CRS and HIPEC for Peritoneal Carcinomatosis:
An update and critical appraisal

K. Van der Speeten, MD, PhD
Pretoria 08/10/16
• 2016 : the Good, the Bad and the Ugly
• Chemosurgery
• The surgery in chemosurgery
• The chemo in chemosurgery
• Rationale for HIPEC
• Do we need HIPEC?
• Now that we have proven the concept, how do we improve it
• Now that we have proven the concept, how do we decrease M&M
• Predicting response & faillure
PERITONEAL CARCINOMATOSIS: PATHOPHYSIOLOGY

Figure 2: Mechanisms of transcoelomic metastasis in ovarian cancer
Step 1: Epithelial ovarian cancer cell (green) detaches after altered gene expression. Step 2: peritoneal or ascitic current (blue arrows) facilitates peritoneal, lymphatic, and haematogenous metastasis. Step 3: immune evasion by complement inhibition and secretion of TGF-β; Step 4: spheroid formation. Step 5: ascites stimulates further metastatic progression. Step 6: peritoneal activation and implantation. FGFR-4=Insulin-like growth factor receptor 4 (IGFR4); PHL=plasminogen activator inhibitor 1; VEGF=vascular endothelial growth factor.
Treating PSM in 2016

“You may run the risks, my friend, but I do the cutting.”

THE GOOD
AND THE
BAD
UGLY
2016 : The Good

Toward Curative Treatment of Peritoneal Carcinomatosis From Nonovarian Origin by Cytoreductive Surgery Combined With Perioperative Intraperitoneal Chemotherapy
A Multi-Institutional Study of 1290 Patients

- There is no long term survival with systemic chemotherapy
- Systemic chemotherapy: bad QoL
- CRS + HIPEC works
- A lot of patients benefit

**Figure 3.** Overall survival rates are illustrated for patients with colorectal peritoneal carcinomatosis (PC), pseudomyxoma peritonei, peritoneal mesothelioma, gastric PC, and PC from appendiceal adenocarcinoma.
2016: The Bad (PALLIATION BY DEFAULT)

- > 50% of patients still die
- CRS + HIPEC doesn’t work good enough
- A lot of patients don’t benefit long enough

Figure 3. Overall survival rates are illustrated for patients with colorectal peritoneal carcinomatosis (PC), pseudomyxoma peritonei, peritoneal mesothelioma, gastric PC, and PC from appendiceal adenocarcinoma.
### Table 3
Factors influencing quality of life at 3, 6 and 12 months in uni and multivariate analysis.

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<tr>
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<th>Baseline – 6 months</th>
<th>Baseline – 12 months</th>
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<td>Deterioration</td>
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<tr>
<td>Gender</td>
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<td>Women</td>
<td>56 (49.56)</td>
<td>57 (50.44)</td>
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<td>Men</td>
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<td>3–4</td>
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<td>&gt;270 min</td>
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Treating PSM in 2016

POOR FELLOW.
HE’S HALF DEAD.

I’M AN
OPTIMIST.
I SAY HE’S
HALF ALIVE!

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CHEMOSURGERY
TREATING PC WITH ‘CHEMOSURGERY’?

- Combined multi-organ resections
- Peritoneectomy-procedures

- Intraperitoneal Chemotherapy

Treatment of MACROSCOPIC disease

Treatment of MICROSCOPIC disease

‘It’s not what the surgeon removes that kills the patients, but what he leaves behind’
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<th>Hyperthermic Intraperitoneal Peroperative Chemotherapy</th>
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<td><strong>BIC</strong></td>
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THE SURGERY IN CHEMOSURGERY
The Surgery in Chemosurgery

- Combined multi-organ resections
- Peritoneectomy-procedures

Treatment of MACROSCOPIC disease
The Surgery in Chemosurgery
The Surgery in Chemosurgery
THE CHEMO IN CHEMOSURGERY
• Hyperthermic Intraperitoneal Peroperative Chemotherapy (HIPEC)

Treatment of MICROSCOPIC disease
The Chemo in Chemosurgery

- Hyperthermic Intraperitoneal Peroperative Chemotherapy (HIPEC)
The Chemo in Chemosurgery

