A look to the future in the management of metastatic and locally advanced gastric cancer

Prof. Dr. Michael Stahl
Department of Medical Oncology
Kliniken Essen-Mitte, Essen, Germany
Gastric cancer in the European Union

- Despite decreasing incidence, more than 34,000 men and 21,000 women died due to gastric cancer in the EU in 2013*
- This is because most tumours were detected at advanced stages in western countries

*Malvezzi M. Ann Oncol 2013;24:792
TREATMENT OF GASTRIC CANCER

1st line therapy in unresectable, or metastatic disease
Effective cytotoxic drugs and drug combinations in gastric cancer 2014

- Cisplatin
- Oxaliplatin
- 5-Fluorouracil
- Capecitabine
- S1
- Docetaxel
- Paclitaxel
- Trastuzumab*

- Cisplatin/5-FU (+trastuzumab*)
- Oxaliplatin/FA/5-FU (OLF)
- Capecitabine/cisplatin (XP) (+trastuzumab*)
- Docetaxel/cisplatin/5-FU (DCF)
- 5-FU/FA/oxaliplatin/docetaxel (FLOT)
- FOLFIRI/FUFIRI
- ECF/ECX/EOF/EOX

*her2-positive tumours, only
Meta-analysis on the efficacy of chemotherapy in advanced gastric cancer

- Individual data of 22 out of 55 published randomised studies (4245 / 9054 patients)
- Comparison of standard therapy with experimental therapy in randomised trials
- Result: statistically significant improvement of survival by experimental therapies.
  However: median survival was increased for 3 weeks, only

The GASTRIC Group et al. Eur J Cancer 2013;49(7):1565-1567
Meta-analysis on the efficacy of chemotherapy in advanced gastric cancer

- 0-2 (control) versus 2-3 (experimental) drug combinations

HR 0.89 (0.80-0.98)

Reprinted from The GASTRIC Group et al. Eur J Cancer 2013;49(7):1565-1567 Copyright (2013), with permission from Elsevier
Importance of starting dose in advanced gastric cancer

- Starting with a reduced dose appears to hamper efficacy of palliative chemotherapy

<table>
<thead>
<tr>
<th>Dose docetaxel</th>
<th>75 mg</th>
<th>60 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose capecitabine</td>
<td>2000 mg</td>
<td>1600 mg</td>
</tr>
<tr>
<td>Pts. (n)</td>
<td>41</td>
<td>50</td>
</tr>
<tr>
<td>Dose reductions due to toxicity of chemotherapy</td>
<td>Doce 50% of pts.</td>
<td>Doce 12% of pts.</td>
</tr>
<tr>
<td></td>
<td>Cape 58% of pts.</td>
<td>Cape 16% of pts.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

| Response rate | 50% | 23.5% |
| Time to progression | 5.6 Mo | 3.7 Mo |
| Overall survival | 10.1 Mo | 7.2 Mo |

TREATMENT OF GASTRIC CANCER

2nd line therapy in unresectable or metastatic disease
## Standards in 2nd line therapy

*30% of pts. without platin-derived in 1st line

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>Median survival time</th>
<th>Experimental arm</th>
<th>Median survival time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cougar-02</td>
<td>BSC</td>
<td>3.6 mo</td>
<td>Docetaxel</td>
<td>5.2 mo #</td>
</tr>
<tr>
<td>AIO</td>
<td>BSC</td>
<td>2.4 mo</td>
<td>Irinotecan</td>
<td>4.0 mo #</td>
</tr>
<tr>
<td>REGARD *</td>
<td>BSC</td>
<td>3.8 mo</td>
<td>Ramucirumab</td>
<td>5.2 mo #</td>
</tr>
<tr>
<td>RAINBOW</td>
<td>Paclitaxel</td>
<td>7.4 mo</td>
<td>Paclitaxel + ramucirumab</td>
<td>9.6 mo #</td>
</tr>
<tr>
<td>WJOG4007</td>
<td>Irinotecan</td>
<td>8.4 mo</td>
<td>Paclitaxel</td>
<td>9.5 mo</td>
</tr>
</tbody>
</table>

