The role of chemoradiotherapy in GE junction and gastric cancer

Karin Haustermans
I have no disclosures
Introduction

Multimodality treatment for locally advanced adenocarcinoma (AC) of the GEJ and stomach

Approaches

- Perioperative chemotherapy:
  - MAGIC (MAGIC-B), FFCD
- Postoperative chemoradiotherapy:
  - Intergroup 0116, ARTIST, CRITICS
- Preoperative chemoradiotherapy:
  - (CROSS), POET
  - Ongoing: TOPGEAR, CRITICS II
Esophageal and GEJ cancer

Limited disease (cT1-T2 cN0 M0)

Locally advanced disease (cT3-T4 or cN1-3 M0)

Squamous cell cancer

- Neoadjuvant chemoradiotherapy
  - Restaging (exclusion of M1)
  - Resection

Definitive chemoradiotherapy

- Follow-up (every 3 months)
  - Salvage resection
  - Resection

Adenocarcinoma

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

- Neoadjuvant chemoradiotherapy

Resection

Resection

Resection

Resection

ESMO PRECEPTORSHIP PROGRAMME

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Subtypes</th>
<th>Primary Therapy</th>
<th>Surgery</th>
<th>Secondary Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERGROUP 0116</td>
<td>556 patients</td>
<td>Gastric - +/-80%</td>
<td>Surgery</td>
<td>CRT: 1x 5-FU/LV, 45 Gy with 5-FU/LV, 2x 5-FU/LV</td>
<td></td>
</tr>
<tr>
<td>MAGIC</td>
<td>503 patients</td>
<td>Eso - 15%</td>
<td>Surgery</td>
<td>CRT: 2x cisplatin/5-FU/LV, 30 Gy with 5-FU/etoposide</td>
<td></td>
</tr>
<tr>
<td>POET</td>
<td>126 patients</td>
<td>GEJ - 100%</td>
<td>Surgery</td>
<td>CRT: 2x XP, 45 Gy with capecitabin, 2x XP</td>
<td></td>
</tr>
<tr>
<td>FFCD</td>
<td>224 patients</td>
<td>Eso - 11%</td>
<td>Surgery</td>
<td>CRT: 2x XP, 45 Gy with capecitabin, 2x XP</td>
<td></td>
</tr>
<tr>
<td>ARTIST</td>
<td>458 patients</td>
<td>Gastric - 100%</td>
<td>Surgery</td>
<td>CRT: 2x XP, 45 Gy with capecitabin, 2x XP</td>
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<tr>
<td>CRITICS</td>
<td>788 patients</td>
<td>Gastric - 83%</td>
<td>Surgery</td>
<td>CRT: 41.4 Gy with carboplatin-paclitaxel</td>
<td></td>
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<tr>
<td>CROSS</td>
<td>366 patients</td>
<td>AC - 75%</td>
<td>Surgery</td>
<td>CRT: 41.4 Gy with carboplatin-paclitaxel</td>
<td></td>
</tr>
</tbody>
</table>
Overview

- Postoperative chemoradiotherapy
- Preoperative chemoradiotherapy
- Palliative radiation
- Technical aspects
Overview

- Postoperative chemoradiotherapy
- Preoperative chemoradiotherapy
- Palliative radiation
- Technical aspects
SWOG 9008/INT 0116

556 patients
Gastric: +/- 80%
GEJ: +/- 20%

RESECTED
STAGE IB-IV (MO)
GASTRIC
ADENOCARCINOMA

--- OBSERVATION

5-FU/LV = fluorouracil/leucovorin

5-FU/LV  5-FU/LV
↓↓↓   ↓↓↓
45 Gy (1.8 Gy/fx) 2D-RT

RADIATION → 5-FU/LV X2
## SWOG 9008/INT 0116

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>Surgery Chemo RT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median DFS</td>
<td>19 months</td>
<td>30 months</td>
<td>0.001</td>
</tr>
<tr>
<td>3 year survival Median survival</td>
<td>40% 27 months</td>
<td>50% 36 months</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Macdonald et al. NEJM 2001
SWOG 9008/INT 0116

- Significant improvement in OS and DFS
- Effect mainly on local failure rate (19 vs 29%)
- Acceptable toxicity
  → new standard?

