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ORIGINAL REPORT

Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Malignant Peritoneal Mesothelioma: Multi-Institutional Experience

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ABSTRACT

Purpose
This multi-institutional registry study evaluated cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) for diffuse malignant peritoneal mesothelioma (DMPM).

Patients and Methods
A multi-institutional data registry that included 405 patients with DMPM treated by a uniform approach that used CRS and HIPEC was established. The primary end point was overall survival. The secondary end point was evaluation of prognostic variables for overall survival.

Results
Follow-up was complete in 401 patients (99%). The median follow-up period for the patients who were alive was 33 months (range, 1 to 235 months). The mean age was 50 years (standard deviation [SD], 14 years). Three hundred eighteen patients (79%) had epithelial tumors. Twenty-five patients (6%) had positive lymph nodes. The mean peritoneal cancer index was 20. One hundred eighty-seven patients (46%) had complete or near-complete cytoreduction. Three hundred seventy-two patients (92%) received HIPEC. One hundred twenty-seven patients (31%) had grades 3 to 4 complications. Nine patients (2%) died perioperatively. The mean length of hospital stay was 22 days (SD, 15 days). The overall median survival was 53 months (1 to 235 months), and 3- and 5-year survival rates were 60% and 47%, respectively. Four prognostic factors were independently associated with improved survival in the multivariate analysis: epithelial subtype ($P < .001$), absence of lymph node metastasis ($P < .001$), completeness of cytoreduction scores of CC-0 or CC-1 ($P < .001$), and HIPEC ($P = .002$).

Conclusion
The data suggest that CRS combined with HIPEC achieved prolonged survival in selected patients with DMPM.

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INTRODUCTION

Malignant mesothelioma is a highly aggressive primary neoplasm of the serosal lining of the pleura, peritoneum, pericardium, or tunica vaginalis.[1] The disease is associated with asbestos exposure, and there has been substantial public interest in recent years, as millions of people have been exposed to asbestos in the environment, especially the workplace. The increasing incidence worldwide is expected to peak in 5 to 10 years.[2] Diffuse malignant peritoneal mesothelioma (DMPM) represents one fourth of all mesotheliomas, and the incidence of DMPM is 300 to 400 occurrences annually in the United States.[3-5] It is characterized macroscopically by thousands of whitish tumor nodules of variable size and consistency that may coalesce to form plaques or masses or that may layer out to uniformly cover the entire peritoneal surface. Although association of asbestos exposure with DMPM has been observed, the pathogenesis of this disease is largely unknown. Patients usually present with advanced disease that causes abdominal pain or distension. As the disease progresses, patients die as a result of intestinal obstruction or terminal starvation within a year. In most patients, DMPM remains localized within the abdominopelvic cavity throughout its course. Few therapeutic advances have occurred in the last century, since the disease was first described by Miller and Wynn[6] in 1908. Systemic

chemotherapy, palliative surgery, and/or total abdominal radiation therapy have been used selectively but have failed to alter the natural history of this disease.[7-13]

Recently, diagnostic and therapeutic aspects of the disease have been re-evaluated as encouraging reports from several centers worldwide on a combined locoregional treatment approach that uses cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have emerged. This new treatment strategy has shown favorable prognosis and has achieved a median survival of up to 60 months and a 5-year survival of 50% in selected patients.[14-22]

However, as the disease is relatively rare, it is difficult to accumulate enough patients to demonstrate procedural safety and efficacy with sufficient statistical power for prognostication of treatment outcomes. A multi-institutional data registry on peritoneal mesothelioma was established, therefore, during the sixth Peritoneal Oncology Meeting in Lyon, France, in November 2008. By February 2009, eight institutions had contributed clinical data to the registry, which provided a total of 405 patients. The primary end point of this study was the overall survival outcome of these patients with DMPM after a treatment strategy that used CRS and perioperative intraperitoneal chemotherapy was administered. The secondary end point was to evaluate the significance of several clinicopathologic and treatment-related prognostic variables for overall survival.

PATIENTS AND METHODS

Ethics approval was obtained from the participating institutions through their institutional review boards or through the chairperson of the ethics committee, who waived the need for patient consent for the study, as individual patients were not identified. The study population was 405 patients who were considered preoperatively to be candidates for CRS and perioperative intraperitoneal chemotherapy for treatment of DMPM between October 1989 and February 2009 from the eight international institutions. The inclusion criteria were peritoneal mesothelioma confirmed by histopathologic examination and a treatment strategy that utilized CRS followed by HIPEC with or without early postoperative intraperitoneal chemotherapy (EPIC). The exclusion criteria were peritoneal mesothelioma secondary to pleural mesothelioma and extra-abdominal metastasis identified during preoperative investigations. Standardized clinical data on consecutive patients from each of the eight institutions were entered onto a central database. Follow-up data from most recent reviews were included, and these consisted of clinical examination and assessment of abdominal-pelvic computed tomography scans. Each institution confirmed that the pooled data represented consecutive operative procedures performed in the study period by participating surgeons.

