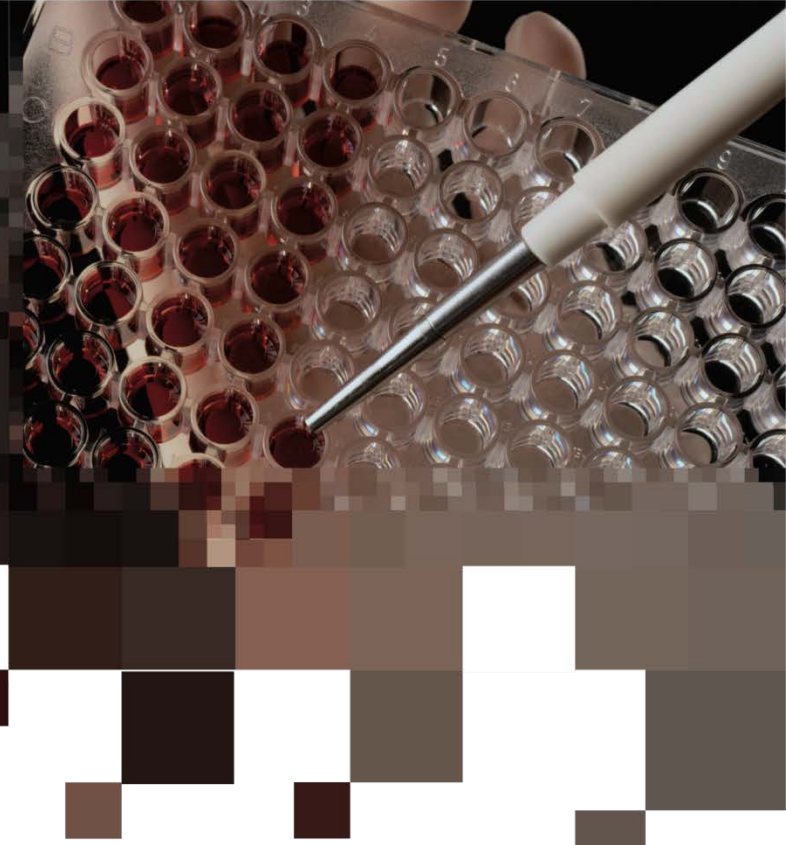
20TH Annual Controversies and Problems in Surgery

Theme: New Techniques and Novel Solution for Common Surgical Problems"

Saturday 08th and Sunday 09th October 2016



CRS and HIPEC for Peritoneal Carcinomatosis :

An update and critical appraisal

K. Van der Speeten, MD, PhD
Pretoria 08/10/16

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- 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

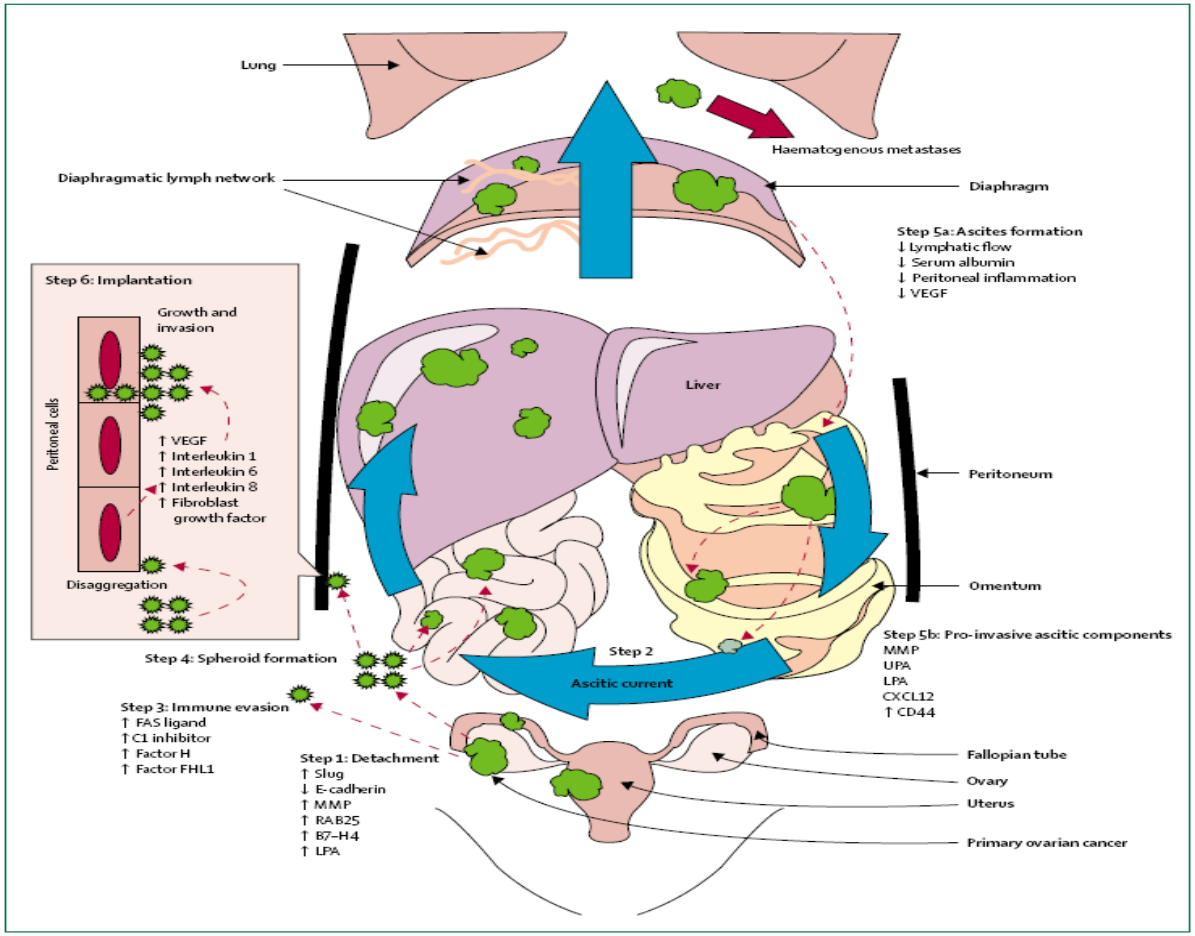
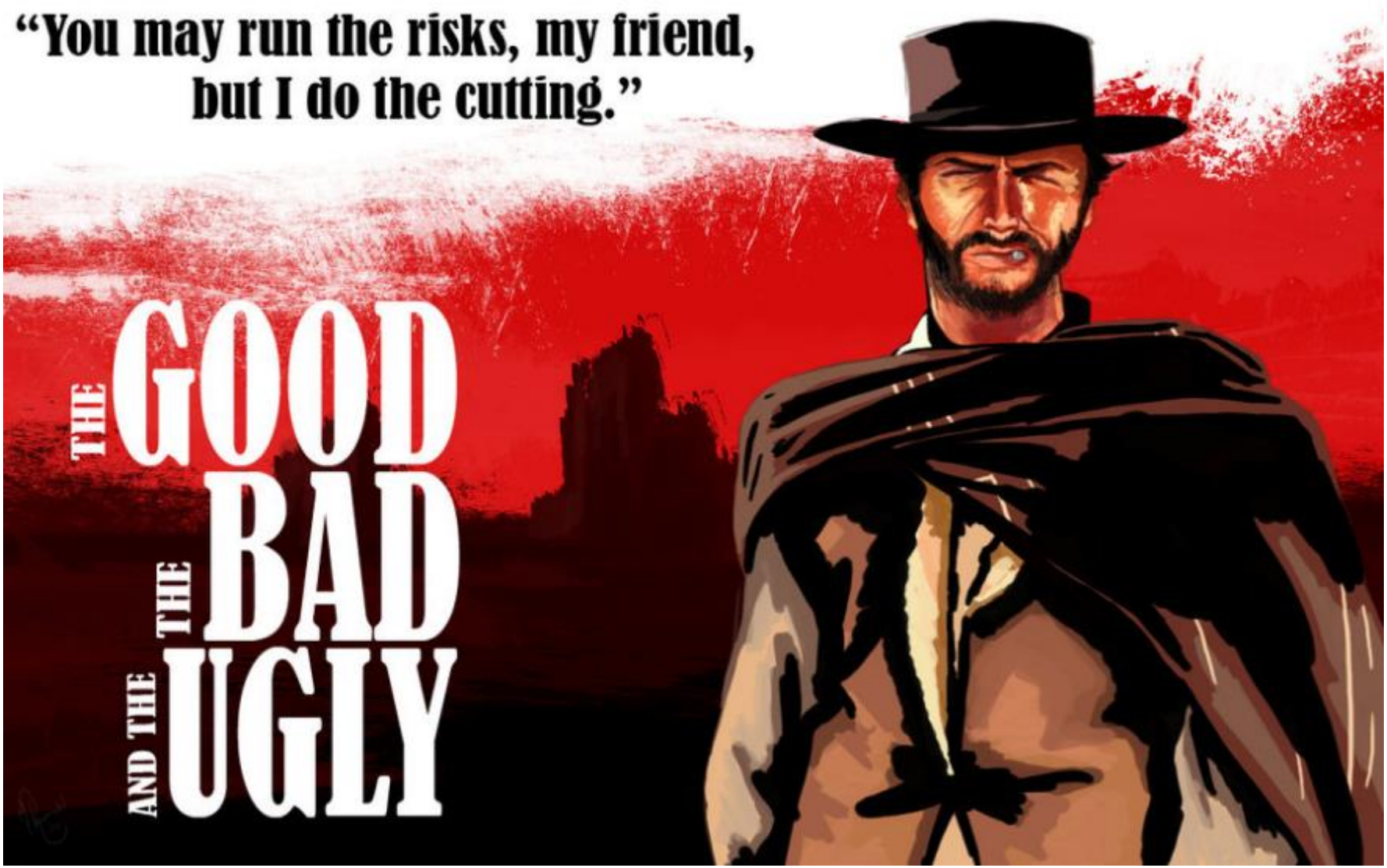


Figure 2: **Mechanisms of transcoelomic metastasis in ovarian cancer**
Step 1: Epithelial ovarian cancer cell (green) detaches after altered gene expression. Step 2: peritoneal or ascitic current (blue arrows) facilitates peritoneal, lymphatic, and haematogenous metastasis. Step 3: immune evasion by complement inhibition and secretion of FAS ligand. Step 4: spheroid formation. Step 5: ascitic components stimulate further metastastic progression. Step 6: peritoneal activation and implantation. B7-H4= Immune costimulatory protein B7-H4; CXCL12=ligand of chemokine (CXC motif) receptor 4 (CXCR4); FHL1= factor H-like protein 1; LPA=lysophosphatidic acid; MMP=matrix metallopeptidase; VEGF=vascular endothelial growth factor.

Treating PSM in 2016



2016 : The Good

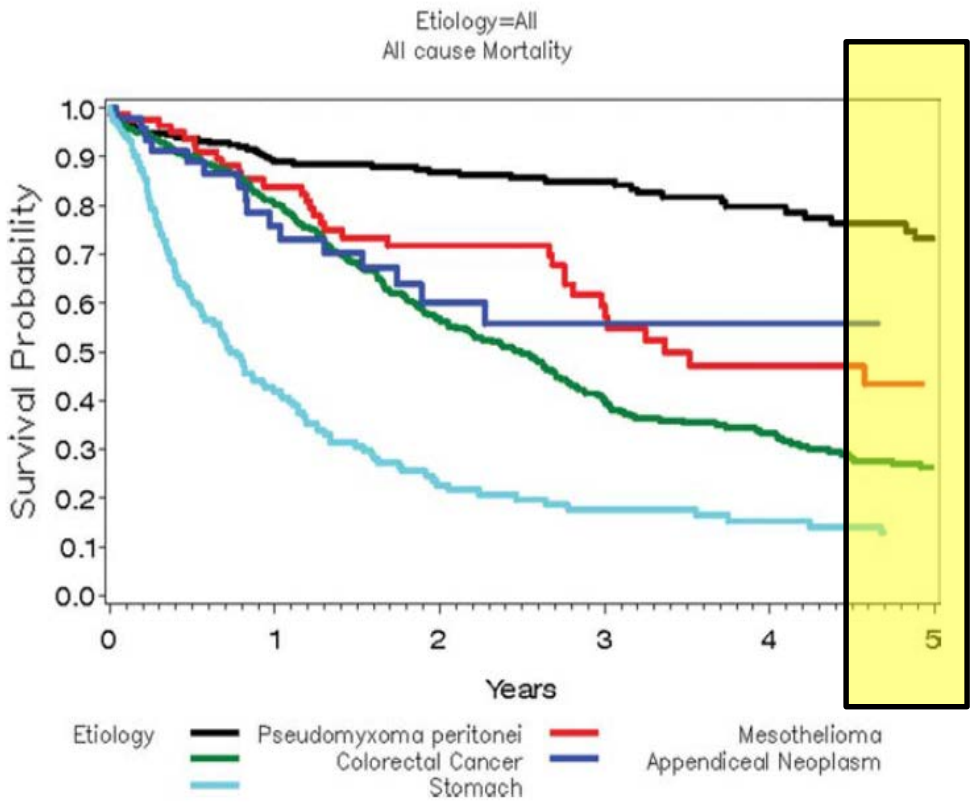


Figure 3. Overall survival rates are illustrated for patients with colorectal peritoneal carcinomatosis (PC), pseudomyxoma peritonei, peritoneal mesothelioma, gastric PC, and PC from appendiceal adenocarcinoma.

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

2016 : The Bad (PALLIATION BY DEFAULT)

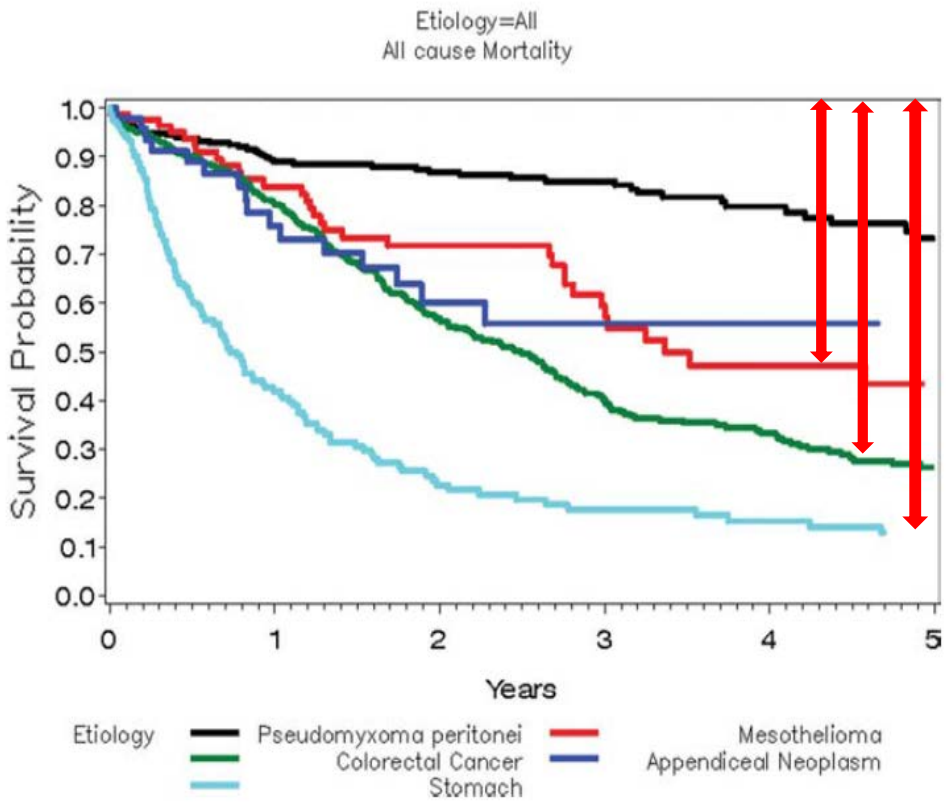


Figure 3. Overall survival rates are illustrated for patients with colorectal peritoneal carcinomatosis (PC), pseudomyxoma peritonei, peritoneal mesothelioma, gastric PC, and PC from appendiceal adenocarcinoma.

Toward Curative Treatment of Peritoneal Carcinomatosis From Nonovarian Origin by Cytoreductive Surgery Combined With Perioperative Intraperitoneal Chemotherapy

A Multi-Institutional Study of 1290 Patients

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

2016 : The Ugly

Quality of life after cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy: A prospective study of 216 patients

G. Passot [a,b], N. Bakrin [a,b], A.S. Roux [c], D. Vaudoyer [a], F.-N. Gilly [a,b], O. Glehen [a,b,*], E. Cotte [a,b]

Table 3
Factors influencing quality of life at 3, 6 and 12 months in uni and multivariate analysis.

		Baseline − 3 months				Baseline − 6 months				Baselin − 12 months			
		Deterioration $N = 85$	No deterioration $N = 75$	P^a	OR (95% CI)[b]	Deterioration $N = 53$	No deterioration $N = 103$	P^a	OR (95% CI)[b]	Deterioration $N = 40$	No deterioration $N = 88$	P^a	OR (95% CI)[b]
Gender	Women	56 (49.56)	57 (50.44)	0.161	–	37 (32.74)	76 (67.26)	0.599	–	30 (32.26)	63 (67.74)	0.688	–
	Men	29 (61.70)	18 (38.30)			16 (37.21)	27 (62.79)			10 (28.57)	25 (71.43)		
Age	mean (std)	57.12 ± 9.89	56.98 ± 10.52	0.879	–	56.76 ± 10.75	57.48 ± 9.88	0.902	–	55.89 ± 9.28	57.51 ± 10.24	0.290	–
Gilly Score	1–2	21 (43.75)	27 (56.25)	0.117	X	18 (37.50)	30 (62.50)	0.588	–	9 (25.00)	27 (75.00)	0.380	–
	3–4	63 (57.27)	47 (42.73)			35 (33.02)	71 (66.98)			30 (32.97)	61 (67.03)		
PCI	0–14	54 (49.54)	55 (50.46)	0.220	–	31 (29.25)	75 (70.75)	0.056	X	20 (22.99)	67 (77.01)	0.003	X
	15–39	30 (60.00)	20 (40.00)			22 (44.90)	27 (55.10)			20 (48.78)	21 (51.22)		
Length of surgery >270 min	No	38 (51.35)	36 (48.65)	0.720	–	20 (28.17)	51 (71.83)	0.142	X	12 (20.00)	48 (80.00)	0.011	3.0 (1.3–6.9)
	Yes	45 (54.22)	38 (45.78)			32 (39.51)	49 (60.49)			27 (40.91)	39 (59.09)		
Major resection	No	23 (46.00)	27 (54.00)	0.223	–	10 (20.00)	40 (80.00)	0.011	X	9 (21.43)	33 (78.57)	0.094	X
	Yes	62 (56.36)	48 (43.64)			43 (40.57)	63 (59.43)			31 (36.05)	55 (63.95)		
CC score	0-1	78 (51.66)	73 (48.34)	0.175	–	50 (33.78)	98 (66.22)	1.0	–	38 (31.15)	84 (68.85)	1.000	–
	2-3	7 (77.78)	2 (22.22)			3 (37.50)	5 (62.50)			2 (33.33)	4 (66.67)		
Grade III-Iv complications	No	48 (50.00)	48 (50.00)	0.332	–	29 (30.85)	65 (69.15)	0.311	–	22 (27.85)	57 (72.15)	0.292	–
	Yes	37 (57.81)	27 (42.19)			24 (38.71)	38 (61.29)			18 (36.73)	31 (63.27)		
Origin	Other	18 (81.82)	4 (18.18)	0.001	7.6 (2.3–25.3)	12 (52.17)	11 (47.83)	0.113	X	6 (54.55)	5 (45.45)	0.065	X
	Colon	25 (65.79)	13 (34.21)		3.2 (1.4–7.6)	14 (38.89)	22 (61.11)			5 (16.67)	25 (83.33)		
	Ovarian	22 (37.29)	37 (62.71)		1.6 (0.7–3.6)	15 (25.00)	45 (75.00)			14 (28.57)	35 (71.43)		
	Peritoneum	20 (48.78)	21 (51.22)			12 (32.43)	25 (67.57)			15 (39.47)	23 (60.53)		
Stoma	No	58 (50.43)	57 (49.57)	0.276	–	30 (26.79)	82 (73.21)	0.002	3 (1.5–6.2)	23 (25.27)	68 (74.73)	0.022	–
	Yes	27 (60.00)	18 (40.00)			23 (52.27)	21 (47.73)			17 (45.95)	20 (54.05)		
Recurrence	No	82 (53.25)	72 (46.75)		–	46 (31.94)	98 (68.06)	0.108	X	22 (23.16)	73 (76.84)	0.001	4.4 (1.8–10.5)
	Yes	3 (50.00)	3 (50.00)			7 (58.33)	5 (41.67)			18 (54.55)	15 (45.45)		

Treating PSM in 2016

CHEMOSURGERY

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TREATING PC WITH ‘ CHEMOSURGERY ‘ ?

