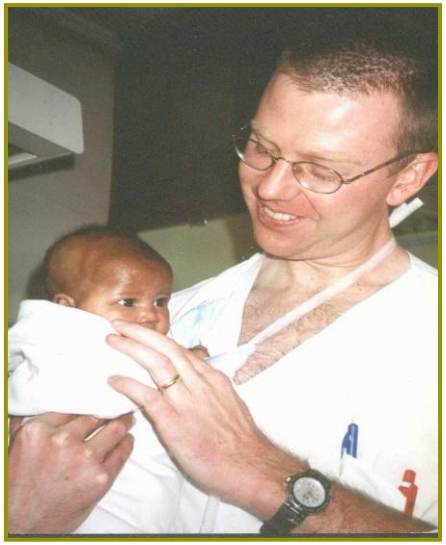
Rationale for the treatment

of

Peritoneal Surface Malignancy

A full circle :acknowledgements



UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

UPPSALA UNIVERSITET

Rationale for the treatment

of

Peritoneal Surface Malignancy

"Nurse, get on the internet, go to SURGERY.COM, scroll down and click on the 'Are you totally lost?' icon."

A *hopeless* operation for a *hopeless* patient with a *hopeless* disease by a *hopeless* surgeon

- Natural history
- Pathofysiology
- Shift of the paradigm
- Pharmacologic rationale
- Pharmacologic variables
- Manipulating variables
- Tumor nodule as endpoint
- Rationale for bidirectional chemotherapy
- Individual drug sensitivity
- Conclusions

Ziekenhuis Oost-Limburg

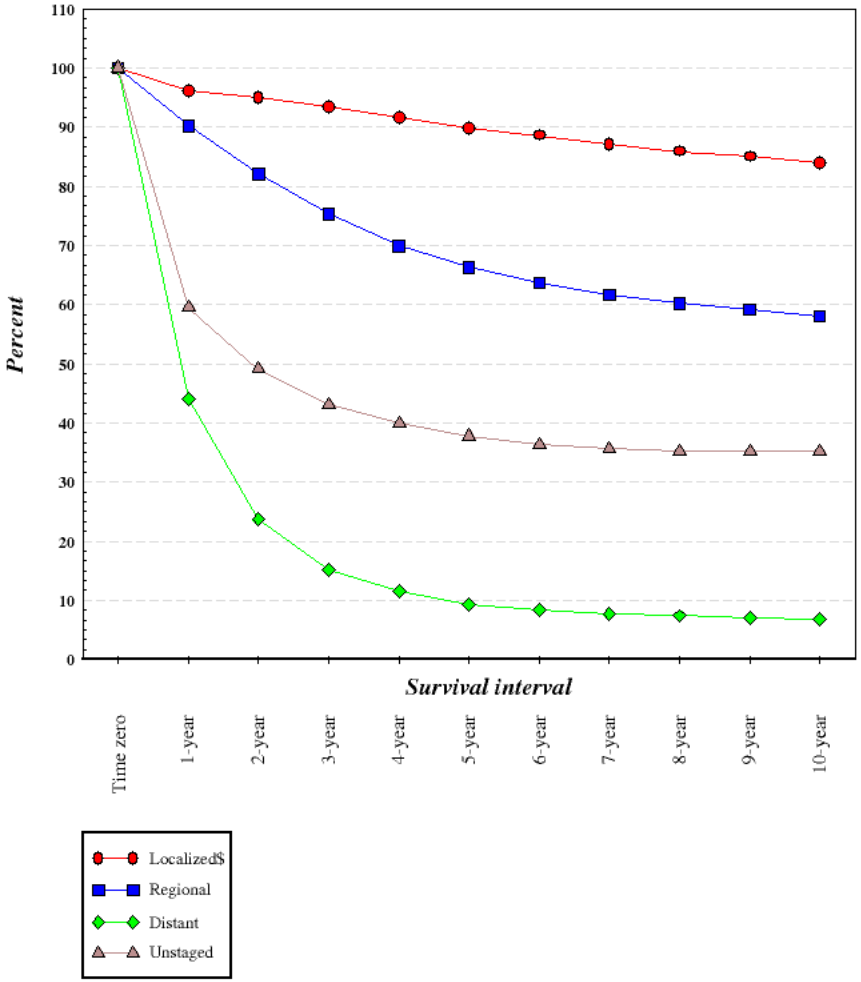
UPPSALA UNIVERSITET

Washington Hospital Center
Washington Cancer Institute

‘ NATURAL ‘

HISTORY

PERITONEAL CARCINOMATOSIS : HOW ARE WE DOING ?



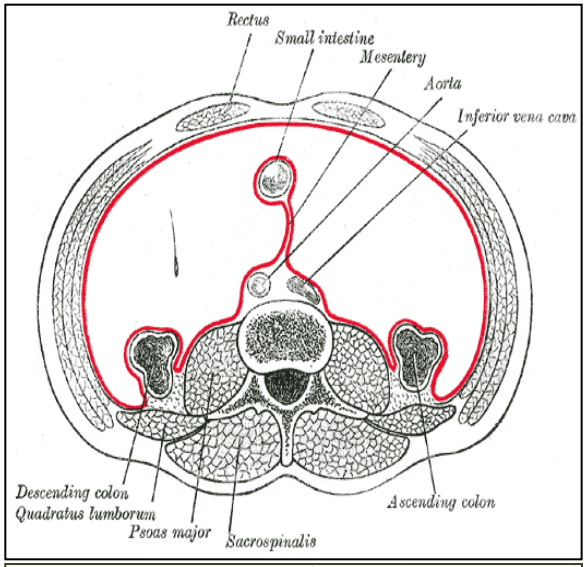
Source : SEER-data, 1988-2010, National Cancer Institute

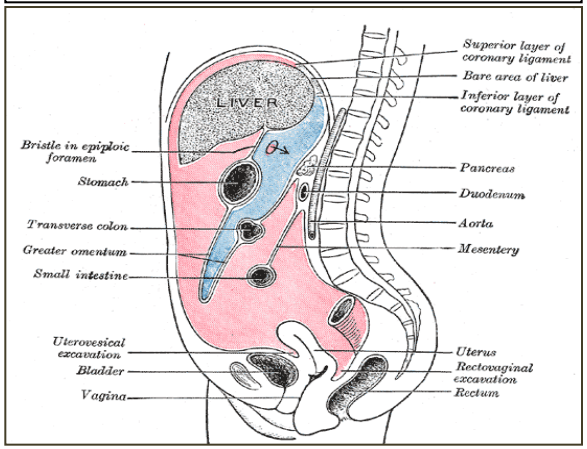
PERITONEAL CARCINOMATOSIS : HOW ARE WE DOING ?

Author	Year	No. patients	Median survival (months)	Tumor
Chu et al	1989	100	2.2-8.5	Non gynecologic
Sadegi et al	2000	370	3.1	Non gynecologic
Jayne et al	2003	349	7.0	Colon Rectum
Verwaal et al	2003	51	12.6	Colon
Elias et al	2009	48	23.9	Colon Rectum
Piccart	2000	680	36.5	Ovary

PATHOFYSIOLOGY

PERITONEAL CARCINOMATOSIS : WHY IS PSM DIFFERENT ?





THEORETICAL PATTERNS OF TUMOR SPREAD

- Direct tumor growth
- Lymfovascular spread
- Exfoliation of tumor cells

Steps in the peritoneal metastatic cascade

1. Liberation of cells from tumor mass
2. Transport throughout the peritoneal cavity
3. Adhesion and invasion
4. Systemic spread

PERITONEAL CARCINOMATOSIS : PATHOPHYSIOLOGY

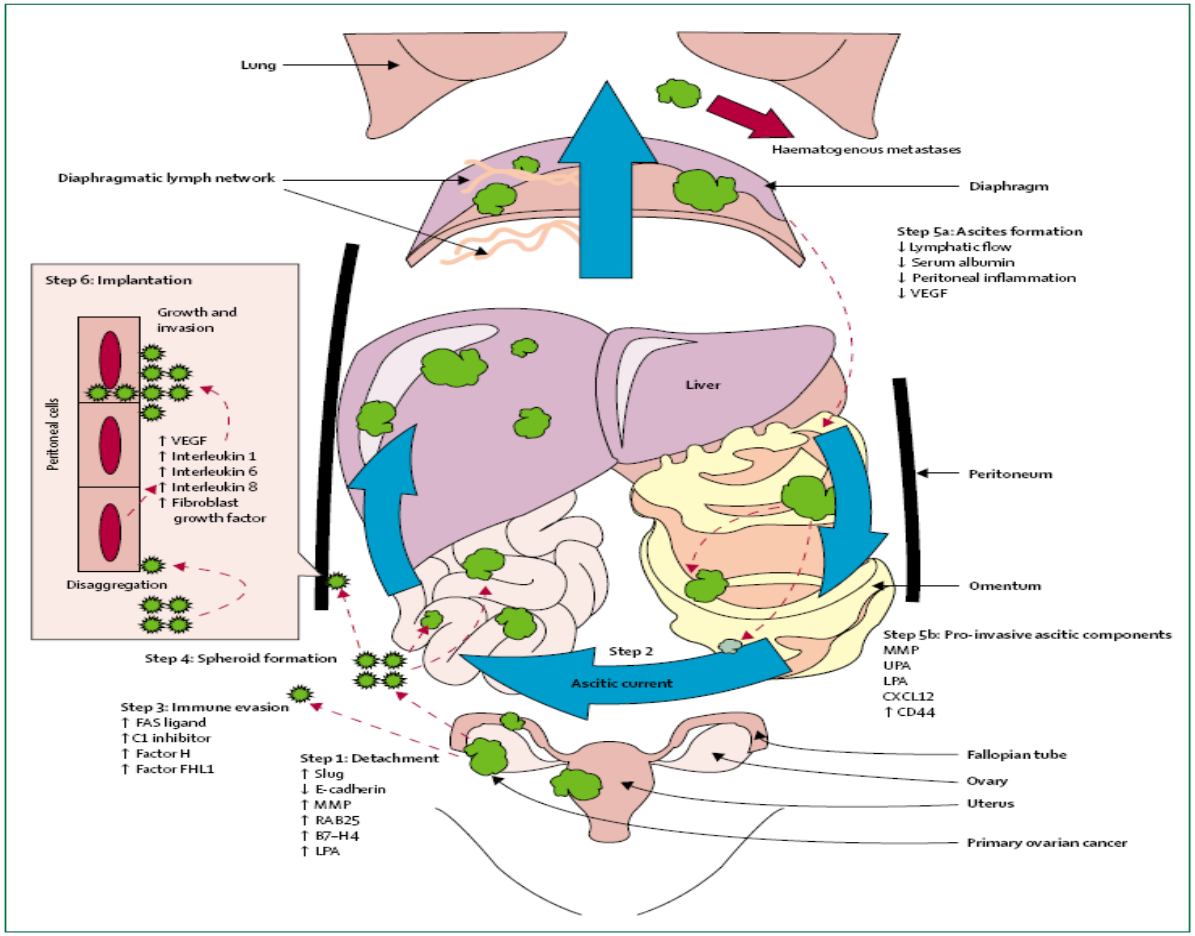
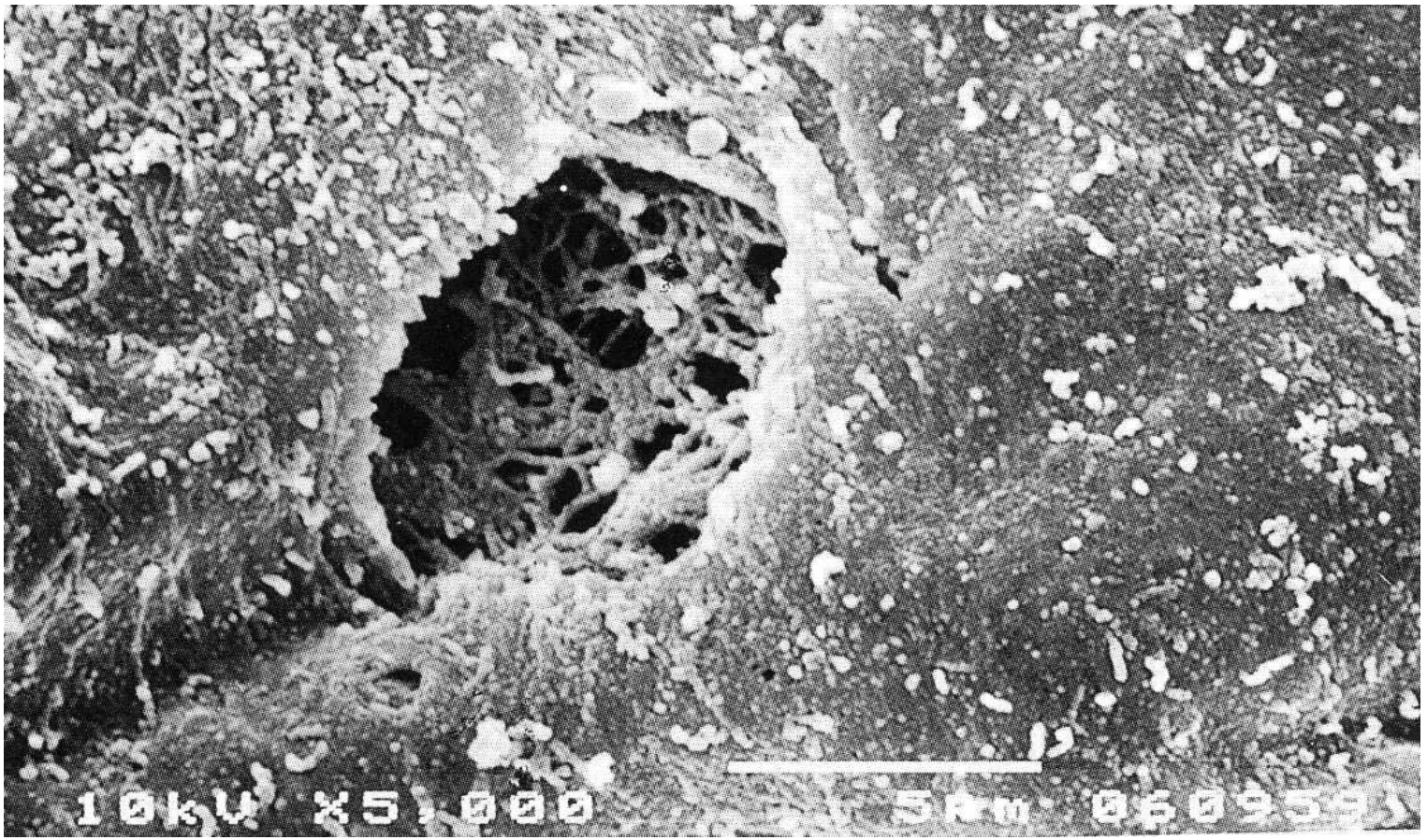


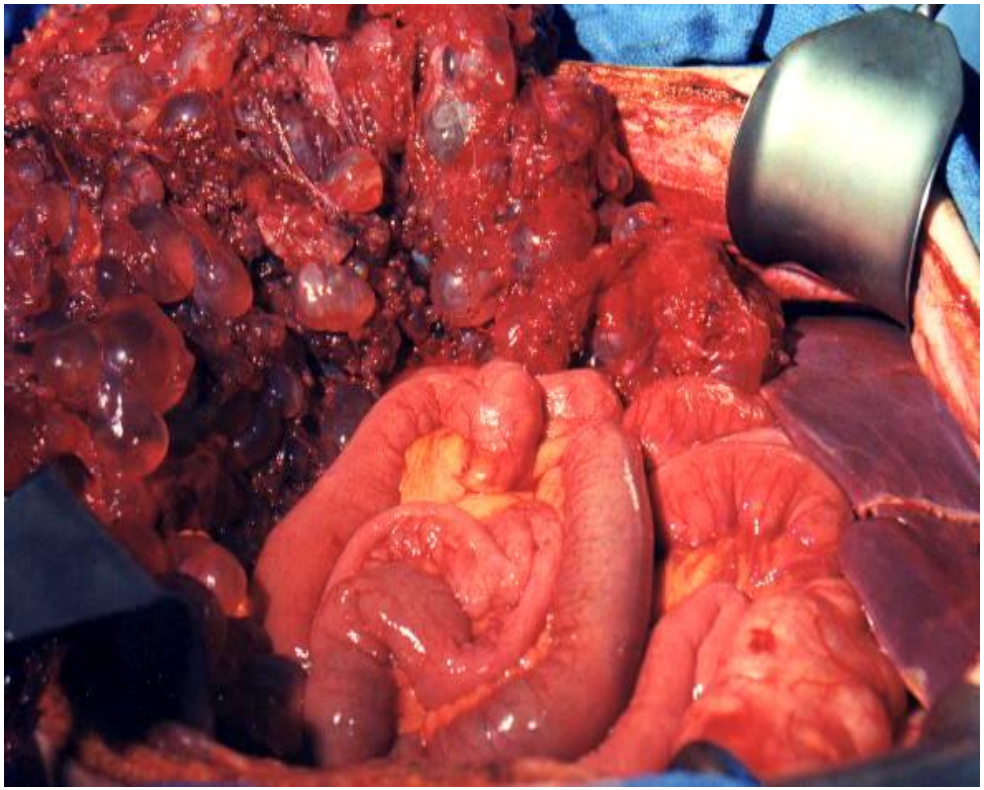
Figure 2: **Mechanisms of transcoelomic metastasis in ovarian cancer**
Step 1: Epithelial ovarian cancer cell (green) detaches after altered gene expression. Step 2: peritoneal or ascitic current (blue arrows) facilitates peritoneal, lymphatic, and haematogenous metastasis. Step 3: immune evasion by 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.