#p<0.05

Wilke H et al. J Clin Oncol GI 2014; 32(3_suppl):LBA7;
Fluoropyrimidine beyond progression is not indicated (first line S1 +/-Platin)

- Toxicity significantly increased with S1

<table>
<thead>
<tr>
<th></th>
<th>S1+ irinotecan</th>
<th>Irinotecan</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response-rate</td>
<td>7.6%</td>
<td>7.4%</td>
<td>ns</td>
</tr>
<tr>
<td>PFS</td>
<td>4.8 mo</td>
<td>4.9 mo</td>
<td>ns</td>
</tr>
<tr>
<td>OS</td>
<td>8.8 mo</td>
<td>9.4 mo</td>
<td>ns</td>
</tr>
</tbody>
</table>

Nishikawa K et al. J Clin Oncol ASCO 2014;32(3_suppl):87
Cisplatin beyond progression?
Cisplatin/irinotecan vs. irinotecan

No difference in overall survival

Reprinted from Higuchi K et al. Eur J Cancer 2014;50(8):1437-1445 Copyright (2014), with permission from Elsevier
Cisplatin beyond progression? Cisplatin/irinotecan vs. irinotecan

PFS significantly improved (p=0.04)

Reprinted from Higuchi K et al. Eur J Cancer 2014;50(8):1437-1445 Copyright (2014), with permission from Elsevier
Improvement in PFS by cisplatin only for patients without cisplatin in 1st line

<table>
<thead>
<tr>
<th>Cisplatin 1st line</th>
<th>Cisplatin 1st line</th>
<th>Cisplatin 1st line</th>
<th>Cisplatin 1st line</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Cis/Iri (n=36)</td>
<td>Irinotecan (n=36)</td>
<td>Cis / Iri (n=28)</td>
<td>Irinotecan (n=27)</td>
</tr>
<tr>
<td>2.8 mo HR 0.80</td>
<td>2.5 mo p=0.35</td>
<td>6.4 mo HR 0.60</td>
<td>4.2 mo p=0.08</td>
</tr>
<tr>
<td>(0.49-1.28)</td>
<td></td>
<td>(0.33-1.08)</td>
<td></td>
</tr>
</tbody>
</table>

Higuchi K et al. Eur J Cancer 2014;50(8):1437-1445
Independent poor prognostic factors to better select patients for 2nd line treatment

- Poor performance status (HR 1.79, p=0.008)
- Haemoglobin <11.5 (HR 1.86, p=0.019)
- CEA > 50 ng/ml (HR 1.86, p=0.004)
- Metastatic sites > 2 (HR 1.72, p=0.006)
- Time to progression after 1st line < 6 months (HR 1.97, p<0.0001)

Catalano V et al. Br J Cancer 2008;99(9):1402-1407
Palliative chemotherapy has proven superiority to best supportive care in 1st and 2nd line.

There are a couple of combinations with similar effectivity.

Choice of drug combination shall be made according to age, performance status and comorbidity of the patient.

Platin/fluoropyrimidin combination is reflecting the standard of care.
TREATMENT OF GASTRIC CANCER

Targeted therapy in advanced gastric cancer
Advances in first line therapy of advanced gastric cancer by improving patient selection - HER-2 overexpression/amplification: TOGA trial

3807 patients screened
810 HER2-positive (22.1%)

HER2-positive GC
(n=584)

5-FU or capecitabatin
+ cisplatin
(n=290)

97% M1 in both arms

5-FU or capecitabatin
+ cisplatin
+ trastuzumab
(n=294)

Stratification factors
• Locally advanced vs. Metastasis
• Gastric vs. ÖGÜ
• Measurable vs. non-measurable
• ECOG PS 0-1 vs. 2
• Capecitabin vs. 5-FU

