Advances in gastric cancer: How to approach localised disease?

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Professor of Medicine
Classical approach to localised gastric cancer

- Surgical resection
- Pathology assessment and estimation of risk
- Treatment based upon classical TNM stage
- Postoperative chemotherapy of doubtful versus no value
- Postoperative chemoradiation
Meta-analysis of trials involving adjuvant chemotherapy versus surgery alone for gastric cancer-1

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>Year</th>
<th>No. trials</th>
<th>No. pts</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hermanns (1) J Clin Oncol</td>
<td>1993</td>
<td>11</td>
<td>2096</td>
<td>0.88</td>
<td>0.78-1.08</td>
<td>No benefit</td>
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<tr>
<td>Earle (2) Eur J Cancer</td>
<td>1999</td>
<td>13</td>
<td>1990</td>
<td>0.80</td>
<td>0.66–0.97</td>
<td>Small survival benefit In N+ patients</td>
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<tr>
<td>Mari (3) Ann Oncol</td>
<td>2000</td>
<td>20</td>
<td>3658</td>
<td>0.82</td>
<td>0.75–.89</td>
<td>Small survival benefit</td>
</tr>
<tr>
<td>Janunger (4) Eur J Surg</td>
<td>2002</td>
<td>21</td>
<td>3962</td>
<td>0.84</td>
<td>0.74–0.96</td>
<td>Very heterogeneous group of trials</td>
</tr>
<tr>
<td>Western</td>
<td></td>
<td></td>
<td></td>
<td>0.96</td>
<td>0.83–1.12</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td></td>
<td></td>
<td>0.58</td>
<td>0.44–076</td>
<td></td>
</tr>
</tbody>
</table>

# Meta-analysis of trials involving adjuvant chemotherapy versus surgery alone for gastric cancer

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<thead>
<tr>
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<th>95% CI</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhao <em>et al.</em> (1) Cancer Investigation</td>
<td>2008</td>
<td>15</td>
<td>3212</td>
<td>0.90</td>
<td>0.84-0.96</td>
<td>Marginal, though significant benefit</td>
</tr>
<tr>
<td>Liu <em>et al.</em> (2) Eur J Surg Oncol</td>
<td>2008</td>
<td>19</td>
<td>2286</td>
<td>0.85</td>
<td>0.80-0.90</td>
<td>Marginal, though significant benefit</td>
</tr>
<tr>
<td>Gastric Group (3) JAMA</td>
<td>2010</td>
<td>17</td>
<td>3871</td>
<td>0.82</td>
<td>0.76-0.90</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

Other trials of adjuvant chemotherapy for localised gastric cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>CT</th>
<th>No. pts control</th>
<th>No. pts CT</th>
<th>5-year survival control</th>
<th>Median survival CT</th>
<th>HR (CI at 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Di Costanzo (1) JNCI 2008</td>
<td>PELF</td>
<td>128</td>
<td>130</td>
<td>48.7%</td>
<td>47.6 %</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No CT</td>
<td></td>
<td></td>
<td></td>
<td>0.64-1.26</td>
</tr>
<tr>
<td>Cascinu (2) JNCI 2007</td>
<td>PELFw</td>
<td>196</td>
<td>201</td>
<td>50%</td>
<td>52%</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FU-LV</td>
<td></td>
<td></td>
<td></td>
<td>0.70-1.29</td>
</tr>
<tr>
<td>De Vita (3) Ann Oncol 2007</td>
<td>ELFE</td>
<td>113</td>
<td>113</td>
<td>43.5%</td>
<td>48%</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No CT</td>
<td></td>
<td></td>
<td></td>
<td>0.69-1.21</td>
</tr>
<tr>
<td>Bajetta (4) Ann Oncol 2002</td>
<td>EAP</td>
<td>137</td>
<td>137</td>
<td>48%</td>
<td>52%</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>5FU-LV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.65-1.34</td>
</tr>
</tbody>
</table>

Why has adjuvant chemotherapy failed to show any positive effect after surgery in gastric cancer?

- Non standard surgery
- High risk of local relapse
- Chemotherapy nor very active in advanced disease: Complete response rate less than 10%
- Heterogeneous samples, low size samples, most patients n-
- Inadequate statistical design
- Prolonged and slow accrual
Meta-analysis of individual data of trials involving adjuvant chemotherapy versus surgery alone for gastric cancer

- Overall survival estimate after any chemotherapy or surgery alone truncated at 10 years

Redrawn from The Gastric Group. JAMA 2010;303:1729–37
Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy versus surgery alone: 5-year follow-up of a randomised phase III trial

Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy versus surgery alone: 5-year follow-up of a randomised phase III trial
The role of radiation in the postoperative setting: Adjuvant chemoradiotherapy for gastric cancer after surgery versus surgery alone: A randomised Phase III Trial

Study design

SURGERY

\[ \downarrow \]

STRATIFICATION

T 1–4
NODES
0, 1–3, >3

\[ \downarrow \]

