MANAGEMENT OF RECURRENT OVARIAN CANCER WITH CRS & HIPEC

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CAUSES OF RECURRENCE

- Tumor biologic behaviour
- Chemo resistance
- Incomplete cytoreduction
While there is not much one can do about the biologic profile of the tumor or its chemoresistance, the factor of cytoreduction can be improved.
INCOMPLETE CYTOREDUCTION

Table 4: Success Rates of Primary Cytoreductive Surgery in Stage III and IV Ovarian Cancer

<table>
<thead>
<tr>
<th>Residual Disease</th>
<th>Stage IIb-IV&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Stage III&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Stage III&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Stage IIIc-IV&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Stage IV&lt;sup&gt;e&lt;/sup&gt;</th>
<th>Stage IV&lt;sup&gt;f&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microscopic</td>
<td>30%</td>
<td>23%</td>
<td>15%</td>
<td>19%</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>0.1-1.0 cm</td>
<td>32%</td>
<td>42%</td>
<td>36%</td>
<td>22%</td>
<td>22%</td>
<td>50%</td>
</tr>
<tr>
<td>&gt; 1 cm</td>
<td>38%</td>
<td>35%</td>
<td>50%</td>
<td>53%</td>
<td>31%</td>
<td>42%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Wimberger et al. 2007.[24]<br>
<sup>b</sup>Winter et al. 2007.[26]<br>
<sup>c</sup>Chi et al. 2006.[28]<br>
<sup>d</sup>Vergote et al. 2010.[30]<br>
<sup>e</sup>Winter et al. 2008.[27]<br>
<sup>f</sup>Rauh-Hain et al. 2011.[29]

due to upper abdomen disease??

PRIMARY CYTOREDUCTION
- **debulking surgery**: surgery aimed to reduce disease burden
- **cytoreductive surgery**: a series of peritoneectomy procedures and visceral resections aimed at the complete removal of tumor from the abdominal cavity

Table 1: Peritoneectomy procedures and resections that are combined to complete a cytoreduction procedure

<table>
<thead>
<tr>
<th>PERITONECTOMY</th>
<th>RESECTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior parietal peritoneectomy</td>
<td>Old abdominal incisions, umbilicus, and epigastric fat pad</td>
</tr>
<tr>
<td>Left upper quadrant peritoneectomy</td>
<td>Greater omentectomy and spleen</td>
</tr>
<tr>
<td>Right upper quadrant peritoneectomy</td>
<td>Tumor on Glisson's capsule of the liver</td>
</tr>
<tr>
<td>Pelvic peritoneectomy</td>
<td>Uterus, ovaries, and rectosigmoid colon</td>
</tr>
<tr>
<td>Omental bursectomy</td>
<td>Gallbladder and lesser omentum</td>
</tr>
</tbody>
</table>
• Gynecologic Oncology Group (GOG):
  • optimal cytoreduction = the largest residual tumor nodule \( \geq 1 \) cm

• for peritoneal surface malignancy surgeons:
  • optimal cytoreduction = residual tumor \( \approx 0 \)


Cytoreductive surgery is a series of peritonectomies and visceral resections
Which surgeon is most suitable to perform these procedures?
(R) SUBDIAPHRAGMATIC PERITONECTOMY
BASE OF (R) SUBDIAPHRAGMATIC PERITONECTOMY

Halkia E, Efstathiou E et al. Management of diaphragmatic peritoneal carcinomatosis. JBUON 2014
## Cancer Cell Entrapment in the Round Ligament of Liver & Gallbladder


<table>
<thead>
<tr>
<th>Tumor Location</th>
<th>Round Ligament</th>
<th>Gallbladder</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resections, n</td>
<td>Macro Pos(+), n</td>
</tr>
<tr>
<td>Pseudomyxoma</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>Ovarian</td>
<td>66</td>
<td>21</td>
</tr>
<tr>
<td>Colon</td>
<td>42</td>
<td>16</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Gastric</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Appendiceal</td>
<td>28</td>
<td>24</td>
</tr>
<tr>
<td>Various</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>180</td>
<td>83</td>
</tr>
</tbody>
</table>
SECONDARY CYTOREDUCTION
Retrospective analysis, 1995 – 2012
N = 41 pts
Mean time from primary to secondary cytoreduction = 33.2m
Complete cytoreduction at the second operation was feasible in 35% and median survival in those patients was 60.3 months VS 10.7 months in patients with incomplete cytoreduction

