Residual Tumor Following Surgery: The Strongest Prognostic Factor or a Myth?

Philipp Harter, MD
Kliniken Essen Mitte
Essen, Germany
What Are Our Questions

• Q1: Prognostic factor residual disease?
• Q2: Differences depending from stage?
• Q3: Differences regarding localization?
• Q4: Could we trust the surgeon?
• Q5: Primary vs interval debulking?
However, Joe Meigs was the first to champion cytoreductive surgery in advanced ovarian cancer to enhance the effects of postoperative radiation therapy.

The Impact of Residual Tumor (RT) on Outcome in Advanced Ovarian Cancer

The impact of residual tumour on outcome in advanced ovarian cancer

Data from an individual patient meta-analysis of three randomised phase III trials with 3,126 patients

5-year survival rate

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Overall survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 mm</td>
<td>100%</td>
</tr>
<tr>
<td>1 mm – 10 mm</td>
<td>75%</td>
</tr>
<tr>
<td>&gt;10 mm</td>
<td>50%</td>
</tr>
<tr>
<td>&gt;10 mm vs 1 mm – 10 mm</td>
<td>1.34 (1.21, 1.49)</td>
</tr>
</tbody>
</table>

Log-rank: \( P < 0.001 \)

HR (95% CI)

- 1 mm – 10 mm vs 0 mm: 2.70 (2.37, 3.07)
- >10 mm vs 1 mm – 10 mm: 1.34 (1.21, 1.49)

The Benefit of Complete Resection Is Independent From Stage of Disease

<table>
<thead>
<tr>
<th>Initial FIGO Stage</th>
<th>No RT</th>
<th>Any RT</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIGO IIIB-IIIB</td>
<td>108.6</td>
<td>48.3</td>
<td>+ 60.3 months</td>
</tr>
<tr>
<td>FIGO IIIC</td>
<td>81.1</td>
<td>34.2</td>
<td>+ 46.9 months</td>
</tr>
<tr>
<td>FIGO IV</td>
<td>54.6</td>
<td>24.6</td>
<td>+ 30.0 months</td>
</tr>
</tbody>
</table>

Median Survival, months

HR = Hazard ratio, reference class for HR is “Any residual tumor”

A5: What Role Does Surgery Play Today?

• Surgical staging should be mandatory and should be performed by a gynecologic oncologist.

• The ultimate goal is cytoreduction to microscopic disease. There is evidence that reduction to ≤1 cm macroscopic disease is associated with some benefit. The term “optimal” cytoreduction should be reserved for those with no macroscopic residual disease.

• Documentation must be provided as to the level of cytoreduction (at least microscopic vs macroscopic).

• Delayed primary surgery following neoadjuvant chemotherapy is an option for selected patients with stage IIC and IV ovarian cancer as included in EORTC 55971.
...Complete Resection Could Partially Compensate For Initial Tumor Spread:

- res. tum. = 0, FIGO IIB-IIIB
- res. tum. = 0, FIGO IIIC
- res. tum. = 0, FIGO IV
- res. tum. > 0, FIGO IIB-IIIB
- res. tum. > 0, FIGO IIIC
- res. tum. > 0, FIGO IV

---
Influence of Extended Procedures to Achieve Complete Resection in Advanced Ovarian Cancer

Log-rank test: \( P<.001 \)

Potential Barriers for Complete Resection—What Is Acceptable?

1. Patient
   - Age
   - Comorbidity

2. Surgeon
   - Lack of expertise in debulking

3. Hospital
   - Lack of operating time
   - Lack of intensive care unit (ICU) beds

4. Tumor
   - Surgical/radiologic findings
Potential Barriers for Complete Resection—What Is Acceptable?

2. Surgeon—inacceptable $\rightarrow$ training, training, training
   
   • Lack of expertise in debulking

---

Potential Barriers for Complete Resection—What Is Acceptable?

3. Hospital—inacceptable
   • Lack of operating time
   • Lack of ICU beds

....but there are not only “external” hurdles

MSKCC analysis—resection rates depending on start of surgery (11:00)

Start before 11:00 was associated with higher complete resection rate, especially in patients with “very” advanced ovarian cancer (OR 0.29 [0.16-1.52]; P<.001 in multivariate analysis)

OR, odds ratio; MSKCC, Memorial Sloan Kettering Cancer Center
Could Preop Diagnostics Be Helpful for Selection?

**CT + PS + Ascites**

Cross-validation of 3 models: UCLA (A), Johns Hopkins (B), Mayo (C) u.a.

<table>
<thead>
<tr>
<th>Study and Model</th>
<th>Original Cohort, %</th>
<th>Cohort A, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sens</td>
<td>Spec</td>
</tr>
<tr>
<td>Cross-validation set</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bristow (model B)</td>
<td>100</td>
<td>85</td>
</tr>
<tr>
<td>Dowdy (model C)</td>
<td>52</td>
<td>90</td>
</tr>
<tr>
<td>Comparative application of other published CT predictor models</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meyer et al. Am J Roentgenol. 1995</td>
<td>58</td>
<td>100</td>
</tr>
<tr>
<td>Qayyum⁸⁸</td>
<td>76</td>
<td>99</td>
</tr>
</tbody>
</table>

Each score is only helpful in the cohort in whom the score was evaluated → generalization not possible → not suitable for routine clinical management

Could Preop Diagnostics Be Helpful for Selection?

