Chemotherapy Considerations In The Treatment of Gastric Cancer

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Albert Einstein College Of Medicine
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Gastric Cancer
U.S. Incidence: 2012

- 21,320 estimated new cases, 10,540 deaths
- 50% fatality rate
- Increasing incidence of proximal tumors
- Decreasing incidence of distal tumors
- 14th in incidence in major malignancies but is the second most common cause of death worldwide

American Cancer Society
What’s New: Gastroesophageal Junction Cancer Staging

• AJCC 6 staging guideline has been criticized as a poor predictor of survival
• Emphasizes the importance of depth of invasion (T) and the involvement of lymph nodes based on anatomic location
• Multiple studies demonstrate the number of involved lymph nodes may better predict survival
Essential changes: Staging: WECC/AJCC 7

• Tumors arising at the esophagogastric junction, or arising in the stomach 5 cm or less from the esophagogastric junction and crossing the esophagogastric junction, are staged using the TNM system for esophageal carcinoma.

• The revised gastric cancer staging system applies to tumors arising in the more distal stomach and to tumors arising in the proximal 5 cm but not crossing the esophagogastric junction.

• T categories have been harmonized with T categories of the esophagus and small and large intestine, with T2 defined as a tumor that invades the muscularis propria, and T3 defined as a tumor that invades the subserosal connective tissue. T4 is now defined as a tumor that invades the serosal (visceral peritoneum) or adjacent structures.

• M1 changed to nonregional lymph node involvement or distant metastasis
Staging: WECC/AJCC 7: Nodal Status Matters

- Addition of N1, N2 and N3 based on # of LN involved (1-3, 4-6 or >6)

Adenocarcinoma Of GE junction and Esophageal Cancer: Siewert Classification and Primary Treatment of ≥cT3

- AEG Type I: adenocarcinoma of distal esophagus
- AEG Type II: tumors of the cardia or esophagogastric junction

AEG Type I and II: Preoperative CT/RT or perioperative chemotherapy

- AEG Type III: subcardial gastric carcinoma

AEG Type III: Perioperative Chemotherapy
Gastric Cancer Primary Treatment of ≥ cT3 or N+

• Perioperative Chemotherapy

• Some favor perioperative chemotherapy for cT2N0
Preoperative Chemoradiation
CROSS Study: Effect of preoperative concurrent chemoradiotherapy on survival of patients with resectable esophageal or esophagogastric junction cancer: Results from a multicenter randomized phase III study

CROSS Study

• Phase III study comparing preoperative chemoradiotherapy (CRT) followed by surgery versus surgery in patients with esophageal or GE junction cancer (T2-3/N0-1)

• Preoperative CRT with weekly paclitaxel 50 mg/m2 and carboplatin AUC = 2 for 5 weeks and concurrent radiotherapy (41.4 Gy in 23 fractions, 5 days per week) followed by surgery versus surgery

• 363 pts were enrolled with adeno/squamous/other carcinoma 273/86/4
## CROSS Study

<table>
<thead>
<tr>
<th></th>
<th>CRT+Surgery</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection Rate</td>
<td>90%</td>
<td>86%</td>
</tr>
<tr>
<td>RO Resection Rate</td>
<td>92.3%</td>
<td>64.9%</td>
</tr>
<tr>
<td>pCR</td>
<td>32.6%</td>
<td>NR</td>
</tr>
<tr>
<td>In-hospital Mortality</td>
<td>3.8%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Median Overall Survival</td>
<td>49 months</td>
<td>26 months</td>
</tr>
<tr>
<td>One, 2 and 3 year survival rates</td>
<td>82%/67%/59%</td>
<td>70%/52%/48%</td>
</tr>
</tbody>
</table>
Overall Survival

