Treatment of surgically resectable colorectal peritoneal metastases

Marcello Deraco M.D.

Responsible Peritoneal Surface Malignancies Program
Liver Resection vs Peritoneal Resection (CRS+HIPEC)

A Simple Tumor Load-Based Nomogram for Surgery in Patients with Colorectal Liver and Peritoneal Metastases

Dominique Elias, MD, PhD¹, Matthieu Faron, MD³, Diane Goëréc, MD, PhD¹, Frédéric Dumont, MD¹, Charles Honoré, MD¹, Valérie Boige, MD², David Malka, MD², and Michel Ducreux, MD, PhD²

¹Department of Oncologic Surgery, Gustave Roussy, Villejuif, France; ²Department of Medical Oncology, Gustave Roussy, Villejuif, France; ³Department of Statistics, Gustave Roussy, Villejuif, France

Livermets | Peritonealmets
--- | ---
Incidences | 25% | 10%
Resectability | ca. 50% | ca. 25%
Postoperative Morbidity (Grade 3 u. 4) | Up to 20% | Up to 30%
Mortality | < 5% | < 5%
5 Years SR | 30-50% | 30-50%
Level of Evidence for Resection | 3 | 2a

CRS/HIPEC (Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy) for treatment of peritoneal carcinosis

Epidemiology

sCT

New Treatments

Results

Liver M+ Peritoneal M+

Patient Selection

Conclusion

EPIDEMIOLOGY

Marcello Deraco M.D. Responsible Peritoneal Surface Malignancies Program
CRS/HIPEC (Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy) for treatment of peritoneal carcinosis

- Epidemiology
- sCT
- New Treatments
- Results
- Liver M+ Peritoneal M+
- Patient Selection
- Conclusion

sCT

Marcello Deraco M.D. Responsible Peritoneal Surface Malignancies Program
Progress in treatments for colorectal cancer peritoneal metastases during the years 2010–2015. A systematic review

Dario Baratti\textsuperscript{a}, Shigeki Kusamura\textsuperscript{a}, Filippo Pietrantonio\textsuperscript{b}, Marcello Guaglio\textsuperscript{a}, Monica Niger\textsuperscript{b}, Marcello Deraco\textsuperscript{a,\star}

\textsuperscript{a} Peritoneal Malignancy Program, Fondazione IRCCS Istituto Nazionale Tumori, via Venezian, 1 20133 Milano, Italy
\textsuperscript{b} Medical Oncology Department, Fondazione IRCCS Istituto Nazionale Tumori, via Venezian, 1 20133 Milano, Italy

**Selected series of systemic chemotherapy for CRC PM**

<table>
<thead>
<tr>
<th>Author (ref.)</th>
<th>Study design</th>
<th>Setting</th>
<th>Patients (no.)</th>
<th>Systemic treatment</th>
<th>Median survival (months)</th>
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<td>Prospective surgical</td>
<td>Treated by complete CRS, or incomplete (n = 9) CRS</td>
<td>50</td>
<td>5FU/FA + OXL or IRI ± BA</td>
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<td>Huang et al. (2014a)</td>
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<td>5FU/FA + OXL or IRI + BA</td>
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<td>50</td>
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<td>Chua et al. (2011)</td>
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<td>5FU/FA + OXL or IRI + OXL; OXL + IRI; IRI alone</td>
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<td>PSA, III-IV</td>
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<td>Overall series</td>
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<td>Pelz et al. (2010)</td>
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<td>PSA, III-IV</td>
<td>19</td>
<td>Best supportive care</td>
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<td>5FU/FA</td>
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<td>20</td>
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<td>108</td>
<td>All treatments</td>
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<td>Franko et al. (2010)</td>
<td>Control arm of non-RCT</td>
<td>Potentially amenable to complete CRS</td>
<td>38</td>
<td>5FU/FA + OXL or IRI ± BA</td>
<td>16.8</td>
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</table>
Role of Chemotherapy in Peritoneal Carcinomatosis in Metastatic Colorectal Cancer

Jan Franko • Charles D. Goldman • Kiran K. Turaga

Only 2% of all patients had PC
CRS/HIPEC (Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy) for treatment of peritoneal carcinosis

Epidemiology
sCT
New Treatments
Results
Liver M+ Peritoneal M+
Patient Selection
Conclusion

NEW TREATMENTS

Marcello Deraco M.D. Responsible Peritoneal Surface Malignancies Program
• Peritoneum is often the only site of CRC metastases;

• Results with sCT are of difficult interpretation and limited benefit;

• Surgery is the standard treatment for solid tumors;

• Surgery when feasible is the standard treatment also for metastases (Liver Metastases);

• Excellent results with Surgery in other PSM (Mesothelioma, Pseudomyxoma and Serous Papillary Peritoneal Carcinoma)
The Concept of Cytoreductive Surgery with Peritonectomy Procedures

• Means a complete removal of all macroscopic tumor in the peritoneal cavity;

• It could require Peritonectomy Procedures eventually associated with intestinal and/or organ resection

<table>
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<tr>
<th>Abdominal regions</th>
<th>Peritonectomies</th>
<th>Visceral resections</th>
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<tr>
<td>Right upper</td>
<td>Right sub-phrenic peritonectomy, Glisson’s capsule dissection</td>
<td>Splenectomy, appendectomy, right colectomy</td>
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<tr>
<td>Left upper</td>
<td>Left sub-phrenic peritonectomy</td>
<td>Gastric antrectomy, cholecystectomy</td>
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<tr>
<td>Antero-lateral</td>
<td>Stripping of paracolic gutters, Greater omentectomy</td>
<td>Sigmoidectomy, hysterectomy, bilateral adnexectomy</td>
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<td>Sub-hepatic</td>
<td>Lesser omentectomy, stripping of the omental bursa</td>
<td>Total gastrectomy</td>
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<tr>
<td>Pelvis</td>
<td>Pelvic peritonectomy</td>
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</table>
Cytoreductive Surgery PC from Mucinous Rectal Cancer
Cytoreductive Surgery PC from Mucinous Rectal Cancer
Cytoreductive Surgery PC from Mucinous Rectal Cancer
Intravenous Administration

