

Provisional Programme Controversies and Problems in Surgery Symposium - University of Pretoria 16TH SYMPOSIUM 05-06 OCTOBER 2012

Technique for Cyto-Reductive Surgery (CRS) and Hyperthermic Intra-Peritoneal Chemotheray (HIPEC)



Marcello Deraco M.D.

Responsible

Peritoneal Surface Malignancies



Presidenza del Consiglio dei Ministri





CLINICAL SCENARIOS











Multistep process in the peritoneal dissemination





Yonemura et al. 2007

Multistep process in the peritoneal dissemination



Yonemura et al. 2007

Distribution of Limphatic Orifices on Peritoneal Surfaces

Region	Limphatic Stomatas	Milky Spots
Omentum	+	+
Falciform Ligament	- F -	+
Douglas	+	+
Diaphragm	+	-
Mesentery	+	_
Appendices Epiploicae	+	-
Liver Capsule	-	-
Parietal Peritoneum	-	-
Splenic Capsule	_	-
Small Bowel Peritoneum	_	_

CLINICAL SCENARIOS



Surgical Technique of Parietal and Visceral Peritonectomy for Peritoneal Surface Malignancies

MARCELLO DERACO, MD,* DARIO BARATTI, MD, SHIGEKI KUSAMURA, MD, PhD, BARBARA LATERZA, MD, AND MARIA ROSARIA BALESTRA, MD

Department of Surgery, National Cancer Institute of Milan, Milan, Italy

Patterns of Peritoneal Cancer Spread

Histologic type	Random proximal distribution	Complete redistribution phenomenon	Widespread cancer distribution
Pseudomyxoma peritonei		+	
Appendix cancer			
Cystoadenocarcinoma G1		+	
Cystoadenocarcinoma G2, G3			+
Adenocarcinoma	+		
Carcinoid	+		
Colorectal cancer			
Mucinous G1, G2, G3			+
Intestinal	+		
Gastric cancer			
Diffuse	+		
Intestinal	+		
Ovarian cancer			
Serous	+		
Mucinous			+
Diffuse malignant mesothelioma		+	

Journal of Surgical Oncology 2009;100:321-328

<u>L-PMP</u>











tumor with complex architecture, high grade cells and stromal invasion

mucin pool



Peritonectomy Procedures

Paul H. Sugarbaker, M.D.

From The Cancer Institute, Washington Hospital Center, Washington, District of Columbia

The Concept of Cytoreductive Surgery

•Means a complete removal of all macroscopic tumor in the peritoneal cavity;

•It could require Peritonectomy Procedures eventually associated with intestinal and/or organ resection

Abdominal regions	Peritonectomies	Visceral resections
Right upper	Right sub-phrenic peritonectomy, Glisson's capsule dissection	
Left upper	Left sub-phrenic peritonectomy	
Antero-lateral	Stripping of paracolic gutters, Greater omentectomy	Splenectomy, appendectomy, right colectomy
Sub-hepatic	Lesser omentectomy, stripping of the omental bursa	Gastric antrectomy, cholecystectomy
Pelvis	Pelvic peritonectomy	Sigmoidectomy, hysterectomy, bilateral adnexectomy
	* •	Total gastrectomy



Heated Intra Peritoneal Chemotherapy (HIPEC)

Is a treatment that allow to expose the abdominal cavity to high drug concentration in hyperthermic condition trought a perfusional procedure.

John Spratt Professor of Surgery University of Louisville



CYTOREDUCTIVE SURGERY

UPPER RIGHT QUADRANT CRS

Diaphragmatic Peritonectomy with Morrison Pouch

Cholecistectomy With Portahepatis Stripping

Kocher manoeuvre

- •Remouval of the gall-bladder from its fundus toward the cystic duct and artery
- •Remouval of the anterior peritoneal surface of the hepato-duodenal
- Ligament
- •Stripping from the under-surface of the porta hepatis
- en bloc remouval of gall-bladder and hepato-duodenal peritoneum are

Lesser Omentectomy

- •Left triangular ligament resection
- •left liver lobe retraction to the right
- •Resection of the hepato-gastric ligament

Gastrectomy

Omental Bursa Peritonectomy

- •Retraction of the caudate lobe
- Identification and dissection of the vena cava
- •Omental bursa is bluntly removed starting from the crus of the right hemidiaphragm

Right Upper Quadrant CRS















UPPER LEFT QUADRANT CRS

•The gastroepiploic vessels and the vascular arcade at the greater gastric curvature are clamped and divided (by the use of Ligasure) close to the stomach wall;

•The left diaphragmatic peritoneum is stripped from the midline to the area beneath the spleen;

•By putting traction on the peritoneum, the spleen is retracted medially with the tail of the pancreas;

•The splenic vessels are exposed therefore from behind and transected where the tail of the pancreas is not surgically traumatized.