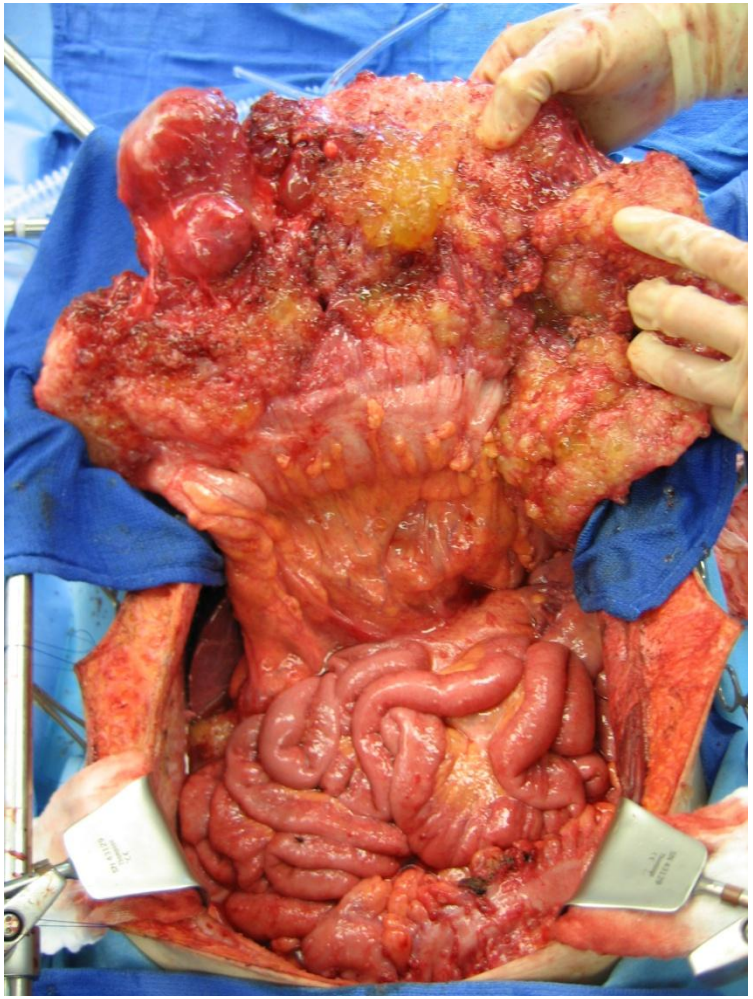
PERITONEAL CARCINOMATOSIS : ‘ MILKY SPOTS ’



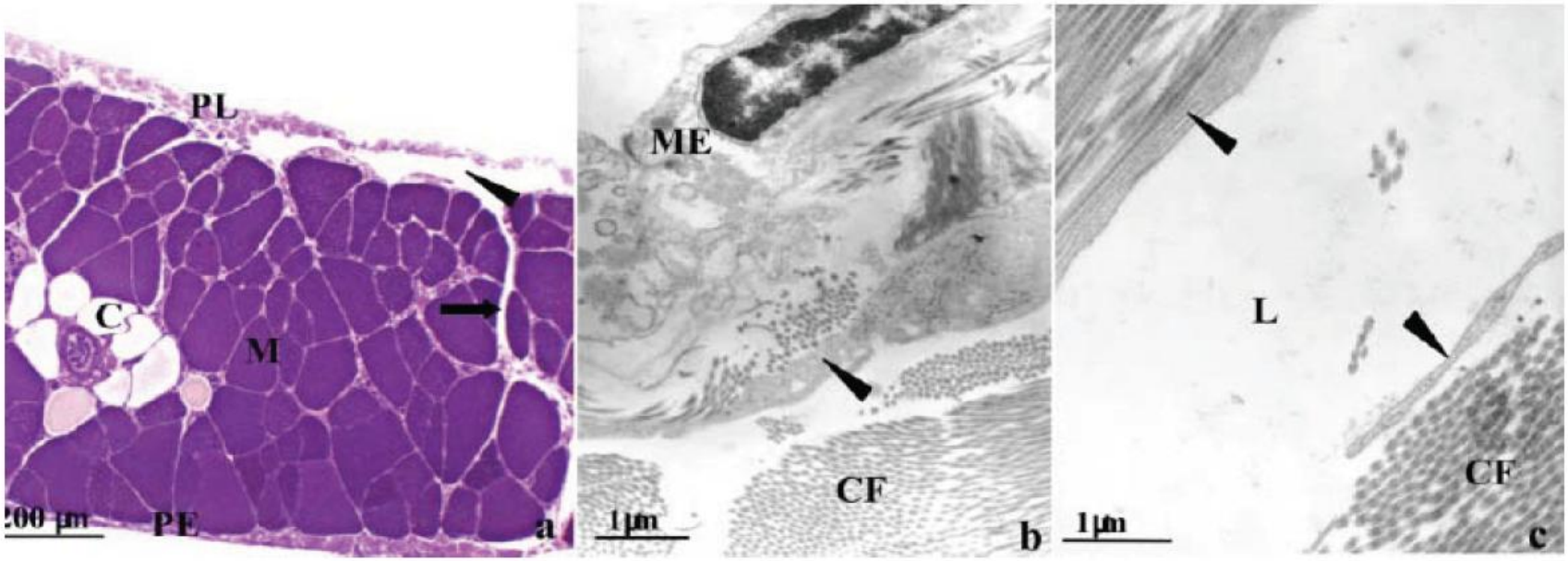
EM magnification of the milky spot. It is 5-10 µm in diameter and connects with submesothelial lymphatic channels (courtesy : Yonemura Y; Peritoneal Dissemination, Maeda Shoten, Kanazawa, Japan, 1998)

PERITONEAL CARCINOMATOSIS : ‘ MILKY SPOTS ’



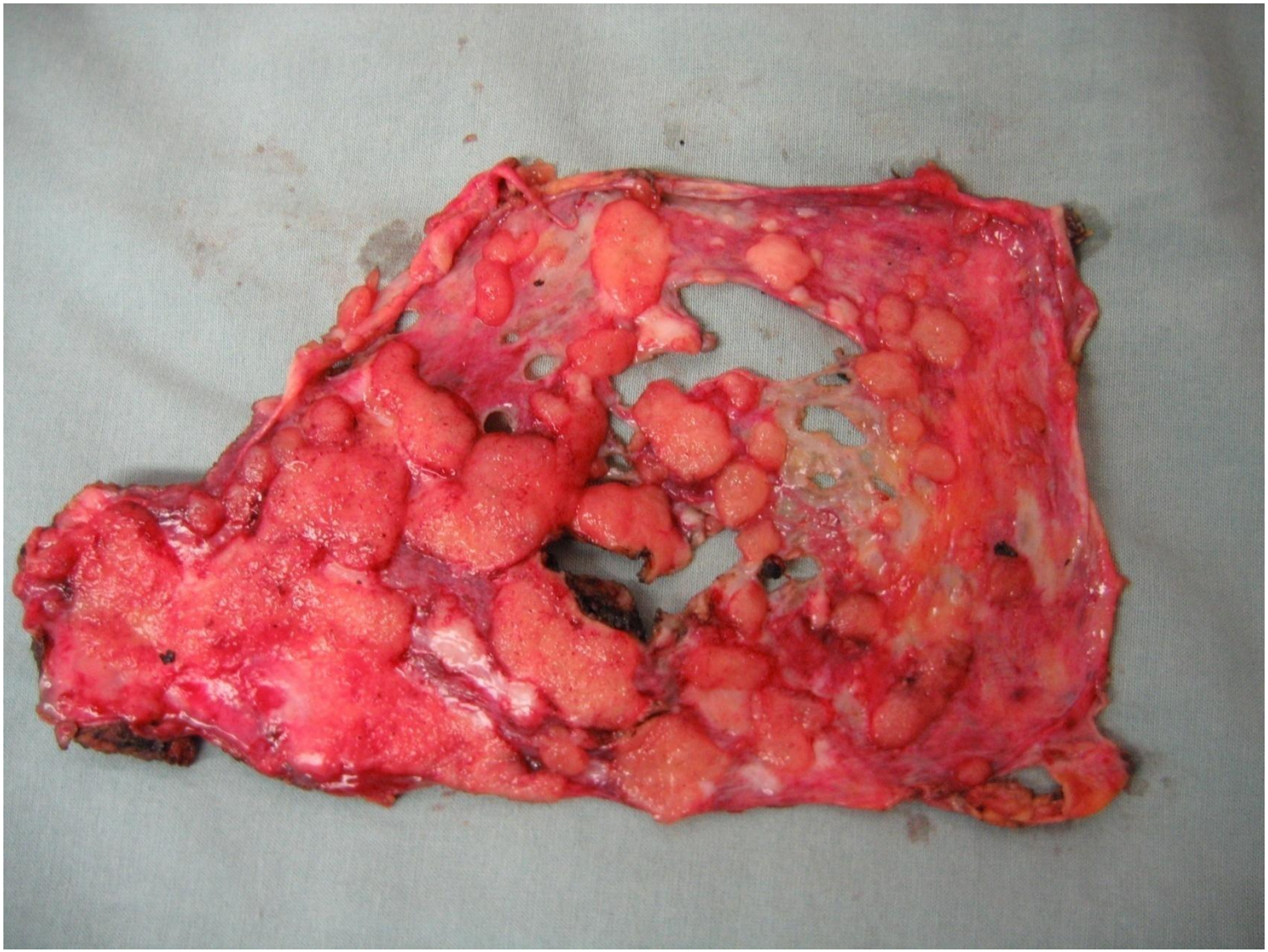


PERITONEAL CARCINOMATOSIS : LYMPHATIC LACUNAE



Lacunae in diaphragmatic mesothelial lining
Grimaldi et al. *Am J Physiol Heart Circ Physiol* 2006

PERITONEAL CARCINOMATOSIS : LYMPHATIC LACUNAE

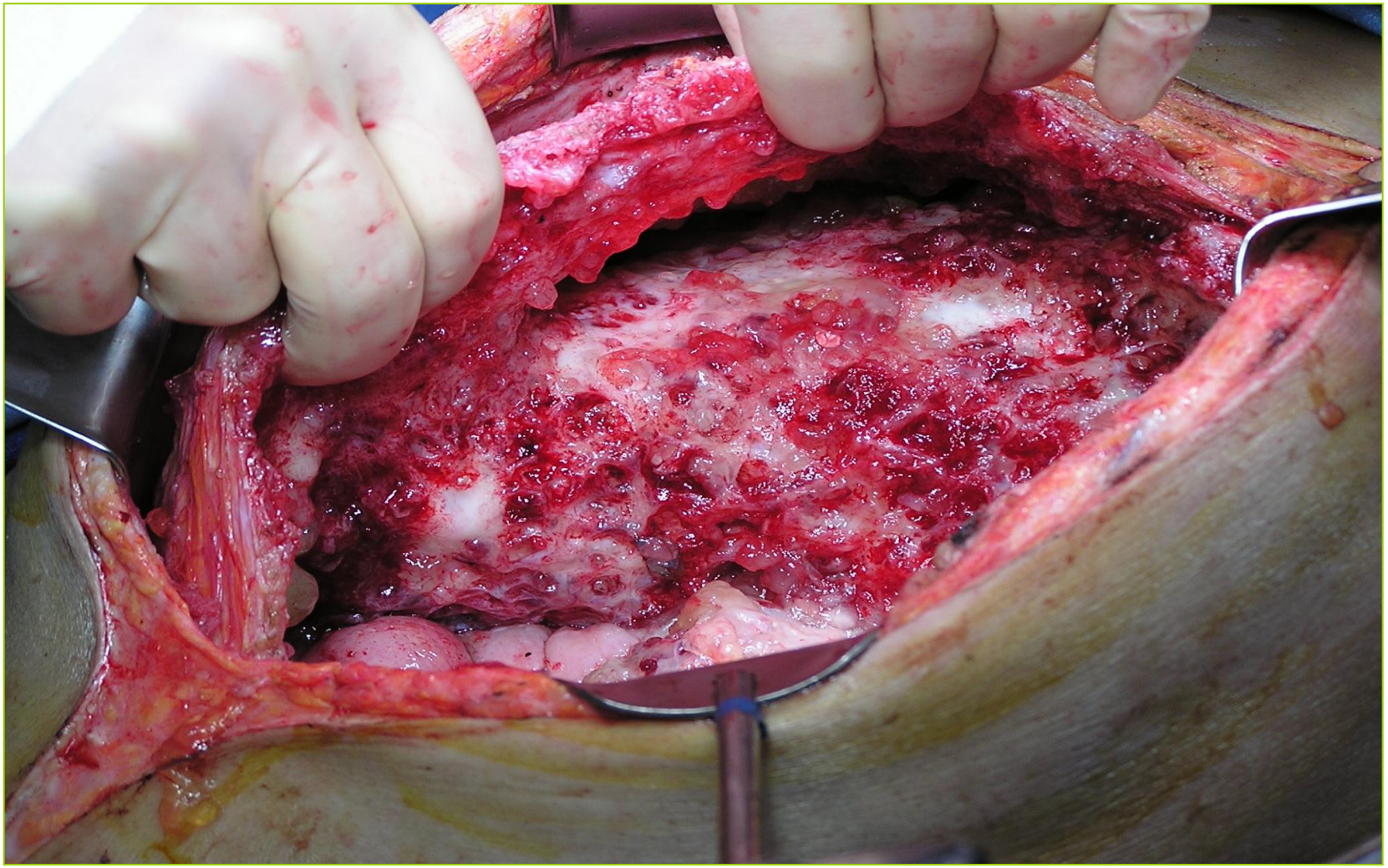


SHIFT

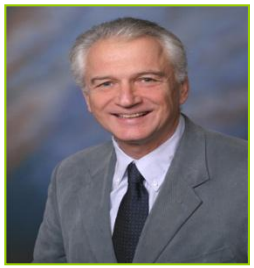
OF THE

PARADIGM

PERITONEAL CARCINOMATOSIS : AGGRESIVE APPROACH ?



