New evolutions for the neo-adjuvant and adjuvant treatment of esophageal cancer

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ESMO Guidelines – Esophageal Cancer

- cTNM staging (endoscopy, EUS, MS-CT, FDG-PET)
- Functional assessment (symptoms, comorbidity, nutritional status, patient preferences)

Limited disease (cT1-T2 cN0 M0)
- Neoadjuvant chemoradiotherapy
- Restaging (exclusion of M1)
- Resection

Locally advanced disease (cT3-T4 or cN1-3 M0)
- Squamous cell cancer
  - Definitive chemoradiotherapy
  - Follow-up (every 3 months)
  - Salvage resection
  - Resection

Adenocarcinoma
  - Perioperative chemotherapy
  - Restaging (exclusion of M1)
  - Resection

Lordick et al. Ann Oncol 2016 Sep;27(suppl 5):v50-v57
Esophageal Cancer – One Disease?

Differences – Adeno- vs Squamous Cell Carcinoma

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

Pohl & Welch. J Natl Canc Inst 2005
Figure 6 | Gradations of molecular subclasses of gastroesophageal carcinoma. Schematic representing shifting proportion of subtypes of gastroesophageal carcinoma.

Esophageal Cancer – Genomic Classification

Figure 4 | Similarity of oesophageal adenocarcinoma and CIN variant of gastric cancer. a. Molecular profiles of head and neck, oesophageal and gastric molecular subtypes by anatomic location across gastroesophageal adenocarcinomas. c. Composite copy number profiles for ESCC, EAC,
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: Esophageal CA
AEG III: Gastric CA

Mariette C Lancet 2011
Agenda

- Chemo vs. radio-chemo for adenocarcinoma
- Surgery vs. definitive chemorad for ESCC
- The role of novel drug regimens
  - Chemotherapy: epirubicin, taxanes
  - Targeted therapy: Anti-VEGF / EGFR / HER2
  - Immunotherapy
- Response-adapted treatment algorithms
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Squamous cell cancer

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- Perioperative chemotherapy
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- Resection
- Salvage resection
- Resection
- Resection

Lordick et al. Ann Oncol 2016 Sep;27(suppl 5):v50-v57
Esophageal Adenocarcinoma – Previous studies

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)
Neoadjuvant R-CTx or CTx

POET Study

N = 59

PLF I  PLF II  PLF III (3 weeks)  Surgery
1  6  7  13  14  17  20-21

N = 60

PLF I  PLF II  15 x 2 Gy in 3 weeks  Surgery

PLF: Cisplatin 50mg/m2, 1h, d 1,15,29. Leucovorin/5-FU 500mg/m2 2h / 2g/m2 24h, d 1,8,15,22,29,36
PE: Cisplatin 50 mg/m2, 1h, d 2+8. Etoposid 80 mg/m2, 1h, d 3-5

Neoadjuvant R-CTx or CTx

POET Study

Overall survival

Local progression free survival (after R0 resection)

Hazard ratio: 0.65, CI 95%: 0.42 - 1.01
log-rank test (two-sided): p-value = 0.055

Arm A: n = 59, 45 events, median = 21.1 months
Arm B: n = 60, 37 events, median = 30.8 months

Hazard ratio: 0.37, CI 95%: 0.16 - 0.85
log-rank test (two-sided): p-value = 0.014

Arm A: n = 48, 18 events, median = NA months
Arm B: n = 45, 8 events, median = NA months

Stahl M et al., Eur J Cancer 2017; 81:183-190
Neoadjuvant R-CTX or CTx

NeoRes Study

Neoadjuvant CTX
Cisplatin 100mg/m² d1 + 5FU 750mg/m² d1-5 x3 RESECTION

Neoadjuvant R-CTX 40,0 Gy (20 x 2Gy)
Cisplatin 100mg/m² d1 + 5FU 750mg/m² d1-5 x3 RESECTION

Neoadjuvant R-CTx or CTx – Propensity Score Matched Analysis

Periop. ECF vs. neoadjuvant CROSS

Ongoing study - ESOPEC

**ESOPEC**

Neoadjuvant Radio-CTX – CROSS Regimen
RESECTION

Primary endpoint: survival
3-year-OS-rate
55% CROSS vs. 68% FLOT)

N=438
T1N1M0 or T2–4aN0–1M0

Perioperative CTX: FLOT* 4 x pre and post
RESECTION

*FLOT = 5-Fluorouracil, Leucovorin, Oxaliplatin, Docetaxel

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Lordick et al. *Ann Oncol* 2016 Sep;27(suppl 5):v50-v57
Squamous Cell Cancer of the Esophagus

