Surgery for recurrent ovarian cancer and palliative surgery

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Imperial College London, UK
Surgery for cytoreduction

- Surgery in platinum sensitive relapse
- *Objective*: complete tumor resection

V.S.

Palliative surgery

- After failure of all conservative treatments
- *Objective*: Improving of QoL
Tumor dissemination patterns at relapse

Field of highest tumor load

- 20.2%
- 24.9%
- 36.5%

Tumor involvement

- 44.8%
- 59.9%
- 72.9%

Site of tumor residuals

- 24.6%
- 27.3%
- 26.6%

Multivisceral surgical techniques at relapse operation

- Partial gastrectomy: 3.5%
- Bowel resection: 58.4%
- Small bowel resection: 41.4%
- Large bowel resection: 44.5%
- Ileostomy: 8.6%
- Colostomy: 7.5%
- Splenectomy: 3.5%
- Cholecystectomy: 2.2%
- Nephrectomy: 1.7%
- Peritonectomy: 49.3%
- Infrared coagulation: 60.1

Charité 2000-2008
Shifting of tumor burden primary to relapsed disease

IMO - Intraoperative Mapping of Ovarian Cancer
Sehouli et al.: Zentralblatt, 2003
No correlation of tumour dissemination patterns in paired primary & relapsed cases

Primary

peritoneal carcinosis
(RR 1.53; 95% CI: 0.89–2.63)

Relapse

bowel involvement
(RR 0.92; 95% CI: 0.65–1.31)

lymph node involvement (RR 1.49; 95% CI: 0.83–2.68)
Indications for surgical cytoreduction at relapse

- Early – platinum resistant/refractory-relapse
  - NO evidence for survival benefit in cytoreduction (except in very rare cases)
  - median OS ≈ 8-9 months
  - low complete resection rates ≈ 30%
  - high surgical morbidity

- Late – platinum sensitive-relapse
  - Significant prolongation of OS and PFS in retrospective trials in tumofree pts
  - High complete tumor resection rates in selected patient population
  - Low/acceptable surgical morbidity and mortality

Cytoreductive surgery for recurrent OC: a meta-analysis

Bristow RE, Puri I, Chi DS. Gynecol Oncol 2009
1100 pts
58 vs.16 mo

Estimated probability


First relapse


Bristow RE, Puri I, Chi DS. Gynecol Oncol 2009

% COMPLETE RESECTION

240 pts
42 vs.17 mo

40 cohorts → 2019 pts
+ 10% Complete resection -→ + 3 months OS

"All or nothing"
Second relapse


Third relapse

Fotopoulou et al. Br J Cancer 2012

406 pts
49 vs. 12 mo

49 pts
43 vs. 13 mo
Residual disease 0 cm < 1 cm < 2 cm > 0 cm, 1 cm, or 2 cm

Expert Rev Anticancer Ther 2009 917-922
**DESKTOP-OVAR I**

Predictive factors for complete tumour resection

<table>
<thead>
<tr>
<th>Pre-op factor</th>
<th>OR</th>
<th>(95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance status (ECOG 0 vs. &gt;0)</td>
<td>2.65</td>
<td>(1.56–4.52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tumour residuals at primary surgery (0 vs. &gt;0)</td>
<td>2.46</td>
<td>(1.45–4.20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>or: initial FIGO (I/II vs. III/IV)</td>
<td>1.87</td>
<td>(1.04–3.37)</td>
<td>0.036</td>
</tr>
<tr>
<td>Ascites (cut-off 500 ml)*</td>
<td>5.08</td>
<td>(1.97–13.16)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*exclusively CA125 (correlation with ascites)

**Multivariate analysis**

Non-significant for a complete resection:

- Site of relapse (pelvis vs. extra-pelvis)
- Therapy-free interval

Is peritoneal carcinosis/multifocal relapse a contraindication for secondary cytoreductive surgery? DESKTOP DATA