Bang YJ et al. The Lancet 2010;376(9742):687-697
TOGA - Overall survival in patients with Her2-positive tumours (IHC2+/FISH+ or IHC3+)

Redrawn from Bang YJ et al. The Lancet 2010;376(9742):687-697
Metastatic gastric cancer: Results with targeted therapies (1st line)

- Only trastuzumab has proven to improve efficacy of chemotherapy in 1st line palliative treatment

<table>
<thead>
<tr>
<th>Chemo-backbone</th>
<th>Targeted drug</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ToGA</td>
<td>PF or PX</td>
<td>Trastuzumab</td>
</tr>
<tr>
<td>REAL-3</td>
<td>EOX</td>
<td>Panitumumab</td>
</tr>
<tr>
<td>EXPAND</td>
<td>PX</td>
<td>Cetuximab</td>
</tr>
<tr>
<td>AVAGAST</td>
<td>PX</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>Yoon 2014</td>
<td>FOLFOX</td>
<td>Ramucirumab</td>
</tr>
</tbody>
</table>

* p<0.05

Bang Y-J *et al.* Lancet 2010; 376(9749):1302;  
Waddell T *et al.* Lancet Oncol 2013;14(6):481;  
Yoon HH *et al.* J Clin Oncol 2014;32(15_suppl):4004

P:Cisplatin  
O:Oxaliplatin  
E:Epirubicin  
X:Capecitabine  
F:5-Fluorouracil
2nd line therapy in patients with Her2-positive tumours: Study design of the TyTAN trial

Efficacy of 2nd line Her2-directed therapy is not proven

- Efficacy of 2nd line: Lapatinib not proven
- Like in 1st line therapy, efficacy may depend on Her2 status

Metastatic gastric cancer: Results with targeted therapies (further lines)

- The combination of paclitaxel and ramucirumab (#) will become a valuable option in 2nd line therapy (# approval awaited in the EU at the end of 2014)

<table>
<thead>
<tr>
<th>Chemo-backbone</th>
<th>Targeted drug</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>REGARD</td>
<td>Placebo</td>
<td>Ramucirumab</td>
</tr>
<tr>
<td>RAINBOW</td>
<td>Paclitaxel</td>
<td>Ramucirumab</td>
</tr>
<tr>
<td>China 2013</td>
<td>Placebo</td>
<td>Apatinib</td>
</tr>
</tbody>
</table>

* p<0.05

Wilke H et al. J Clin Oncol GI 2014; 32(3_suppl):LBA 7;
Trastuzumab is significantly improving the overall survival in patients with advanced gastric carcinomas selected for overexpression/amplification of Her2 protein/gene.

All other targeted drugs failed to improve the results of 1st line palliative chemotherapy (in unselected patients) or even showed a trend to hamper progression free or overall survival (EGFR-inhibitors).
The VEGF-receptor 2 inhibitor ramucirumab alone or in combination with paclitaxel proved to prolong survival of patients with tumour progression during or after 1st line cisplatin/fluoropyrimidine.

The VEGF-receptor 2 tyrosine kinase inhibitor apatinib improved survival of patients in further line of palliative chemotherapy (compared to best supportive care).
New targets and future drugs in gastric cancer: Current randomised trials in Europe

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comparison</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everolimus</td>
<td>Best supportive care</td>
<td>M-TOR</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>Trastuzumab and chemotherapy</td>
<td>HER2</td>
</tr>
<tr>
<td>Rilotumumab</td>
<td>ECX chemotherapy</td>
<td>C-MET</td>
</tr>
<tr>
<td>Cediranib</td>
<td>CF chemotherapy</td>
<td>VEGFR-2</td>
</tr>
<tr>
<td>AZD4547</td>
<td>Paclitaxel</td>
<td>FGFR1-3</td>
</tr>
<tr>
<td>T-DM1</td>
<td>Taxane</td>
<td>Her2</td>
</tr>
</tbody>
</table>
TREATMENT OF GASTRIC CANCER

Resection in metastatic disease
Role for palliative resection of primary tumour and metastases?