Neoadjuvant RCTx + surgery versus definitive RCTx

French Study

German Study


Better local control, but
No survival advantage with the addition of surgery to chemoradiation
ESMO Guidelines – Esophageal Cancer

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Definitive chemoradiotherapy

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Lordick et al. Ann Oncol 2016 Sep;27(suppl 5):v50-v57
Salvage Esophagectomy

*SALV* (n = 308)

**NCRS** (n = 540)

Propensity score matching

*SALV* (n = 308)

**NCRS** (n = 308)

Persistant (n = 234)

Recurrent (n = 74)

* **SALV** = Salvage, **NCRS** = Neoadjuvant ChemoRadiation and planned Surgery

Salvage Esophagectomy

<table>
<thead>
<tr>
<th></th>
<th>SALV</th>
<th>NCRS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality</td>
<td>8.4%</td>
<td>9.3%</td>
<td></td>
</tr>
<tr>
<td>Anastomotic leak</td>
<td>17.2%</td>
<td>10.7%</td>
<td>0.007</td>
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<tr>
<td>3-y-OS</td>
<td>43.3%</td>
<td>40.1%</td>
<td>0.542</td>
</tr>
<tr>
<td>3-y-DFS</td>
<td>39.2%</td>
<td>32.8%</td>
<td>0.232</td>
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</tbody>
</table>

Salvage Esophagectomy

- Persistent versus recurrent disease: HR 1,407
- High mortality (16% vs 6%) in low volume centers
- High mortality (28% vs 4%) after > 55Gy radiation

How to select ESCC patients for a watch-and-wait strategy

Pretreatment work-up and clinical response evaluations include:
- “partial body” or “whole-body” F18-FDG PET-CT
- EGD (with biopsies)
- EUS (with FNA)
- Dedicated CT of neck, thorax, abdomen and pelvis (in pretreatment work-up and on indication)
- External US of the neck (in pretreatment work-up and on indication)

**Noordman BJ et al.** JMIR Res Protoc 2015; 4: 1-11
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Response-adapted treatment algorithms
Histologically confirmed adenocarcinoma lower oesophagus and GOJ (Type I and II)

MDT - resectable following EUS and CT
(excluded T1/2 N0)

OE-5-Study

2 cycles CF (OE-2 Standard)

4 cycles ECX

- **CF**: Two 3-weekly cycles of cisplatin (80mg/m² D1) and 5FU (1g/m² D 1-4)
- **ECX**: Four 3-weekly cycles of epirubicin (50mg/m² D1), cisplatin (60mg/m² D1) and capecitabine (1250mg/m² daily)

**Alderson D et al. ASCO 2015; #4002**
### Median survival (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>CF</th>
<th>ECX</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>2.02</td>
<td>2.15</td>
</tr>
<tr>
<td></td>
<td>(1.80, 2.38) yrs</td>
<td>(1.93, 2.53) yrs</td>
</tr>
<tr>
<td>HR</td>
<td>0.92</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td>(0.79, 1.08)</td>
<td>(0.79, 1.08)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.8582</td>
<td>0.8582</td>
</tr>
</tbody>
</table>

### 3-year survival (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>CF</th>
<th>ECX</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>39%</td>
<td>42%</td>
</tr>
<tr>
<td></td>
<td>(35%, 44%)</td>
<td>(37%, 46%)</td>
</tr>
</tbody>
</table>

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Alderson D et al. ASCO 2015; #4002
**FLOT-4 Study**

Randomized, multicenter, Phase II/III Study

- Gastric or EGJ cancer typ I-III
- Medically and anatomically operable
- cT2-4/cN-any/cM0 or cT-jede/cN+/cM0

Stratification: **ECOG** (0 or 1 vs. 2), **localization** (GÖÜ Type I vs. Type II/III vs. Magen), **age** (< 60 vs. 60-69 vs. ≥70 years) and **nodal status** (cN+ vs. cN-).

