ESMO Clinical Practice Guidelines

Resectable locally advanced oesophagogastric cancer

Clinical Case Discussion

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Honoraria for advisory role, membership in data safety board or lectures for Astellas, Astra Zeneca, Amgen, Biontech, BMS, Elsevier, MSD, Roche, Servier
Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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Minimally invasive surgery for cancer of the oesophagus
Minimally Invasive Oesophagectomy (MIO)

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1969-2017
cTNM, clinical staging tumour, node and metastasis; EUS, endoscopic ultrasound; FDG-PET, fluorodeoxy glucose-positron-emission tomography; MS-CT, multiple-slice helical computed tomography
Oesophageal Cancer

Differences: Adenocarcinoma versus Squamous Cell Carcinoma

- Epidemiology and risk factors
- Location
- Comorbidities
- Survival outcomes
- Biology

Pohl & Welch. J Natl Canc Inst 2005
CIMP, CpG island methylator phenotype; EBV, Epstein-Barr Virus; ESCC, oesophageal squamous cell carcinoma; GEJ, oesophagogastric junction; GS, genomic stability; MSI, microsatellite instability
Siewert’s classification of EGJ tumors

**AEG I**  Adenocarcinoma of the distal esophagus (Barrett cancer)
**AEG II** “True” cardia cancer
**AEG III**  Subcardial cancer of the stomach with infiltration of the cardia

**UICC 8th edition**
AEG I + II: Oesophageal CA
AEG III: Gastric CA

Mariette C. Lancet 2011

AEG, adenocarcinomas of the oesophagogastric junction; CA, carcinoma; EGJ, oesophagogastric junction; UICC, Union for International Cancer Control
cTNM, clinical staging tumour, node and metastasis; EUS, endoscopic ultrasound; FDG-PET, fluorodeoxy glucose-potiton-emission tomography; MS-CT, multiple-slice helical computed tomography
Adeno-CA CTX versus Radio-CTX

Previous studies

- **Neoadjuvant chemotherapy is effective:** OE-2
  
  Sjoquist et al. 2011 (Metaanalysis), Allum et al. 2002 and 2009

- **Neoadjuvant chemoradiation is effective:** CROSS
  
  Sjoquist et al. 2011 (Metaanalysis), Van Hagen et al. 2012, Songun et al. 2015

- **Few direct comparisons of CTX versus R-CTX**
  
  Stahl et al. 2009 / 2017 (POET); Klevebro et al. 2016 (Scandinavian)

CA, carcinoma; CRT, chemoradiotherapy; CTX, chemotherapy; R-CTX, Radio-chemotherapy
FLOT perioperative CTX

- Gastric cancer or adenocarcinoma of the gastro-oesophageal junction type I-III
- Medically and technically operable
- cT2-4/cN-any/cM0 or cT- any/cN+/cM0

Stratification: ECOG (0 or 1 vs. 2), location of primary (GEJ type I vs. type II/III vs. stomach), age (< 60 vs. 60-69 vs. ≥70 years) and nodal status (cN+ vs. cN-).

FLOT x4 - RESECTION - FLOT x4
FLOT: docetaxel 50mg/m², d1; 5-FU 2600 mg/m², d1; leucovorin 200 mg/m², d1; oxaliplatin 85 mg/m², d1, every two weeks

n=716

ECF/ECX x3 - RESECTION - ECF/ECX x3
ECF/ECX: Epirubicin 50 mg/m², d1; cisplatin 60 mg/m², d1; 5-FU 200 mg/m² (or capecitabine 1250 mg/m² p.o. divided into two doses d1-d21), every three weeks

5-FU, 5-fluorouracil; CTX, chemotherapy; ECF, epirubicin, cisplatin and fluorouracil; ECOG, Eastern Cooperative Oncology Group; ECX, epirubicin, cisplatin and capecitabine; FLOT; fluorouracil, leucovorin, oxaliplatin, and docetaxel; GEJ, oesophagogastric junction; p.o., orally; TNM, tumour, node and metastasis

