Annals of Surgical Oncology (© 2006)
DOI: 10.1245/s10434-006-9185-7

Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy in the Management of Peritoneal Surface Malignancies of Colonic Origin: A Consensus Statement

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Received June 2, 2006; accepted June 2, 2006
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Surgical resection remains the hallmark therapy for primary colon cancer. It allows the patients to become clinically disease free, provides proper staging, and determines who should receive adjuvant systemic chemotherapy. Treatment options for patients with unresectable metastatic disease have improved significantly in the past few years. A review of the published data in the treatment of patients with stage IV colorectal cancer, outlining the surgical and medical therapeutic options demonstrates that medical management, with combinations of cytotoxic chemotherapy, and/or biological agents, has resulted in an unprecedented median survival > 20 months. However, these therapeutic combinations are not an optimal therapeutic strategy for all categories of stage IV disease. Systemic treatment alone is no longer appropriate for patients with limited peritoneal dissemination from a primary or recurrent colon cancer. The surgical management of peritoneal surface malignancies of colonic origin with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) has been clearly defined and continues to improve. Better surgical techniques that include peritonectomy procedures, standardized methods to deliver intraoperative hyperthermic intraperitoneal chemotherapy and better patient selection criteria, have resulted in a significant improvement in survival and in morbidity and mortality of the surgical management of this particular group of stage IV colon cancer patients.

MATERIALS AND METHODS

Upon review of the literature, we have identified a subset of patients with metastatic disease confined to the abdomen and with no evidence of hematogenous spread, referred to as peritoneal carcinomatosis without distant disease. Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy with mitomycin C and post-operative systemic chemotherapy, has resulted in a median survival of up to 42 months in these patients when a complete cytoreduction is achieved. On 14–16 January 2006 the first International Symposium on Regional Cancer Therapies was held in Snowmass, Colorado. Surgical options in the management of peritoneal surface malignancies of colonic origin (Table 1), were re-

TABLE 1. *Literature review of most recent updates on cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) in the management of peritoneal surface malignancies of colonic origin*

Chief investigator	Center	Design	Year	Patient (*n*)	HIPEC	Follow-up (months)	Median survival (months)	Survival (%)				
								One year	Two years	Three years	Four years	Five years
Verwaal[1]	Amsterdam	Phase III	2004	54	MMC arm	22	22	67	44	–	–	–
				51	Control arm		13	56	22	–	–	–
Rossi[2]	Padova	Phase II	2003	46	MMC + Cisplatin	15	18	68	31	–	–	–
Di Filippo[3]	SITILO	Phase II	2003	69	MMC	–	–	–	–	27	–	–
Levine[4]	Winston-Salem	Phase II	2004	77	MMC	15	16	56	–	25	–	17
Gilly[5]	Lyon	Phase II	2004	53	MMC	60	13	55	–	32	–	11
Glehen[6]	Multi-centers	Phase II	2004	506	MMC/LOHP	53	19	72	–	39	–	19
Morris[7]	Sydney	Phase II	2005	30	MMC	12	30	71	62	–	–	–
Kecmanovic[8]	Belgrade	Phase II	2005	18	MMC	21	15	–	–	–	–	–
Elias[9]	Villejuif	Phase II	2005	30	LOHP	55	60	97	73	53	49	–
Zoetmulder[10]	Amsterdam	Phase II	2005	117	MMC	46	22	75	–	28	–	19
Sugarbaker[11]	Washington	Phase II	2005	70	MMC	47	33	88	–	44	–	32

MMC mitomycin C; *LOHP* oxaliplatin; *5-FU* 5-fluorouracil

viewed and discussed by some representatives from the major Peritoneal Surface Malignancy Centers from around the world. During a follow up meeting on 24 March 2006 in San Diego, CA, while attending the Society of Surgical Oncology annual meeting, further discussions concluded in agreement on a registry database sheet and using the Peritoneal Cancer Index as a scoring system (Table 2). Based on the analysis of published data, we present a Consensus Statement on the treatment of patients with recurrent and/or metastatic colon cancer with peritoneal involvement (Fig. 1).

Rigorous Diagnostic Work-up

Proper patient selection has been shown to be a crucially important aspect of this treatment plan. Once a patient has been diagnosed with colon cancer with peritoneal involvement, the work-up should include a complete colonoscopic evaluation as well as a CT scan of the chest, abdomen and pelvis with maximum oral and IV contrast to evaluate the extent of peritoneal dissemination. A PET scan can be considered if there is any question of extra-abdominal disease.

