Ann Surg Oncol
DOI 10.1245/s10434-012-2237-2

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – REGIONAL CANCER THERAPIES

Cytoreductive Surgery with Selective Versus Complete Parietal Peritonectomy Followed by Hyperthermic Intraperitoneal Chemotherapy in Patients with Diffuse Malignant Peritoneal Mesothelioma: A Controlled Study

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ABSTRACT

Background. Combined treatment involving peritonectomy procedures, multivisceral resections, and hyperthermic intraperitoneal chemotherapy (HIPEC) has reportedly resulted in survival benefit for peritoneal surface malignancies, including diffuse malignant peritoneal mesothelioma (DMPM). Many unanswered questions remain regarding the surgical options in the management of DMPM. The aim of this case–control study was to assess the impact of the type and extent of parietal peritonectomy on survival and operative outcomes.

Methods. Thirty patients with DMPM undergoing selective parietal peritonectomy (SPP) of macroscopically involved regions, and 30 matched patients undergoing routine complete parietal peritonectomy (CPP), regardless of disease distribution, were retrospectively identified from a prospective database.

Results. Groups were comparable for all characteristics, except for a higher proportion of patients treated before July 2003 and undergoing preoperative systemic chemotherapy in the SPP group. Median follow-up was 86.2 months in the SPP group and 50.3 months in the CPP group. Median overall survival was 29.6 months in the SPP group and not reached in the CPP group; 5-year overall survival was 40.0% and 63.9%, respectively ($P = 0.0269$). At multivariate analysis, CPP versus SPP was recognized as an independent predictor of better prognosis, along with complete cytoreduction, negative lymph nodes, epithelial histology, and lower MIB-1 labelling index. Morbidity and reoperation rates were not different between groups. No operative mortality occurred. In 12 of 24 patients undergoing CPP, pathologic examination detected disease involvement on parietal surfaces with no evident tumor at surgical exploration.

Conclusions. CPP improved survival in patients with DMPM undergoing combined treatment. This information may contribute to standardize surgical options for DMPM and other peritoneal malignancies.

Peritoneal surface malignancies (PSM) include carcinomatosis of gastrointestinal or gynecologic origin and primary peritoneal tumors, such as diffuse malignant peritoneal mesothelioma (DMPM).[1] Once regarded as end-stage metastatic conditions with only palliative options, PSM are increasingly recognized as manifestations of locoregional disease spread. Aggressive surgical cytoreduction, combined with hyperthermic intraperitoneal chemotherapy (HIPEC) to treat the microscopic residual disease, is a new locoregional approach aiming at definitive disease eradication.[2] Several independent clinical trials of combined treatment have reported marked survival improvements, as compared to historical or contemporary nonrandomized controls.[3–9] Furthermore, two randomized and two controlled studies have demonstrated a survival benefit over systemic chemotherapy for colorectal and gastric cancer carcinomatosis.[10–13]

Despite the encouraging results, differences among centers in clinical indications, surgical procedures, and intraperitoneal chemotherapy techniques still hamper any meaningful conclusions regarding the best surgical and comprehensive management of these patients. The surgical

First Received: 16 June 2011

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Published online: 03 February 2012

treatment involves extensive cytoreduction on visceral and/or parietal peritoneal surfaces. In most centers, organ resections are performed only if necessary to preserve sufficient postoperative function, and parietal peritonectomy is limited to surfaces involved by visible tumor.[3–13] In contrast, the main characteristic of our institution's approach consists of performing either selective or systematic complete parietal peritonectomy (CPP) (including both macroscopically involved and normal surfaces), according to the dissemination pattern of the different disease entities being treated.[14]

DMPM is a rare and rapidly fatal malignancy. As a result of a natural history characterized by symptoms, site of progression, and cause of death that are commonly confined to the abdominopelvic cavity, this disease represents a paradigm for the management of peritoneal malignancies of any other origin. Cytoreduction with HIPEC has been recently reported to obtain a median survival of approximately 5 years, as compared with 9–13 months after traditional therapies.[15]

As with other PSM, many unanswered questions remain regarding the surgical options in the management of DMPM. Therefore, we performed a retrospective case-matched study to compare long-term survival in comparable groups of patients with DMPM treated by cytoreductive surgery with selective versus CPP combined with HIPEC. Secondary study end points were operative outcomes and morbidity. Furthermore, the incidence of pathologic disease involvement on parietal surfaces with no evident tumor at surgical exploration was assessed in patients undergoing CPP.