Al-Batran SE. ASCO 2017; abstract 4004
FLOT perioperative CTX

ECF/ECX  FLOT

mOS  35 months  50 months
[27-46]  [38-na]

HR  0.77 [0.63 - 0.94]
p=0.012 (log rank)

OS rate*  ECF/ECX  FLOT
2y  59%  68%
3y  48%  57%
5y  36%  45%

*projected OS rates

CTX, chemotherapy; ECF, epirubicin, cisplatin and fluorouracil; ECX, epirubicin, cisplatin and capecitabine; FLOT; fluorouracil, leucovorin, oxaliplatin, and docetaxel; HR, hazard ratio; OS, overall survival

Al-Batran SE. ASCO 2017; abstract 4004
FLOT perioperative CTX

AEG, adenocarcinomas of the oesophagogastric junction; CI, confidence interval; CTX, chemotherapy; ECF, epirubicin, cisplatin and fluorouracil; ECOG, Eastern Cooperative Oncology Group; ECX, epirubicin, cisplatin and capecitabine; FLOT; fluorouracil, leucovorin, oxaliplatin, and docetaxel; HR, hazard ratio; PS, performance status; TNM, tumour, node and metastasis

P-values stands for test for interaction between treatment and subgroup variable
Adenocarcinoma – next step

CTX, chemotherapy; FLOT; fluorouracil, leucovorin, oxaliplatin, and docetaxel; TNM, tumour, node and metastasis

cTNM, clinical staging tumour, node and metastasis; EUS, endoscopic ultrasound; FDG-PET, fluorodeoxy glucose-positron-emission tomography; MS-CT, multiple-slice helical computed tomography
Squamous cell carcinoma (SCC)

Neoadjuvant R-CTX + surgery versus definitive R-CTX

French Study


German Study


R-CTX, rituximab-chemotherapy
SCC - Salvage surgery

Markar S…..Mariette C. J Clin Oncol 2015; 33: 3866-3873

NCRS, neoadjuvant chemoradiotherapy and planned surgery; SALV, salvage; SCC; squamous cell carcinoma
SCC - Salvage surgery

<table>
<thead>
<tr>
<th></th>
<th>SALV</th>
<th>NCRS</th>
<th>P-value</th>
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<tbody>
<tr>
<td>In-hospital mortality</td>
<td>8.4%</td>
<td>9.3%</td>
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<tr>
<td>Anastomotic leak</td>
<td>17.2%</td>
<td>10.7%</td>
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<tr>
<td>3-y-OS</td>
<td>43.3%</td>
<td>40.1%</td>
<td>0.542</td>
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<tr>
<td>3-y-DFS</td>
<td>39.2%</td>
<td>32.8%</td>
<td>0.232</td>
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</tbody>
</table>

DFS, disease-free survival; NCRS, neoadjuvant chemoradiotherapy and planned surgery; OS, overall survival; SALV, salvage; SCC; squamous cell carcinoma

Markar S…..Mariette C. J Clin Oncol 2015; 33: 3866-3873
Persistent versus recurrent disease: HR 1,407

High mortality (16% vs 6%) in low volume centers

High mortality (28% vs 4%) after > 55 Gy radiation

HR, hazard ratio; SCC, squamous cell carcinoma

Markar S.....Mariette C. J Clin Oncol 2015; 33: 3866-3873
Summary Oesophageal Cancer

- **Neoadjuvant treatment** improves survival in stages II/III oesophageal cancer.
- Clear indication for T3/4 resectable tumours; unclear indication for T2.
- Different recommendations for adenocarcinoma and squamous cell cancer.
- Neoadjuvant radiochemo or chemotherapy for adenocarcinoma.
- Chemoradiotherapy in ESCC (neoadjuvant or definitive).
- Confirmed role for **taxanes** (CROSS: Carbo-paclitaxel; FLOT: FOLFOX + docetaxel).
- Value of **targeted agents and immunotherapy** needs to be established.
- **Response and biology adapted algorithms** to be explored.

ESCC, oesophageal squamous cell carcinoma; FLOT: fluorouracil, leucovorin, oxaliplatin, and docetaxel.