Role of Chemotherapy in Gastric Adenocarcinoma

Dr. Sajeed A
• Adjuvant treatment-NEED?
• What are the options?
• Chemoradiation benefit?
• Chemotherapy alone?
The Need

- The five-year survival rate for patients with completely resected stage I gastric cancer is approximately 70 to 75 percent.
- 35% or less for Stage II and beyond.
Options

• Chemoradiation
• Chemotherapy alone
  – Neoadjuvant/Perioperative
  – Adjuvant

*No consensus for best approach*
• Adjuvant treatment-NEED?
• What are the options?
• Chemoradiation benefit?
• Chemotherapy alone?
Adjuvant Chemoradiation

Over 80% patients develop local recurrence
INT0116

- Largest trial
- After complete curative resection
- Observation/ChemoRT

- 556 patients
- T1-T4, N0-1
- 68% were T3/T4
- 85% nodal disease
INT0116 Regimen

One cycle Chemo FU(425mg/m²) and CaLV (20mg/m²) D1-D5

One month later RT 45Gy/25#. Concurrent FU(400mg/m²) and CaLV (20mg/m²) on D1-D4 and last three days of RT

One month later 2 cycles of FU(425mg/m²) and CaLV (20mg/m²) at monthly interval
• Three-year disease free survival- 48 vs 31%
• Overall survival rates -50 vs 41 %
• median survival - 36 vs 27 months

All favoring ChemoRT
Site of relapse

<table>
<thead>
<tr>
<th>Site</th>
<th>Surgery only (n=177)</th>
<th>Adjuvant ChemoRT(n=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>51 (29%)</td>
<td>23 (19%)</td>
</tr>
<tr>
<td>Regional</td>
<td>127 (72%)</td>
<td>78 (65%)</td>
</tr>
<tr>
<td>Distant</td>
<td>32 (18%)</td>
<td>40 (33%)</td>
</tr>
</tbody>
</table>

Toxicity

• Chemoradiation toxicity- Grade 3 in 41% and Grade 4 in 32%.
• Hematologic toxicity 54%
• GI toxicity- 33%
CALGB 80101

- Compared the INT0116 protocol regimen versus postoperative ECF before and after FU plus concurrent RT
- 546 patients with completely resected gastric or EGJ tumors
- Beyond T2 and Node positive
- ECF arm had lower rates of diarrhea, mucositis, and grade 4 or worse neutropenia.
- Overall survival-not significantly better with ECF
- Not adequately powered
ARTIST trial

458 pts; extended D2 dissection

6 cycles Capecitabine + Cisplatin (XP)

2 cycles Capecitabine + Cisplatin (XP)

ConcChemoRT 45Gy/25# Capecitabine+
Followed by 2 cycle XP
- Capecitabine 2000 mg/m² per day on days 1 to 14
- Cisplatin 60 mg/m² on day 1
- Repeated every 3 weeks

- XP/XRT/XP arm received two cycles of XP capecitabine 1650 mg/m²/d for 5 weeks
- Followed by 2 cycles XP
• Addition of radiotherapy to XP chemotherapy did not significantly prolong DFS (HR 1.352, 95% CI 0.952 - 1.922; P=0.0922)

• Unplanned subgroup analysis showed benefit in N+ disease

Patient selection-Adj ChemoRT

- Any T stage with N+ disease
- T3 N0 and above
• Adjuvant treatment-NEED?
• What are the options?
• Chemoradiation benefit?
• Chemotherapy alone?
Advantage of neoadjuvant

- Down staging
- High risk patients developing distant mets not responding to chemo are spared of morbid procedure
MAGIC trial

- 503 patients with potentially resectable
  - gastric (74 %),
  - distal esophageal (11 %),
  - EGJ adenocarcinomas (15%)
MAGIC trial

- 503 pts
- Surgery
- Surgery+ perioperative ECF
<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epirubicin</td>
<td>50 mg/m² IV</td>
<td>Day 1</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>60 mg/m² IV</td>
<td>Day 1</td>
</tr>
<tr>
<td>Fluorouracil (FU)</td>
<td>200 mg/m² per day IV</td>
<td>Continuous infusion upto 6 months</td>
</tr>
</tbody>
</table>
## Results

<table>
<thead>
<tr>
<th></th>
<th>Surgery+ECF arm</th>
<th>Surgery alone arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curative resection</td>
<td>79%</td>
<td>70%</td>
</tr>
<tr>
<td>Pathological T1/T2</td>
<td>52%</td>
<td>37%</td>
</tr>
<tr>
<td>N0/N1</td>
<td>84%</td>
<td>71%</td>
</tr>
<tr>
<td>Local failure</td>
<td>14%</td>
<td>21%</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>24%</td>
<td>37%</td>
</tr>
<tr>
<td>5yr OS</td>
<td>36%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Only 42 percent were able to complete protocol treatment, including surgery and all three cycles of the postoperative chemotherapy.
French FNLCC/FFCD

• 224 patients with potentially resectable stage II or greater
  – adenocarcinoma of the stomach (n = 55),
  – EGJ (n = 144) or
  – distal esophagus (n = 25)

Randomly assigned to
– two to three cycles of preoperative chemotherapy
– surgery alone

Patients in the chemotherapy arm were to receive three to four cycles of postoperative chemotherapy as well.

