Current approaches to diagnosis and treatment of ovarian cancer
Poznań 24-11-2011 - ESGO Workshop

The role of surgery in treatment of recurrence in epithelial ovarian cancer

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In Europe, 37-41% women with ovarian cancer are alive five years after diagnosis (EUROCARE 2003).

The poor survival associated with ovarian cancer is largely because most women are diagnosed when the cancer is already at an advanced stage (Jemal 2008).
Epidemiology

- Most women with primary ovarian cancer achieve remission on surgery&CHT combination therapy.
- Most women with advanced epithelial ovarian cancer will ultimately develop recurrent disease (Burke 1994; Munkarah 2004).
Epidemiology

- Approximately 22% relapse within 6 months

- whereas most patients experience so-called platinum-sensitive relapse with an interval of more than 6 months after platinum-based chemotherapy
Question (1)

- In a woman with recurrent epithelial ovarian cancer *would you suggest* secondary surgical cytoreduction and chemotherapy compared to chemotherapy alone?
- In terms of effectiveness and safety?
Cytoreductive surgery plus chemotherapy versus chemotherapy alone for recurrent epithelial ovarian cancer
(Review The Cochrane Library 2010, Issue 6)
Galaal K
Cochrane Gynaecological Cancer Group Trials Register, The Cochrane Register of Controlled Trials, MEDLINE and EMBASE up to February 2009.

registers of clinical trials, abstracts of scientific meetings, reference lists of review articles and contacted experts in the field.

RCTs, quasi-randomised trials and non-randomised studies that compared secondary cytoreductive surgery and chemotherapy to chemotherapy alone in women with REOC.
Cochrane review & Greatest threat to the validity

- No current evidence from RCTs to guide clinical practice to determine the efficacy of secondary surgical cytoreduction
- *Publication bias* i.e. studies that did not find the treatment to have been effective may not have been published.
Question (2)

- Which patients were offered cytoreductive surgery for recurrence and what were the surgical achievements?
What was or should be the appropriate endpoint for cytoreductive surgery for recurrence?
Question (4)

- Are there any predictive or prognostic factors regarding surgical outcome in recurrent ovarian cancer?
Does favorable surgical outcome translate into survival benefit in recurrent ovarian cancer?
EORTC Protocol 55963 Lorocson

- Aborted prematurely because of low recruitment
Guidelines (1) : What Is the Role of Cytoreductive Surgery for Recurrent Ovarian Cancer?

- Surgery may be appropriate in selected patients
- No RCT, no level 1 evidence, which demonstrates a survival advantage associated with surgical cytoreduction for women with recurrent ovarian cancer
- Randomized phase 3 trials evaluating the role of surgery in recurrent ovarian cancer are a priority.
- Based on retrospective data, maximum cytoreductive surgery prior to chemotherapy in these patients only leads to a significant extension in survival when the procedure results in an optimal, and preferably complete (no macroscopic residue), debulking.

2010 Gynecologic Cancer InterGroup (GCIG) Consensus Statement on Clinical Trials in Ovarian Cancer
Guidelines (2)

- Experienced and trained surgeons might offer surgery for recurrent disease to individually selected patients after giving information about the potential benefit and about the limited available evidence regarding this strategy.
Systematic reviews/ reviews

- Coleman 2004
- Du Bois 2005
- Hauspy and Covens 2007
- Bristow 2009
- Harter and Du Bois 2010
Limitations of the available literature?

- Most of the studies are retrospective.
- Prospective trials: no definite inclusion criteria are mentioned and there are no control groups.
- Optimal debulking is variously defined.
- Comparing survival is very difficult.
- Recurrence-free interval prior to salvage surgery is variable.
- Detailed data on salvage chemotherapy is not available.
Limitations of the available literature?

- many authors reported series containing mixed types of surgery (cytoreductive surgery for recurrence, secondary debulking surgery during second look procedures, surgery for progressive disease). These mixed series were excluded.
- mixed histologic features (e.g. borderline, micropapillary, and nonepithelial tumors of the ovary).
- Excluded articles reporting only on specific surgical procedures (e.g. hepatic surgery) and article with prior salvage chemotherapy followed by surgery.
Which patients had been offered cytoreductive surgery for recurrence?