HIPEC (SEMI) CLOSED TECHNIQUE
Rationale for HIPEC
“the peritoneal permeability of a number of hydrophylic anticancer drugs after intraperitoneal administration may be considerably less than the plasma clearance of that same drug”

- Pharmacokinetic principle of DOSE INTENSIFICATION
  - function of molecular weight, dose,……
  - two compartment model

DOSE INTENSIFICATION

Fig. 1. Traditional two-compartment model of peritoneal transport, in which transfer of a drug from the peritoneal cavity to the blood occurs across the “peritoneal membrane.” The permeability-area product \((PA)\) governs this transfer and can be calculated by measuring the rate of drug disappearance from the cavity and dividing by the overall concentration difference between the peritoneal cavity and the blood (or plasma). \(C_B\) = the free drug concentration in the blood (or plasma); \(V_B\) = volume of distribution of the drug in the body; \(C_P\) = the free drug concentration in the peritoneal fluid; \(V_P\) = volume of the peritoneal cavity.

Rate of mass transfer = \(PA \times (C_P - C_B)\)
Changes induced by surgical and clinical factors in the pharmacology of intraperitoneal mitomycin C in 145 patients with peritoneal carcinomatosis

Kurt Van der Speeten · O. Anthony Stuart · David Chang · Haile Mahteme · Paul H. Sugarbaker

AUC IP / AUC IV = AUC RATIO …. Measure of efficacy

DO WE NEED HIPEC?
Do we need HIPEC?

Properly Brewed, the
Polyjuice Potion
allows the drinker
to transform himself
temporarily into
the physical form
of another...
Intraoperative hyperthermic intraperitoneal chemotherapy after cytoreductive surgery for peritoneal carcinomatosis in an experimental model

Y. L. B. Klaver¹, T. Hendriks², R. M. L. M. Lomme², H. J. T. Rutten¹, R. P. Bleichrodt² and I. H. J. T. de Hingh³

Fig. 4 Kaplan–Meier survival curves for the three treatment groups. CS, cytoreductive surgery; HIPEC-15, CS + hyperthermic intraperitoneal chemotherapy (HIPEC) with 15 mg/m² mitomycin C; HIPEC-35, CS + HIPEC with 35 mg/m² mitomycin C. \( P = 0.003 \) for CS versus HIPEC-15, \( P < 0.001 \) for CS versus HIPEC-35 (log rank test)
Now that we have proven the concept, how do we further improve it?
Rationale for EPIC
Rationale for EPIC

Add to ____ ml 1.5 % dextrose peritoneal dialysis solution (a) ____ mg 5-fluoruracil (650 mg/m² X ____ m²) (maximum dose 1,500 mg) and (b) 50 meq sodium bicarbonate.

Intraperitoneal fluid volume: 1 liter for patients ≤ 2.0 m², 1.5 liters for > 20 m².

Instill for 5 consecutive days on ____ through ____.

Drain all fluid from the abdominal cavity prior to instillation, then clamp abdominal drains.

Run into abdominal cavity through Tenckhoff catheter as rapidly as possible the chemotherapy solution.

Dwell for 23 h and drain for 1 h prior to next instillation.

Continue to drain the abdominal cavity after final dwell until Tenckhoff catheter is removed.

Use 33 % dose reduction for heavy prior chemotherapy, age greater than 60, extensive intraoperative trauma to small bowel surface or prior radiotherapy.
Fig. 1. 5-Fluorouracil concentrations in peritoneal fluid and plasma after early postoperative intraperitoneal chemotherapy administration (N = 9).
Rationale for Bidirectional Intraoperative Chemotherapy (BIC)
Heated intra-operative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis: pharmacokinetics and tissue distribution


One hour before IPCH we delivered systemic intravenous leucovorin 20 mg/m² and 5-FU 400 mg/m² because 5-FU potentiates the action of oxaliplatin [11]. However, as 5-FU cannot be mixed with oxaliplatin in the peritoneal cavity due to pH incompatibility, it was delivered intravenously. Following this systemic perfusion, tumour and healthy tissue were soaked with 5-FU before the beginning of the IPCH. A low dose of 400 mg/m² was chosen to avoid intensifying the aggressiveness of combined complete cytoreductive surgery and IPCH.
TIMING OF PERIOPERATIVE IV CHEMOTHERAPY

Pharmacologic concept of bidirectional (IV and IP) chemotherapy

Modified from Fujiwara K. Int J Gynecol Cancer 2007, 17, 1-20
FIGURE 2: 5-Fluorouracil concentrations in peritoneal fluid and plasma after intravenous administration during hyperthermic intraperitoneal chemotherapy procedure (N=20).