Standardized Data Form

A blinded, standard, data form was created to retrieve relevant information on the clinical data (ie, age, sex, date of surgery, extent of prior surgical intervention, and performance status); pathologic data (ie, histopathologic subtype, presence of lymph node metastasis, presence of extra-abdominal metastasis, peritoneal cancer index [PCI], and completeness of cytoreduction); and treatment-related data (ie, receipt of HIPEC; receipt of EPIC; duration of surgery; perioperative blood transfusion $>$ 5 units; presence versus absence of cardiac, respiratory, gastrointestinal, renal, and hematologic morbidities; presence versus absence of grades 3 to 4 toxicity according to the National Cancer Institute Common Toxicity Criteria; duration of hospital stay; and receipt of pemetrexed combination chemotherapy). These variables were included in the subsequent data analysis, because they have been found to have significant prognostic values in other studies or because they may have potential clinical implications for future patient management (eg, HIPEC and EPIC).

The volume and extent of the tumor deposits were recorded prospectively by using the PCI.[23] This assessment combines lesion size (0 to 3) with tumor distribution (abdominal-pelvic region, 0 to 12) to quantify the extent of disease as a numerical score (PCI of -0 to 39).[23] Peritonectomy was performed only at the sites of disease involvement with intent to remove all intraperitoneal tumor deposits together with involved peritoneum. CRS was performed according to techniques by Sugarbaker,[24] and the details were described previously. In short, peritonectomy procedures include total anterior parietal peritonectomy, omentectomy with or without splenectomy, right and left subphrenic peritonectomy, pelvic peritonectomy, and lesser omentectomy with or without cholecystectomy.[24] Sites and volumes of the residual disease after CRS also were recorded prospectively by using the completeness of cytoreduction (CC) score.[23] A score of CC-0 indicated no visible evidence of disease; CC-1 indicated residual tumors $\leq$ 2.5 mm in diameter; CC-2 indicated residual tumors between 2.5 mm and 2.5 cm in diameter; and CC-3 indicated residual tumors greater than 2.5 cm in diameter or a confluence of tumor nodules present at any site. It is acknowledged that there were variations in intraperitoneal chemotherapy exposure techniques (ie, open or closed), drugs used, duration, and intraperitoneal temperatures among the institutions. However, all studies shared two of the most important concepts in treatment rationale: maximal CRS to remove macroscopic disease, and intraperitoneal chemotherapy delivered immediately after CRS to eradicate residual tumor cells.

Statistical Analysis

The data were reported on an intention-to-treat basis (ie, all patients selected for the combined procedure, irrespective of CC or HIPEC administration, were included). Perioperative mortality was defined as any death that occurred during the same hospital admission or within 30 days after surgery. Perioperative mortality was included in the overall survival analysis. Overall survival was used as the primary end point, which was determined from the time of surgery. Survival analysis was performed by using the Kaplan-Meier method and was compared by using the log-rank test. For multivariate analysis, a Cox proportional hazards model with forward stepwise selection of covariates and with entering and removing limits of $P < .10$ and $P > .05$ was used. All statistical analyses were performed with the Statistical Package for Social Sciences for Windows (Version 17.5; SPSS GmbH, Munich, Germany). A significant difference was defined as $P < .05$.

RESULTS

Clinicopathologic Data

Between October 1989 and February 2009, a total of 405 patients with peritoneal mesothelioma were judged preoperatively to be candidates for the combined treatment. The follow-up was complete in 401 patients (99%). One hundred seventy-two patients (43%) were deceased at the last time of follow-up. The median follow-up period was 33 months (range, 1 to 235 months). The mean age at the time of CRS was 50 years (standard deviation [SD], 14) years. There were 227 patients (56%) who were men. Three hundred eighteen patients (79%) had epithelial tumors, and 48 patients (12%) had biphasic or sarcomatoid tumors. Twenty-five patients (6%) had lymph node metastases. Twelve patients (3%) had extra-abdominal metastatic disease in the form of disease that penetrated the tendonous portion of the diaphragm, which was resected at the time of CRS. The mean PCI was 20 (SD, 10). One hundred two patients (25%) had CC-0 cytoreduction, 85 patients (21%) had CC-1 cytoreduction, 86 patients (21%) had CC-2 cytoreduction, and 39 patients (10%) had CC-3 cytoreduction at the end of surgery.