Secondary cytoreduction was beneficial to 35% of patients with recurrent disease
**Important point:**

- Optimal secondary cytoreduction in **ASYMPTOMATIC recurrence** offers an OS of 79 months VS 53.9 months in **SYMPTOMATIC recurrence**

**Factors affecting OS:**

- Complete primary cytoreduction
- *Asymptomatic recurrence* = ↑ tumor markers, suspicious diagnostic studies
- Long time from primary cytoreduction to diagnosis of recurrence
975 patients were randomized

- 20% secondary cytoreduction & systemic chemotherapy
- 80% only systemic chemotherapy
- prolonged OS in the secondary cytoreduction group
- Median OS **49.9 months vs. 29.7 months**
- 3-yr survival in the secondary cytoreduction group:
  - residual tumor < 5cm: 72%
  - residual tumor > 5cm: 28%

**Benefit from secondary cytoreduction in well selected patients**
Retrospective study: 159 patients with second recurrence
- 83 patients underwent tertiary cytoreduction & systemic chemotherapy
- 76 patients received only systemic chemotherapy
- Median Survival
  - tertiary cytoreduction & MICROSCOPIC residual disease: 32.9m
  - tertiary cytoreduction & MACROSCOPIC residual disease: 14.6m
  - systemic chemotherapy only: 15m

Even tertiary cytoreduction outbalances treatment with systemic chemotherapy only
In a recent patient series of patients with platinum sensitive recurrence treated with CRS & HIPEC (with paclitaxel), it was reported that the presence of tumors with undifferentiated histology was the only independent factor associated with a reduced disease free survival (DFS), with a 1-year DFS of 77% and a 3-year DFS of 45%, denoting a tendency versus patients who did not undergo HIPEC.
Another recent study correlated response to HIPEC in the treatment of recurrent ovarian cancer to their BRCA status, demonstrating that the benefit from HIPEC is greater in BRCA mutation carriers.
In a recent series of 70 EOC patients, divided in two groups (first recurrence after surgery and adjuvant chemotherapy, six months after chemotherapy versus multiple relapses), survival was similar in the two groups after CRS & HIPEC.


Treatment of peritoneal carcinomatosis from ovarian cancer by surgical cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC).

Robella M¹, Vaira M, Marsanic P, Mellano A, Borsano A, Cinquegrana A, Sottile A, De Simone M.
In ovarian cancer patients with advanced disease, multiple chemotherapy lines (3-9) offer no advantage over 1 or 2 lines, with respect to OS.
n = 49 patients who underwent quarternary cytoreduction
mean OS = 23.05m
mean OS in CC-0 = 43m VS 13.4m in incomplete cytoreduction (p = 0.001)
mean OS of patients who received adjuvant chemotherapy
= 40.5m VS 12.3 m in patients who did not (p < 0.001)
WHEN TO ADMINISTRATE HIPEC?
PATIENT SELECTION

Table 4: Prognostic-predictive factor for “optimal” HIPEC in recurrent EOC.

(i) Age < 65
(ii) Performance status > 80
(iii) Interval from initial diagnosis > 12 months
(iv) Peritoneal Cancer Index < 20
(v) Completeness of Cytoreduction CC-0 or CC-1
(vi) Absence of retroperitoneal lymph nodes
(vii) Platinum-sensitive
Table 1. Timing of HIPEC in the Course of Ovarian Cancer Treatment

<table>
<thead>
<tr>
<th>in combination with cytoreductive surgery (CRS):</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. upfront CRS and HIPEC: as first treatment for newly diagnosed ovarian cancer</td>
</tr>
<tr>
<td>2. interval CRS and HIPEC: after neo-adjuvant chemotherapy without previous resection except for biopsies</td>
</tr>
<tr>
<td>3a. consolidation CRS and HIPEC: after upfront (near) complete CRS and a full course of chemotherapy in patients with a clinically complete response</td>
</tr>
<tr>
<td>3b. secondary CRS and HIPEC: after upfront incomplete CRS followed by chemotherapy in patients with a partial response or stable disease</td>
</tr>
<tr>
<td>4. salvage CRS and HIPEC: for recurrent ovarian cancer after initial complete response to CRS and chemotherapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>without cytoreductive surgery (CRS):</th>
</tr>
</thead>
<tbody>
<tr>
<td>5. palliative HIPEC without CRS for unresectable ovarian cancer with refractory ascites</td>
</tr>
</tbody>
</table>
after CRS and adjuvant chemotherapy and complete response (CR)