HR 0.67  95% CI (0.49 - 0.91)
## Preoperative CRT-ACA

<table>
<thead>
<tr>
<th>Trial</th>
<th>Therapy</th>
<th>Patients</th>
<th>%ACA</th>
<th>%R0</th>
<th>pCR</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stahl</td>
<td>Surgery</td>
<td>94</td>
<td>100</td>
<td>66</td>
<td>--</td>
<td>28% 3y</td>
</tr>
<tr>
<td></td>
<td>CRT-S</td>
<td></td>
<td>72</td>
<td>16</td>
<td></td>
<td>47%</td>
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<tr>
<td>Walsh</td>
<td>Surgery</td>
<td>110</td>
<td>100</td>
<td>NS</td>
<td>--</td>
<td>6% 3y</td>
</tr>
<tr>
<td></td>
<td>CRT-S</td>
<td></td>
<td>NS</td>
<td>25</td>
<td>32%</td>
<td></td>
</tr>
<tr>
<td>Urba</td>
<td>Surgery</td>
<td>100</td>
<td>75</td>
<td>90</td>
<td>--</td>
<td>16% 3y</td>
</tr>
<tr>
<td></td>
<td>CRT-S</td>
<td></td>
<td>88</td>
<td>28</td>
<td>32%</td>
<td></td>
</tr>
<tr>
<td>Tepper</td>
<td>Surgery</td>
<td>56</td>
<td>67</td>
<td>--</td>
<td>--</td>
<td>16% 5 y</td>
</tr>
<tr>
<td></td>
<td>CRT-S</td>
<td></td>
<td>--</td>
<td>16</td>
<td>39%</td>
<td></td>
</tr>
<tr>
<td>Gaast</td>
<td>Surgery</td>
<td>363</td>
<td>73</td>
<td>67</td>
<td>--</td>
<td>48% 3y</td>
</tr>
<tr>
<td></td>
<td>CRT-S</td>
<td></td>
<td>92</td>
<td>32.6</td>
<td>59%</td>
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</table>
# Preoperative CRT-SCC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Therapy</th>
<th>Patients</th>
<th>%SCC</th>
<th>%R0</th>
<th>pCR</th>
<th>Survival</th>
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<tbody>
<tr>
<td>Le Prise</td>
<td>Surgery</td>
<td>86</td>
<td>100</td>
<td>NS</td>
<td>--</td>
<td>14% 3y</td>
</tr>
<tr>
<td></td>
<td>CRT-S</td>
<td></td>
<td></td>
<td>NS</td>
<td>25</td>
<td>19%</td>
</tr>
<tr>
<td>Bossett</td>
<td>Surgery</td>
<td>282</td>
<td>100</td>
<td>90</td>
<td>--</td>
<td>36% 3y</td>
</tr>
<tr>
<td></td>
<td>CRT-S</td>
<td></td>
<td>88</td>
<td>28</td>
<td>23</td>
<td>34%</td>
</tr>
<tr>
<td>Bedenne</td>
<td>CRT-S</td>
<td>259</td>
<td>100</td>
<td>75</td>
<td>23</td>
<td>34% 2y</td>
</tr>
<tr>
<td></td>
<td>CRT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40%</td>
</tr>
<tr>
<td>Stahl</td>
<td>CRT-S</td>
<td>172</td>
<td>100</td>
<td>82</td>
<td>35</td>
<td>31% 3y</td>
</tr>
<tr>
<td></td>
<td>CRT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24%</td>
</tr>
</tbody>
</table>
Neo-adjuvant CRT: Conclusion

• Neo-adjuvant CRT/trimodality therapy is the standard of care for resectable ACA of the esophagus

• CRT alone may be sufficient for certain patients with SCC

• Surgery aids in decrease of local recurrence, but does not improve survival

Assessment of Response Following Neoadjuvant Therapy-Biopsy

• Endoscopic biopsy after CRT has been used to determine response
• 156 patients at MSKCC received CRT for local-regionally advanced esophageal cancer -> biopsy -> resection
• 118 patients had no tumor identified on endoscopic biopsy:
  – 69% had local disease at time of surgery
  – Negative biopsy better predicted a pCR for squamous cell carcinoma versus adenocarcinoma (54.3% vs 13.6% P< 0.001).
  – Nodal status of surgical specimens did not correlate
  – Survival was equivalent

• CONCLUSION: A negative endoscopic biopsy is not a useful predictor of a pCR after CRT, final nodal status, or overall survival

Assessment of Response Following Neoadjuvant Therapy-PET/CT

- PET is useful in restaging after CRT to exclude distant metastasis
- Multiple studies are looking at prognostic value after CRT or chemotherapy
- Preliminary results suggest that PET/CT can potentially be a prognosticator for OS, but data on meaningful prediction of response are lacking
Assessment of Response Following Neoadjuvant Therapy

• CONCLUSIONS:
  • No role for repeat endoscopy with biopsy
  • PET/CT useful for excluding distant disease, but not ready as a prognostic test
Peri-operative Therapy
Peri-operative Rx:

**Advantages**

- Increase rate of curative (R0) resection\(^1\) by tumour downstaging/downsizing
- Eradication of micro-metastatic disease
- Demonstrates in vivo chemo-sensitivity
- Better tolerated than post-operative therapy – MAGIC\(^2\) - 91% pts able to complete pre-op Rx
  - 66% of pts able to commence post-op Rx

**Disadvantages**

- Risk of disease progression during pre-operative treatment
- Definitive surgery may be delayed if significant toxicity occurs
- Risk of increased peri-operative morbidity - **NOT** seen in the MAGIC\(^2\) trial

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1. Boige et al., ASCO 2007 2. Cunningham et al., NEJM 2006

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**Peri-operative chemotherapy is now standard of care in Europe**
MAGIC Trial:
Pre- and Postoperative Chemotherapy

Operable adenocarcinoma of the stomach, gastrooesophageal junction, or lower esophagus
≥ Stage II (M0)

RANDOMIZE

n=250

Chemo*:
Epirubicin + Cisplatin + 5-FU
x 3 cycles

Surgery

Chemo*:
Epirubicin + Cisplatin + 5-FU
X 3 cycles

Surgery

*Epirubicin (50 mg/m² IV bolus on day 1)
Cisplatin (60 mg/m² 4-hour infusion on day 1)
5-FU (200 mg/m²/day continuous infusion on days 1-21)

Tolerability

• A total of 215 patients (86.0 percent of patients who were assigned to receive perioperative chemotherapy, and 90.7 percent of those who started chemotherapy) completed preoperative chemotherapy, of whom 209 proceeded to surgery.