Intraperitoneal Administration

Pestieau SR, J Surg Oncol 2001

HIPEC (Hyperthermic Intra Peritoneal Chemotherapy: Rationale

Temperature: 42.5°C
Mean flow: 700ml/min; Duration: 60-90 min
The American Society of Peritoneal Surface Malignancies Evaluation of HIPEC with Mitomycin C Versus Oxaliplatin in 539 Patients with Colon Cancer Undergoing a Complete Cytoreductive Surgery

ARANCIA PRADA-VILLALVERDE, MD, 1 JESUS ESQUIVEL, MD, 2* ANDREW M. LOWY, MD, 3 MAURIE MARKMAN, MD, 4 TERENCE CHUA, MD, 3 JOERG PELZ, MD, 6 DARIO BARATTI, MD, 7 JOEL M. BAUMGARTNER, MD, 3 RICHARD BERRI, MD, 8 PEDRO BRETCHA-BOIX, MD, 9 MARCELLO DERACO, MD, 7 GUILLERMO FLORES-AYALA, MD, 10 OLIVIER GLEHEN, MD, 11 ALBERTO GOMEZ-PORTILLA, MD, 12 SANTIAGO GONZÁLEZ-MORENO, MD, 13 MARTIN GOODMAN, MD, 14 EVGENIA HALKIA, MD, 15 SHIGEKI KUSUMURA, MD, 7 MECKER MOLLER, MD, 16 GUILLAUME PASSOT, MD, 11 MARC POCARD, MD, 17 GEORGE SALTI, MD, 18 ARMANDO SARDI, MD, 19 MAHESWARI SENTHIL, MD, 20 JOHN SPILIOTIS, MD, 15 JUAN TORRES-MELERO, MD, 21 KIRAN TURAGA, MD, 22 AND RICHARD TROUT, PhD 23

Fig. 2. Survival analysis of 539 patients with a complete cytoreductive surgery comparing HIPEC with MMC vs. Oxaliplatin.

Fig. 3. Survival analysis of 303 patients with a PSDSS I or II and a complete cytoreductive surgery comparing HIPEC with MMC vs. Oxaliplatin.

TABLE IV. Analysis of Agent Comparison with Respect to Survival* for Patients with Complete Cytoreductive Surgery (CC0/CC1) by PSDSS Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PSDSS group 1/2</th>
<th>PSDSS group 3/4</th>
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<td>Agent</td>
<td>N</td>
<td>Median survival (95CI%)</td>
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<tr>
<td>Oxaliplatin</td>
<td>71</td>
<td>28.2 (23.7–NR)</td>
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<td>Mitomycin C</td>
<td>232</td>
<td>54.3 (37.5–76.4)</td>
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</table>
Should the Treatment of Peritoneal Carcinomatosis by Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy Still be Regarded as a Highly Morbid Procedure?

A Systematic Review of Morbidity and Mortality

Terence C. Chua, BScMed (Hons), Tristan D. Yan, BSc (Med), MBBS, PhD, Akshat Saxena, BMedSc, and David L. Morris, MD, PhD

**Mortality:**
Mean 2.9, Range 0-17

**Grade III/IV morbidity:**
Mean 28.8, Range 0-42

TC Chua, Annals of Surgery 2009
CRS/HIPEC (Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy) for treatment of peritoneal carcinosis

RESULTS

Epidemiology  sCT  New Treatments  Results  Liver M+ Peritoneal M+  Patient Selection  Conclusion

Marcello Deraco M.D. Responsible Peritoneal Surface Malignancies Program
• 11,124 patients with CRC
• Stockholm County
• Study period: 1995–2007
• F-U until 2010
• Global incidence PM (sync/met): 924 patients (8.3%)
• PM as only site of metastases: 535 (4.8%)
• Cumulative incidence of metachronous PC: 4.2%
Progress in treatments for colorectal cancer peritoneal metastases during the years 2010–2015. A systematic review

Dario Baratti\textsuperscript{a}, Shigeki Kusamura\textsuperscript{a}, Filippo Pietrantonio\textsuperscript{b}, Marcello Guagliio\textsuperscript{a}, Monica Niger\textsuperscript{b}, Marcello Deraco\textsuperscript{a,\ast}

\textsuperscript{a} Peritoneal Malignancy Program, Fondazione IRCCS Istituto Nazionale Tumori, via Venezian, 1 20133 Milano, Italy
\textsuperscript{b} Medical Oncology Department, Fondazione IRCCS Istituto Nazionale Tumori, via Venezian, 1 20133 Milano, Italy