<table>
<thead>
<tr>
<th></th>
<th>stage</th>
<th>median OS</th>
<th>5-yr OS</th>
<th>median DFS</th>
<th>5-yr DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRS &amp; HIPEC &amp; ACT</strong></td>
<td>III/IV</td>
<td>53.7-130m</td>
<td>42.4%</td>
<td>29.6-82.8m</td>
<td>24.2%</td>
</tr>
<tr>
<td><strong>CRS &amp; ACT</strong></td>
<td>3Cy</td>
<td>48m</td>
<td></td>
<td>14m</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12Cy</td>
<td>53m</td>
<td></td>
<td>22m</td>
<td></td>
</tr>
</tbody>
</table>

- after CRS and adjuvant chemotherapy and partial response (PR) or stable disease (SD)

<table>
<thead>
<tr>
<th>stage</th>
<th>median OS</th>
<th>5-yr OS</th>
<th>median DFS</th>
<th>5-yr DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS &amp; HIPEC &amp; ACT</td>
<td>III</td>
<td>60m</td>
<td>53.8-66.1%</td>
<td>26.4-56m</td>
</tr>
<tr>
<td>CRS &amp; ACT</td>
<td></td>
<td>33.7m</td>
<td></td>
<td>10.7m</td>
</tr>
</tbody>
</table>

THE FIRST RANDOMIZED STUDY ABOUT THE ROLE OF HIPEC IN RECURRENCE

Cytoreductive Surgery and HIPEC in Recurrent Epithelial Ovarian Cancer: A Prospective Randomized Phase III Study

J. Spiliotis, MD, PhD, E. Halkia, MD, PhD, E. Lianos, MD, N. Kalantzi, MD, A. Grivas, MD, E. Efstathiou, MD, and S. Giassas, MD
In an 8-year period (2006-2013), our team has treated 120 women suffering from advanced EOC (IIIc and IV), who recurred after initial treatment with cytoreductive or debulking surgery.

The patients were randomized into two groups, with similar demographic, clinical and therapeutic features.

On the first group of patients (group A, n = 60), cytoreductive surgery was followed by the administration of HIPEC and subsequent systemic chemotherapy.

The second group of patients (group B, n = 60) underwent cytoreductive surgery followed by systemic chemotherapy.
HIPEC TECHNIQUE

- The HIPEC protocols used were:
  - for platinum sensitive disease (n = 34)
    - cisplatin 100 mg/m² AND
    - paclitaxel 175 mg/m²
    delivered for 60 minutes at 42.5°C
  - for platinum resistant disease (n = 26)
    - doxorubicin 35 mg/m² AND
    - paclitaxel 175 mg/m² OR mitomycin 15 mg/m² delivered for 60 minutes at 42.5°C
- On 40 of the patients HIPEC was performed using the open (coliseum) technique, while on the remaining 20 the closed technique was performed.
significantly prolonged OS in the HIPEC group
HIPEC eliminated the difference in OS between platinum resistant and platinum sensitive disease...
...which is significant in the non HIPEC group

- relapse ≤6m vs. >6m, regardless of stage
  - relapse ≤6m: mean survival = 10.2m
  - relapse >6m: mean survival = 15.2m
  - p = 0.002
Moreover, HIPEC eliminated the difference in OS between stage IIIc and IV disease.
DISCUSSION

- This is the first randomized prospective study conducted over a long time period.

- More extensive research is required as to which factors modify platinum resistance in the HIPEC group.
  - doxorubicin?
  - hyperthermia?
  - epigenetics?

- It appears that the implementation of CRS & HIPEC at first recurrence is a possible option in the management of EOC.
CONCLUSIONS
Ovarian cancer management requires a multidisciplinary approach.

What should be taken into consideration in the formation of the management plan are:
- disease stage
- patient performance status
- team experience with cytoreductive surgery

CONCLUSIONS
• The role of systemic chemotherapy is equally important with that of cytoreduction.

• HIPEC appears to prolong survival, but it can only be delivered in specific centres.

• Future directions:
  • new chemotherapeutic agents
  • target therapies
  • CRS education
  • HIPEC in selected cases, after the conduct of phase III RCTs