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

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Cambridge University Hospitals NHS Foundation Trust

ESMO Gastric Cancer Preceptorship Valencia 2018
DISCLOSURES

Honoraria
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
EVOLUTION OF NEOADJUVANT AND PERI-OPERATIVE (CHEMO)THERAPY 2002 - 2017

- OE02 Trial Group, Lancet 2002

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

**CROSS**
Neoadjuvant carbo/taxol+RT-surgery vs surgery alone

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

**OE02**
2x neoadjuvant CF-surgery vs surgery alone

**FFCD/FNCLCC**
CF-surgery-CF vs surgery alone

**Oesophageal and junctional only**

CF, cisplatin + 5-fluourouracil; ECF epirubicin + CF; FLOT. 5-fluorouracil, leucovorin, oxaliplatin, docetaxel
MEDICAL RESEARCH COUNCIL MAGIC TRIAL

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>
<tr>
<td>GOJ</td>
<td>30 (12%)</td>
<td>28 (11%)</td>
</tr>
</tbody>
</table>

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

Eligible patients

3 cycles preoperative ECF (n=250)

Surgery

3 cycles postoperative ECF

Surgery alone (n=253)

Surgery

MAGIC post-operative patient characteristics

<table>
<thead>
<tr>
<th></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>

↑ curative resections
↑ early T stage
↑ early N stage

Peri-operative chemotherapy leads to tumour downstaging

ECF, epirubicin 50mg/m², cisplatin 60mg/m² and continuous 5-fluorouracil 200mg/m²/d
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)

Eligible patients

- 2-3 cycles preoperative CF (n=113)
- Surgery alone (n=111)
  - Surgery
    - 3-4 cycles postoperative CF

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

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**FFCD/ACCORD 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>63</td>
<td>63</td>
</tr>
<tr>
<td><strong>Sex</strong></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><strong>Site of disease</strong></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**

### Eligible patients

- 2-3 cycles preoperative CF (n=113)
  - Surgery alone (n=111)
  - Surgery
  - 3-4 cycles postoperative CF

### Surgery alone (n=111)

- Surgery
  - No resection: 11 (10%)
  - R0: 81 (74%)
  - R1: 6 (5%)
  - R2: 11 (10%)
  - Rx: 1 (1%)

### Surgery

- ypT stage
  - T0: (8%)
  - T1-2: (29%)
  - T3-4: (55%)

- ypN Stage (gastric)
  - N0: 17 (20%)
  - N+: 68 (80%)

### Chemo + surgery

- Surgery
  - No resection: 7 (6%)
  - R0: 95 (87%)
  - R1: 4 (4%)
  - R2: 2 (2%)
  - Rx: 1 (1%)

- ypT stage
  - T0: 3 (3%)
  - T1-2: 38 (39%)
  - T3-4: 57 (58%)

- ypN Stage (gastric)
  - N0: 32 (33%)
  - N+: 66 (67%)

**Peri-operative chemotherapy leads to tumour downstaging**

**CF, cisplatin 100mg/m² and continuous 5-fluorouracil 800mg/m²/d day 1-5 q 28d**
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></th>
<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>
<td>1 cycle: n=11 (10%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 cycles: n=85 (75%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 cycles: n=13 (12%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>87% had minimum 2 cycles</td>
</tr>
<tr>
<td>Surgery</td>
<td>229 (92%)</td>
<td>109 (97%)</td>
</tr>
<tr>
<td>Post-operative chemotherapy</td>
<td>Any chemotherapy: n=137 (55%)</td>
<td>Any chemotherapy: n=54 (50%)</td>
</tr>
<tr>
<td></td>
<td>3 cycles: n=104 (42%)</td>
<td>1 cycle: n=6 (6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 cycles: n=7 (6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 cycles: n=16 (15%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 cycles: n=25 (23%)</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

**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

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-).

n=716

al Batran et al, ASCO 2017
## 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 &gt;=70</td>
<td>62</td>
<td>-</td>
<td>62</td>
<td>-</td>
</tr>
<tr>
<td></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.
## FLOT VS ECX PATHOLOGICAL OUTCOMES

<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>T1</td>
<td>53 (15%)</td>
<td>88 (25%)</td>
<td></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>

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

al Batran et al, ESMO 2017
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 who 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
ESMO GASTRIC CANCER GUIDELINES

