Surgery in Recurrent Ovarian Cancer - an emerging area of evidence -

Andreas du Bois

*Kliniken Essen Mitte (KEM), Germany*
A long and winding road to define the role of surgery in relapsed OC called **AGO-DESKTOP Alley**

**DESKTOP I:** Retrospective multicentre series

1. Identify an appropriate endpoint / goal of surgery
2. Create a hypothetic model for a predictive score to select patients who could achieve the endpoint (allowing patient selection for further studies)

**DESKTOP II:** Prospective international non-interventional study

1. Validation of the DESKTOP I model (AGO score)
2. Descriptive analysis of the selection bias for offering surgery to patients with ROC
3. Description of ROC surgery associated morbidity

**DESKTOP III:** Prospectively randomised controlled phase III trial

1. Evaluation of the impact of ROC surgery on OS
2. acute and delayed morbidity
AGO DESKTOP-OVAR I
Predictive score for successful surgery
( = complete resection), multivariate analysis

<table>
<thead>
<tr>
<th>Pre-surgery variable</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Performance status</strong> (ECOG 0 vs &gt;0)</td>
<td>2.65 (1.56–4.52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Residual disease after 1st surgery</strong> (0 vs &gt;0)</td>
<td>2.46 (1.45–4.20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Ascites</strong> less than 500mL*</td>
<td>5.08 (1.97–13.16)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Exclusively CA-125 CA 125 excluded from analysis due to strong correlation with ascites

Not significant for complete resection in multivariate model
(multivariate model with all significant pre-surgery variables)

- Localisation of recurrent disease (pelvic vs other)
- Therapy-free interval
AGO DESKTOP OVAR II

Frequency of complete resection by applying the AGO score within a prospective validation trial in 524 patients

complete resection in 76% of the study cohort = AGO score could predict with 95% probability
A complete resection in at least 2 out of 3 patients

-> first prospective trial with successful validation of a predictive score

Harter P, du Bois A. Int J Gynecol Cancer 2011
Design: AGO DESKTOP III (ENGOT-ov20; NCT01166737)

Pts. with:
- 1st relapse
- PSROC
- AGO Score +ve

Cytoreductive Surgery with max. effort for complete resection

Platinum-based Combination therapy strongly recommended

R
n = 408

No OP

Immediate Platinum-based Combination therapy strongly recommended

OP Allowed
3rd line

• 1st pt in 9/2010
• Recruitment completed 3/2015
• 407 of 409 pts evaluated (2 screening failures)
### AGO DESKTOP III: Patients’ Characteristics
(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)

<table>
<thead>
<tr>
<th></th>
<th>No surgery</th>
<th>Surgery</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts. (n)</td>
<td>203</td>
<td>204</td>
<td></td>
</tr>
<tr>
<td>Age (median, yrs)</td>
<td>62.2</td>
<td>60.7</td>
<td>0.24</td>
</tr>
<tr>
<td>No prior chemo</td>
<td>2 (1.0%)</td>
<td>2 (1.0%)</td>
<td></td>
</tr>
<tr>
<td>Prior platinum w/o taxan</td>
<td>16 (7.9%)</td>
<td>10 (4.9%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Prior platinum + taxan</td>
<td>182 (89.7%)</td>
<td>191 (93.6%)</td>
<td></td>
</tr>
<tr>
<td>Pt-free-Int. &gt; 12 months</td>
<td>152 (74.9%)</td>
<td>155 (76.0%)</td>
<td>0.80</td>
</tr>
<tr>
<td>CA 125 at study entry:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 70 U/ml</td>
<td>183 (45%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 70 U/ml</td>
<td>197 (48%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>missing</td>
<td>27 (7%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CA 125: Additional data added after ASCO presentation**
**AGO DESKTOP III: Therapy**
(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No 2(^{nd}) surgery</th>
<th>2(^{nd}) Surgery</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non compliant with random arm</td>
<td>8 (3.9%) with OP</td>
<td>12 (5.9%) w/o OP</td>
<td>0.36</td>
</tr>
</tbody>
</table>

**Post-random chemotherapy:**

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>No 2(^{nd}) surgery</th>
<th>2(^{nd}) Surgery</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platinum containing therapy</td>
<td>185 (91.1%)</td>
<td>181 (88.7%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Non-platinum</td>
<td>6 (3.0%)</td>
<td>5 (2.5%)</td>
<td>0.51</td>
</tr>
<tr>
<td>None / missing data</td>
<td>12 (5.9%)</td>
<td>18 (8.8%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>45 (22.2%)</td>
<td>38 (18.6%)</td>
<td>0.32</td>
</tr>
<tr>
<td>PARP Inhibitors</td>
<td>1 (0.5%)</td>
<td>0 (0%)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