Main characteristics of 19 cohort studies of CRS/HIPEC

<table>
<thead>
<tr>
<th>Center (ref.)</th>
<th>Study period</th>
<th>Pts (no.)</th>
<th>CRS</th>
<th>HIPEC</th>
<th>Follow-up (mos.)</th>
<th>Median OS (mos)</th>
<th>5-year OS (%)</th>
<th>Major morb. (%)</th>
<th>Death (%)</th>
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</thead>
<tbody>
<tr>
<td>Eindhoven, ND (Simkens et al., 2015)</td>
<td>2007–13</td>
<td>133</td>
<td>96% CCR 0</td>
<td>MMC</td>
<td>22.9</td>
<td>27.0</td>
<td>NS</td>
<td>24.8</td>
<td>0.8</td>
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<tr>
<td>Wuhan, CH (Huang et al., 2014)</td>
<td>2005–13</td>
<td>60</td>
<td>53% CCR 0%/1</td>
<td>MMC + CDDP</td>
<td>29.2</td>
<td>16.0</td>
<td>22.0</td>
<td>30.0</td>
<td>0</td>
</tr>
<tr>
<td>Villejuiff, FR (Elis et al., 2014)</td>
<td>2000–09</td>
<td>139</td>
<td>100% CCR 0%/1</td>
<td>OXL ± IRI</td>
<td>NR</td>
<td>39.0</td>
<td>39.0</td>
<td>21.6</td>
<td>5.8</td>
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<tr>
<td>Uppsala, SW (Cashin et al., 2014)</td>
<td>2004–10</td>
<td>67</td>
<td>83.6% CCR 0</td>
<td>MMC or OXL±IRI</td>
<td>NR</td>
<td>28.0</td>
<td>NR</td>
<td>39.0</td>
<td>4.0</td>
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<td>Ghent, BE (Ceelen et al., 2014)</td>
<td>2002–12</td>
<td>166</td>
<td>87.3% CCR 0%/1</td>
<td>MMC or OXL</td>
<td>18</td>
<td>27.0</td>
<td>NR</td>
<td>34.9</td>
<td>2.4</td>
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<td>Lyon, FR (Passot et al., 2014)</td>
<td>2005–12</td>
<td>115</td>
<td>100% CCR 0%/1</td>
<td>MMC or OXL (n = 91)(^2)</td>
<td>18.6</td>
<td>36.0</td>
<td>NR</td>
<td>NR</td>
<td>4.0</td>
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<td>Belgrade, SRB (Nikolic et al., 2014)</td>
<td>2005–12</td>
<td>61</td>
<td>NR</td>
<td>OXL</td>
<td>22</td>
<td>51.0</td>
<td>50.5(^3)</td>
<td>NR</td>
<td>NS</td>
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<tr>
<td>Wake-Forest, SC (Blackham et al., 2014)</td>
<td>1991–10</td>
<td>93</td>
<td>100% CCR 0</td>
<td>MMC or OXL</td>
<td>89</td>
<td>33.6</td>
<td>26.0</td>
<td>23.0</td>
<td>5.4</td>
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<tr>
<td>Calgary, CAN (Rivard et al., 2014)</td>
<td>2003–11</td>
<td>68</td>
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<td>MMC + EPIC or OXL</td>
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<td>30.8</td>
<td>43.0(^4)</td>
<td>23.5</td>
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<td>Milan, IT (Baratti et al., 2014)</td>
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<td>101</td>
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<td>MMC + CDDP</td>
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<td>43.2</td>
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<td>3.0</td>
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<td>Candido, IT (Robella et al., 2013)</td>
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<td>50</td>
<td>54% CCR 0%/1</td>
<td>MMC or OXL or MMC+CDDP</td>
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<td>48.1 (15)(^5)</td>
<td>NR</td>
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<td>660</td>
<td>80% CCR 0(^1)</td>
<td>MMC or OXL</td>
<td>41(^1)</td>
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<td>31.0</td>
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<td>3.3(^1)</td>
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<td>23.4</td>
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<td>131</td>
<td>86.1% CCR 0%/1</td>
<td>MMC</td>
<td>27.0</td>
<td>51.0</td>
<td>40.0</td>
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<td>Nice, FR (Benizri et al., 2012)</td>
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<td>100% CCR 0%/1</td>
<td>MMC + OXL±IRI</td>
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<td>36.3</td>
<td>33.0</td>
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<td>3.8</td>
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<td>Nimes, FR (Hompes et al., 2012)</td>
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<td>100% CCR 0%/1</td>
<td>OXL</td>
<td>22.7</td>
<td>NR</td>
<td>88.7(^3)</td>
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<td>Italy(^\prime) (Cavaliere et al., 2011)</td>
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<td>21.0</td>
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<td>MMC ± EPIC (5-FU)</td>
<td>20.0</td>
<td>38.0</td>
<td>48.0(^4)</td>
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<td>NR</td>
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<td>France(^\prime) (Elis et al., 2010)</td>
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<td>30.1</td>
<td>27.0</td>
<td>33.8</td>
<td>3.3</td>
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Critical Reviews in Oncology/Hematology 100 (2016) 209–222
Dutch HIPEC protocol

Study Period: 1995-2012

660 pts PM-CRC

Overall MS: 33 months

Median PFS: 15 months

Three years survival: 46%

Five-year survival: 31%
• Retrospective-cohort, multicentric French study (1990 and 2007)
• 523 patients
• 23 centers
• Overall MS: 30.1 months

Median overall survival was 30.1 months,
Progress in treatments for colorectal cancer peritoneal metastases during the years 2010–2015. A systematic review

Dario Baratti a, Shigeaki Kusamura a, Filippo Pietrantonio b, Marcello Guaglio a, Monica Niger b, Marcello Deraco a, *

a Peritoneal Malignancy Program, Fondazione IRCCS Istituto Nazionale Tumori, via Venezian, 1 20133 Milano, Italy
b Medical Oncology Department, Fondazione IRCCS Istituto Nazionale Tumori, via Venezian, 1 20133 Milano, Italy