272 Enrolled patients
Selected for S-LPS followed by Laparotomic attempt of PDS

38 Excluded patients
- 28 No AEOC (10.3%)
- 10 S-LPS not feasible (3.6%)

234 Eligible patients
Receiving S-LPS followed by laparotomic attempt of PDS

RT = 0
135 patients (57.7%)

RT ≤1 cm
54 patients (23.1%)

RT >1 cm
45 patients (19.2%)

“Modified Fagotti-Score”: 10+ points: 14 patients, none with complete resection

14 patients out of 99 with incomplete resection identified → rate for residual disease >1 cm?

AEOC, advanced epithelial ovarian cancer; PDS, primary debulking surgery; S-LPS, staging laparoscopy
## Could We Trust the Surgeon?

| Correlation Between Postoperative Residual Disease Assessed by the Surgeon or CT |
|-------------------------------------------------|-------------------------------------------------|
| Chi et al.                                      | 52%                                             |
| Sala et al.                                     | 59%                                             |
| Lakhman et al.                                  | 48% with cR0 >1 cm RD on CT                      |
| Lorusso et al.                                  | 20% with cR0 >1 cm RD on CT                      |

### Table:

<table>
<thead>
<tr>
<th>Study</th>
<th>Correlation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chi et al.</td>
<td>52%</td>
<td>Int J Gynecol Cancer 2010</td>
</tr>
<tr>
<td>Sala et al.</td>
<td>59%</td>
<td>Int J Gynecol Cancer 2011</td>
</tr>
<tr>
<td>Lakhman et al.</td>
<td>48% with cR0 &gt;1 cm RD on CT</td>
<td>AJR 2012</td>
</tr>
<tr>
<td>Lorusso et al.</td>
<td>20% with cR0 &gt;1 cm RD on CT</td>
<td>Oncology 2014</td>
</tr>
</tbody>
</table>

Residual disease is the strongest prognostic factor.
Definition by surgeon or radiologist?

Could We Trust the Surgeon?

Multivariate Analysis\textsuperscript{1}
Postoperative CT scan:
HR 2.54 \textit{P}<.001

Multivariate Analysis\textsuperscript{2}
Postoperative CT scan:
HR 8.87 \textit{P}<.0001
Surgical evaluation: HR 1.75 \textit{ns}

Let's Have a Closer Look—The MSKCC Experience

212 patients with advanced OC (1/97 – 12/11) with CT scan 1-7 weeks after surgery:
→ 16 patients/year
→ 51 patients within a trial; indication for CT in the remaining 161 patients?

Complications? Radiologic staging after Sx?

| Residual disease in patients regarded as optimally debulked at surgery. |
|-----------------------------------------------|-----------------|-----------------|
| Patients — R0 resection by surgery            | Reader 1        | Reader 2        |
| (N)                                           | (%)             | (N)             | (%):            |
| N = 104                                       |                 |                 |
| CT-RD                                         | 32 (30.7)       | 34 (32.7)       |
| Supradiaphragmatic disease                    | 12 (11.5)       | 7 (6.7)         |
| Perihepatic                                   | 21 (20.2)       | 13 (12.5)       |
| Perisplenic                                   | 6 (5.8)         | 3 (2.9)         |
| Omental                                       | 9 (8.7)         | 10 (9.6)        |
| Organ metastasis                              | 3 (2.9)         | 5 (4.8)         |

• What was known before/during surgery?
• Correlation to preop CT scan? In 2.4% residual disease indicated by surgeon, not seen in CT
• Upper abdominal/supradiaphragmatic surgery not implemented at least in the first half of study period

Surgeon vs CT?

Standard first-line chemotherapy with or without nintedanib for advanced ovarian cancer (AGO-OVAR 12): a randomised, double-blind, placebo-controlled phase 3 trial

Andreas du Bois, Gunnar Kristensen, Isabelle Ray-Coquard, Alexander Reuss, Sandro Pignata, Nicoletta Colombo, Ursula Denison, Ignace Vergote, Jose M del Campo, Petronella Ottevanger, Martin Heubner, Thomas Minarik, Emmanuel Sevin, Nikolaus de Gregorio, Mariusz Bidziński, Jacobus Pfisterer, Susanne Malander, Felix Hilpert, Mansoor R Mirza, Giovanni Scambia, Werner Meier, Maria O Nicoletto, Line Bjørge, Alain Lortholary, Martin Oliver Sailer, Michael Merger, Philipp Harter, on behalf of the AGO Study Group led Gynecologic Cancer Intergroup (GCIG)/European Network of Gynaecologic Oncology Trials Groups (ENGOT) Intergroup Consortium

1366 patients with upfront surgery and CT before start of systemic treatment

SHOWN at ASCO 2016

Quality Assurance in Advanced (FIGO III-IV) Ovarian Cancer Surgery

Denis Querleu
Surgeon (chair)
Institut Bergonié, Bordeaux (France)