PATIENTS AND METHODS

All the patients included in the present study were treated according to a protocol approved by the institutional ethics committee and signed a written informed consent form. Data for the present analysis were collected from a prospective database.

Patient Population

Eligibility criteria for combined treatment included diagnosis of DMPM made or confirmed in our pathology department according to a standardized protocol including hematoxylin–eosin-stained sections and immunohistochemistry studies; age $\leq$75 years; Eastern Cooperative Oncology Group performance status of $\leq$2; no marked comorbidities; no extra-abdominal or hepatic metastases; and peritoneal disease amenable to potentially complete surgical cytoreduction at preoperative computed tomographic (CT) scan.[16–18]

From August 1996 to May 2011, a total of 136 consecutive patients with peritoneal mesothelioma were operated on by the same surgical team. Second procedures ($n = 5$), multicystic or papillary well-differentiated mesothelioma ($n = 15$), and peritoneal spread from primary pleural mesothelioma ($n = 2$) were excluded from this study. Some of these patients were reported before.[19]

Constitution of Study Groups

Patients undergoing selective or CPP were retrospectively identified. Parietal peritonectomy was categorized into six procedures: right diaphragmatic peritonectomy, left diaphragmatic peritonectomy, pelvic peritonectomy, parietal anterior peritonectomy, greater omentectomy, and lesser omentectomy. Thirty patients who had <6 peritonectomy procedures only in anatomic areas with macroscopic evidence of disease constituted the selective parietal peritonectomy (SPP) group. Patients who were not able to undergo one or more peritonectomy because of unresectable disease were excluded.

For the CPP group, the selection process was divided into two steps. During the first step, patients were selected if they had undergone all six peritonectomies, with at least one of them performed in areas free of macroscopic disease at surgical exploration. Patients with widespread parietal disease were excluded to ensure comparability with the SPP group. During the second step, each patient was matched with a patient in the SPP group according to the following known prognostic factors: histology (epithelial vs. biphasic/sarcomatoid), completeness of cytoreduction, lymph node and metastasis status, peritoneal cancer index, age, and sex. The investigators were blinded to patient outcome during the process.

A number of patients had undergone infracolic omentectomy during previous operations. If gastrocolic ligament resection was performed at the time of combined treatment, this was considered to be a greater omentectomy; if it was not done, patients were included in the SPP group. In the remaining patients, complete omentectomy up to the greater gastric curvature was routinely performed.

Operative Treatment

The operative technique adopted in our center has been described previously.[2,14] Briefly, the goal of the cytoreduction was to remove all visible tumor by means of one to six of the above-mentioned parietal peritonectomy procedures. Small and scattered localizations on the visceral surface were resected by local excision/electrocoagulation. In case of massive and/or deeply infiltrating disease, visceral resections were performed, including cholecystectomy, splenectomy, sigmoid, right or total colectomy, and, in women,

hysterectomy with salpingo-oophorectomy. Clinically suspicious regional (intra-abdominal) lymph nodes were sampled and submitted to pathologic examination.[19] In 27 patients, a median of 2 regions (mean 2.2; range 1–6) and of 4.5 lymph nodes (mean 9.9; range 1–52) were sampled. In the remaining 33 patients, no nodes were sampled or thought to be suspicious for metastatic disease. Nodes were pathologically positive in 9 patients (15%). Iliac lymph nodes were the most commonly involved nodes; four patients had metastatic iliac nodes only, and one had positive bilateral iliac, epigastric, left inguinal, paracaval, and para-aortic nodes, with 21 positive of 52 examined nodes. Four patients had metastatic paracolic ($n = 2$), ileocolic, and mesenteric nodes, respectively.