• 137 patients, 54.8%, subsequently began postoperative chemotherapy.

• Dropouts: death, disease progression, patient preference and postoperative complications.
Downstaging/Resectability

- Preoperative chemotherapy can downstage T and N
- In an intention to treat analysis, R0 resection rate was 71% in the arm for patients receiving preoperative chemotherapy, not significantly better than surgery alone
MAGIC Trial:
Pre- and Postoperative Chemotherapy

Progression-Free Survival (PFS)*
3 years median follow-up

Log rank p=0.0001
HR=0.66
(95% CI: 0.53-0.81)

Patients at risk
CSC 250 159 99 68 46 32 23
S 253 124 57 42 28 15 8

*Included relapse, PD, and death from any cause

MAGIC Trial: Pre- and Postoperative Chemotherapy

Overall Survival (OS)
3 years median follow-up

Log rank p=0.009
HR=0.75
(95% CI: 0.60-0.93)

Patients at risk

<table>
<thead>
<tr>
<th></th>
<th>CSC</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>149</td>
<td>170</td>
</tr>
<tr>
<td>Total</td>
<td>250</td>
<td>253</td>
</tr>
<tr>
<td>Months from Randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>250</td>
<td>168</td>
</tr>
<tr>
<td></td>
<td>253</td>
<td>155</td>
</tr>
</tbody>
</table>

MAGIC Trial: Pre- and Postoperative Chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>CSC (n=250)</th>
<th>S (n=253)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival</td>
<td>24 months</td>
<td>20 months</td>
<td>0.009</td>
</tr>
<tr>
<td>5-year overall survival</td>
<td>36%</td>
<td>23%</td>
<td>--</td>
</tr>
</tbody>
</table>

Adjuvant Chemoradiation
SWOG-9008/INT-0116: Adjuvant Chemoradiation

Resected adenocarcinoma of the stomach or gastroesophageal junction
Stage IB-IV (M0)
N=559

RANDOMIZE

OBSERVATION (n=277)

5-FU/LV (n=282)

RADIATION
4,500 cGy

5-FU/LV

5-FU=5-fluorouracil; LV=leucovorin

Patient Characteristics

• 10% of patients underwent a D2 dissection, 36% underwent a D1 dissection and 54% underwent a D0 dissection

• Only 36 patients had stage IB disease - 18 in each arm. Most of the tumors were in the distal stomach, with 20% located at the GE junction

• 85% had lymph node involvement and over 67% had T3 or T4 staged tumors
SWOG-9008/INT-0116: Adjuvant Chemoradiation

Disease-Free Survival (DFS)

7.4 years median follow-up

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Events</th>
<th>Median DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU/LV+RT</td>
<td>282</td>
<td>193</td>
<td>27 months</td>
</tr>
<tr>
<td>Observation</td>
<td>277</td>
<td>225</td>
<td>19 months</td>
</tr>
</tbody>
</table>

p < 0.0001

SWOG-9008/INT-0116: Adjuvant Chemoradiation

Overall Survival (OS)

7.4 years median follow-up

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Events</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU/LV+RT</td>
<td>282</td>
<td>192</td>
<td>35 months</td>
</tr>
<tr>
<td>Observation</td>
<td>277</td>
<td>214</td>
<td>27 months</td>
</tr>
</tbody>
</table>

p = 0.006

Issues/Criticisms Of INT-116

- The surgery-alone control arm did as well as would be expected.
- The surgery was inadequate, a minimal surgery is a D1 dissection.
- 54% of patients underwent less than a D1 resection.
- An analysis of survival based on the extent of surgical resection performed and found no significant difference.
## SWOG-9008/INT-0116: Adjuvant Chemoradiation

### Sites of First Relapse*

<table>
<thead>
<tr>
<th></th>
<th>Observation (N=177)</th>
<th>5-FU/LV + RT (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>

*Because patients could have relapses at multiple sites, the total numbers of relapses are greater than the numbers of patients in each group who had relapses.

