SURGERY IN OLIGOMETASTATIC GASTRIC CANCER

STEFAN P. MÖNIG
GASTRIC CANCER: WESTERN COUNTRIES

Gastric cancer

EGJ Siewert I-III

German cancer registry

Bollschweiler, Hölscher Cancer 2001
Robert Koch Institut Berlin 2016
42 222 177 patients
60 countries
Gastric cancer: 2019382 pts.

5-y survival (20-40%)

Japan  60%
Korea  69%
Switzerland  32%
GASTRIC CANCER SURVIVAL AT EUROPEAN HIGH VOLUME CENTER

n=1767

Reim et al. J Clin Oncol 2012
Stage IV gastric cancer – proportion of gastric resection and chemotherapy

2007-2014 at the Geneva University Hospital in Switzerland (n=102)

- Surgical resection: 15%
- Chemotherapy (taxane based): 73%
- Surgical resection and chemotherapy: 10%

Cumulative relative survival:
- 1 y: 33.6%
- 2 y: 14.6%
- 3 y: 4.3%

Claassen, .... Chevallay et al. BJS Open 2018
METASTATIC OESOGASTRIC CANCER

CONTROVERSAL DEBATE

„SURGERY OR NO SURGERY“
Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

E. C. Smyth¹, M. Verheij², W. Allum³, D. Cunningham⁴, A. Cervantes⁵ & D. Arnold⁶ on behalf of the ESMO Guidelines Committee

Gastric cancer (Adenocarcinoma)

Operable stage T1 N0
- Consider endoscopic/limited resection

Operable stage >T1 N0
- Preoperative chemotherapy
  - Surgery
  - Adjuvant chemoradiotherapy
  - Adjuvant chemotherapy

Inoperable or metastatic
- Re-assess
- Palliative chemotherapy

HER2-negative: Platinum-fluoropyrimidine-based doublet or triplet regimen
- Consider clinical trials of novel agents
  - Trastuzumab + CF/CX
  - Second-line chemotherapy
  - Best supportive care if unfit for treatment
Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with metastatic oesophageal cancer: a JSMO–ESMO initiative endorsed by CSCO, KSMO, MOS, SSO and TOS


Palliative chemotherapy !

NO SURGERY !!
Concept of conversion surgery in Japan

Stage IV GC

Macroscopic peritoneal Dissemination (-)

Category 1
Potentially resectable metastasis
- resectable
  - One liver metastasis
  - Few paraaortic lymph node
    - 16a2,b1
    - CY1

Neoadjuvant chemotherapy (NAC)

New lesion

Primary and Metastasectomy(R0)

Intensive chemotherapy
- Effective (CR, PR) technically resectable
- No effect

Primary and/or Metastasectomy(R0)

Volume reduction surgery

Palliative chemotherapy

Macroscopic peritoneal Dissemination (+)

Category 3
Incurable and unresectable except certain circumstances of local palliation needs
- Other organ (-)
  - Chemotherapy ± molecular target ± intraperitoneal chemo

Category 4
Non-curable metastasis
- Other organ (+)
  - Chemotherapy ± molecular target ± intraperitoneal chemo
  - Effective (CR, PR)
  - CY0, technically resectable
  - No effect

Yoshida, Kodera et al Gastric Cancer 2016
DUTCH GASTRIC CANCER TRIAL D1 VS. D2 (1989-1993)

SUBGROUP WITH LIMITED METASTASIS / OLIGOMETASTASIS MAY BENEFIT FROM SURGERY

- Patients all 996
- palliative resections 285 (26%)

Survival benefit of Surgery:

*patients < 70 and 1 metastatic site*

## SURGERY VS. PALLIATIVE CHEMOTHERAPY

<table>
<thead>
<tr>
<th>Autor</th>
<th>Jahr</th>
<th>medianes Überleben in Monaten</th>
<th>Metastasektomie</th>
<th>palliative Chemotherapie</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiberio et al.</td>
<td>2014</td>
<td>13,0</td>
<td>3,0</td>
<td></td>
</tr>
<tr>
<td>Mohri et al.</td>
<td>2014</td>
<td>21,9</td>
<td>7,2</td>
<td></td>
</tr>
<tr>
<td>Yang et al.</td>
<td>2013</td>
<td>14,5</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Chen L et al.</td>
<td>2013</td>
<td>22,3</td>
<td>5,5</td>
<td></td>
</tr>
<tr>
<td>Chen S et al.</td>
<td>2012</td>
<td>28,9</td>
<td>13,8</td>
<td></td>
</tr>
<tr>
<td>Miki et al.</td>
<td>2012</td>
<td>33,4</td>
<td>8,7</td>
<td></td>
</tr>
<tr>
<td>Lin et al.</td>
<td>2012</td>
<td>15,0</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Dittmar et al.</td>
<td>2011</td>
<td>48,0</td>
<td>9,0</td>
<td></td>
</tr>
<tr>
<td>Kim et al.</td>
<td>2011</td>
<td>28,0</td>
<td>9,0</td>
<td></td>
</tr>
<tr>
<td>Makino et al.</td>
<td>2010</td>
<td>31,2</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Tiberio et al.</td>
<td>2009</td>
<td>23,0</td>
<td>5,0</td>
<td></td>
</tr>
<tr>
<td>Ueda et al.</td>
<td>2008</td>
<td>24,0</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Cheon et al.</td>
<td>2008</td>
<td>20,0</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Kunieda et al.</td>
<td>2002</td>
<td>7,6</td>
<td>3,3</td>
<td></td>
</tr>
<tr>
<td>Takeda et al.</td>
<td>1990</td>
<td>10,8</td>
<td>5,3</td>
<td></td>
</tr>
<tr>
<td>Okuyama et al.</td>
<td>1985</td>
<td>8,0</td>
<td>3,0</td>
<td></td>
</tr>
</tbody>
</table>
Reduced mortality with minimal-invasive surgery in high volume centers

n=1100 minimally invasive!

ESOPHAGCTOMY Ivor-Lewis 1996-2015
University Hospital of Cologne, Germany Prof. Hölscher
Recent guidelines stage IV standard treatment
- palliative chemotherapy -

\textit{but}

\textbf{German S3-guideline up-date}
Gastric and esophagogastric junction (EGJ) cancer
\textit{Möhler et al. Z Gastroenterol 2019 in preparation}
\textit{Mönig, Gockel et al. Chirurg 2019 in preparation}

\textbf{German S3-guideline up-date}
Esophageal cancer
\textit{Porschen, Hölscher et al. Z Gastroenterol 2019}
\textit{Hölscher et al. Chirurg 2019}

\textit{Oligometastatic disease is part of the up-dated guidelines}
German S3-guideline
Gastric cancer – up date 2019
OLIGOMETASTATIC DISEASE

- Standard treatment is chemotherapy
- No general indication for surgery outside of trials
- Intraoperative detection of oligometastatic disease
  - continue surgery with metastatectomy
Oligometastatic disease

- 764 items in PubMed
- 220 items between 2018 and 2019!

Oligometastasis is a cancer disease state characterized by a limited number of metastatic tumors involving single or few organs and with biological properties that make them potentially amenable to locoregional therapy.
Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial

Kazumasa Fujitani*, Han-Kwang Yang*, Junki Mizusawa, Young-Woo Kim, Masanori Terashima, Sang-Uk Han, Yoshiaki Iwasaki, Woo Jin Hyung, Akinori Takagane, Do Joong Park, Takaki Yoshikawa, Seokyung Hahn, Kenichi Nakamura, Cho Hyun Park, Yukinori Kurokawa, Yung-Jue Bang, Byung Joo Park, Mitsuru Sasako, Toshimasa Tsujinaka, for the REGATTA study investigators†

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy alone (n=86)</th>
<th>Gastrectomy plus chemotherapy (n=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>59 (49-67)</td>
<td>62 (54-66)</td>
</tr>
<tr>
<td><strong>Country</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>46 (53%)</td>
<td>49 (55%)</td>
</tr>
<tr>
<td>South Korea</td>
<td>40 (47%)</td>
<td>40 (45%)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>56 (65%)</td>
<td>61 (69%)</td>
</tr>
<tr>
<td>Female</td>
<td>30 (35%)</td>
<td>28 (31%)</td>
</tr>
<tr>
<td><strong>Non-curable factor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver metastasis (H1)</td>
<td>5 (6%)</td>
<td>11 (12%)</td>
</tr>
<tr>
<td>Peritoneal metastasis (P1)</td>
<td>66 (77%)</td>
<td>65 (73%)</td>
</tr>
<tr>
<td>Para-aortic lymph node</td>
<td>11 (13%)</td>
<td>13 (15%)</td>
</tr>
<tr>
<td>metastasis (16a1/b2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>4 (5%)*</td>
<td>0</td>
</tr>
</tbody>
</table>

Lancet Oncology 2016

Japanese – Korean trial
Surgery without metastasectomy = no benefit!!
Effect of Neoadjuvant Chemotherapy Followed by Surgical Resection on Survival in Patients With Limited Metastatic Gastric or Gastroesophageal Junction Cancer
The AIO-FLOT3 Trial