Closed-abdomen HIPEC was performed for 90 min at a temperature of 42.5°C with cisplatin (45 mg/L) plus doxorubicin (15 mg/L).[20] Perfusate volume was 4–6 L, and average flow was 700 mL/min. The Performer LRT (Rand, Medolla, Italy) extracorporeal circulation device was used.

The size and distribution of disease implants before and after surgical cytoreduction were assessed intraoperatively and prospectively recorded. Peritoneal involvement was scored by the peritoneal cancer index.[21] Completeness of cytoreduction (CCR) was classified as follows: macroscopically complete (CCR-0); nearly complete: residual disease $\leq$2.5 mm in any region (CCR-1); or suboptimal: residual disease >2.5 mm (CCR-2).[20] All resected specimens were submitted to pathologic examination. Tumors were histologically categorized as epithelial, biphasic, or sarcomatoid following the World Health Organization classification.[22] Cell proliferation was assessed by immunohistochemical staining of Ki-67 nuclear antigen with monoclonal antibody MIB-1. Labelling index was expressed as the percentage of MIB-1 positive tumor cells.[15] Postoperative complications occurring within 30 days of the procedure were scored according to the National Cancer Institute *Common Terminology Criteria for Adverse Events,* version 3.0 (http://ctep.cancer.gov/forms/CTCAEv3.pdf).

All patients underwent postoperative follow-up. Physical examination, thoracic/abdominal CT scan, and CA 125 measurements were performed every 3 months during the first 2 years and every 6 months thereafter. Postoperative disease progression was confirmed at surgical exploration or by CT scan/ultrasound-guided biopsy. Alternatively, it was defined according to the Response Evaluation Criteria in Solid Tumor Group.[23]

Statistical Analysis

Categorical variables were described in terms of frequencies and percentages, and continuous variables in terms of mean, standard error, median, and interquartile range. Baseline differences between groups were assessed by Student *t*-test, Chi-square test, or Fisher's exact test, as appropriate. Survival rates were calculated according to the Kaplan–Meier method.[24] Overall survival was calculated from the day of cytoreduction with HIPEC to the time of death due to any cause; progression-free survival (PFS) was dated from the day of cytoreduction with HIPEC to the time of postoperative disease progression. Patients undergoing CCR-2 cytoreduction were considered as having immediate disease progression. Patients with an uneventful postoperative course were censored at the time of the last follow-up visit. The two-tailed log rank test was used to assess the significance of the comparison between survival distributions. Continuous variables were categorized into two classes by using their mean value as cutoff. To detect a 30% survival difference with 90% statistical power and 5% significance level, 60 patients were required. To exclude any residual selection bias, the multivariate analysis of factors deemed statistically significant by univariate analysis was performed by the Cox proportional hazard model.[25] P values of <0.05 were considered significant. All statistical analyses were conducted by SPSS software, version 8.0.0 for Windows (SPSS, Chicago, IL).

RESULTS

Patient characteristics are listed in Table 1. There was no statistical difference between the groups, except for a higher proportion of patients who underwent combined treatment before July 2003 and who had received previous systemic chemotherapy in the SPP group, and obviously a higher number of parietal peritonectomies performed in the CPP group. Median Kaplan–Meier estimated potential follow-up was 86.2 months [95% confidence interval (CI) 64.6–107.8] in the SPP group, and 50.3 months (95% CI 42.7–57.9) in the CPP group.

Median overall survival was 29.6 months (95% CI 9.6–49.6) in the SPP group and was not reached in the CPP group; 5-year overall survival was 40.0% and 63.9%, respectively. The difference was statistically significant ($P = 0.0269$). Survival curves are shown in Fig. 1.

