GASTRIC CANCER: Should all patients be treated with adjuvant and/or neoadjuvant treatment?

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Introduction

- Operable gastric cancer has a poor prognosis
  - Most studies show that 65 -75% of patients who relapse after localised treatment have systemic disease
  - The majority of patients who relapse die of disease within 2 years

- Neoadjuvant and/or adjuvant treatment can improve outcomes....
  .... how can we select the most appropriate treatment option for an individual patient?
## Pre-operative staging

Accurate staging of gastric cancer is essential but can be challenging.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT (thorax, abdomen +/- pelvis)</td>
<td>▪ Detection of local/distant lymphadenopathy &amp; distant metastases</td>
<td>▪ Primary tumour can be difficult to assess</td>
</tr>
<tr>
<td>Endoscopic ultrasound (EUS)</td>
<td>▪ Accurate assessment of T &amp; N stages</td>
<td>▪ Less useful in antral tumours</td>
</tr>
<tr>
<td></td>
<td>▪ Determination of proximal &amp; distal tumour extent</td>
<td></td>
</tr>
<tr>
<td>PET</td>
<td>▪ Improved detection of involved lymph nodes &amp; metastases</td>
<td>▪ May be uninformative in mucinous tumours</td>
</tr>
<tr>
<td>Laparoscopy</td>
<td>▪ To exclude metastatic disease involving the diaphragm/peritoneum</td>
<td>▪ Invasive</td>
</tr>
</tbody>
</table>

Accurate staging requires a combination of these investigations.

Waddell et al, 2013, Annals Oncol, 24 (supp 6) vi 57-63
Early stage disease

- T1 N0 tumours (stage IA) have an excellent prognosis
  - these patients do not require adjuvant and/or neoadjuvant treatment

- However, only 1 in 100 western patients present with stage I disease
  - therefore very few patients are suitable for surgery alone

Depressed gastric lesion confirmed on biopsy as an early gastric cancer

Image from: [www.gastrohep.com](http://www.gastrohep.com), statistics: [www.cancerresearchuk.org](http://www.cancerresearchuk.org)
What is the optimal treatment approach?

Peri-operative chemotherapy?

Adjuvant chemotherapy?

Adjuvant chemoradiotherapy?
Peri-operative chemotherapy

- MAGIC & FFCD trials established peri-operative chemotherapy as an international standard in OG cancer
- Improves OS / PFS & decreases risk of death by 25%

What are the benefits of peri-operative chemotherapy?

1. Systemic chemotherapy decreases risk of distant metastases

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>% distant metastases</th>
<th>Median OS (months)</th>
<th>HR</th>
<th>5yr Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAGIC</td>
<td>253 (S)</td>
<td>37%</td>
<td>20</td>
<td>0.75</td>
<td>23%</td>
</tr>
<tr>
<td></td>
<td>250 (CS)</td>
<td>24% ↓</td>
<td>24</td>
<td></td>
<td>36% ↑</td>
</tr>
<tr>
<td>FFCD</td>
<td>111 (S)</td>
<td>38%</td>
<td>22</td>
<td>0.69</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>113 (CS)</td>
<td>30% ↓</td>
<td>32</td>
<td></td>
<td>38% ↑</td>
</tr>
</tbody>
</table>

What are the benefits of peri-operative chemotherapy?

2. Pre-operative chemotherapy leads to tumour downstaging and increases R0 resection rate:

- MAGIC: 79.3% vs 70.3% (p = 0.03)
- FFCD: 84% vs 73% (p = 0.04)
- Greatest benefit seen in GOJ tumours (HR ~ 0.5)

Does tumour downstaging improve outcomes?

- In oesophageal/junctional adenocarcinoma:
  - Survival is determined by tumour stage after neoadjuvant chemotherapy

![Survival of T3N+ to T2 N-](image)

- Start T3N+ end T2N-
- T2N- no chemo
- Start T3N+ end T3N+

Davies et al, JCO in press
Can peri-operative treatment be improved?

- Trastuzumab has improved survival in HER2 positive metastatic gastric cancer....
  .... is there also a benefit in the neoadjuvant/perioperative setting?

- The phase II HER-FLOT study:
  - Peri-operative 5-FU, oxaliplatin, docetaxel + trastuzumab
  - Interim results of 45 patients:
    - 93.3% R0 resection rate
    - Pathological response:
      - 22.2% pCR rate
      - 24.4% near complete response

Hofheinz et al, 2014, ASCO abstract 4073
Adjuvant chemotherapy

- In Asian patients:
  - Adjuvant S1 or XELOX improves survival in Asian patients following D2 resection
  - S-1 was better tolerated

- In western patients:
  - S1 is poorly tolerated due to CYP2A6 polymorphisms
  - Pre-operative chemotherapy is better tolerated:
    - In the MAGIC trial – 91% completed pre-op chemo but only 50% completed post-op chemo

Adjuvant chemoradiotherapy

- INT-0116 trial: adjuvant chemoradiotherapy improved relapse-free survival and OS
  But... 90% of patients had D0 or D1 resections...
  ....did chemoradiotherapy merely compensate for insufficient lymph node resection?