Treatment-Related Data

Three hundred seventy-two patients (92%) received HIPEC. Twelve patients in the early experience received EPIC, not HIPEC, and seven patients were hemodynamically unstable intraoperatively, so

Table 1. Intraperitoneal Chemotherapy Agents Utilized After Cytoreductive Surgery for Peritoneal Mesothelioma

	Surgery Type			
	HIPEC		EPIC	
Chemotherapy	No.	%	No.	%
Cisplatin + doxorubicin	311	83	16	17
Cisplatin + mitomycin	14	4	—	—
Cisplatin alone	19	5	—	—
Mitomycin	26	7	—	—
Paclitaxel	—	—	77	82
Other	2	1	1	1
Total	372	100	94	100

Abbreviations: HIPEC, hyperthermic intraperitoneal chemotherapy; EPIC, early postoperative intraperitoneal chemotherapy.

HIPEC was withheld. The reasons for not giving HIPEC in the remaining 14 patients were not clear. Three institutions routinely utilized EPIC after HIPEC. Ninety-four patients (23%) received EPIC administered between days 1 and 5 postoperatively. All HIPEC procedures were performed intraoperatively after CRS, but there were variations in exposure techniques (ie, open or closed), drugs used, duration (30 to 120 minutes), and intraperitoneal temperatures (40°C to 43°C). Chemotherapeutic agents used for HIPEC and EPIC are reported in Table 1. The most common HIPEC regimen was cisplatin combined with doxorubicin, and the most common EPIC regimen was paclitaxel. The mean operation duration was 8 hours (SD, 3 hours). Forty-four patients (11%) had a packed-cell transfusion of greater than 5 units. Eleven patients (3%) sustained cardiac complications. Forty-six patients (11%) sustained respiratory complications. Seventy-four patients (18%) experienced bowel-related adverse events. Thirty-nine patients (10%) had renal complications. Twenty-five patients (6%) developed hematologic toxicity. Overall, 188 patients (46%) had perioperative complications, which included 127 patients (31%) who had grades 3 or 4 complications. Nine patients (2%) died perioperatively. The mean length of hospital stay was 22 days (SD, 15 days). Twenty-two patients (5%) received systemic pemetrexed in combination with cisplatin or carboplatin after CRS.

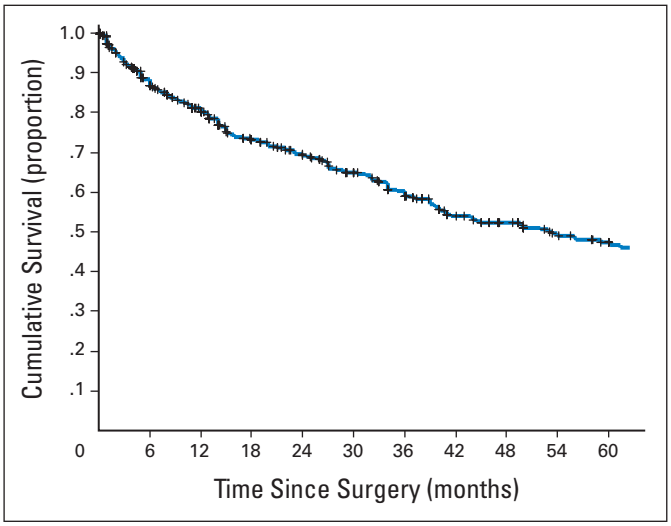

Fig 1. Overall survival after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal mesothelioma (n = 401). (+) Patients who were alive at the last follow-up.

Survival Outcome

The overall median survival was 53 months (range, 1 to 235 months), and the 1-, 3- and 5-year survival rates were 81%, 60%, and 47%, respectively (Fig 1). Univariate analysis identified 10 significant prognostic variables associated with improved survival: age ≤ 50 years ($P = .003$), female sex ($P < .001$), epithelial subtype ($P = .006$), absence of lymph node metastasis ($P = .008$), absence of extra-abdominal metastasis ($P = .013$), PCI ≤ 20 ($P = .002$), CC-0 or CC-1 ($P < .001$), receipt of HIPEC ($P = .049$), packed-cell transfusion of ≤ 5 units ($P = .003$), and absence of cardiac complication ($P = .008$). The remaining 12 prognostic variables were not statistically significant. Tables 2 and 3 demonstrate the significance of clinicopathologic and treatment-related prognostic factors, respectively, for overall survival. One hundred forty-four