Rationale for an aggressive combined surgical – medical approach



Paul Sugarbaker

Frans Zoetmulder

Yutaka Yonemura

Shift of the paradigm

Peritoneal carcinomatosis = distant metastasis

Peritoneal carcinomatosis = regional spread

‘ a locoregional treatment for a locoregional disease makes sense ‘

Sugarbaker PH:Intraperitoneal chemotherapy and cytoreductive surgery for the prevention and treatment of peritoneal carcinomatosis and sarcomatosis.*Dis Colon Rectum* 1994;37 (suppl):S115-22.

PERITONEAL CARCINOMATOSIS : AGGRESSIVE APPROACH

three steps – one procedure

- Combined multi-organ resections
- Peritonectomy-procedures

→ Treatment of MACROSCOPIC disease

- Hyperthermic Intraperitoneal Peroperative Chemotherapy (HIPEC)

→ Treatment of MICROSCOPIC disease

UPPSALA UNIVERSITET

Loco-regional chemotherapy

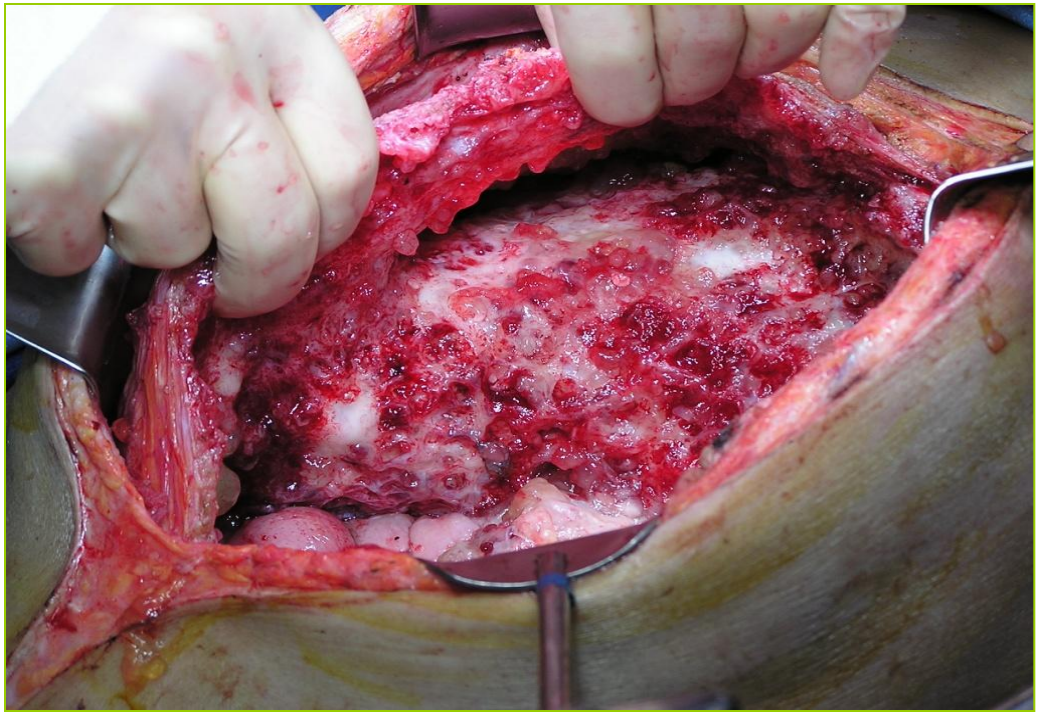
CYTOREDUCTIVE SURGERY + INTRACAVITARY CHEMOTHERAPY

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

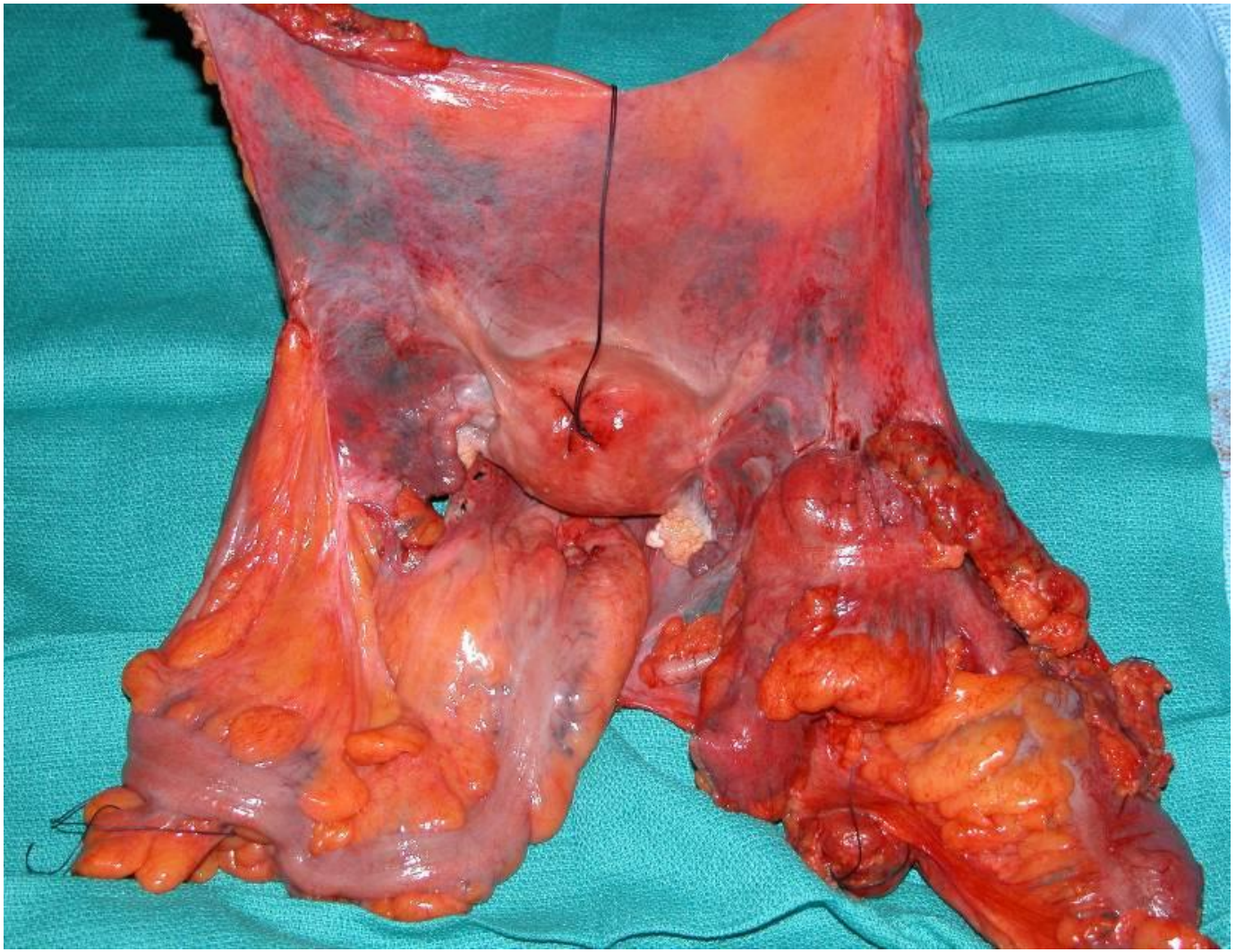
PERITONEAL CARCINOMATOSIS : AGGRESSIVE APPROACH

- Combined multi-organ resections
- Peritonectomy-procedures

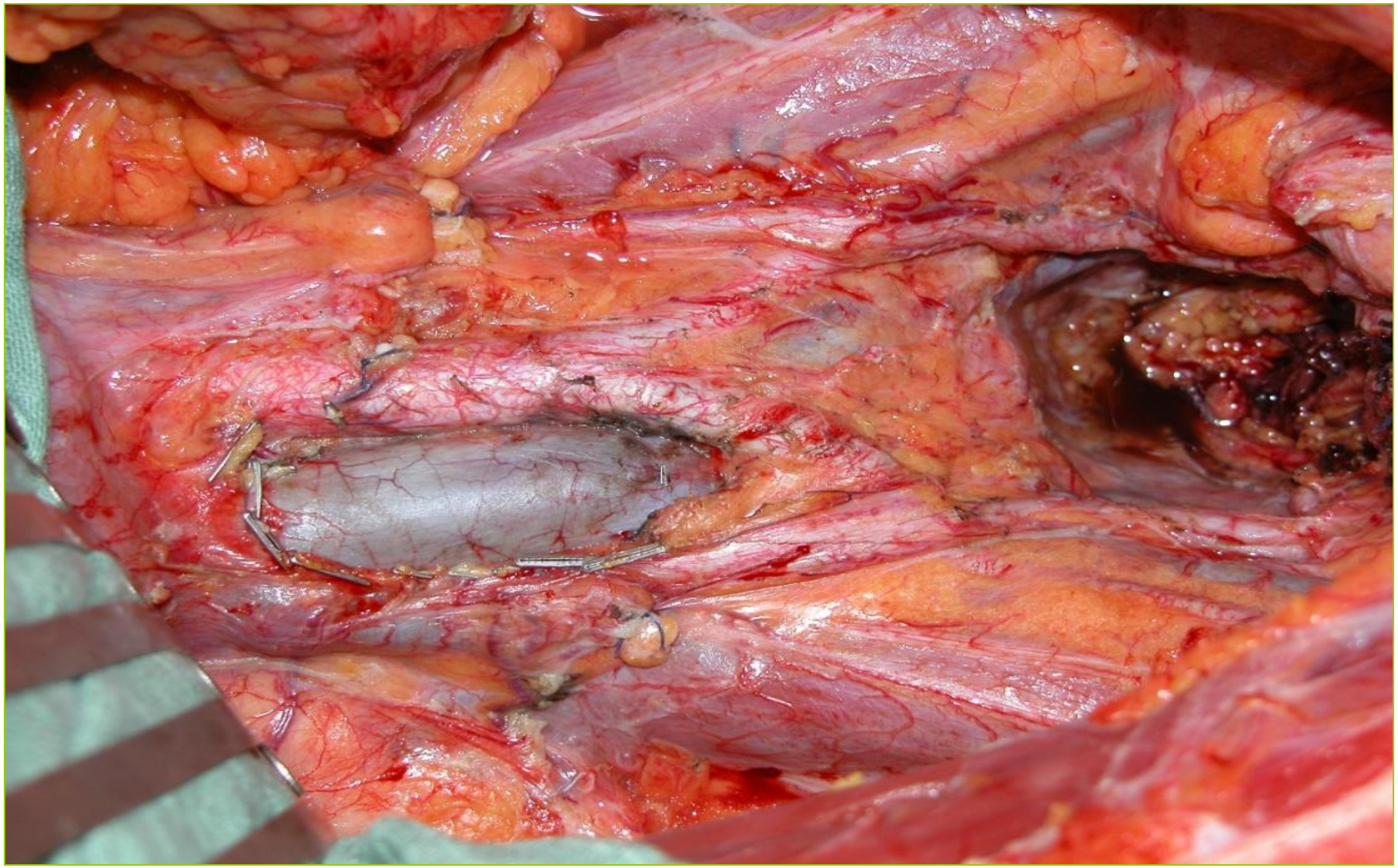
→ Treatment of MACROSCOPIC disease



PERITONEAL CARCINOMATOSIS : AGGRESSIVE APPROACH



PERITONEAL CARCINOMATOSIS : AGGRESSIVE APPROACH

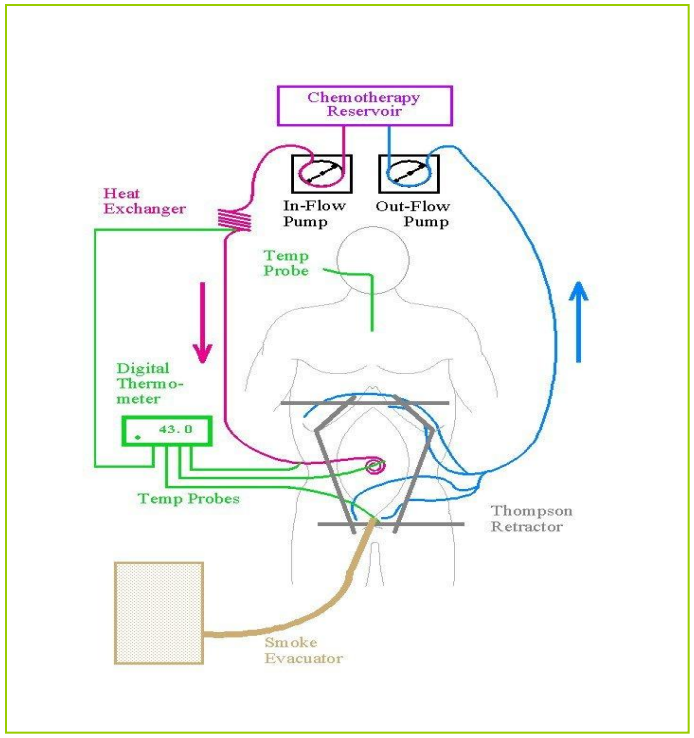


PERITONEAL CARCINOMATOSIS : AGGRESSIVE APPROACH

- Hyperthermic Intraperitoneal

  Peroperative Chemotherapy (HIPEC)

