Management of Peritoneal Surface Malignancy

Irkutsk, Sibiria

9 -11 Aug 2017

Irkutsk Regional Oncology Hospital
Frunze street, House 32
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Rationale for CRS and HIPEC

K. Van der Speeten, MD, PhD
Irkutsk, 09/08/17

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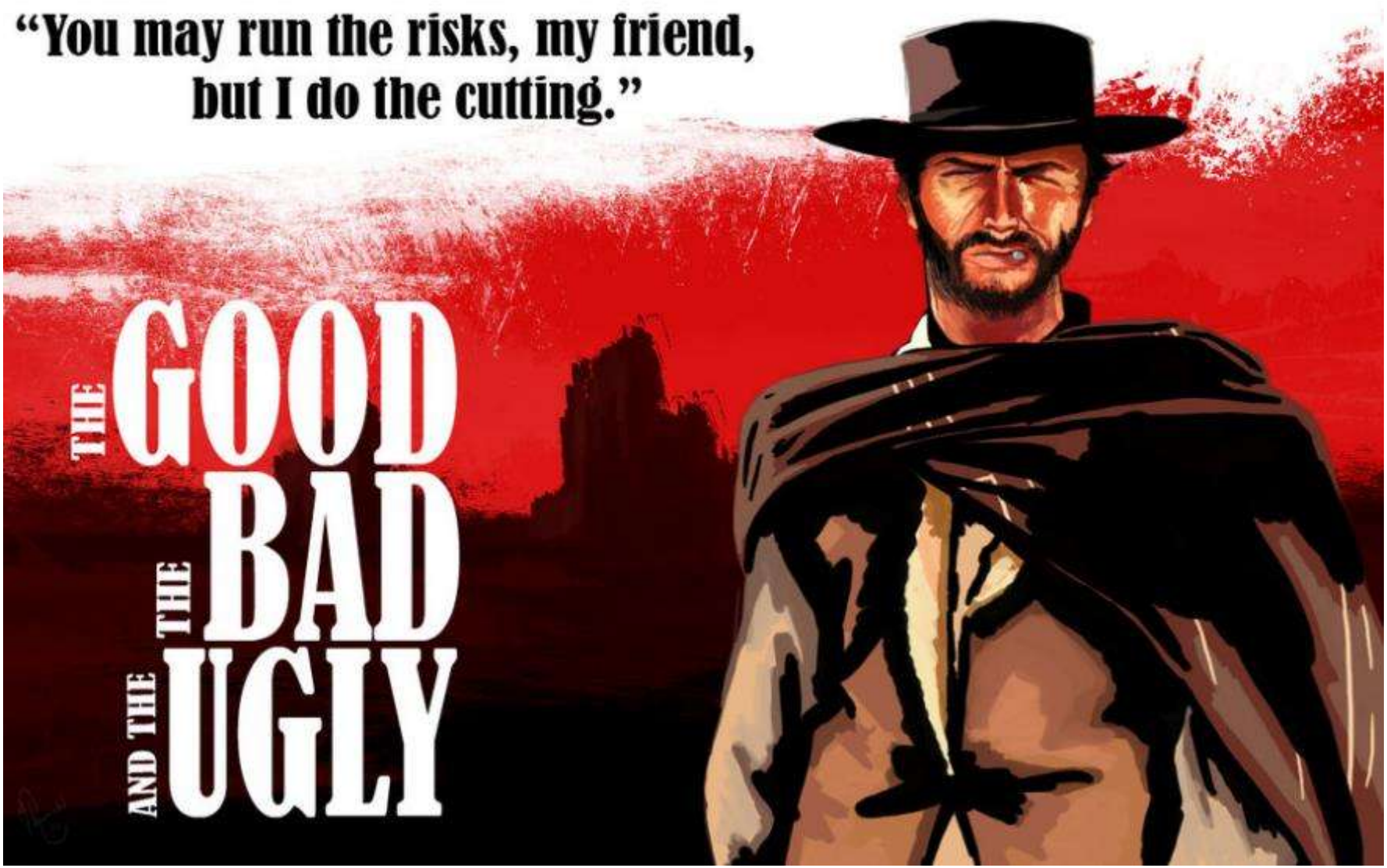
- Background in 2017 : the Good, the Bad and the Ugly
- Chemosurgery
- The surgery in chemosurgery
- The chemo in chemosurgery
- Rationale for HIPEC
- Do we need HIPEC ?
- Do we need Hyperthermia ?
- Rationale for EPIC
- Rationale for BIC
- Too many variables and the need for standardization
- Conclusions

Treating PSM in 2017



2017 : The Good

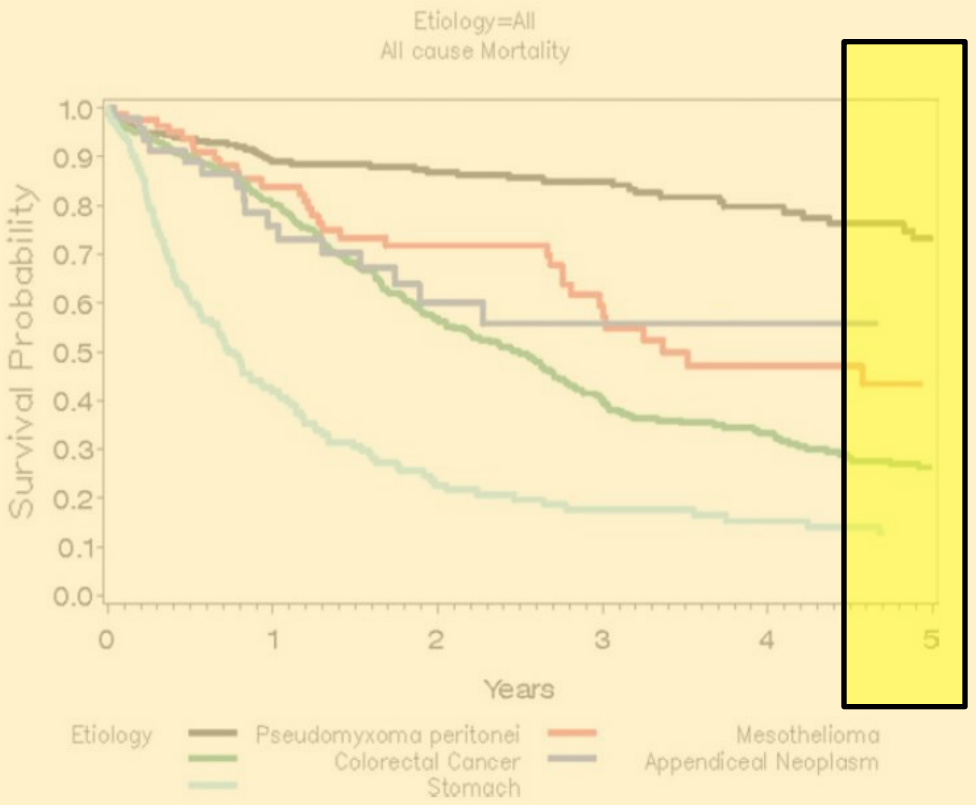


Figure 3. Overall survival rates are illustrated for patients with colorectal peritoneal carcinomatosis (PC), pseudomyxoma peritonei, peritoneal mesothelioma, gastric PC, and PC from appendiceal adenocarcinoma.

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

2017 : The Bad (PALLIATION BY DEFAULT)

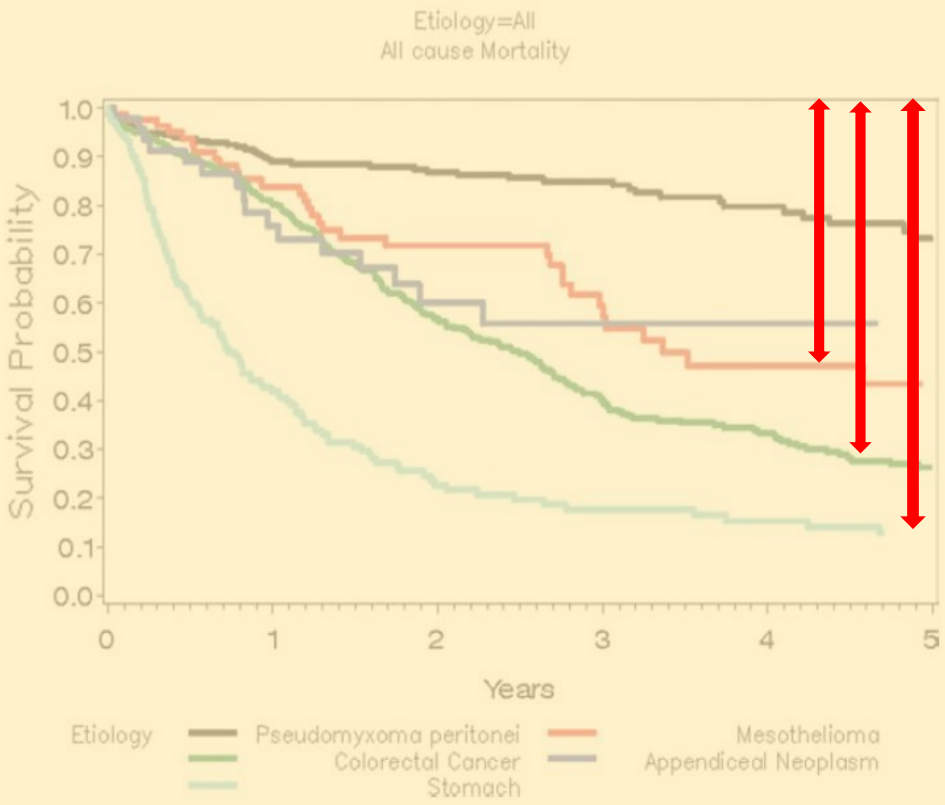


Figure 3. Overall survival rates are illustrated for patients with colorectal peritoneal carcinomatosis (PC), pseudomyxoma peritonei, peritoneal mesothelioma, gastric PC, and PC from appendiceal adenocarcinoma.

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

2017 : 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,c], 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	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)
>270 min	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 2017

CHEMOSURGERY

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TREATING PC WITH ‘ CHEMOSURGERY ‘ ?