Main characteristics of 13 comparative studies of CRS/HIPEC

<table>
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<th>Center (ref.)</th>
<th>Study period</th>
<th>Pts (no.)</th>
<th>CRS</th>
<th>Study design</th>
<th>Factors of comparison</th>
<th>F-up</th>
<th>Overall survival</th>
<th>Major morb. (%)</th>
<th>Mort (%)</th>
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<tr>
<td>Villejuiff, FR (Goéré et al., 2015)</td>
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<td>139</td>
<td>100%</td>
<td>CRS</td>
<td>Controlled</td>
<td>HIPEC or EPIC</td>
<td>60a</td>
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<td>52.0 1</td>
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<td>International (Prada-Villaverde et al., 2014)</td>
<td>85–12</td>
<td>418</td>
<td>94.2%</td>
<td>CRS, HIPEC</td>
<td>Controlled</td>
<td>MMC-based HIPEC</td>
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<td>32.7</td>
<td>7.0 1</td>
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<td>International (Esquivel et al., 2014)</td>
<td>85–12</td>
<td>609</td>
<td>82.3%</td>
<td>CRS, HIPEC</td>
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<td>CRX, HIPEC</td>
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<td>10.0 1</td>
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<td>PSDSS stage I CRS, HIPEC</td>
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<td>45.0 1</td>
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<td>No CRS, HIPEC</td>
<td>75</td>
<td>86.0</td>
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<td>PSDSS stage II CRS, HIPEC</td>
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<td>43.0</td>
<td>–</td>
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<td></td>
<td></td>
<td></td>
<td>No CRS, HIPEC</td>
<td>317</td>
<td>19.0 1</td>
<td>–</td>
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<td></td>
<td>PSDSS stage III CRS, HIPEC</td>
<td>135</td>
<td>28.0</td>
<td>–</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>No CRS, HIPEC</td>
<td>132</td>
<td>6.0 1</td>
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</tr>
<tr>
<td>Nieuwegein (van Oudheusden et al., 2014)</td>
<td>05–13</td>
<td>36</td>
<td>97.2%</td>
<td>CRS, HIPEC</td>
<td>Controlled</td>
<td>Synchr. PM; acute present.</td>
<td>16.2 2</td>
<td>32.1</td>
<td>NS</td>
</tr>
<tr>
<td>Eindhoven, NL</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Amsterdam, NL (Kuijpers et al., 2014)</td>
<td>04–12</td>
<td>113</td>
<td>97.3%</td>
<td>CRS</td>
<td>Matched</td>
<td>Synchr. PM; elective present</td>
<td>N+ primary CRC; periop. sCT</td>
<td>36.1</td>
<td>–</td>
</tr>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>15.0</td>
<td>–</td>
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<tr>
<td>Amsterdam, NL</td>
<td>04–06</td>
<td>39</td>
<td>100%</td>
<td>CRS</td>
<td>Controlled</td>
<td>MMC-based HIPEC</td>
<td>33</td>
<td>37.1</td>
<td>54.0 2</td>
</tr>
<tr>
<td>Leuven, BE (Hompes et al., 2014)</td>
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<tr>
<td>Villejuiff, FR (Braam et al., 2013)</td>
<td>05–12</td>
<td>52</td>
<td>100%</td>
<td>CRS</td>
<td>Matched</td>
<td>Synchr. PM; early HIPEC</td>
<td>49 3</td>
<td>18.0</td>
<td>41.1 2</td>
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<td></td>
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<td></td>
<td>10.0</td>
<td>–</td>
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<tr>
<td>Eindhoven, NL (Braam et al., 2013)</td>
<td>05–12</td>
<td>52</td>
<td>100%</td>
<td>CRS</td>
<td>Matched</td>
<td>Synchr. PM; delayed HIPEC</td>
<td>36 3</td>
<td>32.0</td>
<td>26.0</td>
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<tr>
<td>Uppsala, SW (Cashin et al., 2012c)</td>
<td>06–10</td>
<td>69</td>
<td>–</td>
<td>Controlled</td>
<td>HIPEC</td>
<td>17</td>
<td>49.0</td>
<td>43.0</td>
<td>–</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>10.0</td>
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<td>Uppsala, SW (Cashin et al., 2012b)</td>
<td>05–08</td>
<td>57</td>
<td>100%</td>
<td>CRS</td>
<td>Matched</td>
<td>Synchr. PM; delayed HIPEC</td>
<td>49 3</td>
<td>34.0</td>
<td>40.0</td>
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<td></td>
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<td></td>
<td></td>
<td>20.0</td>
<td>–</td>
</tr>
<tr>
<td>Sidney, AU (Chua et al., 2013)</td>
<td>06–11</td>
<td>16</td>
<td>100%</td>
<td>CRS</td>
<td>Matched</td>
<td>Synchr. PM; delayed HIPEC</td>
<td>36 3</td>
<td>32.0</td>
<td>26.0</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>10.0</td>
<td>–</td>
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<tr>
<td>Villejuiff (Anon, 2016d)</td>
<td>08–07</td>
<td>43</td>
<td>74.4%</td>
<td>CRS</td>
<td>Controlled</td>
<td>HIPEC</td>
<td>38 3</td>
<td>36.5</td>
<td>–</td>
</tr>
<tr>
<td>Montpellier, FR</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pittsburgh, PA (Franko et al., 2010)</td>
<td>01–07</td>
<td>103</td>
<td>97.1%</td>
<td>CRS</td>
<td>Controlled</td>
<td>HIPEC</td>
<td>47.0</td>
<td>42.4</td>
<td>52.4</td>
</tr>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>16.8 3</td>
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</tr>
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</table>

Critical Reviews in Oncology/Hematology 100 (2016) 209–222
## Table 3: Overall Survival Data from Prospectively Randomized Trials and Case Control Studies in Patients With PC of Colorectal Origin After CRS and HIPEC With/Without EPIC

