NEO- AND ADJUVANT TREATMENT FOR GASTRIC CANCER: THE ROLE OF CHEMOTHERAPY

Dr Elizabeth Smyth
Cambridge University Hospitals NHS Foundation Trust

ESMO Gastric Cancer Preceptorship Barcelona 2019
DISCLOSURES

Honoraria
Astellas, BMS, Celgene, Five Prime Therapeutics, Servier, Gritstone Oncology
GASTRIC AND GASTROESOPHAGEAL CANCER NOMENCLATURE

Lower oesophageal, gastroesophageal junction adenocarcinoma → ESMO Oesophageal Cancer Guidelines

Gastric cancer → ESMO Gastric Cancer Guidelines
SURVIVAL FROM OG CANCER WITH SURGERY ALONE

Treatment in addition to surgery is required for most patients

ESMO OESOPHAGEAL CANCER GUIDELINES

NEOADJUVANT AND PERIOPERATIVE CHEMOTHERAPY
AIMS OF NEOADJUVANT AND PERI-OPERATIVE CHEMOTHERAPY

- Downstage the tumour
- Increase R0 resection rate
- Treat micrometastatic disease
- Improve overall survival

Neoadjuvant and perioperative chemotherapy is more commonly used in non-Asian countries where tumours are frequently locally advanced and require downstaging prior to successful resection
1. OE02 Trial Group, Lancet 2002

MAGIC
3x ECF – surgery – 3x ECF vs surgery alone

CROSS
Neoadjuvant carbo/taxol+RT-surgery vs surgery alone
Oesophageal and junctional only

FLOT4/AIO
4x FLOT- surgery – 4x FLOT vs 3x ECX- surgery – 3x ECX

OE02
2x neoadjuvant CF-surgery vs surgery alone
Oesophageal and junctional only

FFCD/FNCLCC
CF-surgery-CF vs surgery alone

CF, cisplatin + 5-fluourouracil; ECF, epirubicin + CF; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, docetaxel
ECF, epirubicin 50mg/m², cisplatin 60mg/m² and continuous 5-fluorouracil 200mg/m²/d

**Eligibility criteria**
- Stage ≥ II gastric, gastroesophageal junction, or lower oesophageal adenocarcinoma (after 1999)
- No metastases
- ECOG 0-1

**MAGIC preoperative patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Surgery alone</th>
<th>Chemo + surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age</strong></td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>191 (75%)</td>
<td>205 (82%)</td>
</tr>
<tr>
<td>Female</td>
<td>62 (25%)</td>
<td>45 (18%)</td>
</tr>
<tr>
<td><strong>Site of disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric</td>
<td>187 (74%)</td>
<td>185 (74%)</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>36 (14%)</td>
<td>37 (15%)</td>
</tr>
</tbody>
</table>
| GOJ              | 30 (12%)      | 28 (11%)
**MEDICAL RESEARCH COUNCIL MAGIC TRIAL**

Eligible patients

- 3 cycles preoperative ECF (n=250)
- Surgery alone (n=253)
- Surgery
- 3 cycles postoperative ECF

<table>
<thead>
<tr>
<th>MAGIC post-operative patient characteristics</th>
<th>Surgery alone</th>
<th>Chemo + surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curative</td>
<td>66/250 (66%)</td>
<td>169/244 (69%)</td>
</tr>
<tr>
<td>Palliative</td>
<td>70/250 (28%)</td>
<td>44/244 (18%)</td>
</tr>
<tr>
<td>Other</td>
<td>17/250 (6%)</td>
<td>27/244 (13%)</td>
</tr>
<tr>
<td>ypT stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>16/193 (8%)</td>
<td>27/172 (16%)</td>
</tr>
<tr>
<td>T2</td>
<td>55/193 (29%)</td>
<td>62/172 (36%)</td>
</tr>
<tr>
<td>T3</td>
<td>106/193 (55%)</td>
<td>75/172 (44%)</td>
</tr>
<tr>
<td>T4</td>
<td>16/193 (8%)</td>
<td>8/172 (4%)</td>
</tr>
<tr>
<td>ypN Stage (gastric)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>42/156 (27%)</td>
<td>42/135 (31%)</td>
</tr>
<tr>
<td>N1</td>
<td>68/156 (43%)</td>
<td>72/135 (53%)</td>
</tr>
<tr>
<td>N2</td>
<td>34/156 (23%)</td>
<td>19/135 (14%)</td>
</tr>
<tr>
<td>N3</td>
<td>12/156 (8%)</td>
<td>2/135 (2%)</td>
</tr>
</tbody>
</table>