But:
- Randomization after surgery
- No optimal surgery: 54% < D1 resection
- RT: careful planning - experience!
- Chemotherapy regimen: not optimal
- Few patients in stage IB (n=39)
- Results not completely in agreement with what was expected on failure pattern
Drawbacks postoperative chemoradiation

- **35% (!) of the RT treatment plans adjusted to avoid toxic effects on critical organs**

- **Still substantial major toxic effects**
  - hematological: 54%
  - gastro-intestinal: 33%

- **Only 64% completed postoperative treatment**

- **Costly treatment**
Quality Control Radiotherapy

- 35% deviations from protocol
  - 10% potentially **lethal** errors
    - 9 heart in field
    - 9 both kidneys in field
    - 5 whole liver in field
- 20% excluding tumor bed
- 20% regional lymph nodes
- 10% anastomosis missed

The ARTIST trial

Enrolled (N = 458)

Randomly assigned (n = 228)
- XP arm (n = 226)
  - Refused before treatment (n = 2)
- Discontinued (n = 54)
  - Refused treatment (n = 20)
  - Documented recurrence (n = 4)
  - Adverse events (n = 20)
  - Others (n = 10)
- Completed planned treatment (n = 172)
- Final analysis (n = 228)

Randomly assigned (n = 230)
- XP/XRT/XP arm (n = 227)
  - Refused before treatment (n = 3)
- Discontinued during XP#1-2 (n = 24)
  - Refused treatment (n = 17)
  - Adverse events (n = 3)
  - Others (n = 4)
  - Discontinued during XRT (n = 3)
  - Adverse events (n = 1)
  - Refused treatment (n = 1)
  - Discontinued during XP#3-4 (n = 12)
    - Adverse events (n = 7)
    - Disease recurrence (n = 2)
    - Refused treatment (n = 2)
    - Others (n = 1)
- Completed planned treatment (n = 188)
- Final analysis (n = 230)
The ARTIST trial

**Figure A**

- **Disease-Free Survival**
- **Time (months)**
- Treatment: XP/XRT/XP, XP
- Event counts: 24, 36, 48, 60
- XP/XRT/XP: N = 230, 55 events
- XP: N = 228, 72 events
- P = 0.0862

**Figure B**

- **Disease-Free Survival**
- **Time (months)**
- Treatment: XP/XRT/XP, XP
- Event counts: 24, 36, 48, 60
- XP/XRT/XP: N = 203, 49 events
- XP: N = 193, 66 events
- P = 0.0365

Lee et al. JCO 2012
788 patients
Gastric: 83%
GEJ: 17%

≥ 87% undergoing D1+

CRITICS

Pre-operative Chemotherapy (3x ECC) → Gastrectomy + lymph node dissection (≥ 15) → Post-operative Chemotherapy (3x ECC)

QoL / Tissue & Blood Banking

Pre-operative Chemotherapy (3x ECC) → Gastrectomy + lymph node dissection (≥ 15) → Chemoradiation 45 Gy / 25 fx + capcitabine + cisplatin

2 weeks 3-6 weeks within 4-12 weeks

3D-CRT/IMRT
ECC: epirubine/cisplatin/capectabine

Dikken et al. BMC Cancer 2011
<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year OS [% (95% CI)]</td>
<td>42 (37-48)</td>
<td>40 (35-46)</td>
</tr>
<tr>
<td>Median OS [months (95% CI)]</td>
<td>43 (31-57)</td>
<td>37 (30-48)</td>
</tr>
</tbody>
</table>
CRITICS

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year PFS [% (95% CI)]</td>
<td>39 (34-44)</td>
<td>38 (33-44)</td>
</tr>
<tr>
<td>Median PFS [months (95% CI)]</td>
<td>28 (20-42)</td>
<td>25 (19-39)</td>
</tr>
</tbody>
</table>