Left Upper Quadrant CRS



SMALL-BOWEL MESENTERY CYTOREDUCTION

•Finding the cleavage space between the serosal layer and the mesenteric fat tissue

- •Stripping by the electrosurgical device and blunt dissection
- •Small disease localizations can be electro-evaporated.













PELVIC CRS

Preservation of the Sigmoid Colon

When only the Douglas pouch is involved by tumorNo tumor invasion of the bowel serosa

Preservation of Uterus and Ovaries

Multicystic and papillary well-differentiated mesothelioma
Low PCI PMP

Preservation of Inferior Mesenteric Vessels

- •The origin of the IMA from the aorta is identified.
- •The mesocolon tissue is dissect
- •The left colic and the sigmoid arteries are sectionated
- •The IMA skeletonise up to its terminal branches in the meso-rectal fat tissue.
- •The rectum is transected distally to the point where the vessels reach the rectum wall





Sigmoid and rectal sparing



Nerve Sparing Peritonectomy



Systematic Aortic and Pelvic Lymphadenectomy Versus Resection of Bulky Nodes Only in Optimally Debulked Advanced Ovarian Cancer: A Randomized Clinical Trial





Journal of the National Cancer Institute, Vol. 97, No. 8, April 20, 2005 ', No. 8, April 20, 2005

Anastomotic techniques

Timing of anastomosis

• Before the HIPEC

Protective ileostomies

- ileo-rectal anastomosis
- lower colo-rectal anastomosis
- complication and re-intervention

Post-Operative follow-up

- 4 abdominal drainages
- 2 torax dreinages
- CVC
- Femoral artery catheter
- Nose-gastric tube for drainage and EN
- Blader catheter



Surgical Technique of Parietal and Visceral Peritonectomy for Peritoneal Surface Malignancies

MARCELLO DERACO, MD,* DARIO BARATTI, MD, SHIGEKI KUSAMURA, MD, PhD, BARBARA LATERZA, MD, AND MARIA ROSARIA BALESTRA, MD

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CRS According to Peritoneal Surface Malignancy

Procedure	Pseudomyxoma peritonei (n = 119)	Peritoneal mesothelioma $(n = 100)$	Other (n = 126)	<i>P</i> -value ^a
Peritonectomies				
Greater omentectomy	114	89	70	< 0.0001
Left sub-diaphragmatic	113	86	24	< 0.0001
Right sub-diaphragmatic	114	87	29	< 0.0001
Pelvic	115	88	48	< 0.0001
Lesser omentectomy	113	74	25	< 0.0001
Total	569	424	196	< 0.0001
Mean	4.78	4.24	1.55	
Median (range)	5 (3-5)	5 (2-5)	2(1-5)	
Visceral resections				
Splenectomy	96	57	17	< 0.0001
Glisson's capsule	64	30	10	< 0.0001
Cholecistectomy	71	21	9	< 0.0001
Total gastrectomy	22	1	6	0.1626
Partial gastrectomy	3	8	5	0.1383
Sigmoidectomy	70	36	36	0.0174
Right colectomy	78	30	27	< 0.0001
Small bowel resection	24	18	22	0.7558
Appendectomy	20	17	6	0.0030
TAH/BSO	17	27	15	0.0839
Other	32	30	20	0.0184
Total	502	270	173	0.0006
Mean	4.22	2.70	1.37	
Median (range)	4 (1-8)	3 (0-7)	2 (0-6)	

Other = abdominal sarcomatosis, primary peritoneal carcinoma, carcinomatosis from gastric, ovarian, and colorectal cancer or other tumor.

^aOther carcinomatosis versus pseudomyxoma peritonei and peritoneal mesothelioma.