Best Systemic Therapy

Patients that are diagnosed as having peritoneal carcinomatosis and other sites of dissemination and that have a good performance status, should receive the best combination of cytotoxic chemotherapy and biological agents. If they have a good response to the systemic therapy and/or if they have limited liver involvement, they may be considered for cytoreductive surgery and intraperitoneal chemotherapy at a later time. There is currently little data to guide us as to whether such chemotherapy is best given before or after cytoreductive surgery and HIPEC. However, we feel that patients should be evaluated by surgical oncologists experienced in these techniques prior to embarking on systemic therapy alone for patients who may be candidates for HIPEC.

Variables Associated with Increased Chances of having a Complete Cytoreduction

Complete cytoreduction means that no macroscopic residual disease was left after the operative procedure. The following are clinical and radiographic variables that are usually associated with increase chances of achieving a complete removal of all tumor greater than 2.5 mm:

(1) ECOG performance status two or less;
(2) no evidence of extra-abdominal disease;
(3) up to three small, resectable parenchymal hepatic metastases;
(4) no evidence of biliary obstruction;
(5) no evidence of ureteral obstruction;
(6) no evidence of intestinal obstruction at more than one site;
(7) small bowel involvement: no evidence of gross disease in the mesentery with several segmental sites of partial obstruction;
(8) small volume disease in the gastro-hepatic ligament.

TABLE 2. *Clinical pathway for the management of peritoneal surface malignancies of colonic origin database sheet*

Institution _____ Patient Number_____ DOB _____ Sex M ____ F ____ Surgeon _____
Date of Cytoreductive Surgery _____ OR Time _____ EBL_____ PRBC's_____ Ascites Drained _____
HIPEC Yes ____ No ____ Open ____ Closed ____ Drug _____ Dose _____Inflow Temp _____
EPIC Yes _____ No _____ Drug _____ Dose _____ Number of Days _____

Cytoreduction Details
Anastomoses _____
SB-SB _____
Gastro-SB_____
SB-Colon _____
Colon-Colon _____
Colon-Rectum _____
SB-Rectum_____
EXTENT OF RESECTIONS
Colon _____SB _____
Low Anterior _____
Spleen _____ Panc _____
Gallbladder_____ Bladder _____
G Oment ____ L Oment ____
Liver mets _____Stomach ____
Uterus _____ Ovaries _____
Other _____
PERITONECTOMIES
Parietal _____
Pelvic _____
Omental Bursa _____
RUQ _____ LUQ _____

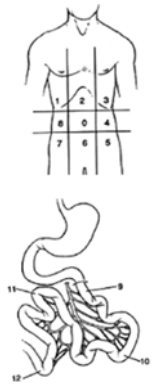
PCI SCORE

CT/Laparosc	Regions	Lesion at Exploration	Lesion Post Surgery
	0 Central		
	1 Right Upper		
	2 Epigastrium		
	3 Left Upper		
	4 Left Flank		
	5 Left Lower		
	6 Pelvis		
	7 Right Lower		
	8 Right Flank		
	9 Upper Jejunum		
	10 Lower Jejunum		
	11 Upper Ileum		
	12 Lower Ileum		
	SCORE		

LESION SIZE SCORE

LS 0	**No Tumor Seen**
LS 1	**Tumor up to 0.5 cm**
LS 2	**Tumor up to 5.0 cm**
LS 3	**Tumor > 5.0 cm or confluence**

	CT	At Exploration	Post Surgery
Zone II Involved Y or N			
Small Bowel Class			



Colostomy: Y____ N____ Permanent: Y_____ N____
Ileostomy: Y ____ N ____ Permanent: Y____ N____

CC SCORING

No Disease :CC 0: _____

<= 0.25 cm : CC 1: _____

0.25-2.5 cm :CC 2: _____

>=2.5 cm :CC 3: _____

RR SCORING

R0: _____ Complete removal of all visible tumor, negative cytology or negative microscopic margins

R1: _____ Complete removal of all visible tumor, positive cytology or microscopic margins

R2a: _____ Minimal residual tumor, nodule (s) <= 0.5 cm

R2b: _____ Gross residual tumor, nodule (s) > 0.5 cm, but <= 2 cm

R2c: _____ Extensive disease remaining, nodule (s) > 2 cm

Institution _____ Patient Number _____ Surgeon _____
Date of Cytoreductive Surgery _____ ICU Length of Stay (LOS)_____ Total Hospital LOS _____

Primary Tumor Stage
Site: R T L S
T____ N_____ M____
Mucinous: Y __ N__
Well Diff _____
Mod Diff _____
Poorly Diff _____
Signet Ring _____
Liver mets _____

Previous Surgeries None ____
Date _____
Procedure 1 _____
Date _____
Procedure 2 _____
Date _____
Procedure 3 _____