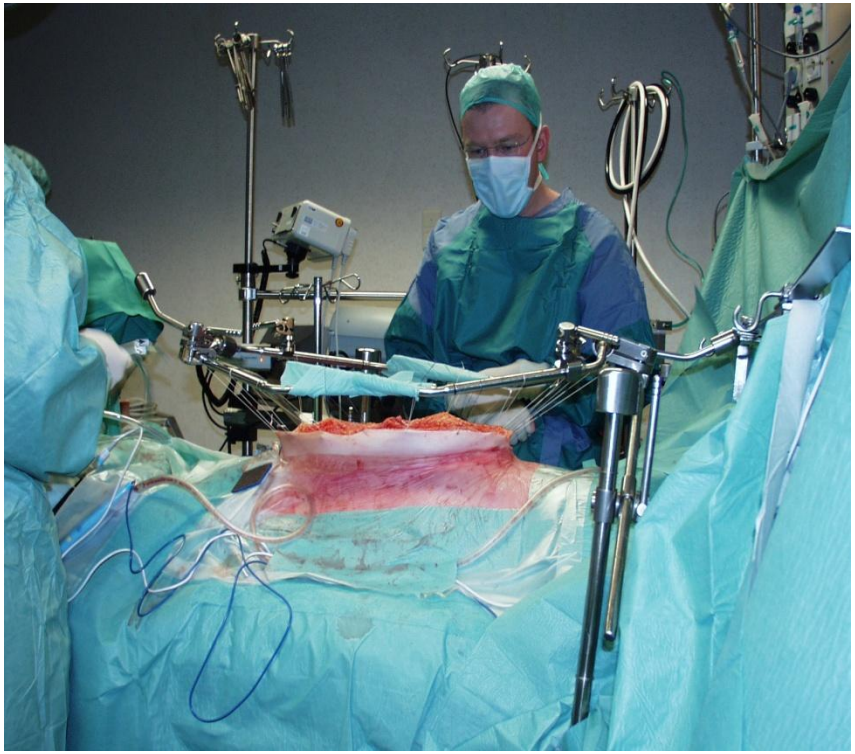
→ Treatment of MICROSCOPIC disease

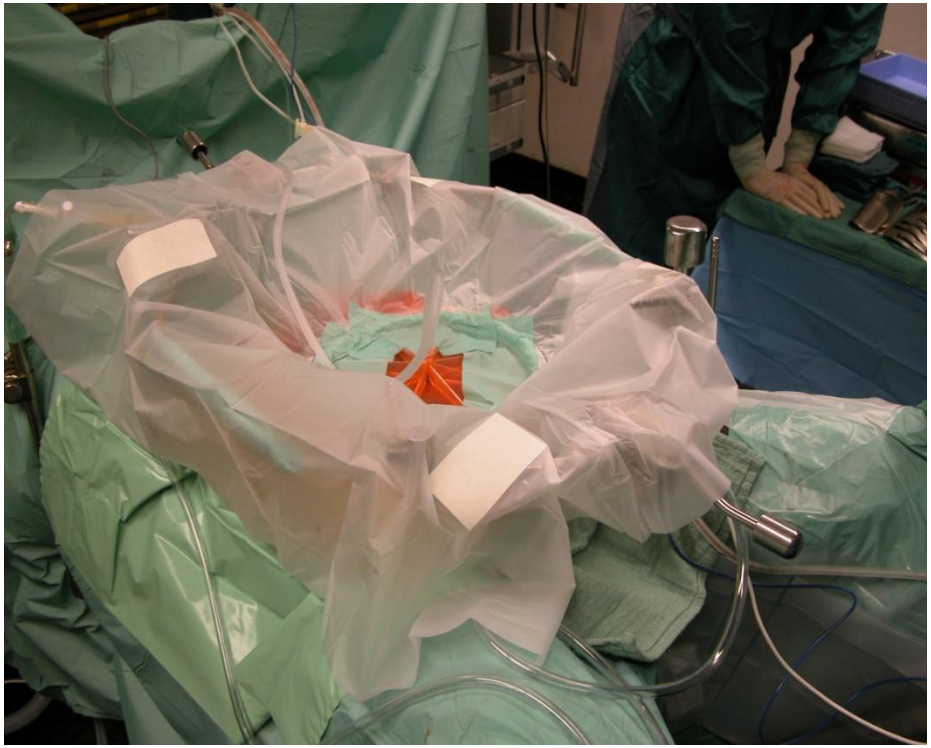


PERITONEAL CARCINOMATOSIS : AGGRESSIVE APPROACH

- Hyperthermic Intraperitoneal

  Peroperative Chemotherapy (HIPEC)





PHARMACOLOGIC

RATIONALE

Ziekenhuis Oost-Limburg

UPPSALA UNIVERSITET

Washington Hospital Center
Washington Cancer Institute

UPPSALA UNIVERSITET

Pharmacokinetic rationale

"***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
- two compartment model

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

DOSE INTENSIFICATION

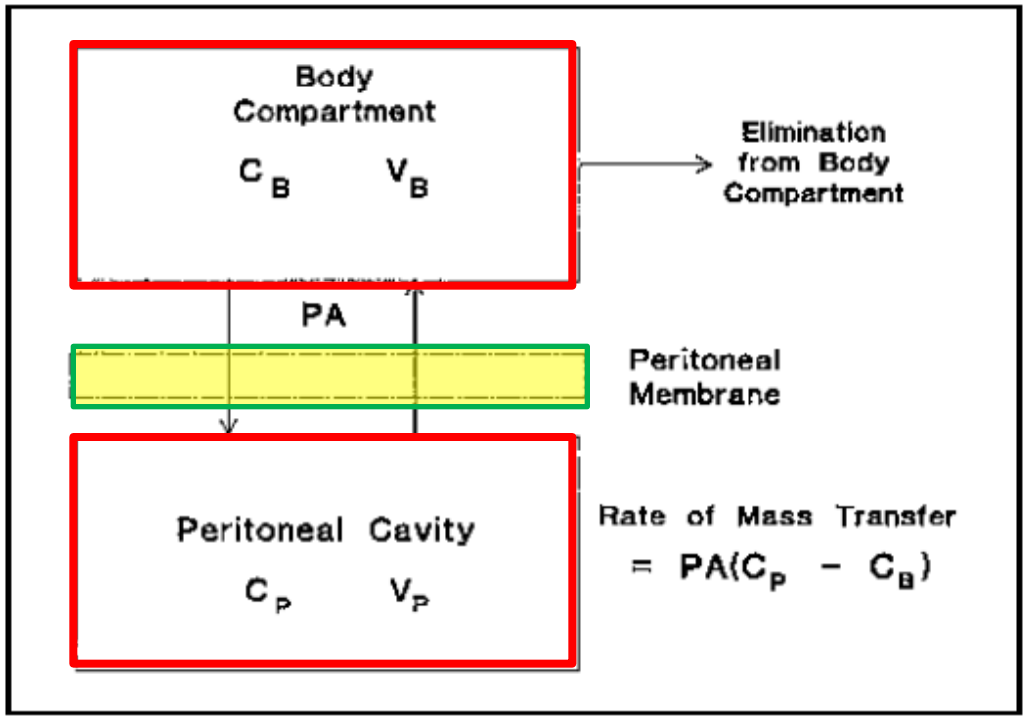
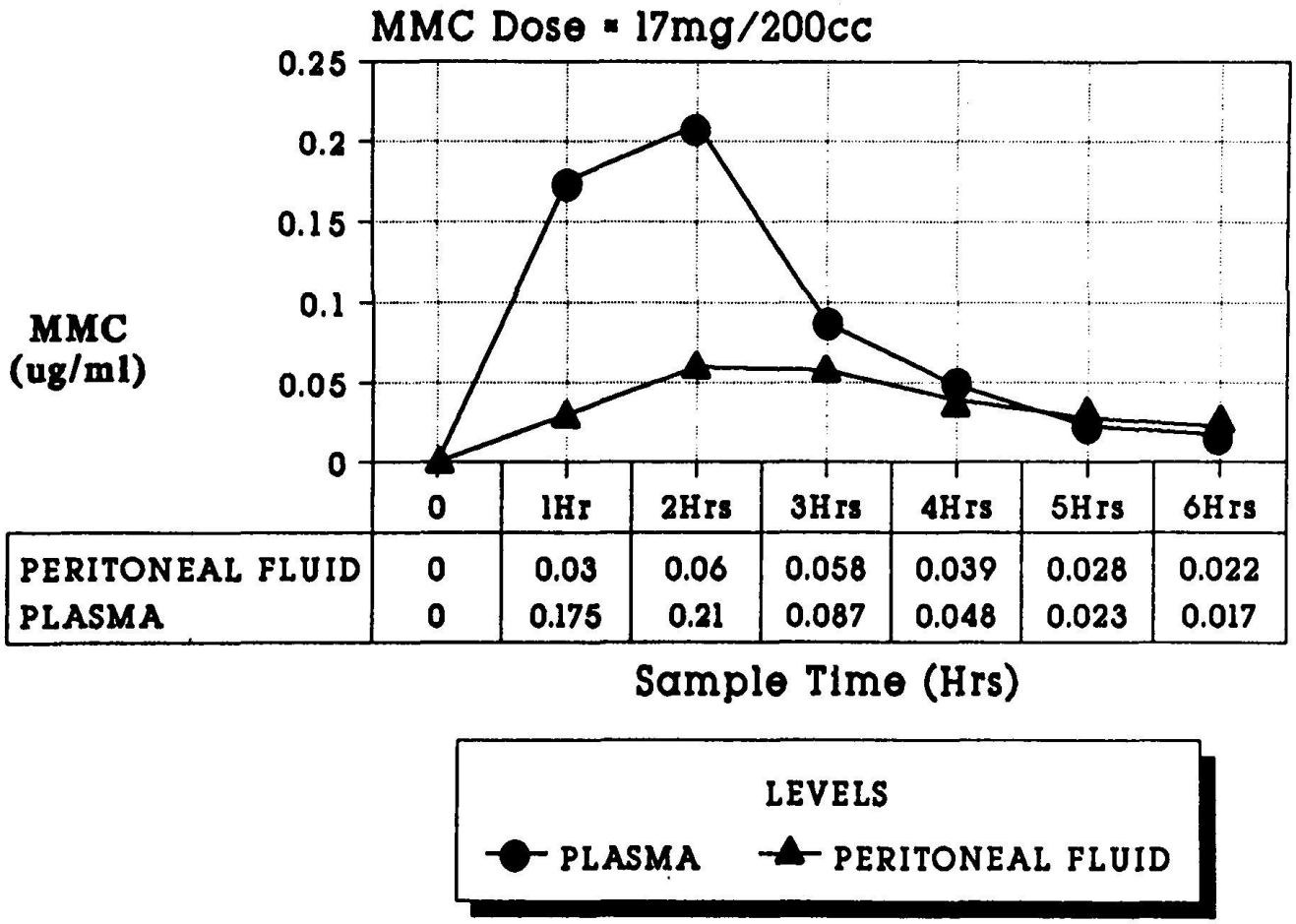


Fig. 1. Traditional two-compartment model of peritoneal transport, in which transfer of a drug from the peritoneal cavity to the blood occurs across the ''peritoneal membrane.'' The permeability-area product (PA) governs this transfer and can be calculated by measuring the rate of drug disappearance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



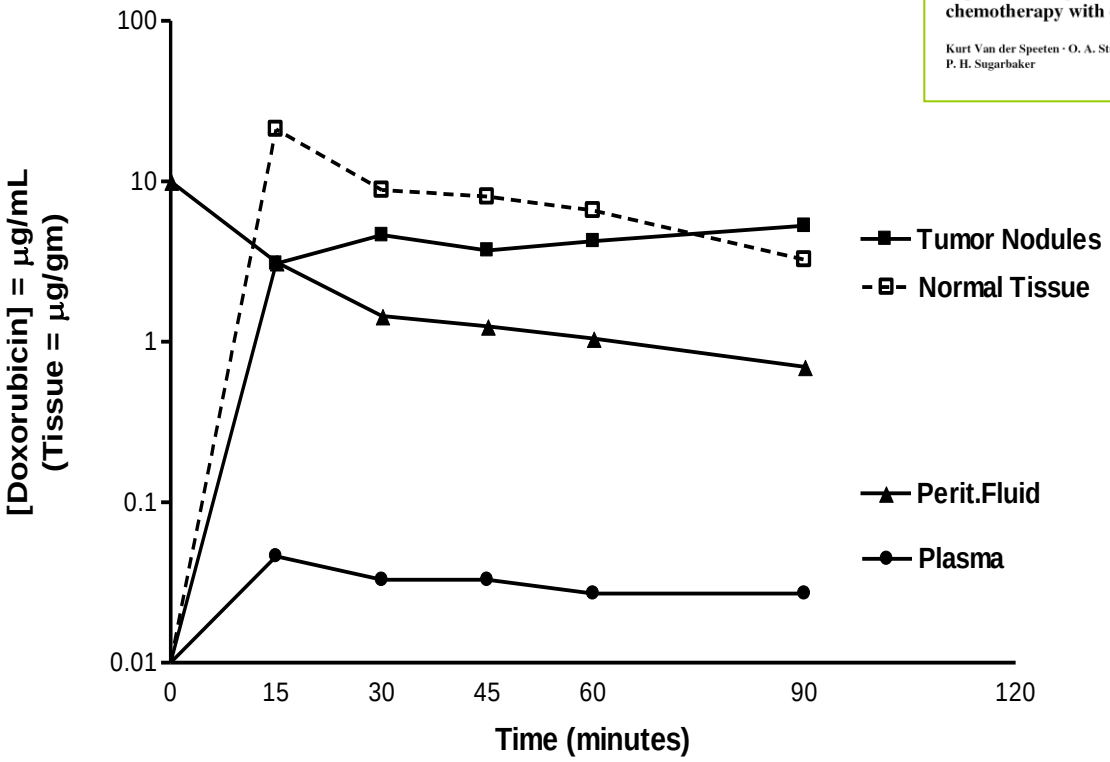
Efficacy versus hematological toxicity

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

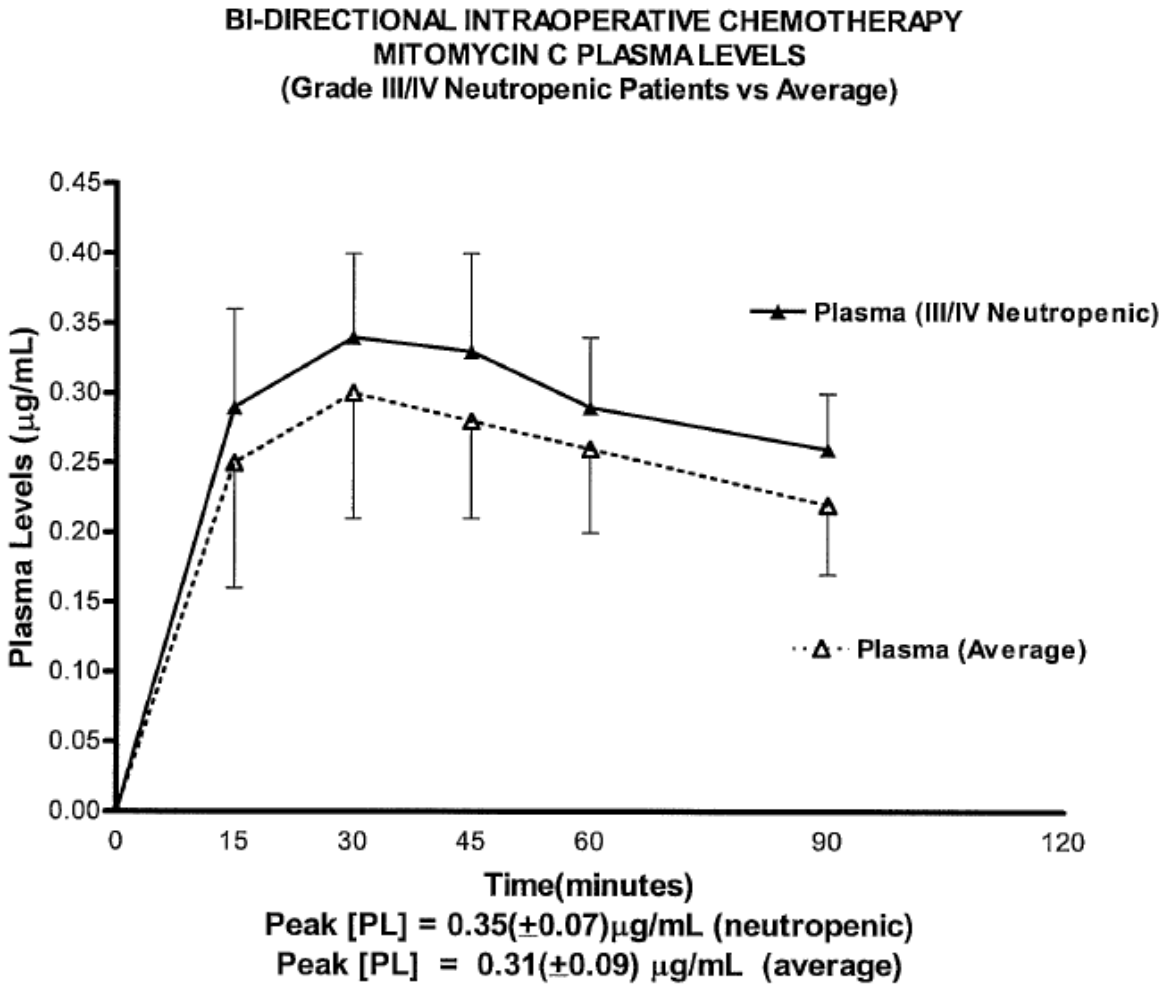


Efficacy

Hematological Toxicity

Doxorubicin levels in tumor nodules versus normal adjacent tissues

Question : do plasmatic levels predict toxicity ?