HIPEC









Intraperitoneal Chemotherapy in the First-line Treatment of Women With Stage III Epithelial Ovarian Cancer

A Systematic Review With Metaanalyses

Study or sub-category	Intraperitoneal n/N	Intravenous n/N		RR (ra 959	andom) % Cl	Weight %	RR (random) 95% Cl
Armstrong, 2006 (8)	101/205	127/210				21.66	0.81 [0.68, 0.97]
Markman, 2001 (9)	109/235	124/227			ł	20.55	0.85 [0.71, 1.02]
Alberts, 1996 (10)	147/267	174/279			ł	33.76	0.88 [0.77, 1.02]
Yen, 2001 (11)	41/55	47/63			•	15.18	1.00 [0.81, 1.23]
Gadduci, 2000 (12)	22/56	30/57	-	-	<u> </u>	4.06	0.75 [0.50, 1.12]
Kirmani, 1994 (14)	19/33	29/50		0	• •••••••••••••••••••••••••••••••••••	4.79	0.99 [0.68, 1.45]
Total (95% Cl)	851	886				100.00	0.88 [0.81, 0.95]
Total events: 439 (Intraperitor	neal), 531 (Intravenous)						
Test for heterogeneity: Chi ² =	3.37, df = 5 (P = 0.64), l ² = 0%	6					
Test for overall effect: Z = 3.	15 (P = 0.002)						
			0.5	0.7	1 1.5	2	
5 year overall su	urvival		Fav	ours treatment	Favours contr	ol	

Study or sub-category	Intraperitoneal n/N	Intravenous n/N		F	R (random 95% Cl)	Weight %	RR (random) 95% Cl
Armstrong, 2006 (8)	149/205	165/210			-		43.86	0.93 [0.83, 1.03]
Markman, 2001 (9)	170/235	180/227					49.46	0.91 [0.82, 1.01]
Gadduci, 2000 (12)	33/56	39/57		7			6.69	0.86 [0.65, 1.14]
Total (95% Cl)	496	494		(100.00	0.91 [0.85, 0.98]
Total events: 352 (Intraperitor	neal), 384 (Intravenous)				-			
Test for heterogeneity: Chi ² =	0.22, df = 2 (P = 0.89), I ² = 0%	6						
Test for overall effect: Z = 2.4	42 (P = 0.02)							
			0.5	0.7	1	1.5	2	
5 year prog	ression free surv	/ival	Fav	ours treatm	nent Fav	ours contro	l.	

CANCER February 15, 2007 / Volume 109 / Number 4

Pharmacokinetics profile of cDDP, Dx and MMC in HIPP

Drug	Molecular weight	AUCpe/ AUCpl	Response rate in normothermia	Tumour penetration
cDDP	300	14	65%	2-2.5 mm
Dx	544	82.9	30%	4-6 cell layers
MMC	334	23,5	N.E.	3 mm
Ozols RF, Cancer Res 1979; Los G, Eur J Cancer 90; Jacquet P, Cancer Chemother Pharmacol 98; Sugarbaker P, Langenbecks Arch Chir 99				

Drug penetration distance from peritoneal surface after IP chemotherapy







Hyperthermic Intraoperative Intraperitoneal Chemotherapy with Cisplatin and Doxorubicin in Patients Who Undergo Cytoreductive Surgery for Peritoneal Carcinomatosis and Sarcomatosis

Phase I Study

Carlo R. Rossi, M.D.¹ Mirto Foletto, M.D.¹ Simone Mocellin, M.D.¹ Pierluigi Pilati, M.D.¹ Michele De Simone, M.D.² Marcello Deraco, M.D.³ Francesco Cavaliere, M. D.⁴ Pietro Palatini, Ph.D.⁵ Fabiola Guasti, M.Se.⁶ Romano Scalerta, M.Se.¹ Mario Lise, M.D.¹ **BACKGROUND.** Hyperthermic intraperitoneal intraoperative chemotherapy (HIIC) combined with cytoreductive surgery (CS) has been proposed as a new multimodal treatment mainly for carcinomatosis of gastrointestinal origin. To evaluate whether this regimen could be used for other tumor types, the authors conducted a Phase I study on HIIC with doxorubicin and cisplatin in patients with peritoneal carcinomatosis or sarcomatosis.