- Combined multi-organ resections
- Peritonectomy-procedures

→ Treatment of MACROSCOPIC disease

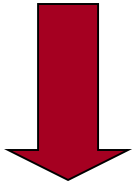
- Intraperitoneal Chemotherapy

→ Treatment of MICROSCOPIC disease

‘ It’s not what the surgeon removes that kills the patients, but what he leaves behind ‘

TREATING PC WITH ‘ CHEMOSURGERY ‘ ?

CYTOREDUCTIVE SURGERY + INTRACAVITARY CHEMOTHERAPY



HIPEC	**H**yperthermic **I**ntraperitoneal **Pe**roperative **C**hemotherapy
EPIC	**E**arly **P**ostoperative **I**ntraperitoneal **C**hemotherapy
BIC	**B**idirectional **I**ntraoperative **C**hemotherapy

THE SURGERY IN CHEMOSURGERY

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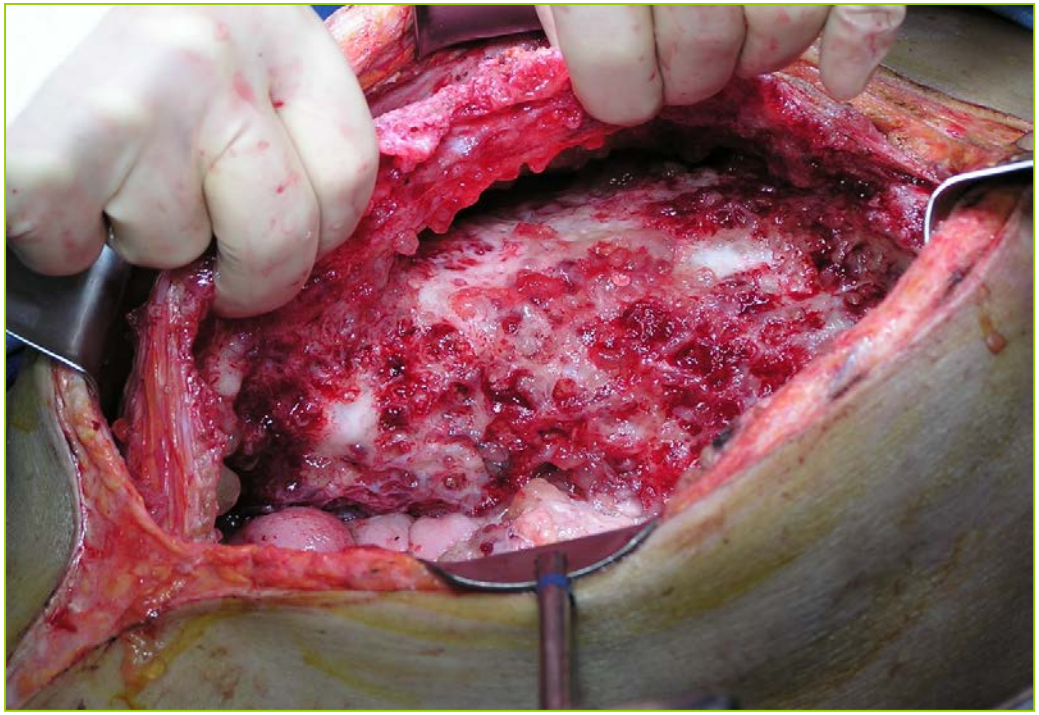
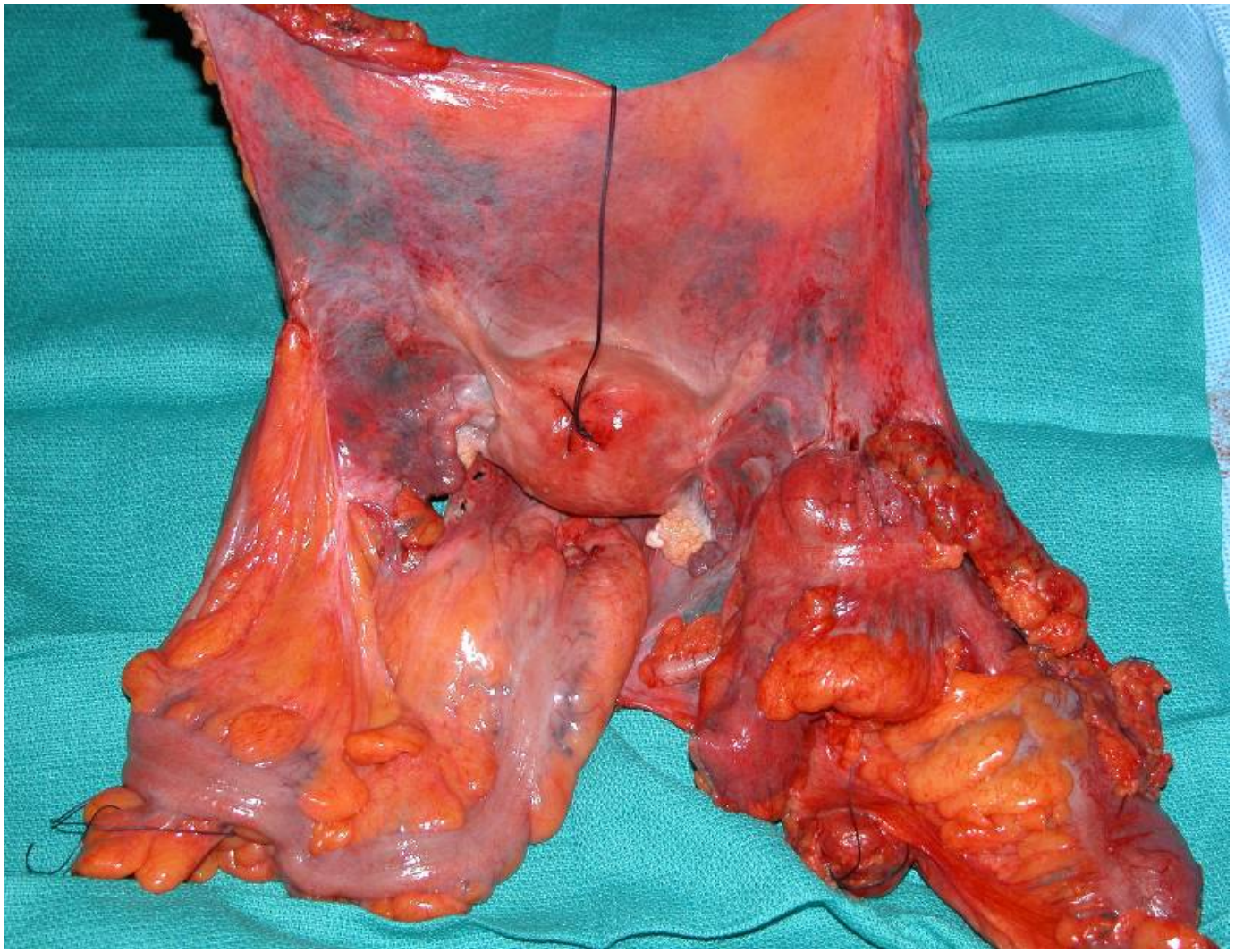
The Surgery in Chemosurgery

- Combined multi-organ resections
- Peritonectomy-procedures

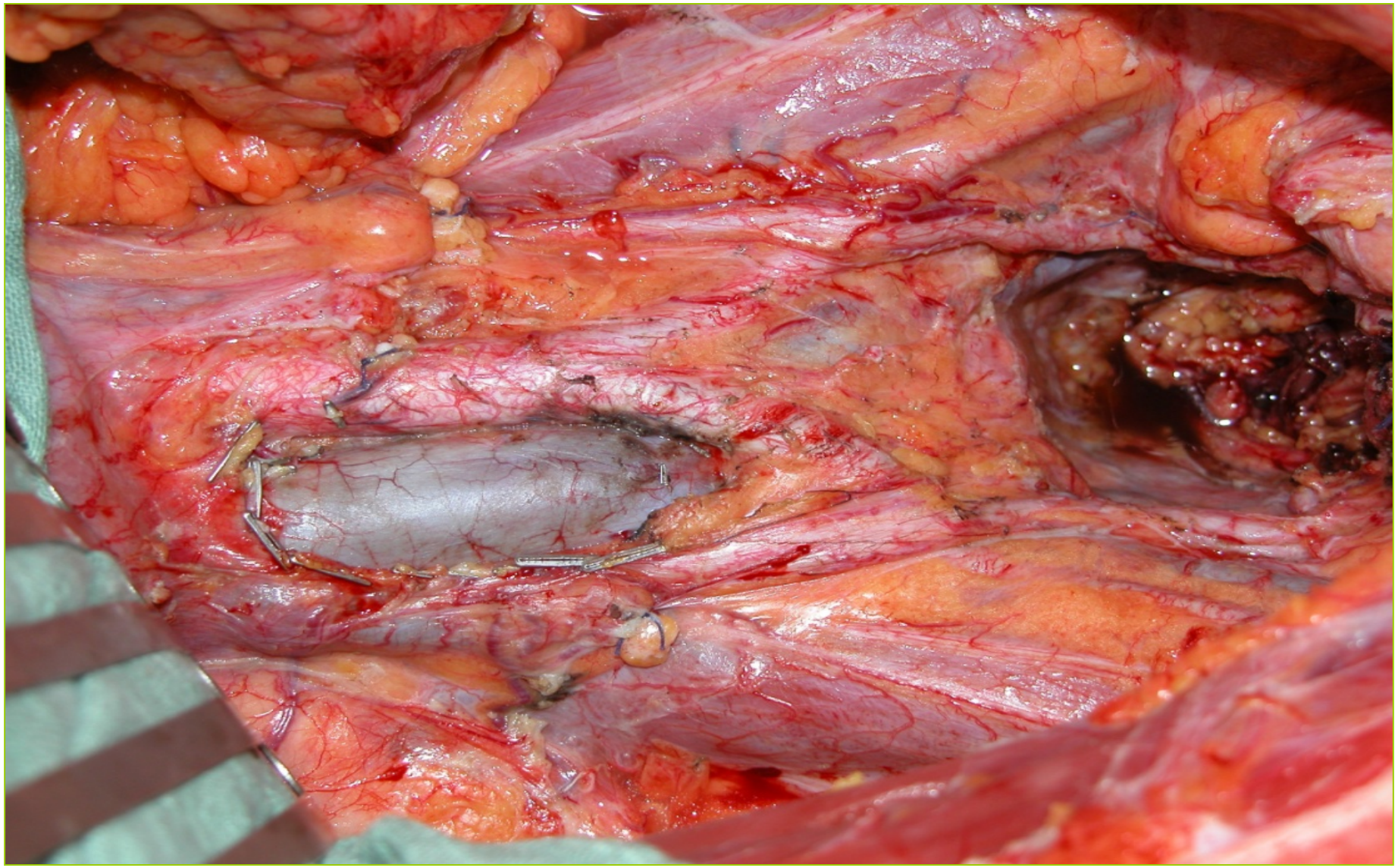
→ Treatment of MACROSCOPIC disease



The Surgery in Chemosurgery



The Surgery in Chemosurgery



THE CHEMO IN CHEMOSURGERY

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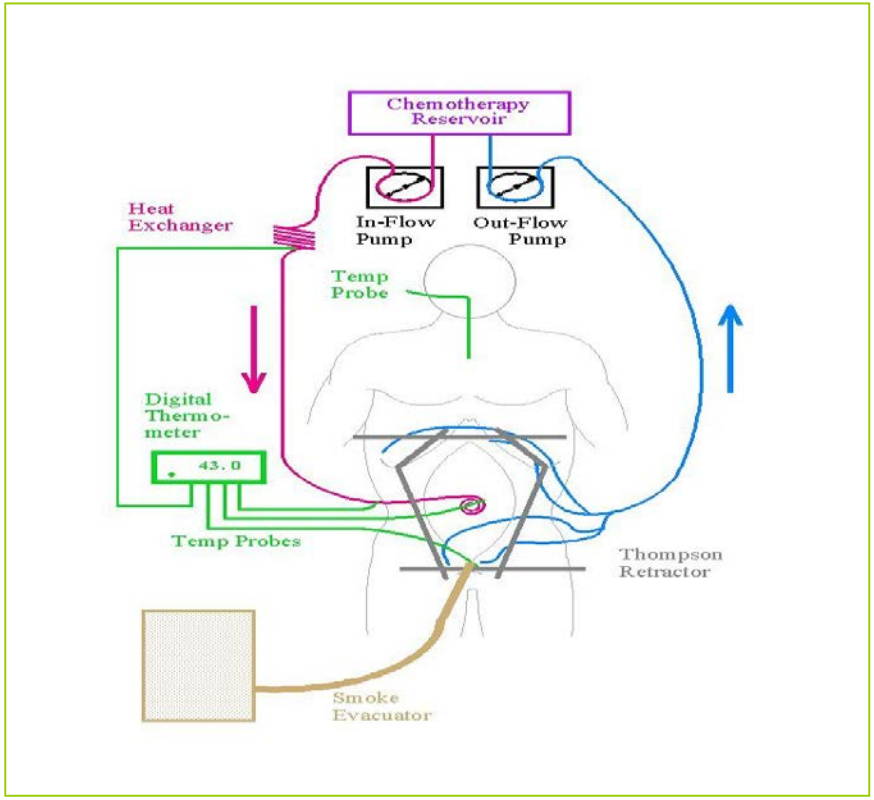
The Chemo in Chemosurgery

- Hyperthermic Intraperitoneal

  Peroperative Chemotherapy (HIPEC)

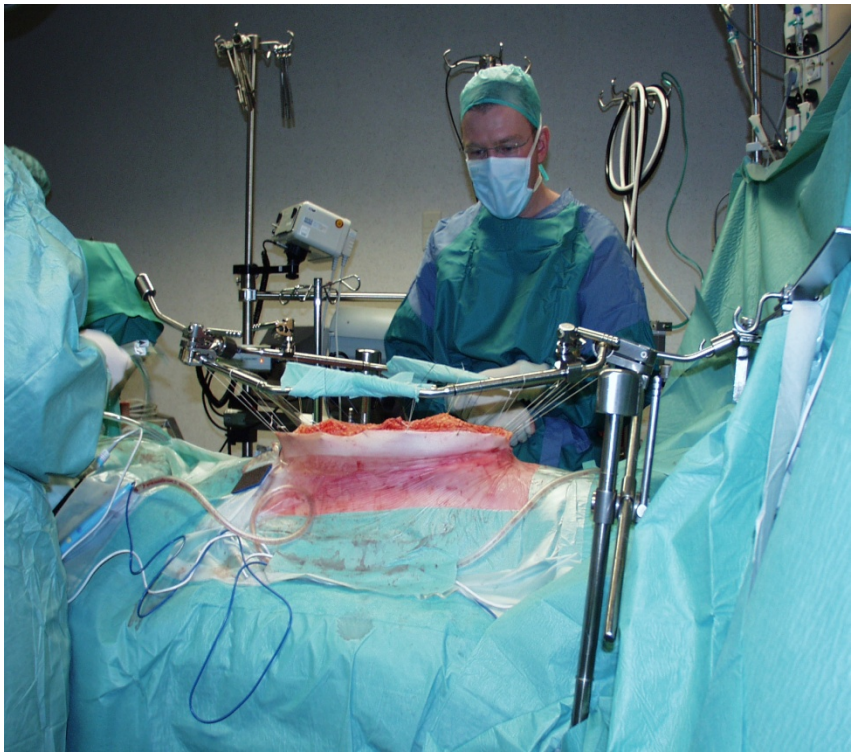
→ Treatment of MICROSCOPIC disease

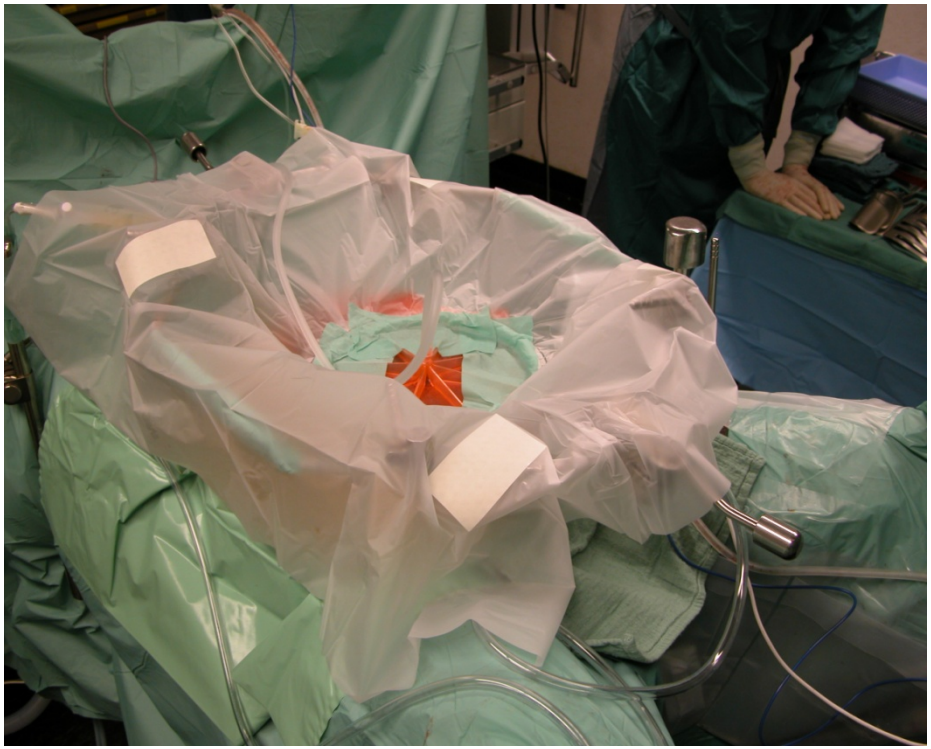


The Chemo in Chemosurgery

- Hyperthermic Intraperitoneal

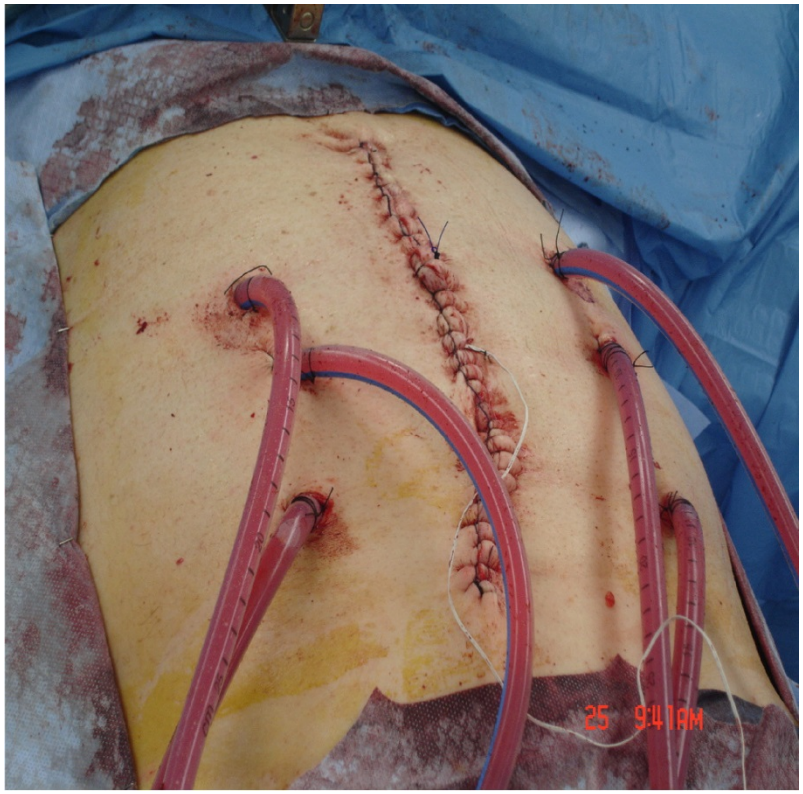
  Peroperative Chemotherapy (HIPEC)