Peri-operative chemotherapy leads to tumour *downstaging*

ECF, epirubicin 50mg/m², cisplatin 60mg/m² and continuous 5-fluorouracil 200mg/m²/d
MEDICAL RESEARCH COUNCIL MAGIC TRIAL

Progression free survival
HR 0.66 (95% CI 0.53 - 0.81)
P=0.0001

Overall survival
HR 0.75 (95% CI 0.60 - 0.93)
P=0.0001

Absolute gain in 5 year survival 13% (23% surgery alone to 36% chemotherapy plus surgery
Median OS benefit approximately 4 months (20 months vs 24 months)

FFCD/FNCLCC TRIAL

Eligible patients

2-3 cycles preoperative CF (n=113)

Surgery alone (n=111)

Surgery

3-4 cycles postoperative CF

Eligibility criteria
Lower oesophageal or GOJ adenocarcinoma (gastric after 1998)
No metastases
ECOG 0-1

FFCD/ACCORD preoperative patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Surgery alone</th>
<th>Chemo + surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>91 (82%)</td>
<td>96 (85%)</td>
</tr>
<tr>
<td>Female</td>
<td>20 (18%)</td>
<td>17 (15%)</td>
</tr>
<tr>
<td>Site of disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric</td>
<td>28 (13%)</td>
<td>27 (9%)</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>15 (25%)</td>
<td>10 (24%)</td>
</tr>
<tr>
<td>GOJ</td>
<td>70 (62%)</td>
<td>74 (67%)</td>
</tr>
</tbody>
</table>

CF, cisplatin 100mg/m² and continuous 5-fluorouracil 800mg/m²/d day 1-5 q 28d
FFCD/FNCLCC TRIAL

Peri-operative chemotherapy leads to tumour downstaging

<table>
<thead>
<tr>
<th>FFCD/FNCLCC post-operative patient characteristics</th>
<th>Surgery alone</th>
<th>Chemo + surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td></td>
<td>↑ curative surgery</td>
</tr>
<tr>
<td>No resection</td>
<td>11 (10%)</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>R0</td>
<td>81 (74%)</td>
<td>95 (87%)</td>
</tr>
<tr>
<td>R1</td>
<td>6 (5%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>R2</td>
<td>11 (10%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Rx</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>ypT stage</td>
<td></td>
<td>↑ early T stage</td>
</tr>
<tr>
<td>T0</td>
<td>(8%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>T1-2</td>
<td>(29%)</td>
<td>38 (39%)</td>
</tr>
<tr>
<td>T3-4</td>
<td>(55%)</td>
<td>57 (58%)</td>
</tr>
<tr>
<td>ypN Stage (gastric)</td>
<td></td>
<td>↑ early N stage</td>
</tr>
<tr>
<td>N0</td>
<td>17 (20%)</td>
<td>32 (33%)</td>
</tr>
<tr>
<td>N+</td>
<td>68 (80%)</td>
<td>66 (67%)</td>
</tr>
</tbody>
</table>

CF, cisplatin 100mg/m² and continuous 5-fluorouracil 800mg/m²/d day 1-5 q 28d
FFCD/FNCLCC TRIAL

Eligible patients

2-3 cycles preoperative CF (n=113)

Surgery alone (n=111)

4-6 week break

Surgery

6-12 week break

3-4 cycles postoperative CF

CF, cisplatin 100mg/m² and continuous 5-fluorouracil 800mg/m²/d day 1-5 q 28d

Absolute benefit in OS 14% (24% surgery vs. 38% chemo + surgery)
1. ~10% of patients will not complete pre-operative chemotherapy
2. Approximately 50% of patients are not fit enough for post operative chemotherapy

<table>
<thead>
<tr>
<th>MAGIC 3 cycles ECF</th>
<th>FFCD/FNCLCC 2-3 cycles CF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-operative chemotherapy</td>
<td>3 cycles: n= 215 (91%)</td>
</tr>
<tr>
<td></td>
<td>2 cycles: n=85 (75%)</td>
</tr>
<tr>
<td></td>
<td>3 cycles: n= 13 (12%)</td>
</tr>
<tr>
<td></td>
<td>87% had minimum 2 cycles</td>
</tr>
<tr>
<td>Surgery</td>
<td>229 (92%)</td>
</tr>
<tr>
<td>Post-operative chemotherapy</td>
<td>Any chemotherapy: n=137 (55%)</td>
</tr>
<tr>
<td></td>
<td>3 cycles: n= 104 (42%)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
NEW HORIZON IN PERI-OPERATIVE CHEMOTHERAPY

