Treatment of metastatic disease confined to the peritoneum - Resection, HIPEC, PIPAC

Hauke Lang
Klinik für Allgemein, Viszeral- und Transplantationschirurgie
Incidence of synchronous Peritoneal carcinomatosis in CRC

Risk factors für PC

- < 60 years
- advanced T-stage
- advanced N-stage
- mucinous tumor
- poor differentiation
- right sided tumor

Lemmens et al., Int J Cancer 2011

4.2% of 12,000, Segelmann et al, Br J Surg 2012
# Multimodal treatment of Peritoneal carcinomatosis in CRC

<table>
<thead>
<tr>
<th>Journal</th>
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- Prospective randomized
- Matched-pair
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- Multinational register
- French register
- Systematic meta-analysis
- Matched-pair
- Prospectiv randomized
- Consensus conference
- Large multicentric retrosp.

**Multimodal Treatment Approaches for Peritoneal Carcinosis in Colorectal Cancer**

### Table 3

<table>
<thead>
<tr>
<th><strong>Author, year</strong></th>
<th><strong>Study</strong></th>
<th><strong>Level of evidence</strong></th>
<th><strong>Therapy (treatment arm vs control arm)</strong></th>
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**Criticism:**

**CRS plus HIPEC** vs **5 FU plus folinic acid**

**Inclusion of appendiceal tumors**

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*SC: systemic chemotherapy; EPIC: early post-operative intraperitoneal chemotherapy; CRS: cytoreductive surgery (peritonectomy); HIPEC: hyperthermic intraperitoneal chemotherapy*

**Piso, Deutsches Ärzteblatt Int. 2011**
Multimodal Treatment Approaches for Peritoneal Carcinosis in Colorectal Cancer

506 patients from 28 institutions

Median survival 19 months
- after complete CRS 32 months
- after incomplete CRS 8 months

Piso, Deutsches Ärzteblatt Int. 2011

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<td>historic comparison group</td>
<td>3b</td>
<td>CRS + EPIC vs. debulking + SC</td>
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<td>32 vs. 14</td>
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<td>Multinational register</td>
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<td>French register</td>
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<td>523</td>
<td>30</td>
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Multimodal Treatment Approaches for Peritoneal Carcinosis in Colorectal Cancer

Study group:
CRS plus HIPEC (Oxaliplatin)

Standard group
(retrospectively included)

Standard chemotherapy
+/- palliative surgery

Elias et al, 2009
**Multimodal Treatment Approaches for Peritoneal Carcinosis in Colorectal Cancer**

Positive prognostic factors:

- complete CRS
- PC limited in extent
- no lymph node invasion
- adjuvant CTx

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<th>Study</th>
<th>Register</th>
<th>CRS + HIPEC</th>
<th>CRN</th>
<th>SC</th>
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<tr>
<td>Lee et al.</td>
<td>Systematic meta-analysis</td>
<td>&gt;2000</td>
<td>15 to 60</td>
<td></td>
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Criticism: HIPEC procedure was done in many variations
(open or closed, duration (30 – 90 minutes), temperature (40°C – 43°C, flow rates, chemotherapy (Mitomycin, Oxaliplatin, Irinotecan +/- 5 FU intravenously))
Completeness of Cytoreduction

CCR 0 (no visible sites)  CCR 1 (only a few deposits that are assumed to be destroyed by HIPEC)

Complete cytoreduction in CRC : CCR-0 (CCR-1)

Survival Probability

Completeness of Cytoreduction
0 mm
< 2.5 mm
≥ 2.5 mm

Time (years)
Extent of Peritoneal Carcinomatosis

### Regions

- 0 Central
- 1 Right Upper
- 2 Epigastrium
- 3 Left Upper
- 4 Left Flank
- 5 Left Lower
- 6 Pelvis
- 7 Right Lower
- 8 Right Flank
- 9 Upper Jejunum
- 10 Lower Jejunum
- 11 Upper Ileum
- 12 Lower Ileum

### Lesion Size Score

- LS 0 No tumor seen
- LS 1 Tumor up to 0.5 cm
- LS 2 Tumor up to 5.0 cm
- LS 3 Tumor > 5.0 cm or confluence

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Piso, Cancer J, 2009
PCI and Prognosis

Peritoneal Cancer Index:
Tumorextent: PCI < 20

D Elias, Journal of Clinical Oncology 2010
Is There a Possibility of a Cure in Patients With Colorectal Peritoneal Carcinomatosis Amenable to Complete Cytoreductive Surgery and Intraperitoneal Chemotherapy?