- Combined multi-organ resections
- Peritonectomy-procedures

→ Treatment of MACROSCOPIC disease

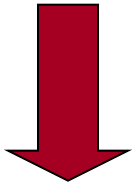
- Intraperitoneal Chemotherapy

→ 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
NIPS	**N**eoadjuvant **I**ntraperitonean and **S**ystemic **C**hemotherapy

THE SURGERY IN CHEMOSURGERY

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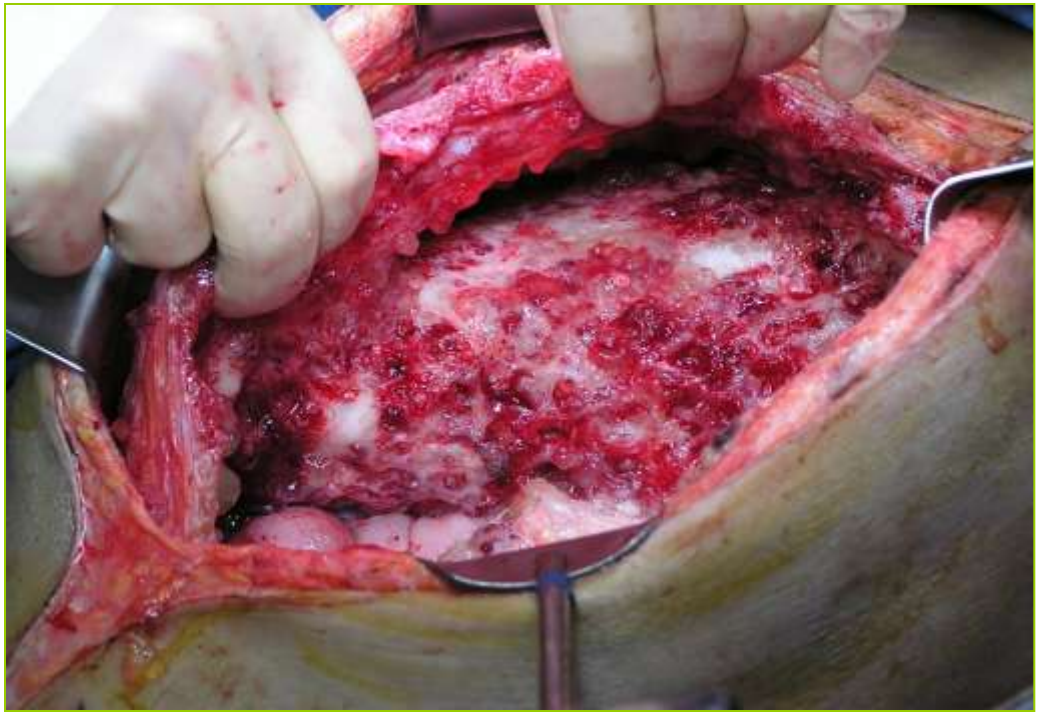
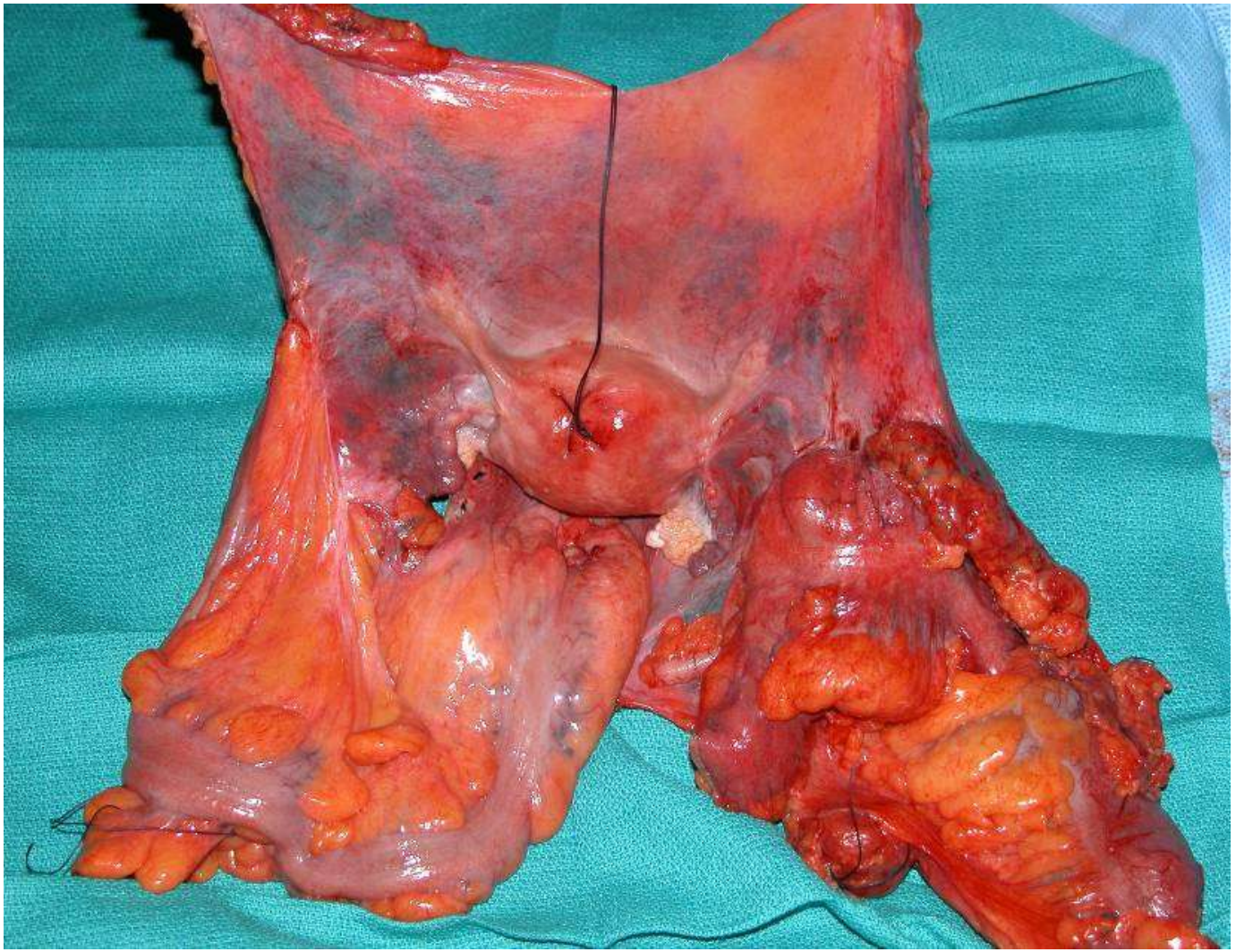
The Surgery in Chemosurgery