- Gastric cancer or adenocarcinoma of the gastro-esophageal junction type I-III
- Medically and technically operable
- cT2-4/cN-any/cM0 or cT-any/cN+/cM0

**Stratification:**
- ECOG (0 or 1 vs. 2), location of primary (GEJ type I vs. type II/III vs. stomach), age (< 60 vs. 60-69 vs. ≥70 years) and nodal status (cN+ vs. cN-).

**FLOT x4 - RESECTION - FLOT x4**
- FLOT: docetaxel 50mg/m², d1; 5-FU 2600 mg/m², d1; leucovorin 200 mg/m², d1; oxaliplatin 85 mg/m², d1, every two weeks

**ECF/ECX x3 - RESECTION - ECF/ECX x3**
- ECF/ECX: Epirubicin 50 mg/m², d1; cisplatin 60 mg/m², d1; 5-FU 200 mg/m² (or capecitabine 1250 mg/m² p.o. divided into two doses d1-d21), every three weeks

n=716

Primary endpoint OS (ITT)

# FLOT Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>ECF/ECX N=360</th>
<th></th>
<th>FLOT N=356</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>62</td>
<td>-</td>
<td>62</td>
<td>-</td>
</tr>
<tr>
<td>&gt;=70</td>
<td>87</td>
<td>24%</td>
<td>85</td>
<td>24%</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>265</td>
<td>74%</td>
<td>268</td>
<td>75%</td>
</tr>
<tr>
<td><strong>ECOG PS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>254</td>
<td>71%</td>
<td>246</td>
<td>69%</td>
</tr>
<tr>
<td>1</td>
<td>103</td>
<td>29%</td>
<td>109</td>
<td>31%</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>1%</td>
<td>1</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GEJ Siewert type 1</td>
<td>85</td>
<td>24%</td>
<td>80</td>
<td>23%</td>
</tr>
<tr>
<td>GEJ Siewert type 2 or 3</td>
<td>115</td>
<td>32%</td>
<td>118</td>
<td>33%</td>
</tr>
<tr>
<td>Stomach</td>
<td>160</td>
<td>44%</td>
<td>158</td>
<td>44%</td>
</tr>
</tbody>
</table>

### FLOT VS ECF/X SURGICAL OUTCOMES

<table>
<thead>
<tr>
<th></th>
<th>ECF/ECX (n=360)</th>
<th>FLOT (n=356)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection surgery</td>
<td>313/360 (87%)</td>
<td>336/356 (94%)</td>
<td>0.001</td>
</tr>
<tr>
<td>R0 resection rate</td>
<td>276/360 (77%)</td>
<td>300/356 (84%)</td>
<td>0.011</td>
</tr>
<tr>
<td>Any surgical complication</td>
<td>188/341 (55%)</td>
<td>188/345 (55%)</td>
<td></td>
</tr>
<tr>
<td>Median duration hospital stay</td>
<td>16 days</td>
<td>15 days</td>
<td></td>
</tr>
<tr>
<td>Death 90 days</td>
<td>26 (8%)</td>
<td>16 (5%)</td>
<td></td>
</tr>
</tbody>
</table>

- Peri-operative FLOT chemotherapy increases the proportion of patients who undergo surgical resection and increases the R0 resection rate compared to ECF/ECX.
- Surgical morbidity and mortality was not increased by use of FLOT chemotherapy.

Peri-operative FLOT chemotherapy increases the proportion of patients have pathological early stage tumours compared to ECF/X.