<table>
<thead>
<tr>
<th>Author, Year of Publication</th>
<th>n</th>
<th>Therapy</th>
<th>Median Survival (Month)</th>
<th>Survival Rates (%), Years</th>
<th>Median DSS (Month)</th>
<th>Median PFS (Month)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospectively Randomized Studies (Evidence Level Ib)(^7)</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Verwaal et al 2003/08(^{24,25})</td>
<td>54</td>
<td>HIPEC</td>
<td>22.3(^a)</td>
<td>46(^b)</td>
<td>22.2</td>
<td>12.6</td>
</tr>
<tr>
<td></td>
<td>51</td>
<td>Control</td>
<td>12.6</td>
<td>-</td>
<td>12.6</td>
<td>7.7</td>
</tr>
<tr>
<td><strong>Case Control Studies (Evidence Level IIIa)(^7)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Elias et al 2009(^{23})</td>
<td>48</td>
<td>HIPEC</td>
<td>62.7(^a)</td>
<td>81</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>Control</td>
<td>23.9</td>
<td>65</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Franko et al 2010(^{21})</td>
<td>67</td>
<td>HIPEC</td>
<td>34.7(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>Control</td>
<td>16.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chua et al 2011(^{22})</td>
<td>110</td>
<td>HIPEC/EPIC</td>
<td>38.0(^a)</td>
<td>92</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>184</td>
<td>Control</td>
<td>9.0</td>
<td>45</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>
Milan NCI: Case matched controlled study comparing CRS vs. CRS + HIPEC in peritoneal metastasis from CRC

- **Aim**: to compare CRS vs. CRS+HIPEC
- **Manual matching using PSDSS**
- **Rate 2:1**
- **N=54 cases of PM from CRC (36 CRS+HIPEC vs. 18 CRS)**

Unpublished Data

Log rank: pvalue=0.042

Log rank: pvalue= non significant
Phase III RCT: Role of HIPEC after CCR0/1 for PC from CRC

Non-randomized patients (n = 131)
- PCI>25: 58
- No macroscopic peritoneal carcinomatosis: 25
- Non resectable: 11
- Liver metastasis: 10
- General contra-indication: 8
- Consent withdrawal: 5
- R2 > 1 mm: 4
- Others: 10

Screened patients (n = 396)

Randomized patients (n = 265)

No systemic chemotherapy received (n = 7)

HIPEC (n = 133)
- Death (n = 4)
  - D30 – Massive pneumonia
  - D30 – Peritoneal hemorrhage
  - D60 – Pulmonary embolism
  - D60 – Sepsis shock

NO HIPEC (n = 132)
- Death (n = 3)
  - D30 – Sepsis shock
  - D30 – Multvisceral failure
  - D60 – Acute respiratory distress

Intent-to-treat population
Morbidity / mortality analysis
Day 30 after surgery

No systemic chemotherapy received (n = 5)

Morbidity / mortality analysis
Day 60 after surgery

33% of non randomized

ACCORD 15/0608 – Prodig 7
CLINICAL SCENARIOS

Metacronous PM-CRC:

• Favorable Prognostic Factors → sCT > CRS/HIPEC
• Unfavorable Prognostic Factors → sCT

Syncronous PM-CRC

• Limited Disease → CRS+HIPEC+sCT
• Extensive → Emergency Managment Only > sCT ± CRS/HIPEC according to Response

CRC with High Risk Probability to develop a PM

• pT4
• Obclusion
• Perforation
• Ovarian M+ Resectable
• Ctm+

Consider for S.L. after first line treatment ± CRS/HIPEC

- 27,632 pts with CRC
- 5638 (20%) with M+
- Patients with PM: 34% of all M+
- Pts with PM alone: 45% of PM
Netherlands Cancer Registry
Study Period: 2005-2012
4430 patients with synchronous PM
297 (6.4%): underwent CRS+HIPEC

MS (months):
• CRS+HIPEC: 32.3
• Palliative chemotherapy: 12.6,
• Palliative surgery: 6.1
• Best supportive care: 1.5
CLINICAL SCENARIOS

Metacronous PM-CRC:
- Favorable Prognostic Factors
  - sCT > CRS/HIPEC
- Unfavorable Prognostic Factors
  - sCT

Synchronous PM-CRC
- Limited Disease
  - CRS+HIPEC+sCT
  - CRS + sCT and Consider for S.L. after first line treatment ± CRS/HIPEC
- Extensive
  - Emergency Management Only > sCT ± CRS/HIPEC according to Response

CRC with High Risk Probability to develop a PM
- pT4
- Obclusion
- Perforation
- Ovarian M+ Resectable
- Ctm+
  - Consider for S.L. after first line treatment ± CRS/HIPEC
Progress in treatments for colorectal cancer peritoneal metastases during the years 2010–2015. A systematic review

Dario Baratti\(^a\), Shigeki Kusamura\(^a\), Filippo Pietrantonio\(^b\), Marcello Guaglio\(^a\), Monica Niger\(^b\), Marcello Deraco\(^a,\)\(^*\)

\(^a\) Peritoneal Malignancy Program, Fondazione IRCCS Istituto Nazionale Tumori, via Venezian, 1 20133 Milano, Italy  
\(^b\) Medical Oncology Department, Fondazione IRCCS Istituto Nazionale Tumori, via Venezian, 1 20133 Milano, Italy