- Combined multi-organ resections
- Peritonectomy-procedures

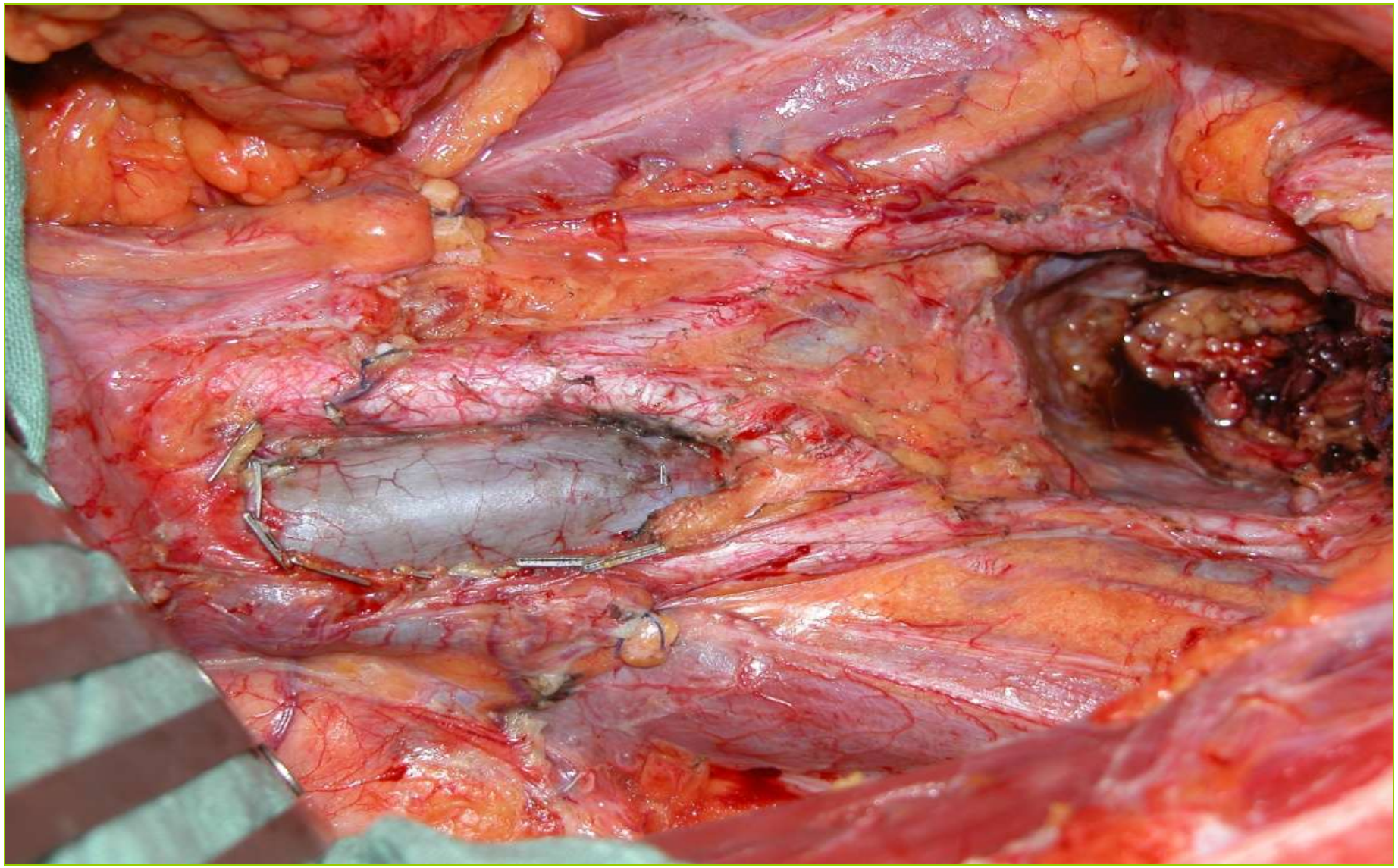
→ Treatment of MACROSCOPIC disease



The Surgery in Chemosurgery



The Surgery in Chemosurgery



THE CHEMO IN CHEMOSURGERY

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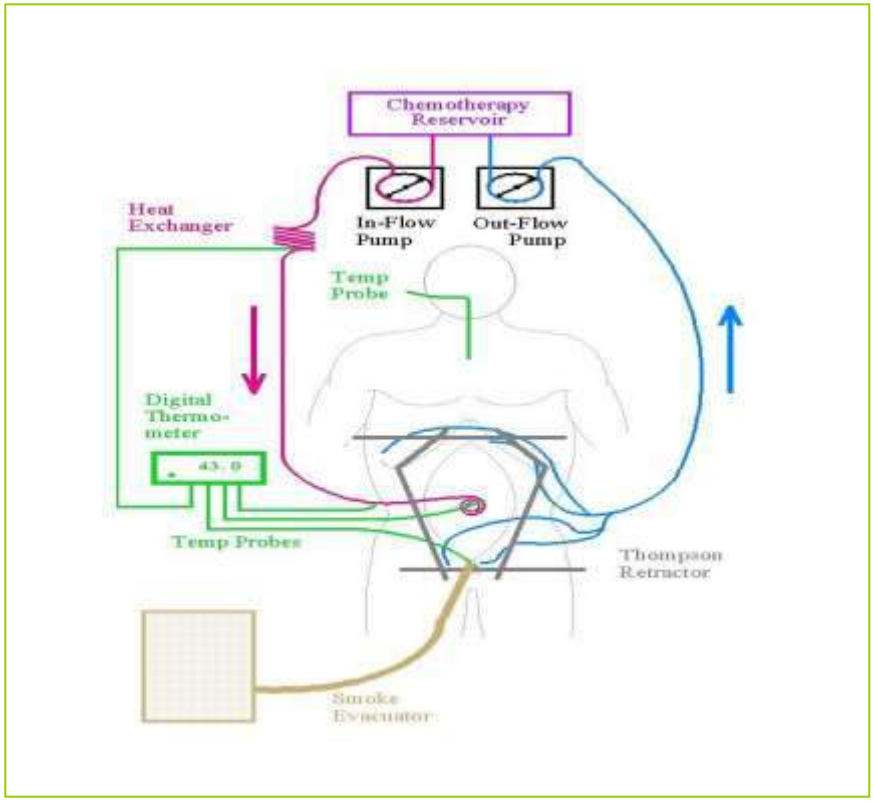
The Chemo in Chemosurgery

- Hyperthermic Intraperitoneal

  Peroperative Chemotherapy (HIPEC)

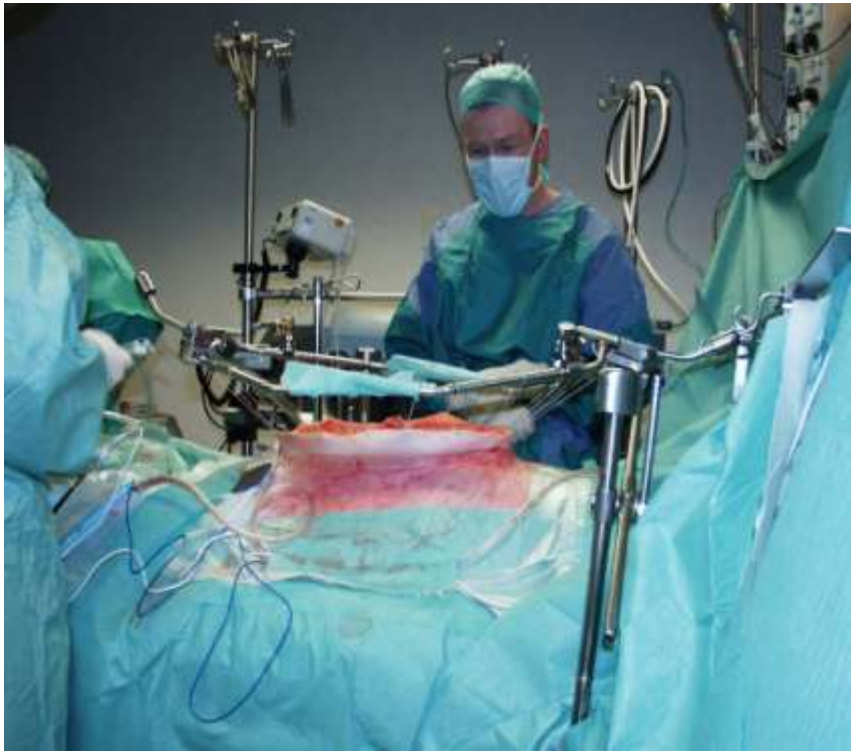
→ Treatment of MICROSCOPIC disease

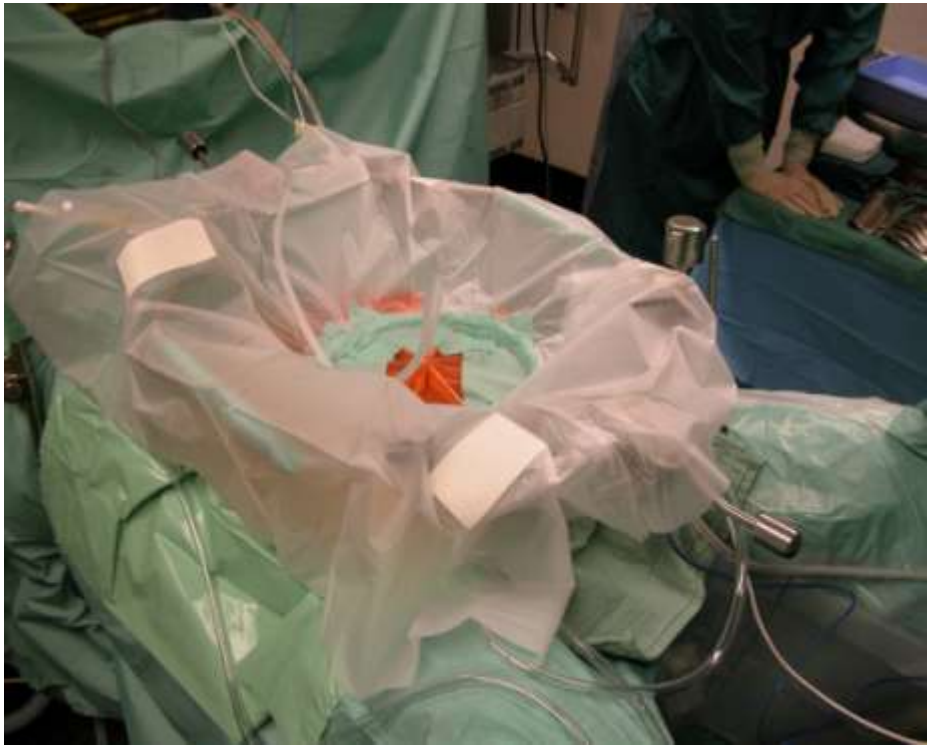


The Chemo in Chemosurgery

- Hyperthermic Intraperitoneal

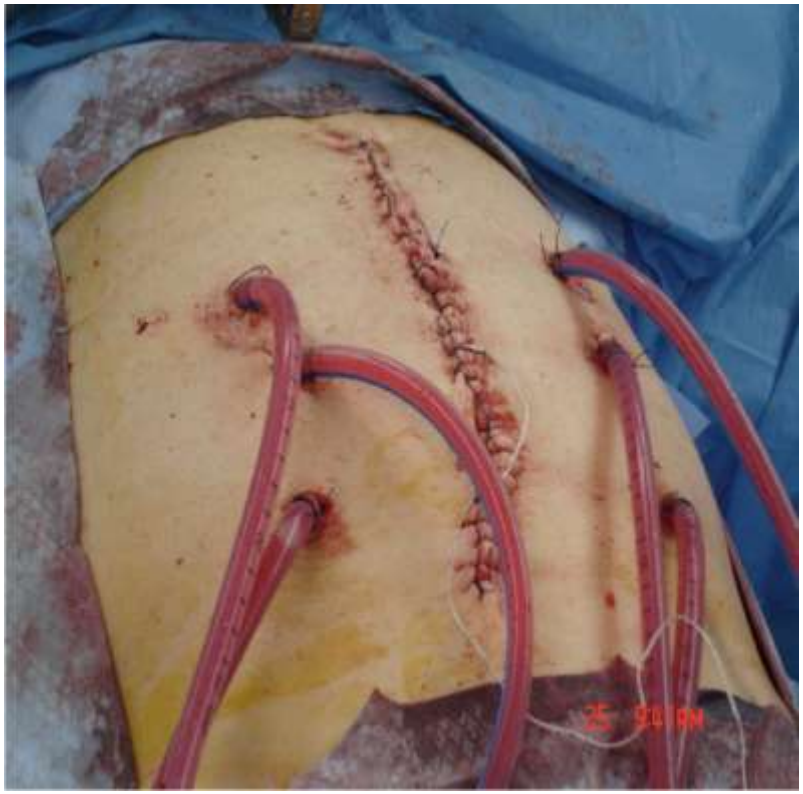
  Peroperative Chemotherapy (HIPEC)