<table>
<thead>
<tr>
<th>ypT stage</th>
<th>ECF/ECX (n=360)</th>
<th>FLOT (n=356)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤T1</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>T2</td>
<td>44 (12%)</td>
<td>44 (12%)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>175 (49%)</td>
<td>165 (46%)</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>47 (13%)</td>
<td>37 (10%)</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>41 (11%)</td>
<td>22 (6%)</td>
<td></td>
</tr>
<tr>
<td>ypN stage</td>
<td></td>
<td></td>
<td>0.029</td>
</tr>
<tr>
<td>N0</td>
<td>146 (41%)</td>
<td>174 (49%)</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>44 (12%)</td>
<td>55 (16%)</td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>54 (15%)</td>
<td>47 (13%)</td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>73 (20%)</td>
<td>57 (16%)</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>43 (12%)</td>
<td>23 (7%)</td>
<td></td>
</tr>
</tbody>
</table>
FLOT IMPROVES PFS AND OS COMPARED TO ECF/X

Projected PFS rates

<table>
<thead>
<tr>
<th></th>
<th>ECF/X</th>
<th>FLOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 year</td>
<td>43%</td>
<td>53%</td>
</tr>
<tr>
<td>3 year</td>
<td>37%</td>
<td>46%</td>
</tr>
<tr>
<td>5 year</td>
<td>31%</td>
<td>41%</td>
</tr>
</tbody>
</table>

Projected OS rates

<table>
<thead>
<tr>
<th></th>
<th>ECF/X</th>
<th>FLOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 year</td>
<td>59%</td>
<td>68%</td>
</tr>
<tr>
<td>3 year</td>
<td>48%</td>
<td>57%</td>
</tr>
<tr>
<td>5 year</td>
<td>36%</td>
<td>45%</td>
</tr>
</tbody>
</table>

Progression free survival
18 months ECF/ECX vs 30 months FLOT
HR 0.75 (0.62-0.91) p=0.003

Overall survival
37 months ECF/ECX vs 50 months FLOT
HR 0.77 (0.63-0.94) p=0.012

## FLOT VS ECF/X TOXICITY

<table>
<thead>
<tr>
<th>Grade 3-4 &gt;5%</th>
<th>ECF/ECX (N=354)</th>
<th>FLOT (N=354)</th>
<th>P-value (Chi-Square)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>13 (4%)</td>
<td>34 (10%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Vomiting</td>
<td>27 (8%)</td>
<td>7 (2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nausea</td>
<td>55 (16%)</td>
<td>26 (7%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>38 (11%)</td>
<td>25 (7%)</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>30 (9%)</td>
<td>63 (18%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>75 (21%)</td>
<td>94 (27%)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>139 (39%)</td>
<td>181 (51%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Sensory</td>
<td>7 (2%)</td>
<td>24 (7%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Thromboembolic</td>
<td>22 (6%)</td>
<td>9 (3%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Anemia</td>
<td>20 (6%)</td>
<td>9 (3%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

### FLOT vs ECF/X Treatment Tolerability

<table>
<thead>
<tr>
<th></th>
<th>ECF/ECX (n=360)</th>
<th>FLOT (n=356)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed pre-operative chemo</td>
<td>327 (91%)</td>
<td>320 (90%)</td>
</tr>
<tr>
<td>Surgery</td>
<td>340 (94%)</td>
<td>336 (94%)</td>
</tr>
<tr>
<td>Started post-operative chemo</td>
<td>187 (52%)</td>
<td>213 (60%)</td>
</tr>
<tr>
<td>Completed protocol post-op chemo</td>
<td>133 (37%)</td>
<td>162 (46%)</td>
</tr>
</tbody>
</table>

- Patients treated with FLOT were more likely to commence post-operative chemotherapy, and those who commenced post-operative FLOT were more likely to complete post-operative chemotherapy.

BENEFIT OF FLOT IN ALL PROGNOSTIC GROUPS
NEOADJUVANT CHEMOTHERAPY FOR SIGNET CELL CANCERS

PRODIGE 19

- Study met primary endpoint
- No detriment to upfront chemotherapy
- However, chemotherapy with FLOT may be associated with improved outcomes
- No contraindication to perioperative chemotherapy in SRC

Eveno et al, ASCO 2019
PERI-OPERATIVE CHEMOTHERAPY: TAKE HOME MESSAGES

FLOT is the new gold standard treatment for patients who receive peri-operative chemotherapy and surgery for operable gastroesophageal cancer

In patients are not suitable for triplet chemotherapy, doublet chemotherapy can be considered
Doublets can be cisplatin or oxaliplatin based

5 year projected OS with FLOT is 45%, therefore there is still more work to do to improve survival for patients treated with peri-operative chemotherapy
ADJUVANT CHEMOTHERAPY
EVOLUTION OF ADJUVANT (CHEMO)THERAPY FOR GASTRIC CANCER 2001 - 2017

