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
SCHEMA

RESECTED STAGE IB-IV (MO) GASTRIC ADENOCARCINOMA

R A N D O M

OBSERVATION

5-FU/LV

5-FU/LV

RADIATION

4,500 cGy

5-FU/LV X2
# 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>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

Gastric Resection (n = 3447)

Excluded 2457 patients with:
- Stage Ia (T1N0) Ib (T2aN0) (n = 1020)
- Stage Ib (T2bN0, T1N1) (n = 409)
- Palliative resection (n = 557)
- PS ECOG ≥ 2 (n = 121)
- Old age (>70) (n = 223)
- Performance N/A (n = 83)
- Double primary cancer (n = 31)
- Recurred AGC (n = 5)
- Other than adenocarcinoma (n = 2)
- Others (n = 6)

Inclusion Criteria
- Curative resection
- Adenocarcinoma
- Stage II – IV (not M1)
- 18 ≤ age ≤ 70
- ECOG ≤ 1

Without CRT (n = 446)

With CRT (n = 544)
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 = 4)
    - Others (n = 4)
  - Discontinued during XRT (n = 3)
    - Adverse events (n = 2)
    - Refused treatment (n = 2)
    - Others (n = 1)
- Completed planned treatment (n = 188)
- Final analysis (n = 230)

A

Disease-Free Survival

Time (months)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>event</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>XP/XRT/XP</td>
<td>230</td>
<td>55</td>
<td>21</td>
<td>44</td>
<td>49</td>
<td>53</td>
<td>55</td>
</tr>
<tr>
<td>XP</td>
<td>228</td>
<td>72</td>
<td>15</td>
<td>39</td>
<td>56</td>
<td>57</td>
<td>70</td>
</tr>
</tbody>
</table>

P = .0862

B

Disease-Free Survival

Time (months)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>event</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>XP/XRT/XP</td>
<td>203</td>
<td>49</td>
<td>10</td>
<td>42</td>
<td>45</td>
<td>47</td>
<td>49</td>
</tr>
<tr>
<td>XP</td>
<td>193</td>
<td>66</td>
<td>14</td>
<td>37</td>
<td>51</td>
<td>52</td>
<td>65</td>
</tr>
</tbody>
</table>

P = .0385
THE ARTIST TRIAL

Fig 2. Disease-free survival. XP, capcitabine plus cisplatin; XPRT, concurrent chemoradiotherapy with capcitabine plus cisplatin.

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>0.740</td>
<td>0.520 to 1.050</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.665</td>
<td>0.392 to 1.129</td>
</tr>
<tr>
<td>1</td>
<td>0.835</td>
<td>0.544 to 1.280</td>
</tr>
<tr>
<td>Gastrectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.753</td>
<td>0.496 to 1.271</td>
</tr>
<tr>
<td>Total</td>
<td>0.701</td>
<td>0.438 to 1.121</td>
</tr>
<tr>
<td>LN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1.359</td>
<td>0.477 to 3.876</td>
</tr>
<tr>
<td>Positive</td>
<td>0.700</td>
<td>0.493 to 0.994</td>
</tr>
<tr>
<td>LN ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.083</td>
<td>0.714</td>
<td>0.407 to 1.252</td>
</tr>
<tr>
<td>≥ 0.083</td>
<td>0.708</td>
<td>0.466 to 1.019</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IB/II</td>
<td>0.876</td>
<td>0.387 to 1.811</td>
</tr>
<tr>
<td>III/IV (M0)</td>
<td>0.703</td>
<td>0.530 to 1.017</td>
</tr>
<tr>
<td>Intestinal</td>
<td>0.442</td>
<td>0.231 to 0.845</td>
</tr>
<tr>
<td>Diffuse</td>
<td>0.826</td>
<td>0.543 to 1.255</td>
</tr>
<tr>
<td>HER2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2+</td>
<td>0.740</td>
<td>0.533 to 1.063</td>
</tr>
<tr>
<td>≥ 3</td>
<td>0.376</td>
<td>0.197 to 0.742</td>
</tr>
<tr>
<td>MET</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2+</td>
<td>0.749</td>
<td>0.534 to 1.060</td>
</tr>
<tr>
<td>≥ 3</td>
<td>1.414</td>
<td>0.196 to 10.197</td>
</tr>
<tr>
<td>MLH1</td>
<td>1.167</td>
<td>0.313 to 4.347</td>
</tr>
<tr>
<td>MLH1 loss</td>
<td>0.789</td>
<td>0.544 to 1.143</td>
</tr>
<tr>
<td>E-cadherin</td>
<td>0.566</td>
<td>0.160 to 2.007</td>
</tr>
<tr>
<td>E-cadherin loss</td>
<td>0.859</td>
<td>0.591 to 1.247</td>
</tr>
</tbody>
</table>