**Eligibility criteria**

- Adequate performance status
- Response to prior treatment
- Estimation of resectability
Which patients had been offered cytoreductive surgery for recurrence?

Results

- Complete debulking rates varied between 9 and 82%
- Mortality rates were between 0% and 3%
- Postoperative morbidity ranged from 8 to 52%
Which patients had been offered cytoreductive surgery for recurrence?

- Proportions of patients not offered cytoreductive surgery was lacking
- Highly selected patient populations because of the exclusion of most patients for whom cytoreductive surgery was believed not to be beneficial.
What should be the appropriate end point for cytoreductive surgery for recurrence?

- Survival benefit only for **completely debulked** patients
- Scarabelli et al., Zang et al. …. indicated a benefit also for so-called optimally debulked patients (<1 cm)
- Different complete resection rates (11% - 81%)

The role of so-called optimal debulking with visible tumor residuals remained controversial.
Are there any predictive or prognostic factors regarding surgical outcome in recurrent ovarian cancer? (systematic reviews)

- presence of symptoms
- elevated cancer antigen (CA-125)
- localization of disease
- number of disease sites (solitary or multiple)
- size of recurrent disease less than 10 cm
- short treatment-free interval (<6m ->1y)
- performance status
The DESKTOP I trial proposed a score for the prediction of complete cytoreduction in recurrent ovarian cancer.

The DESKTOP II trial was planned to verify this hypothesis prospectively in a multicenter setting.

Resectability was assumed if 3 factors were present:

1. complete resection at first surgery
2. good performance status
3. absence of ascites.
End points

- the positive prediction of complete resection in score-positive patients with first relapse
- assessment of selection processes for surgery in dedicated centers
- feasibility and complications of surgery in patients with first or second relapse

Philipp Harter et al. ,Int J Gyn Cancer, Vol 21(2) Feb 2011
Methods:

- Participating centers prospectively enrolled all consecutive patients with platinum-sensitive first or second relapse.
- The score was applied to all patients, but centers were free to decide on therapy. All further therapies were documented, and the outcome of patients was analyzed.
- A 75% complete resection rate in 110 prospectively classified patients had to be achieved to confirm a positive predictive value of 2 or higher of 3 with 95% probability.
Results

08/06 – 03/08: screening of 516 pts with platinum-sensitive 1st or 2nd relapse

AGO score

negative

255 pts (49%)

positive

261 pts (51%)

surgery

NO

113 pts (22%)

YES

148 pts (29%)

1st relapse

NO

19 pts (4%)

YES

study cohort: 129 pts (25%)

Philipp Harter et al. , Int J Gyn Cancer, Vol 21(2) Feb 2011
Baseline characteristics of 129 patients before surgery

- FIGO stage at first diagnosis, n (%)
  - I-II 34 (26)
  - III-IV 95 (74)

- No. mets in preoperative diagnostics, n (%)
  - 1 65 (51)
  - 2 25 (20)
  - 3 11 (9)
  - >3 27 (21)

Philipp Harter et al. ,Int J Gyn Cancer, Vol 21(2) Feb 2011
Baseline characteristics of 129 patients before surgery

- **Tumor locations, n (%)**
  - Pelvis 79 (61)
  - Intra-abdominal above pelvis 54 (42)
  - Retroperitoneal 37 (29)
  - Parenchymal organs 28 (22)
  - Spleen 12 (9)
  - Liver 16 (12)
  - Others 5 (4)
Surgical results

- Residual tumor after surgery for recurrence (mm)
  - 0: 98 (76%)
  - 1: 13 (10%)
  - >10: 18 (14%)

- Residual lesions
  - 1-3: 7 (5)
  - 4-5: 3 (2)
  - >5: 15 (12)
  - carcinomatosis: 21 (16)
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<th>No. Patients</th>
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<td>Mortality within 60 d</td>
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The DESKTOP trial II prognostic factors

- good performance status
- no residual disease after surgery for primary treatment
- early initial FIGO stage
- neither ascites
- nor signs of peritoneal carcinosis

Complete resection was achieved in 81% of patients with all these factors.