### Main characteristics of 6 studies of adjuvant intraperitoneal chemotherapy

<table>
<thead>
<tr>
<th>Author (ref.)</th>
<th>Study period</th>
<th>Pts (no.)</th>
<th>Eligibility</th>
<th>Study design</th>
<th>Adjuvant intraperitoneal chemotherapy</th>
<th>F-up median (mos.)</th>
<th>Overall survival</th>
<th>Peritoneal relapse</th>
<th>Major morbidity</th>
<th>Mort.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lygidakos et al. (2010)</td>
<td>85-06</td>
<td>31 21</td>
<td>Rectal cancer (N_+), neurovascular involvement</td>
<td>Prosp. series</td>
<td>Lap. HIPEC (\times 3) day 22, 47, 730 (5FU/OX/IRI)</td>
<td>NR</td>
<td>100(^1)</td>
<td>3.0(^2)</td>
<td>0(^2)</td>
<td>0</td>
</tr>
<tr>
<td>Noura et al. (2011)</td>
<td>85-06</td>
<td>31 21</td>
<td>Positive peritoneal washing cytology</td>
<td>Controlled</td>
<td>EPIC (MMC) day 1</td>
<td>83.1</td>
<td>88.0(^3)</td>
<td>0.0001</td>
<td>54.3(^5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Tentes et al. (2011)</td>
<td>99-04</td>
<td>67</td>
<td>T3/T4</td>
<td>Controlled</td>
<td>EPIC (5-FU) day 1-5</td>
<td>28.0</td>
<td>40.1(^3)</td>
<td>0.094(^3)</td>
<td>9.5(^4)</td>
<td>0.027(^7)</td>
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<tr>
<td>Virzì et al. (2013)</td>
<td>06-10</td>
<td>12</td>
<td>T4, ovarian/perit M, positive peritoneal washing cytology</td>
<td>Prosp. series</td>
<td>HIPEC (MMC/OX)</td>
<td>17.0</td>
<td>40.5(^3)</td>
<td>0.011</td>
<td>28.0</td>
<td>0.009</td>
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<tr>
<td>Sammartino et al. (2012)</td>
<td>06-08</td>
<td>25</td>
<td>T3/T4, mucinous</td>
<td>Matched</td>
<td>HIPEC (OX)</td>
<td>NR</td>
<td>59.5(^6)</td>
<td>0.04</td>
<td>4.0</td>
<td>&lt;0.03</td>
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<tr>
<td>Sloothaak et al. (2014b)</td>
<td>11-12</td>
<td>10</td>
<td>T4, ovarian/perit M positive peritoneal washing cytology Perforation/obstruct</td>
<td>Prosp. series</td>
<td>HIPEC (MMC)</td>
<td>13.0</td>
<td>52.0(^9)</td>
<td>28.0</td>
<td>8.0</td>
<td>0</td>
</tr>
</tbody>
</table>
Pilot study of adjuvant hyperthermic intraperitoneal chemotherapy in patients with colorectal cancer at high risk for the development of peritoneal metastases

Salvatore Virzi¹, Domenico Iusco¹, Dario Baratti², Serena Bonomi¹, Antonio Grassi¹, Shigeki Kusamura², and Marcello Deraco²

Median follow-up 41.2 ms. (95% CI 29.4-52.9)

OS; P value = 0.04 (Log-rank test)

PFS; P value = 0.01 (Log-rank test)
Trial Comparing Simple Follow-up to Exploratory Laparotomy Plus "in Principle" (Hyperthermic Intraperitoneal Chemotherapy) HIPEC in Colorectal Patients (ProphyloCHIP)

This study is currently recruiting participants.
Verified October 2010 by Institut Gustave Roussy

ClinicalTrials.gov Identifier: NCT01226394

- High-Risk Patients
- Adjuvant systemic chemotherapy
- Re-Do with HIPEC
- Follow-up
- No Re-Do
- Observation

ClinicalTrials.gov
A service of the U.S. National Institutes of Health
CLINICAL SCENARIOS

Metacronous PM-CRC:
• Favorable Prognostic Factors
  \[ \text{sCT} > \text{CRS/HIPEC} \]
• Unfavorable Prognostic Factors
  \[ \text{sCT} \]

Syncronous PM-CRC
• Limited Disease
  \[ \text{CRS+HIPEC+sCT} \]
  \[ \text{CRS + sCT and Consider for S.L. after first line treatment ± CRS/HIPEC} \]
• Extensive
  \[ \text{Emergency Management Only > sCT ± CRS/HIPEC according to Response} \]

CRC with High Risk Probability to develop a PM
• pT4
• Obclusion
• Perforation
• Ovarian M+ Resectable
• Ctm+
  \[ \text{Consider for S.L. after first line treatment ± CRS/HIPEC} \]
CRS/HIPEC (Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy) for treatment of peritoneal carcinosis

Epidemiology  sCT  New Treatments  Results  Liver M+ Peritoneal M+  Patient Selection  Conclusion

Liver METS + Peritoneal METS

Marcello Deraco M.D. Responsible Peritoneal Surface Malignancies Program
LIVER METS + PERITONEAL METS
Patients (1995 and 2010):
• liver metastases (LM)=287
• peritoneal metastasis (PM)=119
• LM + PM= 37

Treatment:
• Neoadjuvant sCT>Surgery>HIPEC in the PM group

Results (5-year OS):
• LM=38.5
• PM=36.5
• LM+PM=26.4
Curative treatment for patients with synchronous liver metastases and peritoneal carcinomatosis of advanced colorectal cancer (aCRC): A multicenter study of the French Association of Surgery

Rea Io Dico: Hôpital Saint-Antoine, APHP, Paris

Patients: 146 (1993 to 2015)
Synchronous liver and peritoneal M+
Mean follow-up: 36 months

Results (OS):
Median OS: 27.2 months; DFS: 9.5 months
• Complete cytoreductive surgery (n = 132): 29 months;
• Incomplete cytoreduction (n = 14): 4 months;
• \( p = 0.0001 \).