- Rapid distribution to ALL body compartments
- Metabolization restricted to plasma compartment
FIGURE 3: 5-Fluorouracil concentrations in plasma, peritoneal fluid and tumor nodules after intravenous administration during hyperthermic intraperitoneal chemotherapy procedure (N=9).
Now that we have proven the concept how do we decrease the Ugly
Table 5. Perioperative Factors and Mortality Outcomes of 24 Institutions Following Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy

<table>
<thead>
<tr>
<th>First Author</th>
<th>Mean Length of Hospital Stay (d)</th>
<th>Mean Length of ICU Stay (d)</th>
<th>Treatment Related Deaths (n)</th>
<th>Mortality (%)</th>
<th>Causes</th>
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<tr>
<td>Glehen et al⁸</td>
<td>11.8</td>
<td>NR</td>
<td>7</td>
<td>3.2</td>
<td>Septic shock, peritonitis, pulmonary embolism, multi-organ failure, aplasia, myocardial necrosis, acute renal failure</td>
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<tr>
<td>Ahmad et al⁷</td>
<td>11*</td>
<td>NR</td>
<td>0</td>
<td>0</td>
<td>Peritonitis, pneumonia, sepsis from bone marrow toxicity</td>
</tr>
<tr>
<td>Schmidt et al¹⁰</td>
<td>25*</td>
<td>5*</td>
<td>3</td>
<td>4.5</td>
<td>Renal failure, multi-organ failure, and bleeding</td>
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<tr>
<td>Kecmanovic et al¹¹</td>
<td>14.2</td>
<td>NR</td>
<td>0</td>
<td>2.8</td>
<td>Duodenal perforation, colic perforation, and sepsis</td>
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<tr>
<td>Yonemura et al¹²</td>
<td>NR</td>
<td>NR</td>
<td>3</td>
<td>0.9</td>
<td>Systemic inflammatory response, fistula, unknown (3), pulmonary embolus, neutropenia</td>
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<tr>
<td>Rufian et al¹³</td>
<td>11*</td>
<td>NR</td>
<td>0</td>
<td>0</td>
<td>Multiorgan failure</td>
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<tr>
<td>Kusamura et al¹⁴</td>
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<td>3</td>
<td>2</td>
<td>0.9</td>
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<tr>
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<td>21*</td>
<td>NR</td>
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<td>4</td>
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<tr>
<td>Tuttle et al¹⁹</td>
<td>9*</td>
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<td>0</td>
<td>0</td>
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*Refers to median.

Unpublished data.
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*Unpublished data.
Positioning
AVC, 54 yrs, ovarian PC, OVHIPEC Trial protocol, CC0 cytoreduction
- Do the positioning yourself
- Modified ‘modified’ lithotomy position
- Regular pausing of the pneumatic compression stockings
Anesthetic pitfalls
SEVERE HYTONATREMIA, HYPERGLYCEMIA, AND HYPERLACTATEMIA ARE ASSOCIATED WITH INTRAOPERATIVE HYPERTHERMIC INTRAPERITONEAL CHEMOPERFUSION WITH OXALIPLATIN

Filip De Somer,¹ Wim Ceelen,² Joris Delanghe,³ Dirk De Smet,¹ Martin Vanackere,¹ Piet Pattyn,² and Eric Mortier⁴

Departments of Cardiac Surgery,¹ Abdominal Surgery,² Central Laboratory,³ and Anaesthesia,⁴ University Hospital Ghent, Ghent, Belgium