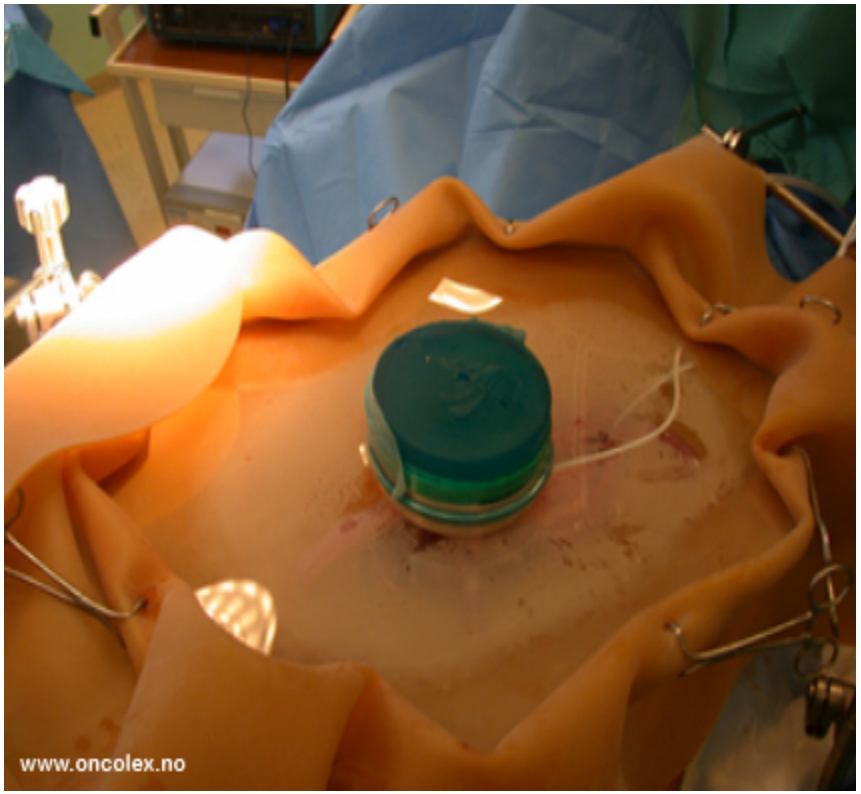




The Chemo in Chemosurgery

HIPEC (SEMI) CLOSED TECHNIQUE





Rationale for HIPEC

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DOSE INTENSIFICATION

"***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

Dedrick RL et al. Cancer Treat Rep 1978; 62(1):673-88.

DOSE INTENSIFICATION

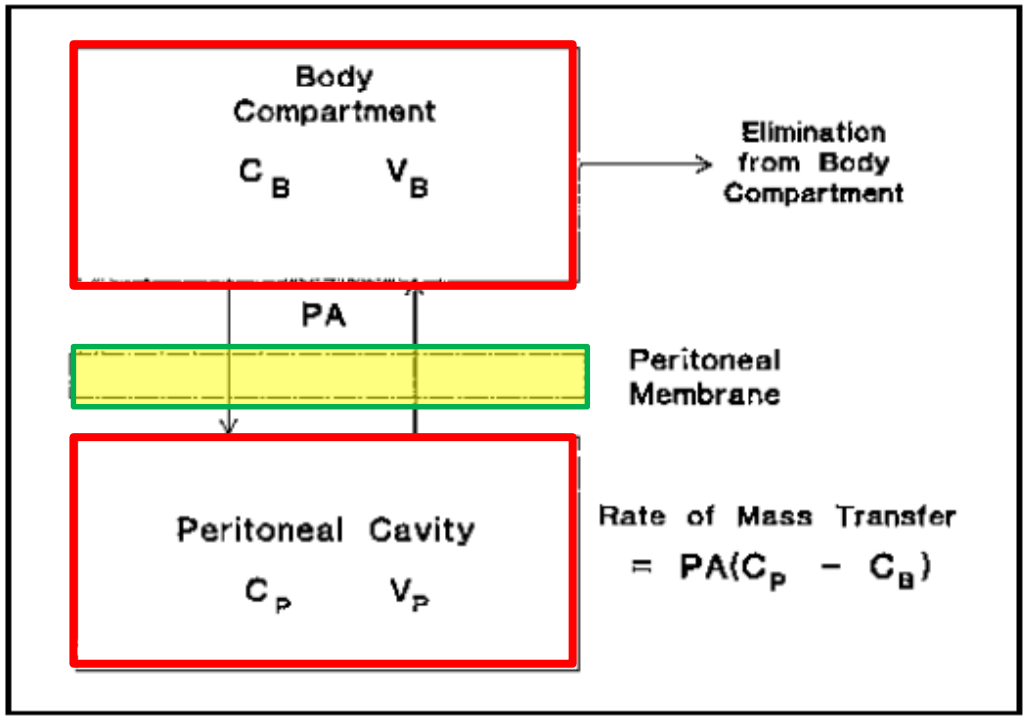


Fig. 1. Traditional two-compartment model of peritoneal transport, in which transfer of a drug from the peritoneal cavity to the blood occurs across the ''peritoneal membrane.'' The permeability-area product (PA) governs this transfer and can be calculated by measuring the rate of drug disappearance 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.

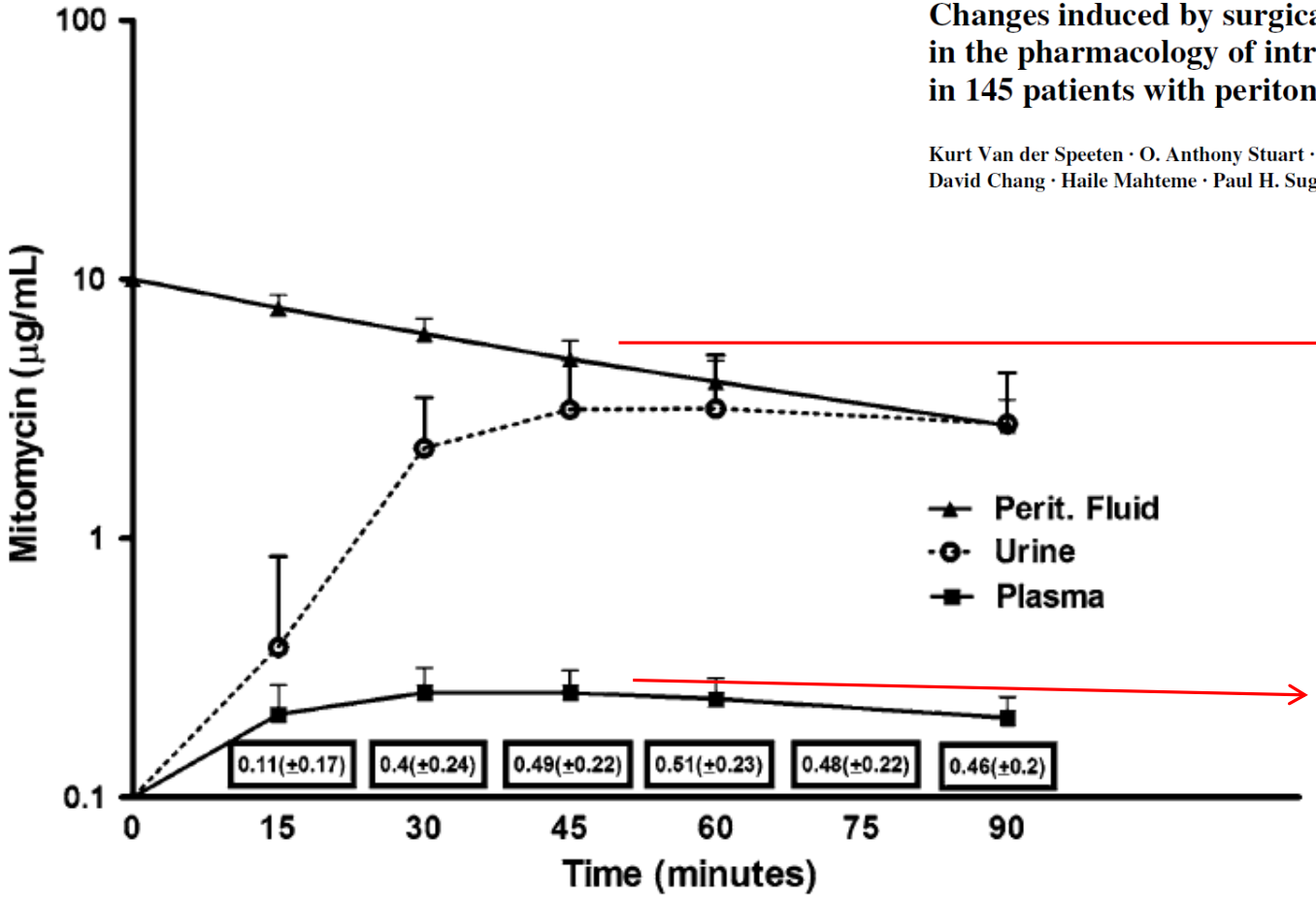
Rate of mass transfer = PA (C_P – C_B)

Journal of the National Cancer Institute, Vol. 89, No. 7, April 2, 1997

DOSE INTENSIFICATION

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



EFFICACY

TOXICITY

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

Cancer Chemother Pharmacol. 2011 Jul; 68(1): 147-56.

DO WE NEED HIPEC ?

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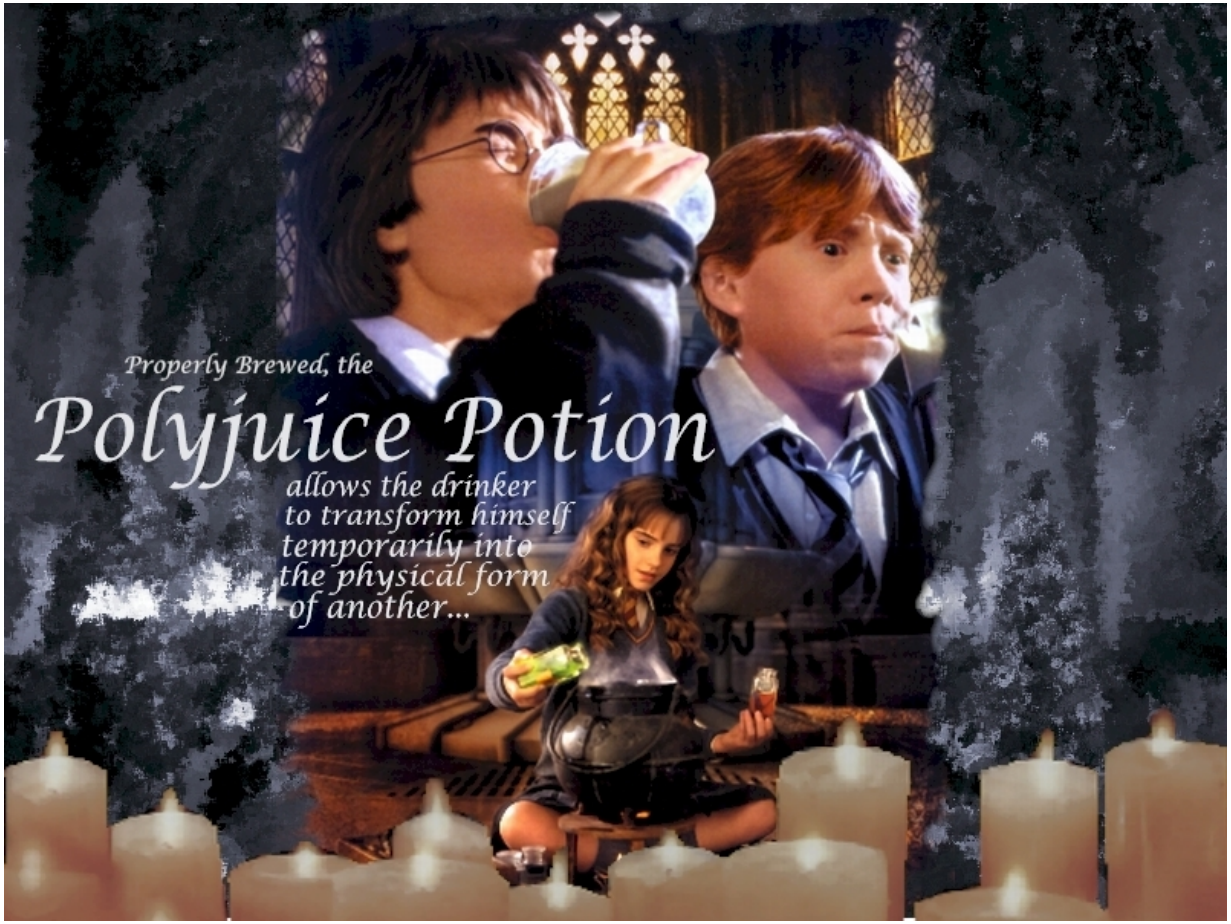
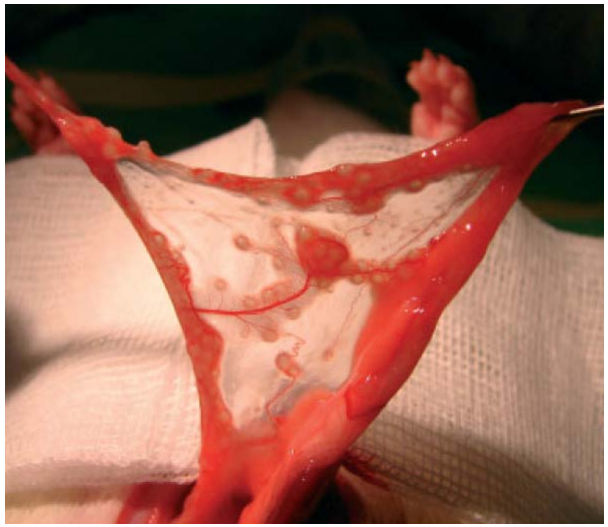
Do we need HIPEC ?

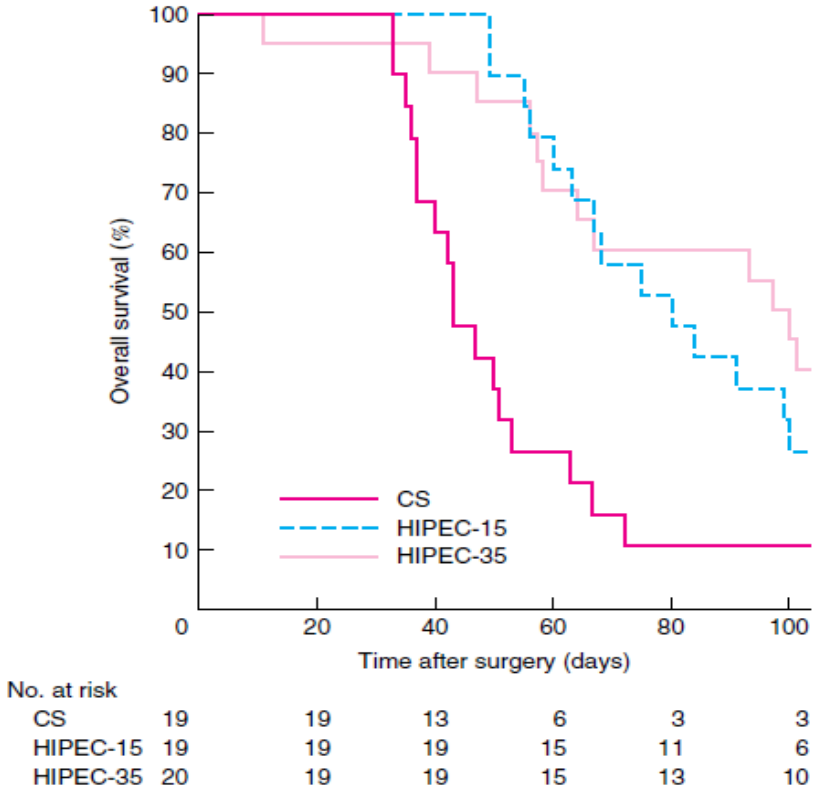


Do we need HIPEC ?