- Identical tumour stage
  - may reflect different biology of the tumour
  - may lead to different prognosis
  - may be managed differently

Clinical stage T3 N+ M1(liver)

Scans: Department of diagnostic and interventional Radiology, Kliniken Essen-Mitte, Essen, Germany, with permission
Strategy of individualised management of metastatic disease based on tumour extension

- FLOT3 study

<table>
<thead>
<tr>
<th>STRATIFICATION</th>
<th>A: resectable disease</th>
<th>B: limited metastatic disease</th>
<th>C: diffuse metastatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>4 x FLOT – OP – 4 x FLOT</td>
<td>8 x FLOT → surgery optional</td>
<td>8 x FLOT</td>
</tr>
</tbody>
</table>

Advanced adenocarcinoma of the stomach or oesophago-gastric junction
- Age ≥ 18 years
- ECOG ≤ 2
- No prior chemotherapy

FLOT: 5-FU, leukovorin, oxaliplatin, docetaxel

n = 252
(A/B/C: 52/68/132)

FLOT-3 Study
Definition of limited metastatic disease

- ECOG 0-1
- Normal value for AP
- Only 1 organ involved (± intraabdominal lymph nodes)
- Less than 5 resectable liver metastases
- No peritoneal metastases, no malignant effusions
- No lymphangiosis pulmonum
Results FLOT-3

<table>
<thead>
<tr>
<th></th>
<th>Arm A</th>
<th>%, n=52</th>
<th>Arm B</th>
<th>%, n=60</th>
<th>Arm C</th>
<th>%, n=127</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation</td>
<td>48</td>
<td>92%</td>
<td>37</td>
<td>62%</td>
<td>15</td>
<td>12%</td>
</tr>
<tr>
<td>OP with curative intent</td>
<td>45</td>
<td>90%</td>
<td>29</td>
<td>48%</td>
<td>7</td>
<td>6%</td>
</tr>
</tbody>
</table>

By permission of Al-Batran S et al. J Clin Oncol ASCO 2011;29(15_suppl):4070
Results FLOT-3

- Complete resection of primary tumour and metastases was performed in 48% of patients with limited metastatic disease
- Patients with complete resection benefit with regard to survival
- The definition of limited and more extended metastatic disease was able to separate patient groups with different prognosis
- Surgery is not a standard of care in metastatic gastric carcinoma
Role for palliative gastrectomy?  
Meta-analysis retrospective trials

HR 0.45 (0.39-0.80)
Problems with data on palliative resection in advanced gastric cancer

- Most of the studies were non-randomised trials
- Heterogeneous patient groups (not all patients with proven distant metastases, with and without chemotherapy, partly combined resection of metastases)
- **Conclusion:** resection of the primary tumour without local problems is not recommended for routine practice
TREATMENT OF GASTRIC CANCER

Perioperative chemotherapy
**Phase III-studies with pre/perioperative chemotherapy**

<table>
<thead>
<tr>
<th></th>
<th>MAGIC</th>
<th>FFCD9703</th>
<th>EORTC40954</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0-resection CT+S vs. S</td>
<td>p = 0.018</td>
<td>p = 0.04</td>
<td>p = 0.036</td>
</tr>
<tr>
<td>Complete preop. CT</td>
<td>86%</td>
<td>87%</td>
<td>65%</td>
</tr>
<tr>
<td>Complete postop. CT</td>
<td>42%</td>
<td>50%</td>
<td>Not planned</td>
</tr>
<tr>
<td>PFS / DFS</td>
<td>p &lt; 0.001</td>
<td>p = 0.003</td>
<td>p = 0.2</td>
</tr>
<tr>
<td>OS</td>
<td>p = 0.009</td>
<td>p = 0.021</td>
<td>p = 0.47</td>
</tr>
</tbody>
</table>

Ychou M *et al.* J Clin Oncol 2011;29(13):1715-1721;
Schuhmacher C *et al.* J Clin Oncol 2010;28(35):5210-5218
Meta-analysis on preoperative chemo-(radio)therapy in oesophageo-gastric cancer