ACTS-GC TRIAL

Eligibility criteria
Stage $\geq$ II (no T1), IIIA or IIIB gastric adenocarcinoma
D2 resection minimum

ACTS-GC patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Surgery alone</th>
<th>Chemo + surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>369 (70%)</td>
<td>367 (71%)</td>
</tr>
<tr>
<td>Female</td>
<td>161 (30%)</td>
<td>162 (29%)</td>
</tr>
<tr>
<td>Stage of cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>282 (53%)</td>
<td>264 (50%)</td>
</tr>
<tr>
<td>III</td>
<td>213 (40%)</td>
<td>224 (42%)</td>
</tr>
<tr>
<td>IV</td>
<td>35 (7%)</td>
<td>40 (8%)</td>
</tr>
</tbody>
</table>

Primary Endpoint
Overall survival
Secondary endpoints
Relapse free survival & safety

S1, 40mg/m2/d x 28 days followed by 2 week break x 1 year

ACTS-GC TRIAL

Updated 5 year survival S1 vs surgery alone
All patients 5 year OS 72% vs. 61%
Stage II 5 year OS 84% vs 71%
Stage IIIA 5 year OS 67% vs 57%
Stage IIIB 5 year OS 50% vs 44%

Post-operative eligible patients

1 year S1 (n=529)
No further treatment (n=530)

Primary Endpoint
Overall survival
Secondary endpoints
Relapse free survival & Safety

Update ESMO 2017 OPAS-1 study
6 months of S1 not inferior to 12 months

CLASSIC TRIAL

Post-operative eligible patients

6 months CapeOx (n=520)

No further treatment (n=515)

Primary Endpoint
3 year disease free survival

Secondary endpoints
Overall survival & safety

Eligibility criteria
Stage ≥ II, IIIA or IIIB gastric adenocarcinoma
D2 resection minimum

CLASSIC patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Surgery alone</th>
<th>Chemo + surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>358 (70%)</td>
<td>373 (72%)</td>
</tr>
<tr>
<td>Female</td>
<td>157 (30%)</td>
<td>147 (28%)</td>
</tr>
<tr>
<td>Stage of cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>261 (51%)</td>
<td>253 (49%)</td>
</tr>
<tr>
<td>III</td>
<td>253 (49%)</td>
<td>266 (51%)</td>
</tr>
<tr>
<td>IV</td>
<td>1 (&lt;1%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

CapeOx, capecitabine 1000 mg/m² bd D1-14, plus oxaliplatin 130 mg/m² iv D1 q3wks

5 year updated survival CapeOx vs surgery alone
All patients 5 year OS 78% vs 69%
Stage II 5 year OS 88% vs 79%
Stage IIIA 5 year OS 70% vs 63%
Stage IIIB 5 year OS 66% vs 45% (compare ACTS GC 50% vs. 44%)

Post-operative eligible patients
6 months CapeOx (n=520)
No further treatment (n=515)

Primary Endpoint
3 year disease free survival
Secondary endpoints
Overall survival & safety

**JACRO-07**

**Post-operative eligible patients**

S1 80mg/m² d1-28 q 6 wks x 1 year (n=459)

Cycle 1: S1 80mg/m² d1-14 q21d
Cycle 2-7: docetaxel 40mg/m² plus S1 80mg/m² d1-14 q21d
Then S1 x 6 months (N=456)

**Primary Endpoint**

3 year relapse free survival

**Secondary endpoints**

Overall survival & safety

**Relapse free survival**

HR, 0.632; 99.99% CI, 0.400 to 0.998; *P < .001*)

3-year RFS of 66% vs 50% in favour of docetaxel-S1

Yoshida et al., JCO 37, no. 15 (May 20 2019) 1296-1304.
**JACRO-07**

**Post-operative eligible patients**

- S1 80mg/m² d1-28 q 6 wks x 1 year  
  \( n = 459 \)

- Cycle 1: S1 80mg/m² d1-14 q21d
- Cycle 2-7: docetaxel 40mg/m² plus S1 80mg/m² d1-14 q21d
- Then S1 x 6 months  
  \( N = 456 \)

**Primary Endpoint**
- 3 year relapse free survival

**Secondary endpoints**
- Overall survival & safety

Overall survival not mature

Kodera et al, ASCO 2018
Neoadjuvant or peri-operative chemotherapy is preferred due to the downstaging effects associated with this.