Intraoperative hyperthermic intraperitoneal chemotherapy after cytoreductive surgery for peritoneal carcinomatosis in an experimental model

Y. L. B. Klaver[1], T. Hendriks[2], R. M. L. M. Lomme[2], H. J. T. Rutten[1], R. P. Bleichrodt[2] and I. H. J. T. de Hingh[1]





No. at risk

CS	19	19	13	6	3	3
HIPEC-15	19	19	19	15	11	6
HIPEC-35	20	19	19	15	13	10

Fig. 4 Kaplan–Meier survival curves for the three treatment groups. CS, cytoreductive surgery; HIPEC-15, CS + hyperthermic intraperitoneal chemotherapy (HIPEC) with 15 mg/m^2 mitomycin C; HIPEC-35, CS + HIPEC with 35 mg/m^2 mitomycin C. $P = 0{\cdot}003$ for CS *versus* HIPEC-15, $P < 0{\cdot}001$ for CS *versus* HIPEC-35 (log rank test)

British Journal of Surgery 2010; **97**: 1874–1880

Now that we have proven
the concept
how do we further improve it

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Rationale for EPIC

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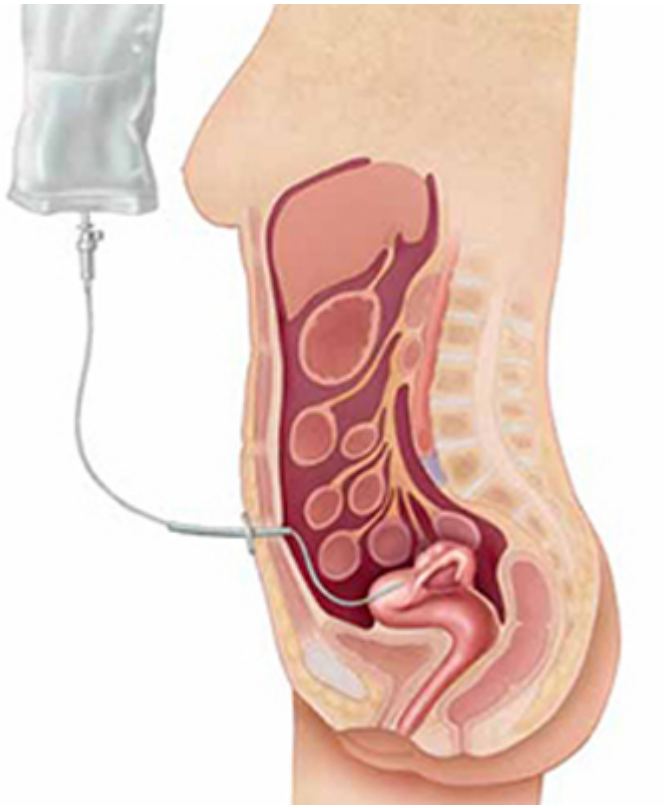
Rationale for EPIC



Add to____ ml 1.5 % dextrose peritoneal dialysis solution (a) _____ mg 5-fluoruracil (650 mg/m^2 X____ m^2) (maximum dose 1,500 mg) and (b) 50 meq. sodium bicarbonate.

Intraperitoneal fluid volume: 1 liter for patients ≤ 2.0 m^2, 1.5 liters for > 20 m^2.

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 chemoterapy 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.

Journal of Surgical Oncology 2010;102:730–735

Rationale for EPIC

Pharmacology of Perioperative 5-Fluorouracil

K. VAN DER SPEETEN, MD,[1]* O.A. STUART, BS,[2] H. MAHTEME, MD, PhD,[3] AND PAUL H. SUGARBAKER, MD, FACS, FRCS[2]
[1]Department of Surgical Oncology, Ziekenhuis Oost-Limburg, Genk, Belgium
[2]Washington Cancer Institute, Washington Hospital Center, Washington, District of Columbia
[3]Department of Surgical Sciences, Section of Surgery, Akademiska Sjukhuset, Uppsala University Hospital, Uppsala, Sweden

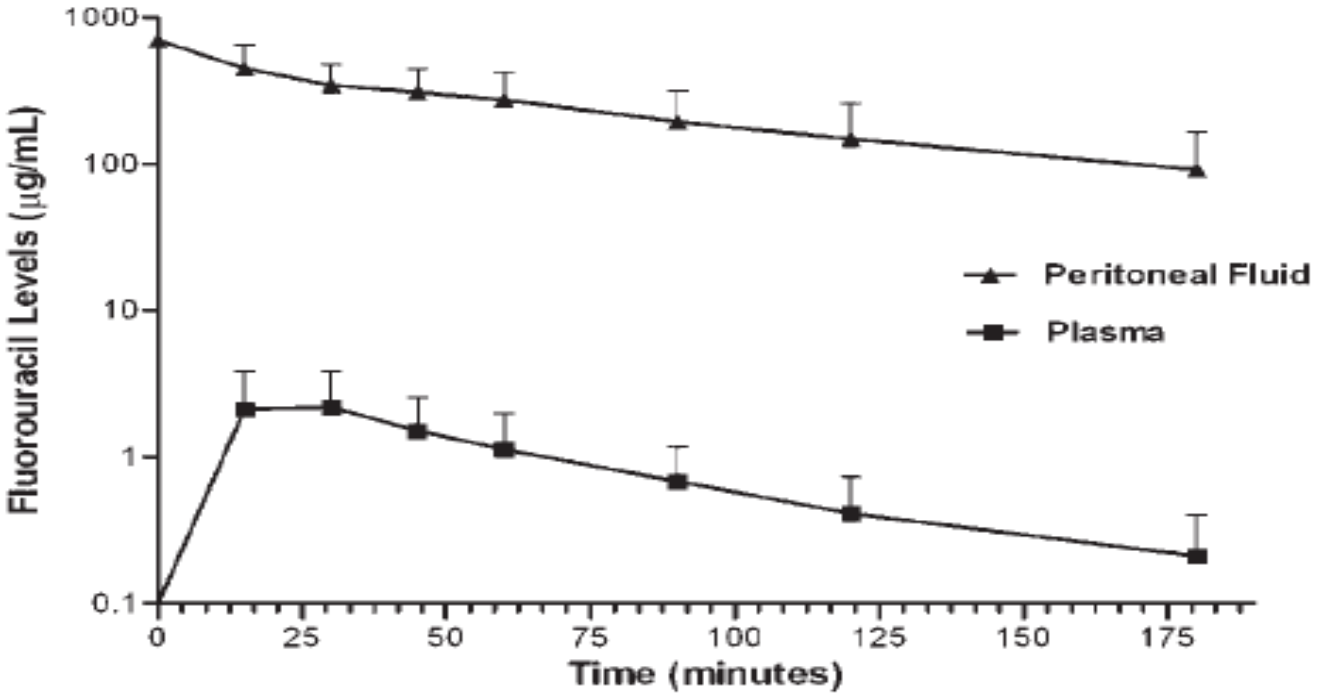


Fig. 1. 5-Fluorouracil concentrations in peritoneal fluid and plasma after early postoperative intraperitoneal chemotherapy administration (N = 9).

Journal of Surgical Oncology 2010;102:730–735

Rationale for Bidirectional Intraoperative Chemotherapy (BIC)

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Introduction : concept of BIC

Heated intra-operative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis: pharmacokinetics and tissue distribution

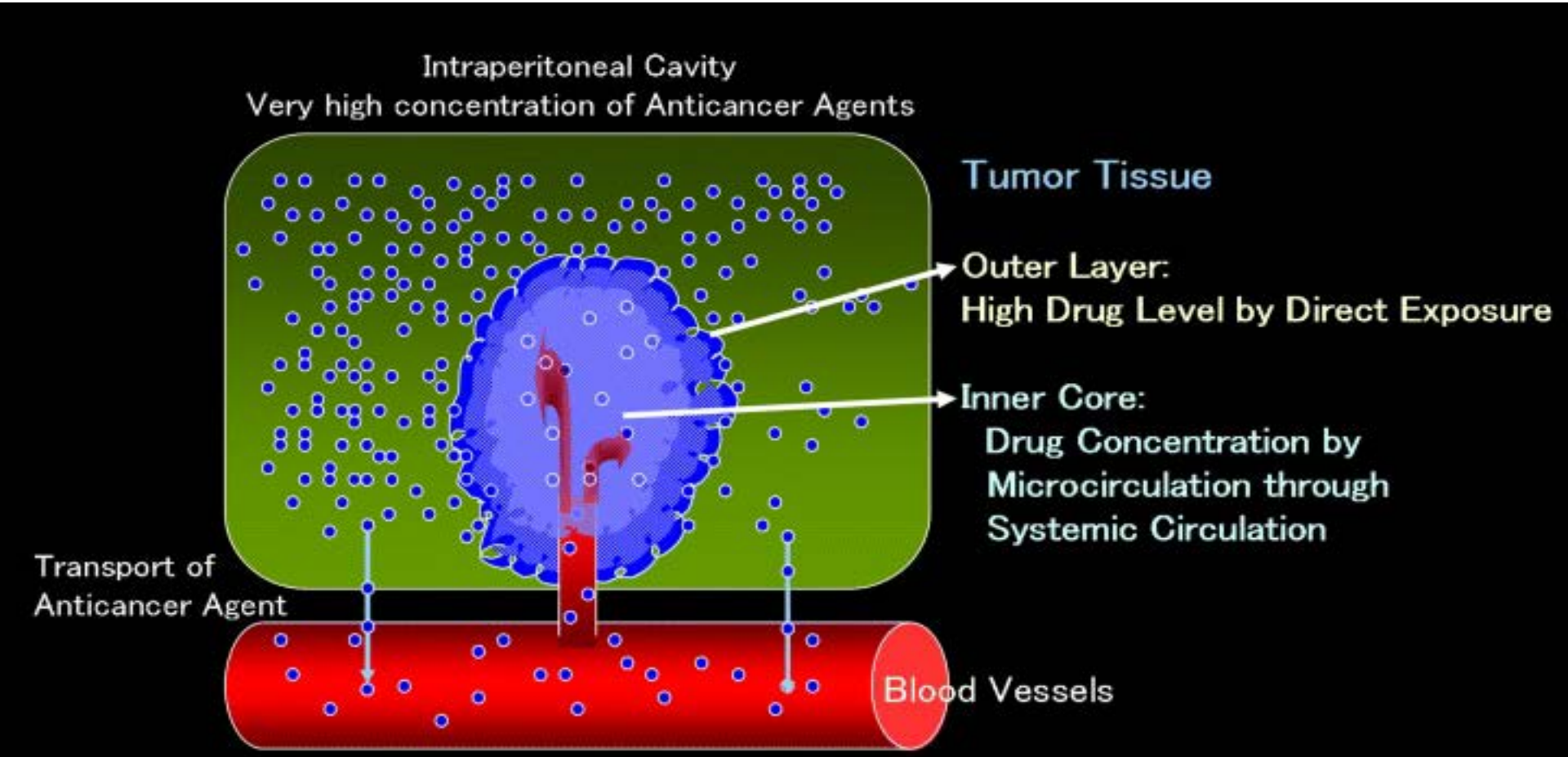
D. Elias*, M. Bonnay, J. M. Puizillou, S. Antoun, S. Demirdjian, A. El Otmany, J. P. Pignon, L. Drouard-Troalen, J. F. Ouellet & M. Ducreux

One hour before IPCH we delivered systemic intravenous leucovorin 20 mg/m^2 and 5-FU 400 mg/m^2 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/m^2 was chosen to avoid intensifying the aggressiveness of combined complete cytoreductive surgery and IPCH.

Annals of Oncology 13: 267–272, 2002

TIMING OF PERIOPERATIVE IV CHEMOTHERAPY

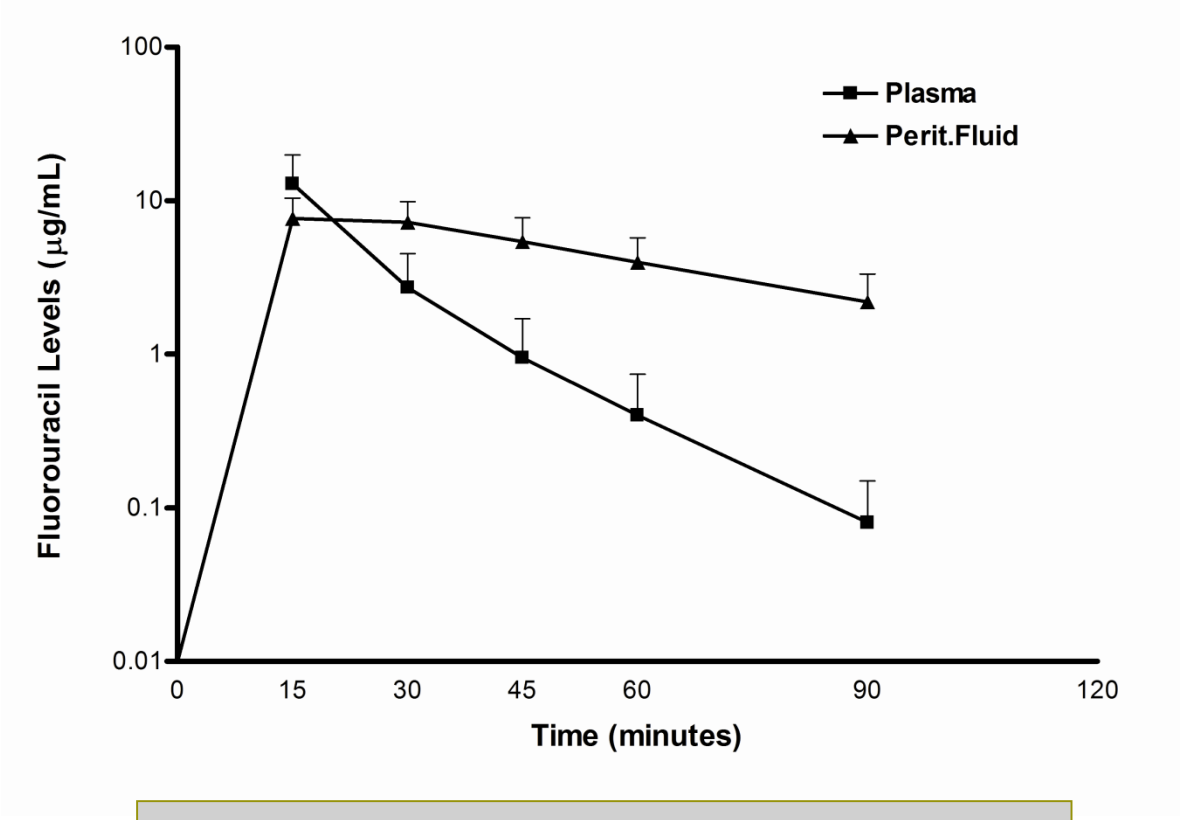
Pharmacologic concept of bidirectional (IV and IP) chemotherapy



Modified from Fujiwara K. Int J Gynecol Cancer 2007,17,1-20

TIMING OF PERIOPERATIVE IV CHEMOTHERAPY

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**

Journal of Surgical Oncology 2010;102:730–735

TIMING OF PERIOPERATIVE IV CHEMOTHERAPY

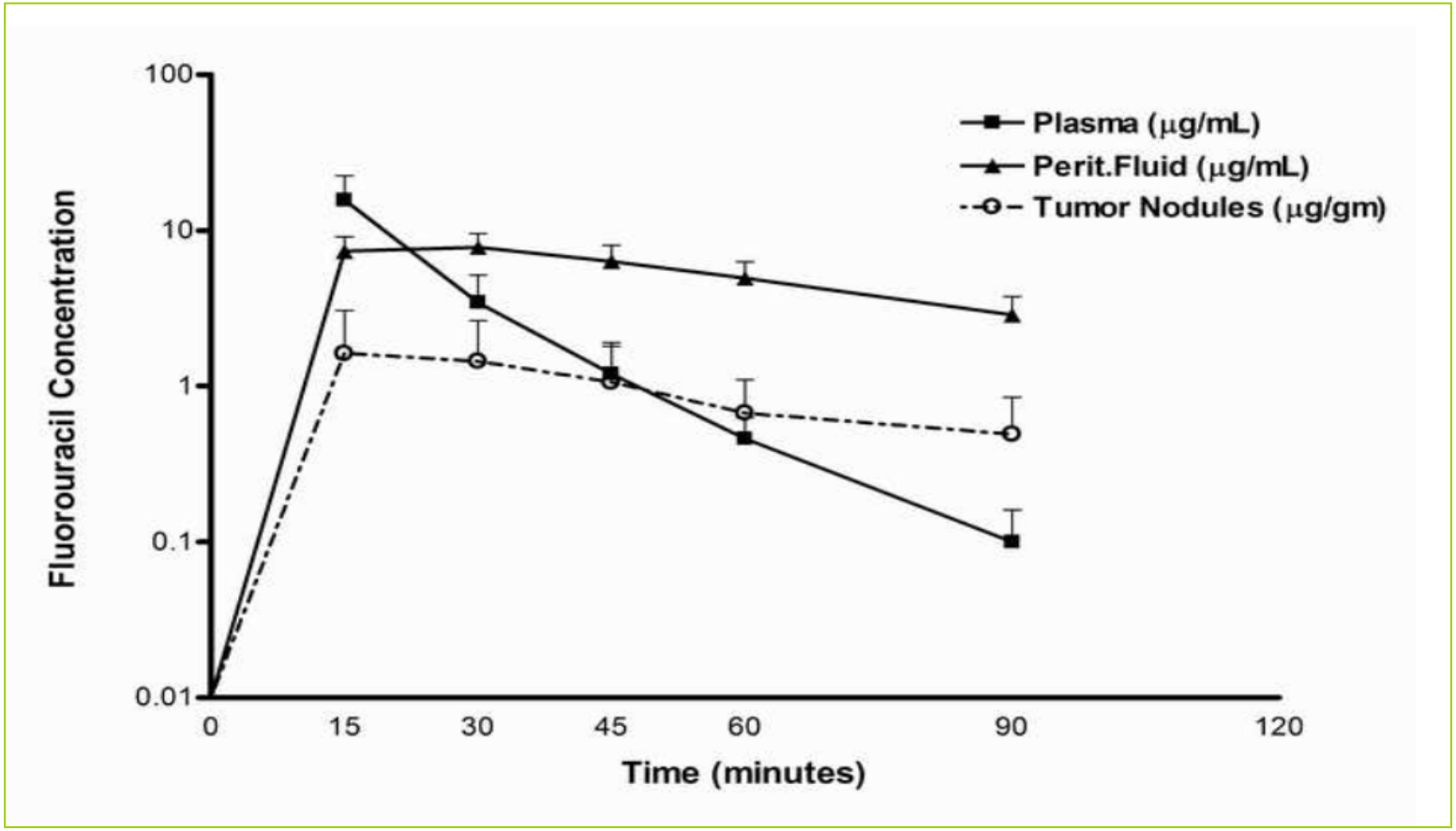


FIGURE 3: 5-Fluorouracil concentrations in plasma, peritoneal fluid and tumor nodules after intravenous administration during hyperthermic intraperitoneal chemotherapy procedure (N=9).

