Perspectives in clinical research for the treatment of peritoneal carcinomatosis in ovarian cancer

Marcello Deraco M.D.

Responsible

Peritoneal Malignancies
Survey of the Society of Gynecologic Oncologists (SGO)

• 45% deferred use of procedures such as:
  – splenectomy +/- distal pancreatectomy,
  – diaphragm stripping +/- full thickness resection
  – excision of grossly positive aortic LN during primary cytoreduction due to concern about morbidity and unproven efficacy

*Eisenkop, Gynecol. Oncol, 2001*
The need to resect a widespread peritoneal carcinomatosis correlates with biological aggressiveness and ↓ survival

but not significantly to justify abbreviation of the operative effort
Survey of the Society of Gynecologic Oncologists (SGO)

Eisenkop, Gynecol. Oncol, 2001
Postoperative Residual Disease Evaluation in the Locoregional Treatment of Peritoneal Surface Malignancy

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DARIO BARATTI, MD,² AND MARCELLO DERACO, MD²

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Hyperthermic Intraperitoneal Chemotherapy With and Without Cytoreductive Surgery for Epithelial Ovarian Cancer

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1 Division of Gynecologic Oncology, James Graham Brown Cancer Center, University of Louisville, Kentucky
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3 Department of Surgery, National Cancer Institute of Milan, Milan, Italy
Would you consider that HIPEC has a role at the time surgery at the following clinical time-points?
Front-line
Summary of ovarian cancer consensus statement

HIPEC was applicable at all the natural history time-points apart from platinum-resistant recurrence. This is a group that has a very poor prognosis and needs further investigation

53% of the panel of experts thought that HIPEC was applicable to use as front-line surgery
Review

“Optimal” cytoreduction for advanced epithelial ovarian cancer: A commentary

Scott M. Eisenkop a,*, Nick M. Spirios b, Wei-Chien Michael Lin a

a Women’s Cancer Center, Southern California, 4835 Van Nuys Blvd., Suite 109, Sherman Oaks, CA 91403, USA
b Women’s Cancer Center, University of Nevada School of Medicine, 3131 La Canada Ave., Suite 110, Las Vegas, NV 89101, USA

Received 8 May 2006

Table 1

<table>
<thead>
<tr>
<th>Author/Years</th>
<th>Primary focus of series</th>
<th>Number of patients</th>
<th>Residual macroscopic disease (number, %)</th>
<th>Median survival (months)b</th>
<th>Estimated 5-year survival (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osumi et al. (1990, 1994)</td>
<td>GOG 52 and 97 IV CDDP/Cytoxan vs. IV CDDP/Cytoxan</td>
<td>349</td>
<td>IIIb,c</td>
<td>None: 9 (25.4%), ≤0.1 cm: 250 (71.4%)</td>
<td>&gt;48</td>
<td>NA b</td>
</tr>
<tr>
<td>Eisenkop et al. (1992)</td>
<td>Surgical with multiple adjuvant regimens (87% Pt-based)</td>
<td>250</td>
<td>IIIICJv</td>
<td>None: 23 (11.2%), ≤1 cm: 109 (43.6%), &gt;1 cm: 113 (42.5%)</td>
<td>60</td>
<td>~59%</td>
</tr>
<tr>
<td>Maki et al. (1995)</td>
<td>Surgical with multiple adjuvant regimens (78% Pt-based)</td>
<td>455</td>
<td>IIIb,c</td>
<td>None: 45 (9.9%), ≤2 cm: 78 (17.1%), &gt;2 cm: 332 (73.0%)</td>
<td>18</td>
<td>~18%</td>
</tr>
<tr>
<td>Albert et al. (1996)</td>
<td>GOG 104P CDDP/IV Cytosan vs. IV CDDP/IV Cytosan</td>
<td>546</td>
<td>IIIb,c</td>
<td>None: 139 (25.4%), ≤0.5 cm: 254 (46.5%), ≥0.5 cm: 153 (28.0%)</td>
<td>76</td>
<td>~52%</td>
</tr>
<tr>
<td>Le et al. (1997)</td>
<td>Surgical with adjuvant Pt-based chemotherapy</td>
<td>330</td>
<td>IIIb,c</td>
<td>None: 51 (15.4%), ≤2 cm: 59 (27.8%), &gt;2 cm: 190 (57.5%)</td>
<td>21</td>
<td>~15%</td>
</tr>
<tr>
<td>Mishe et al. (1997)</td>
<td>Surgical with adjuvant Pt-based chemotherapy</td>
<td>152</td>
<td>IIIb,c, IV</td>
<td>None: 46 (30.3%), ≤2 cm: 92 (60.5%), &gt;2 cm: 14 (9.2%)</td>
<td>36</td>
<td>~34%</td>
</tr>
<tr>
<td>Ovolo et al. (2003)</td>
<td>GOG 158 IV Carboplatin vs. IV CDDP/Taxol</td>
<td>792</td>
<td>IIIb,c</td>
<td>None: 211 (35.2%), ≤1 cm: 511 (64.5%), &gt;1 cm: 75 (9.8%)</td>
<td>46</td>
<td>~38%</td>
</tr>
<tr>
<td>Eisenkop (2003)</td>
<td>Surgical with adjuvant Pt-based chemotherapy</td>
<td>408</td>
<td>IIIe</td>
<td>None: 351 (66.6%), ≤1 cm: 41 (10.0%)</td>
<td>76</td>
<td>~56%</td>
</tr>
<tr>
<td>Ven Guo et al. (2003)</td>
<td>Surgical with adjuvant Pt-based chemotherapy + radiotherapy</td>
<td>119</td>
<td>IIIb,c, IV</td>
<td>None: 22 (18.4%), ≤10 cm: 25 (21.0%), &gt;10 cm: 50 (41.0%), 101-300 cm: 26 (21.8%), 300-1000 cm: 31</td>
<td>28</td>
<td>~30%</td>
</tr>
<tr>
<td>Alettio et al. (2006)</td>
<td>Surgical with adjuvant Pt-based chemotherapy</td>
<td>194</td>
<td>IIIe</td>
<td>None: 48 (23.7%), ≤1 cm: 80 (41.3%), &gt;1 cm: 52 (26.7%)</td>
<td>22</td>
<td>~30%</td>
</tr>
<tr>
<td>Chi et al. (2006)</td>
<td>Surgical with adjuvant Pt-based chemotherapy</td>
<td>465</td>
<td>IIIe</td>
<td>None: 67 (14.7%), ≤0.5 cm: 76 (15.1%), ≤0.6-1.0 cm: 99 (21.3%), &gt;1.0-2.0 cm: 53 (11.4%), &gt;2 cm: 176 (37.8%)</td>
<td>34</td>
<td>~25%</td>
</tr>
</tbody>
</table>