Unpublished data

Question : is ‘ P ‘ influenced by our surgery ?

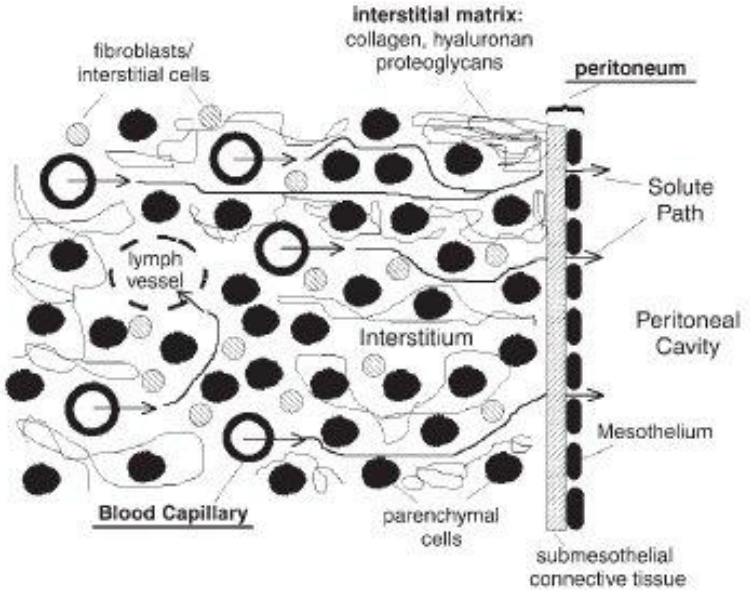


Fig. 1. Peritoneal barrier modeled as blood and lymph capillaries distributed within a tissue space made up of parenchymal cells, interstitial cells, and matrix molecules. The peritoneum, made up of a single layer of mesothelial cells and underlying connective tissue, separates the fluid in the cavity from the underlying tissue space but does not provide a significant barrier to transport. The major resistances to transport are the capillary endothelium and the cell-matrix system surrounding the exchange vessels.

Question : is P influenced by our surgery ?

Peritoneal Barrier Function

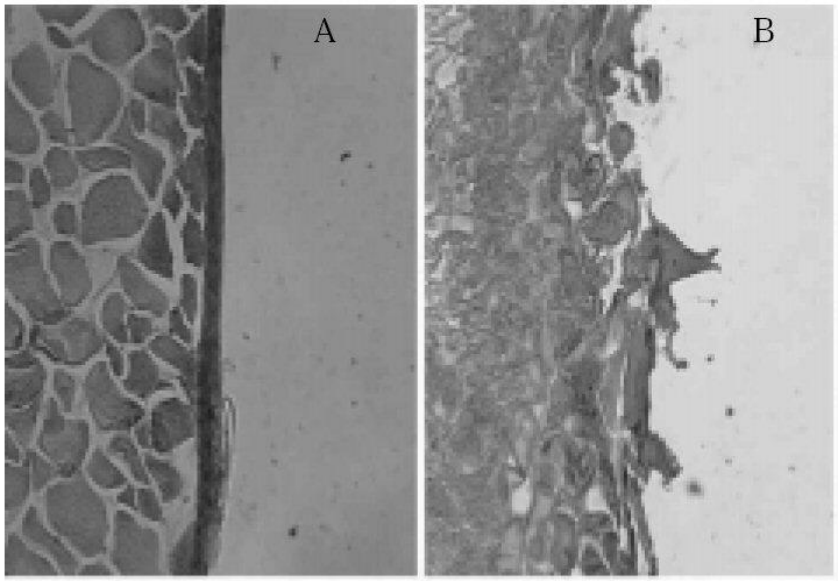


Figure 4 — H&E stain of frozen sections of rat demonstrating the presence (A) or absence (B) of peritoneum.

Flessner et al PDI 2003

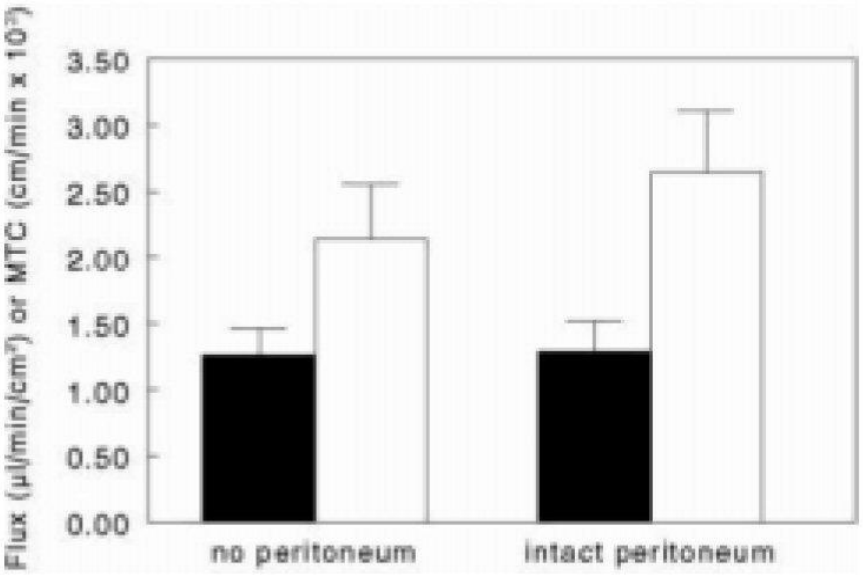


Figure 5 — Osmotic filtration into the transport chamber and loss of mannitol: effect of the presence of peritoneum. The results of one-way ANOVA demonstrate no significance of the presence of the peritoneum for osmotic volume flux (µL/minute/cm^2, $n = 9$, $p > 0.9$, solid bars) or mass transfer coefficient for mannitol (MTC; cm/minute, $n = 9$, $p > 0.4$, open bars).

Question : is P influenced by our surgery ?

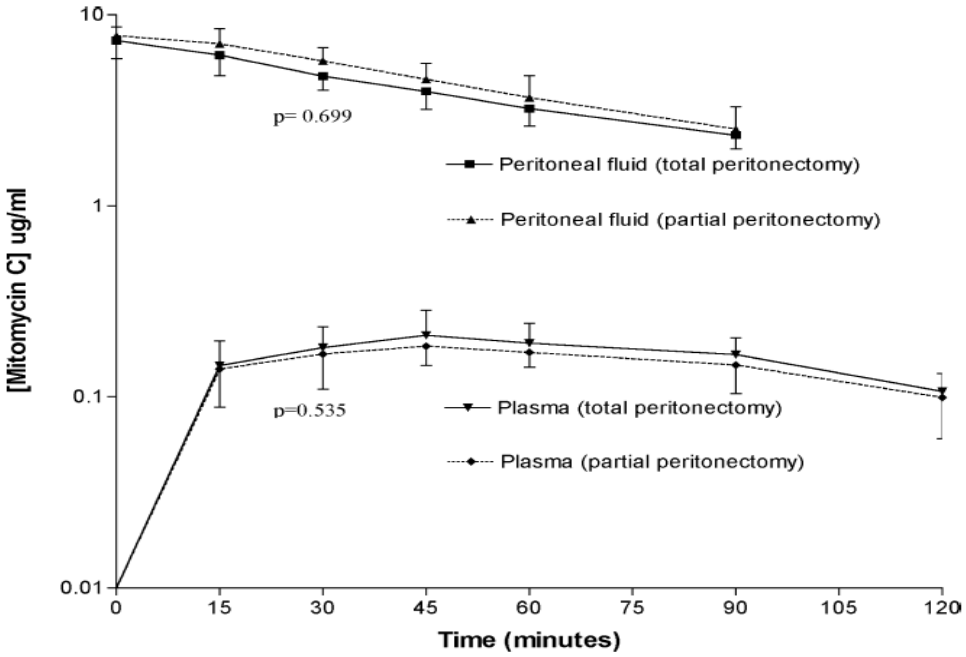
Cancer Chemother Pharmacol (2003) 52: 108–112
DOI 10.1007/s00280-003-0626-8

ORIGINAL ARTICLE

Vinicius de Lima Vazquez · O. Anthony Stuart
Faheez Mohamed · Paul H. Sugarbaker

Extent of parietal peritonectomy does not change intraperitoneal chemotherapy pharmacokinetics

Fig. 2 Peritoneal and plasma concentration curves of heated intraoperative mitomycin C. The means ± SD of five patients in each group are shown



PHARMACOLOGIC VARIABLES

PHARMACOLOGIC VARIABLES

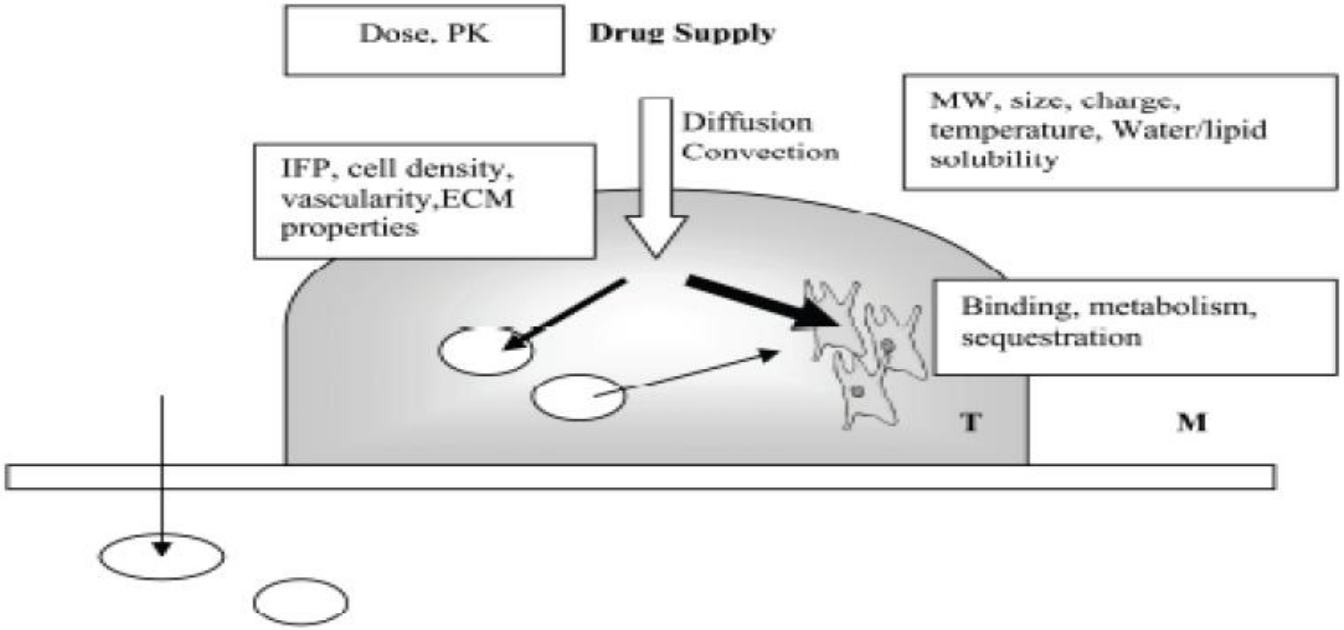
Pharmacokinetic VR	Pharmacodynamic VR
• DOSE	• TUMOR NODULE SIZE
• VOLUME	• DENSITY
• DURATION	• VASCULARITY
• CARRIER SOLUTION	• INTERSTITIAL FLUID PRESSURE
• PRESSURE	• BINDING
• MOLECULAR WEIGHT	• TEMPERATURE

‘ what the drug does to the body ‘

‘ what the body does to the drug ‘

PHARMACOLOGIC VARIABLES

Determinants of efficacy of IP chemotherapy



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

Manipulating

Pharmacologic Variables

PK- VARIABLE : PRESSURE

High Intra-abdominal Pressure Enhances the Penetration and Antitumor Effect of Intraperitoneal Cisplatin on Experimental Peritoneal Carcinomatosis

Philippe Esquis, MD,† David Consolo, MD,‡ Guy Magnin, MD,‡ Philippe Pointaire, MD,‡ Philippe Moretto, MD,§ Maria Dolores Ynsa, MD,§ Jean-Luc Beltramo, PhD,‖ Carole Drogoul,¶ Michel Simonet,** Laurent Benoit, MD,*† Patrick Rat, MD,† and Bruno Chauffert, MD*††*

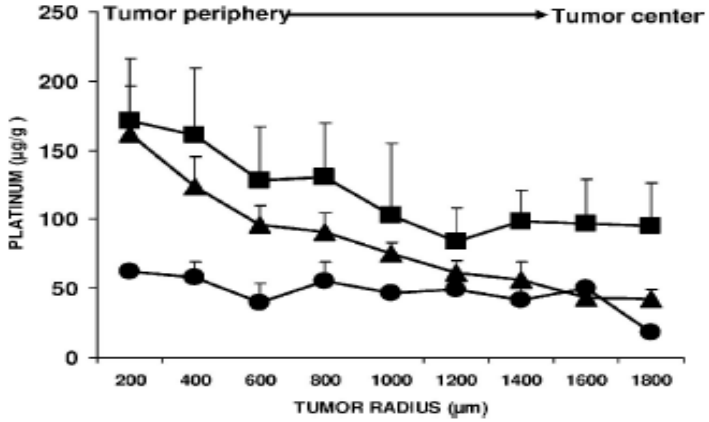


FIGURE 3. Distribution of platinum into peritoneal tumor nodules after conventional IP or IAP cisplatin treatment. Rats with 21-day-old carcinomatosis (4 per group) were treated with cisplatin through a conventional intraperitoneal injection (IP) or an intraperitoneal infusion with increased intra-abdominal pressure (22 mm Hg for 1 hour; IAP). Local platinum concentration was measured along the radii of peritoneal tumor nodules by the PIXE method. The platinum distribution in 400 × 800 μm^2 analyzed areas was plotted from the periphery to the tumor center. In conventionally treated IP groups, the cisplatin concentration in the peritoneal liquid was either 250 mg/L in 20 mL isotonic saline (5 mg/rat; 15 mg/kg; ●), or 1875 mg/L in 20 mL isotonic saline (37.5 mg/rat; 112.5 mg/kg; ▲) to compare groups exposed to the same concentration or the same total dose of cisplatin. Cisplatin concentration was 250 mg/L in 150 mL isotonic saline (37.5 mg/rat; 112.5 mg/kg) for the IAP-treated group (■). Each point is the mean of 4 determinations ± SD. A significant difference among the 3 IP treatments was detected ($P = 0.0125$, Kruskal-Wallis test). The Mann-Whitney test indicated that the difference between both of the upper curves was only significant between a depth of 1400 and 1800 µm ($P = 0.0421$).