HR 0.99 (95% CI 0.82–1.19); p=0.92
Overview

- Postoperative chemoradiotherapy
- Preoperative chemoradiotherapy
- Palliative radiation
- Technical aspects
Preoperative treatment

- **Rationale/potential advantages**
  - Enhance resectability
  - Assess response in primary tumour
  - Improve local control
  - Treat micrometastases early
  - Better tolerance than postoperative treatment

- **Potential disadvantages**
  - Staging less adequate
  - Increased postoperative morbidity
  - Disease progression
Pre- versus postoperative

<table>
<thead>
<tr>
<th>Tolerance adjuvant treatment</th>
<th>Proportion in study</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG/INT 0116</td>
<td>CRT: 65%</td>
</tr>
<tr>
<td>ARTIST</td>
<td>CT: 75% - CRT 81.7%</td>
</tr>
<tr>
<td>CRITICS</td>
<td>CT: 47% - CRT 52%</td>
</tr>
</tbody>
</table>

ESMO PRECEPTORSHIP PROGRAMME
GEJ tumors involving the GEJ whose epicenter is within the proximal 2 cm of the cardia (Siewert types I/II)

Cancers whose epicenter is more than 2 cm distal from the GEJ will be staged using the Stomach Cancer TNM and Stage even if the GEJ is involved.

All cardia cancers not involving the GEJ will be staged using the Stomach Cancer TNM
Preoperative chemoradiation GEJ and gastric

- Gastric cancer: no randomized phase III trials available
- GEJ cancer: mostly included in esophageal cancer studies: phase III trials available
Preop CRT vs preop CT

HR: 0.88 (95% CI 0.76-1.01); p=0.07

Preop CRT seems to work better!

Sjoquist et al. Lancet Oncol 2011
CROSS trial

- Randomized phase III trial
- AC or SCC
- Stage II or III: T2-3/N0-1/M0 (CT scan + EUS + PET Scan)
- WHO PS 0-1, weight loss < 10%, T length < 8 cm
- Primary objective: Overall survival + QOL

Paclitaxel 50mg/m² + carboplatin AUC2 weekly x 5 wks + RT 41.4 Gy

366 patients
Esophagus: +/- 73%
GEJ: +/- 24%

Van der Gaast. ASCO 2010
## CROSS trial

<table>
<thead>
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<th>CRT + Surgery</th>
<th>Surgery</th>
<th>p-value</th>
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<tbody>
<tr>
<td>N</td>
<td>178</td>
<td>188</td>
<td></td>
</tr>
<tr>
<td>Age [Median (range)]</td>
<td>60 (36-79)</td>
<td>36-73</td>
<td></td>
</tr>
<tr>
<td>Histology [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AC</td>
<td>134 (75)</td>
<td>141 (75)</td>
<td></td>
</tr>
<tr>
<td>SCC</td>
<td>41 (23)</td>
<td>43 (23)</td>
<td></td>
</tr>
<tr>
<td>T3 [n (%)]</td>
<td>150 (84)</td>
<td>147 (78)</td>
<td></td>
</tr>
<tr>
<td>Surgery [n (%)]</td>
<td>168 (94)</td>
<td>186 (99)</td>
<td>0.01</td>
</tr>
<tr>
<td>Postoperative mortality [n (%)]</td>
<td>6 (4)</td>
<td>8 (4)</td>
<td></td>
</tr>
<tr>
<td>R0 resection [n (%)]</td>
<td>148 (92)</td>
<td>111 (69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>pCR [n (%)]</td>
<td>47 (29)</td>
<td>-</td>
<td>-</td>
</tr>
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</table>
CROSS trial

Patterns of recurrence

HR: 0.47 (95% CI 0.35-0.64)
HR: 0.37 (95% CI 0.23-0.59)
HR: 0.52 (95% CI 0.38-0.73)