a Extrapolated from inspection of survival curve.
b Not available.
• 81 cohorts of patients with stage III/IV EOC (6,885 pts)
• Statistically significant correlation between percent maximal CRS and log median survival time
• Correlation remained significant after controlling for all other variables (P < .001)
• Each 10% increase in maximal CRS -> 5.5% increase in median survival time.

Intraperitoneal chemotherapy in the first-line treatment of women with stage III epithelial ovarian cancer: a systematic review with metaanalyses

Elit L, Oliver TK, Covens A, Kwon J, Fung MF, Hirte HW, Oza AM.
Intraperitoneal chemotherapy in the first-line treatment of women with stage III epithelial ovarian cancer: a systematic review with metaanalyses

Elit L, Oliver TK, Covens A, Kwon J, Fung MF, Hirte HW, Oza AM.

5 year progression free survival
Primary cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy in the Stage III / IV epithelial ovarian cancer: a multicentric prospective phase II randomised study

Proponent: NCI of Milan Italy, 2008
Proposal 1

Stage III/IV ovarian cancer

Cytoreducible disease according to CT scan

Cytoreduction with RD<5mm

Random

HIPEC

Systemic first line chemotherapy

Systemic first line chemotherapy
Objectives 1

Primary endpoint

Progression free survival

Secondary endpoint

toxicity, morbidity, mortality

Overall survival
Elegibility criteria

- Epithelial invasive ovarian carcinoma / carcinoma of fallopian tube stage III/IV
- Absence of visceral metastasis
- Age < 75 years
- Adequate hematopoiesis
- Adequate renal function
- Performance status (ECOG) 0, 1 or 2
- Informed consent
- Cytoreducible disease according to CT scan
Sample size calculation 1

- Significance level : 20% (one-tailed)
- Power : 80%
- 5 year-progression free survival : 30%
- Survival difference : 12.6%
- Number of patients/arm: 110
Duration of study

- Duration of accrual time: 3 years
- Maximum duration of follow up: 5 years
Proposal 2

Stage III/IV ovarian cancer

Random

CRS aiming micr RD + HIPEC

Systemic first line chemotherapy

CRS aiming RD<1cm

Systemic first line chemotherapy
Objectives 2

**Primary endpoint**
- Progression free survival

**Secondary endpoint**
- Toxicity, morbidity, mortality
- Overall survival
Sample size calculation 2

- Significance level: 20% (two-tailed)
- Power: 80%
- 5 year-progression free survival: 15%
- Survival difference: 15%
- Number of patients/arm: 70
Duration of study 2