Individual patient data:

HR 0.80 (0.69-0.93) in favour of preoperative therapy

Reprinted from Ronellenfitsch U et al. Eur J Cancer 2013;49(15):3149-318 Copyright (2013), with permission from Elsevier
Patients benefit from preoperative chemo-as well as chemoradiotherapy

<table>
<thead>
<tr>
<th>Subset criterion</th>
<th>Periop Chemo events/N</th>
<th>Surgery events/N</th>
<th>HR (95% CI)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>Subset Diff.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing of regimen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-operative</td>
<td>&gt; 409*626</td>
<td>&gt; 448*640</td>
<td>0.81</td>
<td>[0.68,0.95]</td>
<td>p = 0.92</td>
<td></td>
</tr>
<tr>
<td>Pre- and post-operative</td>
<td>367/596</td>
<td>407/590</td>
<td>0.80</td>
<td>[0.70,0.91]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chemotherapeutic agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonplatinum, nonanthracycline</td>
<td>52/121</td>
<td>52/110</td>
<td>0.89</td>
<td>[0.64,1.23]</td>
<td>p = 0.24</td>
<td></td>
</tr>
<tr>
<td>Platinum based, nonanthracycline</td>
<td>&gt; 551*824</td>
<td>&gt; 612*808</td>
<td>0.80</td>
<td>[0.72,0.89]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracycline based, nonplatinum</td>
<td>24/27</td>
<td>21/29</td>
<td>1.40</td>
<td>[0.78,2.53]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platinum and anthracycline based</td>
<td>149/250</td>
<td>170/253</td>
<td>0.75</td>
<td>[0.60,0.93]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chemo-/radiotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pure chemotherapy</td>
<td>&gt; 626*1024</td>
<td>&gt; 693*1009</td>
<td>0.83</td>
<td>[0.75,0.91]</td>
<td>p = 0.38</td>
<td></td>
</tr>
<tr>
<td>Radiochemotherapy</td>
<td>150/198</td>
<td>162/191</td>
<td>0.70</td>
<td>[0.50,0.99]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sort of data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individual patient data</td>
<td>375/525</td>
<td>402/524</td>
<td>0.80</td>
<td>[0.66,0.97]</td>
<td>p = 0.87</td>
<td></td>
</tr>
<tr>
<td>Aggregated data</td>
<td>&gt; 401*697</td>
<td>&gt; 453*676</td>
<td>0.81</td>
<td>[0.72,0.92]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reprinted from Ronellenfitsch U et al. Eur J Cancer 2013;49(15):3149-318 Copyright (2013), with permission from Elsevier
Meta-analysis on preoperative chemo-(radio)therapy in oesophago-gastric cancer

- Patients with EGJ adenocarcinomas benefit most (overall survival)

<table>
<thead>
<tr>
<th>Location</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophagus N=473</td>
<td>0.87</td>
<td>0.73-1.05</td>
</tr>
<tr>
<td>EGJ N=470</td>
<td>0.69</td>
<td>0.54-0.87</td>
</tr>
<tr>
<td>Stomach N=828</td>
<td>0.94</td>
<td>0.82-1.06</td>
</tr>
</tbody>
</table>

Meta-analysis on preoperative chemo-(radio)therapy in oesophago-gastric cancer

- Increased postoperative morbidity with chemotherapy. Mortality not changed

Reprinted from Ronellenfitsch U et al. Eur J Cancer 2013;49(15):3149-318 Copyright (2013), with permission from Elsevier
Results of phase III-studies with pre/perioperative chemotherapy

- Preoperative chemotherapy was consistently able to increase the rate of complete resection.
- This was not translated into improved survival in all of the randomised studies.
- Meta-analysis confirms the value of preoperative chemotherapy.
- The role of the postoperative part of chemotherapy is still unclear.
Preoperative therapy should focus on the rate of major histologic response because this appears to impact long term survival.