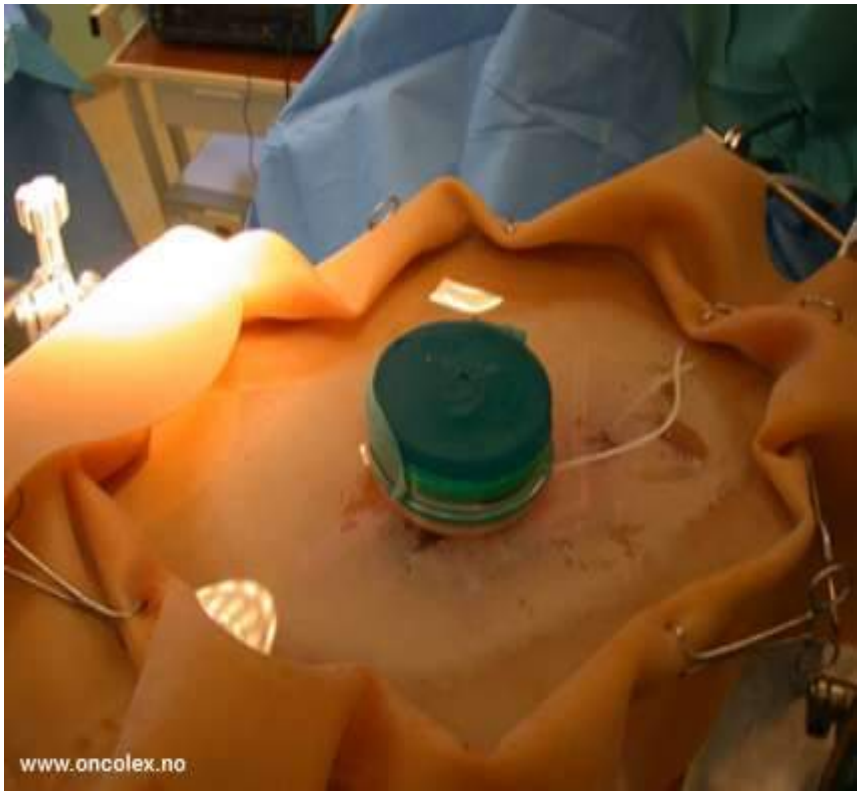




The Chemo in Chemosurgery

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

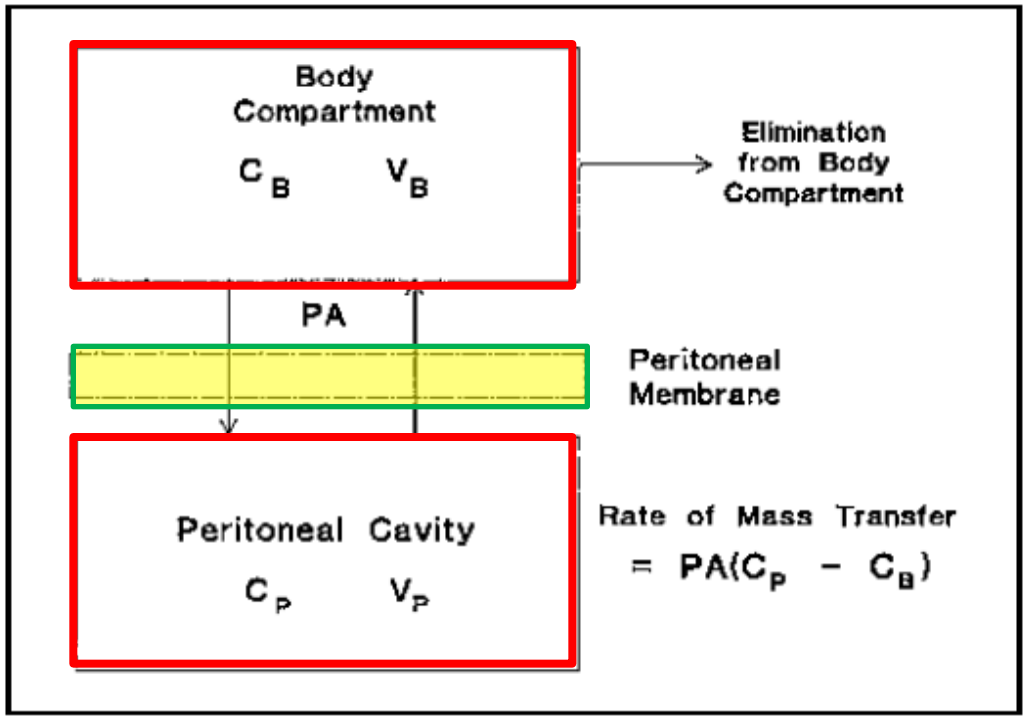
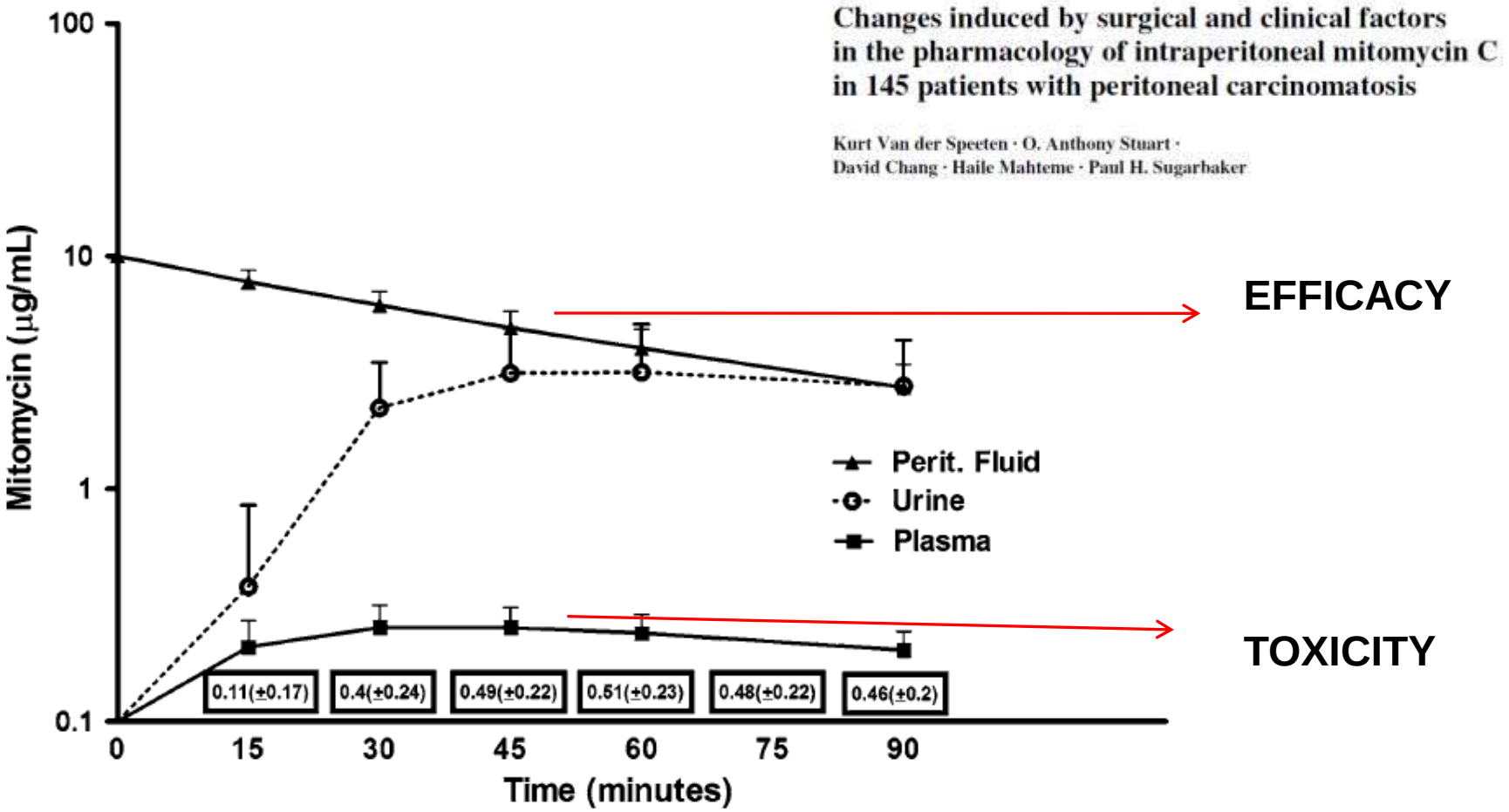


Fig. 1. Traditional two-compartment model of peritoneal transport, in which transfer of a drug from the peritoneal cavity to the blood occurs across the ''peritoneal membrane.'' The permeability-area product (PA) governs this transfer and can be calculated by measuring the rate of drug disappearance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