• Duration of accrual time: 3 years
• Maximum duration of follow up: 5 years
• The current evidence supporting the intraperitoneal approach in the treatment of ovarian cancer indicates the conduction of a trial testing CRS+HIPEC as front line treatment

• CRS+HIPEC is a complex procedure requiring a high expertise and a particular technical resource

• This implies that the conduction of the protocol should be done only in specialized centers
Interval Debulking
Proposal 3

Unresectable Stage III/IV ovarian cancer

Neoadjuvant sCT

Cytoreducible disease according to CT scan

Cytoreduction with RD<5mm

R

HIPEC

Systemic first line chemotherapy

Systemic first line chemotherapy

Systemic first line chemotherapy
Second Line
OVARIAN CANCER CONSENSUS

Would you consider HIPEC following completion of front-line surgery and chemotherapy

- front-line platinum-taxane therapy with no macroscopic disease at the 2nd surgery and frozen sections are negative?

  - 28% yes
  - 72% no

- patient that had received 6 cycles of front-line IP cisplatin/paclitaxel?

  - 33% yes
  - 67% no

www.peritonealworkshop2006.com
Stage III / IV epithelial ovarian cancer with macroscopic residual disease after 1st line Chemotherapy: a multicentric prospective randomised study comparing loco regional approach + systemic chemotherapy vs systemic chemotherapy alone

Interim Analysis 2006
Raspagliesi, F, Deraco M, Kusamura S, Mariani L
Study Design

Stage III/IV ovarian cancer

Surgery + 1st line CHT

Partial response + Cytoreducible disease

Complete response

RANDOM

Secondary CRS + HIPEC

2nd line CHT

Relapse within 6 mths after 1st line CHT

2nd line CHT
CTCAE v3 classification criteria (Up to 3 months from the procedure)

- Morbidity rate G3-5: 57%
- Mortality rate: 28%

Poor patient accrual
Consolidation
OVARIAN CANCER CONSENSUS

Would you consider HIPEC for consolidation following completion of front-line surgery and chemotherapy

Front-line platinum-taxane therapy when there is small volume disease found at second look surgery?

- 89% no
- 11% yes

www.peritonealworkshop2006.com
Effects of intraperitoneal hyperthermic chemotherapy in ovarian cancer

Ki Sung Ryu, a Jae Hoon Kim, b Hyun Sun Ko, c Jin Woo Kim, c Woong Shick Ahn, c Yong Gyu Park, d Seung Jo Kim, e and Joon Mo Lee, e,*

a Saint Mary’s Hospital, The Catholic University of Korea, Seoul, South Korea
b Youngdong Severance Hospital College of Medicine, Seoul, South Korea
c Department of Obstetrics and Gynecology, Kangnam Saint Mary’s Hospital, The Catholic University of Korea, Seoul, South Korea
d Department of Biostatistics, The Catholic University of Korea, Seoul, South Korea
e Comprehensive Gynecological Cancer Center, College of Medicine, Bundang CHA Hospital, Pochon CHA University, South Korea

Received 24 June 2003

Comparison of disease-free survival and survival data between the IPHC and control groups according to stage

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients</th>
<th>Median disease-free survival (months)</th>
<th>5-year disease-free survival (%)</th>
<th>Median survival (months)</th>
<th>5-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Stages Ic + II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPHC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21</td>
<td>a</td>
<td>69.6</td>
<td>a</td>
<td>78.43</td>
</tr>
<tr>
<td>No</td>
<td>22</td>
<td>a</td>
<td>77.8</td>
<td>a</td>
<td>89.64</td>
</tr>
<tr>
<td>Stage III</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPHC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>35</td>
<td>a</td>
<td>26.4</td>
<td>26.9</td>
<td>60.9</td>
</tr>
<tr>
<td>No</td>
<td>39</td>
<td>a</td>
<td>6.1</td>
<td>10.3</td>
<td>22.3</td>
</tr>
</tbody>
</table>

* Not available data because of variable clinical courses.
Treatment of ovarian cancer with paclitaxel- or carboplatin-based intraperitoneal hyperthermic chemotherapy during secondary surgery

Jeong Hoon Bae a, Joon Mo Lee a,*, Ki Sung Ryu a, Yong Seok Lee a, Yong Gyu Park b, Soo Young Hur c, Woong Shik Ahn a,d, Seong Eun Namkoong a

