Barrett esophagus
British Society of Gastroenterology guidelines on the diagnosis and management of Barrett’s oesophagus

Rebecca C Fitzgerald, 1 Massimiliano di Pietro, 1 Krish Ragunath, 2 Yeng Ang, 3 Jin-Yong Kang, 4 Peter Watson, 5 Nigel Trudgill, 6 Praful Patel, 7 Philip V Kaye, 8 Scott Sanders, 9 Maria O’Donovan, 10 Elizabeth Bird-Lieberman, 11 Pradeep Bhandari, 12 Janusz A Jankowski, 13 Stephen Attwood, 14 Simon L Parsons, 15 Duncan Loft, 16 Jesper Lagergren, 17 Paul Moayyedi, 18 Georgios Lyraizopoulos, 19 John de Caestecker 20

ACG Clinical Guideline: Diagnosis and Management of Barrett’s Esophagus

Nicholas J. Shaheen, MD, MPH, FACP 1, Gary W. Falk, MD, MS, FACP 2, Prasad G. Iyer, MD, MSc, FACP 3 and Lauren Gerson, MD, MSc, FACP 4

Am J Gastroenterol advance online publication, 3 November 2015; doi:10.1038/ajg.2015.322
• Definition?

BSG:

ACG:
• Definition?

BSG:

Barrett’s oesophagus is defined as an oesophagus in which any portion of the normal distal squamous epithelial lining has been replaced by metaplastic columnar epithelium, which is clearly visible endoscopically (≥1 cm) above the GOJ and confirmed histopathologically from oesophageal biopsies (Recommendation grade C).

ACG:

BE should be diagnosed when there is extension of salmon-colored mucosa into the tubular esophagus extending ≥1 cm proximal to the gastroesophageal junction (GEJ) with biopsy confirmation of IM (strong recommendation, low level of evidence).
• What are the arguments for and against IM as prerequisite for the Dg?
• What are the arguments for and against IM as prerequisite for the Dg?
  
- Intestinal metaplasia is biologically more unstable


- Possible sampling error (false negativ Bx)

  Harrison R et al. Detection of intestinal metaplasia in Barrett’s esophagus: an observational comparator study suggests the need for a minimum of eight biopsies. Am J Gastroenterol 2007

- Evolution of IM over the time

  Gatenby PA et al. Relevance of the detection of intestinal metaplasia in non-dysplastic columnar-lined oesophagus. Scand J Gastroenterol 2008
• What are the arguments for and against IM as prerequisite for the Dg?
  - < 50 of endoscopically resected OAC have IM

Takubo K et al. Cardiac rather than intestinal-type background in endoscopic resection specimens of minute Barrett adenocarcinoma. Hum Pathol 2009.
• What are the arguments for and against IM as prerequisite for the Dg?
  - < 50 of endoscopically resected OAC have IM

Takubo K et al. Cardiac rather than intestinal-type background in endoscopic resection specimens of minute Barrett adenocarcinoma. Hum Pathol 2009.

• Is IM of the cardia of concern?
• What are the arguments for and against IM as prerequisite for the Dg?
  - < 50% of endoscopically resected OAC have IM IM

Takubo K et al. Cardiac rather than intestinal-type background in endoscopic resection specimens of minute Barrett adenocarcinoma. Hum Pathol 2009.

• Is IM of the cardia of concern?
  - No, 20% of people harbour IM

• How is the distal esophageal and endoscopically defined?
• How is the distal esophageal and endoscopically defined?

The proximal limit of the longitudinal gastric folds with minimal air insufflation is the easiest landmark to delineate the GOJ and is the suggested minimum requirement (Recommendation grade B).
• How is the distal esophageal and endoscopically defined?

The proximal limit of the longitudinal gastric folds with minimal air insufflation is the easiest landmark to delineate the GOJ and is the suggested minimum requirement (Recommendation grade B).

• Is this a potential Barrett esophagus?
• How is the distal esophageal and endoscopically defined?

The proximal limit of the longitudinal gastric folds with minimal air insufflation is the easiest landmark to delineate the GOJ and is the suggested minimum requirement (Recommendation grade B).

• Is this a potential Barrett esophagus?

No!
• What describes the Prague Classification?
What describes the Prague Classification?
• What should be further recorded?
• What should be further recorded?