Median OS (months):
- 0 mm: nyr
- 1–10 mm: 17.9
- >10 mm: 19.8

Tumorfree operated pts

\[ p = 0.96, \text{HR: } 0.98 \text{ (95%CI: } 0.37 \text{ – 2.6)} \]

Is peritoneal carcinosis/ multifocal relapse a contraindication for secondary cytoreductive surgery? TCS DATA

Interaction of surgical effort and tumorbiology

<table>
<thead>
<tr>
<th>Tumorfree operated patients</th>
<th>median OS</th>
<th>95%-CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>46.0</td>
<td>27.94 - 64</td>
</tr>
<tr>
<td>no</td>
<td>51.0</td>
<td>37.8 – 64.5</td>
</tr>
<tr>
<td>Total</td>
<td>47.0</td>
<td>36.4 – 57.6</td>
</tr>
</tbody>
</table>
AGO-DESKTOP II: An International Multicentre GCIG Trial
Prospective Validation of a Predictive Score for Resectability in Platinum-Sensitive ROC

Frequency of complete resection in AGO-Score positive pts.

Score positive
1st relapse

Score positive
2nd relapse

p < 0.05

76

68

DESKTOP Hypothesis

DESKTOP II = positive
Positive AGO score predicts complete resection in more than 2 out of 3 pts

Timing of Surgery: when to operate?

- CA125 driven follow up?
- Asymptomatic vs symptomatic relapse?
- Operate too early (reduction of QoL) vs too late (low PS)
- Is the retrospective evidence a result of tumorigenesis or of surgical effort?

A matter of calendar??
Taking into consideration all parameters: radicality and quality of previous surgery, residual length of bowel, etc
Candidates for surgery

- Rarely relapse diagnosed by symptoms

\[\text{CA-125 elevation 5 months before clinical relapse!} \]

\[\text{* only } \sim 6\% \text{ with surgery for recurrent disease} \]
Diagnosis of 1st relapse by CA125+ PET-CT -> Surgery + Chemo

Diagnosis of 1st relapse by symptoms + ascites -> chemotherapy

2nd relapse

Real benefit by earlier diagnosis and surgery?

By Harter P
AGO-OVAR DESKTOP III (Protocol AGO - OVAR OP.4)

A randomized trial evaluating cytoreductive surgery in patients with platinum-sensitive recurrent ovarian cancer

408 Pts with + AGO-Score

Stratification:
- Platinum-free-interval
  - 6-12 vs > 12 months
- 1st line platinum based ctx: yes vs no

RANDOM

Cytoreductive surgery

RANDOM

no surgery

* Recommended platinum-based chemotherapy regimens:
  - carboplatin/paclitaxel
  - carboplatin/gemcitabine
  - carboplatin/pegliposomal doxorubicin
  - or other platinum combinations in prospective trials
<table>
<thead>
<tr>
<th>Centre / group</th>
<th>AGO</th>
<th>25</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>GINECO</td>
<td>94</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>AGO Austria</td>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Centre / group</th>
<th>GEICO</th>
<th>28</th>
</tr>
</thead>
<tbody>
<tr>
<td>MITO/MANGO</td>
<td>26</td>
<td></td>
</tr>
</tbody>
</table>

**TOTAL:** 409 patients
GOG 0213: Secondary Cytoreduction

- Epithelial Ovarian, Fallopian, or Peritoneal Cancer
- One prior therapy, Platinum-free interval > 6 months
- Primary Endpoint: OS

**I** Maximal Secondary Cytoreduction

- Carboplatin AUC=5
- Paclitaxel 175 mg/m\(^2\) x 6-8
- (No further therapy)

**II** No Secondary Surgery

- Carboplatin AUC=5
- Paclitaxel 175 mg/m\(^2\) x 6-8
- Bevacizumab 15 mg/kg
- Bevacizumab 15 mg/kg (Until progression)

**III** Not Surgical Candidate

- Carboplatin AUC=5
- Paclitaxel 175 mg/m\(^2\) x 6-8
- Bevacizumab 15 mg/kg
- Bevacizumab 15 mg/kg (Until progression)
### AGO-DESKTOP II – PERIOPERATIVE MORBIDITY