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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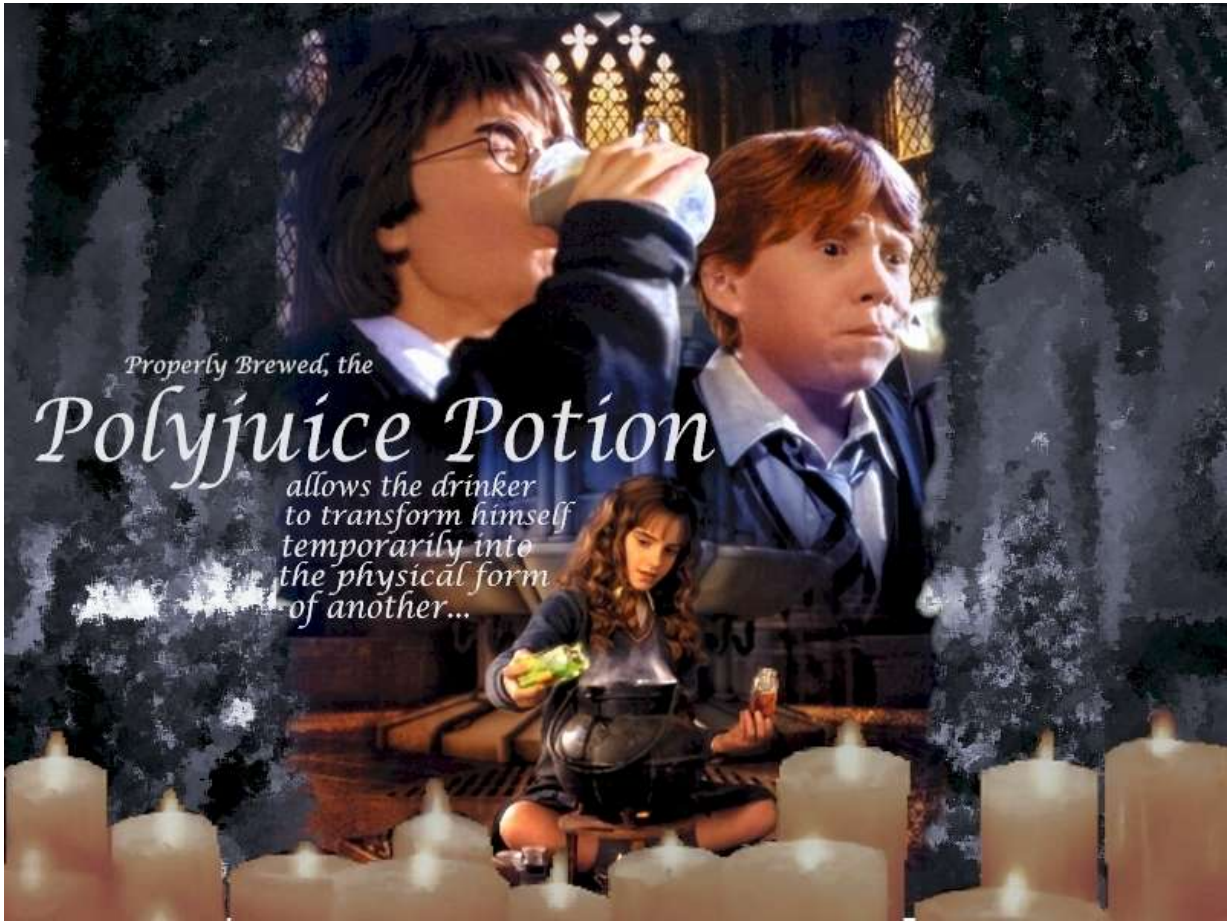
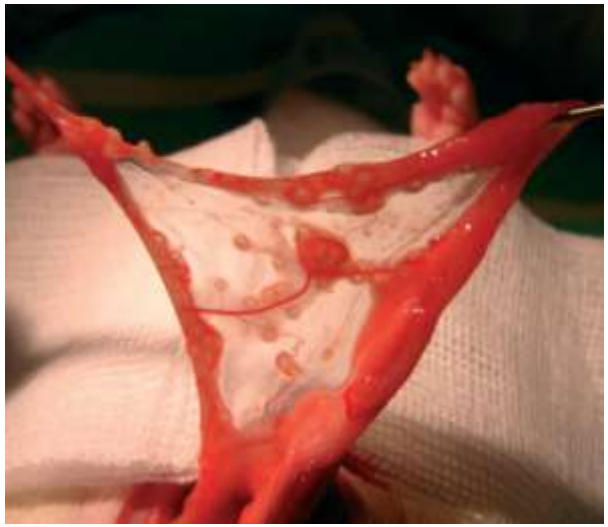
Do we need HIPEC ?

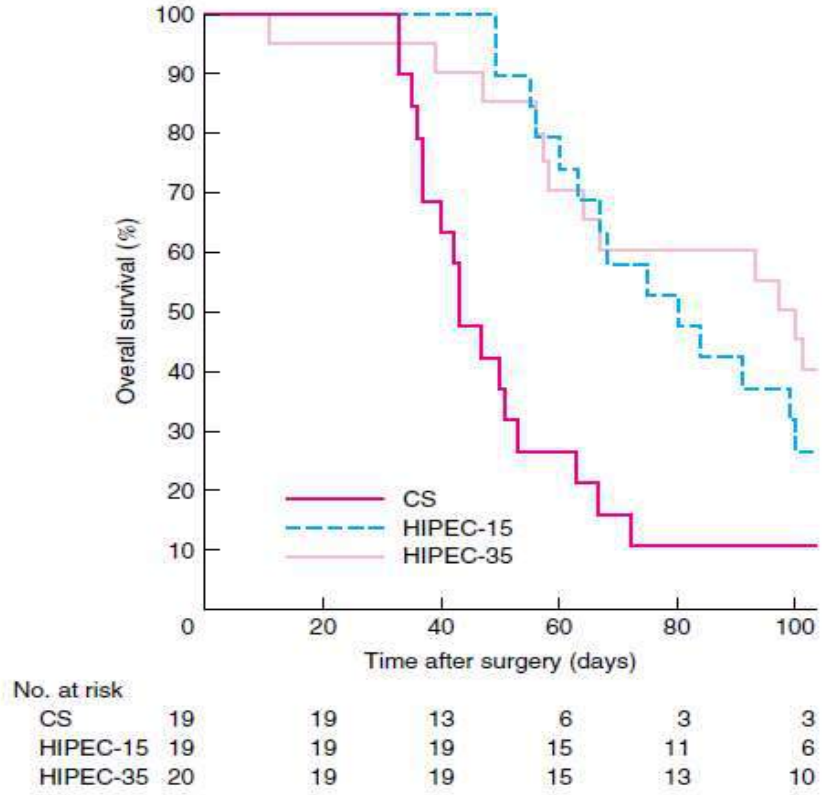


Do we need HIPEC ?

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]





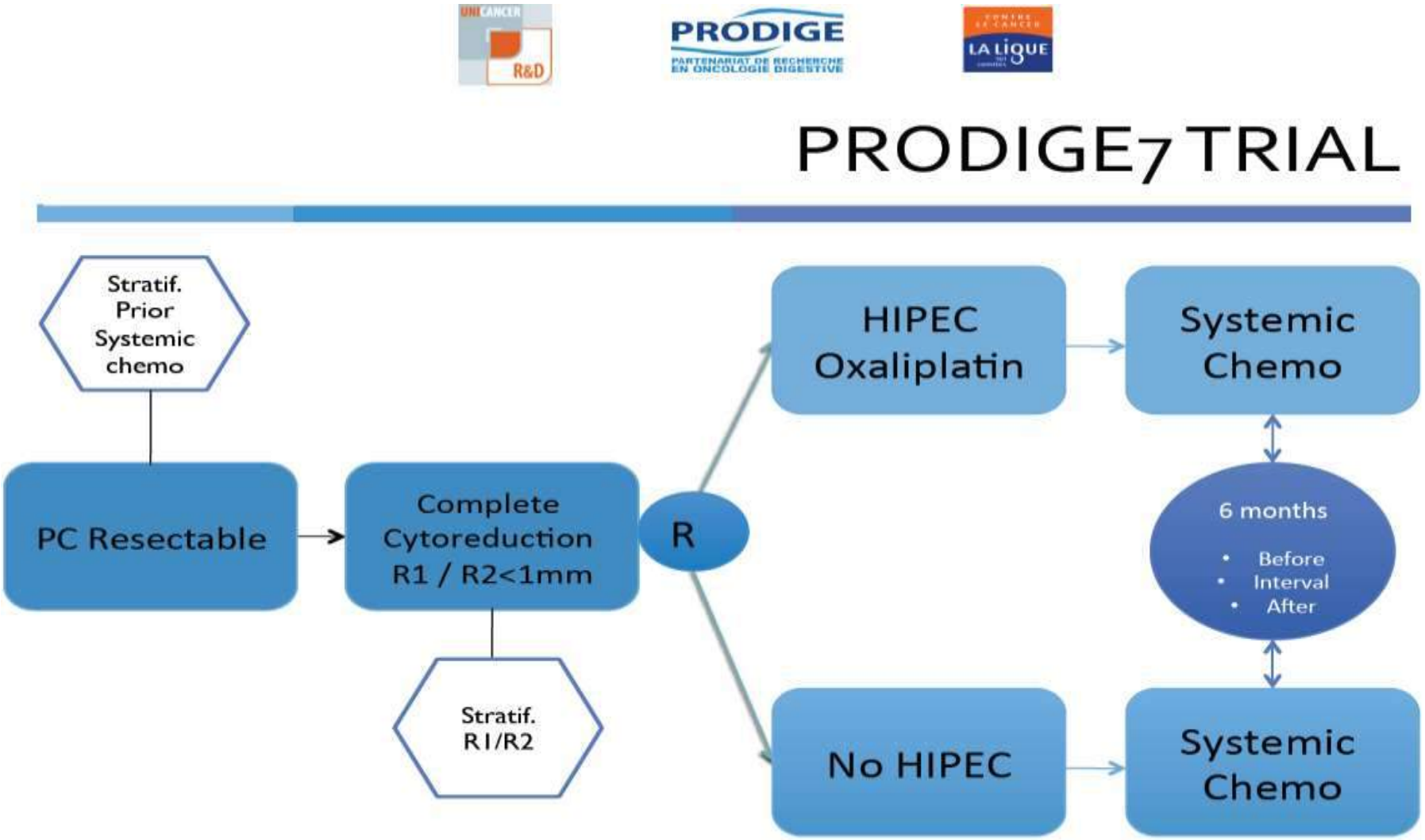
No. at risk

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

Do we need HIPEC ?



DO WE NEED

HYPERTHERMIA ?

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Do we need hyperthermia ?

1. T° is cytotoxic on its own
2. T° improves chemotherapy penetration
3. T° augments the cytotoxic effect of some drugs

ROLE OF HYPERTHERMIA ?

Rationale for Heating Oxaliplatin for the Intraperitoneal Treatment of Peritoneal Carcinomatosis

A Study of the Effect of Heat on Intraperitoneal Oxaliplatin Using a Murine Model

Nelson Piché, MD, François A. Leblond, PhD, Lucas Sidéris, MD, Vincent Pichette, MD, Pierre Drolet, MD, Louis-Philippe Fortier, MD, Andrew Mitchell, MD, and Pierre Dubé, MD

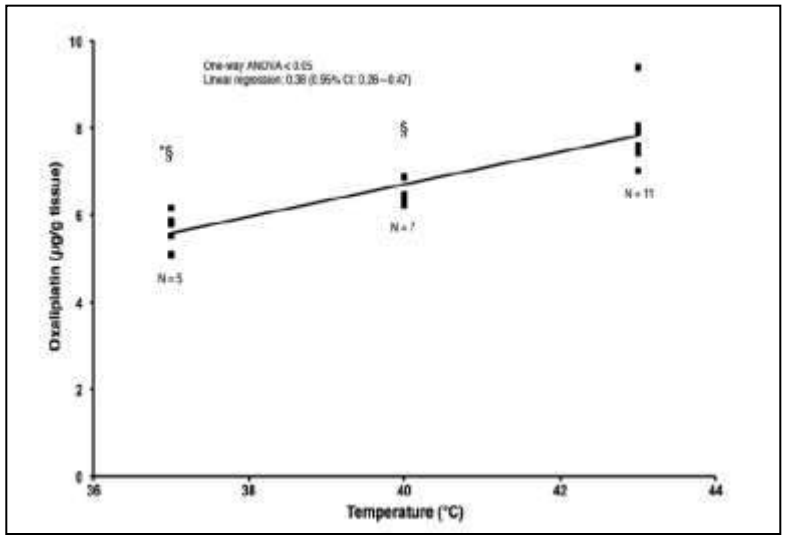
Objective: To study the effect of heat on the absorption of intraperitoneal (IP) oxaliplatin using a murine model.