Oppedijk et al. JCO 2014
## CROSS trial

### Patterns of recurrence

Table 3. Tumor Recurrences in Relation to Radiation Target Volumes in Patients Undergoing CRT Plus Surgery (n = 213)

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>Infield</th>
<th>Outfield</th>
<th>Borderline</th>
<th>Unknown</th>
<th>Total</th>
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<tbody>
<tr>
<td>LRR only</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Distant only</td>
<td>0</td>
<td>43</td>
<td>0</td>
<td>1</td>
<td>44</td>
</tr>
<tr>
<td>LRR plus distant</td>
<td>9</td>
<td>11</td>
<td>3</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>56</td>
<td>5</td>
<td>2</td>
<td>74</td>
</tr>
</tbody>
</table>

Abbreviations: CRT, chemoradiotherapy; LRR, locoregional recurrence.

*Factor only available in the CRT + S arm and therefore not suitable for multivariable analysis.
“Because a substantial percentage of patients in the chemoradiotherapy-surgery group in the present study (22%) had a GE-junction tumor, we favor preoperative chemoradiotherapy for such patients”
## POET trial

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Arm A</th>
<th></th>
<th>Arm B</th>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. %</td>
<td>No. %</td>
<td></td>
<td>No. %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with resection</td>
<td>49</td>
<td>100.0</td>
<td>45</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>pT0 N0 M0</td>
<td>1</td>
<td>2.0</td>
<td>7</td>
<td>15.6</td>
<td>.03*</td>
</tr>
<tr>
<td>pT1-4 N0 M0</td>
<td>17</td>
<td>34.7</td>
<td>22</td>
<td>48.9</td>
<td></td>
</tr>
<tr>
<td>pT0-4 N0 M0*</td>
<td>18</td>
<td>36.7</td>
<td>29</td>
<td>64.4</td>
<td>.01*</td>
</tr>
<tr>
<td>pTall N M0</td>
<td>27</td>
<td>55.1</td>
<td>14</td>
<td>31.1</td>
<td></td>
</tr>
<tr>
<td>pTall N M1</td>
<td>4</td>
<td>8.2</td>
<td>2</td>
<td>4.5</td>
<td></td>
</tr>
</tbody>
</table>

Fisher’s exact test.

*Bold text indicates data summarized from patients with pT0 N0 M0 and pT1-4 N0 M0.

![Overall Survival (probability)](image)

*Stahl et al., JCO 2009*
POET trial

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

Overall survival (%)

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 - 0.86
log-rank test (two-sided): p-value = 0.014
Preoperative chemoradiotherapy

- **RESPONDERS** (30%-50%)
  - increased resectability rate
  - reduced locoregional recurrences
  - prolonged survival

- **NON-RESPONDERS** (50%-70%)
  - worse prognosis compared to surgery alone
Ongoing studies
TOPGEAR

Currently recruiting patients
- 120 patients phase II → results published
- 500 patients phase III
- cT1N1 or cT3-4N+
- AC GEJ (Sievert I/II) or gastric

Primary endpoint: 5y OS

Estimated Primary Completion Date: December 2020
TOPGEAR: statistical considerations

Assumptions made for sample size calculations

- 5 y survival 40% for standard arm (chemotherapy alone)
- 5 y survival 50% for experimental arm (CRT)
- alpha=0.05 (2-sided)
- beta=0.80

Target sample size = 620
CRITICS II

DOC = docetaxel/oxaliplatin/capecitabine

Preoperative chemotherapy
4x DOC q3 wks

Preoperative chemotherapy
2x DOC q3 wks

Chemoradiation ‘CROSS-regimen’
(45 Gy in 1.8 Gy/fx)

Chemoradiation ‘CROSS-regimen’
(45 Gy in 1.8 Gy/fx)

D2 surgery

D2 surgery

D2 surgery
NEO-AEGIS

Currently recruiting patients:
- 574 patients
- cT2-3N0-1
- AC esophagus or GEJ

CROSS => MAGIC

Primary endpoint: 2y and 3y OS

Estimated Primary Completion Date: January 2024
Overview

- Postoperative chemoradiotherapy
- Preoperative chemoradiotherapy
- Palliative radiation
- Technical aspects
Palliative radiation