<table>
<thead>
<tr>
<th>Finding</th>
<th>Reporting system</th>
<th>Nomenclature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrett’s oesophagus length</td>
<td>Prague classification</td>
<td>CnMn (where n is length in cm)</td>
</tr>
<tr>
<td>Barrett’s islands</td>
<td>Describe distance from the incisors and length in cm</td>
<td>Descriptive in the text</td>
</tr>
<tr>
<td>Hiatus hemia</td>
<td>Distance between diaphragmatic pinch and GOJ</td>
<td>yes/no; cm</td>
</tr>
<tr>
<td>Visible lesions</td>
<td>Number and distance from incisors</td>
<td>yes/no; cm</td>
</tr>
<tr>
<td>Classification of visible lesions</td>
<td>Paris classification</td>
<td>0-Ip, protruded pedunculated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0-I s, protruded sessile</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0-II a, superficial elevated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0-II b, flat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0-II c, superficial depressed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0-III, excavated</td>
</tr>
<tr>
<td>Biopsies</td>
<td>Location and number of samples taken</td>
<td>n cm (distance from incisors) Xn</td>
</tr>
</tbody>
</table>

GOJ, gastro-oesophageal junction.
• Biopsy protocol and important aspects of sampling?
• Biopsy protocol and important aspects of sampling?

- Targeted biopsies from visible lesions
- 4 Quadrant biopsies every 2 cm
- Optimize visualisation (Inspection of the OGJ by inversion if possible, careful flushing, acetic acid, starting distal and basal, inspection time!)
Screening/surveillance

• «Optimal» disease for a screening?
Screening/surveillance

• «Optimal» disease for a screening?
- Disease with a high morbidity/mortality
- A early diagnosis leads to improved survival
- High prevalence of the disease in a certain population
- High positive and negative predictive values of the test
- Cost effective and well tolerated test/treatment
Screening

• What is the prevalence of BE?
Screening

• What's the prevalence of BE?
  - 1.5% (≈15% if GERD)
Screening

• What is the prevalence of BE?
  - 1.5% (≈15% if GERD)

• What are the risk factors of BE?
Screening

• What's the prevalence of BE?
  - 1.5% (≈15% if GERD)

• What are the risk factors of BE?
  - Male gender, caucasian ethnicity
  - Older age
  - History of GERD
  - Possible cigarette smoking
  - Family history
  - Abdominal adiposity
• Is screening recommended?
• Is screening recommended?

Screening with endoscopy is not feasible or justified for an unselected population with gastro-oesophageal reflux symptoms (Recommendation grade B).

Endoscopic screening can be considered in patients with chronic GORD symptoms and multiple risk factors (at least three of age 50 years or older, white race, male sex, obesity). However, the threshold of multiple risk factors should be lowered in the presence of a family history including at least one first-degree relative with Barrett’s or OAC (Recommendation grade C).
Surveillance

• Is there evidence I for surveillance?
Surveillance

- Is there evidence I for surveillance?
  - No, BOSS trial awaited
• What are the most important arguments for the surveillance?
• What are the most important arguments for the surveillance?
  - OAC has a very poor overall 5 year survival < 20%
  - OAC detected by screening have an earlier stage and better survival rate
• What are the most important arguments for the surveillance?
- OAC has a very poor overall 5 year survival < 20%
- OAC detected by screening have an earlier stage and better survival rate

⇒ Usefullness of surveillance proved?
• What are the most important arguments for the surveillance?
- OAC has a very poor overall 5 year survival < 20%
- OAC detected by screening have an earlier stage and better survival rate

⇒ Usefullness of surveillance proved?
- No!
• Why?
• Why?
- Length time bias:
- Lead time bias:

- Disease onset
- Detectable by screening
- Appearance of 1st symptoms
- Survival after diagnosis
- Survival after screening

Apparent increase in life expectancy or lead time
• Is surveillance recommended?
Although RCT data are lacking, given the evidence from the published studies that surveillance correlates with earlier staging and improved survival from cancer, surveillance is generally recommended (Recommendation grade B).

Endoscopic monitoring with histopathological assessment of dysplasia is the only current method of surveillance with sufficient evidence to be recommended (Recommendation grade B).
• What’s the incidence of OAC in BE?
• What’s the incidence of OAC in BE?

- 0.16%/year

- 0.12%/year

- 0.33%/year
• What are the risk factors for malignant progression?
• What are the risk factors for malignant progression?
- Advancing age
- Male gender
- Smoking (HR ≈ 2)!
- Length of Barrett esophagus
- Ulcers, strictures and nodules!
- Lack of PPI, NSAID/ASS, Statins
• What are the risk factors for malignant progression?
  - Advancing age
  - Male gender
  - Smoking (HR ≈ 2)!
  - Length of Barrett esophagus
  - Ulcers, strictures and nodules!
  - Lack of PPI, NSAID/ASS, Statins

Metaanalysis of cohort studies
• Is chemoprevention indicated?
• Is chemoprevention indicated?