Park et al, JCO 2015
CRITICS

Design

Preoperative chemotherapy
3x ECC q 3 wks → D1 + surgery → 3x ECC q 3 wks

Preoperative chemotherapy
3x ECC q 3 wks

“MAGIC” (3x ECC)
Epirubicine /Cisplatin /Capecitabine
³ 15 Lymph nodes
no splenectomy

Chemoradiation
45 Gy/25 fx + capecitabine dd
 cisplatin 1-5x pw
3D-CRT/IMRT

Stratified for:
- Center
- Histological type
- Localisation of tumor
Postoperative chemoradiation

- **Meta-analysis**

**Overall survival**

- Hallissey
- Shchepotin
- Zhang
- Skorpad
- Skorpad
- RT v Obs
- HR: 0.77 (95% CI 0.66-0.90); p=0.001
- Moertel
- Int 0116
- ChemoRT v Obs
- HR: 0.75 (95% CI 0.63-0.89); p<0.001
- Bamias
- Kwon
- Yu
- ARTIST
- Zhu
- ChemoRT v Chemo
- HR: 0.83 (95% CI 0.67-1.03); p=0.087

**Disease-free survival**

- Moertel
- Int 0116
- ChemoRT v Obs
- HR: 0.66 (95% CI 0.55-0.76); p<0.001
- Bamias
- Kwon
- Yu
- ARTIST
- Zhu
- ChemoRT v Chemo
- HR: 0.77 (95% CI 0.65-0.91); p=0.002

HR: 0.75 (95% CI 0.63-0.89); p<0.001

HR: 0.66 (95% CI 0.55-0.78); p=0.002

Ohri et al, Int J Radiat Oncol Biol Phys 2013
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
The esophagus includes the GE-junction.

A tumor of which the epicentre is within 5 cm of the GE-junction and which extends into the esophagus is classified and staged as an esophageal tumor.
Preoperative chemoradiotherapy

TABLE 1. Overview of Phase III Randomized Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Study treatments</th>
<th>Regimen</th>
<th>Histology</th>
<th>Median survival (months)</th>
<th>Overall survival (%)</th>
<th>PCR rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walsh et al, 1996</td>
<td>103</td>
<td>Surgery versus surgery and CRT</td>
<td>Concurrent cisplatin + 5-fluorouracil and RT to 40.0 Gy</td>
<td>103 (100%) adenocarcinoma</td>
<td>11.0 versus 16.0</td>
<td>(3-yr) 6% versus 32%*</td>
<td>25</td>
</tr>
<tr>
<td>Urba et al, 2001</td>
<td>100</td>
<td>Surgery versus surgery and CRT</td>
<td>Concurrent cisplatin + 5-fluorouracil + vinblastine and RT to 45.0 Gy</td>
<td>25 (25%) SCC, 75 (75%) adenocarcinoma</td>
<td>17.6 versus 16.9</td>
<td>(3-yr) 16% versus 30%</td>
<td>28</td>
</tr>
<tr>
<td>Burmeister et al, 2005</td>
<td>256</td>
<td>Surgery versus surgery and CRT</td>
<td>Concurrent cisplatin + 5-fluorouracil and RT to 35.0 Gy</td>
<td>95 (37%) SCC, 156 (62%) adenocarcinoma, 3 (1%) mixed or other</td>
<td>22.2 versus 19.3</td>
<td>NR</td>
<td>16</td>
</tr>
<tr>
<td>Tepper et al, 2008</td>
<td>56</td>
<td>Surgery versus surgery and CRT</td>
<td>Concurrent cisplatin + 5-fluorouracil and RT to 50.4 Gy</td>
<td>14 (25%) SCC, 42 (75%) adenocarcinoma</td>
<td>21.5 versus 53.8</td>
<td>(5-yr) 16% versus 39%*</td>
<td>40</td>
</tr>
<tr>
<td>van Hagen et al, 2012</td>
<td>368</td>
<td>Surgery versus surgery and CRT</td>
<td>Concurrent carboplatin + paclitaxel and RT to 41.4 Gy</td>
<td>84 (23%) SCC, 275 (75%) adenocarcinoma, 7 (2%) undifferentiated</td>
<td>49.4 versus 24.0</td>
<td>(5-yr) 47% versus 34%*</td>
<td>29</td>
</tr>
</tbody>
</table>