**Post-event surgery after 2\(^{nd}\) relapse** (within 3 mos after 2\(^{nd}\) relapse)

<table>
<thead>
<tr>
<th>Surgery Type</th>
<th>No 2(^{nd}) surgery</th>
<th>2(^{nd}) Surgery</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 (11%)</td>
<td>9 (5.4%)</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td></td>
<td>median</td>
<td>Quartiles 25-75%</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>--------</td>
<td>-----------------</td>
<td></td>
</tr>
<tr>
<td>Duration of surgery (minutes)</td>
<td>222</td>
<td>150 – 300</td>
<td></td>
</tr>
<tr>
<td>Bowel resection</td>
<td></td>
<td>33.3%</td>
<td></td>
</tr>
<tr>
<td>Stoma diversion temporary / permanent</td>
<td></td>
<td>3.5% / 3.5%</td>
<td></td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>250</td>
<td>50 - 500</td>
<td></td>
</tr>
<tr>
<td>RBC transfusion</td>
<td></td>
<td>20.3%</td>
<td></td>
</tr>
<tr>
<td>Fever &gt; 38\°C</td>
<td></td>
<td>4.8%</td>
<td></td>
</tr>
<tr>
<td>Antibiotic treatment</td>
<td></td>
<td>19.0%</td>
<td></td>
</tr>
<tr>
<td>Peri-OP thrombosis / embolism</td>
<td></td>
<td>1.1% / 0</td>
<td></td>
</tr>
<tr>
<td>Re-laparotomy</td>
<td></td>
<td>3.2%</td>
<td></td>
</tr>
<tr>
<td>Macroscopic complete resection rate</td>
<td></td>
<td>72.5%</td>
<td></td>
</tr>
</tbody>
</table>

AGO DESKTOP III: Surgery
(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)

Presented by: Andreas du Bois
AGO & KEM Essen, Germany
AGO DESKTOP III: Outcome 1 (Mortality / OS)
(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)

<table>
<thead>
<tr>
<th></th>
<th>No surgery</th>
<th>Surgery</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>30-days mortality (%)</td>
<td>-</td>
<td>-</td>
<td>Peri-OP 1</td>
</tr>
<tr>
<td>60-days mortality (%)</td>
<td>1 pt (0.49%)</td>
<td>-</td>
<td>Peri-OP 2</td>
</tr>
<tr>
<td>90-days mortality (%)</td>
<td>1 pt (0.49%)</td>
<td>1 pt (0.49%)</td>
<td>Peri-OP MAYO</td>
</tr>
<tr>
<td>6 months mortality (%)</td>
<td>5 pts (2.46%)</td>
<td>1 pt (0.49%)</td>
<td>End of 2\textsuperscript{nd} line thx</td>
</tr>
</tbody>
</table>

- The observed pooled 2-YSR was 83% and much higher than the assumed 2-YSR in the overall trial population.
- According to the trial protocol a planned interim analysis took place after observation of 122 OS events. The local significance level was set to alpha=0.0052 for a two-sided test – which was not met (O’Brien-Fleming group sequential plan).
AGO DESKTOP III: Outcome 2 (PFS) (AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>No surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>19.6 mos</td>
<td>14.0 mos</td>
</tr>
<tr>
<td>Δ median PFS</td>
<td></td>
<td>5.6 mos</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.66 (0.52 – 0.83)</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