There is not yet sufficient evidence to advocate acid suppression drugs as chemopreventive agents (Recommendation grade C).
Use of medications to suppress gastric acid production is recommended for symptom control (Recommendation grade A).
PPIs have the best clinical profile for symptomatic management (Recommendation grade A).

- AspECT trial awaited

26. Patients with BE should receive once-daily PPI therapy. Routine use of twice-daily dosing is not recommended, unless necessitated because of poor control of reflux symptoms or esophagitis (strong recommendation, moderate level of evidence).
• Is chemoprevention indicated?

  There is not yet sufficient evidence to advocate acid suppression drugs as chemopreventive agents (Recommendation grade C).
  Use of medications to suppress gastric acid production is recommended for symptom control (Recommendation grade A).
  PPIs have the best clinical profile for symptomatic management (Recommendation grade A).

- AspECT trial awaited

• Is fundoplicatio indicated?
- Is chemoprevention indicated?

There is not yet sufficient evidence to advocate acid suppression drugs as chemopreventive agents (Recommendation grade C).

Use of medications to suppress gastric acid production is recommended for symptom control (Recommendation grade A).

PPIs have the best clinical profile for symptomatic management (Recommendation grade A).

- AspECT trial awaited

- Is fundoplicatio indicated?

Antireflux surgery is not superior to pharmacological acid suppression for the prevention of neoplastic progression of Barrett's oesophagus (Recommendation grade C).

Antireflux surgery should be considered in patients with poor or partial symptomatic response to PPIs (Recommendation grade A).
• What’s the likelihood to die from an Barrett – unrelated cause in patients without dysplasia?
• What’s the likelihood to die from an Barrett – unrelated cause in patients without dysplasia?
  - > 90%

• What’s the likelyhood to die from an Barrett – unrelated cause in patients without dysplasia? -> 90%


• What’s the risk of progression of dysplasia?
• What’s the likelyhood to die from an Barrett – unrelated cause in patients without dysplasia? 
- > 90%


• What’s the risk of progression of dysplasia?

The risk of cancer progression for patients with nondysplastic is ~0.2–0.5% per year.
For patients with low-grade dysplasia (LGD) the annual risk of progression to cancer is ~0.7% per year.
For patients with high-grade dysplasia (HGD), the annual risk of neoplastic progression is ~7% per year.
• How is the surveillance proposed?
• How is the surveillance proposed?

ECOG score 0-2 (self care possible)

- Maximum length <3cm
  - Gastric metaplasia
    - Repeat OGD*
      - Length <3cm
        - Gastric metaplasia
          - Consider discharging
    - Repeat OGD every 3 to 5 years

- Maximum length <3cm
  - Intestinal metaplasia
    - Repeat OGD every 2 to 3 years

- Maximum length ≥3cm

Clinical review of patient fitness and preference
• How is low grade dysplasia defined?
• How is low grade dysplasia defined?
• How is high grade dysplasia defined?
• How is high grade dysplasia defined?
• Is the interobserver agreement good for dysplasia?
• Is the interobserver agreement good for dysplasia?
  - No, especially for low grad dysplasia

Dysplasia confirmed by two GI pathologists is currently the best tissue biomarker for the assessment of cancer risk (Recommendation grade B).
• Is the interobserver agreement good for dysplasia?
  - No, especially for low grad dysplasia

  Dysplasia confirmed by two GI pathologists is currently the best tissue biomarker for the assessment of cancer risk (Recommendation grade B).

• How it could be improved?
  - Immunostaining with p53
• Is the interobserver agreement good for dysplasia?
  - No, especially for low grad dysplasia

  *Dysplasia confirmed by two GI pathologists is currently the best tissue biomarker for the assessment of cancer risk (Recommendation grade B).*

• How it could be improved?
• Is the interobserver agreement good for dysplasia?
  - No, especially for low grad dysplasia

_Dysplasia confirmed by two GI pathologists is currently the best tissue biomarker for the assessment of cancer risk (Recommendation grade B)._  

• How it could be improved?
  - Immunostaining with p53
Aberrant p53 protein expression is associated with an increased risk of neoplastic progression in patients with Barrett’s oesophagus.


Abstract

OBJECTIVE: The value of surveillance for patients with Barrett’s oesophagus (BO) is under discussion given the overall low incidence of neoplastic progression and lack of discriminative tests for risk stratification. Histological diagnosis of low-grade dysplasia (LGD) is the only accepted predictor for progression to date, but has a low predictive value. The aim of this study was therefore to evaluate the value of p53 immunohistochemistry for predicting neoplastic progression in patients with BO.

