General Remarks on the Esophagogastric Junction (EGJ)
Prof. Marco Novelli
Definition of EGJ
Definition of EGJ
Natural variation of true EGJ and squamo-columnar junction of up to 20mm!

No fixed structure. Moves proximally or distally depending on in-/exspiration
Hiatal hernia as seen from corpus
Columnar lined oesophagus (CLO) = «Barrett’s mucosa»

- True increase in prevalence (not just bc. increased endoscopy) incl. assoc. carcinoma

- Interesting:
  H. pylori infection is thought to be protective against CLO (lack of H.p. causes lower pH?)

- *Def.*: The replacement of the lower oesophageal squamous mucosa by metaplastic glandular mucosa as a result of GERD
Figure 5.1 A definitive diagnosis of columnar-lined oesophagus (CLO) can be made from this biopsy specimen. There is glandular mucosa with a squamous island on the surface with juxtaposed native oesophageal structures, a submucosal gland and its duct beneath. In serial sections, the gland duct will lead into, and form, the squamous island.
Figure 5.2 Typical columnar-lined oesophagus (CLO) mucosa seen in a biopsy. There is predominant cardiac-type epithelium (right) and intestinalised epithelium (left). Occasional specialised fundic-type glands are also present at right. This is the typical ‘patchwork’ mucosa of CLO.
What kind of goblets?

• Difficult to differentiate
  
  – «True» CLO vs. gastric intestinal metaplasia
  
  – Some data suggest that MUC-1 and MUC-6 may be quite specific for CLO goblets, but poor sensitivity.
  
  – CK7 and CK20 not helpful
• “No goblets, no Barrett’s” no longer set in stone:

  – Classic (long segment) CLO is essentially an *endoscopic* diagnosis (UK, Japan)

  – Short and ultrashort segment CLO entirely *pathological* diagnosis
Forget goblets in classic CLO

• Sampling issue

• Non-goblet cell population shows molecular changes similar to the ones in goblets

• Well-defined risk of neoplasia in those with CLO but without goblets

N. Shepherd:
«Powerful grounds to abolish demonstration of goblets for the diagnosis of CLO»
Figure 5.1 A definitive diagnosis of columnar-lined oesophagus (CLO) can be made from this biopsy specimen. There is glandular mucosa with a squamous island on the surface with juxtaposed native oesophageal structures, a submucosal gland and its duct beneath. In serial sections, the gland duct will lead into, and form, the squamous island.
Squamous islands
Figure 5.5 A hybrid gland beneath intestinalised surface mucosa.

Squamous islands

Hybrid gland
• Histology becomes *corroborative* of an endoscopic diagnosis of CLO
  – Information essential, e.g. hiatal hernia?

• Histology more of use when endoscopic features are equivocal, esp. in short-segment disease

• Category reporting strategy (similar to Wotherspoon, Lerner etc.)
**PRAGUE CRITERIA**

For Endoscopically Suspected Esophageal Columnar Metaplasia/Barrett's Esophagus

Developed by the Barrett's Oesophagus Subgroup of the International Working Group for the Classification of Reflux Oesophagitis (IWGCO)

1. Ensure Hiatus Hernia Is Recognised By Distinguishing Diaphragmatic Hiatal Impression From Gastroesophageal Junction

2. Locate Gastroesophageal Junction By Depth Of Endoscope Insertion* At Level Of:
   - tops of gastric mucosal folds
   - sphincter “pinch”
   = 36 cm

3. Look For Displacement Of Squamocolumnar Junction Above Gastroesophageal Junction

4. Measure Depth Of Endoscope Insertion* At The Most Proximal Circumferential Extent Of Suspected Columnar Metaplasia*  
   = 33 cm

5. Measure Depth Of Endoscope Insertion* At The Maximum Extent Of Suspected Columnar Metaplasia*  
   = 29 cm

6. Subtract the Depth of Insertion for Circumferential and Maximum Extents from the Depth of Endoscope Insertion at the Gastroesophageal Junction:
   - $36 cm - 33 cm = C3$
   - $36 cm - 29 cm = M7$
   - Prague C3 and M7