Now that we have proven
the concept
how do we decrease the Ugly

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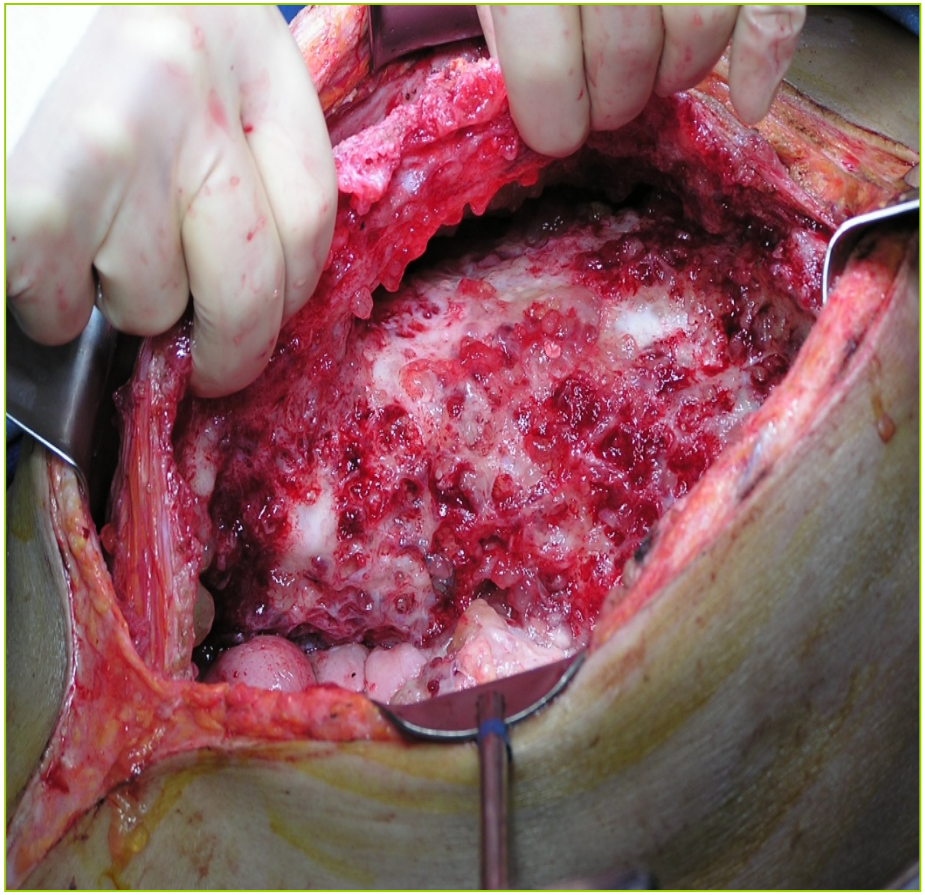


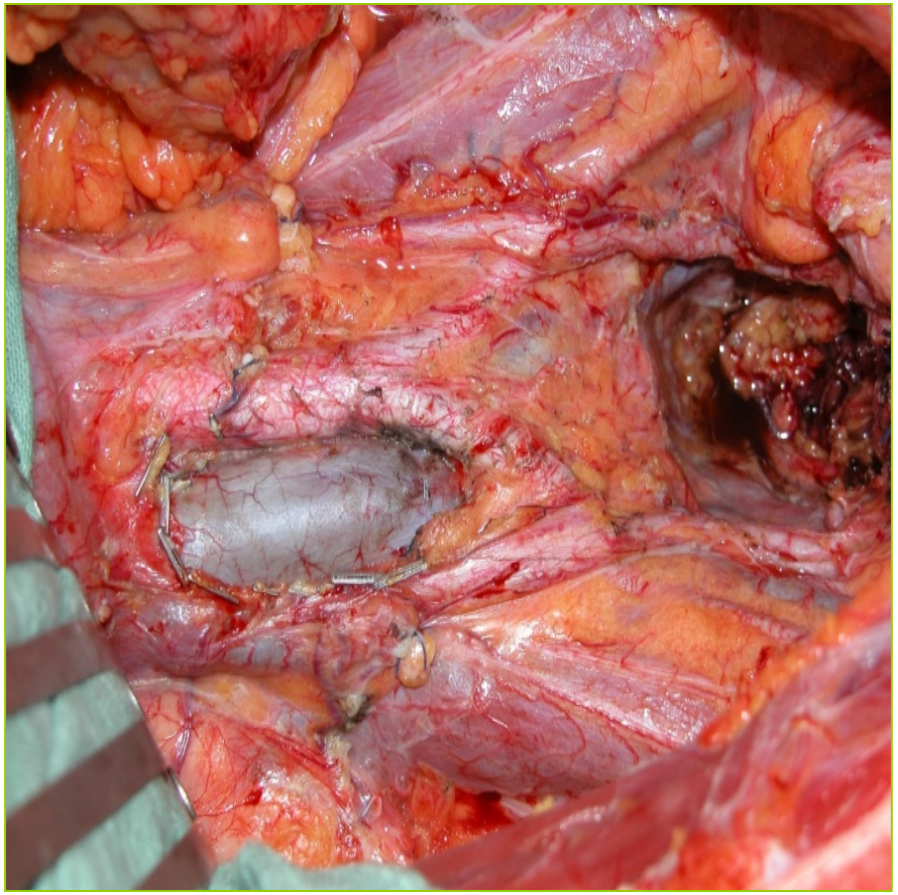


TABLE 5. Perioperative Factors and Mortality Outcomes of 24 Institutions Following Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy

First Author	Mean Length of Hospital Stay (d)	Mean Length of ICU Stay (d)	Treatment Related Deaths (n)	Mortality (%)	Causes
Glehen et al[8]	11.8	NR	7	3.2	Septic shock, peritonitis, pulmonary embolism, multi-organ failure, aplasia, myocardial necrosis, acute renal failure
Ahmad et al[9]	11*	NR	0	0	—
Schmidt et al[10]	25*	5*	3	4.5	Peritonitis, pneumonia, sepsis from bone marrow toxicity
Kecmanovic et al[11]	14.2	NR	0	0	—
Yonemura et al[12]	NR	NR	3	2.8	Renal failure, multi-organ failure, and bleeding
Rufian et al[13]	11*	NR	0	0	—
Kusamura et al[14]	23	3	2	0.9	Duodenal perforation, colic perforation, and sepsis
Sugarbaker et al[15]	21*	NR	7	2	Systemic inflammatory response, fistula, unknown (3), pulmonary embolus, neutropenia
Roviello et al[16]	29	NR	1	1.6	Multiorgan failure
Zanon et al[17]	NR	NR	1	4	Pulmonary embolus
Cavaliere et al[18]	NR	NR	4	3.3	NR
Tuttle et al[19]	9*	NR	0	0	—
Capone et al[20]	48*	NR	5	17	NR
Elias et al[21]	24	NR	4	4	Postinhalation lung infection (3), ischaemic gut
Levine et al[22]	15	2	22	4.4	Wound infection, haematologic toxicity, sepsis, respiratory failure, anastomotic leak, pneumonia, enterocutaneous fistula
Smeenk et al[23]	17*	NR	18	5.8	NR
Kianmanesh et al[24]	27	NR	1	2.3	NR
Helm et al[25]	11.5	NR	1	6	Pulmonary embolus
Gusani et al[26]	12*	3*	2	1.6	Unknown, died of the malignancy
van Leeuwen et al[27]	15*	1*	1	1	Cerebral infarction
Di Giorgio et al[28]	22	2	2	4	Pulmonary embolus (2)
Harrison et al[29]	7	NR	0	0	—
Ceelen et al[30]	19*	3*	0	0	—
Morris†	31	5	5	2	Sepsis and multiorgan failure (5)
Range	7–48	1–5	0–22	0–17	—
Mean	19	3	3.7	2.9	—

*Refers to median.
†Unpublished data.

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

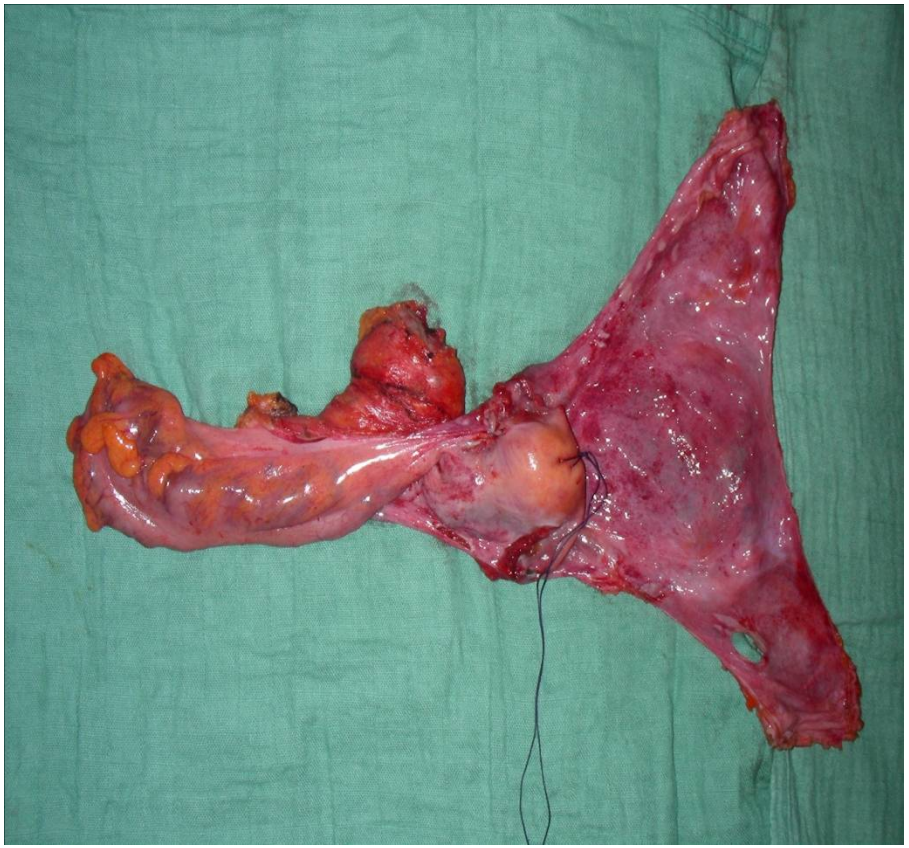
TABLE 6. Perioperative Morbidity Outcomes of 24 Institutions Following Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy

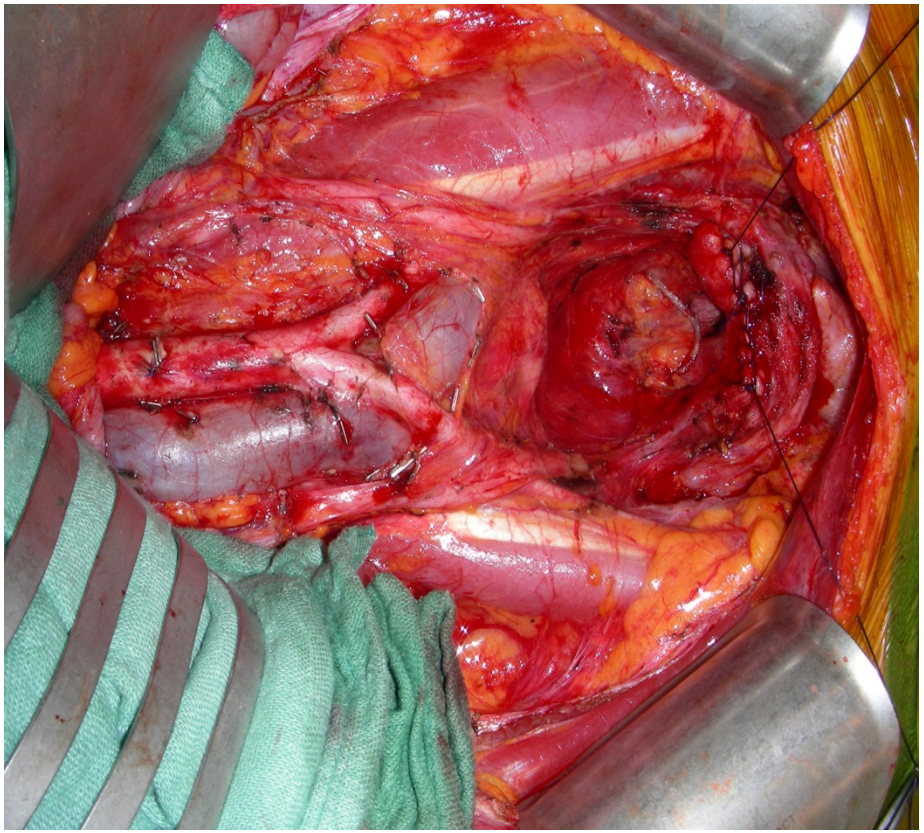
First Author	Combined Major or Grade III/IV Morbidity (%)	Re-Operation (%)	Sepsis (%)	Fistula (%)	Abscess (%)	Hematological Toxicity (%)	Ileus (%)	Renal Insufficiency (%)	Perforation (%)	DVT/PE (%)	Anastomotic Leak (%)
Glehen et al[8]	25	NR	3	7	7	5	5	1	1	3	NR
Ahmad et al[9]	26	6	0	9	9	0	2	0	3	3	0
Schmidt et al[10]	NR	22	6	7	7	3	0	2	2	0	9
Kecmanovic et al[11]	0	0	0	0	0	11	17	0	0	0	0
Yonemura et al[12]	NR	NR	—	1	6	—	—	2	2	—	6
Rufian et al[13]	36	6	0	0	0	0	3	0	3	0	0
Kusamura et al[14]	12	NR	2	1	NR	1	2	NR	3	0.5	8
Sugarbaker et al[15]	14	11	NR	2	1	NR	NR	NR	NR	2	2
Roviello et al[16]	28	8	0	9	3	9	2	3	NR	0	NR
Zanon et al[17]	NR	8	0	0	0	0	0	4	0	0	8
Cavaliere et al[18]	23	NR	NR	NR	NR	20	NR	NR	5	NR	3
Tuttle et al[19]	NR	0	0	11	11	0	0	0	0	9	0
Capone et al[20]	27	NR	NR	NR	17	NR	10	7	10	NR	7
Elias et al[21]	52	23	NR	23	8	11	86	3	0	NR	0
Levine et al[22]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Smeenk et al[23]	51	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kianmanesh et al[24]	NR	5	NR	9	14	NR	14	7	NR	NR	NR
Helm et al[25]	NR	22	11	6	6	28	0	0	0	6	0
Gusani et al[26]	30	NR	4	2	4	NR	NR	NR	0	2	7
van Leeuwen et al[27]	43	18	8	5	9	7	2	0	3	2	4
Di Giorgio et al[28]	26	13	0	9	0	0	0	0	0	2	0
Harrison et al[29]	NR	NR	0	0	5	0	10	0	0	0	5
Ceelen et al[30]	24	10	0	0	0	0	0	0	4	0	4
Morris*	43	16	14	13	37	0	8	1	5	3	NR
Range	0–52	0–23	0–14	0–23	0–37	0–28	0–86	0–7	0–10	0–9	0–9
Mean	28.8	11.2	3	5.7	7.2	5.6	9.5	1.7	2.2	1.9	3.5

*Unpublished data.

Positioning

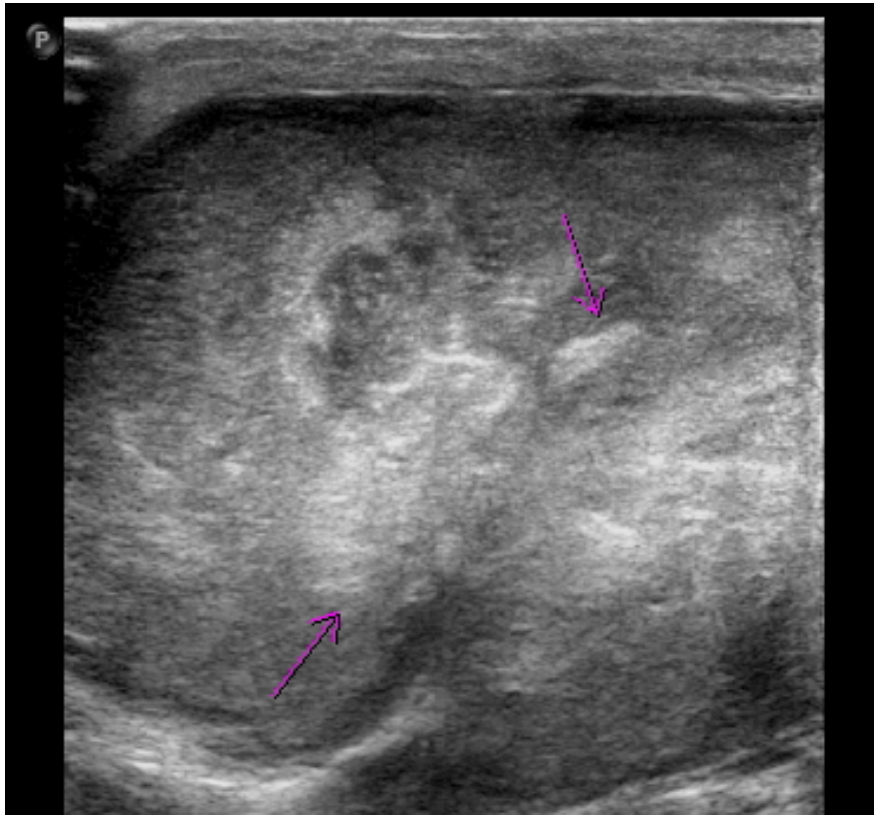
CASE-REPORT

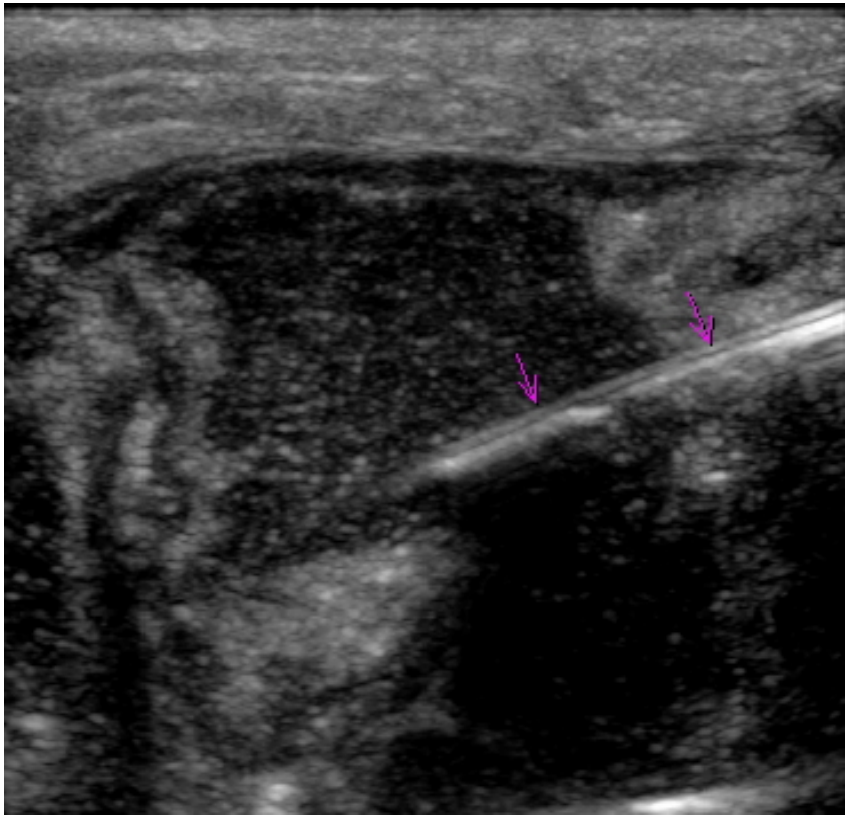




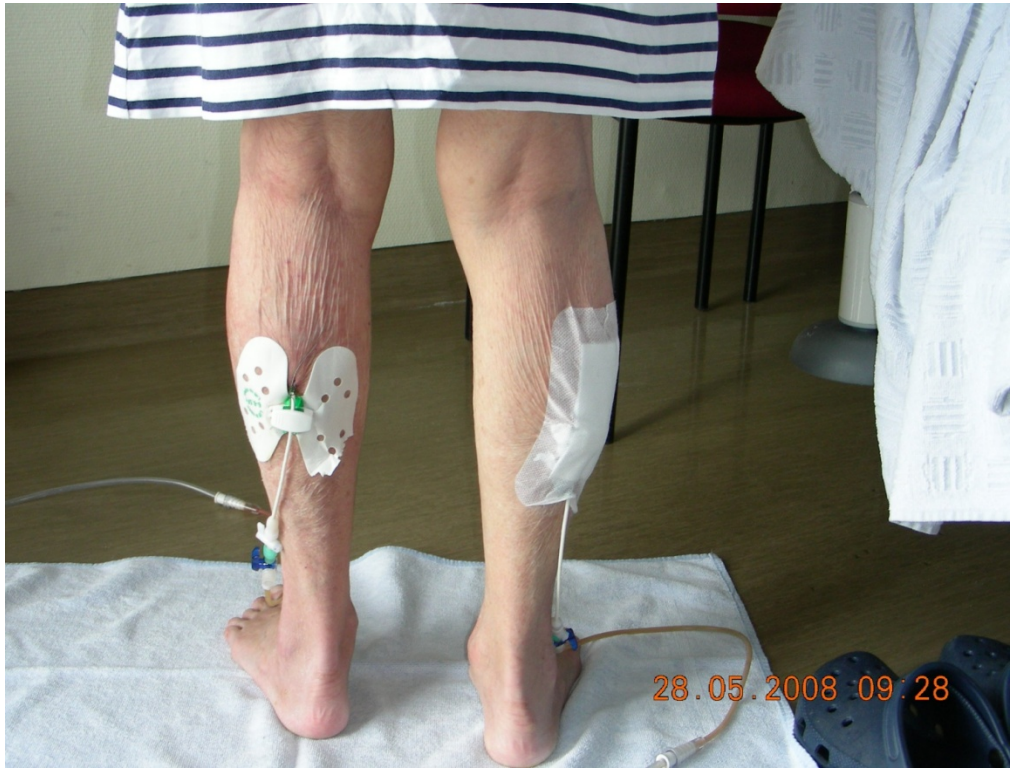
AVC, 54 yrs, ovarian PC, OVHIPEC Trial protocol, CC0 cytoreduction