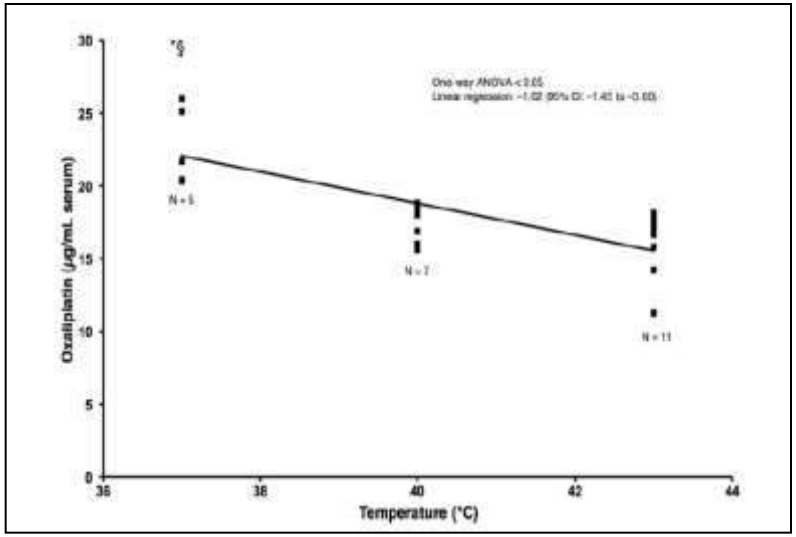
Background: Because of its efficiency in the systemic treatment of colorectal cancer, oxaliplatin is currently used in hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal carcinomatosis. However, its properties when administered by the IP route have not been well characterized by preclinical studies.

Methods: Under general anesthesia, 35 Sprague–Dawley rats were submitted to 3 different doses of IP oxaliplatin (460, 920, and 1840 mg/m^2) at 3 different perfusion temperatures (37, 40, and 43°C) during 25 minutes. At the end of perfusion, samples in different compartments (peritoneum, portal blood, and systemic blood) were harvested and the concentrations of oxaliplatin were measured by high performance liquid chromatography.

Results: As the dose of IP oxaliplatin was increased, higher concentrations were observed in every compartment. When the temperature of IP oxaliplatin was increased, it resulted in an increase of its peritoneal concentration (linear regression 0.38; 95% CI: 0.28–0.47) and in a decrease of its systemic blood (linear regression –1, 02; 95% CI: –1.45 to –0.60) and portal blood (linear regression –1.08; 95% CI: –1.70 to –0.47) concentrations.

Conclusion: Proportionally to the dose administered, IP oxaliplatin leads to high concentration of drug in peritoneal tissues. Furthermore, heat enhances peritoneal tissue concentration of Oxaliplatin while reducing its systemic absorption. This last effect may possibly lead to decreased systemic toxicity. These observations support the use of oxaliplatin for HIPEC.





Annals of Surgery • Volume 254, Number 1, July 2011

ROLE OF HYPERTHERMIA ?

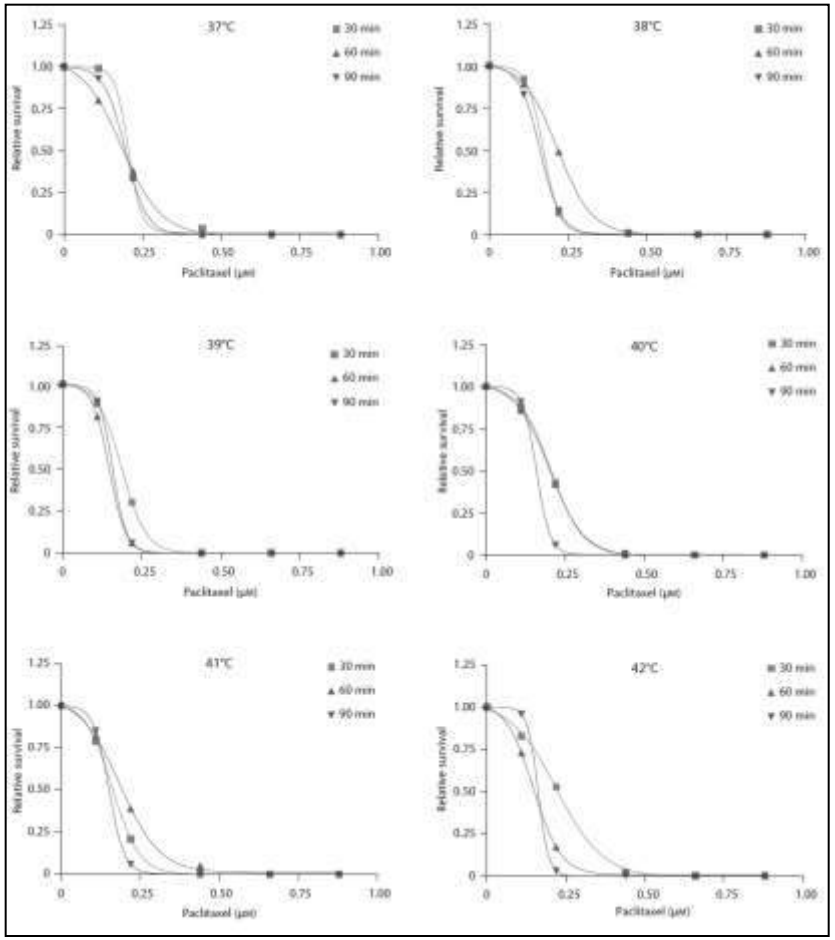
The Cytotoxic Effect of Combined Hyperthermia and Taxane Chemotherapy on Ovarian Cancer Cells: Results of an in vitro Study

M. Muller[a, b] M. Chérel[b] P.-F. Dupré[a] S. Gouard[b] M. Collet[a] J.-M. Classe[b, c]

[a]Unit of Gynecological and Mammary Oncologic Surgery, Centre Hospitalier Universitaire Augustin Morvan, Brest, [b]Research Center against Cancer, Angers INSERM Unit 892, Université de Nantes, Nantes, and [c]Department of Oncologic Surgery, Centre René Gauducheau, Nantes Saint-Herblain, France

Abstract

Purpose: Hyperthermic intraperitoneal chemotherapy (HIPEC) is under continuous evaluation as a potential treatment for ovarian cancer. The purpose of this study was to evaluate the effect of chemotherapy, drug concentration and temperature. ***Materials and Methods:*** We examined the combined effects of hyperthermia and taxane chemotherapy on the clonogenic survival of the human ovarian carcinoma SHIN-3 cell line in vitro. ***Results:*** When hyperthermia was combined with chemotherapy, the median lethal dose (LD50) was equivalent regardless of the duration of exposure, and was independent of the exposure temperature. Taxanes showed a similar LD50 over the temperature range tested. ***Conclusions:*** In our study, hyperthermia does not increase the cytotoxic effects of taxanes, at least for the concentrations and durations tested.



Eur Surg Res 2012;48:55–63

Do we need hyperthermia ?

Hyperthermia and Intraperitoneal Chemotherapy for the Treatment of Peritoneal Carcinomatosis

An Experimental Study

Yvonne L. B. Klaver, MD, Thijs Hendriks, PhD,† Roger M. L. M. Lomme,† Harm J. T. Rutten, MD, PhD,* Robert P. Bleichrodt, MD, PhD,† and Ignace H. J. T. de Hingh, MD, PhD**

TABLE 1. Tumor Score Before Cytoreduction and Results of Cytoreductive Surgery

Group	CS	HIPE	IPEC	HIPEC
Preoperative weight (g) (mean, SD)	264 (16)	265 (10)	264 (15)	261 (12)
Tumor score per site (median, range)				
Subcutaneous	1 (0–1)	1 (0–2)	1 (0–1)	1 (0–3)
Inoculation site intraabdominal	1 (0–3)	1 (0–1)	1 (0–1)	1 (0–1)
Greater omentum	1 (1–1)	1 (1–2)	1 (1)	1 (1–1)
Liver hilus	1 (1–2)	1 (1–2)	1 (0–2)	1 (1–2)
Liver surface	0 (0–1)	0 (0–0)	0 (0–0)	0 (0–1)
Spleen	1 (0–1)	1 (0–1)	1 (0–2)	1 (1–1)
Mesentery	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)
Fatpad left	0 (0–1)	0 (0–2)	0 (0–2)	0 (0–2)
Fatpad right	0 (0–3)	0 (0–1)	0 (0–1)	0 (0–1)
Diaphragm	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)
Parietal peritoneum	0 (0–1)	0.5 (0–1)	0.5 (0–2)	0 (0–1)
Overall PCI (mean, SD)	5.9 (2.0)	6.6 (2.0)	5.8 (1.9)	6.1 (1.6)
Splenectomy (n)				
Yes	0	1	2	2
No	20	19	18	18
Completeness of resection (n)				
R1	18	17	18	19
R2a	2	3	2	1
R2b	0	0	0	0

HIPE = CS + perfusion with NaCl at 41°C, IPEC = CS + perfusion with mitomycin at 37°C, HIPEC = CS + perfusion with mitomycin at 41°C. R1 = no macroscopic residual tumor after cytoreduction, R2a = residual tumor <2.5 mm after cytoreduction, R2b = residual tumor >2.5 mm after cytoreduction.

Do we need hyperthermia ?

