The role of chemoradiotherapy in GE junction and gastric cancer

Karin Haustermans
Overview

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

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

RESECTED
STAGE IB-IV (MO)
GASTRIC
ADENOCARCINOMA

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

5-FU/LV = fluorouracil/leucovorin

45 Gy (1.8 Gy/fx) 2D-RT

Macdonald et al. NEJM 2001
Post-operative Chemoradiotherapy

INT 0119 - SWOG 9008

<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>p=0.001</td>
</tr>
<tr>
<td>3y survival Med. Survival</td>
<td>40% 27 months</td>
<td>50% 36 months</td>
<td>p=0.03</td>
</tr>
</tbody>
</table>

Macdonald J et al, NEJM 2001
Post-operative Chemoradiotherapy

**INT 0116:**
- Significant improvement in overall survival and disease free survival
- 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 post-operative 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: gastric cancer

- Enrolled (N = 456)
  - 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)
  - XP/XRT/XP arm (n = 230)
    - 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 = 2)
      - 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 = 172)
  - Final analysis (n = 228)
  - Completed planned treatment (n = 188)
  - Final analysis (n = 230)

- N+ patients (N = 396)

Lee et al, JCO 2012
CRITICS: design

788 patients
Gastric: 83%
GEJ: 17%

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

≥ 87% undergoing D1+

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

QoL / Tissue & Blood Banking

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

Dikken et al. BMC Cancer 2011
CRITICS: results

**Results: Overall Survival**

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year OS (%)</td>
<td>40.8</td>
<td>40.9</td>
</tr>
<tr>
<td>Median OS (yrs)</td>
<td>3.5</td>
<td>3.3</td>
</tr>
</tbody>
</table>
CRITICS: results

Results: Progression-Free Survival

![Graph showing progression-free survival probability over years with two curves labeled CT and CRT. The Log-rank test p-value is 0.99.]

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year PFS (%)</td>
<td>38.5</td>
<td>39.5</td>
</tr>
<tr>
<td>Median PFS (yrs)</td>
<td>2.3</td>
<td>2.5</td>
</tr>
</tbody>
</table>
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 post-operative

<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>
UICC TNM 8th edition (2017)

- 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 CRT GEJ and Gastric Cancer

- Gastric cancer: no randomized phase III trials available

- GEJ cancer -> mostly included in esophageal studies: phase III trials available
Preop CRT seems to work better!

Sjoquist et al, Lancet Oncol 2011
Resectable Esophageal or GE junction Cancer CROSS Study

- Resectable esophageal adenocarcinoma 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 → Surgery

Surgery
### Resectable Esophageal or GE junction Cancer CROSS Study

Randomized Phase III study - Netherlands

<table>
<thead>
<tr>
<th></th>
<th>CRT + surgery</th>
<th>Surgery</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>175</td>
<td>188</td>
<td></td>
</tr>
<tr>
<td>Median Age</td>
<td>60</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Histology SCC/Adeno (%)</td>
<td>23/74</td>
<td>23/74</td>
<td></td>
</tr>
<tr>
<td>T3 N0 or N1 (%)</td>
<td>79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery (resection) (%)</td>
<td>90</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>Postoperative mortality (%)</td>
<td>3,4</td>
<td>3,8</td>
<td></td>
</tr>
<tr>
<td>R0 Resection</td>
<td>92,3</td>
<td>67</td>
<td>&lt; 0,002</td>
</tr>
<tr>
<td>pCR (%)</td>
<td>32</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

van Hagen et al., NEJM 2012
CROSS Study

A. Neoadjuvant chemoradiotherapy vs Surgery alone. Log-rank test $p=0.003$

B. SCC, neoadjuvant chemoradiotherapy plus surgery vs SCC, surgery alone, AC, neoadjuvant chemoradiotherapy plus surgery vs AC, surgery alone. Log-rank tests $p=0.008$, $p=0.038$.

Shapiro et al. Lancet Oncol 2015
CROSS Study

- 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)
CROSS Study

- Patterns of recurrence

In total only 11 (5%) infield recurrences
→ preop CRT reduces LRR rate!
“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</th>
</tr>
</thead>
<tbody>
<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.

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

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

Stahl et al. Eur J Cancer 2017
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: design

Currently recruiting patients

- 120 patients Phase II
- 500 patients Phase III
- cT1N1 or cT3-4N+

Leong et al. BMC Cancer 2015
CRITICS II

Primary endpoint: event-free survival

Estimated Primary Completion Date: October 2020

DOC = docetaxel/oxaliplatin/capecitabine
Neo-AEGIS

Currently recruiting patients:
- 574 patients
- cT2-3N0-1 (TNM 7)
- adenocarcinoma
- esophagus or GEJ

CROSS >> MAGIC

Primary endpoint: 2y and 3y OS

Estimated Primary Completion Date: January 2024

Operable adenocarcinoma

CRT 41.4 Gy Carbo-taxol

Surgery

Chemo ECF x 3

Surgery

Chemo ECF x 3

ECF = epirubicin/cisplatin/5-FU or capecitabine
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
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
- ...
Radiotherapy: 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
"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”
IMRT has a lower incidence of cardiac and unknown related deaths.
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.

IMRT

PBT

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>
</tr>
</thead>
<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>

Conclusions GEJ cancer

- Major tumor bulk in esophagus or tumors at transition (Siewert type 1 and 2):
  - Strategy of preoperative CRT

- Major tumor bulk in stomach (Siewert type 3):
  - Strategy of peri-operative CT

Level II evidence (CROSS/POET)
If sub-optimal surgery (<D1) or N+ disease

Consider (optimized) post-operative chemoradiation

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

Level II evidence (INT0116/ARTIST)
A multidisciplinary approach is essential in the treatment of this disease!

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