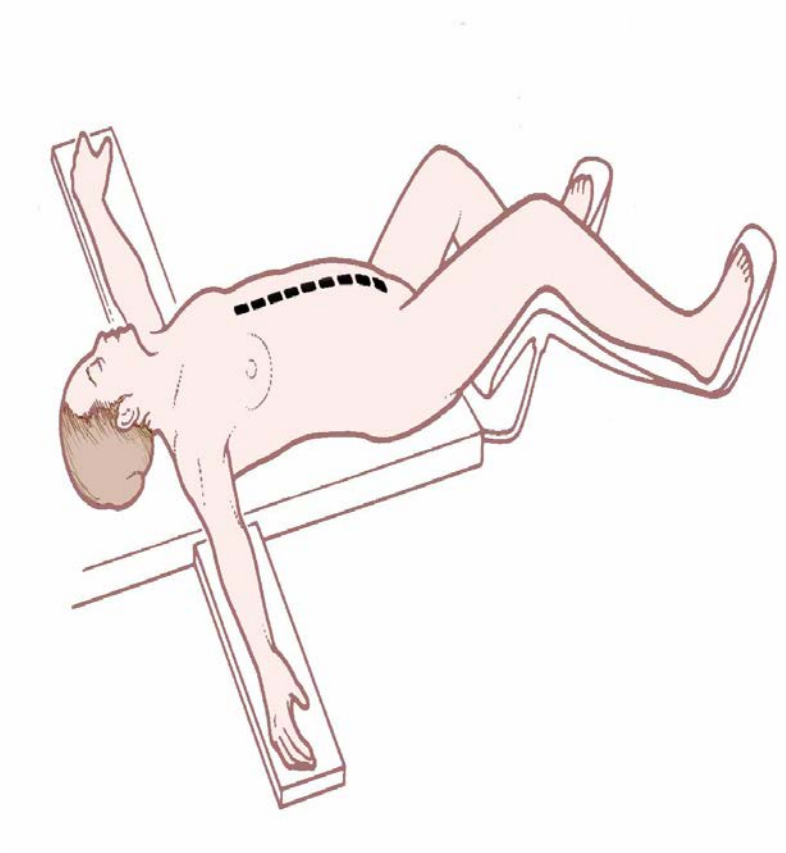
CASE-REPORT





CASE-REPORT





- **Do the positioning yourself**
- **Modified ‘modified’ lithotomy position**
- **Regular pausing of the pneumatic compression stockings**

Anesthetic pitfalls

SEVERE HYPONATREMIA, 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 Mortier[4]

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

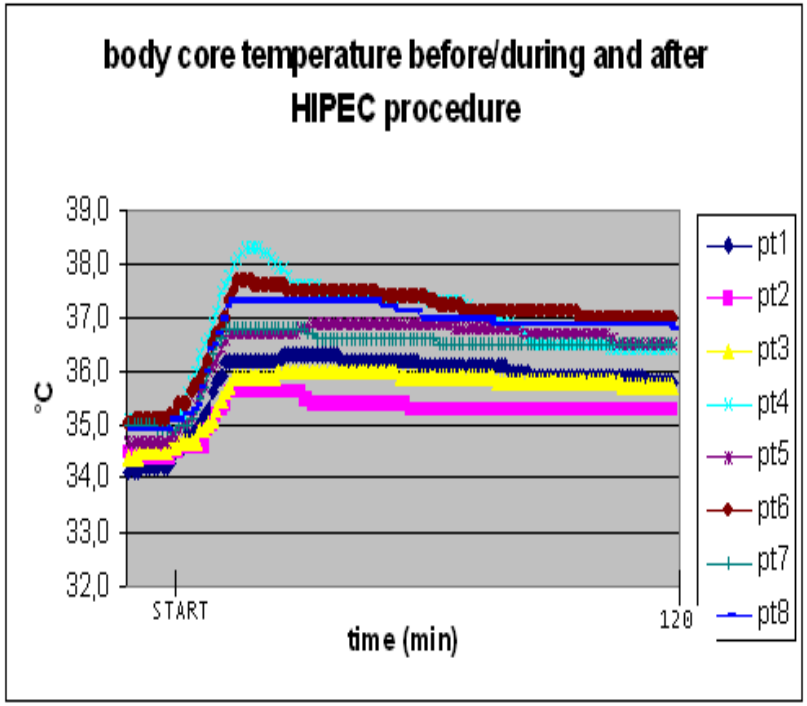
CASE REPORT

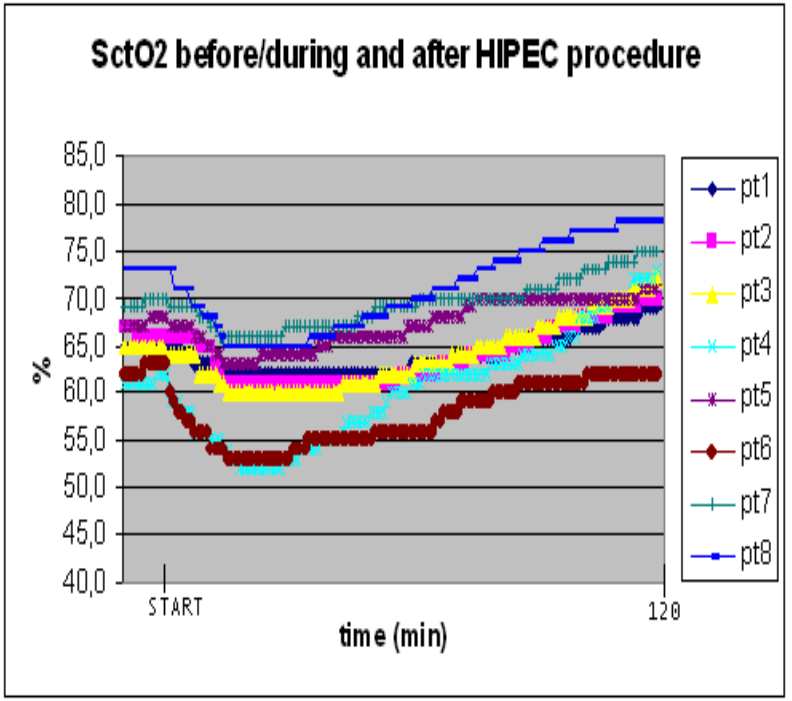
Ventricular tachycardia during hyperthermic intraperitoneal chemotherapy

C. A. Thix,[1] I. Königsrainer,[2] R. Kind,[3] P. Wied[1] and T. H. Schroeder[1]

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

MONITORING OF BRAIN OXYGENATION DURING HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC) PROCEDURES





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.

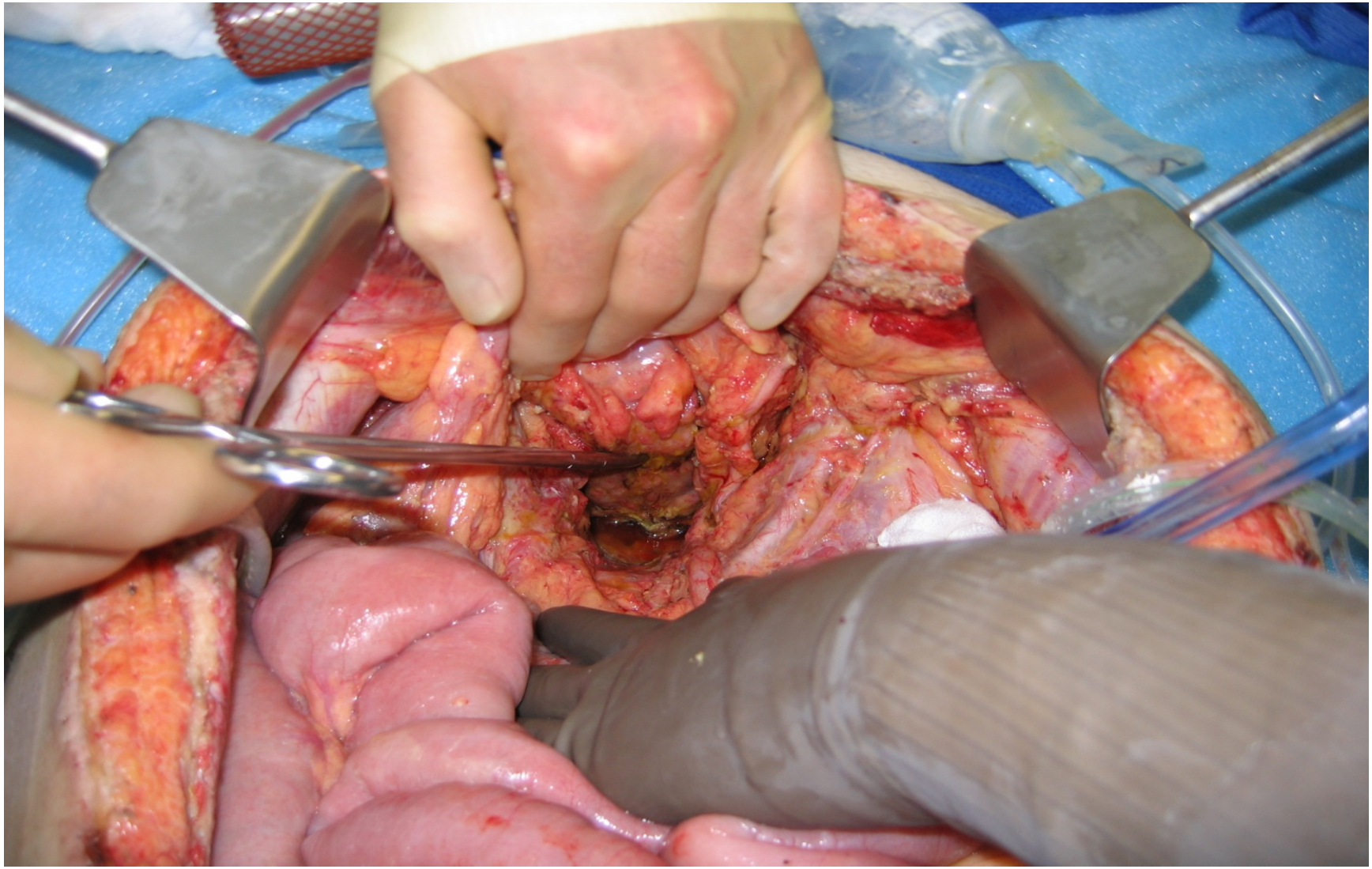
Eur J Anaesthesiol 2009; 26 (Suppl 45): 44.

- proper training of anesthesiologists is mandatory
- Train the whole team !!!

Anastomotic

Leaks

CASE-REPORT



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

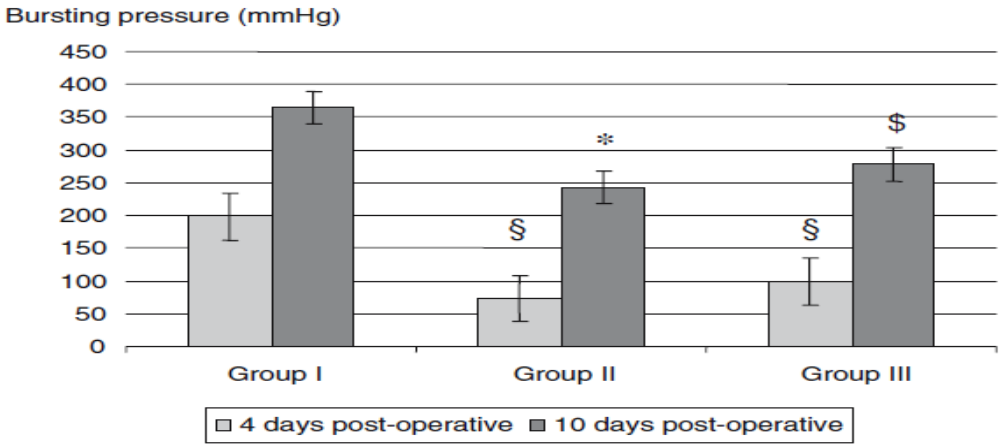


Fig. 1 Anastomotic strength post-operatively. The median are given for bursting pressure. (Group I: control without treatment; group II: anastomosis was performed before HIPEC; group III: anastomosis was performed before HIPEC) (§: group III vs group I, $p=0.028$; *: group II vs group I, $p=0.03$; $: group II and group III vs group I, $p=0.24$; Kruskal–Wallis)

Int J Colorectal Dis 2007; 22(8):941-7

Cytoreductive Procedures—Strategies to Reduce Postoperative Morbidity and Management of Surgical Complications With Special Emphasis on Anastomotic Leaks

JOACHIM JAEHNE, MD, PhD, MBA*
Department of General and Visceral Surgery, Diakoniekrankenhaus Henriettenstiftung gGmbH, Marienstrasse, Hannover, Germany

TABLE III. Synopsis of Treatment Options of Anastomotic Leaks After Multivisceral Resections in Peritonectomy and HIPEC

Anastomotic leak	1st treatment option	2nd treatment option
Esophago-jejunostomy	Conservatively; interventional therapy of subphrenic abscess	Resection of the anastomosis
Gastro-jejunostomy	Resection and new anastomosis	Oversewing
Duodenal stump	Oversewing, Rouy-en-Y anastomosis	Interventional therapy
Small bowl	Resection and new anastomosis	Fistula development
Colon anastomosis	Diversion operation	Resection and new anastomosis, eventually percutaneous drainage
Rectal anastomosis	Diversion operation	New anastomosis percutaneous/transabdominal drainage VAC therapy

- **Protect all low rectal anastomoses**
- **More than 2 anastomoses: protect**
- **Aggressive treatment of all leakage**

J. Surg. Oncol. 2009;100:302–305.

Hematologic toxicity

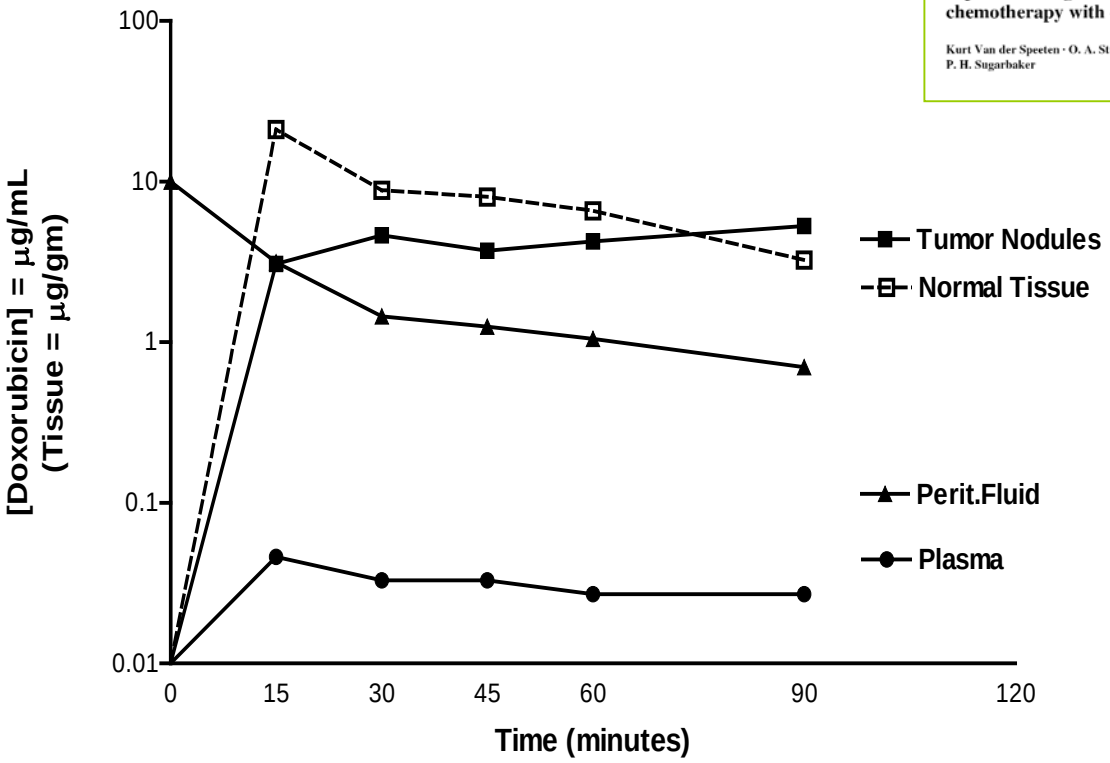
Efficacy versus hematological toxicity

Cancer Chemother Pharmacol
DOI 10.1007/s00280-008-0800-0

ORIGINAL ARTICLE

A pharmacologic analysis of intraoperative intracavitary cancer chemotherapy with doxorubicin