Regression grade 1a / 1b

Grading according to Becker

Regression grade 2

Regression grade 3

Cumulative survival vs Overall survival_ab_CTx

P = 0.043

p < 0.001

Redrawn from Ott K and Lordick F. Chirurg 2009;80(11):1028-1034
### PCR-rates with different chemotherapy combinations (phase II-studies)

- 3-drug combinations including a taxane seem to be more active
- Results of phase III comparisons are pending

<table>
<thead>
<tr>
<th>Study</th>
<th>Pts. n</th>
<th>Chemotherapy</th>
<th>pCR rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC 2009</td>
<td>34</td>
<td>ECX</td>
<td>5.9%</td>
</tr>
<tr>
<td>Lorenzen 2008</td>
<td>24</td>
<td>Gastro-Tax</td>
<td>17.4%</td>
</tr>
<tr>
<td>Al-Batran 2008</td>
<td>46</td>
<td>FLOT</td>
<td>17.4%</td>
</tr>
<tr>
<td>Thuss 2009</td>
<td>44</td>
<td>DCX</td>
<td>15.9%</td>
</tr>
<tr>
<td>AIO 2011</td>
<td>51</td>
<td>DCX</td>
<td>13.7%</td>
</tr>
</tbody>
</table>
Which perioperative chemotherapy should be used?  
Phase III: ECF/ECX vs. FLOT

<table>
<thead>
<tr>
<th>ECF / ECX</th>
<th>FLOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Sign. more thromboembolic events</td>
<td>- Sign. more neutropenia</td>
</tr>
<tr>
<td>- More delays/dose reductions</td>
<td>+ Postoperative chemotherapy applied more often</td>
</tr>
<tr>
<td>- More postoperative deaths</td>
<td></td>
</tr>
</tbody>
</table>

Safety-analysis after 300 patients

TREATMENT OF GASTRIC CANCER

Adjuvant chemo(radio)therapy
Meta-analysis on survival with adjuvant chemotherapy

- Individual studies in “the West” negative
- Meta-analyses show small but significant improvement
- 5-year OS 49.6% → 55.3%; HR 0.83
Adjuvant chemoradiotherapy significantly improved OS

More than half of the patients did not have at least D1-lymphadenectomy (European standard)

Meta-analysis confirms the role of LN-dissection for efficacy of adjuvant therapy

- Int 0116 (subgroup)
  - Hallissey: HR=0.73 [0.56-0.95] p=0.021
  - Skoropad*: HR=0.79 [0.62-1.01] p=0.056
  - Skoropad: HR=0.83 [0.64-1.07] p=0.146
- Int 0116 (subgroup)
  - Kwon: HR=0.78 [0.68-0.91] p=0.001
  - Zhu: HR=0.73 [0.56-0.95] p=0.021

Adjuvant chemo- versus chemoradiotherapy

- **Adjuvant ChemoRadiotherapy Trial In Stomach Tumours (ARTIST)**

- D2 resected gastric adenocarcinoma
- pStage Ib to IV(M0)
- Stratified by (1) stage, (2) type of surgery (STG vs. TG)

- Primary endpoint: 3-y DFS

Disease-free survival

- 141 recurrence events occurred
- Hazard ratio 0.740 (95% CI, 0.520-1.050)
- $P=0.9222$

Disease-free survival: By lymph node status

- In 396 patients with LN+ disease, 3-y DFS was 76% vs. 72% (P=0.04) \(^1\)

Adjuvant therapy in gastric cancer

- The overall benefit with adjuvant therapy accounts for 5-10% at five years.
- This appears to be less than with pre/perioperative therapy (10-15%).
- Chemoradiotherapy improved survival in patients with limited resection compared to observation.
- It remains unclear, whether adjuvant chemo-radiation is superior to chemotherapy alone.
NEW PERSPECTIVES IN THE TREATMENT OF GASTRIC CANCER

Should we treat all types of gastric cancer in the same way?
Different incidence of gene-alterations in different types of gastric cancer