The GASTRIC group meta-analysis suggests a 5.8% absolute OS benefit at 5 years (55.3% to 49.6%) for patients treated with adjuvant chemotherapy.

CHEMOTHERAPY VS CHEMORADIOOTHERAPY
An ongoing debate

For **GASTRIC** adenocarcinomas peri-operative chemotherapy (FLOT) is preferred to post-operative chemotherapy or post-operative chemoradiotherapy because:

- More patients are able to receive chemotherapy before surgery than afterwards.
- Downstaging due to chemotherapy increases rates of R0 resections

However, in cases where surgery has been performed without neoadjuvant chemotherapy, adjuvant treatment may be considered.

For **GASTROESOPHAGEAL JUNCTIONAL (Siewert Type I/II)** and **OESOPHAGEAL** adenocarcinoma, perioperative chemotherapy and neoadjuvant chemoradiotherapy are both reasonable choices. Patients selection for treatment depends on the characteristics of the patient, the tumour and local expertise.
Pre-operative eligible patients (ADC and OSCC)

Cisplatin 100mg/m² + 5FU 750mg/m²³ D1-5 q3w x3 (n=90)

SAME CHEMOTHERAPY + RT 40Gy (20 x 2Gy) (n=91)

Primary endpoint: pathological CR

The NeoRes study treated patients with oesophageal SCC and adenocarcinoma including gastroesophageal junction. Although underpowered for survival, no difference was suggested in OS for chemotherapy vs chemoradiotherapy treated patients, nor in subgroup analysis. Surgical complications were more severe, but not more frequent in patients treated with chemoradiotherapy.

NeoRes Study Outcomes

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0</td>
<td>58 (74%)</td>
<td>68 (87%)</td>
</tr>
<tr>
<td>Path CR</td>
<td>7 (9%)</td>
<td>22 (28%)</td>
</tr>
<tr>
<td>30 day mortality</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

Eligible patients from prospectively maintained databases
OAC or Siewert I/II GEJ

Neoadjuvant chemotherapy plus surgery
N=221

Neoadjuvant chemoradiotherapy plus surgery
N=221

**Study Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>nCT</th>
<th>nCRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0</td>
<td>165 (78%)</td>
<td>204 (92%)</td>
</tr>
<tr>
<td>Path CR</td>
<td>11 (5%)</td>
<td>59 (27%)</td>
</tr>
<tr>
<td>30 day mortality</td>
<td>1.4%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Leak</td>
<td>6.8%</td>
<td>23.1%</td>
</tr>
</tbody>
</table>

RETROSPECTIVE

This multicentre European analysis matched patients with resectable oesophageal and Siewert Type I and II junctional cancers treated with neoadjuvant chemotherapy or chemoradiotherapy. Compared with chemotherapy CRT is associated with improvements in R0 resection rates and pathological complete response, but not in overall survival.

With the exception of anastomotic leaks, morbidity and post-operative mortality were not different between the groups.

Trials which will answer this question
Chemo vs CRT

Neo-Aegis (NCT01726452): Same design (n=594)

N=438
T1N1M0 or T2–4aN0–1M0

Neoadjuvant Radio-CTX – CROSS Regimen RESECTION

Primary endpoint: survival
3-year-OS-rate
55% CROSS vs. 68% FLOT

Perioperative CTX: FLOT* 4 x pre and post RESECTION

Trials which will answer this question
Peri-operative chemo vs peri-operative chemo +RT

TOPGEAR

Eligibility
Resectable stomach or gastroesophageal adenocarcinoma

Preoperative chemotherapy
Chemotherapy ECF/X (FLOT) 2 cycles
Chemotherapy ECX/X (FLOT) 3 cycles

Preoperative radiotherapy (1 arm only)
Chemoradiotherapy 45Gy + 5FU/X

Postoperative chemotherapy
Chemotherapy ECF/X (FLOT) 3 cycles
Chemotherapy ECX/F FLOT 3 cycles