- 209 patients
- Inoperable
- 12 Gy SD vs stent
- BT more effect on dysphagia
- BT less complications
- QoL better after BT

Homs et al. Lancet 2004
Overview

- Postoperative chemoradiotherapy
- Preoperative chemoradiotherapy
- Palliative radiation
- Technical aspects
Technical aspects

- Total dose, dose per fraction, total treatment time
- Target volume/OAR
- Technique
- Motion
Radiation schedules used

- 35 Gy in 2.3 Gy fractions over 3 weeks
- 45 Gy in 1.5 Gy fractions over 3 weeks
- 40 Gy in 2.7 Gy fractions over 3 weeks
- 41.4 Gy in 1.8 Gy fractions over 5 weeks
- ...
Clinical target volume

110 - Paraoesophageal LN
111 - Supradiaphragmatic LN

20 - LN in the oesophageal hiatus of the diaphragm
4sa - LN along the short gastric vessels

3 - LN along the lesser curvature
4sb - LN along the left gastroepiploic vessels
7 - LN along the left gastric artery

5 - Suprapyloric LN,
9 - LN around the celiac artery
10 - LN at the splenic hilum
11p - LN along the proximal splenic artery
11d - LN along the distal splenic artery
12 a, b, p - LN in the hepatoduodenal ligament

Matzinger et al. Radiather Oncol 2009
"We gave PTV coverage and lung sparing higher priority than the other structures"

IMRT plans reduced the amount of lung treated compared to 3D-CRT

“No clinically meaningful differences were observed with respect to irradiated volumes of spinal cord, heart, liver, or total body integral doses”
3D-CRT, IMRT, VMAT

Zhang et al. Radiat Oncol 2015
IMRT has a lower incidence of cardiac and unknown related deaths

Renal toxicity

- 44 patients:
  - In 35: APPA, at least 2/3 of 1 kidney shielded
  - In 9: 3D dose planning, multiple beams, at least 2/3 of 1 kidney should receive 40% or less of 45 Gy
  - Tc99m-thiatide renography

Renal toxicity

- IMRT: n = 31
- 3D conformal: n = 25
- APPA: n = 31
How about protons?

Schematic depth dose diagram of a proton beam Bragg peak, the spread out Bragg peak and a megavoltage X-ray beam. The grey shaded areas indicate the extent of dose reduction.

Courtesy of Matt Palmer, MD Anderson
Impact of radiation dose to OAR on postoperative complications and outcome

<table>
<thead>
<tr>
<th></th>
<th>Pulmonary</th>
<th>GI</th>
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<tbody>
<tr>
<td>3D-CRT</td>
<td>30.3%</td>
<td>28.4%</td>
</tr>
<tr>
<td>IMRT</td>
<td>23.8%</td>
<td>18.3%</td>
</tr>
<tr>
<td>PBT</td>
<td>13.9%</td>
<td>18.1%</td>
</tr>
</tbody>
</table>
Breathing motion
Conclusions GEJ cancer

- Major tumor bulk in esophagus or tumors at transition (Siewert I/II):
  - Strategy of preoperative CRT

- Major tumor bulk in stomach (Siewert III):
  - Strategy of peri-operative CT

Level II evidence (CROSS, POET)
Conclusions gastric cancer

- If sub-optimal surgery (<D1) or N+ disease:
  consider (optimized) post-operative chemoradiation

- Indications: (T2b), T3, T4 or N+ M0

- Preoperative chemoradiation? (TOPGEAR, NEO-AEGIS)

Level II evidence (INT0116/ARTIST)
Conclusions

A multidisciplinary approach is essential in the treatment of this disease!

– Which type of treatment?
– Which drugs?
– Which total dose of radiation/fractionation?
– What volume to irradiate?
– What kind of operation?