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>Intestinal type</th>
<th>Diffuse type</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>LOH, mutation</td>
<td>30-40%</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>DCC</td>
<td>LOH</td>
<td>60%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>E-Cadherin</td>
<td>Mutation LOH</td>
<td>?</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>FGFR-2</td>
<td>Amplification</td>
<td>2%</td>
<td>35%</td>
</tr>
</tbody>
</table>

Different gene expression in cell lines of Lauren’s intestinal and diffuse type, respectively

Prognosis of gastric cancer according to histology versus gene profiling

Tumours with concordance of histology and gene profile

Survival based on gene profile (when discordant with histology)

HR 1.79 (1.28-2.51)  HR 1.83 (1.02-3.30)

Figure 3. Intrinsic genomic subclasses are prognostic. Kaplan–Meier plots of survival in (A) all patients (HR, 1.79; 95% CI, 1.28–2.51; \( P = .001 \)) and (B) when the intrinsic classification and Lauren’s classes are discordant (HR, 1.83; 95% CI, 1.02–3.30; \( P = .04 \)).

Should we use different drugs for different types of gastric cancer?

- Chemosensitivity \textit{in vitro} according to gene profiling

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Should we use different drugs for different types of gastric cancer?

- Chemosensitivity *in vitro* according to gene profiling

Molecular characterisation revealed four different types of GC (EBV+, microsatellite unstable, genomic stable, cromosomal unstable) (Nature 2014; 513:209)

These types are differently represented in the different parts of the stomach

Their sensitivity to classical chemotherapy and the options for targeted therapy appear to be different, which has to be prospectively evaluated
Comprehensive molecular characterisation

Retrospective data seemed to show that patients with signet ring carcinomas may not benefit from perioperative chemotherapy.

Median survival: 14.0 vs. 12.8 months, p=0.04
3-year survival rate: 13.1% versus 3.6%

Retrospective study on signet ring carcinomas (France 1997-2010)

There is no obvious difference in prognostic factors between treatment groups

<table>
<thead>
<tr>
<th></th>
<th>Surgery (n=753)</th>
<th>CT + surgery (n=171)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal tumours</td>
<td>60%</td>
<td>80%</td>
<td>ns</td>
</tr>
<tr>
<td>Stage III</td>
<td>54%</td>
<td>59%</td>
<td>ns</td>
</tr>
<tr>
<td>D1 / D2 – dissection</td>
<td>31% / 43%</td>
<td>40% / 41%</td>
<td>ns</td>
</tr>
<tr>
<td>Gastrectomy</td>
<td>58%</td>
<td>64%</td>
<td>ns</td>
</tr>
</tbody>
</table>

Retrospective study on signet ring carcinomas (France 1997-2010)

- However: most patients of both groups received chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Surgery (n=702)</th>
<th>CT + surgery (n=162)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with preoperative chemotherapy</td>
<td>0</td>
<td>100%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Patients with adjuvant chemotherapy</td>
<td>67%</td>
<td>35%</td>
<td>ns</td>
</tr>
</tbody>
</table>

Is it time to treat signet ring carcinoma differently?

- Retrospective data appear to show that preoperative chemotherapy may not work.
- Instead of evaluating the role of preoperative chemotherapy the study was rather comparing pre- vs. postoperative chemotherapy.
- Other groups were not able to reproduce this data (Ott K, JCO 2014; 32:abstract 106).
- At this time we do not have the data to support the use of biologic features of gastric cancer for guiding chemotherapy.
New perspectives in treatment of gastric cancer: Identifying new targets

- First results hint at the fact that so called immune checkpoint inhibition by PD-1 or PDL-1 antibodies may be an attractive principle for gastric cancer (Keynote 012 study, Muro K, ESMO 2014, LBA 15)

- Targeting cancer stem cells by inhibiting the STAT-3 and the beta-catenin pathway appears promising, particularly in gastric cancer and a phase III trial has been launched in pre-treated patients (BRIGHTER)
THANK YOU!