Kurt Van der Speeten · O. A. Stuart · H. Mahteme · P. H. Sugarbaker

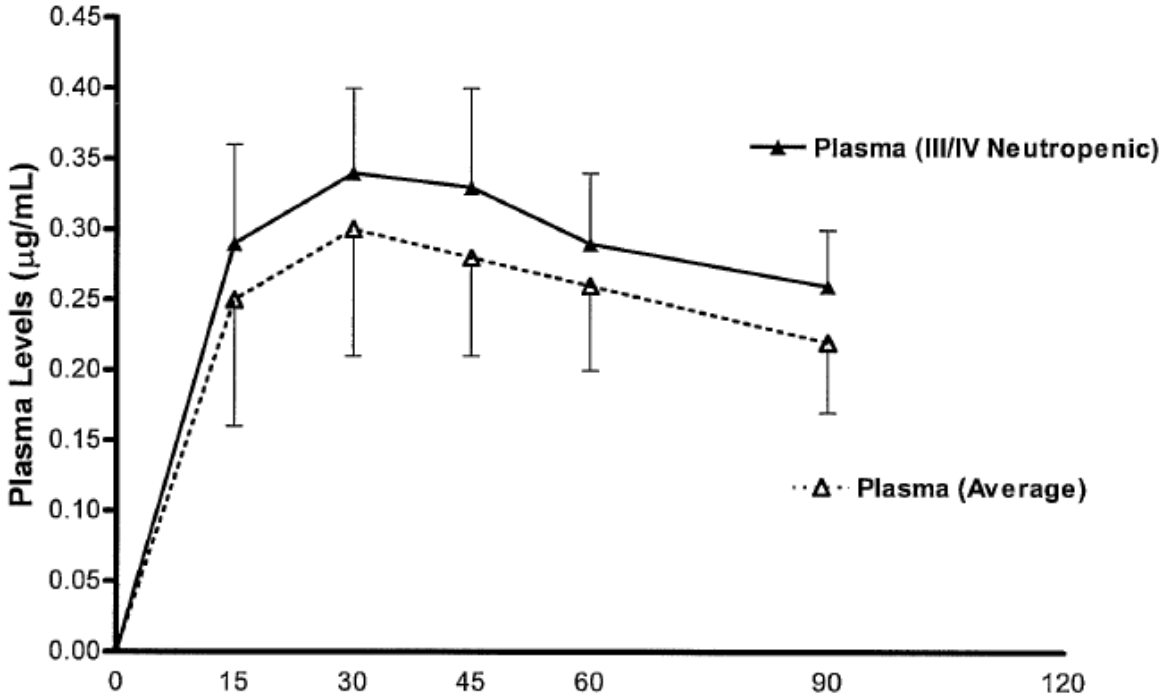


Efficacy

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)



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

Unpublished data

M & M

Learning curve

Ziekenhuis Oost-Limburg

UPPSALA UNIVERSITET

Washington Hospital Center
Washington Cancer Institute

Learning Curve in Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

BIJAN N. MORADI III, MS AND JESUS ESQUIVEL, MD, FACS*
St. Agnes Hospital, Baltimore, Maryland

TABLE I. Overview of Studies Done on the Learning Curve of CRS With PIC

Refs.	Study design	Comparison groups, year range, number of patients (n)	Factors analyzed	Number of surgeons (n)	Same surgical team	Conclusions, learning curve?
Smeenk et al. [3]	Retrospective	Group 1 = 1996–1998 (n = 73); Group 2 = 1999–2002 (n = 121); Group 3 = 2003–2006 (n = 129)	Number of abdominal regions affected, Simplified Peritoneal Cancer Index Score, completeness of cytoreduction, morbidity, duration of hospital stay, and survival	2	Yes	Yes, the zenith of the curve being reached after 130 procedures and reflecting patient selection and treatment expertise
Yan et al. [6]	Retrospective	Group 1 = 1997–2004 (n = 70); Group 2 = 2004–2006 (n = 70)	Perioperative morbidity, delayed morbidity, perioperative mortality, transfusion requirement, length of operation, length of hospital stay, and 2-year survival	1	Yes	Yes, it is improved after 70 cases and addresses that there is a need for concentration of services
Cavaliere et al. [8]	Retrospective	n = 37	Completeness of cytoreduction, length of surgery, and 2-year survival	2	Yes	Yes, the zenith occurs after 19 months of conducting CRS with HIPEC
Moran [7]	Retrospective	Group 1 = 1994–2000 (n = 33); Group 2 = 2000–2002 (n = 33); Group 3 = 2002–2002 (n = 34)	Completeness of cytoreduction, major morbidity, and perioperative mortality	1	Yes	Yes, main components are decision-making and technical factors. Can be reduced by team work and two surgeons

CRS, cytoreductive surgery; PIC, perioperative intraperitoneal chemotherapy; HIPEC, hyperthermic intraperitoneal chemotherapy.

- **Don’t reinvent the wheel; ‘surf’ on the global learning curve**

Journal of Surgical Oncology 2009;100:293–296

Predicting

Response
&
Faillure

Ziekenhuis Oost-Limburg

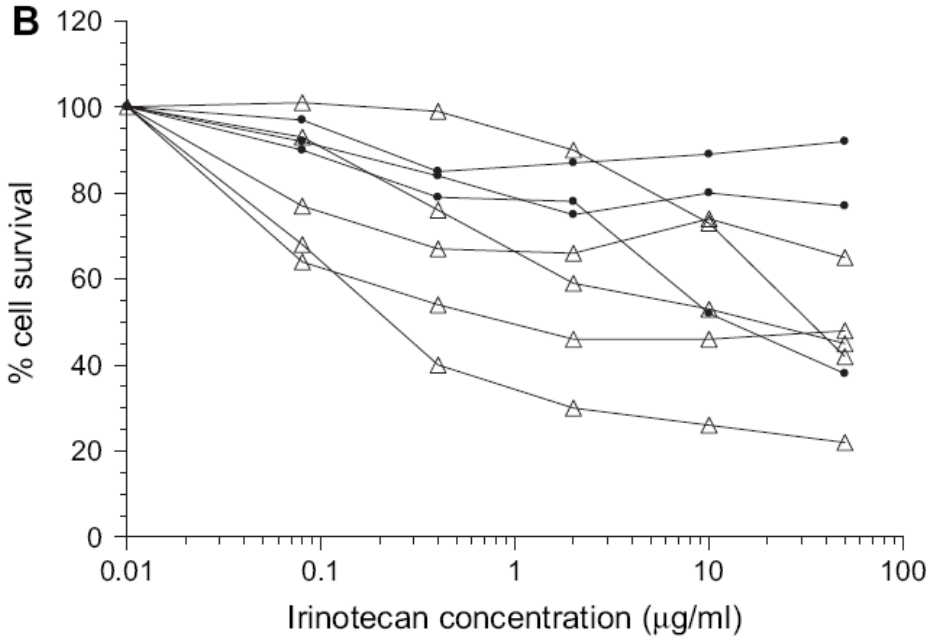
Washington Hospital Center
Washington Cancer Institute

universiteit hasselt

Trick 1

Heterogeneous activity of cytotoxic drugs in patient samples of peritoneal carcinomatosis

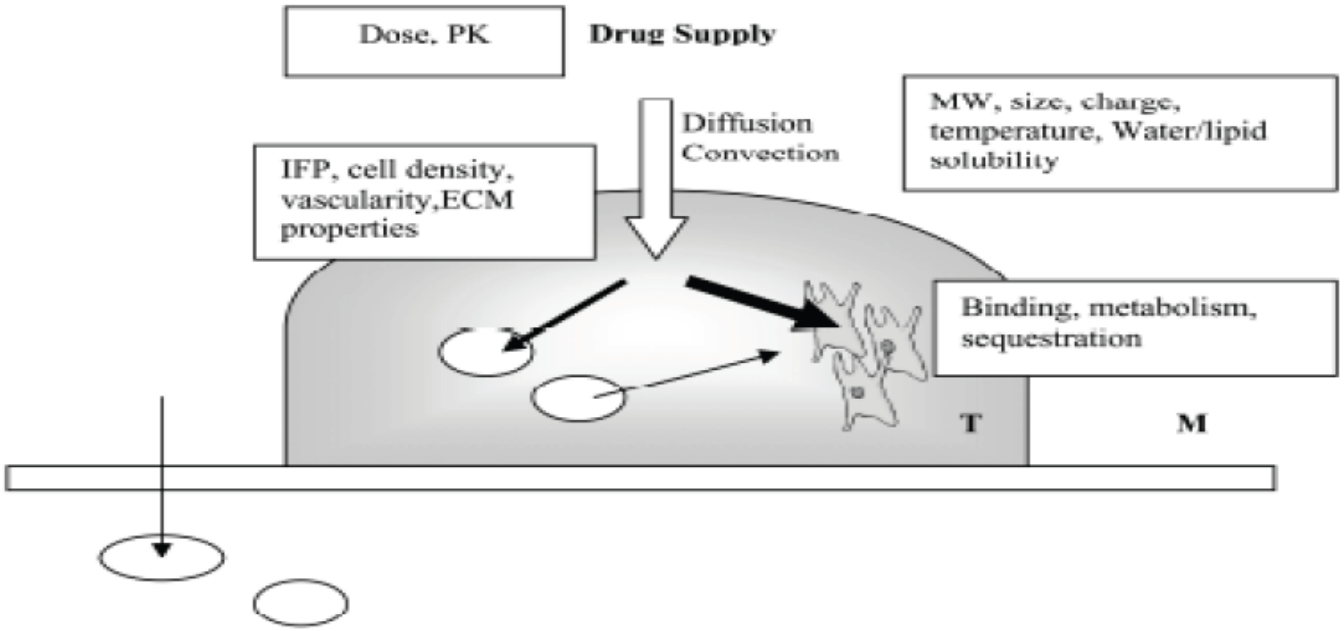
H. Mahteme [a], A. von Heideman [b], B. Grundmark [c], B. Tholander [d], L. Påhlman [a], B. Glimelius [b,d], R. Larsson [c], W. Graf [a], P. Nygren [b,*]



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.

PHARMACOLOGIC VARIABLES

Determinants of efficacy of IP chemotherapy



Question : do peritoneal drug levels accurately predict efficacy ? **NO**

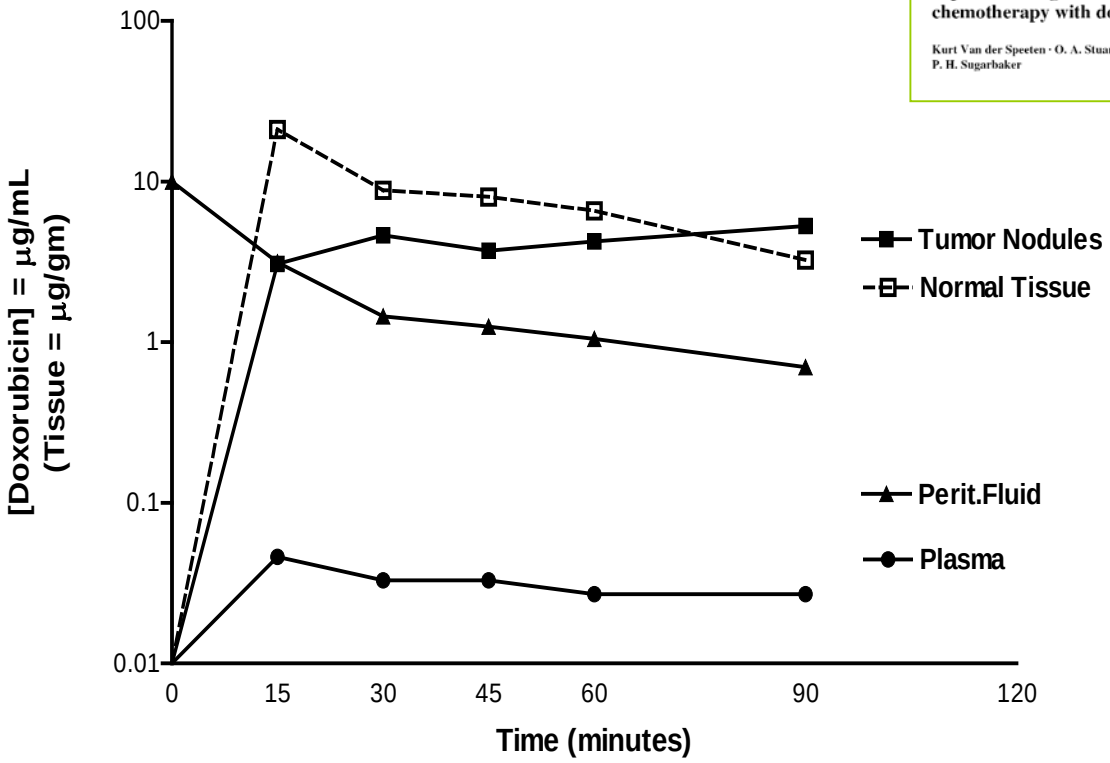
TUMOR NODULE AS PHARMACOLOGIC ENDPOINT

Cancer Chemother Pharmacol
DOI 10.1007/s00280-008-0800-0

ORIGINAL ARTICLE

A pharmacologic analysis of intraoperative intracavitary cancer chemotherapy with doxorubicin

Kurt Van der Speeten · O. A. Stuart · H. Mahteme · P. H. Sugarbaker



Doxorubicin levels in peritoneal fluid, plasma, tumor nodules and adjacent tissue

TUMOR NODULE AS PHARMACOLOGIC ENDPOINT

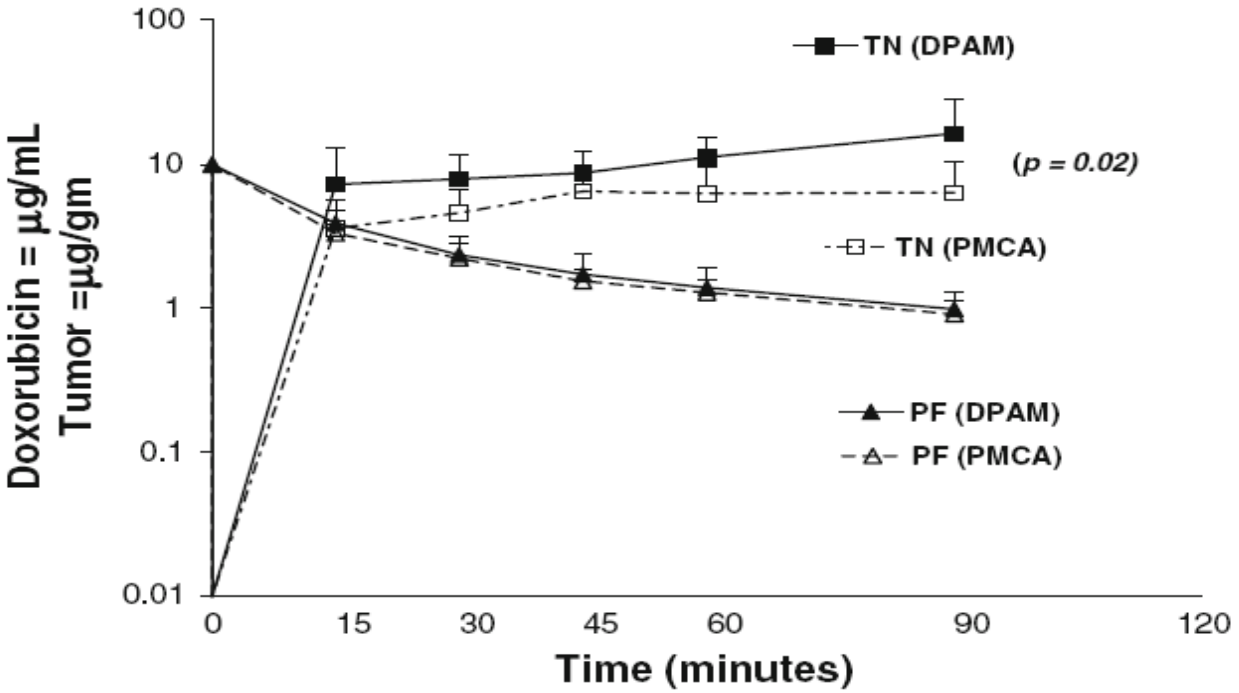


Fig. 3 Doxorubicin levels in appendiceal tumor tissue showing diffuse peritoneal adenomucinosis (*DPAM*) versus peritoneal mucinous carcinomatosis (*PMCA*). Peritoneal fluid concentrations are also shown. *TN* tumor nodule, *PF* peritoneal fluid

PREDICTING RESPONSE +/- FAILLURE

Gene Expression Profiling of Peritoneal Metastases from Appendiceal and Colon Cancer Demonstrates Unique Biologic Signatures and Predicts Patient Outcomes

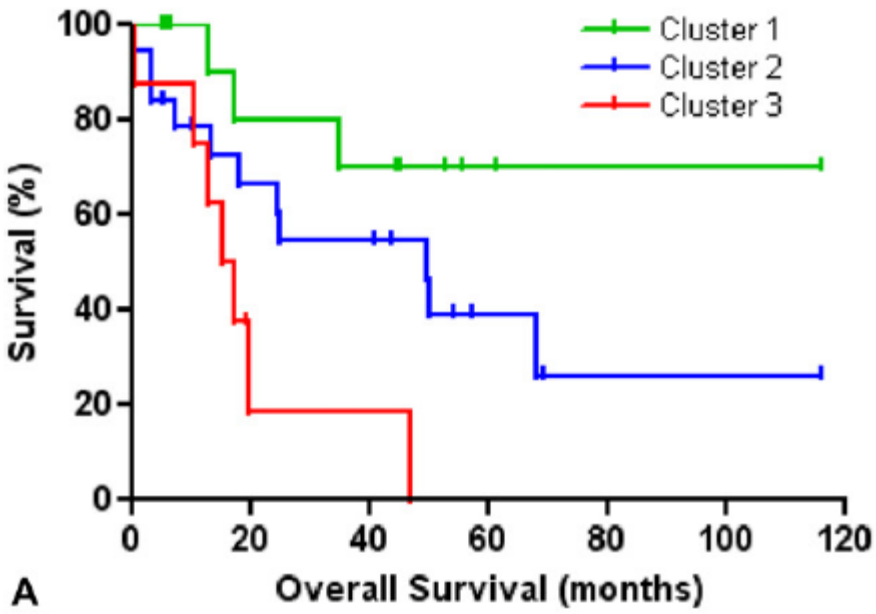
Edward A Levine, MD, FACS, Dan G Blazer III, MD, FACS, Mickey K Kim, BS, Perry Shen, MD, FACS, John H Stewart IV, MD, FACS, Cynthia Guy, MD, David S Hsu, MD, PhD

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 restratified 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)



J Am Coll Surg 2012;214:599–607.

PREDICTING RESPONSE +/- FAILLURE

Int J Oncol. 2012 Apr;40(4):960-4. doi: 10.3892/ijo.2012.1334. Epub 2012 Jan 16.

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.

