Esophageal cancer: Biology, natural history, staging and therapeutic options

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Anatomy

Esophageal cancer

Cardia cancer (Type I-III)

(Subcardial) Stomach cancer
### Anatomy / Definitions

<table>
<thead>
<tr>
<th>Siewert Type</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mediastinal Stations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Paratracheal</td>
<td>4%</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>2. Carinal</td>
<td>10%</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>3. Left bronchial</td>
<td>15%</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>4. Right bronchial</td>
<td>19%</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>5. Para-aortic</td>
<td>20%</td>
<td>2%</td>
<td>-</td>
</tr>
<tr>
<td>6. Middle and lower paraesophageal</td>
<td>55%</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Abdominal Stations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Right paracardial</td>
<td>41%</td>
<td>46%</td>
<td>-</td>
</tr>
<tr>
<td>9. Left paracardial</td>
<td>32%</td>
<td>50%</td>
<td>-</td>
</tr>
<tr>
<td>10. Left gastric</td>
<td>60%</td>
<td>65%</td>
<td>24%</td>
</tr>
<tr>
<td>11. Lesser curve</td>
<td>14%</td>
<td>65%</td>
<td>41%</td>
</tr>
<tr>
<td>12. Common hepatic</td>
<td>3%</td>
<td>16%</td>
<td>17%</td>
</tr>
<tr>
<td>13. Splenic artery</td>
<td>6%</td>
<td>30%</td>
<td>28%</td>
</tr>
<tr>
<td>14. Coeliac axis</td>
<td>5%</td>
<td>30%</td>
<td>-</td>
</tr>
</tbody>
</table>

**Siewert, Type I:** "Esophageal cancer" (80% Barrett)

**Siewert, Type II:** "True" cardia cancer (stomach)

**Siewert, Type III:** "Gastric cancer"
"In the Western world, distal esophageal and GE adenocarcinoma is increasing in incidence faster than any other type of gastrointestinal cancer"

(Blot, Jama 1991)

Metaplasia – Dysplasia - Adenocarcinoma

Reflux/Barrett

Alcohol, smoking, obesity, dietary deficiency, Helicobacter pylori, oro-pharyngeal cancer, …
Staging & Resectability assessment

AJCC & UICC staging correlate to longterm survival, but estimates need improvement..

AJCC does not accurately predict survival in patients receiving multimodal therapy
(Rizk, J Clin Oncol 2007)

Malignant LN
Total number of examined LN
(Rizk, J Thorac Cardiovasc Surg 2006)
Genes/molecules with prognostic impact

<table>
<thead>
<tr>
<th>Gene/Molecule</th>
<th>Prognostic Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>cyclin D1</td>
<td>E-cadherin</td>
</tr>
<tr>
<td>beta-catenin</td>
<td>uPA</td>
</tr>
<tr>
<td>EGFR, Her-2/Neu</td>
<td>MMP-1,3,7,9</td>
</tr>
<tr>
<td>APC, TGF-beta</td>
<td>TIMP</td>
</tr>
<tr>
<td>Endoglin</td>
<td>T( h )1/T( h )2 balance</td>
</tr>
<tr>
<td>CTGF, P53, Bcl-2</td>
<td>CRP, Cox-2</td>
</tr>
<tr>
<td></td>
<td>NF-kappaB</td>
</tr>
</tbody>
</table>

The best prognostic estimate is probably a combination of:
- several biomarkers
- macroscopically and microscopically
description of tumor extent and lymph node involvement

(Lagarde, Ann Surg Oncol 2007)
Staging & Resectability assessment

Multidisciplinary teams are associated with improved outcome in esophageal cancer
(Stephens, Dis Esophagus 2006)

High-volume referral centers detect more metastases in EC than regional centers
(van Vliet, Am J Gastroenterol 2006)
Staging & Resectability assessment

Esophageal cancer

- Poor general condition/severe co-morbidity → Palliation
- CT/PET-CT (Thorax/abdomen)

EUS

- Neo-adjuvant therapy NOT indicated
- Neo-adjuvant therapy Indicated → PET-CT
  - 2-3 weeks therapy
  - 2-3 weeks therapy → PET-CT

Laparoscopy + LUS (Thoracoscopy)

- Non-Responders
- Responders
  - Con’t Neo-adjuvant therapy

Adjuvant therapy

Resection
**Staging: Cost-effectiveness**

- **CT+US vs EUS vs CT+LAP vs EUS+LAP/LUS**

  **EUS+LAP/LUS superior to CT based strategies**

  (Mortensen, Surg Endosc 2000)

- **CT vs EUS-FNA vs PET-CT vs Thoracoscopy/la.p.sc vs combined strategies**

  **EUS-FNA + CT most inexpensive strategy**

  (Using PET-CT in stead of CT increased the figures, but was also more expensive)

Don’t forget the neck!