UPPSALA UNIVERSITET

Pharmacokinetic variables

Laparoscopic HIPEC: initial experience; opportunities and limitations

Kurt GF Van der Speeten, M.D
Departement of Digestive Surgery, Ziekenhuis Oost-Limburg, Genk - Belgium

Ziekenhuis Oost-Limburg

Introduction

Peritoneal carcinomatosis is a common manifestation of colorectal tumors and is second to metastatic liver disease as cause of death. 25% of patients with peritoneal involvement have no systemic metastasis (1). In the last two decades aggressive resection of all macroscopic peritoneal carcinomatosis, followed by hyperthermic intraperitoneal peroperative chemotherapy (HIPEC) established itself as a new treatment modality with encouraging results (2-3). Until now this technique required an extensive laparotomy for full exploration and peritonectomy. The possibility of performing a laparoscopic peritonectomy and HIPEC was recently explored in an animal model (4). We report the first clinical case of laparoscopic assisted peritonectomy and HIPEC in a patient with limited peritoneal metastasis of an appendiceal carcinoma. The main objective is to demonstrate the feasibility and safety of this novel procedure.

Methods

A 45-years old patient was admitted to the emergency department with a 3-day history of right iliac fossa (RIF) pain and nausea. On clinical examination there was localized peritonitis confined to the RIF. Biochemistry and imaging studies confirmed the clinical diagnosis of acute appendicitis. A laparoscopic exploration and appendectomy was performed. Peroperative findings included: perforated appendicitis with diffuse contamination of the abdominal cavity and two hard nodules on the peritoneal surface of the RIF at a distance of the appendix itself at that time interpreted as local inflammatory changes. A laparoscopic appendectomy and lavage was performed. Cultures of the abdominal fluid were negative. Post-operative stay was uneventful. Anatomopathology of resected specimen unexpectedly revealed an invasive well-differentiated appendiceal carcinoma located at the perforated top of the appendix. In retrospect the lesions on the peritoneum of the RIF were considered potential peritoneal metastases. Staging was performed by CEA, liver ultrasound, helical CT-scan and PET-scan. No evidence of distant metastasis was encountered. Repeat laparoscopy was performed after 3 weeks. Patient was positioned in modified lithotomy-position. Five Versaport 5-12mm trocars® (Tyco Healthcare Group, Norwalk, Connecticut USA) were positioned and secured at the umbilicus and in the four quadrants (figure 1). The incisions of the previous laparoscopy were deliberately avoided. An extensive laparoscopic staging of the peritoneal surface including the bursa omentalis minor using a 45°-angled scope was performed and confirmed the two suspect lesions on the peritoneum of the RIF (figure 2); the peritoneal carcinomatosis index (PCI) according to Sugarbaker was established(5). A laparoscopic peritonectomy of the RIF and right flank was performed using the coagulating hook and forceps (figure 3). Pneumoperitoneum was helpful in exposing the peritoneum for an adequate stripping. The pneumoperitoneum was then deflated, the umbilical trocar was after rinsing the incision with povidone-iodine replaced by a handassist-device (Lapdisc®, Ethicon Endo Surgery, Cincinnati USA) (figure 4). 2 abdominal irrigation circuits were established through the 4 trocars. The inflow catheters were placed in the left subphrenic space and the Douglas cavity. The outflow catheters were at the top connected to a small plastic cage to avoid sticking to viscus and thus obstructing the abdominal perfusion (figure 5). The trocars at this point were positioned vertically and attached to an Omnitract-retractor. 6 temperature probes (Sorin Biomedica) and 3 pressure transducers (Baxter) were used as monitoring devices during the HIPEC (Figure 6). Before starting the HIPEC, 5-fluorouracil (5FU) 400 mg/m² with folinic acid 20 mg/m² was administered by IV. The surgeons hand was positioned through the Lapdisc® and the abdomen was filled with heated dextrose 5% at 43°C (figure 7). The hydroperitoneum was built up to a pressure of 10mm Hg. The roller pumps were started at a flow of 1.8 l/m and through a stirring motion of the surgeons hand a uniform temperature profile of 42° C. on all probes was reached. Subsequently Oxaliplatin 460 mg/m² was added to the abdominal irrigation circuit for 30 minutes. Intra-abdominal temperature, pressure and vital signs of the patient were monitored throughout the HIPEC. After 30 minutes the perfusate was aspirated and the abdomen flushed with normal saline. By adding methylen-blue to the perfusate we could confirm an adequate exposure of all peritoneal surfaces to the perfusate. The trocars and Lapdisc® were removed and the incisions irrigated with povidone-iodine before closing (figure 8). In addition a full thickness excision of the trocar sites of the initial appendectomy was performed.

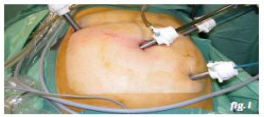


fig.1


fig.2


fig.3

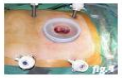


fig.4


fig.5

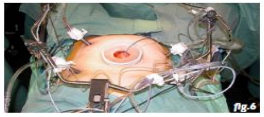


fig.6

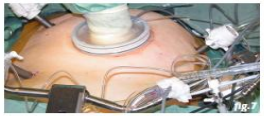


fig.7

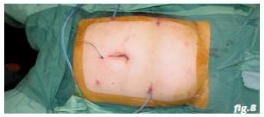


fig.8

Results

The PCI assessed during staging laparoscopy was 3. Laparoscopic peritonectomy was successful and R1-resection was achieved. The duration of the whole procedure was 145 min. The target intra-abdominal temperature of 43° was achieved after 17 min. A uniform homogeneous temperature and pressure profile could be sustained during the laparoscopic HIPEC. A flow of >2l/min was recorded throughout the procedure. No leaks of irrigation fluid through trocars or Lapdisc® were noted. The perfusate was recovered without contamination in a closed circuit bag. During laparoscopic HIPEC repeated blood samples were obtained. These revealed hyperglycemia/hyponatremia which was treated with an insulin-drip. The postoperative stay was uneventful, liquids were started the evening of surgery and solid intake the next day. No wound infection was observed. Patient was discharged on postoperative day 4. A blood sample on day 7 was within normal limits. After 7 months follow up there is no evidence of recurrent disease. Anatomopathology confirmed peritoneal metastasis of the appendiceal carcinoma in the resected peritonectomy specimen. Unexpectedly viable tumor cells were encountered in one of the excision specimens of the initial trocar sites of the appendectomy.

Discussion

Until recently, peritoneal carcinomatosis of colorectal origin was considered systemic disease beyond the scope of curability. The last two decades saw the emergence of arguments in favor of considering PC as a step between local disease and systemic spread (6) and the rise of cytoreductive surgery and HIPEC as a treatment option with a curative intent. The role of laparoscopy in treating peritoneal carcinomatosis has yet to be defined. Laparoscopy HIPEC has been explored in palliation of debilitating malignant ascites with excellent successrates as to resolution of the ascites in our institution and others (7). So far laparoscopic peritonectomy and HIPEC were not attempted in a potential curative setting. Recent animal studies by Ferron et al.(4) indicated that laparoscopic peritonectomy and HIPEC could be performed safe and efficient in an animal model. There are suggestions in literature that the increased pressure during laparoscopic HIPEC might add to penetration depth of the chemotherapeutic solution (8,9). We suggest with this first clinical case-report that laparoscopic peritonectomy and HIPEC is safe and feasible in treating limited peritoneal carcinomatosis with curative intent. It is clear that extensive peritoneal involvement will never be an indication for laparoscopic peritonectomy and HIPEC. Fase I-II studies are required for further validating this technique.
Lessons learned from HIPEC in gastric surgery suggest a benefit of HIPEC in an neoadjuvant setting in high risk patients with no peritoneal metastasis at the time of curative surgery (10). In an era were laparoscopy is validated as a tool in resecting colonic and gastric malignancies; laparoscopic HIPEC might be of benefit in preventing peritoneal metastases in high risk patients (positive cytology, immunocytohistochemistry,...).

References

1. Moody RD, Mine C, Kim TA, Bentrem A, Chadhry JT. Potentially curative surgery of colon cancer: patterns of failure and survival. J Clin Oncol 1988; 6: 106-116.
2. Elias D, Pocard M, Gilly F, et al. Preliminary results of intraperitoneal chemoperfusions with oxaliplatin in peritoneal carcinomatosis of colorectal origin. Ejc 2004; 11: 422-26.
3. Verwaal VJ, Van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol 2003; 21: 3737-43.
4. Ferron G, Gouraz Fraisse A, Classe JM, Querleu D. Feasibility of laparoscopic peritonectomy followed by intraperitoneal chemoperfusion: an experimental study. Gynecol Oncol 2005; 99: 258-61.
5. Sugarbaker PH. Peritonectomy procedures. Ann Surg Oncol 1995; 2: 226-37.
6. Sugarbaker PH. Management of peritoneal surface malignancy: the surgeon's role. Langenbecks Arch surg 1999; 384: 576-87.
7. Gonzalez R, et al. Laparoscopic intraperitoneal hyperthermic chemotherapy for palliation of debilitating malignant ascites. Eur J Surg Oncol. 2006; 32(6): 682-5.
8. Jacquet P, Stuart OA, Chang D, Sugarbaker PH. Effects of intraabdominal pressure on pharmacokinetics and tissue distribution of doxorubicin after intraperitoneal administration. Anticancer Drugs 1996; 7(7): 796-803.
9. Lopez P, et al. High intra-abdominal pressure enhances the penetration and antitumor effect of intraperitoneal cisplatin on experimental peritoneal carcinomatosis. Am Surg 2006; 72(4): 325-31.
10. Yonemura Y, et al. Hyperthermic intraperitoneal chemotherapy after curative gastrectomy for treatment of locally advanced gastric cancer. Ann Surg Oncol 2006; 13(5): 618-26.
11. Glehen O, Gilly FN, Arvieux C, et al. Peritoneal carcinomatosis from gastric cancer: a multivariate analysis of prognostic factors and the value of cytoreductive surgery. Ann Surg Oncol 2010; 17(9): 2370-7.
12. Yan TD, Black D, Savady R, et al. A systematic review on the efficacy of cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma. Ann Surg Oncol 2007; 14(2): 543-52.
13. Elias D, Gilly F, Boutitie F, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol 2010; 28(1): 63-8.
14. Glehen O, Kwiatkowski F, Sugarbaker PH, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. J Clin Oncol 2004; 22(16): 3284-92.
15. Elias D, Lefevre JH, Chevalier J, et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. J Clin Oncol 2009; 27(5): 681-5.
16. Yan TD, Black D, Sugarbaker PH, et al. A systematic review and meta-analysis of the morbidity and survival following cytoreductive surgery and perioperative intraperitoneal chemotherapy for ovarian peritoneal carcinomatosis. Gynecol Oncol 2007; 107(1): 133-9.

UPPSALA UNIVERSITET

Pharmacokinetic variables

Journal of Surgical Oncology 2009;100:331–334

Laparoscopic Hyperthermic Intraperitoneal Peroperative Chemotherapy (HIPEC) in the Management of Refractory Malignant Ascites: A Multi-Institutional Retrospective Analysis in 52 Patients

M. VALLE, MD,[1] K. VAN DER SPEETEN, MD,[2]* AND A. GAROFALO, MD, PhD[1]
[1]*Department of Surgical Oncology, Digestive Branch, "Regina Elena National Cancer Institute", Rome, Italy*
[2]*Department of Surgical Oncology, Ziekenhuis Oost-Limburg, Genk, Belgium*

Malignant ascites is a debilitating condition affecting cancer patients in their terminal stage of disease. Recently, laparoscopic hyperthermic intraperitoneal peroperative chemotherapy (HIPEC) was introduced as a new approach. From September 2001 to August 2008, 52 patients were treated with this new modality. No treatment-related mortality was observed. Median survival was 98 days. One patient developed a clinical recurrence. Laparoscopic HIPEC is a safe and effective method for palliating malignant ascites
J. Surg. Oncol. 2009;100:331–334.

UPPSALA UNIVERSITET

Pharmacokinetic variables

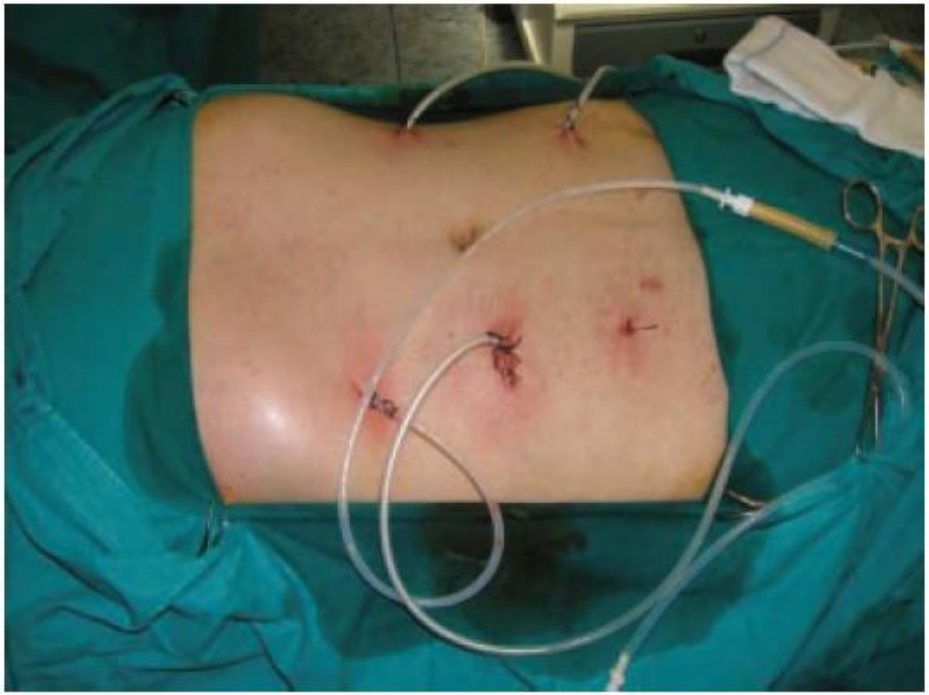


Fig. 1. Inflow an outflow catheters in place and secured, through trocar port incisions after laparoscopic adhesiolysis.

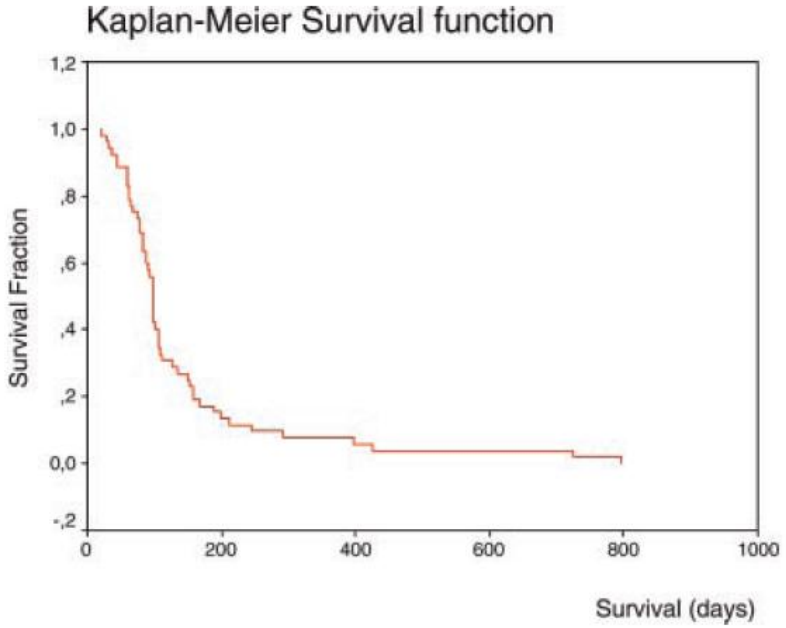


Fig. 3. Kaplan–Meier survival function of 52 patients treated with laparoscopic HIPEC in the palliation of malignant ascites.