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients in intensive care unit</td>
<td>67</td>
<td>52%</td>
</tr>
<tr>
<td>Days intensive care unit [median]</td>
<td>2</td>
<td>range: 1-20</td>
</tr>
<tr>
<td>No of pts adm. packed blood cells</td>
<td>55</td>
<td>44%</td>
</tr>
<tr>
<td>No of pts with at least one complication</td>
<td>42</td>
<td>33%</td>
</tr>
<tr>
<td>Infections requiring antibiotic treatment</td>
<td>31</td>
<td>24%</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>14</td>
<td>11%</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>10</td>
<td>8%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4</td>
<td>3%</td>
</tr>
<tr>
<td>Others</td>
<td>7</td>
<td>5%</td>
</tr>
<tr>
<td>Re-laparotomy</td>
<td>14</td>
<td>11%</td>
</tr>
<tr>
<td>Bowel leakage/perforation</td>
<td>6</td>
<td>5%</td>
</tr>
<tr>
<td>Abscess/infection</td>
<td>3</td>
<td>2%</td>
</tr>
<tr>
<td>Bleeding</td>
<td>3</td>
<td>2%</td>
</tr>
<tr>
<td>Fistula</td>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>Thrombosis / Embolism</td>
<td>3</td>
<td>2% / 4</td>
</tr>
<tr>
<td>Other severe complications</td>
<td>12</td>
<td>9%</td>
</tr>
<tr>
<td>Mortality within 60 days</td>
<td>1</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

## Surgical morbidity

<table>
<thead>
<tr>
<th>Primary Surgery</th>
<th>Year</th>
<th>Patients [n]</th>
<th>Mortality [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aletti</td>
<td>2006</td>
<td>194</td>
<td>1.5</td>
</tr>
<tr>
<td>Chi</td>
<td>2010</td>
<td>141</td>
<td>1.4</td>
</tr>
<tr>
<td>Harter</td>
<td>2011</td>
<td>187</td>
<td>2.3</td>
</tr>
<tr>
<td>Sehouli</td>
<td>2011</td>
<td>332</td>
<td>3.1</td>
</tr>
<tr>
<td>Gerestein</td>
<td>2009</td>
<td>pop. based</td>
<td>3.7</td>
</tr>
<tr>
<td><strong>Surgery for relapse</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DESKTOP II</td>
<td>2011</td>
<td>129</td>
<td>0.8</td>
</tr>
<tr>
<td>Chi</td>
<td>2006</td>
<td>153</td>
<td>0</td>
</tr>
<tr>
<td>Tian</td>
<td>2010</td>
<td>123</td>
<td>0</td>
</tr>
<tr>
<td>Sehouli</td>
<td>2010</td>
<td>240</td>
<td>3.8</td>
</tr>
<tr>
<td>Oksefjell</td>
<td>2010</td>
<td>217</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
Palliative surgery
• Chemotherapy: Epothilone, Pemetrexed (Alimta), TLK 286, ...
• Antibodies: Anti-Epcam, ACA125, ...
• EGFR: Gefitinib, Erlotinib, Cetuximab,..
• Antiangiogenesis and VEGF: Bevacizimab, DXMAA, VEGF trap, PI GFab, ..
• c-erb-family (Trastuzumab, pertuzumab, TAK-165, CP724,714, 2C4, IMC-225, EMD72000), Lapatinib (GW572016),
• FTI (Lonafarnib, SCH6636, R115777, BMS214662),
• Raf-1 (Bay 43-90006), MEK (CI-1040), Erbitux, ...
• M-tor inhibitors
• Multiple targets: Enzastaurin, ...