Multivariate analysis recognized CPP versus SPP as an independent factor for better overall survival, along with completeness of cytoreduction, epithelial histology, nodal status (with borderline significance), and MIB-1 positive cells >10%. The results of univariate and multivariate analyses are shown in Table 2. Treatment period and previous systemic chemotherapy were forced into the model because of the significant distribution difference between groups, but they did not reach significance. In a separate analysis, CPP correlated to better survival in patients undergoing CCR-0 ($P = 0.039$) and CCR-1 ($P = 0.028$)

TABLE 1 Patient characteristics

Characteristic	Category	Selective parietal peritonectomy ($n = 30$)	Complete parietal peritonectomy ($n = 30$)	*P*
Sex	Male	12	13	1.000
	Female	18	17	
Age	Mean (SD)	47.4 (12.1)	50.7 (15.8)	0.309
	Median (IQ range)	49.5 (40.0–55.0)	54.0 (36.0–65.0)	
ECOG	0	25	23	0.748
	1–2	5	7	
Previous surgery	≤1 abdominopelvic region dissected	26	23	0.506
	>1 abdominopelvic region dissected	4	7	
Previous systemic chemotherapy	No	15	24	0.029
	Yes	15	6	
	Cis/carboplatin + pemetrexed	1	2	
	Cis/carboplatin containing	9	2	
	Doxorubicin + ifosfamide	4	2	
	Other	1	–	
Interval from diagnosis to HIPEC	Mean (SD)	9.2 (13.3)	11.6 (22.2)	0.624
	Median (IQ range)	6.3 (3.1–8.2)	3.9 (2.5–7.9)	
PCI	Mean (SD)	18.2 (7.9)	19.7 (9.7)	0.516
	Median (IQ range)	18 (13–23)	20.5 (12–29)	
Histology	Epithelial	25	25	1.000
	Biphasic	5	5	
Lymph nodes	Positive	5	4	0.731
	Negative	6	11	
	Not sampled	19	15	
Metastases	Present[a]	3	3	1.000
	Absent	27	27	
CCR	0	12	9	0.751
	1	10	12	
	2	8	9	
MIB-1	>10% positive cells	14	14	1.000
	≤10% positive cells	16	16	
Treatment period	Before 2003/07/01	16	7	0.033
	After 2003/07/01	14	23	
Parietal peritonectomy procedures	Mean (SD)	3.47 (1.83)	6 (0.0)	0.001
	Median (IQ range)	4 (1–5)	6	
Visceral resections	Mean (SD)	2.33 (1.71)	3.06 (1.76)	0.107
	Median (IQ range)	2 (1–4)	3 (2–4)	

SD standard deviation, *IQ* interquartile, *HIPEC* hyperthermic intraperitoneal chemotherapy, *PCI* peritoneal cancer index, *ECOG* Eastern Cooperative Oncology Group performance score, *CCR* completeness of cytoreduction (*CCR-0* no macroscopic residual disease, *CCR-1* residual disease ≤2.5 mm in any region, *CCR-2* residual disease >2.5 mm)

[a] Partial diaphragm involvement not detected at preoperative computed tomographic scan

cytoreduction, but not CCR-2 cytoreduction ($P = 0.449$) (Fig. 2).

Median PFS was 14.4 months (95% CI 5.3–23.4) in the SPP group and was not reached in the CPP group; 5-year PFS was 24.9% and 54.3%, respectively ($P = 0.0334$). At multivariate analysis, longer PFS correlated to CPP [hazard ratio (HR) 0.18; 95% CI 0.06–0.56; $P = 0.002$] and epithelial histology (HR 4.93; 95% CI 1.44–16.94; $P = 0.023$).