Rectal primary tumor, PCI of 13 or more, positive nodal status of the primitive tumor and more than 3 LM were not identified as independent factors for poor OS.
CRS/HIPEC (Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy) for treatment of peritoneal carcinosis

PATIENT SELECTION

Marcello Deraco M.D. Responsible Peritoneal Surface Malignancies Program
- Experience with HIPEC
- Certification
- Tumorboard
- HIPEC Register

- No extraabdominal metastases
- No small bowel disease
- PCI

- Histology
- Response on Chemo

- Age
- General condition
- Motivation
- Postoperative QoL

- Disease Extension
- Tumor biology
- Patient related data
- Center

- Experience with HIPEC
- Certification
- Tumorboard
- HIPEC Register
CRS/HIPEC (Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy) for treatment of peritoneal carcinosis

PATIENT SELECTION

- PCI
- Cytoreduction
- Histology
- Response on Chemo
- Patient Condition

Marcello Deraco M.D. Responsible Peritoneal Surface Malignancies Program
Lesion size score

<table>
<thead>
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<th>LSS-0</th>
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<td>LSS-1</td>
<td>&lt;0.5</td>
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<tr>
<td>LSS-2</td>
<td>0-5-5</td>
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<tr>
<td>LSS-3</td>
<td>&gt;5</td>
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</table>

Table 6: Correlation Between the PCI and the Survival of Patients With PC from Colorectal Cancer Treated With CRS and HIPEC

<table>
<thead>
<tr>
<th>Reference</th>
<th>PCI</th>
<th>Median Survival (Months)</th>
<th>Survival Rates (%) Years</th>
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<tbody>
<tr>
<td></td>
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</tr>
<tr>
<td>Pestieau and Sugarbaker 2000</td>
<td>≤ 10</td>
<td>48.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>50</td>
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<tr>
<td></td>
<td>11-20</td>
<td>24.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>&gt; 20</td>
<td>12.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
</tr>
<tr>
<td>Glehen et al 2004</td>
<td>&lt; 13</td>
<td>34.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>92</td>
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<tr>
<td></td>
<td>≥ 13</td>
<td>14.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>62</td>
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<tr>
<td>Kecmanovic et al 2005</td>
<td>≤ 13</td>
<td>16.8&lt;sup&gt;a&lt;/sup&gt;</td>
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</tr>
<tr>
<td></td>
<td>&gt; 13</td>
<td>6.9&lt;sup&gt;a&lt;/sup&gt;</td>
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</tr>
<tr>
<td>Yan et al 2008</td>
<td>≥ 10 - &lt; 20</td>
<td>29</td>
<td>63</td>
</tr>
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<td></td>
<td>≥ 20</td>
<td>27</td>
<td>80</td>
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<td>Elias et al 2010</td>
<td>1-6</td>
<td>40.0</td>
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<td>7-12</td>
<td>29.0</td>
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<td>13-19</td>
<td>25.0</td>
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<td>&gt; 19</td>
<td>18.0</td>
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<td>Cavaliere et al 2011</td>
<td>&lt; 11</td>
<td>23.0 (31&lt;sup&gt;b&lt;/sup&gt;&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>18.5</td>
</tr>
<tr>
<td></td>
<td>11-20</td>
<td>16.0 (19&lt;sup&gt;b&lt;/sup&gt;&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>7</td>
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<tr>
<td></td>
<td>&gt; 20</td>
<td>11.0 (14&lt;sup&gt;b&lt;/sup&gt;&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>0</td>
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</tbody>
</table>
173 patients treated with CCRS and HIPEC;
Study Period: 2003-2012;
5-year OS: 42 %;
5-years Recurrence-free survival: 14 %;
Median OS: 41 months;
Median recurrence free survival: 17.7 months;
Mean PCI: 10.2 (±6.8).
PATIENT SELECTION

- PCI
- Cytoreduction
- Histology
- Response on Chemo
- Patient Condition

Marcello Deraco M.D. Responsible Peritoneal Surface Malignancies Program
# Current Status of Cytoreductive Surgery With Hyperthermic Intraperitoneal Chemotherapy in Patients With Peritoneal Carcinomatosis from Colorectal Cancer

Thomas Weber, Mark Roitman, Karl H. Link

## Table 5: Correlation Between the CCR and the Survival of Patients with PC from Colorectal Cancer Treated with CRS and HIPEC

<table>
<thead>
<tr>
<th>Reference</th>
<th>Completeness of Cytoreduction</th>
<th>Median OS (Month)</th>
<th>Survival Rates (%)</th>
<th>Years</th>
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Completeness of Cytoreduction:

Peritoneal Colorectal Carcinomatosis Treated With Surgery and Perioperative Intraperitoneal Chemotherapy: Retrospective Analysis of 523 Patients From a Multicentric French Study

Dominique Elias, François Gilly, Florent Boutilie, François Quenet, Jean-Marc Bereder, Baudouin Mansvelt, Gérard Lorimier, Pierre Dubè, and Olivier Glehen

- Retrospective-cohort, multicentric French study (1990 and 2007)
- 523 patients
- 23 centers
CRS/HiPEC (Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy) for treatment of peritoneal carcinosis

PATIENT SELECTION

- PCI
- Cytoreduction
- Histology
- Response on Chemo
- Patient Condition

Marcello Deraco M.D. Responsible Peritoneal Surface Malignancies Program
Period time; April 2005-December 2013

Patients Referred for CRS+HIPEC: 351

Patients with SRCC histology: 20 (5.7%).

CRS+HIPEC performed in:
  • 16 pts with SRCC (80%)
  • 252 pts with other histology (331=76.1%).
“Influence of molecular alterations on site-specific (ss) time to recurrence (TTR) following adjuvant therapy in resected colon cancer (CC) (Alliance Trial N0147)”

Ryan Eldredge Wilcox, Qian Shi, Frank A. Sinicrope, Daniel J. Sargent, Nathan R. Foster, Jeffrey P. Meyers, Richard M. Goldberg, Suresh Nair, Anthony Frank Shields, Emily Chan, Sharlene Gill, Morton S. Kahlenberg, Steven R. Alberts; Mayo Clinic, Rochester, MN; North Central Cancer Treatment Group, Rochester, MN; Mayo Clinic, Rochester, MN, Rochester, MN; The Ohio State University Comprehensive Cancer Center, Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH; Lehigh Valley Health Network, Allentown, PA; Karmanos Cancer Institute, Detroit, MI; Vanderbilt University Medical Center, Nashville, TN; British Columbia Cancer Agency, Vancouver, BC, Canada; Surg Onc Assocs of South Texas, San Antonio, TX

✓ Biological Patterns and Time to Tumor Recurrence following adjuvant therapy in stage III patients (3098 pts) were analyzed

✓ BRAF V600E mutation (poor prognostic marker) has a significant association with shorter TTR for peritoneal metastases

Abstract N. 3590 Wilcox et al. (ASCO 2015)
CRS/HIPEC (Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy) for treatment of peritoneal carcinosis

PATIENT SELECTION

- PCI
- Cytoreduction
- Histology
- Response on Chemo
- Patient Condition

Marcello Deraco M.D. Responsible Peritoneal Surface Malignancies Program
Is preoperative chemotherapy related to the survival of patient operated for peritoneal colorectal carcinomatosis and can it induce complete pathological response?