CASE REPORT

Ventricular tachycardia during hyperthermic intraperitoneal chemotherapy

C. A. Thix,¹ I. Königsrainer,² R. Kind,³ P. Wied¹ and T. H. Schroeder¹

¹ Department of Anaesthesiology and Critical Care Medicine, 2 Department of General, Visceral, and Transplantation Surgery, 3 Maquet Cardiovascular at the Department of Cardiothoracic and Vascular Surgery, Tuebingen University Hospital, Tuebingen, Germany
CONCLUSIONS
This is the preliminary report on non-invasive, absolute cerebral oxygenation monitoring during HIPEC procedures, where rapid increase in body temperature may be induced. These rapid increases in body temperature may result in mismatches in cerebral perfusion to cerebral metabolism ratio, possible inducing inadequacy of cerebral perfusion. However, more data are required to elucidate the relationship between rapid increases in body temperature and adequacy of cerebral perfusion, as monitored by cerebral oximetry.
- proper training of anesthesiologists is mandatory
- Train the whole team !!!
Anastomotic Leaks
Hyperthermic intraperitoneal chemoperfusion (HIPEC) decrease wound strength of colonic anastomosis in a rat model

J. O. W. Pelz · J. Doerfer · M. Decker · A. Dimmler · W. Hohenberger · T. Meyer

Fig. 1 Anastomotic strength post-operatively. The median are given for bursting pressure. (Group I: control without treatment; group II: anastomosis was performed before HIPEC; group III: anastomosis was performed before HIPEC) (§: group III vs group I, p=0.028; *: group II vs group I, p=0.03; $: group II and group III vs group I, p=0.24; Kruskal–Wallis)
Protect all low rectal anastomoses
More than 2 anastomoses: protect
Aggressive treatment of all leakage
Hematologic toxicity
Efficacy versus hematological toxicity

Doxorubicin levels in tumor nodules versus normal adjacent tissues
BI-DIRECTIONAL INTRAOPERATIVE CHEMOTHERAPY
MITOMYCIN C PLASMA LEVELS
(Grade III/IV Neutropenic Patients vs Average)

Plasma Levels (μg/mL)

Time (minutes)

Peak [PL] = 0.35(±0.07) μg/mL (neutropenic)
Peak [PL] = 0.31(±0.09) μg/mL (average)
M & M

Learning curve
Don’t reinvent the wheel; ‘surf’ on the global learning curve
Predicting Response & Faillure
Conclusions: The activity in vitro of cytotoxic drugs commonly used in IPC for PC is very heterogeneous. Efforts for individualizing drug selection for PC patients undergoing IPC seem justified.
Determinants of efficacy of IP chemotherapy

Question: do peritoneal drug levels accurately predict efficacy? **NO**
Doxorubicin levels in peritoneal fluid, plasma, tumor nodules and adjacent tissue

**TUMOR NODULE AS PHARMACOLOGIC ENDPOINT**

Doxorubicin levels in peritoneal fluid, plasma, tumor nodules and adjacent tissue
Fig. 3  Doxorubicin levels in appendiceal tumor tissue showing diffuse peritoneal adenomucinosis (DPAM) versus peritoneal mucinous carcinomatosis (PMCA). Peritoneal fluid concentrations are also shown. TN tumor nodule, PF peritoneal fluid
Gene Expression Profiling of Peritoneal Metastases from Appendiceal and Colon Cancer Demonstrates Unique Biologic Signatures and Predicts Patient Outcomes

Edward A Levine, MD, FACS, Dan G Blazer III, MD, FACS, Mickey K Kim, BS, Perry Shen, MD, FACS, John H Stewart IV, MD, FACS, Cynthia Guy, MD, David S Hsu, MD, PhD

BACKGROUND: Treatment of peritoneal metastases from appendiceal and colon cancer with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) shows great promise. Although long-term disease-free survival is achieved in some cases with this procedure, many patients have recurrence. Oncologists have treated such recurrences of appendiceal cancer similarly to colorectal carcinoma, which has been largely ineffective. This study uses gene expression analysis of peritoneal metastases to better understand these neoplasms.

STUDY DESIGN: From a prospectively maintained database and tissue bank, 41 snap frozen samples of peritoneal metastases (26 appendiceal, 15 colorectal) from patients undergoing HIPEC with complete cytoreduction and more than 3 years of follow-up underwent global gene expression analysis. Distinct phenotypes were identified using unsupervised hierarchical clustering based on differential gene expression. Survival curves stratified by genotype were generated.

RESULTS: Three distinct phenotypes were found, 2 consisting of predominantly low grade appendiceal samples (10 of 13 in Cluster 1 and 15 of 20 in Cluster 2) and 1 consisting of predominantly colorectal samples (7 of 8 in Cluster 3). Cluster 1 consisted of patients with good prognosis and Clusters 2 and 3 consisted of patients with poor prognosis (p = 0.006). Signatures predicted survival of low- (Cluster 1) vs high-risk (Cluster 2) appendiceal (p = 0.04) and low-risk appendiceal (Cluster 1) vs colon primary (Cluster 3) (p = 0.0002).