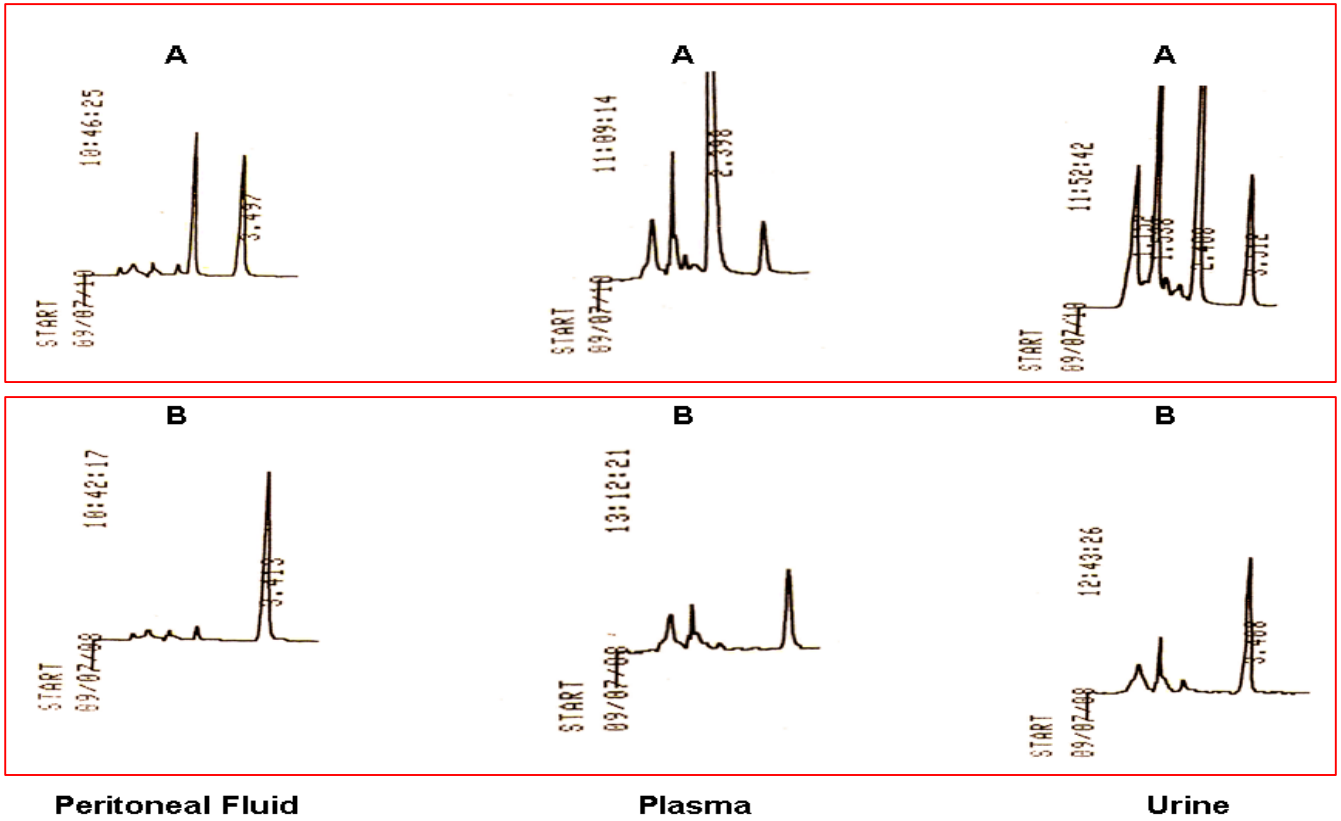
Source

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

PROBABLY



Peritoneal Fluid | Plasma | Urine

Normal patient

Non-metabolizer

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 shows the HPLC chromatogram of a single patient who had failure to metabolize the drug. Six patients (4%) had this unusual mitomycin C chromatogram

PREDICTING RESPONSE +/- FAILLURE

Pharmacology of Perioperative Intraperitoneal and Intravenous Chemotherapy in Patients with Peritoneal Surface Malignancy

Kurt Van der Speeten, MD, PhD[a,b,*], O. Anthony Stuart, BS[c], Paul H. Sugarbaker, MD, FRCS[c]

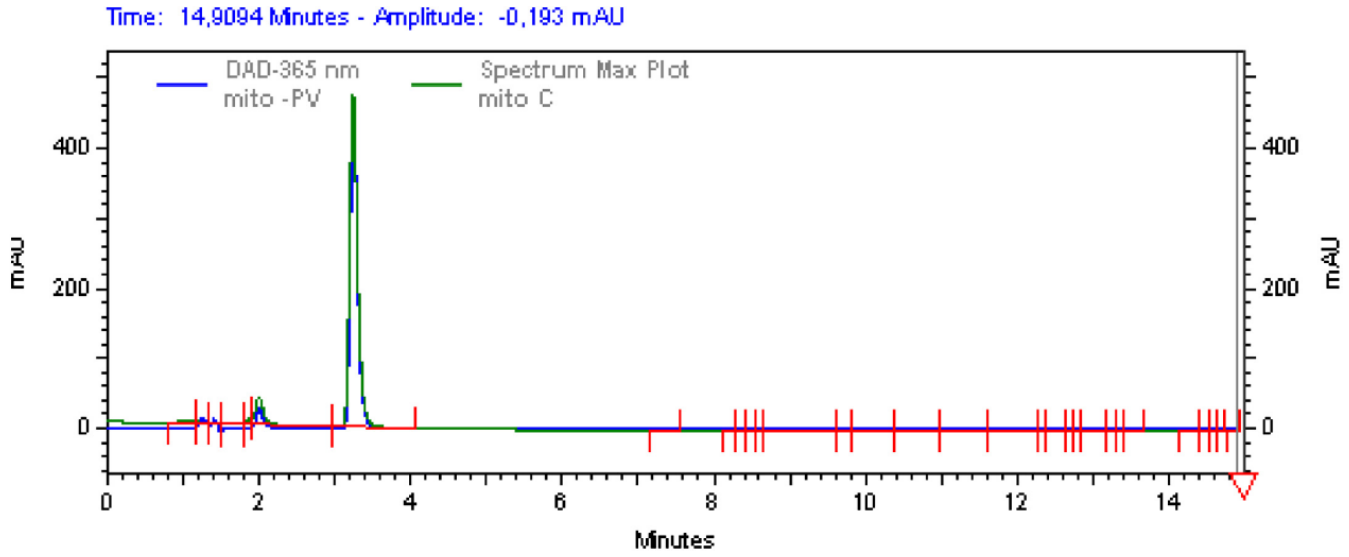
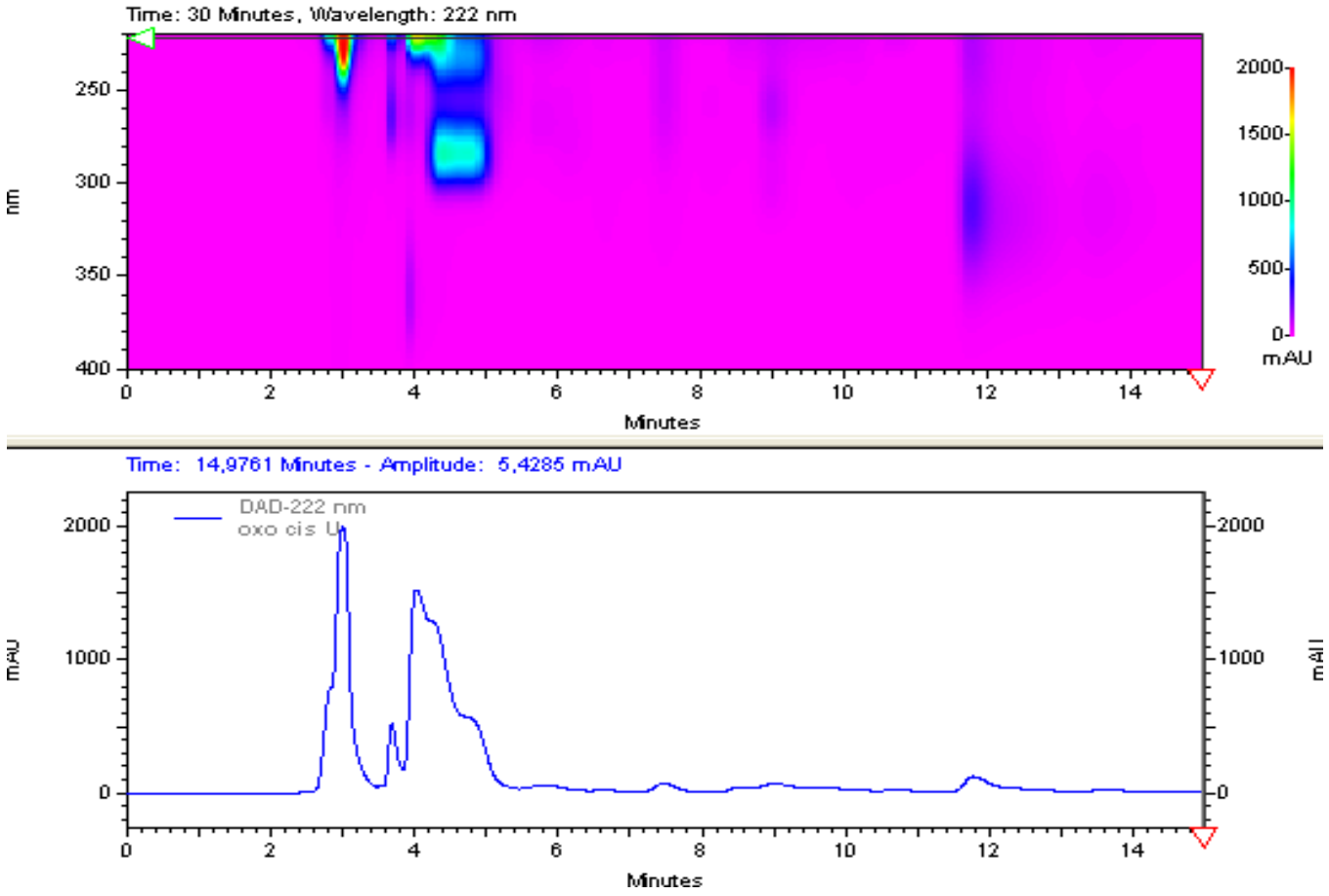


Fig. 7. Representative mitomycin C chromatogram in peritoneal fluid of a PSM patient during HIPEC at 75 minutes. Similar monospiked chromatograms were recovered from plasma, urine, and peritoneal fluid throughout HIPEC. The patient recurred at the peritoneal cavity 3 months after CRS and HIPEC.

Surg Oncol Clin N Am 21 (2012) 577–597

PREDICTING RESPONSE +/- FAILLURE

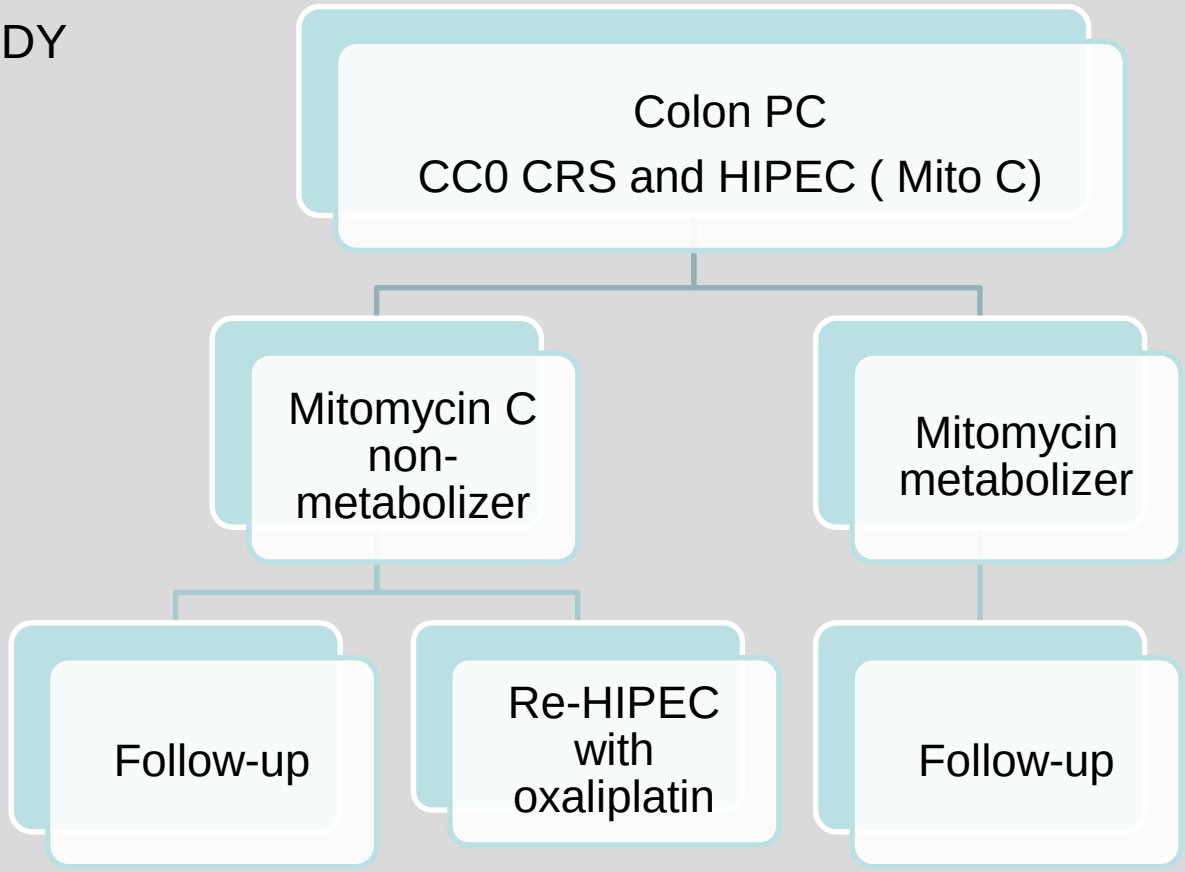
Rabbit model; mito c non metabolizer, oxaliplatin metabolizer



Unpublished data

PREDICTING RESPONSE +/- FAILLURE

PILOT STUDY



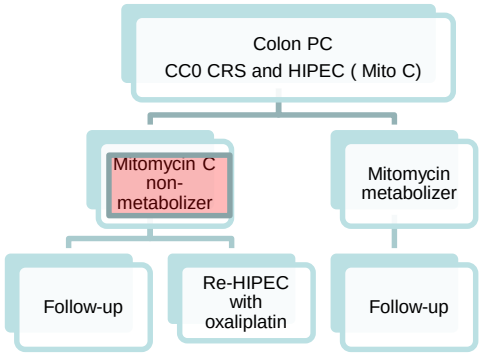
Unpublished data, 50 patients, accrual completed

PREDICTING RESPONSE +/- FAILLURE

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

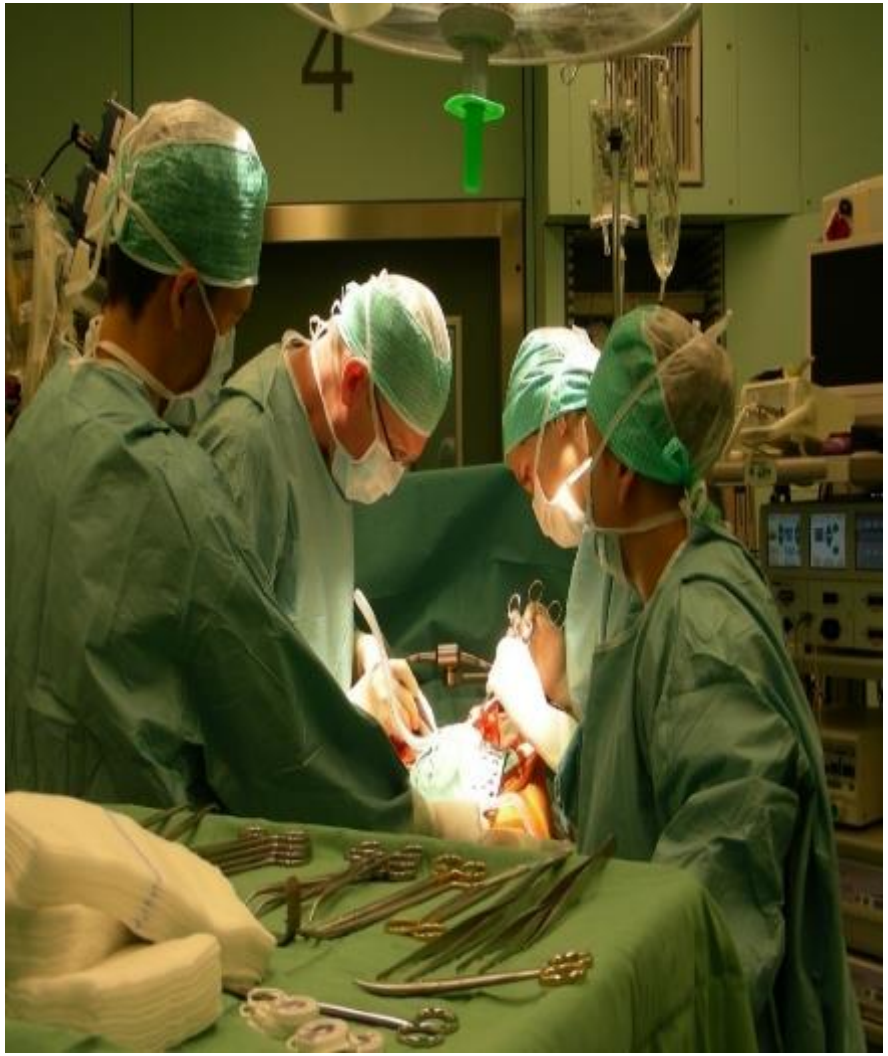


Unpublished data

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



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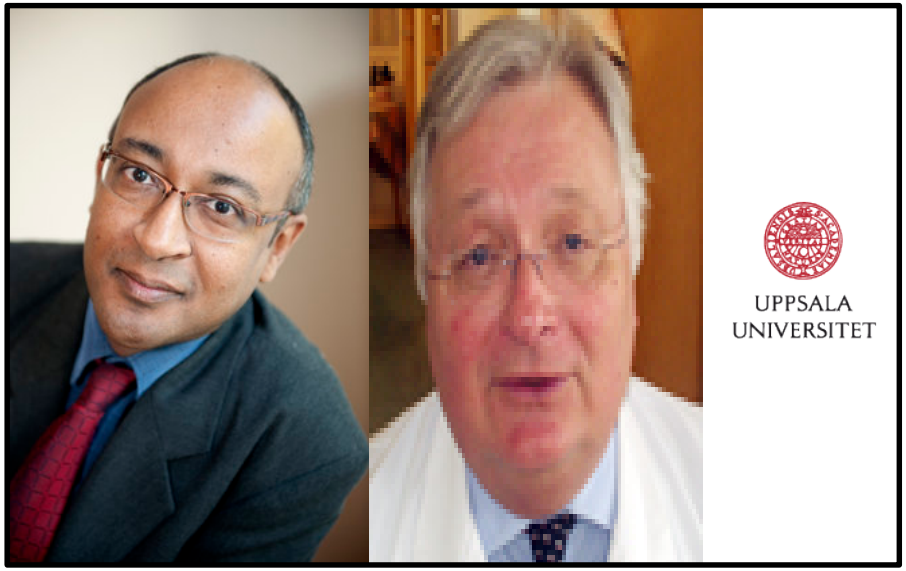
universiteit hasselt

Acknowledgements



Travel Fellowship

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

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THANK YOU