Operative outcomes are detailed in Table 3. CPP was associated with longer operative time and shorter hospital stay, with a trend for higher number of blood red cell units

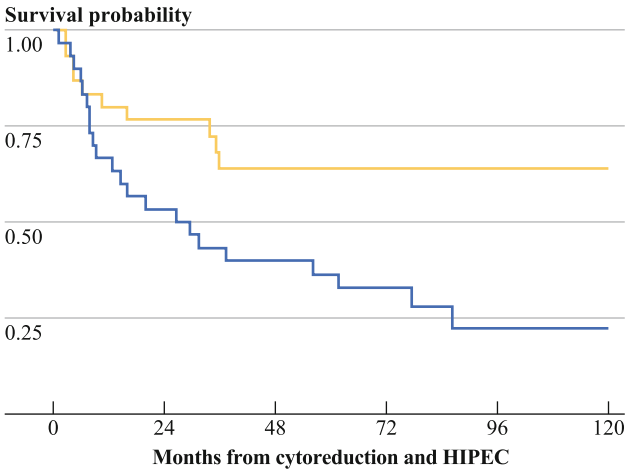

FIG. 1 Overall survival in patients undergoing surgical cytoreduction with selective (*blue line*) or complete (*yellow line*) parietal peritonectomy, combined with hyperthermic intraperitoneal chemotherapy (HIPEC). The difference was statistically significant ($P = 0.027$, log rank test)

transfused. The SPP group experienced more grade 3–5 surgical complications as well as grade 3–5 systemic toxicity and reoperation, but this did not reach statistical significance; overall, 21 major adverse events occurred in 15 patients in CPP group and 11 major adverse events occurred in 8 patients in CPP group ($P = 0.110$).

Pathologic findings of 24 patients of CPP group are shown in Table 4. In 19 of 35 parietal surface specimens with no evident tumor at surgical exploration, pathologic examination detected microscopic ($n = 12$) or macroscopic ($n = 7$) disease involvement. Overall, in 12 of 24 patients for whom accurate pathologic data were available, residual disease on parietal peritoneum would have been unnoticed (and not removed) with a selective approach of parietal peritonectomy.

DISCUSSION

Improved survival after surgical cytoreduction and locoregional perioperative chemotherapy has been reported,

TABLE 2 Operative outcomes and adverse events

Complication	Overall series ($n = 60$)	Selective parietal peritonectomy ($n = 30$)	Complete parietal peritonectomy ($n = 30$)	*P*
Anastomotic leakage	2	1	1	
Bowel perforation	5	4	1	
Hemorrhage	2	1	1	
Pancreatic leakage	1	1		
Wound abscess	1	1		
Cardiac arrest	1	1		
Pulmonitis	3	2	1	
Glaucoma	1	1		
Renal failure	7	5	2	
Hematologic toxicity	*5*	3	2	
Pancreatitis	1		1	
Sepsis	3	1	2	
Grade 3–5 surgical morbidity	17	11	6	0.252
Grade 3–5 systemic toxicity	11	8	3	0.181
Overall grade 3–5 adverse events	23	15	8	0.110
Reoperation	7	5	2	0.424
Operative time, mean (SD)	559.6 (125.3)	519.5 (118.6)	599.7 (120.7)	0.012
Median (IQ range)	552 (480–660)	497.5 (420–600)	600 (540–660)	
Hospital stay, mean (SD)	23.4 (13.2)	27.3 (15.8)	19.7 (8.9)	0.035
Median (IQ range)	19 (10.0–49.2)	23.5 (15.0–36.0)	17.0 (14.2–21.5)	
Blood red cell unit, mean (SD)	2.26 (2.37)	2.13 (2.92)	2.40 (1.69)	0.067
Median (IQ range)	2 (0–4)	1.5 (0–3.0)	3.0 (0–4.0)	
Fresh frozen plasma unit, mean (SD)	6.65 (4.66)	6.44 (4.32)	6.83 (5.01)	0.756
Median (IQ range)	6 (4–8.2)	6 (4–8)	5 (4–9)	