Salah-Eddin Al-Batran, MD; Nils Homann, MD; Claudia Pauligk, PhD; Gerald Illerhaus, MD; Uwe M. Martens, MD; Jan Stoehtmacher, MD; Harald Schmalenberg, MD; Kim B. Luley, MD; Nicole Prasniker, MD; Matthias Egger, MD; Stephan Probst, MD; Helmut Messmann, MD; Markus Moehler, MD; Wolfgang Fischbach, MD; Jörg T. Hartmann, MD; Frank Mayer, MD; Heinz-Gert Höffkes, MD; Michael Koenigsmann, MD; Dirk Arnold, MD; Thomas W. Kraus, MD; Kersten Grimm, MD; Stefan Berkhoff, MD; Stefan Post, MD; Elke Jäger, MD; Wolf Bechstein, MD; Ulrich Ronellenfitsch, MD; Stefan Mönig, MD; Ralf D. Hofheinz, MD

Figure 1. CONSORT Diagram
Locally advanced and metastatic gastric and juntional adenocarcinoma
age ≥ 18 y.
ECOG ≤ 2
No chemotherapy before

A: neoadjuvant
B: limited metastatic
C: diffuse metastatic

4xFLOT – OP – 4xFLOT
8xFLOT → OP possible
8xFLOT → palliative

Primary endpoint: overall survival (OS) arm B vs arm C: HR 0.55,
Power 80% → n=250

Al-Batran et al. JAMA Oncol 2017
- **Arm A** Primary operable:
  - Every T, Every N, M0 (operable)  (*neoadjuvante*)

- **Arm B** Limited Metastasis (LM):
  - Implication of maximal one organ (+/- intra-abdominal LN)
  - ECOG 0 or 1
  - Ø Diffuse peritoneal carcinomatosis
  - Ø Lymphangiosis of the lung
  - <5 Liver metastasis

- **Arm C** Diffuse Metastasis (DM):
  - All other category with distant metastasis (M1)  (*palliative*)
<table>
<thead>
<tr>
<th>Oligometastatic arm</th>
<th>Limited metastatic (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (Range)</td>
<td>63 (28-79)</td>
</tr>
<tr>
<td>Gender Male</td>
<td>44 (73.3%)</td>
</tr>
<tr>
<td>Female</td>
<td>16 (26.7%)</td>
</tr>
<tr>
<td>cT stage cT1</td>
<td></td>
</tr>
<tr>
<td>cT2</td>
<td>5 (8.3%)</td>
</tr>
<tr>
<td>cT3</td>
<td>33 (55%)</td>
</tr>
<tr>
<td>cT4</td>
<td>10 (16.7%)</td>
</tr>
<tr>
<td>cN stage cN-</td>
<td></td>
</tr>
<tr>
<td>cN+</td>
<td>3 (5.0%)</td>
</tr>
<tr>
<td>57 (95.0%)</td>
<td></td>
</tr>
<tr>
<td>Site Primary</td>
<td></td>
</tr>
<tr>
<td>AEG I</td>
<td>13 (19.7%)</td>
</tr>
<tr>
<td>AEG II</td>
<td>27 (40.9%)</td>
</tr>
<tr>
<td>AEG III</td>
<td>4 (6.1%)</td>
</tr>
<tr>
<td>Corpus</td>
<td>12 (18.2%)</td>
</tr>
<tr>
<td>Antrum</td>
<td>9 (13.6%)</td>
</tr>
<tr>
<td>Site Metastases</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>11 (18.3%)</td>
</tr>
<tr>
<td>Spleen</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>Lung</td>
<td>10 (16.7%)</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>4 (6.7%)</td>
</tr>
<tr>
<td>Bone</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>Distant lymph</td>
<td>36 (60.19%)</td>
</tr>
<tr>
<td>Retraperitone.</td>
<td>27 (45%)</td>
</tr>
</tbody>
</table>
## Surgical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Arm A (operable)</th>
<th>Arm B (limited metastatic)</th>
<th>Arm C (extensive metastatic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients total</td>
<td>52</td>
<td>67</td>
<td>133</td>
</tr>
<tr>
<td>Patients proceeded to surgery</td>
<td>49 (94,2%)</td>
<td><strong>36 (53,7%)</strong></td>
<td>15 (11,3%)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transthoracic esophagectomy</td>
<td>12 (24,5%)</td>
<td>2 (5,6%)</td>
<td>2 (13,3%)</td>
</tr>
<tr>
<td>Gastrectomy + Transhiatal Esophagus Resection</td>
<td>10 (20,4%)</td>
<td>17 (47,2%)</td>
<td>4 (26,7%)</td>
</tr>
<tr>
<td>Gastrectomy</td>
<td>24 (49,0%)</td>
<td>14 (38,9%)</td>
<td>8 (53,3%)</td>
</tr>
<tr>
<td>Laparotomy without resection because</td>
<td>3 (6,1%)</td>
<td>2 (5,6%)</td>
<td>1 (6,7%)</td>
</tr>
<tr>
<td>Missing values</td>
<td>1 (2,8%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Median (months): 26.7 (9.1-NA)
Median (months): 8.4 (4.1-10.4)
Median (months): 22.9 (16.5-NA)
Median (months): 15.9 (7.1-22.9)
HYPOTHESIS