TUMOR NODULE

AS

PHARMACOLOGIC

ENDPOINT

UPPSALA
UNIVERSITET

Washington
Hospital Center
Washington
Cancer Institute

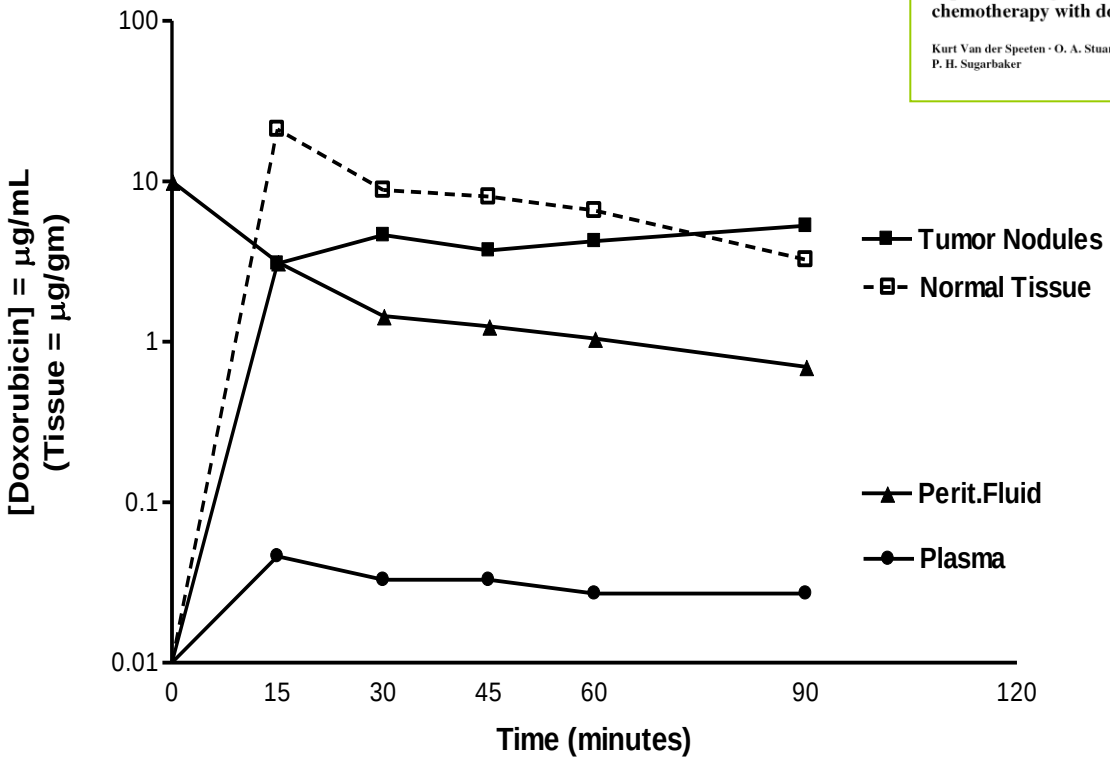
TUMOR NODULE AS PHARMACOLOGIC ENDPOINT

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

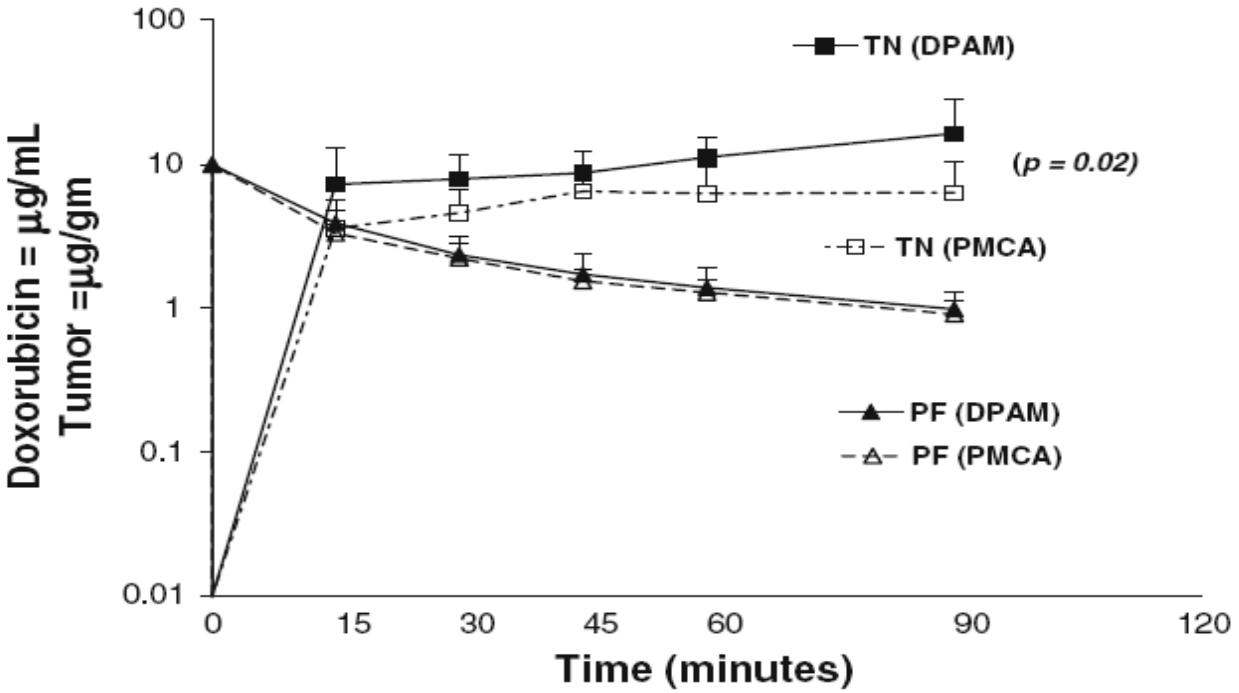
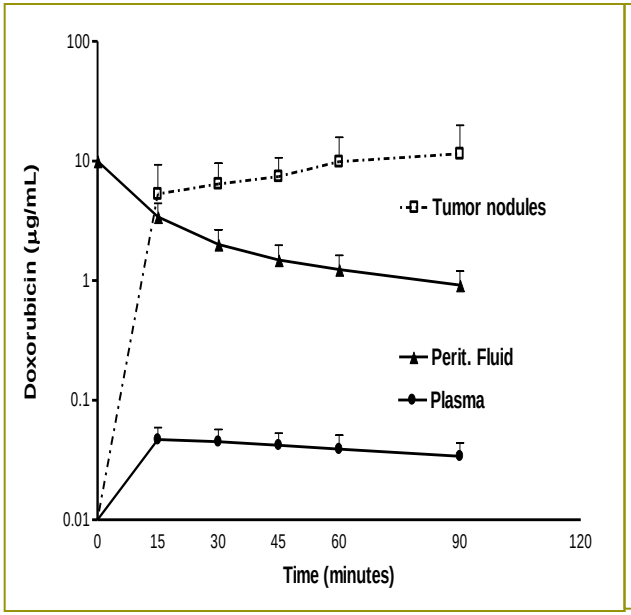
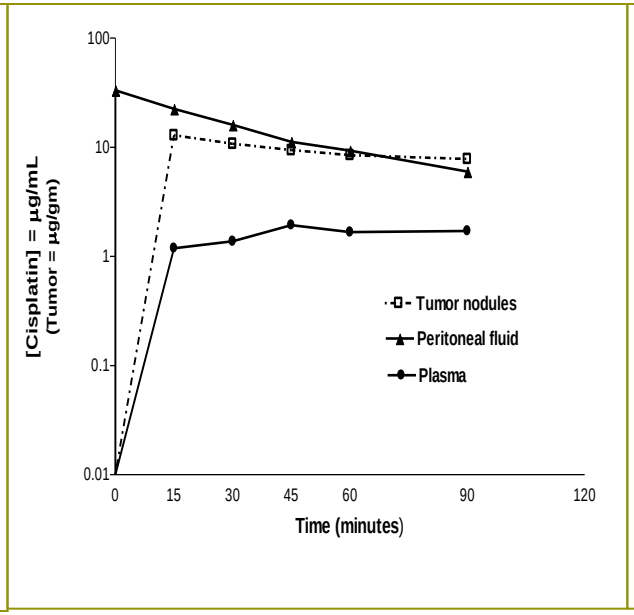
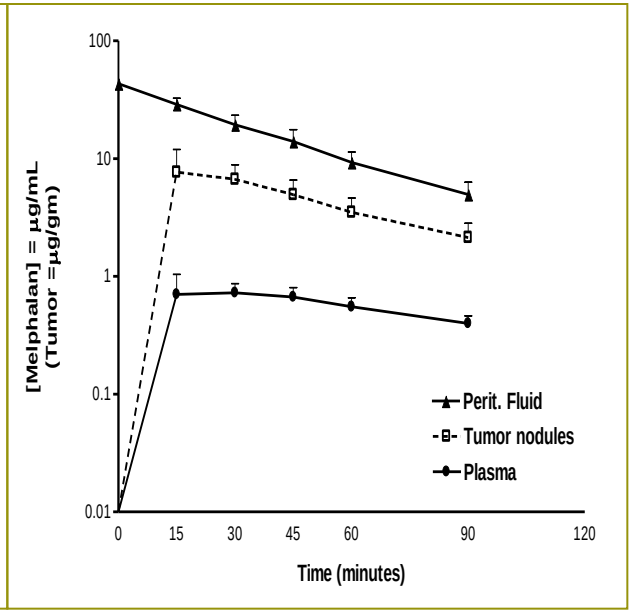


Fig. 3 Doxorubicin levels in appendiceal tumor tissue showing diffuse peritoneal adenomucinosis (*DPAM*) versus peritoneal mucinous carcinomatosis (*PMCA*). Peritoneal fluid concentrations are also shown. *TN* tumor nodule, *PF* peritoneal fluid

TUMOR NODULE AS PHARMACOLOGIC ENDPOINT







DOXORUBCIN

CISPLATIN

MELPHALAN

Rationale for Bidirectional Intraoperative Chemotherapy (BIC)

Ziekenhuis Oost-Limburg

UPPSALA UNIVERSITET

Washington Hospital Center
Washington Cancer Institute

Introduction : concept of BIC

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

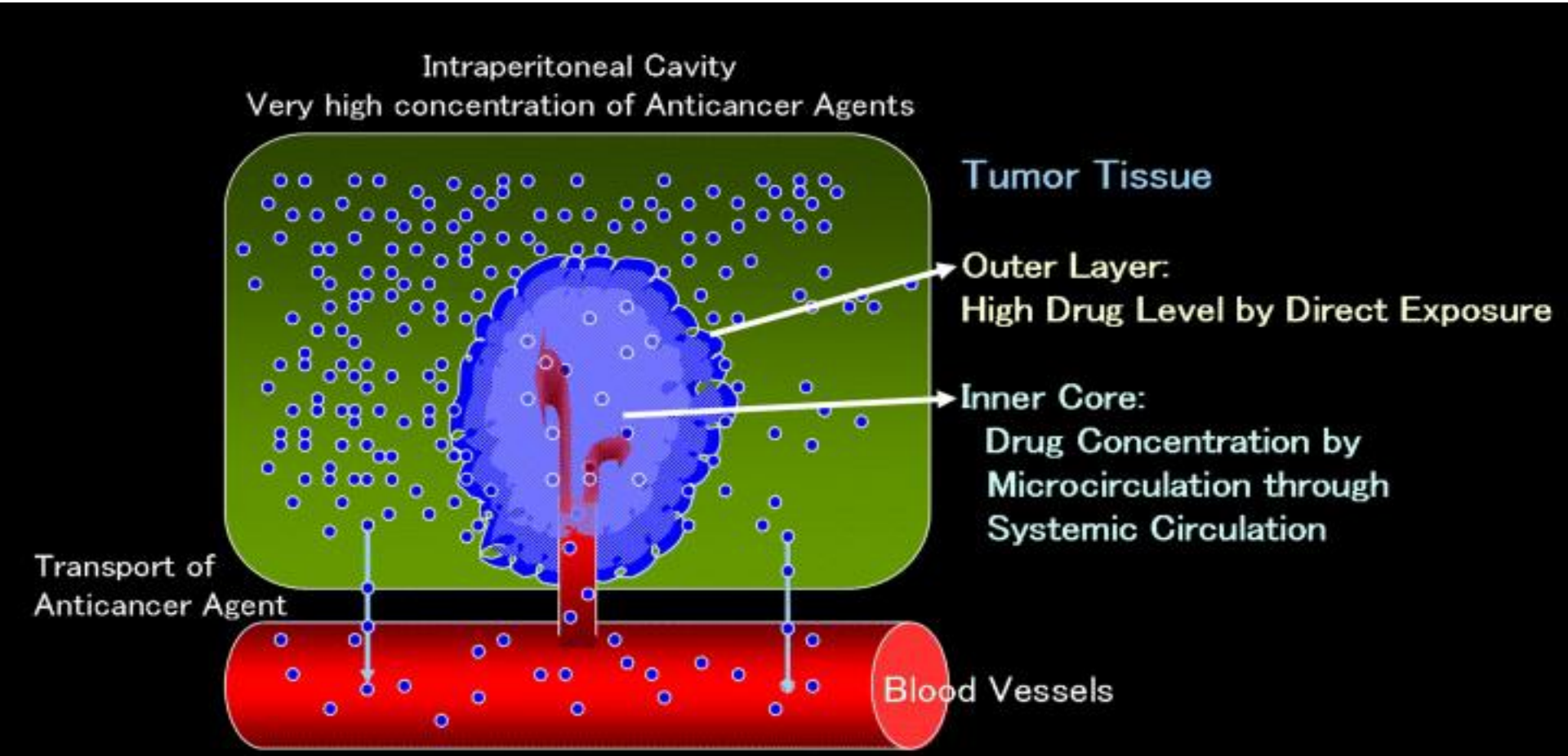
D. Elias*, M. Bonnay, J. M. Puizillou, S. Antoun, S. Demirdjian, A. El Otmany, J. P. Pignon, L. Drouard-Troalen, J. F. Ouellet & M. Ducreux

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

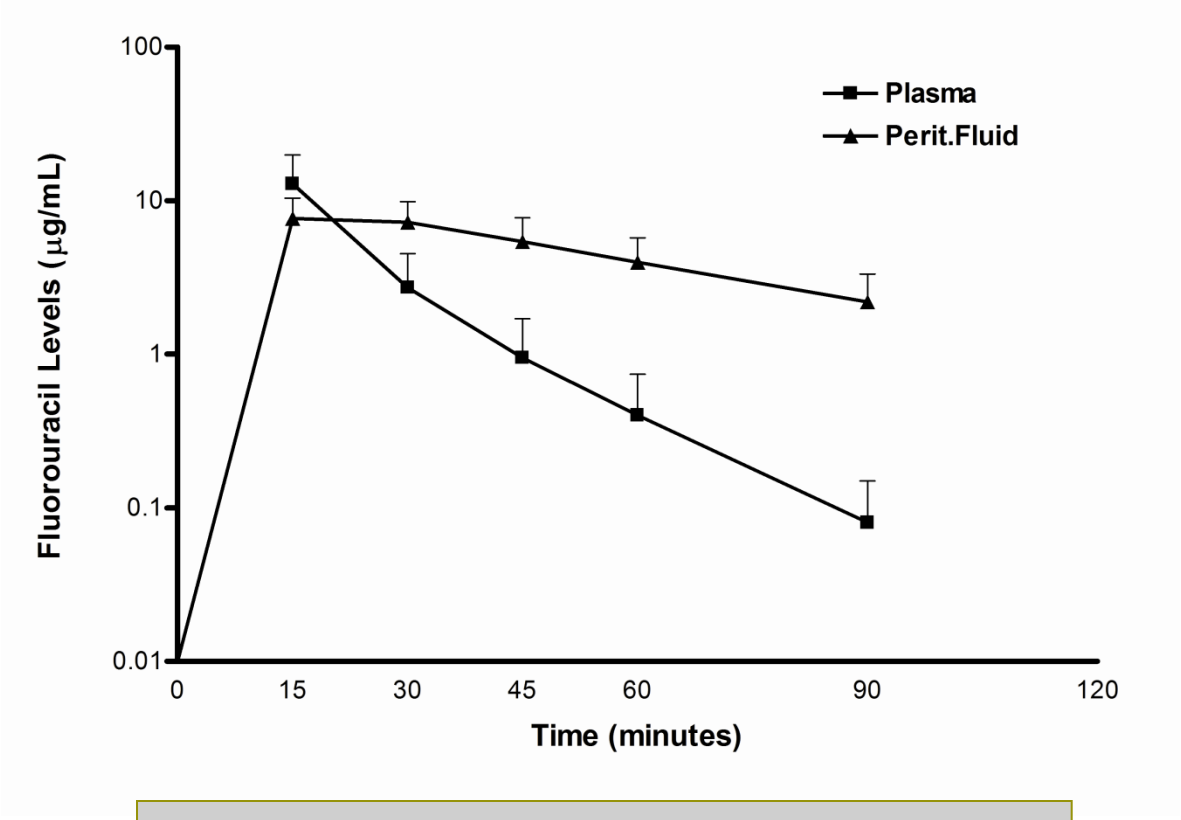
Pharmacologic concept of bidirectional (IV and IP) chemotherapy