Gastric Cancer

Operable stage T1 NO

Consider endoscopic/limited resection

Operable stage >T1 NO

Preferred pathway

Preoperative chemotherapy

Surgery

Adjuvant chemotherapy

Adjuvant chemoradiotherapy

Postoperative chemotherapy

Surgery

Palliative chemotherapy

HER2-negative: Platinum+ fluoropyrimidine-based doublet or triplet regimen

HER2-positive: Trastuzumab + CF/CX

Second-line chemotherapy

Re-assess

Inoperable or metastatic

Best supportive care if unfit for treatment

Consider clinical trials of novel agents

EVOLUTION OF ADJUVANT (CHEMO)THERAPY FOR GASTRIC CANCER 2001 - 2017

ACTS-GC
12 months adjuvant S1 vs surgery alone

CLASSIC
6 months capecitabine/oxaliplatin vs. surgery alone

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

GASTRIC Group Meta-analysis

ACTS-GC TRIAL

Eligibility criteria
- Stage ≥ II (no T1), IIIA or IIIB gastric adenocarcinoma
- D2 resection minimum

Post-operative eligible patients
- 1 year S1 (n=529)
- No further treatment (n=530)

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 patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Surgery alone</th>
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</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>

ACTS-GC TRIAL

- 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

**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%

CLASSIC TRIAL

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

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

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

CLASSIC TRIAL

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

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

**JACRO-07**

**Post-operative eligible patients**

S1 80mg/m² d1-28 q6 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: 0.400-0.998]  
p = 0.0007 (stratified log-rank test)

3-year RFS  
- S-1 49.5%  
- S-1/docetaxel 65.9%

Kodera et al, ASCO 2018
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

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. CHEMORADIOThERAPY
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.
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.

CHEMOTHERAPY VS CHEMORADIOThERAPy

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

Neoadjuvant chemotherapy plus surgery
N=221

Neoadjuvant chemoradiotherapy plus surgery
N=221

CHEMOTHERAPY VS CHEMORADIOTHERAPY

Propensity matched analysis neoadjuvant chemotherapy vs CRT

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>

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 anastamotic 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)

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**
- Chemoradiotherapy
  - 45Gy + 5FU/X

**1 arm only**
- Chemoradiotherapy

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

**SURGERY**

**FLOT to replace ECF/X**

BIOMARKERS FOR PERIOPERATIVE CHEMOTHERAPY
EvoLution of (NeO)AdjuVant treatment 2002 - 2017

- **2001**: INT-0116
  - Adjuvant bolus 5FU/RT
  - 20% junctional adenocarcinoma

- **2002**: OE02
  - 2# neoadjuvant CF
  - Oesophageal and junctional only

- **2006**: MAGIC
  - 3 + 3# peri-operative ECF

- **2006**: CLASSIC
  - Adjuvant CapeOx
  - Oesophageal and junctional only

- **2007**: ACTS-GC
  - Adjuvant S1

- **2011**: CROSS
  - Neoadjuvant carbo/taxol+RT
  - Oesophageal and junctional only

- **2012**: FFCD/FNCLCC
  - Peri-operative CF

- **2017**: FLOT4/AIO
  - 4 + 4# peri-operative FLOT
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)

<table>
<thead>
<tr>
<th>TRG 1-2 and node negative</th>
<th>Subjects</th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRG 1-2 and node positive</td>
<td>15</td>
<td>6</td>
<td>1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TRG 3-4-5 and node negative</td>
<td>19</td>
<td>5</td>
<td>0.78 (0.23 to 2.56)</td>
<td>.676</td>
</tr>
<tr>
<td>TRG 3-4-5 and node positive</td>
<td>64</td>
<td>50</td>
<td>3.44 (1.44 to 8.21)</td>
<td>.005</td>
</tr>
</tbody>
</table>

**EORTC VESTIGE Study design**

**Control arm:** Postoperative chemotherapy (completion of the perioperative tx) according to standards: Fluoropyrimidine/platinum based (CF/CFX/ECF/ECX/0EOX/04OEX/CapeOx/FL0T/DCF).

**Experimental arm:**
Nivolumab 3mg/kg q2w x 1y
Ipilimumab 1mg/kg q6wk x 1y

- Gastric or EGI adenocarcinoma stage Ib-IV
- Completed pre-operative chemo with a fluoropyrimidine-platinum containing regimen
- Duration of neoadjuvant chemotherapy: 6 weeks - 12 weeks
- Total or partial gastrectomy with at least D1 LND; Minimum of 15 lymph nodes evaluated
- Age ≥ 18 years
- 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

CI: F. Lordick

MSI FOR PERSONALISED TREATMENT IN RESECTABLE GC

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.
PD-L1 AS A BIOMARKER IN OPERABLE GC:
PROGNOSTIC AND PREDICTIVE EFFECTS OF MSI AND PD-L1 IN CLASSIC

Choi et al, Ann Surg 2018

PD-L1 is prognostic in MSS patients in the trial as a whole

MSS only

Chemo appears to benefit MSS PD-L1 negative patients > MSS PD-L1 positive
PROGNOSTIC AND PREDICTIVE GENE SIGNATURES IN CLASSIC

PROGNOSTIC POST-CHEMOTHERAPY GENE SIGNATURE MAGIC

Prognostic gene selection

Smyth, Sadanandam et al, accepted, Annals of Oncology
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.