LIMITED METASTASIS

+ INTENSIVE CHEMOTHERAPY

→ GOOD RESPONSE

+ SURGERY WITH METASTASECTOMY

→ CURATIVE ?!
Problem:

No data from randomised trials!! (except REGATTA trial)
The RENAISSANCE (AIO-FLOT5) trial: effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction – a phase III trial of the German AIO/CAO-V/CAOGI
Randomized phase III trial

Patient number: 271 to be recruited
≥176 to be randomized (88 into each arm)

**Lead Coordinating Investigator (LKP)**
Prof. Dr. med. Salah-Eddin Al-Batran

**Lead Coordinating Investigator Surgery**
Prof. Dr. med. Stefan P. Mönig

**Radiation Therapy Consultant**
Prof. Dr. med. Claus Rödel

**Projekt Management**
Dr. Daniel Müller; Dr. Claudia Pauligk

**eCRF**
Anneke Neuhaus, Trium Analysis Online GmbH

**Monitoring**
Karin Scheffler, mca24.de

and the AIO study group
Definition of limited metastasis
Renaissance trial / German S3-guideline

1. Retroperitoneal lymph node metastases (RPLM)
   (para-aortal, intra-aorto-caval, parapancreatic, mesenterial etc.)
   
   or/and

2. maximal 1 organ metastasis with or without RPLM
   
   I. Localized peritoneal carcinomatosis: (PCI ≤ 6) or
   II. Liver: max. 5 resectable metastases or
   III. Lung: unilateral involvement, resectable or
   IV. Uni- or bilateral “Krukenberg”-tumors without further PC or
   V. Uni- or bilateral adrenal gland metastasis or
   VI. Extra-abdominal lymph node metastases (supraclavicular or cervical) or
   VII. Localized bone metastases (one radiation field) or
   VIII. Other limited metastasis (according investigator and review committee)
ENDPOINTS

Primary

   Overall Survival

Secondary

   • Quality of life (QoL) adjusted OS
   • QoL-response
   • QoL mean scores
   • OS in patients with lymph node metastases only
   • Progression free survival (PFS): time interval from randomization until disease progression or disease recurrence after surgery or death of any cause
   • Surgical morbidity and mortality
   • Toxicity
**STUDY DESIGN**

**Patient characteristics**
- Histologically confirmed limited metastatic gastric or GEJ adeno-carcinoma
- Medical and technical operability of the primary
- Metastatic lesions are resectable or can be controlled by local ablative procedure
- No prior chemotherapy and no prior tumor resection

**Screening:**
- Tumor status
- QoL

**Re-Staging:**
- Tumor status
- QoL

**Follow-up assessments**
(tumor status, QoL)
- Every 3 months → until progression

**Central evaluation**
- Progression: drop-out

**Randomization**
- Arm A: 4 cycles FLOT
- Arm B: 4 – 8 cycles FLOT

**Surgery**
- n = 88

**4 – 8 cycles FLOT**
- n = 88

**Follow-Up PFS**

**Follow-Up OS**

**Survival status**
- Every 3 months

**n = 271**
- First Patient In: 09.02.2016
- Current Enrollment (06/2019)
  - Screened: 123
  - Patient eligible: 105 / 271
  - Randomized: 74 / 176
  - Surgery: 40
SURGIGAST
PALLIATIVE GASTRIC RESECTION PLUS CTX VS. CTX ALONE IN STAGE IV GASTRIC CANCER

Ongoing amendment to the RENAISSANCE trial inclusion criteria
(French FREGAT group)

G. Piessen et al. 2019
• Standard treatment stage IV gastric cancer 2019: chemotherapy

• Although not yet recommended by most guidelines, surgery with low postoperative mortality may improve survival in patients with synchronous limited metastatic disease (oligometastatic)

• In patients that show a good response after induction chemotherapy, resection of the primary tumor and metastases may be beneficial

• Ongoing randomized clinical trials should be awaited to determine the use of surgery for limited metastatic gastric cancer