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

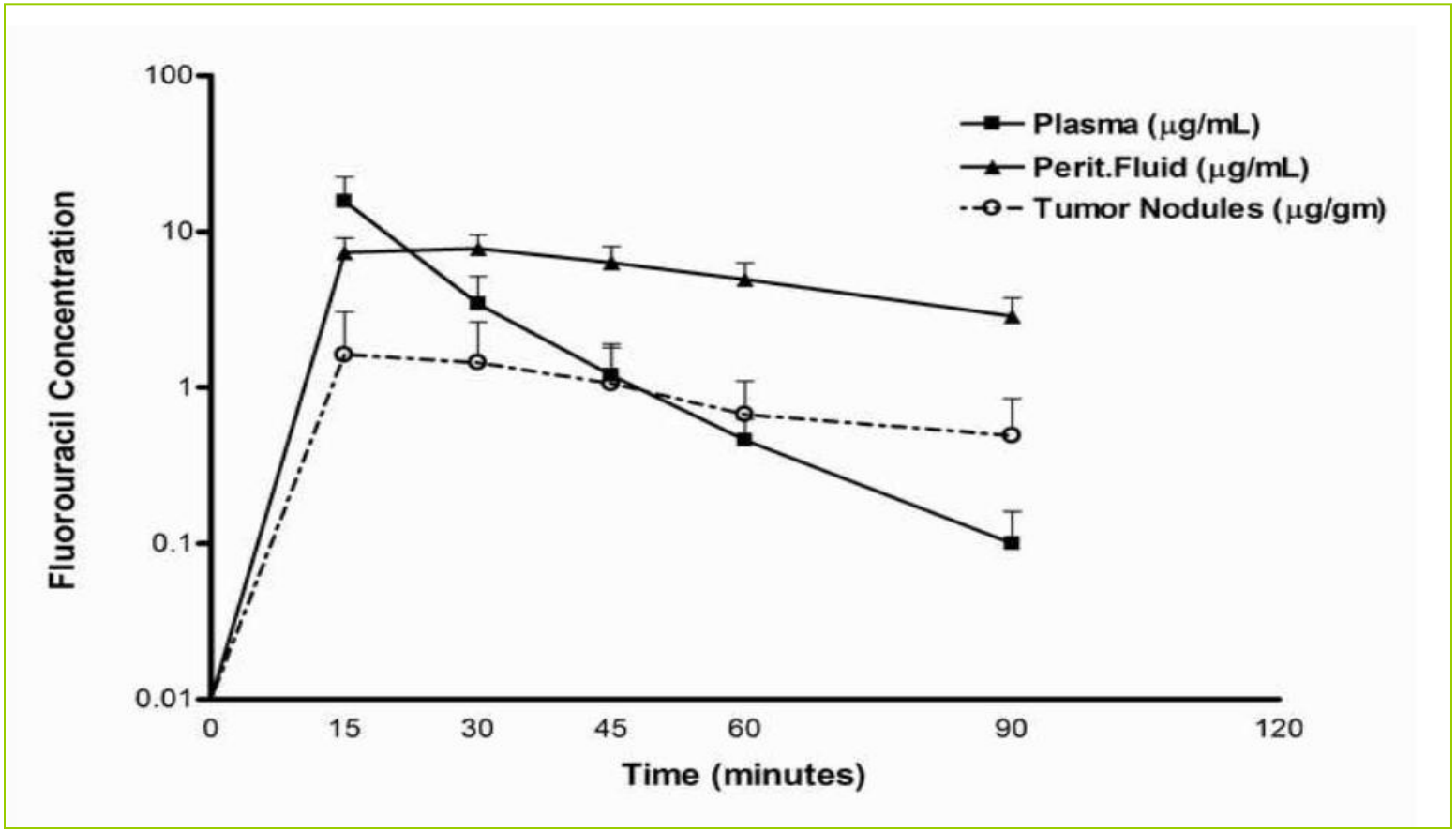


FIGURE 3: 5-Fluorouracil concentrations in plasma, peritoneal fluid and tumor nodules after intravenous administration during hyperthermic intraperitoneal chemotherapy procedure (N=9).

TIMING OF PERIOPERATIVE IV CHEMOTHERAPY

Rationale for **intravenous** administration of 5-fluorouracil *(augmentative drug)*

- Rapid distribution to all body compartments (including peritoneal cavity)
- Metabolisation confined to plasma compartment
- Pharmacokinetic advantage

Timing of intravenous chemotherapy emerges as a new variable

- Pharmacological ‘sink’ phenomenon in the artificial ascites
- Ideal situation for drug synergism with intraperitoneal chemotherapy
- Normothermic administered IV 5-FU = subject to IP hyperthermic augmentation

INDIVIDUAL

DRUG SENSITIVITY

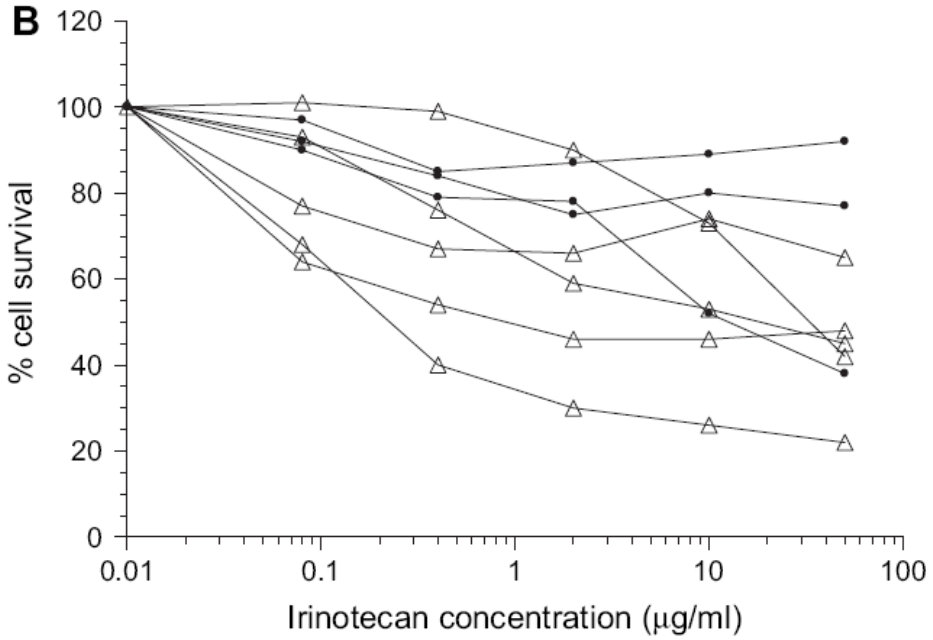
UPPSALA
UNIVERSITET

Washington
Hospital Center
Washington
Cancer Institute

INDIVIDUAL DRUG SENSITIVITY

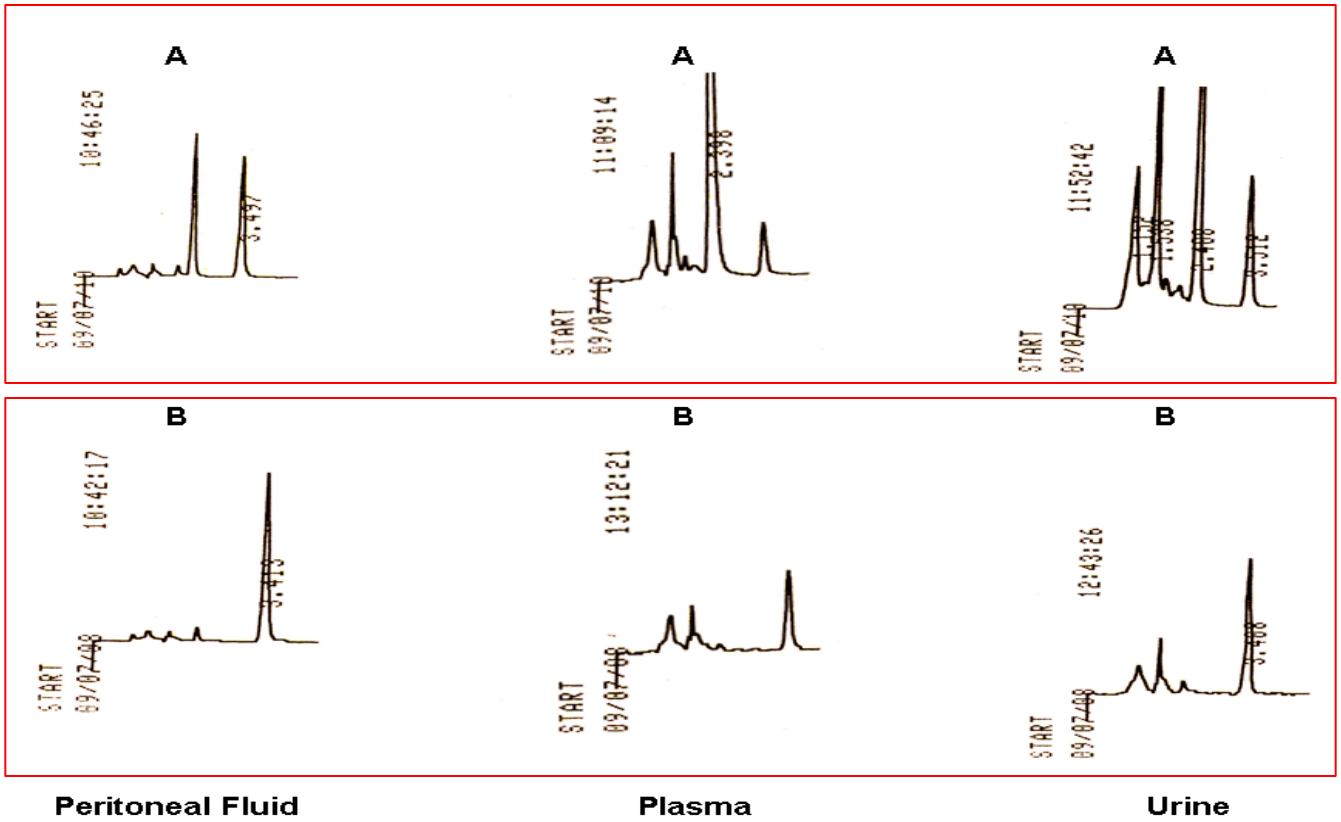
Heterogeneous activity of cytotoxic drugs in patient samples of peritoneal carcinomatosis

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.

NON-METABOLIZERS



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

TIME

FOR

A NEW CONCEPTUAL MODEL

Ziekenhuis Oost-Limburg

UPPSALA UNIVERSITET

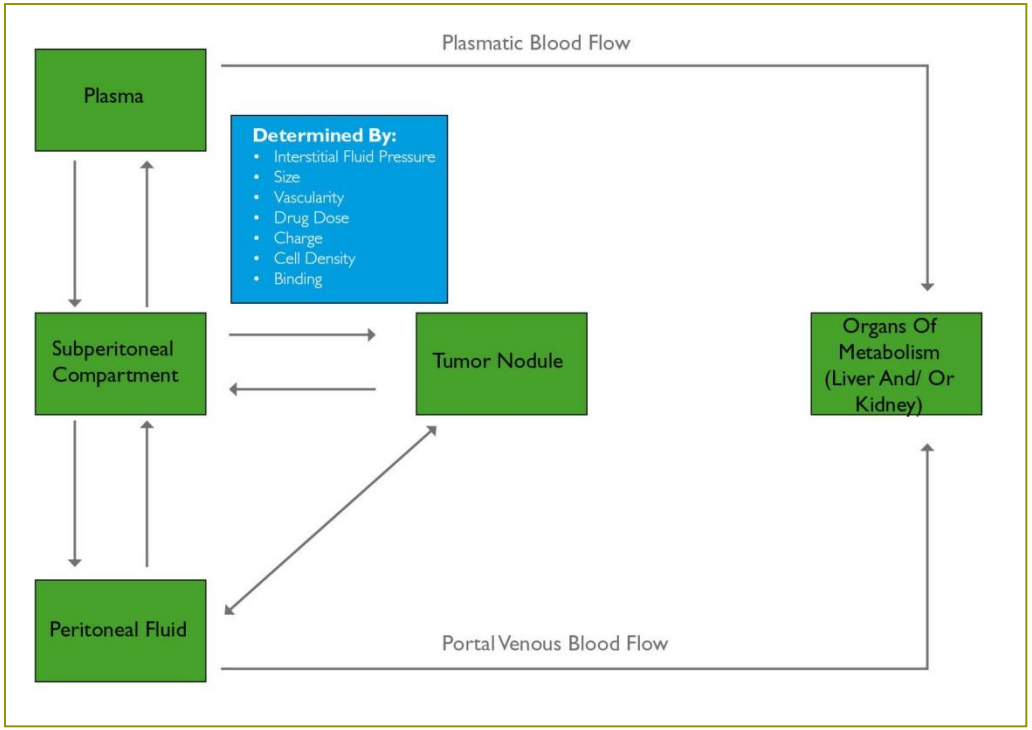
Washington Hospital Center
Washington Cancer Institute

CONCEPTUAL MODEL OF PERIOPERATIVE CHEMOTHERAPY

REVIEW ARTICLE

Pharmacokinetics and Pharmacodynamics of Perioperative Cancer Chemotherapy in Peritoneal Surface Malignancy

Kurt Van der Speeten, MD, Oswald A. Stuart, BS,† and Paul H. Sugarbaker, MD†*



CONCLUSIONS

Ziekenhuis Oost-Limburg

UPPSALA UNIVERSITET

Washington Hospital Center
Washington Cancer Institute

PERITONEAL CARCINOMATOSIS : CONCLUSIONS

- PSM is a locoregional disease and as such warrants a locoregional approach.
- CRS addresses macroscopic disease and the subsequent intraperitoneal chemotherapy eliminates residual microscopic disease
- Dose intensification (IP/IV) is the driving force
- Tumor nodules emerges as the pharmacologic endpoint
- Timing of IV chemotherapy emerges as a new pharmacologic variable
- Individual drug sensitivity ?

THANK YOU