Chemotherapy: number of cycles and regimen

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Number of cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control group</td>
</tr>
<tr>
<td></td>
<td>N=29</td>
</tr>
<tr>
<td>Combination chemotherapy</td>
<td></td>
</tr>
<tr>
<td>1. Platinumb – taxane c</td>
<td>158</td>
</tr>
<tr>
<td>2. Platinum–cyclophosphamide</td>
<td>92</td>
</tr>
<tr>
<td>3. Platinum–topotecan</td>
<td>8</td>
</tr>
<tr>
<td>4. CAP d</td>
<td>36</td>
</tr>
<tr>
<td>5. Miscellaneous</td>
<td>40</td>
</tr>
</tbody>
</table>

Single chemotherapy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Number of cycles</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Topotecan</td>
<td>36</td>
<td>21</td>
</tr>
<tr>
<td>2. Taxane</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total number of cycles</td>
<td>371</td>
<td>524</td>
</tr>
</tbody>
</table>

Fig. 3. Overall survival in stage III ovarian cancer.


*Control vs. IPHC, b carboplatin or cisplatin, c paclitaxel or docetaxel, d cyclophosphamide/doxorubicin/cisplatin. Abbreviation: SD, standard deviation.
Recurrence
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.
Cytoreduction combined with intraperitoneal hyperthermic perfusion chemotherapy in advanced/recurrent ovarian cancer patients: The experience of National Cancer Institute of Milan

F. Raspagliesi a, S. Kusamura ad, J.C. Campos Torres d, G.A. de Souza d, A. Ditto a, F. Zanaboni a, R. Younan b, D. Baratti b, L. Mariani c, B. Laterza c, M. Deraco a.

a Department of Surgery—Gynaecology Unit, National Cancer Institute of Milan, Milan, Italy
b Department of Surgery—Melanoma and Sarcoma Unit, National Cancer Institute of Milan, Via Venerini 1, 20133 Milan, Italy
c Department of Statistics and Biometry, National Cancer Institute of Milan, Milan, Italy
d Department of Obstetrics and Gynaecology, School of Medical Science, State University of Campinas UNICAMP, Campinas, SP, Brazil

Accepted 2 March 2006

Overall

Median: 32 months

Progression free

Median: 11 months
Secondary Cytoreductive Surgery in Patients with Platinum-Sensitive Recurrent Ovarian Cancer

Pierluigi Benedetti Panici, MD, Antonio De Vivo, MD, Filippo Bellati, MD, Natalina Manci, MD, Giorgia Perniola, MD, Stefano Basile, MD, Ludovico Muzii, MD, and Roberto Angioli, MD

Department of Obstetrics and Gynecology, University of Rome “La Sapienza,” Via del Policlinico, 555, 00161 Rome, Italy

Department of Obstetrics and Gynecology, University Campus Bio-Medico of Roma, Via Longoni, 83, 00100 Rome, Italy

FIG. 1. Overall survival of patients who underwent secondary surgical cytoreduction (n = 47).

FIG. 2. (A) Cumulative survival determined by residual tumor (RT) at secondary surgical cytoreduction (SCR). Solid line: RT = 0; dashed line RT > 0. (B) Cumulative survival determined by CA-125 at SCR. Solid line CA-125 < 35 UI/mL; dashed line CA-125 > 35 UI/mL.
## Secondary CRS in Platin responder patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N°</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Patients</td>
<td>25</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>2</td>
</tr>
<tr>
<td>IIIa</td>
<td>0</td>
</tr>
<tr>
<td>IIIb</td>
<td>4</td>
</tr>
<tr>
<td>IIIc</td>
<td>17</td>
</tr>
<tr>
<td>IV</td>
<td>2</td>
</tr>
<tr>
<td>BMI mean (range)</td>
<td>23.7 (18-31.6)</td>
</tr>
<tr>
<td>Età mean (anni) (range)</td>
<td>52 (43-63)</td>
</tr>
<tr>
<td>PS ECOG mean (range)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Ca125 mean (UI/ml) (range)</td>
<td>134.4 (8.7-434)</td>
</tr>
<tr>
<td>PFI mean (mesi) (range)</td>
<td>26 (7-67)**</td>
</tr>
<tr>
<td>Recurrence</td>
<td></td>
</tr>
<tr>
<td>1st</td>
<td>24 (96 %)</td>
</tr>
<tr>
<td>2nd</td>
<td>1 (4 %)</td>
</tr>
</tbody>
</table>

CRS+HIPEC (Oxaliplatin)
Outcomes

Median follow up
13 mts (1-35)

6 pts (24%) recurred

TtP
9 mts (1-31)

DFS
12.5 mts (7-17)
Platin sensitive Recurrent ovarian cancer

Cytoreducible disease according to CT scan

Cytoreduction with RD<5mm

Random

HIPEC

Systemic first line chemotherapy

Systemic first line chemotherapy

Proposal 4