Presented by: Andreas du Bois
AGO & KEM Essen, Germany
<table>
<thead>
<tr>
<th>Trials</th>
<th>Treatment</th>
<th>med. PFS (mos)</th>
<th>PFS gain (mos)</th>
<th>HR / p-value</th>
<th>OS (mos)</th>
<th>HR / p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICON 4 (n = 802)</td>
<td>Platinum</td>
<td>9</td>
<td>3</td>
<td>0.76</td>
<td>24</td>
<td>0.82</td>
</tr>
<tr>
<td>Lancet 2003</td>
<td>Platinum + Paclitaxel</td>
<td>12</td>
<td>3</td>
<td>&lt; 0.001</td>
<td>29</td>
<td>P = 0.02</td>
</tr>
<tr>
<td>AGO OVAR 2.5 (n = 366)</td>
<td>Carboplatin</td>
<td>5.8</td>
<td>2.8</td>
<td>0.72</td>
<td>17.3</td>
<td>0.96</td>
</tr>
<tr>
<td>JCO 2006</td>
<td>Gem/Carboplatin</td>
<td>8.6</td>
<td>2.8</td>
<td>p = 0.003</td>
<td>18</td>
<td>P = 0.73</td>
</tr>
<tr>
<td>CALYPSO (n = 976)</td>
<td>Carboplatin + Paclitaxel</td>
<td>9.4</td>
<td>1.9</td>
<td>0.82</td>
<td>33.0</td>
<td>0.99</td>
</tr>
<tr>
<td>JCO 2010</td>
<td>Carboplatin + PLD</td>
<td>11.3</td>
<td>2.8</td>
<td>p = 0.005</td>
<td>30.7</td>
<td>P = 0.94</td>
</tr>
<tr>
<td>OCEANS (n = 484)</td>
<td>Gem/Carboplatin</td>
<td>8.4</td>
<td>4.0</td>
<td>0.48</td>
<td>33.6</td>
<td>0.96</td>
</tr>
<tr>
<td>JCO 2012, Gyn Onc 2015</td>
<td>Gem/Carbo + Bevacizumab</td>
<td>12.4</td>
<td>4.0</td>
<td>p &lt; 0.0001</td>
<td>32.9</td>
<td>P = 0.65</td>
</tr>
<tr>
<td>ICON6 (n = 456)</td>
<td>Platinum + Paclitaxel</td>
<td>8.7</td>
<td>2.4</td>
<td>0.56</td>
<td>21</td>
<td>0.77</td>
</tr>
<tr>
<td>Lancet 2016</td>
<td>Chemo + cediranib + maintenance cediranib</td>
<td>11.1</td>
<td>2.4</td>
<td>p &lt; 0.0001</td>
<td>26.3</td>
<td>P = 0.11</td>
</tr>
<tr>
<td>GOG 213 (n = 674)</td>
<td>Carboplatin – Paclitaxel</td>
<td>10.4</td>
<td>3.4</td>
<td>0.63</td>
<td>37.3</td>
<td>0.829 (0.823)*</td>
</tr>
<tr>
<td>Lancet Onc in press 2017</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P = 0.056 (P = 0.044)*</td>
</tr>
<tr>
<td></td>
<td>Carbo-Paclitaxel + Bev</td>
<td>13.8</td>
<td></td>
<td>p &lt; 0.0001</td>
<td>42.2</td>
<td></td>
</tr>
<tr>
<td>DESKTOP III</td>
<td>Platin-based +/- surgery</td>
<td>14.0</td>
<td>5.6</td>
<td>0.66</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>ASCO 2017</td>
<td></td>
<td>19.6</td>
<td></td>
<td>p &lt; 0.001</td>
<td>n.a.</td>
<td></td>
</tr>
</tbody>
</table>
AGO DESKTOP III: Outcome 3 (PFS by surgical outcome)
(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)

<table>
<thead>
<tr>
<th></th>
<th>Median PFS [mos]</th>
<th>Δ PFS [mos]</th>
<th>HR (95% CI)</th>
<th>P-value Wald-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>No surgery</td>
<td>14.0</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Surgery but with</td>
<td>13.7</td>
<td>- 0.3</td>
<td>0.98 (0.71 – 1.35)</td>
<td>0.8952</td>
</tr>
<tr>
<td>residual tumor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery with</td>
<td>21.2</td>
<td>+ 7.2</td>
<td>0.56 (0.43 – 0.72)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>complete resection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Presented by: Andreas du Bois
AGO & KEM Essen, Germany
AGO DESKTOP III: Outcome 4 (TFST = time to 3rd line) (AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>No surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median TFST</td>
<td>21.0 mos</td>
<td>13.9 mos</td>
</tr>
<tr>
<td>Δ median TFST</td>
<td></td>
<td>7.1 mos</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.61 (0.48 – 0.77)</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>
AGO DESKTOP III: Conclusions 1
(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)

- 1st randomized controlled trial on 2nd cytoreductive surgery in ROC
- OS in this patients cohort treated in selected centres is better than expected.
- 2nd surgery in pts with AGO Score positive PSROC resulted in:
  - a meaningful PFS and TFST advantage of 5.6 and 7.1 months
  - a PFS gain at least comparable with all published positive phase III trials in 2nd line therapy for PSROC so far.
  - no increase in short-term mortality (30-180 d) and morbidity (60 d)
- 2nd surgery should be discussed with all AGO Score +ve PSROC pts.
AGO DESKTOP III: Conclusions 2
(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)

• a benefit of surgery was exclusively seen in pts. with complete resection (CR) indicating the importance of selecting both:
  
  - **the right centre** with capability to achieve a CR in the majority of pts.
  