Charles S Fuchs et al. # 4003
CALGB 80101 – Adjuvant Chemoradiation

- North America: Intergroup study

**Randomize**

- 5-FU/LV x 1 → 5-FU IV CI RT → 5-FU/LV x 2
- ECF x 1 → 5-FU IV CI RT → ECF x 2

N = 540
Stratification by T stage, N stage, < or ≥ 7 examined lymph nodes
Primary endpoint: improvement in overall survival

PRESENTED AT: ASCO Annual Meeting
## CALGB 80101 – Adverse Events ≥ 3

<table>
<thead>
<tr>
<th>Condition</th>
<th>5FU/LV</th>
<th>ECF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>17%</td>
<td>15%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15%</td>
<td>7%</td>
</tr>
<tr>
<td>Mucositis</td>
<td>15%</td>
<td>7%</td>
</tr>
<tr>
<td>Dehydration</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>16%</td>
<td>13%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11%</td>
<td>13%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>52%</td>
<td>48%</td>
</tr>
<tr>
<td>Grade ≥ 4 Neutropenia</td>
<td>33%</td>
<td>19%</td>
</tr>
<tr>
<td>Death</td>
<td>3% (8)</td>
<td>0% (1)</td>
</tr>
</tbody>
</table>
CALGB 80101 – Disease-free Survival

Disease Free Survival by Arm

Proportion Surviving Disease-Free

Years from Study Entry

ECF

5-FU

P, log rank = 0.99
CALGB 80101 – Overall Survival

Overall Survival by Arm

Proportion Surviving

Years from Study Entry

P, log rank = 0.80
CALGB 80101 – Discussion

GISCAD adjuvant PELF vs FU

Cascinu et al. JNCI 2007; 99: 601-607
Adjuvant Chemotherapy
Yung-Jue Bang et al. LBA 4002
CLASSIC – Adjuvant Chemotherapy

- Asia: Korea, China, Taiwan
- Surgical technique: D2 resection

Randomization

- Surgically (D2) resected Stage II, IIIA, or IIIB* GC, 6 weeks prior to randomization
- No prior chemotherapy or radiotherapy

- 8 cycles of XELOX (6 months) n = 520
  - Capecitabine: 1,000 mg/m² bid, d1–14, q3w
  - Oxaliplatin: 130 mg/m², d1, q3w

- Observation: No adjuvant therapy n = 515

- Primary endpoint: 3-year DFS‡
- Secondary endpoints: overall survival and safety profile
CLASSIC – Overall Survival

HR = 0.74 (95% CI 0.53–1.03)

P = .0775

XELOX, n = 520
Observation n = 515

No. left

<table>
<thead>
<tr>
<th></th>
<th>XELOX</th>
<th>Observation</th>
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<tr>
<td>0</td>
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<td>515</td>
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<td>6</td>
<td>468</td>
<td>458</td>
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<tr>
<td>12</td>
<td>451</td>
<td>441</td>
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<td>18</td>
<td>395</td>
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<tr>
<td>48</td>
<td>16</td>
<td>12</td>
</tr>
</tbody>
</table>

ITT population
Median follow-up 34.4 months (range 16–51)
CLASSIC – Primary Endpoint Met (3-year DFS at Interim Analysis)

3-year DFS

HR = 0.56 (95% CI 0.44–0.72)

P < .0001

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>XELOX</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>520</td>
<td>515</td>
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<tr>
<td>6</td>
<td>443</td>
<td>414</td>
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<td>12</td>
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<td>30</td>
<td>22</td>
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<tr>
<td>48</td>
<td>10</td>
<td>6</td>
</tr>
</tbody>
</table>

ITT population
Median follow-up 34.4 months (range 16–51)
CLASIC – Discussion

ATCS-GC (Japan): S-1 vs. surgery alone

Relapse-free survival

Overall survival

HR = 0.62 (95% CI, 0.50 to 0.77)
P < 0.001

HR = 0.68 (95% CI, 0.52 to 0.87)
P = 0.003

CLASSIC – Discussion

GASTRIC Group Meta-analysis

Figure 3. Overall Survival Estimate After Any Chemotherapy or Surgery Alone Truncated at 10 Years

6% difference at 5 years
HR = 0.82; p < 0.001

The Gastric Group. JAMA 2010; 303: 1729-1737
CLASSIC – Discussion

• D2 resection (Classic): median 42 lymph nodes examined (range 9-127)

<table>
<thead>
<tr>
<th>US INT 0116 (SWOG 9008)</th>
<th>UK MAGIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macdonald et al. 2001</td>
<td>Cunningham et al. 2006</td>
</tr>
<tr>
<td>D2-Resection</td>
<td>D2-Resection</td>
</tr>
<tr>
<td>10%</td>
<td>41%</td>
</tr>
<tr>
<td>D1-Resection</td>
<td>D1-Resection</td>
</tr>
<tr>
<td>36%</td>
<td>19%</td>
</tr>
<tr>
<td>D0-Resection</td>
<td>Other Resections</td>
</tr>
<tr>
<td>54%</td>
<td>40%</td>
</tr>
</tbody>
</table>
Summary Adjuvant Gastric Cancer

N America
Adjuvant R-CTx
45 Gy + 5FU/LV

Europe
Perioperative CTx
(Epirubicin)-Platin-5FU

Asia
Adjuvant CTx
S-1 or Capox
Gastric Cancer – Discussion

Does the surgical approach determine the optimal adjuvant treatment strategy?