In general, data are in support of preoperative chemoradiation
Preoperative chemoradiotherapy

- **Meta-analysis**

  All-cause mortality for chemoradiotherapy vs surgery alone:

  Similar survival benefit between tumor type subgroups

  9% reduction in overall mortality at 2 years and NNT=11

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Chemoradiotherapy (total)</th>
<th>Surgery alone (total)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td>498</td>
<td>467</td>
<td>0.80 (0.68-0.93)</td>
</tr>
<tr>
<td>Nygaard</td>
<td>53</td>
<td>25</td>
<td>0.76 (0.45-1.28)</td>
</tr>
<tr>
<td>Apinop</td>
<td>35</td>
<td>34</td>
<td>0.80 (0.48-1.34)</td>
</tr>
<tr>
<td>Le Priez</td>
<td>45</td>
<td>41</td>
<td>0.85 (0.50-1.46)</td>
</tr>
<tr>
<td>Urba</td>
<td>13</td>
<td>12</td>
<td>0.83 (0.36-1.89)</td>
</tr>
<tr>
<td>Bosset</td>
<td>148</td>
<td>145</td>
<td>0.96 (0.73-1.27)</td>
</tr>
<tr>
<td>Walsh</td>
<td>29</td>
<td>32</td>
<td>0.74 (0.46-1.18)</td>
</tr>
<tr>
<td>Burmeister</td>
<td>44</td>
<td>48</td>
<td>0.68 (0.40-1.15)</td>
</tr>
<tr>
<td>Lee</td>
<td>51</td>
<td>50</td>
<td>0.55 (0.36-0.84)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>498</td>
<td>467</td>
<td>0.80 (0.68-0.93)</td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2=5.31, df=8 \) (p=0.72); \( I^2=0\% \)

Test for overall effect: \( Z=2.90 \) (p=0.004)

<table>
<thead>
<tr>
<th>Adenocarcinoma</th>
<th>Chemoradiotherapy (total)</th>
<th>Surgery alone (total)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urba</td>
<td>37</td>
<td>38</td>
<td>0.69 (0.42-1.14)</td>
</tr>
<tr>
<td>Walsh</td>
<td>58</td>
<td>55</td>
<td>0.58 (0.38-0.88)</td>
</tr>
<tr>
<td>Burmeister</td>
<td>80</td>
<td>77</td>
<td>0.64 (0.46-1.45)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>175</td>
<td>170</td>
<td>0.75 (0.59-0.95)</td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2=3.11, df=2 \) (p=0.21); \( I^2=36\% \)

Test for overall effect: \( Z=2.40 \) (p=0.02)