Philipp Harter et al. ,Int J Gyn Cancer, Vol 21(2) Feb 2011
Does favorable surgical outcome translate into survival benefit in recurrent ovarian cancer?

- The median survival in completely debulked patients ranged from 16 to 100 months.
- Most series of cytoreductive surgery for recurrent ovarian cancer did not report median survival far exceeding the ICON4/AGO-OVAR 2.2.
- The lack of randomized trials makes it impossible to conclude whether a more favorable outcome in series with high rates of complete debulking could be attributed to biology (i.e., selection bias) or to surgical efforts.
Which prognostic factors are associated with prolonged survival in patients who received cytoreductive surgery for recurrent ovarian cancer?

- Complete debulking was one of the strongest predictors for survival in all five multivariate analyses performed on this question.

- The proportions of patients with less than 6 months ranged from 0 to 13.5% only.

DESKTOP I trial

- The DESKTOP trial showed a benefit for a treatment-free interval exceeding 6 months but no difference when intervals longer than 6 months were compared in the univariate analysis.
meta-analysis Bristow 2009

- Forty cohorts of patients with recurrent ovarian cancer (2019 patients) meeting study inclusion criteria
- MEDLINE database (1983–2007)
- Simple and multiple linear regression analyses
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<th>Author</th>
<th>Reference</th>
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<th>Accrual interval (months)</th>
<th>N (total)</th>
<th>Age (median)</th>
<th>Median overall survival (months)</th>
<th>Disease-free interval (months)</th>
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<td>≤0.5</td>
<td>80.2</td>
<td>55.6</td>
</tr>
</tbody>
</table>
Bristow 2009

- The mean weighted median disease-free interval prior to cytoreductive surgery was 20 months.
- Mean weighted median overall post-recurrence survival time was 30 months.
- Mean proportion of patients in each cohort undergoing complete cytoreductive surgery was 52.2%.
<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>95% confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year of publication</td>
<td>0.43 to 1.82</td>
<td>0.002</td>
</tr>
<tr>
<td>Accrual interval</td>
<td>(−)0.05 to 0.10</td>
<td>0.51</td>
</tr>
<tr>
<td>Median age</td>
<td>(−)0.85 to 1.24</td>
<td>0.71</td>
</tr>
<tr>
<td>Median disease-free interval</td>
<td>(−)0.33 to 1.03</td>
<td>0.31</td>
</tr>
<tr>
<td>Localized disease</td>
<td>(−)1.63 to 2.78</td>
<td>0.609</td>
</tr>
<tr>
<td>Ascites</td>
<td>(−)9.13 to 0.47</td>
<td>0.089</td>
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<tr>
<td>Serous histology</td>
<td>(−)0.52 to 6.58</td>
<td>0.09</td>
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<tr>
<td>Grade 3 tumor</td>
<td>(−)1.51 to 4.59</td>
<td>0.32</td>
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<tr>
<td>Surgery before chemotherapy</td>
<td>(−)23.67 to 22.91</td>
<td>0.974</td>
</tr>
<tr>
<td>Bowel resection</td>
<td>(−)2.90 to 0.51</td>
<td>0.129</td>
</tr>
<tr>
<td>Optimal cytoreduction</td>
<td>0.90 to 4.49</td>
<td>0.004</td>
</tr>
<tr>
<td>Complete cytoreduction</td>
<td>1.29 to 4.38</td>
<td>0.00008</td>
</tr>
</tbody>
</table>
Simple linear regression analysis: median cohort survival time plotted against the proportion of patients in each cohort undergoing complete cytoreductive surgery.
only statistically significant clinical variable **independently** associated with post-recurrence survival time was the proportion of patients undergoing complete cytoreductive surgery (p=0.019).

After controlling for all other factors, each **10% increase in the proportion of patients undergoing complete cytoreductive surgery** was associated with a 3.0 month increase in median cohort survival time.

For this **select group** of patients, the surgical objective should be resection of all macroscopic disease.
Abundant retrospective series report prolongation of survival with secondary cytoreductive surgery in recurrent ovarian cancer.