François Planchamp
Methodologist (co-chair)
Institut Bergonié, Bordeaux (France)
Quality Management Programs Improve Outcome:

Treatment Period and Overall Survival

QI 1. Rate of Complete Surgical Resection

<table>
<thead>
<tr>
<th>TYPE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>OUTCOME</td>
<td>indicator.</td>
</tr>
<tr>
<td>COMPLETE</td>
<td>abdominal surgical resection is defined by the absence of remaining macroscopic lesions after careful exploration of the abdomen. Whenever feasible, localized thoracic disease is resected. Surgery can be decided upfront, or planned after neoadjuvant chemotherapy. However, the quality assurance program must take into account that patients who can be operated upfront with a reasonable complication rate benefit most from primary debulking surgery.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SPECIFICATIONS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(i) Complete resection rate:</td>
<td></td>
</tr>
<tr>
<td>Numerator:</td>
<td>number of patients with advanced ovarian cancer undergoing complete surgical resection.</td>
</tr>
<tr>
<td>Denominator:</td>
<td>all patients with advanced ovarian cancer referred to the center.</td>
</tr>
<tr>
<td>(ii) Proportion of patients who are operated upfront (based on evidence from the EORTC 55971 trial, only patients presenting with low metastatic volume (peritoneal metastases less than 5 cm in diameter) are considered; patients with unresectable parenchymal metastases are excluded):</td>
<td></td>
</tr>
<tr>
<td>Numerator:</td>
<td>patients who are offered upfront surgery.</td>
</tr>
<tr>
<td>Denominator:</td>
<td>all patients not previously treated.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TARGET(S)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(i) Complete resection rate:</td>
<td></td>
</tr>
<tr>
<td>Optimal target:</td>
<td>&gt; 65%.</td>
</tr>
<tr>
<td>Minimum required target:</td>
<td>&gt; 50%.</td>
</tr>
<tr>
<td>(ii) Proportion of patients who are operated upfront:</td>
<td>&gt; 80%</td>
</tr>
</tbody>
</table>
Does Resection Status After Interval Debulking Influence Prognosis?

Prognostic classes influenced by surgery:

**Optimal prognosis:** Complete resection at upfront surgery

**Improved prognosis:** RD 1-10 mm at upfront sx or CR at IDS

**Suboptimal prognosis:** RD >10 mm upfront sx or any residuals at IDS

Could Preop Chemo Help to Improve Prognosis in Inoperable Patients?

Clinical CR: ~15% (out of patients with response → PD excluded: 20%?)
Pathologic complete response (cPR): 6.5%

- Response to chemo is a prognostic effect—mainly chemo or chemo + surgery?
- Could this limited effect really improve operability?
  - Yes, higher resection rates at IDS (EORTC, CHORUS)
  - Does IDS improve prognosis in inoperable patients?

CR, complete response; macroPR, macroscopic pathologic response; microPR, microscopic pathologic response

Interval Debulking Surgery After Incomplete Surgery

Design GOG 152 (550 patients)

Primary Surgery
RD >1 cm

→ 3 x PT → CR PR NC → Randomization

IDS by GO with “max. effort”

Despite surgery by GO with max. effort

off study

PT: Cisplatin 75 mg/m² Paclitaxel 135 mg/m² 24 h d1 q 21

GO, gynecologic oncologist; NC, no change; PR, partial response
IDS cannot compensate for residual disease after primary surgery, if primary surgery was performed with maximum effort

→ Tumor defined residual disease >1 cm at primary surgery has to be accepted!
→ Limited prognostic effect of residual disease after IDS (rate of CR 35%)

Interval Debulking Surgery—The Mother of This Concept
Design EORTC-IDS Trial (425 Patients)

Benefit by interval debulking performed in a center after primary surgery/biopsy elsewhere…..

Residual Disease After PDS and IDS

Significant difference favoring upfront surgery in patients with complete resection and residual disease!

Subgroup stage IV:
- PDS: 15% CR, median OS 62 months
- IDS: 35% CR, median OS 32 months

TRUST – Trial on Radical Upfront Surgical Therapy

Pts. with ovarian-, fallopian-tube or peritoneal-cancer FIGO stage IIIB, IIIC and resectable stage IV

- **Primary Endpoint**: OS ITT population
- **Secondary Endpoints**: PFS, resection rates, M'nM after 6 months, QoL, "fragility Index"
- **Strata**: FIGO stage (III / IV), group/country, ECOG 0 vs 1
- **Defined qualification process for participating centers to ensure high surgical quality** (>50% complete resection rate, >36 procedures/year)
Residual Tumor Following Surgery: The Strongest Prognostic Factor or a Myth?

- A fact at primary surgery

- A kind of a myth at interval debulking

- Therefore, the aim should always be complete or at least significant cytoreduction at primary surgery

- Every other strategy has to be justified

- If you are unable to achieve <1 cm at primary surgery → don‘t try again!

- Referral to the center has to be done before any invasive procedure

- In case of referral after primary surgery elsewhere, consider IDS