CONCLUSIONS: This study represents the first use of gene expression profiling for appendiceal cancer, and demonstrates genomic signatures quite distinct from colorectal cancer, confirming their unique biology. Consequently, therapy for appendiceal lesions extrapolated from colonic cancer regimens may be unfounded. These phenotypes may predict outcomes guiding patient management. (J Am Coll Surg 2012;214:599–607. © 2012 by the American College of Surgeons)
MUC2 protein expression status is useful in assessing the effects of hyperthermic intraperitoneal chemotherapy for peritoneal dissemination of colon cancer. Fujishima Y, Goi T, Kimura Y, Hirono Y, Katayama K, Yamaguchi A.

Source
First Department of Surgery, University of Fukui, 23-3 Eiheiji-cho, Yoshida-gun, Fukui, Japan.

Abstract
We conducted a molecular biological investigation to determine the outcomes of hyperthermic intraperitoneal chemotherapy (HIPEC) treatment, and whether it is effective in all cases for patients with peritoneal dissemination of colon cancer. In the HIPEC group, the 3-year survival rate was 39.2%, whereas in the non-HIPEC group the 3-year survival rate was 15.6%. MUC2 expression was investigated in the HIPEC group, in patients positive for MUC2 expression, and the 3-year survival rate was 0.0%, while in patients negative for MUC2 expression, the 3-year survival rate was 61.1%. In addition, as a result of introducing MUC2-siRNA into a colon cancer cell line with high expression of the MUC2 gene, the cell death rate from heat and anticancer agents increased 40% in comparison with colon cancer cells in which scrambled siRNA had not been introduced. HIPEC therapy is thought to be effective in prolonging survival in patients with peritoneal dissemination of colon cancer, and MUC2 expression is thought to be useful as an indicator to assess its effectiveness in colon cancer cells.
Unmetabolized mitomycin C. In the top portion is a representative HPLC chromatogram of mitomycin C and its metabolites in peritoneal fluid, plasma and urine. This pattern of the chromatogram was observed in a great majority of patients. The lower graphs show the HPLC chromatogram of a single patient who had failure to metabolize the drug. Six patients (4%) had this unusual mitomycin C chromatogram.
Pharmacology of Perioperative Intraperitoneal and Intravenous Chemotherapy in Patients with Peritoneal Surface Malignancy

Kurt Van der Speeten, MD, PhD,*, O. Anthony Stuart, BS, Paul H. Sugarbaker, MD, FACS

Time: 14,906.4 Minutes - Amplitude: -0.193 mAU

Fig. 7. Representative mitomycin C chromatogram in peritoneal fluid of a PSM patient during HIPEC at 75 minutes. Similar monospiked chromatograms were recovered from plasma, urine, and peritoneal fluid throughout HIPEC. The patient recurred at the peritoneal cavity 3 months after CRS and HIPEC.
PREDICTING RESPONSE +/- FAILURE

Rabbit model; mito c non metabolizer, oxaliplatin metabolizer
PILOT STUDY

Colon PC
CC0 CRS and HIPEC (Mito C)

Mitomycin C non-metabolizer
Follow-up

Mitomycin metabolizer
Re-HIPEC with oxaliplatin
Follow-up

Unpublished data, 50 patients, accrual completed
PRELIMINARY RESULTS

14 mitomycin non-metabolizers identified

5/7 recurred in follow-up arm
1/7 recurred in re-HIPEC arm
Median follow-up: 15 months
CONCLUSIONS

• CRS + HIPEC provides very encouraging clinical results in PSM of colorectal and appendiceal origin

• Systemic therapy alone offers no long term survival

• Completeness of cytoreduction

• Acceptable morbidity-mortality

• Aggressively treat all complications

• Reduce the learning curve: side-to side training.

• Move IP chemotherapy up in the timeline of colorectal and appendiceal patients at high risk of PSM
Acknowledgements
Travel Fellowship

- 6000 Euro
- 6 months
- Let us learn from each other
THANK YOU