SD standard deviation, *IQ* interquartile

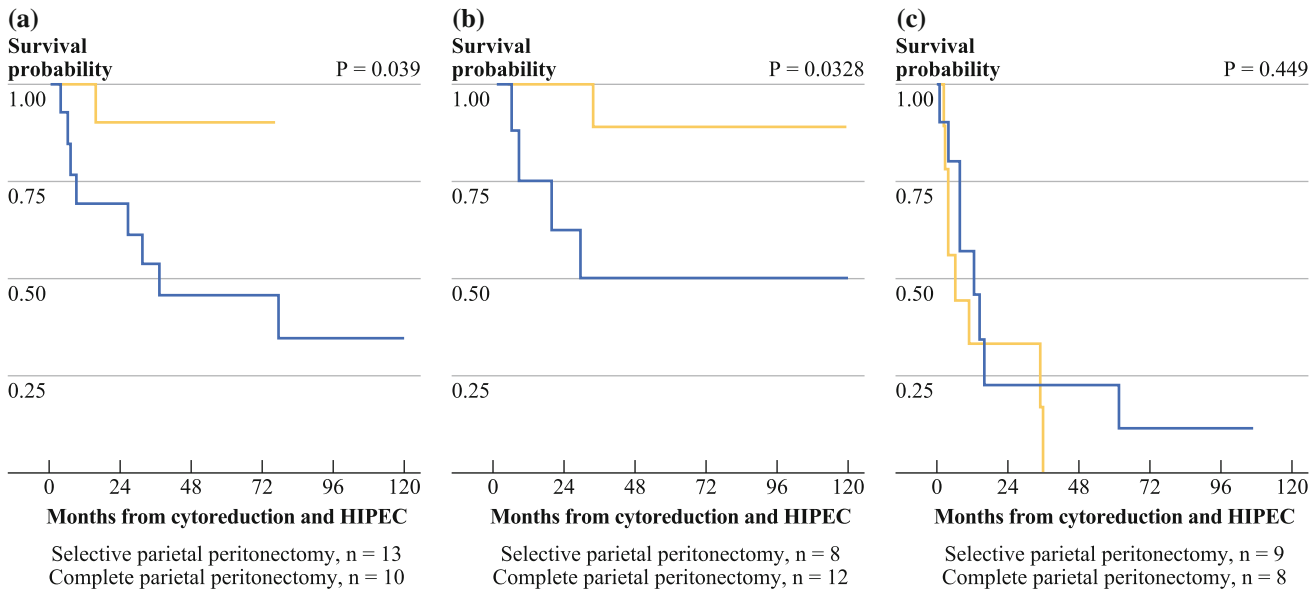

FIG. 2 Overall survival in patients undergoing cytoreductive surgery with selective (*blue line*) or complete (*yellow line*) parietal peritonectomy, combined with hyperthermic intraperitoneal chemotherapy (HIPEC), according to the completeness of cytoreduction. **a** Macroscopically complete cytoreduction ($P = 0.039$). **b** Near-complete cytoreduction, residual disease ≤2.5 mm ($P = 0.038$). **c** Suboptimal cytoreduction, residual disease >2.5 mm ($P = 0.449$)

resulting in an increasing interest in using comprehensive strategies to treat PSM.[3–9] A common feature of these studies is that outcome is predominantly determined by the completeness of the cytoreduction and inherent tumor characteristics, such as tumor load and biological aggressiveness. To our knowledge, this is the first study to demonstrate the prognostic impact of a surgical factor. In comparable groups of patients with peritoneal mesothelioma, CPP was associated with longer survival, with no increase in operative risk and an average 80-minute increase in operative time.

The concept of systematic CPP, regardless of disease distribution, is new. This is particularly relevant for patients with limited parietal disease, as CPP is generally accepted for widespread involvement, except in colorectal and gastric cancer carcinomatosis, where high-volume disease is a common contraindication for treatment. So far, poor data are available on the correlation between prognosis and the quality of surgical cytoreduction. In our institution, a better understanding of the biological behavior of PSM has gradually evolved into a more liberal approach to surgically remove parietal surfaces where tumor deposits are not macroscopically detectable. Because HIPEC and visceral cytoreduction were highly standardized in our protocol (organ resections were strictly performed only when massive involvement made superficial excision ineffectual), such a surgical policy allowed us to assess the impact on survival of selective versus complete peritonectomy.