Abdelkader Taibi: CHU Limoges France and French Multicentric group

Rationale:
• CT scan or MRI, is not accurate enough for imaging a response using RECIST criteria
• Blazer or tumor regression grade (TRG)

Patients: 23 treated with Neoadjuvant sCT

Results:
Pathology
• Blazer classification, complete, major and minor PR = 17.5%, 52% and 30.5%
• TRG, PR was considered major, partial and absent in 61%, 9% and 30%

Median OS:
• Patients with a complete or major response = 54 months
• Patients with minor response = 21.5 months
• ($p < 0.05$).
PATIENT SELECTION

- PCI
- Cytoreduction
- Histology
- Response on Chemo
- Patient Condition

Marcello Deraco M.D. Responsible Peritoneal Surface Malignancies Program
The American Society of Peritoneal Surface Malignancies (ASPSM) Multiinstitution Evaluation of the Peritoneal Surface Disease Severity Score (PSDSS) in 1,013 Patients with Colorectal Cancer with Peritoneal Carcinomatosis

Jesus Esquivel, MD1, Andrew M. Lowy, MD2, Maurie Markman, MD3, Terence Chua, MD4, Joerg Pelz, MD5, Dario Baratti, MD6, Joel M. Baumgartner, MD7, Richard Berri, MD7, Pedro Bretcha-Boix, MD8, Marcello Deraco, MD8, Guillermo Flores-Ayala, MD9, Olivier Glehen, MD10, Alberto Gomez-Portilla, MD11, Santiago González-Moreno, MD12, Martin Goodman, MD13, Evgenia Halkia, MD14, Shigeki Kusamura, MD6, Mecker Moller, MD15, Guillaume Passot, MD16, Marc Pocard, MD16, George Salti, MD17, Armando Sardi, MD18, Maheswari Senthil, MD19, John Spilloitis, MD14, Juan Torres-Melero, MD20, Kiran Turaga, MD21, and Richard Trout, PhD22

Clinical | CT- PCI | Histology
---|---|---
No symptoms | PCI < 10 (Low) | G1 G2 N- L- V-
Mild symptoms | PCI 10-20 (Medium) | G2 N+ and/or L+ and/or V-
Severe symptoms | PCI > 20 (High) | G3 Signet Ring

Score | Stage
---|---
2-3 | Stage I
4-7 | Stage II
8-10 | Stage III
>10 | Stage IV

<table>
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<tr>
<th>PSDSS</th>
<th>Median Srv. Mts</th>
<th>Median Srv. Mts</th>
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</table>
CRS/HIPEC (Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy) for treatment of peritoneal carcinosis

Epidemiology  sCT  New Treatments  Results  Liver M+ Peritoneal M+  Patient Selection  Conclusion

CONCLUSION

Marcello Deraco M.D. Responsible Peritoneal Surface Malignancies Program
• **CRS**, defined as removal of macroscopic peritoneal disease, combined with **HIPEC**, is the treatment that is indicated for selected patients with **moderate- to small-volume PM** secondary to CRC;

• CRS and HIPEC should be **avoided** in patients who are **unlikely to undergo a complete or near-complete resection**;

• CRS and HIPEC **should not be offered at institutions where there is insufficient knowledge or insufficient skill**;

• **Integration** of this treatment strategy into the total care of the patient with PM from colorectal cancer has become a necessary matter of discussion for **multidisciplinary teams**

• **Developing centers** should seek support from **established teams** to assist in their development while gaining experience in these techniques;
Core Curriculum 2013

Section 1. Basic Principles of Oncology
1.1 Carcinogenesis
1.2 Carcinogens
1.3 Epidemiology of Cancer
1.4 Screening for Cancer
1.5 Clinical Trials and Research Methods
1.6 Radiation Biology
1.7 Principles of Chemotherapy and targeted molecular therapies
1.8 Palliative and end of life care
1.9 Psycho-Oncology and Communication Skills

Section 2. Disease Site Specific Oncology
2.1 Breast Cancer
2.2 Colorectal Cancer
2.3 Thoracic Cancer
2.4 Upper Gastro-intestinal Cancer (Oesophageal, Gastric, GIST, Small Bowel)
2.5 Skin Cancer and Melanoma
2.6 Urological Malignancies
2.7 Endocrine Malignancies, (thyroid, parathyroid, adrenal and pancreatic endocrine)
2.8 Peritoneal Surface Malignancies

Section 3. General Clinical Skills
Section 4. Training Recommendations.
4.1 Training Programme Content
4.2 Multidisciplinary Team Meetings
4.3 Surgery
4.4 Consulting/Clinic
4.5 Research
4.6 Appraisal and mentoring
4.7 Teaching and Education
4.8 Facilities

Section 5. Eligibility Criteria for the EBSoQ Examination in Surgical Oncology

Co-Directors:
• Marcello Deraco
• Santiago Gonzales Moreno
THANK YOU FOR YOUR ATTENTION

M. GUAGLIO

Peritoneal Surface Malignancies: Surgical Team