- Overall survival
- Disease-free survival

n = 107

PCI 4 (3-16)

n = 14 remained disease free

- Resection
- HIPEC
- PIPAC
Peritonectomy procedures

Peritonectomy RUQ
Lesser omentectomy CHE
Right colectomy

Peritonectomy LUQ
Gastrectomy
Omentectomy Splenectomy
Anterior parietal peritonectomy

Peritonectomy small pelvis, Rectosigmoid resection, Hysterectomy

Sugarbaker et al, Ann Surg 1999
Tirkes T et al. Radiographics 2012
Diagnosed for colon cancer 12/2011

- 12/2011 sigmoid cancer (left colectomy)
- 02 – 07/2012 adjuvant CTx (FOLFOX)
- 05/2014 „ovarian mass“, diagnosed as CRC metastases (PC) by percutaneous puncture
- 08 – 10/2014 FOLFIRI
- 12/2014 lap. appendectomy (histology: PC from CRC)
- 02/2015 peritoneectomy plus HIPEC (PCI)
- Surgery
  - Omentectomy, cholecystectomy, peritoneectomy lower abdomen and pelvis, hysterectomy, adnexectomy, rectal resection
Selection criteria for multimodal treatment

- No extensive small bowel disease, max. one bowel stenosis (PET-CT, CT, laparoscopy)
- No biliary/ureteral obstruction due to tumor penetration
- No involvement of the gastrohepatic ligament > 5cm (CT)
- Good Performing status (ECOG 1 or 2)
- No severe co-morbidities

Piso, Cancer J, 2009
Case, female; diagnosed for colorectal cancer 2/2015; PCI 16

- Omental cake
- Parietal carcinomatosis

Parietal carcinomatosis

Omental cake
Primary tumor in the transverse colon
Small bowl with only very few small lesions
Typical tumor formation in Douglas' space
En bloc colectomy, omentectomy, splenectomy
Selection criteria for multimodal treatment

- PCI < 20 (CT, PET-CT)
- No extra-abdominal metastases
- Up to 3 peripheric resectable liver metastases

- Patient motivation
- Informed consent
- At least acceptable QoL predictable

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Piso, Cancer J, 2009
PRIMARY TUMOR
appendix, colon/high-grade histology/recurrent disease-free interval > 6 months, limited disease

PCI<20
(CT, PET-CT)

No extra-abdominal metastases

Up to 3 peripheric resectable liver metastases

• Patient motivation
• Infrom consent
• At least acceptable QoL predictable

± good response to prior chemotherapy

TUMOR BOARD
± neoadjuvant systemic chemotherapy

LAPAROTOMY
resectability criteria fullfilled

CRS

CCRO-1

HIPEC

± adjuvant systemic chemotherapy

FOLLOW-UP

No extensive small bowel disease, max. one bowel stenosis
(PET-CT, CT, laparoscopy)

No biliary/ureteral obstruction due to tumor penetration

No involvement of the gastrohepatic ligament > 5cm (CT)

Good Performing status
(ECOG 1 or 2)
No severe co-morbidities

Piso, Cancer J, 2009
Mortality:
Mean 2.9,
Range 0-17

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

= Hyperthermic intraperitoneal chemotherapy
# Hypertherme Intraoperative Intraperitoneale Chemotherapie

<table>
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<tr>
<th>Table 1</th>
<th>Properties of cytotoxic agents used during intraoperative or early postoperative intraperitoneal chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td><strong>Molecular weight (Daltons)</strong></td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td><strong>Platinum compounds</strong></td>
<td></td>
</tr>
<tr>
<td>Cisplatin&lt;sup&gt;84&lt;/sup&gt;</td>
<td>300.1</td>
</tr>
<tr>
<td>Carboplatin&lt;sup&gt;85&lt;/sup&gt;</td>
<td>371.3</td>
</tr>
<tr>
<td>Oxaliplatin&lt;sup&gt;86&lt;/sup&gt;</td>
<td>397.3</td>
</tr>
<tr>
<td><strong>Antimicrotubule agents</strong></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel&lt;sup&gt;87&lt;/sup&gt;</td>
<td>853.9</td>
</tr>
<tr>
<td>Docetaxel&lt;sup&gt;88&lt;/sup&gt;</td>
<td>861.9</td>
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<tr>
<td><strong>Topoisomerase interactive agents</strong></td>
<td></td>
</tr>
<tr>
<td>Mitoxantrone&lt;sup&gt;89&lt;/sup&gt;</td>
<td>517.4</td>
</tr>
<tr>
<td>Doxorubicin&lt;sup&gt;90&lt;/sup&gt;</td>
<td>543.5</td>
</tr>
</tbody>
</table>