AND MANY MANY OTHERS
43-year-old patient
Bowel obstruction and fistula under Avastin treatment
Platinum resistant ov ca relapse
67y

Platinum refractory relapse after catumaxomab treatment ip.
42y
Platinum refractory ovarian cancer
4 mo after initial diagnosis
Taxol weekly induced bowel perforation with peritonitis and ileus
Salvage Surgery Due To Bowel Obstruction in Advanced or Relapsed Ovarian Cancer Resulting in Short Bowel Syndrome and Long-Life Total Parenteral Nutrition

Surgical and Clinical Outcome

Christina Fotopoulou, PhD, MD,*† Elena Ioana Braicu, MD,* Sara-Lea Kwee,* Marc Kuhberg, MD,* Rolf Richter,* Klaus Pietzner, MD,* Aarne Feldheiser, MD,‡ Marcus Bahra, MD,§ Sven Christian Schmidt,§ and Jalid Sehouli, PhD, MD*

<table>
<thead>
<tr>
<th>TABLE 2. Data of Perioperative Management, Operative Mortality and Morbidity (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median (Range)</strong></td>
</tr>
<tr>
<td>Operation time, min</td>
</tr>
<tr>
<td>Transfusion of erythrocyte concentrates, U</td>
</tr>
<tr>
<td>Length of stay in intensive care unit, d</td>
</tr>
<tr>
<td>Length of hospital stay, d</td>
</tr>
<tr>
<td>Intestinal length</td>
</tr>
<tr>
<td>&lt;1 m</td>
</tr>
<tr>
<td>&gt;1 m</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Any major complications</th>
<th>19 (51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>4</td>
</tr>
<tr>
<td>Pleura effusion</td>
<td>3</td>
</tr>
<tr>
<td>Relaparotomy</td>
<td>12</td>
</tr>
<tr>
<td>Anastomotic insufficiency</td>
<td>5</td>
</tr>
<tr>
<td>Abscess, secondary wound healing</td>
<td>1</td>
</tr>
<tr>
<td>Postoperative bleeding</td>
<td>2</td>
</tr>
<tr>
<td>Intestinal perforation</td>
<td>1</td>
</tr>
<tr>
<td>Rupture of abdominal wall closure</td>
<td>1</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>1</td>
</tr>
</tbody>
</table>

30 day operative mortality: 10%
QoL & Survival

- Median OS: 5.6 months (range, 0.1-49 months)
- 1-year and 2-year OS: 18.3% and 8.1%
- Within a median FU- period of 5 mo (range, 0.2-49 months), 4 patients (10.8%) are still alive.

- No significant differences in survival were seen between patients with or without major complications, tumor residuals, or residual intestinal length of less than 1 m versus greater than 1 m.

**TABLE 4. Assessment of the Quality of Life of the 4 Alive Patients With EOC Who Underwent Salvage Surgery Resulting in SBS According to the SF-12 Health Survey Validated Questionnaire**

<table>
<thead>
<tr>
<th></th>
<th>Patients With EOC</th>
<th>Healthy Population</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-12 physical score, mean (SD)</td>
<td>36.68 (2.2)</td>
<td>50 (10)</td>
<td>0.009</td>
</tr>
<tr>
<td>SF-12 psychological score, mean (SD)</td>
<td>21.36 (6.5)</td>
<td>50 (10)</td>
<td>0.017</td>
</tr>
</tbody>
</table>

The physical and mental scores of the patients were significantly lower than the scores of the general healthy population.

Fotopoulou et al. IJGC 2013
Epithelial Ovarian Cancer Surgery in the Era of Personalised Medicine

Novel targeted approaches allowing to extend the window of opportunities for platinum resistance relapse?

Caris Target Now
Sequenom
Exome Seq
Expression Microarray
Surgery at relapse

• No value of cytoreuction in „platinum resistant“ patients apart from palliation

• OS and PFS prolongation in tumorfree operated patients (retrospective), data from prospective trials awaited

• Therapeutic decisions individualized and tailored to patients prior treatments, tumor dissemination pattern and patients overall status

• At emergency situations after failure of conservative measures: en-block resection techniques; avoidance of numerous anastomoses; ileostomy/colostomy preferred.