Upper GIT IV
Gastric cancer

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• Introduction
• Classification
• Morphogenesis
• Problems
  – Intraepithelial neoplasia
  – Surveillance
  – EGJ
• Predictive factors
Gastric cancer

• Fifth most common malignancy worldwide
  – 70% in developing countries

• Third leading of cancer death worldwide
  – Far East
  – Central and East Europe

Classification

- Adenocarcinoma
  - Papillary
  - Tubular
  - Mucinous
  - Poorly cohesive
  - Mixed
  - Adenosquamous
  - With lymphoid stroma (medullary)
  - Hepatoid
  - Squamous
Classification

• Laurén
  – Intestinal
  – Diffuse
  – Mixed
  – Indeterminate

• Ming
  – Expanding
  – Infiltrative

• Mulligan
  – Mucus
  – Intestinal
  – Pyloro-cardiac

• Carneiro
  – Morphology/Immuno phenotype
Classification: meaning

- **Intestinal**
  - „Epidemic“
  - Men, > 60y
  - Antrum
  - Cohesive
  - Liver metastasis
  - Gastritis, HP, IM
  - Longer surviving

- **Diffuse**
  - „Endemic“
  - Women, < 60y
  - Corpus
  - Dysc., SR (CDH)
  - Diffuse metastasis
  - Sup. Gastritis (?)
  - Poorer prognosis (?)
Correa cascade
„Currently used classifications... take into consideration the presence of Paneth cells (complete metaplasia) or crescent architecture changes, dedifferentiation, and degree of absence of Paneth cells (incomplete metaplasia)“

„Endoscopic surveillance should be offered to patients with extensive... intestinal metaplasia (i.e... intestinal metaplasia in the antrum and corpus)“

Dinis-Ribeiro et al., Endoscopy, 2012
Intraepithelial neoplasia (dysplasia)

• No dysplasia
• Indefinite for dysplasia
  – Reactive changes, decreasing from basis to surface
  – NB: this is **not** a final diagnosis
• Dysplasia
  – Low-grade, high-grade
  – Intestinal, gastric type
  – Adenoma if protruding and/or elevated
• Intramucosal carcinoma
Dysplasia: special cases

• Foveolar dysplasia
• Pyloric-type dysplasia

• Dysplasia in FGP, HP
  – FAP?

• Signet-ring cell carcinoma in-situ
  – HGC

Dysplasia: management

• **LG-dysplasia**
  - Regression up to 75%
  - 0-23% malignant transformation
  - Surveillance

• **HG-dysplasia**
  - Regression up to 16%
  - 60-85% malignant transformation
  - Endoscopic mucosal resection

*Alfaro & Lauwers, Adv Anat Pathol, 2011*
Early gastric cancer

- Limited to mucosa (pT1a) and submucosa (pT1b)
- Biologically stable
- Very good prognosis (5-ys surv. > 90%)
Early gastric cancer

- <60ys, size>$20mm$, SM invasion >500mm, ulceration, type IIb, IIc, III, SR histology high risk node metastasis

- Conservative treatment
  - Endoscopic mucosal resection
  - Endoscopic submucosal dissection

*Alfaro & Lauwers, Adv Anat Pathol, 2011*
Oeso-gastric junction

„The EGJ is defined differently by anatomists, physiologists, endoscopists and pathologist“

Marsman et al., JSO, 2005
TNM 7th Edition

- **Oesophagus**
  - T1. Tumour invades lamina propria or submucosa
  - T2. Tumour invades muscularis propria
  - T3. Tumour invades adventitia
  - T4. Tumour invades adjacent structures

- **Stomach**
  - T1. Tumour invades lamina propria or submucosa
  - T2. Tumour invades muscularis propria or subserosa
    - T2a. Tumour invades muscularis propria
    - T2b. Tumour invades subserosa
  - T3. Tumour penetrates serosa (visceral peritoneum) without invasion of adjacent structures
  - T4. Tumour invades adjacent structures
“...if the epicentre of a tumour is within 5 cm of the oesophagogastric junction and extends into the distal oesophagus, the tumour should be staged as an oesophageal carcinoma“

WHO, 2010

Sehdev and Catenacci, Discov Med, 2014
Predictive factor(s)
<table>
<thead>
<tr>
<th>Her2 Status in GC</th>
<th>Predictive Value</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC0/FISH+</td>
<td>1.0</td>
<td>0.92</td>
</tr>
<tr>
<td>IHC1+/FISH+</td>
<td>0.8</td>
<td>1.24</td>
</tr>
<tr>
<td>IHC2+/FISH+</td>
<td>0.6</td>
<td>0.75</td>
</tr>
<tr>
<td>IHC3+/FISH+</td>
<td>0.4</td>
<td>0.58</td>
</tr>
<tr>
<td>IHC3+/FISH-</td>
<td>0.2</td>
<td>0.83</td>
</tr>
</tbody>
</table>

**Median OS (months)**

- IHC0/FISH+: 61, 7.2 vs 10.6
- IHC1+/FISH+: 70, 10.2 vs 8.7
- IHC2+/FISH+: 159, 10.8 vs 12.3
- IHC3+/FISH+: 256, 12.3 vs 17.9
- IHC3+/FISH-: 15, 17. vs 17.5

**Event**

- FC + T: 11.8 vs 13.8, 0.74, p=0.0046

Assessment of HER2 protein overexpression and HER2 gene amplification in metastatic gastric cancer should be performed using FDA-approved tests specifically for gastric cancers due to differences in gastric vs. breast histopathology, including incomplete membrane staining and more frequent heterogeneous expression of HER2 seen in gastric cancers. Study 7 demonstrated that gene amplification and protein overexpression were not as well correlated as with breast cancer.

http://www.accessdata.fda.gov
How to test

- **Immunohistochemistry**
  - 0 - 1+ negative
  - 3+ positive
  - 2+ „equivocal“

- **ISH (FISH, CISH, SISH)**
  - Ratio HER2/CEP17 < 2.0 negative
  - Ratio HER2/CEP17 ≥ 2.0 positive
IHC

HER2/CEP17: 1.3

FISH

HER2/CEP17: 9.6
IHC

0,1+<br>ISH+

2+<br>Trastuzumab

3+
CMET

- IHC „Score“, semiquantitative
- > 50% 2+-3+ Positiv
- If not evaluable/not sure, then FISH
„Eine (neo)adjuvante Therapie mit zielgerichteten Substanzen alleine oder in Kombination mit Chemotherapie soll ausserhalb von Studien nicht durchgeführt werden“

S-3 Leitlinien zum Magenkarzinom, 2013
Literatur

• Bosman et al. (eds.), *WHO Classification of Tumours of the Digestive System*, 4th ed., Lyon, IARC, 2010
• AWMF, DKG, *S-3 Leitlinie zur Diagnostik und Therapie der Adenokarzinome des Magens und ösophagogastralen Übergangs*, Berlin, 2012
• Gomez-Martìn et al., *Cancer Lett*, 2014;351:30-40