Asia: Radical resection (D2)
Adjuvant chemotherapy

Sub-radical resection (≤ D 1)
Adjuvant chemoradiation
Treatment of Metastatic Disease
Chemotherapy for Advanced Gastric Cancer (meta-analysis)

Chemotherapy versus Best Supportive Care
Overall Survival

<table>
<thead>
<tr>
<th>Study</th>
<th>No. (Chemotherapy)</th>
<th>No. (BSC)</th>
<th>Hazard Ratio (fixed)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murad 1993⁹</td>
<td>30</td>
<td>10</td>
<td>0.33</td>
<td>0.17 to 0.64</td>
</tr>
<tr>
<td>Prorhon 1995¹⁰</td>
<td>21</td>
<td>20</td>
<td>0.25</td>
<td>0.13 to 0.47</td>
</tr>
<tr>
<td>Scheithauer 1996¹¹</td>
<td>52</td>
<td>51</td>
<td>0.49</td>
<td>0.33 to 0.74</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>103</td>
<td>81</td>
<td>0.39</td>
<td>0.28 to 0.52</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 3.32$, ($P = .19$)
Test for overall effect: $Z = 6.15$ ($P < .00001$)

6 months improvement

Combination Therapy vs Single Agent

<table>
<thead>
<tr>
<th>Study</th>
<th>Combination Chemotherapy</th>
<th>Single-Agent Chemotherapy</th>
<th>Hazard Ratio (fixed)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cullinan 1985&lt;sup&gt;14&lt;/sup&gt;</td>
<td>51</td>
<td>51</td>
<td>0.90</td>
<td>0.61 to 1.33</td>
</tr>
<tr>
<td>De Lisi 1986&lt;sup&gt;20&lt;/sup&gt;</td>
<td>42</td>
<td>43</td>
<td>1.16</td>
<td>0.26 to 5.15</td>
</tr>
<tr>
<td>Levi 1986&lt;sup&gt;23&lt;/sup&gt;</td>
<td>94</td>
<td>93</td>
<td>0.58</td>
<td>0.43 to 0.77</td>
</tr>
<tr>
<td>Cullinan 1994&lt;sup&gt;15&lt;/sup&gt;</td>
<td>183</td>
<td>69</td>
<td>0.90</td>
<td>0.69 to 1.16</td>
</tr>
<tr>
<td>Loehrer 1994&lt;sup&gt;13&lt;/sup&gt;</td>
<td>64</td>
<td>94</td>
<td>0.85</td>
<td>0.61 to 1.19</td>
</tr>
<tr>
<td>Colucci 1995&lt;sup&gt;19&lt;/sup&gt;</td>
<td>35</td>
<td>36</td>
<td>0.70</td>
<td>0.42 to 1.16</td>
</tr>
<tr>
<td>Barone 1998&lt;sup&gt;18&lt;/sup&gt;</td>
<td>36</td>
<td>36</td>
<td>0.89</td>
<td>0.55 to 1.42</td>
</tr>
<tr>
<td>Yamamura 1998&lt;sup&gt;22&lt;/sup&gt;</td>
<td>37</td>
<td>34</td>
<td>0.88</td>
<td>0.55 to 1.41</td>
</tr>
<tr>
<td>Popov 2002&lt;sup&gt;21&lt;/sup&gt;</td>
<td>30</td>
<td>30</td>
<td>0.86</td>
<td>0.32 to 2.29</td>
</tr>
<tr>
<td>Ohtsu 2003&lt;sup&gt;16&lt;/sup&gt;</td>
<td>175</td>
<td>105</td>
<td>1.04</td>
<td>0.82 to 1.32</td>
</tr>
<tr>
<td>Bouche 2004&lt;sup&gt;17&lt;/sup&gt;</td>
<td>89</td>
<td>45</td>
<td>0.65</td>
<td>0.45 to 0.95</td>
</tr>
</tbody>
</table>

Total (95% CI): 836, 636

Test for heterogeneity: $\chi^2 = 12.30$, ($P = .27$)
Test for overall effect: $Z = 3.28$ ($P = .001$)
5FU, Anthracyclines and Platinum

