Suspicious appendiceal findings & adenocarcinoma of appendix

Jörg Pelz

Department of General-, Visceral-, Vascular- and Pediatric Surgery
University Würzburg
Stapel A, Chirurg 2013
“Natural history studies show that peritoneal carcinomatosis (PC) is uniformly fatal, with median survival attaining 6-9 months (1)”

Publication JCO 2010

(1) Sadeghi B et al.
(5 FU)
New Chemo in GI Tumoren

- 1985: 5-FU / FS
- 1990: Irinotecan
- 1995: Oxaliplatin, Capecitabin
- 2000: Docetaxel
- 2005: Cetuximab, Bevacizumab
- 2010: Imatinib, Sunitinib, Erlotinib, Panitumumab, Trastuzumab

Nib’s = TKI
Mab’s = mAk
Survival in metastatic CRC

- Best supportive Care: ca. 6 M.
- 5-FU: 10-12 M. (~15%)
- 5-FU + Irinotecan/Oxaliplatin: 14-16 M. (~50%)
- 5-FU + Combination + Antibody (Bevacizumab, Cetuximab/Panitumumab KRAS<sup>WT</sup>) + Resection of the metastasis: > 24 M. (~70%)

mOS = median Survival
RR = Response (n. RECIST-Criteria)
Randomized Trial of Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy Versus Systemic Chemotherapy and Palliative Surgery in Patients With Peritoneal Carcinomatosis of Colorectal Cancer

By Vic J. Verwaal, Serge van Ruth, Eelco de Bree, Gooike W. van Slooten, Harm van Tinteren, Henk Boot, and Frans A.N. Zoetmulder

J Clin Oncol 2003, 21: 3737-3743

n = 105, Appendix n=18, Colon n=75, Rectum n=12

Surgery + HIPEC + Ctx
n=54

MS 22,3 months

(Surgery) + Ctx
n=51

MS 12,6 months

p=0.032

HIPEC: 35 mg/m² MMC, 40-41°C

Ctx: 5FU 400 mg/m², LV 80 mg/m²
Complete Cytoreductive Surgery Plus Intraperitoneal Chemohyperthermia With Oxaliplatin for Peritoneal Carcinomatosis of Colorectal Origin

Dominique Elias, Jérémy H. Lefevre, Julie Chevalier, Antoine Brouquet, Frédéric Marchal, Jean-Marc Classe, Gwenaël Ferron, Jean-Marc Guillot, Pierre Meeus, Diane Goërë, and Julia Bonastre


n = 96, Colorectal

Surgery + HIPEC + Ctx
n=48
(prospectiv)
MS  62,7 months

(Surgery) + Ctx
n=48
(retrospectiv)
MS  23,9 months

P<0.05

HIPEC: 460 mg/m² Oxaliplatin
43°C for 30 minutes; synchron iv. 5FU 400 mg/m², LV 80 mg/m²
Ctx:best systemic chemotherapy
Therapy

Surgery + HIPEC + Ctx
n=54
MS 22.3 months

(Surgery) + Ctx
n=51
MS 12.6 months

Control

(Surgery) + Ctx
n=48 (prospectiv)
MS 62.7 months

(Surgery) + Ctx
n=48 (retrospectiv)
MS 22.3 months

Patient selection?
Best Chemotherapy?

Verwaal et al.

Elias et al.
Benefit in multimodal treatment for peritoneal carcinomatosis
Problems in comparing

patients with peritoneal carcinomatosis

- Different tumors (Histology, PCI)
- Different Therapies (Surgery, Chemo, HIPEC)
- Different Chemo (BSC, 5FU/L, combination)
Cave: don’t compare apples and oranges!!
Evaluation of a Peritoneal Surface Disease Severity Score in Patients With Colon Cancer With Peritoneal Carcinomatosis


Key factors:

Histology
Peritoneal carcinomatosis index (PCI)
Clinical Symptoms
<table>
<thead>
<tr>
<th>Symptoms</th>
<th>PCI</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>no</td>
<td>PCI &lt; 10</td>
<td>G1, G2 N-</td>
</tr>
<tr>
<td></td>
<td>0 point</td>
<td>1 point</td>
</tr>
<tr>
<td></td>
<td>1 point</td>
<td>1 point</td>
</tr>
<tr>
<td>mild</td>
<td>PCI 10-20</td>
<td>G2 N+</td>
</tr>
<tr>
<td></td>
<td>1 point</td>
<td>3 points</td>
</tr>
<tr>
<td></td>
<td>3 points</td>
<td>3 points</td>
</tr>
<tr>
<td>severe</td>
<td>PCI &gt; 20</td>
<td>every G3 Signet ring</td>
</tr>
<tr>
<td></td>
<td>6 points</td>
<td>7 points</td>
</tr>
<tr>
<td></td>
<td>7 points</td>
<td>9 points</td>
</tr>
<tr>
<td>Score</td>
<td>PSDS</td>
<td>Proposed Therapy</td>
</tr>
<tr>
<td>-------</td>
<td>-------</td>
<td>-------------------------------------------------------</td>
</tr>
<tr>
<td>2-3</td>
<td>Stage I</td>
<td>CRS/HIPEC</td>
</tr>
<tr>
<td>4-7</td>
<td>Stage II</td>
<td>Neo-adjuvant Rx for 3 months, then CRS/HIPEC</td>
</tr>
<tr>
<td>8-10</td>
<td>Stage III</td>
<td>Protocol</td>
</tr>
<tr>
<td>&gt;10</td>
<td>Stage IV</td>
<td>Palliativ (no CRS/HIPEC)</td>
</tr>
</tbody>
</table>
Impact of Cytoreduction on Survival of Carcinoma Peritonei and Hyperperitoneas

Terence C. Chuah

Complete cytoreduction (n = 77)

Incomplete cytoreduction (n = 12)

Complete cytoreductive surgery only (n = 6)
Complete cytoreductive surgery and EPIC (n = 15)

Complete cytoreduction and HIPEC (n = 56)
Easy !?
Case report I

M.F. female, 43 years

Appendix carcinoma (pT2, pN1 (1/35), G2) DD: 07/10
Synchronous Peritoneal carcinomatosis (PCI 6) **PSDSS II**

08-11/2010
Neoadjuvante/palliative Chemotherapy FOLFOX
CRS (CC-0) and HIPEC (Oxaliplatin ip and 5FU/L iv)
and adjuvant systemic chemo (FOLFOX)

Peritoneal recurrence and multiple Liver metastasis
3 month after adjuvant Chemotherapy
DOD 22 months after HIPEC
Case report I
Case report I
Case report I
Case report II

R.B. female 65 years

Appendixcarcinoma (pT4, pN2 (7/30), signet ring PD:07/09
Synchronous Peritonealcarzinomatosis

Involvement of the small bowel (PCI 20) **PSDSS IV**

Since 08/09 palliative Chemotherapy (FOLFOX)

CT-morphologic Stable Disease for 2 years in good quality of
life. Since 08/11 progression, DOD 01/13

Survival 36 months !  ???
Individual (bad)success

Different outcome within same groups
Do we need other selection factors?

Role of Resistance mechanisms in different Tumors?
HSP-Expression depends on Temperature
(Hyperthermia-Model: In vitro – Expression after 30 min. Regeneration)

RT-qPCR

<table>
<thead>
<tr>
<th>Temperature</th>
<th>HSP70</th>
<th>HSP72</th>
<th>HSP90</th>
<th>HSP27</th>
</tr>
</thead>
<tbody>
<tr>
<td>37°C</td>
<td>120,5%</td>
<td>98,8%</td>
<td>47,2%</td>
<td></td>
</tr>
<tr>
<td>39°C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>41°C</td>
<td></td>
<td></td>
<td></td>
<td>61,3%</td>
</tr>
<tr>
<td>43°C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cell proliferation (MTS-Test)

Western Blot

- HSP70/72
- Beta-Aktin
Hyperthermia and intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis: an experimental study.

Treatment:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS only,</td>
<td>63 d</td>
</tr>
<tr>
<td>CS + HIPEC (MMC at 41°C),</td>
<td>121 d</td>
</tr>
<tr>
<td>CS + ip MMC at 37°C,</td>
<td>n.r. (126 d follow up)</td>
</tr>
<tr>
<td>CS + ip saline perfusion at 41°C.</td>
<td>57 d</td>
</tr>
</tbody>
</table>

The effectiveness of intraoperative intraperitoneal perfusion after CS is highly dependent on the presence of chemotherapeutic agents in the perfusate but not on hyperthermia.

A trend towards improved outcomes is demonstrated from treatment of patients with PC from colorectal cancer using modern systemic chemotherapy (up to 36 months).

Cytoreductive Surgery + HIPEC improved outcomes compared to systemic chemotherapy alone.

The PSDSS appears to be a useful tool in patient selection and prognostication in PC of colorectal origin.

Repair mechanisms (HSPs) and induced chemotherapy-resistence (ABC-transporter) inhibit the HIPEC-induced tumor cell apoptosis.
Thank you!

Department of General-, Visceral-, Vascular- and Pediatric Surgery
University Würzburg