Hyperthermia and Intraperitoneal Chemotherapy for the Treatment of Peritoneal Carcinomatosis

An Experimental Study

Yvonne L. B. Klaver, MD, Thijs Hendriks, PhD,† Roger M. L. M. Lomme,† Harm J. T. Rutten, MD, PhD,* Robert P. Bleichrodt, MD, PhD,† and Ignace H. J. T. de Hingh, MD, PhD**

Conclusions: The effectiveness of intraoperative intraperitoneal perfusion after CS is highly dependent on the presence of chemotherapeutic agents in the perfusate but not on hyperthermia. The need to include hyperthermia in the adjuvant intraoperative treatment after CS for PC should be further investigated.

Annals of Surgery • Volume 254, Number 1, July 2011

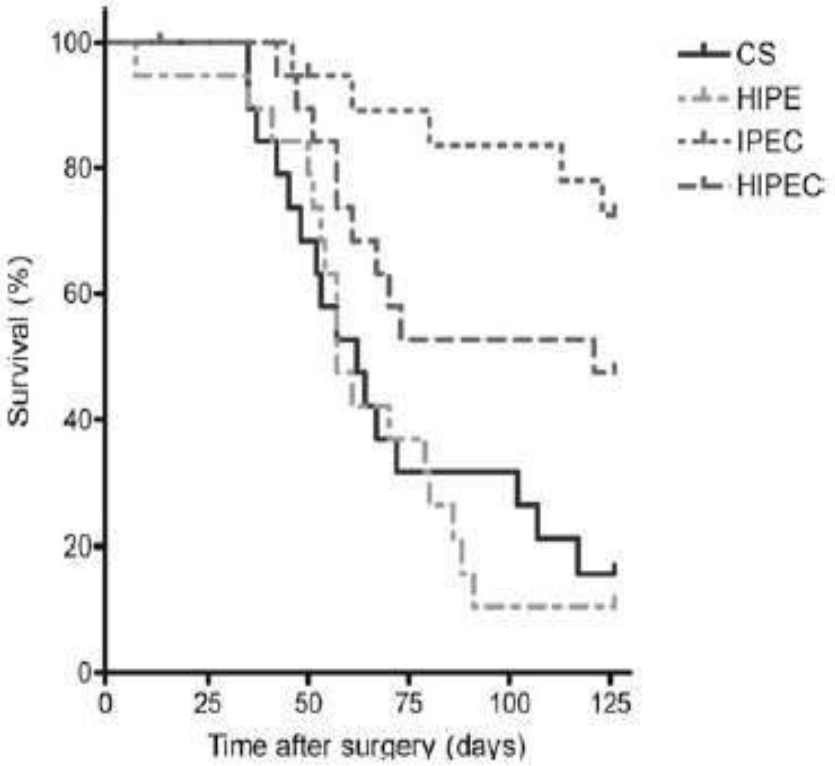


FIGURE 4. Kaplan–Meier survival curves, per group. CS, cytoreductive surgery, HIPE = CS + perfusion with NaCl at 41°C; IPEC = CS + perfusion with mitomycin at 37°C; HIPEC = CS + perfusion with mitomycin at 41°C. CS vs. HIPEC: $P = 0.022$, CS vs. IPEC: $P = 0.002$, hazard ratio 0.36, 95% CI 0.19–0.69, CS vs. HIPE: nonsignificant.

Rationale for EPIC

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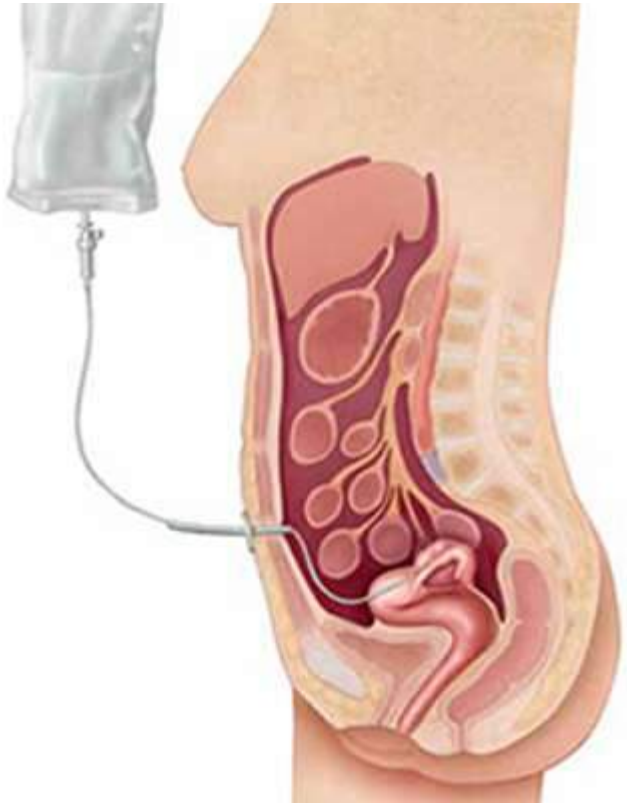
Rationale for EPIC



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

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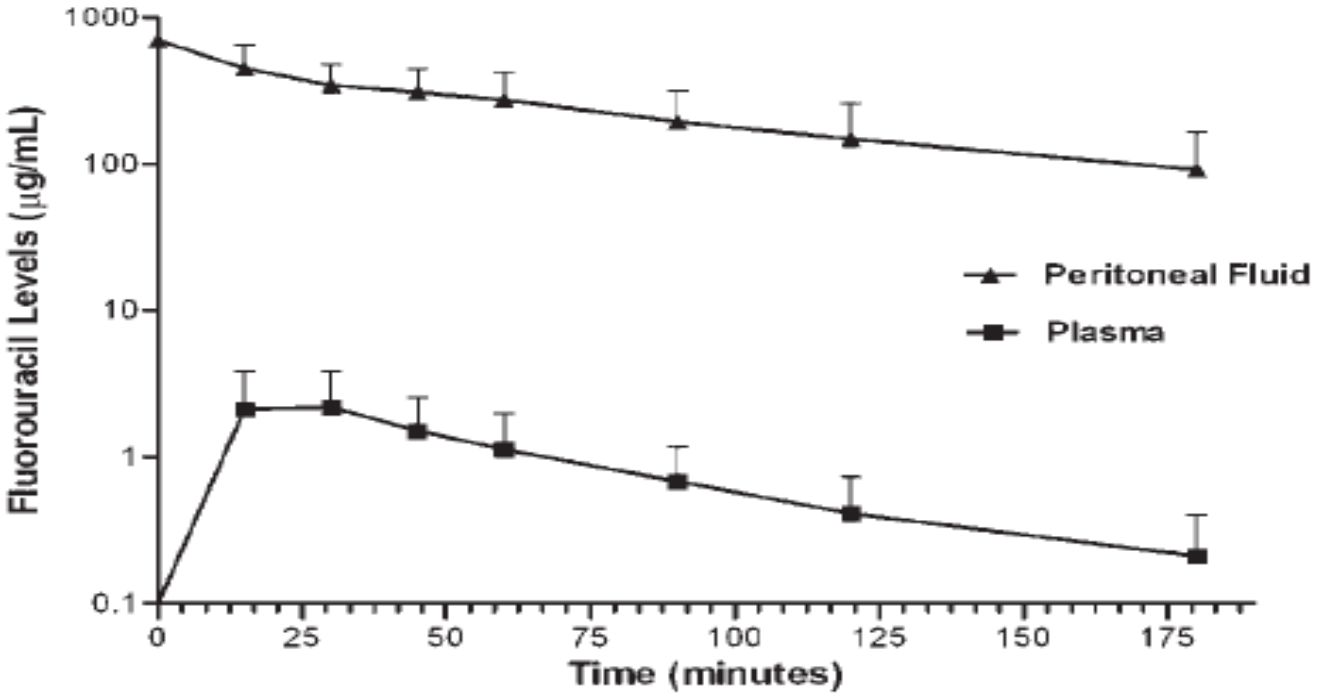

Fig. 1. 5-Fluorouracil concentrations in peritoneal fluid and plasma after early postoperative intraperitoneal chemotherapy administration (N = 9).