The present study may affect the surgical decision making for DMPM and possibly for other malignancies. On the basis of tumor penetration depth of HIPEC under experimental conditions, cytoreduction leaving residual disease ≤2.5 mm has been generally considered adequate.[1,2] More recently, the survival advantage of macroscopically complete cytoreduction, compared to millimetric residual disease, has been demonstrated in DMPM, peritoneal sarcomatosis, and colorectal and gastric cancer carcinomatosis.[6,8,9] Our results suggest the need for maximal surgical efforts to limit as much as possible the inherently marginal nature of surgical cytoreduction in PSM. This kind of surgery can never reach microscopically adequate resection margins, but it can approximate it, and this was shown to be of value in DMPM.

In the present series, selective stripping of macroscopically involved parietal regions would have resulted in 50% of patients with residual tumor remaining on parietal surfaces. Theoretically, extensive cytoreduction can improve the chances of responding to subsequent HIPEC by removing chemotherapy-resistant clones and dormant tumor cells, thus stimulating any remaining cells to undergo mitosis and become more susceptible to antiblastic drugs.[26] The most important benefit, however, is the consistent inverse relationship between the amount of residual disease and survival. In line with our findings, investigators from the Netherlands Cancer Institute recommend routine oophorectomy during cytoreduction for peritoneal carcinomatosis of colorectal and appendiceal origin because approximately 30% of patients with no evident involvement have microscopic ovarian metastases, and ovarian involvement correlates with reduced disease-free survival.[27]

Disease involving hepatic hilum and small bowel with its mesentery is a limiting factor for complete cytoreduction

TABLE 3 Univariate and multivariate analysis of factors influencing overall survival

Variable	Category	Median survival, mo	*P* (log rank test)	HR (95% CI)	*P* (Cox model)
CCR	0	NR	0.001	2.44 (1.45–3.97)	0.001
	1	NR			
	2	10.5			
Histology	Epithelial	77.5	0.010	3.37 (1.42–7.97)	0.006
	Biphasic	16.0			
Lymph nodes	Negative	NR	0.047	2.67 (0.93–7.70)	0.069
	Positive/not assessed	35.1			
Metastases	Yes	NR	0.552		
	No	56.3			
PCI	≤20	NR	0.027	0.88 (0.38–2.05)	NS
	>20	31.4			
Peritonectomy	Selective	29.6	0.027	0.46 (0.21–0.99)	0.048
	Complete	NR			
MIB-1	>10% positive cells	16.0	0.003	2.87 (1.17–7.01)	0.020
	≤10% positive cells	NR			
Sex	Male	NR	0.535		
	Female	35.9			
Age, y	>52	37.3	0.876		
	≤51	77.5			
ECOG	0	37.3	0.583		
	1–3	NR			
Interval of diagnosis by HIPEC	≤10.4 months	NR	0.612		
	>10.4 months	37.3			
Previous surgery	≤1 abdominopelvic region dissected	37.3	0.379		
	>1 abdominopelvic region dissected	77.5	0.769		
Previous systemic chemotherapy	Done	37.3	0.918	2.49 (0.92–6.76)	NS
	Not done	61.5			
Treatment period	Before 2003/07/01	NR	0.178	3.27 (0.93–11.46)	NS
	After 2003/07/01	31.4			

HR hazard ratio, *CI* confidence interval, *NR* not reached, *ECOG* Eastern Cooperative Oncology Group performance score, *HIPEC* hyperthermic intraperitoneal chemotherapy, *PCI* peritoneal cancer index, *CCR* completeness of cytoreduction (*CCR-0* no macroscopic residual disease, *CCR-1* residual disease ≤2.5 mm in any region, *CCR-2* residual disease >2.5 mm)