NO TREATMENT

CT+ CT-RT + CT

Adjuvant chemoradiotherapy for gastric cancer after surgery versus surgery alone: A randomised Phase III Trial

Figure 2. Relapse-free Survival among All Eligible Patients, According to Treatment-Group Assignments.
Adjuvant chemoradiotherapy for gastric cancer after surgery *versus* surgery alone: A randomised Phase III Trial

**Figure 1.** Overall Survival among All Eligible Patients, According to Treatment-Group Assignment.

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Adjuvant chemoradiotherapy for gastric cancer after surgery versus surgery alone: Long term data of a randomised Phase III Trial
The role of radiation in the postoperative setting: Adjuvant cisplatin and capecitabine *versus* chemoradiation for gastric cancer after surgery: A randomised Phase III Trial

Registered (N = 458)

- Randomly assigned to XP (n = 228)
  - Submitted tissue for biomarker
    - XP (n = 204)
    - XPRT (n = 211)
  - Treated with XP (n = 226)
    - Completed XP (n = 172)
      - Relapse (n = 79)
      - Alive (n = 10)
      - No relapse (n = 149)
      - Alive (n = 149)
  - Treated with XPRT (n = 227)
    - Completed XPRT (n = 188)
      - Relapse (n = 62)
      - Alive (n = 5)
      - No relapse (n = 168)
      - Alive (n = 164)
The role of radiation in the postoperative setting: Adjuvant cisplatin and capecitabine versus chemoradiation for gastric cancer after surgery: A randomised Phase III Trial

The role of radiation in the postoperative setting: Adjuvant cisplatin and capecitabine versus chemoradiation for gastric cancer after surgery: A randomised Phase III Trial

Fig 2. Disease-free survival. XP, capecitabine plus cisplatin; XPRT, concurrent chemoradiotherapy with capecitabine plus cisplatin.

Fig 3. Overall survival. XP, capecitabine plus cisplatin; XPRT, concurrent chemoradiotherapy with capecitabine plus cisplatin.
The role of radiation in the postoperative setting: Adjuvant cisplatin and capecitabine versus chemoradiation for gastric cancer after surgery: A randomised Phase III Trial

Treatment for localised gastric cancer: What is standard of care?

- Algorithm for the management of gastric cancer

Gastric cancer (adenocarcinoma)

Operable Stage T1N0

Consider endoscopic/limited resection

Operable Stage >T1N0

Preferred pathway

Preoperative chemotherapy

Surgery

Post-operative chemotherapy

Surgery

Adjuvant chemoradiation

Adjuvant chemotherapy

Localised gastric cancer: Aims of neoadjuvant therapy

- To increase R0 resection rate
- Early treatment of micrometastases
- To reduce locoregional relapses
- Biological studies
Eligible patients:
- Adenocarcinoma of the stomach or lower third of the oesophagus (from 1999), suitable for curative resection
- Non-metastatic disease
- Stage II or greater

Primary
Overall survival

Secondary
Progression-free survival
Surgical resectability
Quality of Life

Chemotherapy (ECF):
- Epirubicin 50 mg/m², IV day 1
- Cisplatin 60 mg/m², IV day 1
- 5-FU 200 mg/m²/day, continuous infusion, days 1-21
(cycles repeated every 3 weeks)

Recruitment: July 1994-April 2002

Pre-operative chemotherapy and surgery trial profile

CSC
N=250

Commenced pre-operative chemotherapy
N=237 (95%)

Completed pre-operative chemotherapy
N=215 (86%)

Proceeded to surgery
N=219 (88%)

S
N=253

Proceeded to surgery
N=240 (95%)

### MAGIC Trial: Postoperative morbidity/mortality

<table>
<thead>
<tr>
<th></th>
<th>CSC</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative deaths</td>
<td>6% (14/219)</td>
<td>6% (15/240)</td>
</tr>
<tr>
<td>Postoperative complications</td>
<td>46%</td>
<td>46%</td>
</tr>
<tr>
<td>Median duration of post-operative hospital stay</td>
<td>13 days</td>
<td>13 days</td>
</tr>
</tbody>
</table>

MAGIC Trial results

**PFS**

- Logrank p-value = 0.0001
- Hazard Ratio = 0.66
  (95% CI 0.53 - 0.81)

**Overall**

- Logrank p-value = 0.009
- Hazard Ratio = 0.75
  (95% CI 0.60 - 0.93)

<table>
<thead>
<tr>
<th></th>
<th>2 year survival</th>
<th>5 year survival</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSC</td>
<td>50%</td>
<td>36%</td>
<td>24 mo</td>
</tr>
<tr>
<td>S</td>
<td>41%</td>
<td>23%</td>
<td>20 mo</td>
</tr>
</tbody>
</table>

**Benefit to CSC arm**

- 9%
- 13%
- 4 mo

- On multivariate analysis, treatment effect unchanged after adjustment for age, performance status, site of primary and gender

- Hazard ratio for death
  - Adjusted: 0.74 (95%CI: 0.59-0.93)
  - Unadjusted: 0.75

MAGIC: Conclusions

- In operable gastric and lower oesophageal cancer, perioperative chemotherapy:
  - Leads to downsizing of primary tumour
  - Significantly improves progression-free survival
  - Significantly improves overall survival

Can MAGIC be compared to INT0116?