Infusional FU 800 mg/m² daily for five days plus cisplatin 100 mg/m² on day 1 or 2, every four weeks
Results

• Neoadjuvant chemotherapy were significantly more likely to undergo R0 resection (84 versus 73 percent)

• 35 percent reduction in the risk of disease recurrence at 5.7 yr median follow up

• five-year survival 38 versus 24 percent
META ANALYSIS

• Twelve RCTs with a total of 1,820 patients were included

• neoadjuvant chemotherapy
  – overall survival (OR 1.32, 95% CI 1.07-1.64)
  – progression-free survival (OR 1.85, 95% CI 1.39-2.46)
  – Higher R0 resection rate (OR 1.38, 95% CI 1.08-1.78)
  – no significantly worsen rates of complications

Patient Selection for NACT

• Patients of any age with a performance status of 0 or 1
• Histologically proven adenocarcinoma of the stomach
• stage T2 or higher
• locally advanced inoperable disease
Adjuvant Chemotherapy

• Many trials have evaluated adjuvant chemotherapy
• Different regimen
• Mostly negative results when overall survival was end point
JAPANESE S-1 trial

• Japanese ACTS-GC trial
• 1059 patients with stage II or III gastric cancer - curative surgery with D2 lymphadenectomy
• randomly assigned to
  – Post op six months of S1 (80 to 120 mg daily for four weeks, repeated every six weeks for one year)
  – surgery alone
Result

• Five-year overall survival better with S-1 (72 versus 61 percent)

CLASSIC Trial

- Capecitabine in combination with oxaliplatin
- 1035 patients with stage II, IIIA, or IIIB gastric
  - Randomly assigned to eight 21-day cycles of capecitabine (1000 mg/m² twice daily in days 1 to 14) plus oxaliplatin (130 mg/m² on day 1)
  - surgery alone after D2 gastrectomy

• Only 67 percent of the patients assigned to chemotherapy received all eight cycles
• Adverse events led to chemotherapy dose modifications in 90 percent of patients.
• Median follow-up of 34 months,
  • improvement in three-year disease-free survival (74 versus 59 percent, HR for death 0.56, 95% CI 0.44-0.72)
  • five-year overall survival 78 versus 69 percent, HR for death 0.66 percent, 95% CI 0.51-0.85

Noh SH, Park SR, Yang HK, et al. Adjuvant capecitabine and oxaliplatin (XELOX) for gastric cancer after D2 gastrectomy: Final results of the CLASSIC trial (abstract)
### Cochrane Meta analysis

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival (OS)</td>
<td>HR 0.85 (0.80 to 0.90)</td>
<td>7523 (34 studies)</td>
</tr>
<tr>
<td>Disease Free Survival</td>
<td>HR 0.79 (0.72 to 0.87)</td>
<td>4133 (15 studies)</td>
</tr>
</tbody>
</table>

# Cochrane Meta analysis

<table>
<thead>
<tr>
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<th>No of participants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemobased OS - 5-FU based chemotherapy OS</strong></td>
<td>HR 0.88 (0.83 to 0.94)</td>
<td>5694 (28 studies)</td>
</tr>
<tr>
<td><strong>Chemobased OS - Platinum-based chemotherapy OS</strong></td>
<td>HR 0.9 (0.81 to 1)</td>
<td>1504 (9 studies)</td>
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<tr>
<td><strong>Chemobased DFS - Platinum-based chemotherapy DFS</strong></td>
<td>HR 0.89 (0.75 to 1.06)</td>
<td>969 (4 studies)</td>
</tr>
</tbody>
</table>

Optimal Chemo regimen not established
Comparison between Chemotherapy vs. Chemoradiation
## Chemotherapy vs. ChemoRT – Meta analysis

<table>
<thead>
<tr>
<th>Author/Study</th>
<th>Number</th>
<th>Nodal dissection</th>
<th>End points reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bamias et al</td>
<td>143</td>
<td>56% D0 44% D1-2</td>
<td>OS, DFS</td>
</tr>
<tr>
<td>Kwon et al</td>
<td>61</td>
<td>D2</td>
<td>OS, DFS</td>
</tr>
<tr>
<td>Yu et al</td>
<td>68</td>
<td>31% D1 69% D2</td>
<td>OS, DFS</td>
</tr>
<tr>
<td>ARTIST</td>
<td>458</td>
<td>D2</td>
<td>DFS</td>
</tr>
<tr>
<td>Zhu et al</td>
<td>351</td>
<td>D2</td>
<td>OS, DFS</td>
</tr>
</tbody>
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Who benefits from adjuvant radiation therapy for gastric cancer? A meta-analysis.
Patient selection-Adj. Chemotherapy

- Any T stage with N+ disease
- T3 N0 and above
Conclusion

- Optimal way to integrate combined modality is yet to be defined.

- Institutional / Patient preference

- Upfront curative resection- INT0116 as treatment protocol

- Prior to surgery- MAGIC trial protocol
THANK YOU