<table>
<thead>
<tr>
<th>Study</th>
<th>FU/P/Anthracyline</th>
<th>FU/Anthracyline</th>
<th>Hazard Ratio (fixed)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG 1988</td>
<td>85</td>
<td>162</td>
<td>0.86, 0.67 to 1.11</td>
<td></td>
</tr>
<tr>
<td>Kikuchi 1990</td>
<td>32</td>
<td>33</td>
<td>0.58, 0.36 to 0.95</td>
<td></td>
</tr>
<tr>
<td>Cocconi 1994</td>
<td>88</td>
<td>55</td>
<td>0.69, 0.51 to 0.93</td>
<td></td>
</tr>
<tr>
<td>Cullinan 1994</td>
<td>51</td>
<td>132</td>
<td>1.07, 0.80 to 1.44</td>
<td></td>
</tr>
<tr>
<td>Webb 1997</td>
<td>98</td>
<td>101</td>
<td>0.78, 0.64 to 0.95</td>
<td></td>
</tr>
<tr>
<td>Roth 1999</td>
<td>54</td>
<td>56</td>
<td>0.74, 0.55 to 0.99</td>
<td></td>
</tr>
<tr>
<td>Cocconi 2003</td>
<td>100</td>
<td>100</td>
<td>0.90, 0.77 to 1.05</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>508</td>
<td>639</td>
<td>0.83, 0.76 to 0.91</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 8.39$, ($P = .21$)

Test for overall effect: $Z = 4.01$ ($P < .0001$)
Selection of patients for chemotherapy

- Patients of good performance status (ECOG 0-1) more likely to respond to chemotherapy\(^1\) and have improved median survival\(^1,2\)
- Linitus plastica is a feature of poor prognosis\(^1\)
- Response rate is lower in patients with peritoneal carcinomatosis\(^3\)
- Co-morbidities must be considered

REAL 2

Untreated advanced oesophageal, OGJ or gastric cancer n=1002

Randomised

Epirubicin Cisplatin + infused 5-FU (ECF)
Epirubicin + cisplatin + capecitabine (ECX)
Epirubicin + oxaliplatin + 5-FU (EOF)
Epirubicin + oxaliplatin + capecitabine (EOX)

Primary Endpoints:
- Non-inferiority for survival
  - Capecitabine compared to Fluorouracil
  - Oxaliplatin compared to Cisplatin
- Overall survival amongst the four regimens

Cunningham et al., NEJM 2008
REAL-2 - Results

Capecitabine is non-inferior to infused 5FU

Toxicity:
More G3/4 neutropenia (uncomplicated) hand foot syndrome

Oxaliplatin is non-inferior to cisplatin

Toxicity:
Less G3/4 neutropenia (uncomplicated) thromboembolism, alopecia
More G3/4 diarrhoea G3/4 peripheral neuropathy

Cunningham et al., NEJM 2008
Survival: ECF v EOX

<table>
<thead>
<tr>
<th>Arm</th>
<th>OS (m)</th>
<th>1 year survival (95% CI)</th>
<th>p-value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECF</td>
<td>9.9</td>
<td>37.7 (31.8-43.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EOX</td>
<td>11.2</td>
<td>46.8 (40.4-52.9)</td>
<td>0.020</td>
<td>0.80 (0.66-0.97)</td>
</tr>
</tbody>
</table>

**Improved efficacy of EOX compared to ECF for survival**

**EOX now an accepted first-line therapy option**

Cunningham et al., NEJM 2008
CALGB 80403 / ECOG 1206: Randomized Phase II Study of Standard Chemotherapy + Cetuximab for Metastatic Esophageal Cancer

PC Enzinger, BA Burtness, DR Hollis, D Niedzwiecki, DH Ilson, AB Benson 3rd, RJ Mayer, RM Goldberg
Stratification:
- ECOG 0-1 vs 2
- ADC vs. SCC

Primary endpoint RR

**ARM A: (ECF + cetuximab); 1 cycle = 21 days**
- Cetuximab 400 → 250mg/m2 IV, weekly
- Epirubicin 50 mg/m2 IV, day 1
- Cisplatin 60mg/m2 IV, day 1
- Fluorouracil 200mg/m2/day, days 1-21

**ARM B: (IC + cetuximab); 1 cycle = 21 days**
- Cetuximab 400 → 250mg/m2 IV, weekly
- Cisplatin 30 mg/m2 IV, days 1 and 8
- Irinotecan 65 mg/m2 IV, days 1 and 8

**ARM C: (FOLFOX + cetuximab); 1 cycle = 14 days**
- Cetuximab 400 → 250mg/m2 IV, weekly
- Oxaliplatin 85 mg/m2 IV, day 1
- Leucovorin 400 mg/m2, day 1
- Fluorouracil 400 mg/m2 IV bolus, day 1
- Fluorouracil 2400 mg/m2 IV over 46hrs (days 1-2)
Overall Survival

- Median OS:
  - ECF-C: 11.5 months
  - IC-C: 8.9 months
  - FOLFOX-C: 12.4 months
Conclusions