PATIENTS AND METHODS. Thirty-one patients with peritoneal carcinomatosis or sarcomatosis (PCS) were enrolled for the study. After completion of CS, HIIC was administered with drug doses that were increased for each consecutive cohort following a three-patient cohort scheme. Thereafter, the accrual was stopped when Grade 4 locoregional or systemic toxicity was observed. The maximum tolerated dose (MTD) was considered the dose in the previous triplet. Drug pharmacokinet-



Open symbols = DXR

Filled symbols = CDDP



Drugs, Carrier Solutions and Temperature in Hyperthermic Intraperitoneal Chemotherapy

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Drug	Molecular weight	AUCpe/ AUCpl	Tumour penetration	Dose for HIPEC	Mechanism of hyperthermic modulation
Doxorubicin	580	87.9	4-6 cell layers	15.25mg/L of perfusate ^a	Enhanced tissue absorption; increased Dx aglycon concentration
Caelyx				100mg/m2 ^b	
Mitomycin C	334	23.5	NA	35mg/m2	Enhanced tissue absorption; cell membrane permeability alteration; increased activation and intracellular alkylation, inhibition of DNA damage repair
Mitoxantrone	517	5.6 - 15.2	5-6 cell layers	28mg/m2 °	yes
Cisplatin	300	14	2-2.5 mm	300mg/m2 ^b	Enhanced tissue absorption; increased DNA adduct formation; increased activity at low pH; Increased production of O2 radicals; reduction of cisplatin resistance
Carboplatin	371	1.9 - 5.2	0.2-0.5 mm	1000mg/m2 ^b	Enhanced tissue absorption; increased DNA adduct formation;
Oxaliplatin	397	16	1-2 mm	200mg/m2 ^b	Enhanced tissue absorption
Paclitaxel	854	1000*	NA	175mg/m2 °	Increased disruption of microtubules system and apoptosis
Gemcitabine	300	12.5 -26.8	NA	120mg/m2 ^d	Enhanced tissue absorption; activation to triphosphate metabolite; inhibition of DNA damage repair

Hyperthermic Intraperitoneal Chemotherapy: Nomenclature and Modalities of Perfusion

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25,0%

METHDOLOGICAL CONSENSUS HIPEC modality

62,5%

Open abdominal technique



- Semi-opened technique
- No sufficient evidence for elect the best technique



3.1%

6.3%

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

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HIPEC: Closed Abdomen Technique

Advantages

- Minimizes exposure of OR staff to chemotherapy
- Easier to achieve high perfusion temperatures
- The higher intrabdominal pressure might lead to increased convection-driven drug penetration of macromolecular agents such as TNF-α inside the tumour
- The higher intra-abdominal pressure enhance the tissue uptake of some chemotherapies

Leunig M, et al. *Cancer Res* 92; Milosevic MF et al. *Int J Radiat Oncol Biol Phys* 99; Jain RK, et al. *Cancer Res* 88; Jacquet P, et al. Anticancer Drugs. 96

HIPEC: Closed technique

Disadvantages

- Uneven heat distribution that can result in increased toxicity
- does not allow to treat all surfaces at risk.
- Morbidity rate: 12%-30% (Open technique 27-39%)

Elias D, et al. 2000, 2005; Loggie et al. 2000; Kusamura et al. 2006; Glehen et al. 2003; Stephen et al. 1999; Witkamp et al. 2001; Verwaal et al. 2004; Shen et al. 2004; Schmidt U et al. 2005



Consensus Statement on the Loco Regional Treatment of Colorectal **Cancer With Peritoneal Dissemination**

JESUS ESQUIVEL, MD, FACS,¹* DOMINIQUE ELIAS, MD,² DARIO BARATTI, MD,³ SHIGEKI KUSAMURA, MD, PhD,³ AND MARCELLO DERACO, MD³

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PCI as a Prognostic Indicators of Survival



Lesion size score	cm
LSS-0	No detectable
LSS-1	<0.5
LSS-2	0-5-5
LSS-3	>5

Sugarbaker, Ann Surg 1995









Yan-Deraco Cancer in Press



CC-Score as a Prognostic Indicators of Survival











Dominique Elias, J Clin Oncol 28:63-68. © 2009

Multidimensional Analysis of the Learning Curve for Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy in Peritoneal Surface Malignancies

Shigeki Kusamura, MD, PhD, Dario Baratti, MD, and Marcello Deraco, MD

CRS + HIPEC Procedures: 490 (Personal: >600)



Kusamura, Baratti and Deraco, Annals of Surgery, 2012

8TH INTERNATIONAL WORLD CONGRESS ON PERITONEAL SURFACE MALIGNANCIES

Management of Peritoneal Sufface Malignancy: a Multidisciplinary challenge



BCTLIN, GERMANY OCTOBER 31st -NOVEMBER 2ND 2012



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Congress venue: www.Langenbeck-Virchow-Haus.de, Berlin