  - **and the right pts** (eg. AGO Score selects app 50% of PSROC pts)

• so far, our data do not support more aggressive follow-up. The role of CA125 and time of relapse diagnosis is subject of further analysis.

• hopefully, further follow-up will show that this PFS benefit translates into OS
A question which became even more important after DESKTOP III:

How to identify the “right” clinic for surgery in recurrent ovarian cancer
<table>
<thead>
<tr>
<th>Procedures in ROC surgery</th>
<th>HSK/KEM series*</th>
<th>Mayo series**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 217 pts (%)</td>
<td>N= 192 pts (%)</td>
</tr>
<tr>
<td>Bowel resection</td>
<td>41.0</td>
<td>29.2</td>
</tr>
<tr>
<td>any</td>
<td></td>
<td></td>
</tr>
<tr>
<td>large bowel</td>
<td>37.3</td>
<td></td>
</tr>
<tr>
<td>small bowel</td>
<td>12.9</td>
<td></td>
</tr>
<tr>
<td>Diverting stoma</td>
<td>8.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>13.4</td>
<td>17.2</td>
</tr>
<tr>
<td>Pancreatic tail resection</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>Liver partial resection</td>
<td>15.7</td>
<td>11.5</td>
</tr>
<tr>
<td>Lymphadenectomy</td>
<td>56.7</td>
<td></td>
</tr>
<tr>
<td>any</td>
<td></td>
<td></td>
</tr>
<tr>
<td>groins</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>pelvic</td>
<td>38.2</td>
<td>16.7</td>
</tr>
<tr>
<td>para-aortic</td>
<td>38.2</td>
<td>24.5</td>
</tr>
<tr>
<td>Upper abdomen LNE</td>
<td>8.2</td>
<td>5.7</td>
</tr>
<tr>
<td>above diaphragm</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Diaphragmatic peritoneum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial</td>
<td>24.0</td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>19.8</td>
<td>19.8</td>
</tr>
<tr>
<td>full thickness</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>Abdominal wall</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>urinary bladder / ureter</td>
<td>5.1</td>
<td>6.3</td>
</tr>
<tr>
<td>resection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrectomy</td>
<td>2.3</td>
<td></td>
</tr>
</tbody>
</table>

*Harter P, ..., du Bois A. Gynecol Oncol 2014, **Janco J, ...., Cliby W, Gynecol Oncol 2016
Quality Assurance in Advanced (FIGO III-IV) Ovarian Cancer Surgery

European Society of Gynaecologic Oncology Quality Indicators for Advanced Ovarian Cancer Surgery

Denis Querleu, MD,* François Planchamp, MSc,* Luis Chiva, MD,† Christina Fotopoulou, MD,‡ Desmond Barton, MD,§ David Cibula, MD,¶ Giovanni Aletti, MD,‖ Silvestro Carinelli, MD,¶ Carien Creutzberg, MD,# Ben Davidson, MD, PhD,** Philip Harter, MD,†† Lene Lundvall, MD,‡‡ Christian Marth, MD,§§ Philippe Morice, MD, PhD,||| Arash Rafii, MD, PhD,¶¶ Isabelle Ray-Coquard, MD, PhD,### Andrea Rockall, MD,‡ Cristina Sessa, MD,*** Ate van der Zee, MD,††† Ignace Vergote, MD,‡‡‡ and Andreas du Bois, MD,‡‡‡

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10 quality indicators certification process
STUDY OF PRIMARY RADICAL CYTOREDUCTIVE SURGERY FOR ADVANCED EPITHELIAL OVARIAN CANCER

TRUST

Protocol ID: AGO-OVAR OP.7

A prospectively randomised open multi-centre study
A project of the AGO study group

TRUST Quality Control Manual

Version: V01MASTER international
Date: 02.03.2016

Authors: S. Mahner, A. du Bois
The right patient

- performance status / age / co-morbidity
- motivation

The right disease presentation

- initially resectable (if max. effort was tried)
- ascites < 500 ml
- no irresectable lesions (eg. imaging/laparoscopy)

The right centre

- resources (intensive care unit, transfusion unit)
- interdisciplinar and interprofessional peri-op management

The right surgical team

- skills & experience
- training (numbers)
- motivation