FLOT to replace ECF/X

BIOMARKERS FOR PERIOPERATIVE CHEMOTHERAPY
EVOLUTION OF (NEO)ADJUVANT TREATMENT 2002 - 2017

MAGIC
3 + 3# peri-operative ECF

ACTS-GC
Neoadjuvant S1

CROSS
Neoadjuvant carbo/taxol+RT
Oesophageal and junctional only

FLOT4/AIO
4 + 4# peri-operative FLOT

2001

OE02
2# neoadjuvant CF
Oesophageal and junctional only

2002

INT-0116
Adjuvant bolus 5FU/RT
20% junctional adenocarcinoma

2006

OE02
Adjuvant S1

2007

CLASSIC
Adjuvant CapeOx

2011

FFCD/FNCLCC
Peri-operative CF

2012

2017
NEGATIVE TRIALS OF (NEO)ADJUVANT TREATMENT 2012-2016

More is not always better

CALGB 80101
Adjuvant ECX-RT-ECX not better than 5FU/LV-RT

ARTIST
Adjuvant CX-RT-CX not better than adjuvant CX

CRITICS
Pre-op ECX then post op ECX-RT not better than pre- and post op ECX

None of the following were effective in improving overall survival

Intensification of chemo in adjuvant chemo-RT (CALGB 80101)
Addition of RT to adjuvant chemo (ARTIST)
Intensification of adjuvant chemotherapy (ITACA-S)
Intensification of neoadjuvant treatment with anthracycline (OEO5)
Addition of RT to standard peri-operative treatment (CRITICS)
Addition of bevacizumab (ST03)

RISK STRATIFICATION USING TUMOUR REGRESSION GRADING

Lymph nodes are the most important prognostic marker following chemotherapy and surgical resection.

**MAGIC OS by TRG & lymph node status**

![Graph showing survival rates](image)

**EORTC VESTIGE Study design**

- **Control arm:** Postoperative chemotherapy (completion of the perioperative bi) according to standards: Fluoropyrimidine/platinum based (CEF/EC/ECF/ECX/EDX/FL/FOX/ CapeOx/FL such as DCF).
- **Experimental arm:** Nivolumab 3mg/kg q2w x 1y + ipilimumab 1mg/kg q6w x 1y

Follow-up:
- Clinical examination and CT scan of the chest and abdomen every 3 months during year 1 and 2 following randomization
- and then every 6 months until year 5 or death or documented recurrence

**Smyth et al, J Clin Oncol. 2016 Aug 10;34(23):2721-7.**
MSI FOR PERSONALISED TREATMENT IN RESECTABLE GC

MAGIC Trial

CLASSIC Trial

No benefit to perioperative chemotherapy in MSI-H gastric cancer, possible detriment observed (small numbers)

No benefit to adjuvant chemotherapy in MSI-H gastric cancer

Smyth et al, JAMA Oncol. 2017 Sep 1;3(9):1197-1203.
Choi et al., Ann Surg; 2018,
META-ANALYSIS OF MSI ACROSS PERIOPERATIVE AND ADJUVANT TRIALS

Pietrantonio et al, JCO, in press
PROGNOSTIC AND PREDICTIVE GENE SIGNATURES IN CLASSIC

Prognostic

Patients with resectable gastric cancer (stage II-III)

- Low-risk group
- Immune high (GZMB+WAR5+)
- Intermediate-risk group
- Stem-like low (SFRP4-)

Patients with resectable gastric cancer (stage II-III)

- Remainder
- No-benefit group
- Immune high (GZMB+WAR5+)
- High-risk group
- Epithelial low (CDX1-)

Predictive

Overall survival (%)

- Low risk
- Intermediate risk
- High risk

Intermediate risk vs low risk:

- HR\textsubscript{univariate} 1.60 (95% CI 0.91-2.83), p=0.11
- HR\textsubscript{multivariate} 1.92 (95% CI 1.08-3.39), p=0.026

High risk vs low risk:

- HR\textsubscript{univariate} 2.16 (95% CI 1.22-3.80), p=0.0078
- HR\textsubscript{multivariate} 2.36 (95% CI 1.33-4.18), p=0.0032

Adjuvant chemotherapy

- HR\textsubscript{univariate} 0.47 (95% CI 0.30-0.75), p=0.0015
- HR\textsubscript{multivariate} 0.46 (95% CI 0.29-0.74), p=0.0012

Surgery only

- HR\textsubscript{univariate} 0.93 (95% CI 0.62-1.38), p=0.72
- HR\textsubscript{multivariate} 0.90 (95% CI 0.60-1.36), p=0.63
BIOMARKERS

Take home messages

- Lymph node metastases are a more important prognostic marker than tumour regression grade

- Mismatch repair deficient tumours do not appear to benefit from perioperative or neoadjuvant chemotherapy

- Gene signatures show promise for selection for chemotherapy, however require prospective validation.
Cambridge Biomedical Campus