Previous Chemotherapy None _____
Date _____
Regimen 1 _____
Date _____
Regimen 2 _____
Date _____
Regimen 3 _____
Previous XRT: Y ____ N ____

Cytoreduction Path
Mucinous: Y_____ N_____
Well Diff: _____
Mod Diff:_____
Poorly Diff: _____
Signet Ring: _____
Lymph nodes _____
Liver mets: Number _____ Resected _____

Cytology: Positive____ Neg ____ N/A ____

Cytoreduction Morbidity
Pancreatitis Y ____ N ____
Fistula Y ____ N ____
Leak Y ____ N ____
PE Y ____ N ____
DVT Y ____ N ____
Re-Op Y ____ N ____
Cause _____
Hematologic Y ____ N ____
_____
Death Y ____ N ___
Death Cause _____
Re-admission Y ____ N ____
Cause _____
Other _____

Follow-up Status
Date _____
Status _____
Recurrence Site_____
Date _____
Status _____
Recurrence Site_____

Others
Pre Op CEA _____ Date _____
Post Op CEA _____ Date _____

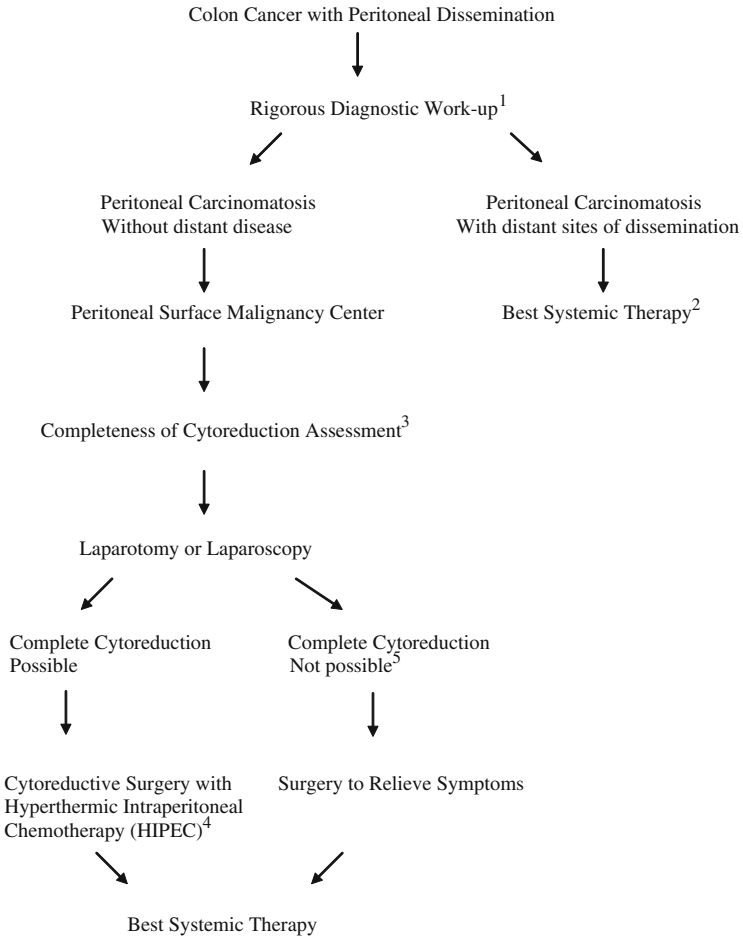


FIG. 1. Clinical pathway for the management of peritoneal surface malignancies of colonic origin.

Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

Cytoreductive surgery will include peritonectomy procedures in order to remove all visible tumor. If a complete cytoreduction, CC-0/CC-1 by the completion of cytoreduction score or a *R*0/*R*1 by the *R* scoring system is achieved (see Table 2), then the patients will undergo hyperthermic intraperitoneal chemotherapy (HIPEC) with mitomycin C (15–35 mg/m^2) with a target intraperitoneal temperature of 39–42°C for 60–120 min. Whether an open or closed method for the chemotherapeutic perfusion is used, and whether or not early post-operative intraperitoneal chemotherapy (EPIC) with 5 days of 5-FU is used, will be the surgeon's preference. In those patients with symptomatic ascites in whom an adequate cytoreduction could not be achieved, HIPEC could be performed at the discretion of the surgeon with the intention of palliating the intractable ascites. Although mitomycin C is the most commonly used drug, we recognized that oxaliplatin is being used more frequently with very promising results.

Complete Cytoreduction Not Possible

In those patients with clear evidence of incomplete cytoreduction, surgery should be performed to relieve symptoms at the discretion of the operating surgeon.

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