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

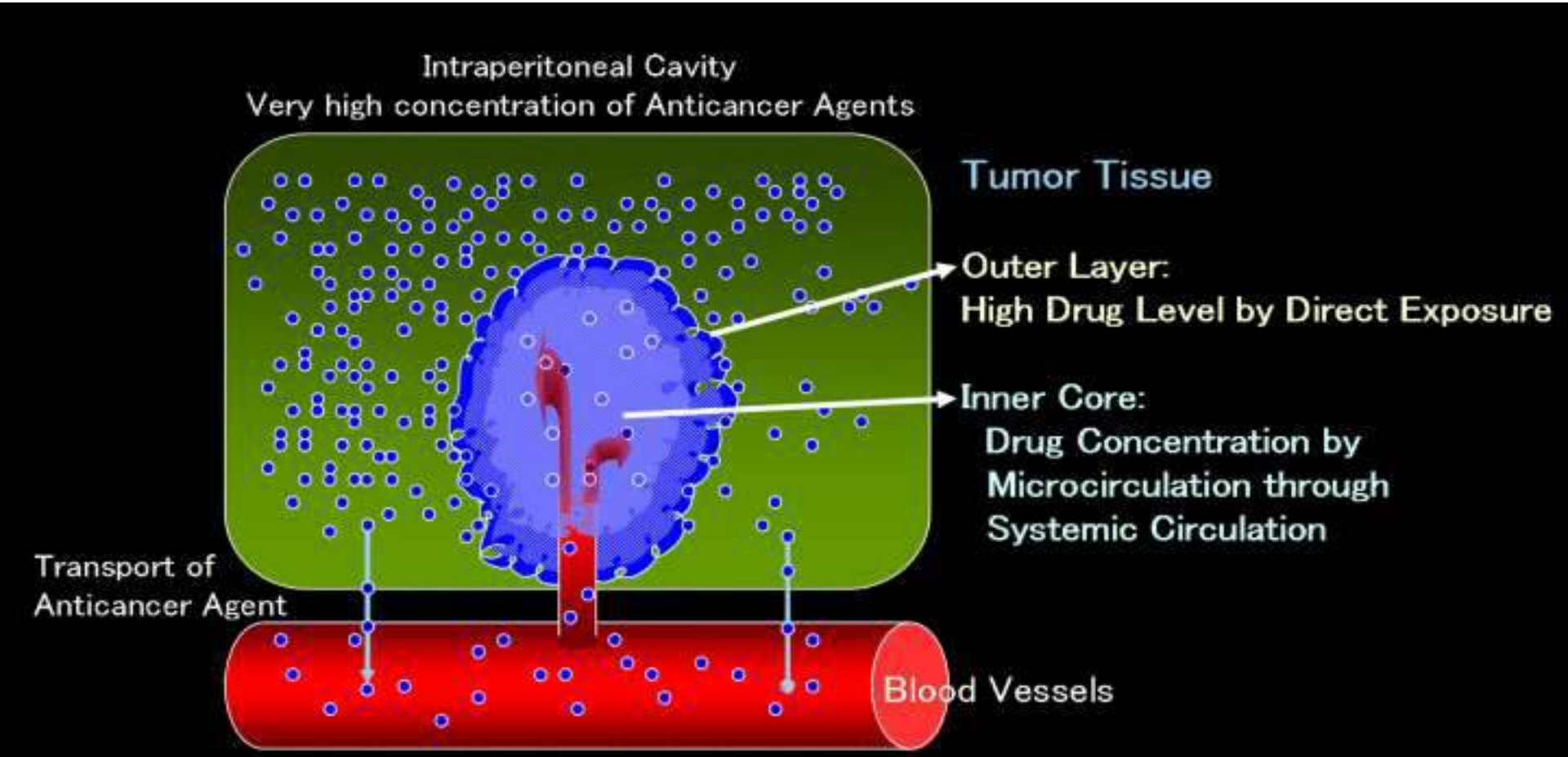
D. Elias*, M. Bonnay, J. M. Puizillou, S. Antoun, S. Demirdjian, A. El Otmany, J. P. Pignon, L. Drouard-Troalen, J. F. Ouellet & M. Ducreux

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

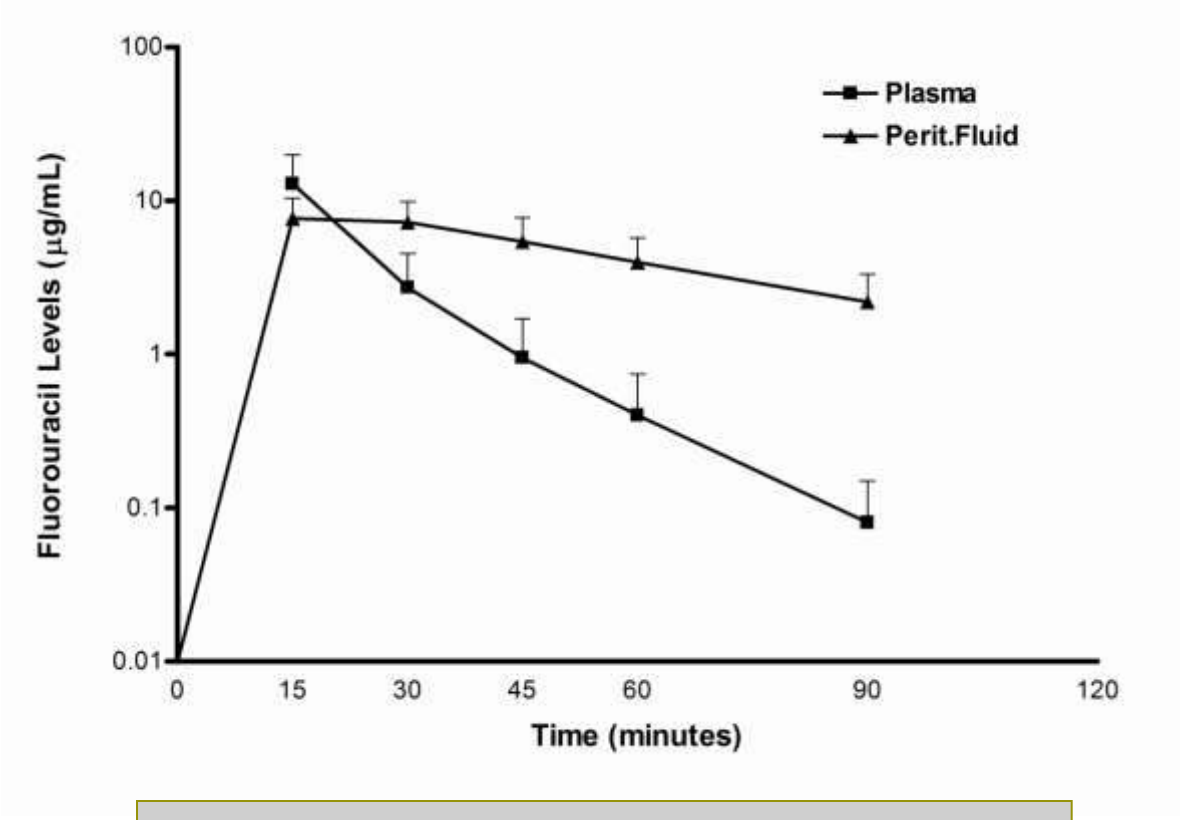
Pharmacologic concept of bidirectional (IV and IP) chemotherapy



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

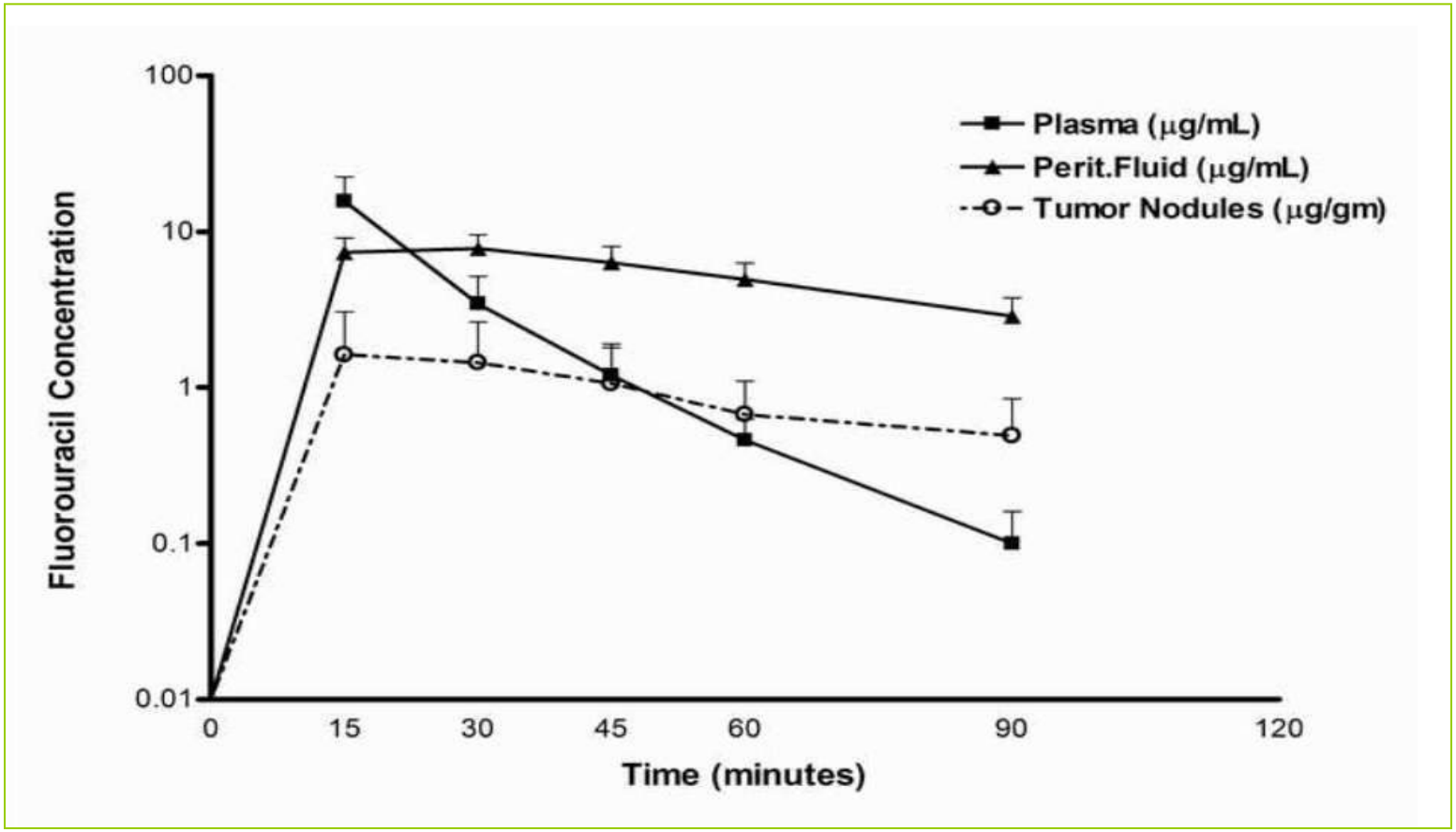


FIGURE 3: 5-Fluorouracil concentrations in plasma, peritoneal fluid and tumor nodules after intravenous administration during hyperthermic intraperitoneal chemotherapy procedure (N=9).

THE PROBLEM

TOO MANY VARIABLES

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Where things went wrong…

esso

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PHARMACOLOGIC VARIABLES

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

‘ what the drug does to the body ‘

‘ what the body does to the drug ‘

- Build more clinical (RCT and registries) data based on the current IP chemotherapy regimens (see handouts with 'recipes'

- Build more pharmacologic data 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

CONCLUSIONS

- Perioperative chemotherapy in combination with cytoreductive surgery has a proven clinical result
- There is a clear pharmacologic rationale for IP chemotherapy
- Cytoreduction alone is not enough (Prodige 7 pending)
- The IP chemo is more important than the hyperthermia
- Carefully consider pharmacokinetic and non-pharmacokinetic variables
- Further progress should come from correlating the clinical and pharmacologic database