HR: 0.78 (95% CI 0.70-0.88); p<0.0001

HR: 0.80 (95% CI 0.68-0.93); p=0.004

HR: 0.75 (95% CI 0.59-0.95); p=0.02
Preop CRT vs preop CT

Preop CRT seems to work better

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

<table>
<thead>
<tr>
<th></th>
<th>Chemoradiotherapy (total)</th>
<th>Chemotherapy (total)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stahl</td>
<td>60</td>
<td>59</td>
<td>0.67 (0.41-1.08)</td>
</tr>
<tr>
<td>Burmeister</td>
<td>39</td>
<td>36</td>
<td>0.96 (0.53-1.74)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>99</td>
<td>95</td>
<td>0.77 (0.53-1.26)</td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2=0.84$, df=1 (p=0.36); $I^2=0%$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z=1.36$ (p=0.17)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled trials (indirect)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect</td>
<td>980</td>
<td>1046</td>
<td>0.90 (0.77-1.04)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>980</td>
<td>1046</td>
<td>0.90 (0.77-1.04)</td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z=1.42$ (p=0.15)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1079</td>
<td>1141</td>
<td>0.88 (0.76-1.01)</td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2=1.38$, df=2 (p=0.50); $I^2=0%$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z=1.83$ (p=0.07)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: $\chi^2=0.53$, df=1 (p=0.46); $I^2=0%$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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

Van der Gaast et al., ASCO 2010
### Resectable Oesophageal 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>4,3</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
B  Survival According to Tumor Type and Treatment Group

Proportion Surviving

Follow-up (mo)

No. at Risk

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC, CRT+surgery</td>
<td>134</td>
<td>107</td>
<td>87</td>
<td>53</td>
<td>34</td>
<td>18</td>
</tr>
<tr>
<td>AC, surgery alone</td>
<td>141</td>
<td>99</td>
<td>73</td>
<td>50</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>SCC, CRT+surgery</td>
<td>41</td>
<td>35</td>
<td>30</td>
<td>21</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>SCC, surgery alone</td>
<td>43</td>
<td>29</td>
<td>19</td>
<td>11</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>359</td>
<td>270</td>
<td>209</td>
<td>135</td>
<td>82</td>
<td>40</td>
</tr>
</tbody>
</table>

van Hagen et al., NEJM 2012
### CROSS study

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Univariate Hazard Ratio (95% CI)</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>P Value for Adjusted Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>0.657 (0.495–0.871)</td>
<td>0.665 (0.500–0.884)</td>
<td>0.005</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.913 (0.482–1.729)</td>
<td>0.928 (0.487–1.766)</td>
<td>0.82</td>
</tr>
<tr>
<td>Male</td>
<td>0.612 (0.446–0.841)</td>
<td>0.614 (0.447–0.845)</td>
<td>0.003</td>
</tr>
<tr>
<td>Histologic type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0.627 (0.056–6.970)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>0.732 (0.524–0.998)</td>
<td>0.741 (0.536–1.024)</td>
<td>0.07</td>
</tr>
<tr>
<td>Squamous-cell carcinoma</td>
<td>0.453 (0.243–0.844)</td>
<td>0.422 (0.226–0.788)</td>
<td>0.007</td>
</tr>
<tr>
<td>Clinical N stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.414 (0.234–0.732)</td>
<td>0.422 (0.239–0.747)</td>
<td>0.003</td>
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<tr>
<td>1</td>
<td>0.793 (0.567–1.108)</td>
<td>0.807 (0.576–1.130)</td>
<td>0.21</td>
</tr>
<tr>
<td>Could not be determined</td>
<td>0.552 (0.066–4.602)</td>
<td></td>
<td></td>
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<tr>
<td>WHO performance score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.617 (0.452–0.844)</td>
<td>0.625 (0.456–0.857)</td>
<td>0.004</td>
</tr>
<tr>
<td>1</td>
<td>0.864 (0.433–1.726)</td>
<td>0.898 (0.753–1.631)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

---

van Hagen et al., NEJM 2012
Preoperative chemoradiotherapy

- **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 V, JCO 2014
Preoperative chemoradiotherapy

- **CROSS trial**
  - Patterns of recurrence

  ![Table 3](image)

- In total only 11 (5%) infield recurrences
  - preop CRT reduces LRR rate!