* To the nearest centimeter
* Squamous and columnar islands do NOT contribute to measures of extent
* To the nearest centimeter, except when areas of columnar metaplasia are estimated to be less than 1 cm, report this as <1 cm

Source: J Gastroenterol Hepatol © 2008 Blackwell Publishing
Figure 4. Video still of endoscopic Barrett’s esophagus showing an area classified as C2M5. C: extent of circumferential metaplasia; M: maximal extent of the metaplasia (C plus a distal “tongue” of 3 cm).
Dysplasia in CLO

– 2 GI histopathologists to review all diagnoses of dysplasia and indefinite for dysplasia.

– Reason for use of “indefinite for dysplasia” should be provided.

– p53 immunostaining may improve the diagnostic reproducibility of a diagnosis of dysplasia.
p53

• Potentially useful but need to “know” your own lab’s p53

• Significant staining pattern
  – Strong staining
  – Absent staining

Dysplasia does not always demonstrate a significant staining pattern.

Mutations resulting in deletion or truncation of the protein will not be detected by immunohistochemistry.
Significant p53 staining may not always indicate a mutation, but in some cases could represent wild-type overexpression.
In some cases non dysplastic epithelium shows a significant staining pattern. This suggests the changes in p53 expression or mutation antedate the dysplasia seen on histology.

-> limited use of p53 immunohistochemistry
Dysplasia in CLO

- 2 tier system
  - low grade
  - high grade
  - indefinite for dysplasia

- Impossible to define strict criteria low vs. high grade

- Variation in grading even among experts; poor interobserver variability

- Lack of maturation toward surface is single most useful criterion for diagnosis of dysplasia
  - but: basal crypt dysplasia-like atypia (BCDA) possible rare form of dysplasia) -> «indefinite»

- Abrupt transition favors dysplasia
Dysplasia in CLO

Low grade:

- Similar to mild/moderate dysplasia in colonic adenomas
- Mitotic activity may be substantial
- Atypical mitoses may be present!

**Figure 5.9** Low grade dysplasia in columnar-lined oesophagus. The sharp cut-offs between non-neoplastic foveolar-type epithelium and truly dysplastic epithelium, especially at the surface, are a helpful feature for the diagnosis of true low grade dysplasia.
Dysplasia in CLO

High grade:

• Severe cytological atypia
• Pronounced cellular dysorganisation
• Complex architectural changes
• Intraluminal necrotic debris

Figure 5.10 High grade dysplasia in columnar-lined oesophagus. There are notable cytological abnormalities with a villiform architecture.
Dysplasia in CLO

• «Indefinite for dysplasia» if not possible to confidently rule out dysplasia

1. Inflammation and regenerative changes

2. Polymorphism of juxtaposed cell-types (patchwork mucosa)

3. Artefact (crush, tangential sectioning)

4. Squamous reepithelialisation (obscures maturation)
Figure 5.8 Squamous re-epithelialisation in high grade dysplastic columnar-lined oesophagus. The latter diagnosis is clear for the epithelium at the extreme left but the unwary pathologist might regard the isolated glands underneath the surface squamous epithelium as representing invasive adenocarcinoma beneath native oesophageal squamous mucosa.
Basal crypt dysplasia-like atypia BCDA

Crypt dysplasia with surface maturation
Dysplasia and Carcinoma in CLO

- Distinction dysplasia – carcinoma not always clear cut

- Variation among experts and among countries:
  - Japan: Emphasis on cytological atypia, disruption of basement membrane not required for carcinoma!
  - West: Emphasis on architectural changes, unequivocal infiltration.
Dysplasia and Carcinoma in CLO

• EU/USA guidelines:

  high-grade dysplasia -> oesophagectomy (mortality/morbidity!)