- Selection bias
- Publication bias
- Subsequent therapies
- … confounding factors for survival.
- … and if this selected group of patients would respond to chemotherapy at the same way as they do with surgery?
SECOND-LINE TREATMENT OF PARTIALLY-PLATINUM-SENSITIVE RECURRENT OVARIAN CANCER: A MANGO - PIEMONTE E VALLE D'AOSTA CANCER NETWORK ITALIAN MULTICENTRIC RETROSPECTIVE STUDY

A. Ferrero, L. Fuso, R. Fossati, B. Sostegni, O. Nicoletto, A. Gadducci, F. Raspagliesi, A. Testa, N. Colombo, A.A. Lissoni, P. Zola, MaNGO, Piemonte e Valle d'Aosta Cancer Network, Italy
Results: recruitment

- 524 first recurrences, 213 partially platinum-sensitive

2. Ospedale Biella
3. Ospedale Vincenzo Cervello - Palermo
4. Ospedale Giovanni Agnelli Pinerolo
4. Ospedale San Luigi-Orbassano
5. Ospedale Sant'Anna
5. Policlinico Bari
6. AOUS San G.Battista-Torino
7. AOU Maggiore della Carità - Novara
9. Ospedale Varese
10. Ospedali civili di Brescia
11. IOV IRCCS Padova
16. Ginecologia Oncologica Università Pisa
17. Istituto Nazionale Tumori Milano
18. Mauriziano
24. Università Cattolica Sacro Cuore-Roma
25. Istituto Europeo di Oncologia di Milano
47. Ospedale San Gerardo Monza
213. Total
Results: overall survival

<table>
<thead>
<tr>
<th>Regime</th>
<th>Total N</th>
<th>N of Events</th>
<th>Censored</th>
</tr>
</thead>
<tbody>
<tr>
<td>platino</td>
<td>95</td>
<td>54</td>
<td>41</td>
</tr>
<tr>
<td>non platino</td>
<td>104</td>
<td>71</td>
<td>33</td>
</tr>
<tr>
<td>Overall</td>
<td>199</td>
<td>125</td>
<td>74</td>
</tr>
</tbody>
</table>

Chi-Square: 17.067, df: 1, Sig: .000
Chi-Square: 22.685, df: 1, Sig: .000
Chi-Square: 21.897, df: 1, Sig: .000
With the limits of a retrospective study, PLATINUM-BASED TREATMENT BETTER than Non-Platinum in “partially platinum-sensitive disease” (PFI 6-12 months) …

It has been proposed that extending the platinum-free interval with intervening non-platinum therapy could increase the efficacy of a later re-treatment with platinum in platinum-sensitive recurrent ovarian cancer

- This hypothesis is based on data from small series (Gore 1990, Markman 1991)

- The hypothesis has been questioned by the SOCRATES study, that retrospectively assessed the pattern of care of a cohort of patients with recurrent platinum-sensitive ovarian cancer in the years 2000-2002 in 37 Italian centres (Pignata S et al., Oncology 2006)
The objective of this trial is the efficacy determined through analysis of overall survival (OS) of the different sequence (CP→PLD vs PLD→CP) in recurrent ovarian cancer patients with platinum-free interval 6-12 months.
Summary (1)

- As management of ovarian cancer has recently evolved to a treatment of a 'chronic disease', surgery (which has a definite role in primary therapy) should be considered.
Summary (2)

- Patients with favorable characteristics such as a long disease-free interval, good performance status, a single or few small intra-abdominal recurrences *may* benefit from secondary cytoreduction.

- A prospective randomized study is needed
WHAT IS THE ROLE OF CYTOREDUCTIVE SURGERY FOR RECURRENT OVARIAN CANCER?

- There is no level I evidence to demonstrate a survival advantage associated with surgical cytoreduction in women with recurrent ovarian cancer.

Randomized phase 3 trials:
2 such trials were open to accrual within GCIG member groups (GOG 213 and AGO-OVAR DESK-TOP 3).

Until data from these trials have matured, the evidence regarding this question is based almost entirely on retrospective cohort studies.

2010 Gynecologic Cancer InterGroup (GCIG) Consensus Statement on Clinical Trials in Ovarian Cancer
Future directions

2010 Gynecologic Cancer InterGroup (GCIG)

Consensus Statement
WHAT IS THE ROLE OF CYTOREDUCTIVE SURGERY FOR RECURRENT OVARIAN CANCER?