### Table 2

Pharmacokinetic data and characteristics of cytostatic drugs for intraperitoneal use in colorectal cancer with peritoneal carcinosis

<table>
<thead>
<tr>
<th>Cytostatic</th>
<th>Dosage intraperitoneal (mg/m²)</th>
<th>Combination with IV 5-FU</th>
<th>Depth of Penetration (mm)</th>
<th>Synergy with hyperthermia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxaliplatin</td>
<td>200–460</td>
<td>possible</td>
<td>1–2</td>
<td>present</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>50–250</td>
<td>no data available</td>
<td>1–3</td>
<td>present</td>
</tr>
<tr>
<td>Mitomycin</td>
<td>20–35</td>
<td>possible</td>
<td>2</td>
<td>present</td>
</tr>
<tr>
<td>5-FU</td>
<td>400–650</td>
<td>not applicable</td>
<td>0.2</td>
<td>not present</td>
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5-FU = 5-fluorouracil; modified according to Ceelen et al. (1)

Piso, Deutsches Ärzteblatt Int. 2011
Hypertherme Intraoperative Intraperitoneale Chemotherapie
- PIPAC

= Pressurized intraperitoneal chemotherapy
- Laparoscopic approach: 12 mmHg intraperitoneal pressure, 30 min.

- Chemotherapy: colon: Oxaliplatin 92 mg/m2 body surface;

- Device : MIP®, Reger Medizintechnik (CE-certified, class 2A)
- High-pressure injector: any industry-standard injector up to 20 bar
1. An artificial hydrostatic intraperitoneal pressure is created

2. Gas/aerosol repartition within a closed volume is homogeneous

3. PIPAC can be repeated
Therapy within the framework of regulatory studies PIPAC-OV1 (NCT01809379) and PIPAC-GA1 (NCT01854255) as well of as off-label use according to German AMG.

5.11.2011 to 2.5.2014: 483 PIPAC + 7 PITAC in 253 patients
556 procedures including primary and secondary non-access (11.9%)

Palliative indication in pretreated, platin-resistant peritoneal carcinomatosis, primary CRS and HIPEC not indicated

Mortality zero in the last 383 consecutive procedures
Local toxicity is acceptable, systemic toxicity is minimal
Quality of life appears to be preserved, 1y SR for CRC 70%
PIPAC is not expensive, limited due to max. number of PIPAC sessions

Prof. Reymond, Marien Hospital, Ruhr-University Bochum
Cytoreductive surgery plus hyperthermic perioperative chemotherapy to treat peritoneal metastases from colorectal cancer: standard of care or an experimental approach?

Paul H Sugarbaker*, David P Ryan*

Credits
- Long-term survival in 30% of patients
- Patients with minimum carcinomatosis experience best survival
- Morbidity (12%) and mortality (1%) at experienced centres is acceptable
- Favourable results of treatment continue to be reported from many different institutions in the oncology literature

Debits
- The surgical technology is complex and requires an extended learning curve
- Surgical series contain patients who have received many different chemotherapy regimens and who are at many different timepoints in their treatment
- The one randomised trial was flawed, primarily by the inclusion of patients with appendiceal tumours
- Whether the procedure is causally related to long-term survival or if surgeons select patients likely to survive long term is unclear
In patients with an **isolated** and **limited** peritoneal carcinomatosis, **without** extraabdominal metastases and **low PCI** (peritoneal cancer index, < 20) cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy **can** be performed.

A pre-requisite is **complete macroscopic** cytoreduction.

The treatment should be performed in **specialized centers**. If possible, patients should be included in studies.

http://www.krebsgesellschaft.de/download/ll_krk.pdf
Thank you!