  future:
  chromo-endoscopy, narrow band imaging, autofluorescence endoscopy

  -> EMR +- ablative therapy
Carcinoma
Carcinoma

- Oesophageal?
- Gastric?
- of EGJ?
Classification of adenocarcinoma of the oesophagogastric junction

J. R. Siewert
H. J. Stein

British Journal of Surgery 1998, 85, 1457–1459

"We have defined and described adenocarcinomas of the oesophagogastric junction as tumours that have their centre within 5 cm proximal and distal of the anatomical cardia and have differentiated the following three distinct tumour entities within this area\(^1,3\):"

<table>
<thead>
<tr>
<th>Type I tumour</th>
<th>Adenocarcinoma of the distal oesophagus which usually arises from an area with specialized intestinal metaplasia of the oesophagus (i.e. Barrett’s oesophagus) and which may infiltrate the oesophagogastric junction from above.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type II tumour</td>
<td>True carcinoma of the cardia arising from the cardiac epithelium or short segments with intestinal metaplasia at the oesophagogastric junction; this entity is also often referred to as ‘junctional carcinoma’.</td>
</tr>
<tr>
<td>Type III tumour</td>
<td>Subcardial gastric carcinoma which infiltrates the oesophagogastric junction and distal oesophagus from below.</td>
</tr>
</tbody>
</table>

Siewert classification of EGJ tumors

Type I

Type II

Type III

5 cm

1 cm

0 cm

-2 cm

-5 cm
Siewert classification of EGJ tumors

- Type I
- Type II
- Type III

Mediastinal LN
Abdominal LN

cm
TNM 5th/6th ed.

No separate TNM for EGJ

Stomach cancer

<5cm

Oesophageal cancer

<5cm
TNM Classification of malignant Tumours – Fifth Edition 1997

Oesophagus

- pT2
- pT3

Stomach

- pT2
- pT2

Colorectum

- pT2
- pT3
Oesophagus

Stomach

Colorectum

pT2  pT3

Mucosa  Submucosa

Muscularis propria

Subserosa  Serosa

pT2  pT3  pT2  pT3  pT2  pT3
TNM 7th ed.

Still no separate TNM for EGJ, but doesn’t matter…

Stomach TNM = Oesophagus TNM

<5cm
Assessment of invasion
Colorectal carcinoma
Benign glands in Barrett’s often extend in between bundles of smooth muscle
Pseudo-invasion in high grade dysplasia
Early oesophageal adenocarcinoma often lacks a desmoplastic stroma
pT staging of early adenocarcinoma
# Oesophageal adenocarcinoma T staging, TNM 7

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>High-grade dysplasia</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades lamina propria, muscularis mucosae, or submucosa</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor invades lamina propria or muscularis mucosae</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor invades submucosa</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades muscularis propria</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades adventitia</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades adjacent structures</td>
</tr>
<tr>
<td>T4a</td>
<td>Resectable tumor invading pleura, pericardium, or diaphragm</td>
</tr>
<tr>
<td>T4b</td>
<td>Unresectable tumor invading other adjacent structures, such as the aorta, vertebral body, and trachea</td>
</tr>
</tbody>
</table>
Significance of the Depth of Tumor Invasion and Lymph Node Metastasis in Superficially Invasive (T1) Esophageal Adenocarcinoma

T1a – lamina propria. T1b – muscularis mucosae. T1c – superficial submucosa. T1d – deep submucosa.

Double muscularis mucosae in 87.5% Barrett’s patients and none of the non-Barrett’s patients!!

• Mostly pT1
• Submucosal invasion?
• May be difficult to assess as splaying/reduplication of muscularis mucosa)
**Staging of EMRs**

**pT1a**

- M1 – Limited to the epithelial layer (HGD/IMC).
- M2 – Invades the lamina propria.
- M3 – Invades into but not through the muscularis mucosae.

**pT1b**

- Sm1 – Infiltrates submucosa <500 microns.
- Sm2 – Infiltrates submucosa <1000 microns.
- Sm3 – Infiltrates submucosa ≥1000 microns.
Danke