<table>
<thead>
<tr>
<th></th>
<th>MAGIC(^1) (N=503)</th>
<th>INT116(^2) (N=556)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peri-op chemo + surgery N=250</td>
<td>Surgery only N=253</td>
</tr>
<tr>
<td>2 year survival</td>
<td>50%</td>
<td>41%</td>
</tr>
<tr>
<td>5 year survival</td>
<td>36%</td>
<td>23%</td>
</tr>
<tr>
<td>Median survival</td>
<td>24 months</td>
<td>20 months</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.75 (0.60–0.93)</td>
<td>0.76 (0.62–0.93)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>P=0.009</td>
<td></td>
</tr>
</tbody>
</table>

Direct comparison of results is difficult due to different inclusion criteria and different time of randomisation.


\(^*\)Estimated from curve
Perioperative chemo: FNLCC 94012-FFCD 9703 Trial

Randomisation N=224

CT + S

FP (\(^*\)) x 2/3 every 28 days
4 – 6 weeks
Resection
4 – 6 weeks
FP x 3/4 or no treatment

Follow-up

Within 4 weeks
Resection

S

*5-Fluorouracil  800 mg/m\(^2\) d1-5* + Cisplatin 100 mg/m\(^2\) day 1

Trial accrual 1995-2003
Median FU 5.7 yrs

Perioperative chemo: FNLCC 94012-FFCD 9703 Trial

**PFS***

Logrank p value = 0.0033  
Hazard Ratio = 0.65  
(95% CI 0.48-0.89)

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<table>
<thead>
<tr>
<th>Data</th>
<th>Periop CT</th>
<th>Surgery</th>
<th>Benefit to CSC arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 year survival</td>
<td>58%</td>
<td>47%</td>
<td>10%</td>
</tr>
<tr>
<td>5 year survival</td>
<td>38%</td>
<td>24%</td>
<td>14%</td>
</tr>
<tr>
<td>Median survival</td>
<td>29 mo</td>
<td>20 mo</td>
<td>9 mo</td>
</tr>
</tbody>
</table>

On multivariate analysis, treatment effect unchanged after adjustment for age, performance status, site of primary and gender

Prognostic variables in Cox multivariate analysis:
- Preoperative CT
- Gastric location

Median follow up: 5.7 years

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Summary of trials of perioperative chemotherapy for localised gastric cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>CT</th>
<th>No. pts control</th>
<th>No. pts CT</th>
<th>5-year survival control</th>
<th>5-year survival CT</th>
<th>HR (CI at 95%)</th>
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</thead>
<tbody>
<tr>
<td>Cunningham N Eng J Med 2006</td>
<td>ECF</td>
<td>253</td>
<td>250</td>
<td>23%</td>
<td>36%</td>
<td>0.75 (0.60-0.93) p=0.009</td>
</tr>
<tr>
<td>Ychou J Clin Oncol 2011</td>
<td>CDDP</td>
<td>111</td>
<td>113</td>
<td>24%</td>
<td>38%</td>
<td>0.69 (0.50-0.95) p=0.021</td>
</tr>
</tbody>
</table>

Neoadjuvant chemotherapy in gastric cancer: Conclusions

- Perioperative chemotherapy:
  - Induces downstaging
  - May increase the R0 resection rate
  - Prolongs disease free survival
  - Improves overall survival

- Evidence level I based upon 2 well designed and properly conducted randomised trials
- Preoperative therapy is better tolerated than postoperative
- Localised gastric cancer requires a multidisciplinary team approach
- Further research on biological predictive factors is needed
Currently recommended approach to localised gastric cancer

- Clinical assessment and staging
- Multidisciplinary team discussion
- Preoperative treatment in all patients with clinical stage II and III
- Surgical resection after chemotherapy
- Pathology assessment and estimation of risk
- Postoperative chemotherapy if tolerated
- Participation in trials
Treatment for localised gastric cancer: What is standard of care?

Algorithm for the management of gastric cancer

Gastric cancer (adenocarcinoma)

- Operable Stage T1N0
  - Consider endoscopic/limited resection
  - Preoperative chemotherapy
  - Surgery
  - Post-operative chemotherapy

- Operable Stage >T1N0
  - Preferred pathway
  - Surgery
  - Adjuvant chemoradiation
  - Adjuvant chemotherapy

Advances in gastric cancer: How to approach localised disease? Conclusions

- Multidisciplinary approach needed for localised disease: Preoperative treatment preferred
- Quality of surgery essential
- Radiotherapy for localised disease still experimental
THANK YOU!