and hence survival. Limited dissection can be applied to the bowel surface, and a minimal length should be preserved to maintain sufficient postoperative function. Therefore, the most obvious criticism of our study is that even the most extensive parietal peritonectomy cannot remove residual tumor on crucial visceral sites, which may result in disease recurrence. However, CPP versus SPP correlated with better outcome in patients with microscopic or minimal residual disease, but not in those undergoing grossly incomplete cytoreduction, presumably because locoregional chemotherapy is largely ineffective in this setting. As in sarcoma surgery, these data suggest that a resection leaving microscopic residual tumor over a critical structure, but complete for the rest, might be definitely better than a cytoreduction leaving microscopic disease in multiple areas.[28] Although it is virtually impossible to remove all the microscopic tumor from the small bowel surface, an aggressive cytoreduction all around, with minimal residual disease over these critical structures, might be better than less aggressive cytoreduction overall just because of one critical spot.

The current knowledge of PSM dissemination patterns supported our choice to perform CPP in DMPM. High-grade cancer cells disseminate within the coelomic cavity as a result of highly efficient mechanisms of mesothelial adhesion, implantation, invasion, and growth. Their molecular profile (E-cadherin downregulation, expression of matrix proteinases, CD-44, motility, and angiogenic factors) enables them to invade directly peritoneal surfaces.[29,30] Implants from these aggressive malignancies are in close proximity to the primary tumor and randomly

TABLE 4 Surgical and pathologic findings in 24 patients undergoing cytoreduction with routine complete parietal peritonectomy and hyperthermic intraperitoneal chemotherapy

Parietal peritoneum region	Macroscopic tumor at surgical exploration ($n = 109$)				Negative at surgical exploration ($n = 35$)			
	Pathologic diagnosis				Pathologic diagnosis			
	Macroscopic tumor	Microscopic tumor	No tumor	Total	Macroscopic tumor	Microscopic tumor	No tumor	Total
Right diaphragmatic	18	1	1	20	–	2	2	4
Left diaphragmatic	10	2	2	14	4	5	1	10
Parietal anterior	19	–	–	19	1	1	3	5
Pelvic	17	1	2	20	1	2	1	4
Greater omentum	19	–	2	21	1	–	2	3
Lesser omentum	13	2	–	15	–	2	7	9
Total	95	6	7	–	7	12	16	–

involve nearby surfaces.[26] Conversely, low- to moderate-grade malignancies, such as peritoneal mesothelioma and pseudomyxoma peritonei, merely distribute throughout the abdominopelvic cavity by gravity, peritoneal fluid flows, and bowel movements following a predictable stepwise pattern. The omentum, diaphragmatic peritoneum, and Douglas pouch, characterized by numerous lymphatic orifices (milky spots) and discontinuous mesothelial lining, are their preferential locations for implantation.[26,30] Ubiquitous intracavitary malignant cell diffusion may occur in the early phase of the disease. Furthermore, DMPM is a primary peritoneal-based cancer.

An additional criticism of this investigation may involve its retrospective nature. This limitation is minimized by the comparative study design, with well-balanced case and control groups. A far greater proportion of patients undergoing SPP was treated during the early years of the study period. This necessarily reflects the evolution of our surgical policy. Several groups have suggested the existence of a learning curve for performing these demanding procedures, which may contribute to improve both operative and long-term outcomes in the more recently treated CPP group. Nevertheless, the survival analysis demonstrated that better prognosis was not sensitive to treatment period.

Analogously, a higher proportion of patients in the SPP group had received systemic chemotherapy before referral to our center. Because most of the patients were treated with cisplatin/carboplatin with or without pemetrexed-based schedules, this raises concern as to the possible role of prior chemotherapy in inducing resistance to HIPEC, thus adversely affecting prognosis. However, the lack of univariate and multivariate correlation with survival do not seem consistent with this hypothesis.

In conclusion, this retrospective case-matched comparison suggests that CPP may improve survival in patients with DMPM undergoing cytoreduction and HIPEC. Future prospective studies are needed to confirm these findings and to assess their possible implications in other PSM management.

ACKNOWLEDGMENT Supported in part by grants from the Italian Association for Cancer Research (AIRC) and the Italian Health Ministry.

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