- Data from retrospective studies suggest a benefit of surgery on disease-specific survival in patients who are optimally cytoreduced and suggest that cytoreductive surgery may be appropriate in selected patients with recurrent ovarian cancer.
In 76% of the 524 patients enrolled in DESKTOP OVAR II, complete surgical resection of disease was achieved. The AGO score predicted complete resection in 2 of every 3 patients.
HOW DO WE DEFINE DISTINCT PATIENT POPULATIONS IN NEED OF SPECIFIC THERAPEUTIC APPROACHES?

- distinct patient populations for clinical trial enrollment should be based on the interval from last platinum therapy and on the time to progression.
- It was recognized that the PFI is determined by the frequency and the type of investigations patients received. The PFI is defined from the last date of platinum dose until progressive disease is documented.
- Each trial should specify how progression was defined (i.e., CA-125 alone, radiological or symptomatic recurrence).

2010 Gynecologic Cancer InterGroup (GCIG) Consensus Statement on Clinical Trials in Ovarian Cancer
SHOULD END POINTS FOR TRIALS WITH RECURRENT DISEASE VARY FROM THOSE OF FIRST-LINE TRIALS?

- There was consensus that phase 3 trials in patients with late relapse (ie, PFI >12 months) should be large enough to detect clinically meaningful differences in both PFS and OS.

2010 Gynecologic Cancer InterGroup (GCIG) Consensus Statement on Clinical Trials in Ovarian Cancer
IS CA-125 PROGRESSION ALONE SUFFICIENT FOR ENTRY/ELIGIBILITY INTO CLINICAL TRIALS?

- Patients with recurrent disease on the basis of CA-125 alone are eligible for clinical trials, although it was accepted that there does not seem to be any significant survival benefit associated with initiating chemotherapy in asymptomatic patients with an elevated CA-125 alone, based on the results of MRC OV05/EORTC 55955 study.17
Overall survival

**Median:**
- Early: 25.7 months (95% CI 23.0–27.9)
- Delayed: 27.1 months (95% CI 22.8–30.9)

HR 0.98 (95% CI 0.80–1.20), p=0.85

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Early</th>
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</tr>
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<tbody>
<tr>
<td>0</td>
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<td>264</td>
</tr>
<tr>
<td>6</td>
<td>247</td>
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<tr>
<td>12</td>
<td>211</td>
<td>203</td>
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<tr>
<td>18</td>
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<tr>
<td>60</td>
<td>15</td>
<td>16</td>
</tr>
</tbody>
</table>

Lancet. 2010 Oct 2;376(9747):1155-63
Phase III GOG 213

Recurrent Ovarian, PPT, or FT Cancer; TFI ≥ 6 months

Surgical Candidate?

Yes

Randomize

Surgery

No Surgery

Chemotherapy Randomization

No

Randomize

Carboplatin / Paclitaxel

Carboplatin / Paclitaxel / Bevacizumab

Bevacizumab

http://www.gcig.icgs.org/ClinicalTrials.html
AG0-OVAR DESKTOP III (Protocol AGO - OVAR OP.4)

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

Strata:

Platinum-free-interval
6-12 vs > 12 months

1st line platinum based chx: yes vs no

Cytoreductive surgery

No surgery

* Recommended platinum-based chemotherapy regimens:
- carboplatin/paclitaxel
- carboplatin/gemcitabine
- carboplatin/pegliposomal doxorubicin
- or other platinum combinations in prospective trials
Primary objective: Overall survival

Secondary objectives:
- Progression-free survival
- Quality of Life: EORTC QLQ 30 and NCCN FOSI
- Rate of complete resection as prognostic factor
- Complication rates of surgery
- Exploratory analysis of surgical characteristics and chemotherapy
AGO-OVAR DESKTOP III (Protocol AGO - OVAR OP.4)

Datamanagement and Randomisation: Fax and e-CRF (MACRO)

Central Monitoring

Statistics: HR 0.7 favouring surgery

Sample size: 408 patients/244 events

Recruitment: 36 months

Participating groups from GCIG: AGO,

Again no full funding - participating groups have to pay local costs.
Thank you