- ARTIST trial (n = 458):
  - 6 cycles of adjuvant XP versus 2 cycles of XP followed by chemoradiotherapy and a further 2 cycles of XP
  - All patients had a D2 resection
  .... no improvement in disease-free survival with the addition of chemoradiotherapy

Lee et al. 2012, JCO, 3: 268-273
MacDonald et al. NEJM, 2001, 345(10): 725-730
Are there subgroups of patients who gain particular benefit?

- Adjuvant XELOX improved DFS in N1/2 but not N0 disease

<table>
<thead>
<tr>
<th>Nodal status</th>
<th>Count</th>
<th>DFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>103</td>
<td>0.90 (0.41-1.97)</td>
</tr>
<tr>
<td>N1</td>
<td>621</td>
<td>0.62 (0.44-0.89)</td>
</tr>
<tr>
<td>N2</td>
<td>311</td>
<td>0.45 (0.31-0.66)</td>
</tr>
</tbody>
</table>

← favours XELOX   favours surgery →

- But... no interaction was found between adjuvant S-1 and any characteristic

- Adjuvant chemoradiotherapy:
  - Marginally improves 3-year DFS in node-positive patients
    - (77.5% vs 72.3%, p = 0.0365)

Factors to consider when selecting a treatment approach

- Geographical variations in biology and prognosis
  - 5 year overall survival after surgery alone:
    - 23 – 24% in Western patients
    - 61 – 69% in Asian patients

- Tumour site and size:
  - ↑ risk of positive margins in:
    - Proximal gastric tumours
    - Locally advanced, bulky tumours
  - Faster recovery time for distal subtotal gastrectomy

## Suggested approach for operable gastric cancer

<table>
<thead>
<tr>
<th>Setting</th>
<th>Treatment</th>
<th>Rationale</th>
</tr>
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<tbody>
<tr>
<td>Early-stage disease</td>
<td>Surgery alone</td>
<td>Low risk of metastatic disease</td>
</tr>
<tr>
<td>Western patients</td>
<td>Peri-operative chemotherapy</td>
<td>↑R0 resection rate &amp; improved OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment of micrometastatic disease</td>
</tr>
<tr>
<td></td>
<td>Post-operative chemoradiotherapy</td>
<td><strong>Limited indications:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Patients understaged prior to resection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- No neoadjuvant chemo received</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Local control at risk (R1 resection, &lt; D2 resection)</td>
</tr>
<tr>
<td>East Asian patients</td>
<td>Adjuvant chemotherapy</td>
<td>Improved OS for optimally resected patients</td>
</tr>
</tbody>
</table>
### Selected ongoing clinical trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Planned accrual</th>
<th>Treatment</th>
<th>Research question</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST03 (phase II/III)</td>
<td>1140</td>
<td>Peri-operative chemo +/- bevacizumab</td>
<td>Does bevacizumab improve the efficacy of peri-operative chemo?</td>
</tr>
<tr>
<td>CRITICS (phase III)</td>
<td>788</td>
<td>Peri-operative chemo vs neoadjuvant chemo + post-op CRT</td>
<td>Does the addition of post-op CRT improve outcomes for patients treated with neoadjuvant chemo?</td>
</tr>
<tr>
<td>ITACA-S2 (phase III)</td>
<td>1180</td>
<td>Peri-op chemo (+/- post-op CRT) vs post-op chemo (+/- post-op CRT)</td>
<td>To evaluate the benefit of the addition of post-op CRT and to compare peri-op with post-op chemo</td>
</tr>
<tr>
<td>TOXAG (phase II)</td>
<td>40</td>
<td>Adjuvant CRT with capecitabine, oxaliplatin + trastuzumab</td>
<td>Is the addition of trastuzumab to adjuvant CRT safe?</td>
</tr>
<tr>
<td>POTENT (phase III)</td>
<td>724</td>
<td>Adjuvant S-1 vs S-1 + oxaliplatin</td>
<td>Does the addition of oxaliplatin improve the efficacy of adjuvant chemo?</td>
</tr>
</tbody>
</table>
Conclusions

- The benefit of peri-operative chemotherapy for GOJ/gastric cancer has been clearly established by RCTs.

- Adjuvant chemotherapy has been shown to benefit Asian patients.

- Chemotherapy and chemoradiotherapy have significant toxicities – further research is needed to identify the patients most likely to benefit and the optimal treatment schedule.