DESIGN: We conducted a case-control study within a prospective cohort of 720 patients with BO. Patients who developed high-grade dysplasia (HGD) or oesophageal adenocarcinoma (OAC) were classified as cases and patients without neoplastic progression were classified as controls. P53 protein expression was determined by immunohistochemistry in more than 12 000 biopsies from 635 patients and was scored independently by two expert pathologists who were blinded to long-term outcome.

RESULTS: During follow-up, 49 (8%) patients developed HGD or OAC. P53 overexpression was associated with an increased risk of neoplastic progression in patients with BO after adjusting for age, gender, Barrett length and oesophagitis (adjusted relative risks (RR(a)) 5.6; 95% CI 3.1 to 10.3), but the risk was even higher with loss of p53 expression (RR(a) 14.0; 95% CI 5.3 to 37.2). The positive predictive value for neoplastic progression increased from 15% with histological diagnosis of LGD to 33% with LGD and concurrent aberrant p53 expression.

CONCLUSIONS: Aberrant p53 protein expression is associated with an increased risk of neoplastic progression in patients with BO and appears to be a more powerful predictor of neoplastic progression than histological diagnosis of LGD.
• How should we manage dysplasia?
• How should we manage dysplasia?
• What about the SURF trial?
• What about the SURF trial?
• What about the SURF trial?

Figure 2. Management of nonnodular Barrett’s esophagus (BE). *Although endoscopic eradication therapy is associated with a decreased rate of progression, surveillance upper endoscopy at 1-year intervals is an acceptable alternative. The above schema assumes that the T1a esophageal adenocarcinoma (EAC) displays favorable characteristics for endoscopic therapy, including well-differentiated histology and lack of lymphovascular invasion. EGD, esophagogastroduodenoscopy; HGD, high-grade dysplasia; LGD, low-grade dysplasia; PPI, proton pump inhibitor.
• What are the therapeutic options with HGD?
• What are the therapeutic options with HGD?

**Diagram:**

- **OGD in tertiary referral centre**
  - Macroscopically visible lesion
    - Endoscopic resection
      - HGD or T1a cancer
        - Plan RFA after complete eradication of visible neoplasia
      - T1b cancer
        - Surgery
  - Flat lining throughout after careful inspection with HRE
    - Schedule RFA treatment*
      - T1b sm1 with features of good prognosis
      - Consider endoscopic therapy if patient at high surgical risk
• Risk of lymph node metastasis in T1?
• Risk of lymph node metastasis in T1?
  - T1a: 0-10%
  - T1b SM1: conflicting data, if R0L0 an poor surgical candidate => endoscopic resection
  - T1b SM2-3: Risk up to 46% => Surgery
• What should be done after curative endoscopic resection?
• What should be done after curative endoscopic resection?
- Eradication of BE (>80 have remaining dysplasia, 20% metachronous lesions in 2 years
• What should be done after curative endoscopic resection?
  - Eradication of BE (>80 have remaining dysplasia, 20% metachronous lesions in 2 years)
• Is (PET)-CT indicated if early esophageal cancer is supposed?
• What should be done after curative endoscopic resection?
  - Eradication of BE (>80 have remaining dysplasia, 20% metachronous lesions in 2 years)

• Is (PET)-CT indicated if early esophageal cancer is supposed?
  - No
• What should be done after curative endoscopic resection?
  - Eradication of BE (>80 have remaining dysplasia, 20% metachronous lesions in 2 years)
• Is (PET)-CT indicated if early esophageal cancer is supposed?
  - No
• What about EUS?
• What should be done after curative endoscopic resection?
  - Eradication of BE (>80 have remaining dysplasia, 20% metachronous lesions in 2 years)
• Is (PET)-CT indicated if early esophageal cancer is supposed?
  - No
• What about EUS?
  - Can be done, but frequent over- (15–25%) and understaging (4–12%) of T1 vrs T2
Since EUS can both overstage and understage T1 lesions, its routine use cannot be recommended for staging before ER for suspected early lesions (Recommendation grade B).

In selected cases where the endoscopist cannot exclude advanced stage on the basis of endoscopic appearance of nodular lesions, EUS with or without FNA is recommended to inform the therapeutic decision (Recommendation grade C).

EUS with or without FNA of visible lymph nodes is recommended in selected cases with T1b (sm1) disease on staging ER for which endoscopic therapy is selected, because of the significant risk of lymph nodal involvement (Recommendation grade C).
• How should we follow up the patients?
• How should we follow up the patients?
  - Every 3 month for 1 year, than yearly
  - Biopsies of the prior extend of BE (burried dysplasia!)
• How should we follow up the patients?
  - Every 3 month for 1 year, than yearly
  - Biopsies of the prior extend of BE (burried dysplasia!)