Barrett-Esophagus

Reiner Wiest
Definition - Diagnosis
How is the end of the distal esophagus defined?
How is the end of the distal esophagus defined?

easiest landmark to delineate the GEJ are proximal limit of longitudinal gastric folds at minimal air insufflation and is the suggested as minimal requirement

optional: but not more accurate palisade vessels at the distal end of the esophagus
How is Barrett-esophagus defined?
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BSG:

ACG:
How is Barrett-esophagus defined?

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oesophagus is defined as an oesophagus in which any portion of the normal distal squamous epithelial lining has been replaced by *metaplastic columnar epithelium*, which is clearly visible endoscopically (≥1 cm) above the GOJ and confirmed histopathologically from oesophageal biopsies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:
How is Barrett-esophagus defined?

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oesophagus is defined as an oesophagus in which any portion of the normal distal squamous epithelial lining has been replaced by **metaplastic columnar epithelium**, which is clearly visible endoscopically (≥1 cm) above the GOJ and confirmed histopathologically from oesophageal biopsies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 is the relevance of presence of IM?
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Of the types of metaplastic columnar epithelium in the oesophagus, intestinal is the most biologically unstable with the greatest risk of neoplastic progression through dysplasia to adenocarcinoma

Higher incidence of HGD and cancer in IM (0.38 vs 0.07 %)

IM should be taken into account for surveillance!

Smith Am J Surg Pathol 1984
Bhat J Nat Cancer Inst 2011

Bhat J Nat Cancer Inst 2011
Is this a Barrett-esophagus?
Is this a Barrett-esophagus?
Irregular Z-Line

- Squamocolumnar junction appears with tongues of columnar epithelium shorter than 1 cm and with no confluent columnar-lined segment
- Often harbours IM but with unclear significance
- No Bx recommended
- If Bx are taken labelling as GOJ important
- No surveillance in IM at the cardia or irregular Z-Line
- Whether there is IM or not
How to scope a Barrett-esophagus?
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- Equipment: HD-monitor, -scope, cap
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- Mucus clearance (aqua-jet) plus
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- **Near-Focus-function**

- **Retroflexion in cardia**
- **Long enough inspection time**
- **Particularly “danger” zone**
- **First biopsy most important**
Barrett-Esophagus-Carcinom: NBI + Near Focus
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Well-differentiated Adeno-Carcinoma
T1a N0L0V0 G1 R0
Barrett-Esophagus-Carcinom: NBI + Near Focus

Well-differentiated Adeno-Carcinom
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Barrett esophagus: 3 steps to do (see, capture …….)
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Near Focus
Barrett esophagus: 3 steps to do (see, capture ……)

How long does it take for “loss-of-whitening”?
Barrett esophagus: 3 steps to do (see, capture ……)

How long does it take for “loss-of-whitening”? 

Up to 2 min (for Dysplasia)
Barrett esophagus: 3 steps to do (see, capture ……)
GE-junction – normal or not?
Barrett-Esophagus-Carcinom
Barrett-Esophagus-Carcinom

Moderate differentiated Adeno-Carcinom
T1a N0L0V0 G2 R0
The big 5: What do you need to document in Barrett-report?
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1. Extent of BE: Prag-Classification + any separate island
2. Visible lesion: size, Paris-classification and location in cm from incisors and clockwise orientation
3. Presence or absence of Esophagitis/GERD: Los Angeles classification Hiatal hernie ? (Hill-Classification)
4. Biopsies: locations (in cm from incisors), numbers
5. Photo-documentation of landmarks, lesions
Prague-criteria and classification
Prague-criteria and classification

Maximal extent of metaplasia: $M = 5.0 \text{ cm}$

Circumferential extent of metaplasia: $C = 2.0 \text{ cm}$

True position of GEJ: $\text{Origin} = 0.0 \text{ cm}$
Epidemiology- Cancer Risk
<table>
<thead>
<tr>
<th>BE</th>
<th>indefinite</th>
<th>LGD</th>
<th>HGD</th>
<th>adenocarcinoma</th>
</tr>
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</table>

**Incidence ratio of AC 11.3**

---
What are pre-/incidence of BE?
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- Prevalence of Barrett: 1.3-1.6 % overall (Zagari Gut 2008)
  - Asymptomatic: 1,4 % Symptomatic GERD: 2,3 %
    *but < 40 % of CA do not have GERD*
  - High risk: 13,2 %

