Multidisciplinary interactive session

Management of localized gastric cancer

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Disclosures

I have participated in Advisory Boards and I have been paid for giving educational lectures in satellite symposia by Roche, Genentech, Merck Serono, Bayer and Sanofi during the last two years.
Multidisciplinary interactive session
Management of localized gastric cancer
Case Presentation

72 year old female PS 1
No relevant previous diseases
Unspecific epigastric discomfort for 2 months
Significant asthenia and weight loss for 3 months
Occasional vomiting and fullness after eating small amounts of food

A diagnostic test was done: gastroscopy
Gastroscopy:
An ulcerated and infiltrating lesion of 5 cm was detected in the corpus/antrum of the stomach.

Multiple biopsies were done.

Poorly differentiated adenocarcinoma of the stomach of intestinal type

**Staging procedures were ordered**
Multidisciplinary interactive session
Management of localized gastric cancer
Case Presentation

Chest CT-scan: no lung or mediastinal mets

Abdominal and pelvic CT-scan:
No liver mets or peritoneal mets
Thickening of the whole gastric wall without invasion of any surrounding local structures
Multiple perigastric lymph nodes of 2 cm size, but no extraperigastric and paraortic lymph nodes.

A laparoscopy and an endoscopic ultrasonography were not considered

\text{cT3 cN+ cM0}
Surgical resection
Pathology assessment and estimation of risk
Treatment based upon classical TNM stage
Postoperative Chemotherapy of limited value
Postoperative Chemoradiation if D0-D1
## META-ANALYSIS OT TRIALS INVOLVING ADJUVANT CHEMOTHERAPY 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 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>
</tr>
<tr>
<td>Earle 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>
</tr>
<tr>
<td>Mari Ann Oncol</td>
<td>2000</td>
<td>20</td>
<td>3658</td>
<td>0.82</td>
<td>0.75-0.89</td>
<td>Small survival benefit</td>
</tr>
<tr>
<td>Januger 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>
<tr>
<td>Meta-analysis</td>
<td>Year</td>
<td>No. Trials</td>
<td>No. Pts</td>
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<td>95% CI</td>
<td>Conclusions</td>
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<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Zhao et al 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 P: 0.001</td>
</tr>
<tr>
<td>Liu et al 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 P&lt; 0.0001</td>
</tr>
<tr>
<td>Gastric Group 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>
**Figure 3.** Overall Survival Estimate After Any Chemotherapy or Surgery Alone Truncated at 10 Years

![Graph showing survival rates]

- **HR 0.82**
- **Δ5.7%**
- **Adj. Chemotherapy:** 55.3%
- **Surgery alone:** 49.6%

**No. at risk**
- Any chemotherapy: 1924, 1688, 1385, 1217, 1080, 929, 709, 526, 390, 297, 243
- Surgery alone: 1857, 1568, 1300, 1092, 952, 782, 583, 407, 267, 172, 138

Log-rank $P < .001$
## RECENT TRIALS OF ADJUVANT CT FOR LOCALIZED GASTRIC CA IN WESTERN COUNTRIES

<table>
<thead>
<tr>
<th>Trial</th>
<th>CT</th>
<th>Nr. Pts</th>
<th>Nr. Pts</th>
<th>5-year Survival Control</th>
<th>Median Survival CT</th>
<th>HR (CI at 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Di Constanzo 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 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 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 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>
POSTOPERATIVE CHEMOTHERAPY IN LOCALIZED GASTRIC CANCER

• LIMITED VALUE, IF ANY
• HRs BY 0.90
• NON SIGNIFICANT EFFECT IN MOST SINGLE TRIALS
• BUT...
  – NONSTANDARDIZED SURGERY
  – MANY SINGLE TRIALS UNDERPOWERED
  – HYPOTETIC BENEFIT OVERESTIMATED
  – STRATIFIED BY MANY AND DIFFERENT CLINICAL OR PATHOLOGICAL FACTORS
  – HETEROGENEOUS POPULATION ACCRUED
  – N NEGATIVE PATIENTS PREDOMINATE
  – SELECTED POPULATION OF PATIENTS WELL ADAPTED TO TOTAL OR PARTIAL GASTRECTOMY
  – BIOLOGICAL PREDICTIVE FACTORS UNKOWN AND THEREFORE NOT APPLIED TO STRATIFICATION
D2 LYMPHADENECTOMY ALONE OR WITH PARA-AORTIC NODAL DISSECTION FOR GASTRIC CANCER

TRIAL DESIGN
SURGERY
RANDOMIZED
N= 1059
STRATIFIED
STAGE II, IIIA, IIIB
S1 40 MG/M² BID

NO TREATMENT
ADJUVANT CHEMOTHERAPY FOR GASTRIC CANCER WITH S1: AN ORAL FLUOROPYRIMIDINE
ADJUVANT CHEMOTHERAPY FOR GASTRIC CANCER CONTROL VS XELOX (CLASSIC)

HR: 0.74 p<.0001
DFS at 3 yr: 74% vs 59%

HR: 0.72 p=0.049
OS at 3 yr: 83% vs 78%
TRIAL DESIGN
SURGERY
RANDOMIZED
N= 556
STRATIFIED
T 1-4
NODES 0, 1-3, >3
NO TREATMENT
ChT+ ChRT +

Clear benefit in disease free and overall survival with median follow-up of 6 years. Risk reduction of death by 24%.