• All 3 regimens > 40% RR
• IC-C: appeared to have lowest response and survival & most adverse events
• ECF-C: appeared to have highest response, but highest treatment-related mortality and most treatment-related modifications
• FOLFOX-C: good response and survival and best tolerated
AVAGAST: A Randomized Double-Blind, Placebo-Controlled Phase III Study

Locally advanced or metastatic gastric cancer

Primary endpoint OS

Cape 1000 mg/m² oral bid, d1–14, 1-week rest
Cisplatin 80 mg/m² d1
Bevacizumab 7.5 mg/kg d1
Maximum of 6 cycles of cisplatin
Cape and bevacizumab/placebo until PD
Conclusions

• Primary endpoint of OS not met
• Secondary efficacy endpoints (PFS, best ORR) significantly improved, indicating clinical activity of bev + chemo in AGC
• Apparent greater benefit in America>Europe>Asia
• No unexpected / new safety signals for bev
• Further analysis ongoing, including preplanned biomarker analysis
HER2 Expression in Gastric/GEJ Cancer

- According to the ToGA trial, approximately 22% of patients with gastric/GEJ cancer are HER2+.\(^1\)

  - HER2 status should be included in the diagnostic protocol for metastatic GC

<table>
<thead>
<tr>
<th>Incidence of HER2 Expression by IHC or FISH(^1-6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All GC tumors</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>13%-23%</td>
</tr>
<tr>
<td>Histology</td>
</tr>
<tr>
<td>Intestinal</td>
</tr>
<tr>
<td>16%-34%</td>
</tr>
<tr>
<td>Diffuse</td>
</tr>
<tr>
<td>6%-7%</td>
</tr>
<tr>
<td>Mixed</td>
</tr>
<tr>
<td>20%</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td>14%</td>
</tr>
<tr>
<td>Primary tumor location</td>
</tr>
<tr>
<td>GEJ</td>
</tr>
<tr>
<td>25%-34%</td>
</tr>
<tr>
<td>Gastric</td>
</tr>
<tr>
<td>9%-20%</td>
</tr>
</tbody>
</table>

DFS=disease-free survival; FISH=fluorescence in situ hybridization; IHC=immunohistochemistry; OS=overall survival.

Herceptin in GC: ToGA Trial Design
Phase III, randomized, open-label, international, multicenter study

**Stratification factors**
- Advanced vs metastatic
- GC vs GEJC
- Measurable vs nonmeasurable
- ECOG PS 0-1 vs 2
- Capecitabine vs 5-FU

**Endpoints**
- Primary: overall survival
- Secondary: PFS, TTP, ORR, duration of response, safety

---

Advanced GC or GEJC (n=3801)*

**Randomize**

HER2+ advanced GC (n=584)

5-FU or capecitabine† + cisplatin (n=290)

Until disease progression, unacceptable toxicity, or withdrawal of consent.

5-FU or capecitabine† + cisplatin + Herceptin 8 mg/kg loading dose, followed by 6 mg/kg q3wk to PD (n=294)

---

*810 HER2+ (22.1%).
† Chosen at investigator’s discretion.
5-FU=5-fluorouracil; CI=continuous infusion; ECOG PS=Eastern Cooperative Oncology Group performance status; GEJC=gastroesophageal junction cancer; ORR=overall response rate; PD=progressive disease; PFS=progression-free survival; TTP=time to progression.

## ToGA Trial: Overall Survival

<table>
<thead>
<tr>
<th>Final Overall Survival</th>
<th>Herceptin + Chemotherapy*</th>
<th>Chemotherapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=298)</td>
<td>(n=296)</td>
<td></td>
</tr>
<tr>
<td>No. deaths (%)</td>
<td>167 (56.0%)</td>
<td>184 (62.2%)</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>13.5 (95% CI: 11.7-15.7)</td>
<td>11.0 (95% CI: 9.4-12.5)</td>
</tr>
<tr>
<td></td>
<td>HR=0.73 (95% CI: 0.60-0.91)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*P value=0.0038</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Updated Overall Survival†</th>
<th>Herceptin + Chemotherapy*</th>
<th>Chemotherapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=298)</td>
<td>(n=296)</td>
<td></td>
</tr>
<tr>
<td>No. deaths (%)</td>
<td>221 (74.2%)</td>
<td>227 (76.7%)</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>13.1 (95% CI: 11.9-15.1)</td>
<td>11.7 (95% CI: 10.3-13.0)</td>
</tr>
<tr>
<td></td>
<td>HR=0.80 (95% CI: 0.67-0.97)</td>
<td></td>
</tr>
</tbody>
</table>

Please see full prescribing information for **Boxed WARNINGS** and additional important safety information.

* Capecitabine or 5-fluorouracil (at investigator’s discretion) plus cisplatin.
† 2-sided; comparing with the nominal significance level of 0.0193.
‡ Updated OS analysis was conducted 1 year after the final analysis
Cl=confidence interval.