  *Westhoff, Gastrointest Endosc 2005; Ronkainen, Gastroenterology 2005*
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• In 2013 500 new diagnosed esophageal cancers
  (Krebsregister Schweiz)
Incidence of Adenocarcinoma
Incidence of Adenocarcinoma among patients with Barrett’s
Incidence of Adenocarcinoma among patients with Barrett’s Esophagus
Incidence of Adenocarcinoma among patients with Barrett’s Esophagus
lower than in historical data
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0.12 % vs 0.5 %
Incidence of Adenocarcinoma among patients with Barrett’s Esophagus

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Frederik Hvid-Jensen et al. N Engl J
Incidence of Adenocarcinoma among patients with Barrett’s Esophagus

lower than in historical data

0.12 % vs 0.5 %

follow up: 5.2 years

What risk factors for BE development do you know – when to screen?
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- male gender,
- caucasian ethnicity
- older age (> 50 ly; OR ≈1.5-2.0 each 10y-increment)
- GERD (chronic > 5y OR≈ 3, > 10y OR ≈6
- cigarette smoking (OR ≈ 2)
- abdominal/Central obesity (OR ≈2)
- axial hernia (OR for long-segment BE ≈12)

positive family history – up to OR 12
(at least one first-degree relative with BE or AC)
in case of pos FA lower threshold
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What are risk factors for Adenocarcinoma-development in Barrett's esophagus?
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What are risk factors for Adenocarcinoma-development in Barrett's esophagus?

- Length of Barrett-mucosa
- Advancing age
- Central obesity
- Smoking
- Ulcers, strictures and nodules!
- Lack of PPI, NSAID/ASS, Statins

Plus ..... Krishnamoorti et al. CGH 2018
Biopsy-regimen / recommendations
Biopsy-regimen / recommendations

Endoscopic report should include number of biopsy samples

**Seattle protocol:**
four-quadrant random biopsies (=4) every 2 cm in addition to targeted biopsies on macroscopically visible lesions
If < 2 cm also try to get 8 biopsies

Levine DS, Blount PL Am J Gastroenterol 2000

Adherence low! -> centres
What potential biomarkers for increased risk in BE do you know?
What potential biomarkers for increased risk in BE do you know?

- DNA content abnormalities
- Chromosomal abnormalities
- Gene mutations
- Methylation changes
- Aberrant p53 expression

But:

no single biomarker is adequate for risk stratification.....
What is the risk for progression to HGD/cancer in BE without dysplasia?
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**Annual progression rate:**
- 0.3% for cancer
- 0.5% for HGD

Cumulative over time
- Extreme high NNT to prevent one cancer

De Jonge et al. Gut 2010
What you know about agreement of pathologists on dysplasia – e.g. LGD?
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Correctly diagnosing LGD is tough

Consensus diagnosis (3 pathologists):

- high risk of progression

agreement between any two pathologists

Kappa -0.4 to 0.28 = poor

Skacal AJG 2000
146 LGD pts reviewed by 2 expert pathologists

- 110 pts NDBE (75%)
- 14 pts Indef (10%)
- 22 pts LGD (15%)

Median FU of 51 months

- 0.49% per patient year
- No HGD/Ca
- 42% HGD/Ca 13.4% per pnt yr

Curvers et al. AJG 2010
146 LGD pts reviewed by 2 expert pathologists

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LGD: overdiagnosed but underestimated

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Curvers et al. AJG 2010
What is the risk for progression to HGD/cancer in dependency on degree of dysplasia?
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<table>
<thead>
<tr>
<th></th>
<th>EAC</th>
<th>HGD</th>
</tr>
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<tbody>
<tr>
<td>LGD: incidental/all</td>
<td>0.5%</td>
<td>1.7%</td>
</tr>
<tr>
<td>uni- vs. multifocal (for EAC or HGD)</td>
<td>1.4% vs. 3.5%</td>
<td></td>
</tr>
<tr>
<td>HGD: any type</td>
<td>7-19%</td>
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What is the likelihood to die of a BE-unrelated cause in non-dysplastic BE?
What is the likelihood to die of a BE-unrelated cause in non-dysplastic BE?

> 90%

Meta-Analysis from 7930 patients

Incidence rate of fatal AC

3/1000 person-years

only 7% of deaths from AC

Sikkema et al. CGH 2010
Treatment and Surveillance
How is surveillance recommended in non-dysplastic BE?

ECOG score 0-2 (self care possible) – fit for endoscopy

- Maximum length <3cm
- Gastric metaplasia

- Maximum length <3cm
- Intestinal metaplasia

- Maximum length ≥3cm
How is surveillance recommended in non-dysplastic BE?