Oppedijk V, JCO 2014
“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”

van Hagen et al., NEJM 2012
### POET trial

#### Patients with resection

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Arm A</th>
<th></th>
<th>Arm B</th>
<th></th>
<th>P</th>
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<tbody>
<tr>
<td>Patients with resection</td>
<td>49</td>
<td>100.0</td>
<td>45</td>
<td>100.0</td>
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<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.

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Stahl et al., JCO 2009
Preoperative chemoradiotherapy

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

- **NON-RESPONDERS** (50%-70%)
  - worse prognosis compared to surgery alone
ELIGIBILITY: RESECTABLE ADENOCARCINOMA OF STOMACH OR GOJ STAGE IB (T1N1) – IIIc, (T3.4 and/or N + ve)

RANDOMISATION

GROUP 1
CONTROL ARM

ECF (or ECX) x 3
REPEATED EVERY 21 DAYS

GROUP 2

ECF (or ECX) x 2
REPEATED EVERY 21 DAYS

PREOP CRT
45 Gy + CI 5-FU (or X)

SURGERY (D1)

ECF (or ECX) x 3
REPEATED EVERY 21 DAYS
Study Design and Key Objectives

Study design:

This is a multicentre, prospective, randomised, stratified, phase II/III clinical trial.

Primary objective:

To investigate whether the addition of chemoradiotherapy to chemotherapy is superior to chemotherapy alone in the neoadjuvant setting by improving pCR rates in the first instance (Part I), and subsequently overall survival (Part II), in patients undergoing adequate surgery (minimum D1 dissection) for resectable gastric and gastroesophageal junction cancer.
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
- accrual rate approximately 140 patients per year

Target sample size = 752
Overview

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

THESE SCHEDULES CANNOT BE REGARDED AS STANDARD!
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
3D vs. IMRT Comparison

“In general, \( V_{40} \) and \( V_{50} \) were kept to <50 and <30%, respectively, for the heart.”

“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”
Postoperative complications related to radiation dose to organ at risk

- Higher rates of postoperative pulmonary complications (ARDS, PNA) when large lung volumes receive low doses
  - Total Lung V10 $\geq 40\%$ vs $<40\%$: 35% vs 8% ($p=0.014$) (Lee HK et al. 2003)
  - NTCP modeling associated postoperative pulmonary complications to the amount of total lung spared from doses $\geq 5$ Gy (Tucker SL et al., 2006)
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.
Results from a prospective trial (n = 62) at MD Anderson

A. Total Lung DVH

B. Heart DVH

<table>
<thead>
<tr>
<th></th>
<th>TL Mean</th>
<th>Cord Max</th>
<th>Liver Mean</th>
<th>Heart Mean</th>
<th>Esc. Mean</th>
<th>PTV Mean</th>
<th>PTV %</th>
<th>PTV Max</th>
<th>CTV Mean</th>
<th>GTV Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average (54)*</td>
<td>634</td>
<td>3125</td>
<td>373</td>
<td>1329</td>
<td>2139</td>
<td>5291</td>
<td>97</td>
<td>5699</td>
<td>5325</td>
<td>5328</td>
</tr>
<tr>
<td>Distal (42)</td>
<td>567</td>
<td>3095</td>
<td>375</td>
<td>1318</td>
<td>2077</td>
<td>5302</td>
<td>97</td>
<td>5691</td>
<td>5332</td>
<td>5328</td>
</tr>
<tr>
<td>Mid (11)</td>
<td>893</td>
<td>3714</td>
<td>253</td>
<td>1507</td>
<td>2853</td>
<td>5241</td>
<td>96</td>
<td>5652</td>
<td>5281</td>
<td>5308</td>
</tr>
<tr>
<td>Prox (2)</td>
<td>592</td>
<td>2756</td>
<td>0</td>
<td>1.7</td>
<td>1253</td>
<td>5349</td>
<td>92</td>
<td>6100</td>
<td>5480</td>
<td>5526</td>
</tr>
</tbody>
</table>

* Data for 8 pts couldn't be restored during the de-archiving process
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)
Conclusions gastric cancer

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?