# ToGA Trial: Secondary Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Herceptin + chemotherapy* (n=294)</th>
<th>Chemotherapy alone* (n=290)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months</td>
<td>6.7</td>
<td>5.5</td>
<td>0.71 (0.59-0.85)</td>
<td>0.0002</td>
</tr>
<tr>
<td>ORR, %</td>
<td>47.3</td>
<td>34.5</td>
<td>—</td>
<td>0.0017</td>
</tr>
<tr>
<td>Median duration of response, months</td>
<td>6.9</td>
<td>4.8</td>
<td>—</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CBR, %</td>
<td>78.9</td>
<td>69.3</td>
<td>—</td>
<td>0.0081</td>
</tr>
</tbody>
</table>

Please see full prescribing information for **Boxed WARNINGS** and additional important safety information.

* Capecitabine or 5-FU (at investigator's discretion) plus cisplatin.

CBR=Clinical benefit rate; ORR=overall response rate.

Advanced Gastric Cancer

- 1st line chemotherapy prolongs survival
- 1st line chemotherapy improves symptom control


Established standard 1st line:
Platin-fluoropyrimidine-combinations

Park et al. # 4004
Is there a role for second-line chemotherapy?
2nd line Chemotherapy (SLC)
Park et al. #4004

Screening & consent for RCT

- Refused RCT, but prefer SLC
  - 2:1 randomization
    - SLC
    - SLC
    - BSC
    - BSC

- Willing to participate RCT
  - 2:1 randomization
    - SLC
    - SLC
    - BSC
    - BSC

- Refused RCT, but prefer BSC

Docetaxel or irinotecan

RCT: randomized controlled trial
PPT: patient-preference trial

N = 202

ClinicalTrials.gov, NCT00821990
Survival (Park et al. #4004)

Median f/u (95% CI): 17 mo (16-18 mo)

- SLC + BSC
  - Median: 5.1 mo
  - 95% CI: 4.0-6.2

- BSC alone
  - Median: 3.8 mo
  - 95% CI: 3.0-4.6

Log-rank
P=0.009
# Post progression chemotherapy

## German AIO Study

<table>
<thead>
<tr>
<th></th>
<th>Irinotecan (n = 21)</th>
<th>BSC (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom improvement</strong></td>
<td>44%</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Survival (median)</strong></td>
<td>4 mon</td>
<td>2.4 mon</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>P = 0.0027</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR = 0.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>95% CI [0.25-0.92]</td>
</tr>
</tbody>
</table>

Thuss-Patience P. *Eur J Cancer*, 2011; accepted for publication
2nd line chemotherapy has a proven benefit in advanced gastric cancer and should be offered to patients with an acceptable Karnofksy PS and motivation to receive further chemotherapy.
Current randomised phase III trials

**ST03 (MAGIC-B)**
- Resectable adenocarcinoma of the stomach or Type III OGJ
  - ECX x3 → Surgery → ECX x3
  - ECX + bevacizumab x3 → Surgery → ECX + bevacizumab x3

**CRITICS:**
- Resectable adenocarcinoma of the stomach or Type III OGJ
  - ECX x3 → Surgery → ECX x3
  - ECX x3 → Surgery → CX + RT 45Gy

**REAL3**
- Untreated advanced adenocarcinoma or undifferentiated carcinoma of the oesophagus, OGJ or stomach
  - EOX
  - EOX panitumumab
What have we learned about localized gastric/GE cancers?

- Surgical approach determines the optimal adjuvant treatment strategy
  - Asia: Radical resection (D2)
  - U.S.: Sub-radical resection (≤ D 1)
- Adjuvant chemotherapy
- Adjuvant chemoradiation

- Awaiting data on adjuvant CRT vs. chemotherapy
  - ARTIST (capecitabine/cisplatin compared with resected gastric cancer with D2 nodal dissection trial - when surgery is controlled, is adjuvant radiation necessary?)

- Is a neoadjuvant approach feasible and better?
  - Neoadjuvant much more likely to receive therapy (SAKK)
  - EORTC 40954 – 3 months neoadjuvant chemo trends towards better outcomes
  - No randomized neoadjuvant CRT gastric studies reported yet
    - Attempts have been aborted secondary to low accrual

- Data with targeted therapies, more aggressive chemotherapy
  - MAGIC 2 – ECF +/- bevacizumab
Gastro-esophageal Cancers: Advanced disease

- Marginal differences between doublets and triplets that perhaps do not justify the differences in toxicities.

- Trastuzumab should be considered as an option added to a platinum and 5FU in the presence of Her-2 overexpression
  - Capecitabine + oxaliplatin +/- lapatinib
  - All patients with gastric and GEJ ACA should have her2neu status assessed

- 2nd line Irinotecan has a proven benefit in advanced gastric cancer and should be offered to patients with a PS 0-2

- No role for Bevacizumab in gastric cancer
Thank you!!