Type of surgery: D2 resection less than 10%

Planning of Radiation to be modified after central review in 35% of cases due to minor/minor deviations

POSTOPERATIVE CHEMORADIOOTHERAPY FOR LOCALISED GASTRIC CANCER: UPDATED RESULTS

HR: 0.68

HR: 0.49

CRITICS (ChemoRadiotherapy after Induction ChemoTherapy in Cancer of the Stomach) Trial

**Quality assurance**
- Surgery: surgical audit to individual surgeons
- Pathology: pathology audit to individual pathologists
- Radiotherapy:
  - check of RT plan before start of treatment
  - RT atlas

At least 15 nodes, No splenectomy

Tissue banking

Postoperative Chemotherapy 3x ECC

QoL

D1 + surgery

Preoperative chemotherapy 3x ECC

Preoperative chemotherapy 3x ECC

Chemoradiation 45 Gy/25fx + Capecitabine + Cisplatin
DISADVANTAGES OF POST-OPERATIVE TREATMENT

Efficacy of treatment used is unknown

Treatment appears to be less well tolerated after major surgery

Commencement of post-operative treatment may be delayed by slow recovery from surgery or peri-operative morbidity

Important morbidity related with total gastrectomy, specially altered nutritional status
POTENTIAL ADVANTAGES FOR PRE-OPERATIVE TREATMENT

Tumour downstaging/downsizing prior to surgery
  Reduction of microscopic marginal involvement with tumour
  Increase likelihood of curative resection
Eliminating disseminated micrometastatic disease and achieving systemic control
Demonstrates in vivo sensitivity to systemic treatment
Improvement of tumour related symptoms
Better tolerated than post-operative therapy
More patients may benefit from therapy
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

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

Primary
Overall survival

Secondary
Progression-free survival
Surgical resectability
Quality of Life

Study entry and randomization
S arm
N=253

CSC arm
N=250

Pre-operative chemotherapy:
3-6 weeks

Post-operative chemotherapy:
6-12 weeks

Surgery

S arm

CSC arm

www.esmo2012.org
# Postoperative Morbidity/Mortality

<table>
<thead>
<tr>
<th></th>
<th>CSC</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative deaths</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>(14/219)</td>
<td>(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>

Cunningham et al NEJM 2006
**MAGIC TRIAL: SURVIVAL**

**PFS**

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

<table>
<thead>
<tr>
<th>2 year survival</th>
<th>5 year survival</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CSC</strong></td>
<td>50%</td>
<td>36%</td>
</tr>
<tr>
<td><strong>S</strong></td>
<td>41%</td>
<td>23%</td>
</tr>
<tr>
<td><strong>Benefit to CSC arm</strong></td>
<td>9%</td>
<td>13%</td>
</tr>
</tbody>
</table>

*Included relapse, PD and death from any cause.*

**Overall**

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

- 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

Cunningham et al NEJM 2006
### 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 (95% CI)</td>
<td>0.75 (0.60-0.93)</td>
<td></td>
</tr>
<tr>
<td></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 randomization.

---

1. Cunningham NEJM 2006
2. MacDonald NEJM 2001; 2004 GI Cancers Symposium

\(^*\)Estimated from curve
PERIOPERATIVE CHEMO: FNLCC 94012-FFCD 9703 TRIAL

Randomization 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

S

Resection

Trial accrual 1995-2003

Median FU 5.7 yrs

*5-Fluorouracil 800 mg/m2 d1-5*

+ Cisplatin 100 mg/m2 day 1

Ychou et al J Clin Oncol 2011; 29:1715
PERIOPERATIVE CHEMO: FNLCC 94012-FFCD 9703 TRIAL

![Kaplan-Meier curve showing overall survival from date of random assignment.](image)

**2 year survival** | **5 year survival** | **Median survival**
--- | --- | ---
Periop CT | 58% | 38% | 29 mo
Surgery | 47% | 24% | 20 mo
Benefit to CSC arm | 10% | 14% | 9 mo

Ychou et al J Clin Oncol 2011; 29:1715
# SUMMARY OF TRIALS OF PERIOPERATIVE CHEMOTHERAPY FOR LOCALIZED GASTRO-ESOPHAGEAL CANCER

<table>
<thead>
<tr>
<th>Trial</th>
<th>CT</th>
<th>Nr. Pts Control</th>
<th>Nr. Pts CT</th>
<th>5-year Survival Control</th>
<th>5-year Survival CT</th>
<th>HR (CI at 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cunningham</strong></td>
<td>ECF</td>
<td>253</td>
<td>250</td>
<td>23%</td>
<td>36%</td>
<td>0.75 (0.60-0.93)</td>
</tr>
<tr>
<td>NEJM 2006</td>
<td>No CT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=.009</td>
</tr>
<tr>
<td><strong>Ychou</strong></td>
<td>CDDP</td>
<td>111</td>
<td>113</td>
<td>24%</td>
<td>38%</td>
<td>0.69 (0.50-0.95)</td>
</tr>
<tr>
<td>JCO 2011</td>
<td>5-FU</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=.021</td>
</tr>
<tr>
<td><strong>Allum</strong></td>
<td>CDDP</td>
<td>402</td>
<td>400</td>
<td>17.1%</td>
<td>23%</td>
<td>0.84 (0.72-0.78)</td>
</tr>
<tr>
<td>JCO 2009</td>
<td>5-FU</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=.03</td>
</tr>
</tbody>
</table>

*Esophageal only*
CURRENT APPROACH TO LOCALISED GASTRIC CANCER

Clinical staging with CT-Scan/endoscopic ultrasonography

Preoperative Chemotherapy if cT3-4 or cN+

Surgical resection

Pathology assessment and estimation of risk

Postoperative Chemotherapy if feasible
FUTURE DIRECTIONS IN THE TREATMENT OF LOCALISED GASTRIC CANCER

– More active systemic treatment combinations, including targeted therapies
– Defining role of radiotherapy in relation to systemic therapy
– Diagnostic/assessment
– Assessing response to treatment earlier (i.e. role of PET)
– Translational: prognostic and predictive markers