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Repeat OGD*

Length <3cm
Gastric metaplasia

Consider discharging

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0.05 % malignant conversion per annum

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  - Repeat OGD every 3 to 5 years

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- Maximum length ≥3cm
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Repeat OGD every 3 to 5 years

- Maximum length ≥3cm

Repeat OGD every 2 to 3 years
Chemoprevention in barrett-esophagus – what to do?
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PPI-therapy: at least once daily
Most likely twice daily better in delaying AC/HGD
Aspirin 300mg in combination with high-dose PPI
strongest protective effect

Lancet 2018: 392: 400ff
Plus Editorial Hvid et al. Lancet 2018
Figure 4  Surveillance flow chart for dysplastic Barrett’s oesophagus (BO). A pathological finding of indefinite for dysplasia does not exclude the presence of dysplasia, therefore a 6-month follow-up is warranted. Six-monthly surveillance and endoscopic treatment are generally recommended for low-grade and high-grade dysplasia, respectively. MDT, multidisciplinary team; OGD, oesophagogastroduodenoscopy.
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What to do when LGD is confirmed?
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RCT: RFA vs. surveillance (3 year follow-up)

Phoa et al. JAMA 2014
What are the therapeutic options for HGD?
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- **OGD in tertiary referral centre**
- **Macroscopically visible lesion**
  - Endoscopic resection
  - HGD or T1a cancer
    - Plan RFA after complete eradication of visible neoplasia
  - T1b cancer
  - T1b sm1 with features of good prognosis
  - Consider endoscopic therapy if patient at high surgical risk
- **Flat lining throughout after careful inspection with HRE**
What are the therapeutic options for HGD?

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      - **T1b cancer**
        - Surgery
  - **Flat lining throughout after careful inspection with HRE**
    - **Schedule RFA treatment***
      - **T1b sm1 with features of good prognosis**
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When is EMR/ESD curative? when further treatment needed?
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- T1a or T1b
- sm1
- G1 or 2
- L0
- V0
- R0
When is EMR/ESD curative?  
when further treatment needed?

all features

- T1a or T1b
- sm1
- G1 or 2
- L0
- V0
- R0

any of features

- T1b with
- > sm1
- undifferentiated
- L+
- V+
- R1 deep margin
When is EMR/ESD curative? When further treatment needed?

- **T1a or T1b**
  - sm1
  - G1 or 2
  - L0
  - V0
  - R0

- **T1b with**
  - > sm1
  - undifferentiated
  - L+
  - V+
  - R1 deep margin

**Lymph node positivity**
- < 2%

Any of features
Rate of LN-positivity in early BE-cancer

Manner et al. CGH 2013
Rate of LN-positivity in early BE-cancer

Manner et al. CGH 2013
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<table>
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<tr>
<th>Features</th>
<th>Sm 2</th>
<th>Sm 3</th>
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<tbody>
<tr>
<td>Low risk: G1-2,L0,V0..</td>
<td>8.3%</td>
<td>28.6%</td>
</tr>
<tr>
<td>High-risk: any other</td>
<td>26.3%</td>
<td>37.5%</td>
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Rate of LN-positivity in early BE-cancer

Diagnostic accuracy

T1b vs. 1a EUS best modality
LN+ EUS-FNA + CT/MR (DWI)
NPV suboptimal
(55 - 90 %)

Manner et al. CGH 2013
Is (PET)-CT indicated if early esophageal cancer is supposed?

Not strictly

What about EUS?

Can be done, but frequent over- (15–25%) and understaging (4–12%) of T1 vrs T2
What to do after successful curative EMR?

Eradication of BE

at best by RFA

> 80% have remaining dysplasia, 20% metachronous lesions in 2 years
How to follow-up after curative EMR (HGD/EAC)
How to follow-up after curative EMR (HGD/EAC)

every 3 month for 1 year,
then 6-months in second year
afterwards annually

biopsies of the prior extend of BE
(buried dysplasia!)
4-quadrant every 1 cm !!
and always also from GEJ
How to follow-up after BE-ablation for LGD?
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Every 6 months in first year then annually
How to follow-up after BE-ablation for LGD?

Every 6 months in first year then annually

What is the recurrence rate after BE-ablation?
How to follow-up after BE-ablation for LGD?

Every 6 months in first year
then annually

What is the recurrence rate after BE-ablation?

> 20% at 2-3 years
Up to 25% with HGD/EAC
• 68 year old male patient.
• C9M10 BE with a subtle visible abnormality upon WLE.
• Treatment: piecemeal endoscopic resection.
Desmin stain

- Muscularis
- Adenocarcinoma
- Submucosa
• Poorly differentiated adenocarcinoma.
• Signet-ring cells.
• Submucosal infiltration.
• Vaso-invasion.

Esophagectomy

T1sm3 G3 V1 L1 N1
If you doubt cut it out!
Every hint on visible lesion
when ever you think of that there is something different go for EMR