23% had Siewert type I
33% had Siewert type II/III

**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, q2w

**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 Capecitabin 1250 mg/m² p.o. geteilt in 2 doses d1-d21), q2w

Al-Batran et al. *J Clin Oncol* 2017; 35(suppl): #4004
Survival ECF/ECX versus FLOT

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

Median follow-up time: 43 months

Al-Batran et al. *J Clin Oncol* 2017; 35(suppl): #4004
STO-3 Study

Caveat: anastomotic leaks (30 events vs 69)

Increased rate in pts undergoing esophagectomy

Anti-EGFR - Cetuximab

RTOG 0436
Carbo/Paclitaxel-RTx +/- Cetuximab

SAKK 75/08
Cis/Docetaxel-RTx +/- Cetuximab

Ilson D et al. ASCO 2014
Ruhstaller T et al. ASCO 2017

Conflicting results about the addition of anti-egfr targeting agents to chemorad
Ongoing neoadjuvant studies

- **EORTC 1203 - INNOVATION**
  - FLOT / FOLFOX +/- Trastuzumab +/- Trastuzumab/Pertuzumab

- **AIO-FLOT6 - PETRARCA**
  - FLOT +/- Trastuzumab/Pertuzumab

- **RTOG 1010**
  - Carbo/Paclitacel + RTX +/- Trastuzumab
Immunotherapy – Checkpoint Inhibitors

Checkmate 577 phase III

**Adjuvant Nivolumab** versus placebo following nRCTx + surgery

Kelly et al. ASCO 2017, #TPS 212

Keynote MK3475

**Periop. Pembro** + 5FU / Cisplatin in EGJ + GC

https://clinicaltrials.gov/ct2/show/NCT02918162

EORTC 1707 - VESTIGE

**Adjuvant Nivolumab + Ipilimumab** following nCTx + surgery in high-risk ypT N+ or R1 resected EGJ or GC

AIO-STO 0317 DANTE

**Perioperative FLOT +/- Atezolizumab** in gastric and eg junction
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Early Detection of Non-Response

Can PET help to tailor treatment according to response?

PET

CTx

Pre-operative chemotherapy

Resection

negative predictive value 95%
positive predictive value 53%

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Early Detection of Non-Response

Determination of a „cut-off“: -35% decrease of SUV

Early Response PET – MUNICON I

**Response definition:** Decrease of the SUV\textsubscript{mean} \( \frac{PET\text{d14}}{PET\text{baseline}} > 35\% \)


AEG: adenocarcinoma of the esophago-gastric junction; C: cisplatinum; d: day CTX: chemotherapy PET: positron emission tomography; SUV: standard uptake value

**Lordick et al.** *Lancet Oncol* 2007 Sep; 8: 797-805
Early Response PET – MUNICON I

MUNICON 1 Study

PET-Responder

PET-Non-Responder
No further treatment

Survival time [months]

Pre MUNICON Experience

PET-Responder

PET-Non-Responder
Further treatment

Survival

Lordick et al. Lancet Oncol 2007 Sep; 8: 797-805

Ott et al. J Clin Oncol 2006; 10;24:4692-8
CALGB 80803
PI: Karyn Goodman

T3/4 or N1 Esophageal Adenocarcinoma.

Induction Chemo:
- FOLFOX6 days 1,15, 22
- Carbo/Taxol days 1,8,22,29

PET Scan day 29-35

PET-responders: ≥ 35% SUV decrease: continue same chemo + concurrent RT (5040cGy)

Surgical resection 6 weeks post-RT

PET- nonresponders: < 35% SUV decrease: Cross over to alternate chemo + RT (5040cGy)

Hypothesis: changing chemo in PET nonresponding patients will improve pCR during chemo + RT

Goodman K et al. ASCO-GI 2017; abstract 1
PET-based Treatment Stratification in Adeno-CA

AGITG DOCTOR
PI: Andrew Barbour

Barbour A et al. *ESMO* 2016 [selected oral presentation]
PET-based Treatment Stratification in ESCC

EORTC/Nordic NEEDS Trial
PI: Maren Knödler / Magnus Nilsson

Oesophageal SCC
Resectable Disease
T1-2 N+ or T3-4 Nany, M0
ECOG-PS 0-1

PET → Induction CT → PET → R

Arm A: CROSS
RCT + OE

Arm B: RCT
RCT alone

SCC, squamous cell cancer; PET, positron emission tomography; CT, chemotherapy; R, randomisation; RCT, radiochemotherapy; OE, oesophagectomy.
Summary and Outlook

- **Neoadjuvant treatment** improves survival in st. II / III esophageal cancer
- Clear indication for **T3/4 resectable tumors**; unclear indication for T2
- Different recommendations for **ESCC and adenocarcinoma**
- Clear role for **chemoradiation in ESCC** (neoadjuvant or definitive)
- Chemoradiation or chemotherapy for adenocarcinoma
- Confirmed role for **taxanes** in both histologies
- Value of **targeted agents and immunotherapy** needs to be established
- **Response assessment** to be explored for individualization of treatment