10-15% of the patients have malignant supraclavicular nodes

(Van Vliet, J Surg Oncol 2007)

US-FNA is cheap and simple
Staging & Resectability assessment

Esophageal cancer

Neck US (FNA)

CT/PET-CT (Thorax/abdomen)

EUS

Disseminated disease

Poor general condition/severe co-morbidity

Palliation

Neo-adjuvant therapy indicated

Neo-adjuvant therapy NOT indicated

Laparoscopy + LUS (Thoracoscopy)

Resection

Adjuvant therapy

Responders

Con’t Neo-adjuvant therapy

Non-Responders

PET-CT

2-3 weeks therapy
Treatment options

**Intended Curative**

*Esophagectomy or resection of distal esophagus/proximal stomach*

*Endoscopic Mucosal Resection (EMR)*

*Definitive chemoradiotherapy*

**Palliative**

*Relieving dysphagia*

*Prolonging survival (chemotherapy)*

*Symptomatic treatment*
Treatment

- (left-sided) Thoraco-abdominal resection
- Transhiatal resection
- Combined abdominal and right sided thoracotomy (Lewis-Tanner)
- Abdominal resection (selected type (II)/III)
Surgical Treatment

Combined abdominal and right sided thoracotomcy

OPEN resection

THORACOSCOPIC/
LAPAROSCOPIC
resection
Minimally invasive surgery

Virtual CT thoracoscopy simulation

(Morita, Abdom Imaging 2007)

Virtual CT laparoscopic simulation

Thoracoscopic and Laparoscopic Ultrasound (TUS / LUS) may provide important information during minimally invasive procedures.
Minimally invasive surgery

Open vs Thoracoscopic assisted vs Minimally invasive

Median blood loss: Minimally invasive < Assisted < Open
Operating time: Assisted < Open < Minimally invasive
Median hospitalization: Minimally invasive < Assisted < Open
Advanced disease: Open > Minimally invasive > Assisted
Stricture formation: Open < Assisted < Minimally invasive
Survival and lymph node clearance: no differences

(Smithers, Ann Surg 2007)
EMR in cancers invading the muscularis mucosa is controversial...

(retrospective, multicentre study, N0, n=104 (111 lesions)

86 patients no further treatment
2 (1.9%) developed LN mets.
1 (1%) organ mets.
23 (20.7%) local recurrence
5-y cause-specific survival was 95%

(Katada, Endoscopy 2007)
Neo-Adjuvant Treatment

Mucinous cancer and Signet-ring cell cancer seem to have improved response to neo-adjuvant CRT

(Chirieac, Clin Cancer Res 2005)

(and neo-adjuvant therapy may provide a better chance of R0 resection in large GE junction tumors)

Neo-adjuvant therapy + surgery > surgery alone in esophageal cancer, but there may be an increased operative risk

(Gebski, Lancet Oncol 2007)
Size (proportion) of residual carcinoma after CRT in esophageal cancer is significantly correlated with patterns of locoregional and distant failure

(Rothagi, Cancer 2005)

Therefore, we need to find the responders within a few weeks of treatment!

PET-CT is superior to other imaging modalities regarding the identification of responders to neoadjuvant therapy

(Wong, Abdom Imaging 2007)
Neo-Adjuvant Treatment

Esophageal cancer

- Neck US (FNA)
- CT/PET-CT (Thorax/abdomen)
- EUS

- Poor general condition/severe co-morbidity
- Disseminated disease

Palliation

Neo-adjuvant therapy Indicated

- PET-CT
- 2-3 weeks therapy

- PET-CT

Responders

- Con’t Neo-adjuvant therapy

Non-Responders

Adjuvant therapy

Resection
Prognostic factors following surgery

Preoperative morbidity (but not age) is important
(Johansson, J Gastrointest Surg 2000)

30-d morbidity and mortality are lower in high-volume centers
(Dimick, Ann Thorac Surg 2001)

30-d mortality < 5% in experienced centers
Prognostic factors following surgery

Size, differentiation and subtype
  T stage
  N stage
Vascular invasion
Perineural and lymphatic invasion

Ratio: Invaded/removed lymph nodes

Residual tumor (R1/R2)
  - proximal margin
  - distal margin
  - circumferential margin (< 1mm)

(Saha, Dis Esophagus 2001)
(Dexter, Gut 2001)
(Griffiths, Eur J Surg Oncol 2006)
Prognostic factors following surgery

**En-bloc vs transhiatal resection**

50% vs 25% 5-y survival

(Sihvo, Am J Gastroenterol 2004)

En-bloc > Transhiatal

...if 1-8 positive nodes!

(>8 positive nodes: n.d.)

(Johansson, Arch Surg 2004)
Palliative

Relieving dysphagia (APC/SEMS)
Conclusion

Multidisciplinary evaluation & treatment

High-volume centers

Individual staging and tailored treatment

Identification of responders/non-responders to neo-adjuvant (adjuvant) therapy

Focus on molecular, genetic and other factors regarding diagnosis, classification and treatment