Table 2. Univariate Analysis of Clinicopathologic Factors Affecting Survival

Variable	No. of Patients	Median Survival (months)	*P*
Total	401	53	
Age at the time of surgery, years			.003
≤ 50	194	67	
> 50	207	40	
Sex			< .001
Male	227	36	
Female	174	119	
Date of surgery			.434
Before September 2003	201	50	
After September 2003	200	53	
Extent of prior surgery			.635
Limited dissection or biopsy	176	50	
Previous surgical debulking	75	32	
Unknown	150		
Performance status			.628
≤ 2	247	53	
> 2	38	44	
Unknown	116		
Histologic subtype			.006
Epithelial	318	63	
Biphasic/sarcomatoid	48	16	
Unknown	35		
Lymph node metastasis			.008
Present	25	20	
Absent	376	56	
Extra-abdominal metastasis			.013
Present	12	20	
Absent	389	56	
Peritoneal cancer index			.002
≤ 20	158	119	
> 20	133	39	
Unknown	110		
Completeness of cytoreduction score			< .001
0	102	94	
1	85	67	
2	86	40	
3	39	12	
Unknown	89		

Table 3. Univariate Analysis of Treatment-Related Factors Affecting Survival

Variable	No. of Patients	Median Survival (months)	*P*
Total	401	53	
HIPEC			.049
Yes	372	56	
No	29	23	
EPIC			.580
Yes	94	64	
No	307	50	
Duration of surgery, hours			.480
≤ 8	140	66	
> 8	142	54	
Unknown	119		
Blood transfusion, units			.003
≤ 5	357	56	
> 5	44	29	
Cardiac complication			.008
Yes	11	21	
No	390	54	
Respiratory complication			.742
Yes	46	41	
No	355	53	
Gastrointestinal complication			.870
Yes	74	44	
No	327	54	
Renal complication			.632
Yes	39	61	
No	362	53	
Hematologic complication			.243
Yes	25	36	
No	376	54	
Grade of morbidity			.205
I to II	274	56	
III to IV	127	41	
Length of hospital stay, days			.567
≤ 21	218	50	
> 21	163	56	
Unknown	20		
Pemetrexed combination chemotherapy			.117
Yes	22	76	
No	379	53	

Abbreviations: HIPEC, hyperthermic intraperitoneal chemotherapy; EPIC, early postoperative intraperitoneal chemotherapy.

patients had open technique, and 228 patients had closed technique. Subgroup analyses showed no survival differences between the two HIPEC delivery techniques ($P = .160$) and between the HIPEC chemotherapeutic regimens used ($P = .091$).

Four prognostic factors were independently associated with improved survival in the multivariate analysis: epithelial subtype (hazard ratio [HR], 27.547; 95% CI, 2.905 to 10.360; $P < .001$), absence of lymph node metastasis (HR, 13.929; 95% CI, 1.749 to 6.017; $P < .001$), CC-0 to CC-1 (HR, 24.222; 95% CI, 2.008 to 5.054; $P < .001$), and HIPEC (HR, 9.489; 95% CI, 0.219 to 0.713; $P = .002$).

DISCUSSION

In the past, no uniform treatments were suggested for patients with DMPM, and survival was largely dependent on the histopathologic subtype of the disease. Several studies have reported reduced survival outcome associated with biphasic or sarcomatoid subtype compared with outcomes associated with the epithelial subtype.[14-22] A lack of prognostic indicators for optimal patient selection is not surprising. As the disease is rare, most centers have insufficient number of patients, and the treatments employed in these patients have varied greatly. Most studies in the current literature have relatively small samples; therefore, the clinical implications of these reports are limited. This registry represents, to our knowledge, the largest collaborative effort to demonstrate clinical outcomes of patients with peritoneal mesothelioma who were treated by a combined strategy. This allows a more thorough and precise analysis of clinicopathologic and treatment-related prognostic parameters.

Women have a better prognosis than men. Direct exposure to asbestos was apparent in men, but it was less apparent in women.[3,5] It is possible that this difference in causation is at least partially responsible for the difference in survival between men and women. Acherman et al[25] reported that women seldom presented with weight loss; a lack of this important poor prognostic symptom suggested less advanced disease. Also, women often sought medical attention with gynecologic complaints caused by DMPM. Diagnoses as a result of nonspecific gynecologic symptoms may have resulted in earlier interventions.[14] A recent study showed that women had more favorable histopathologic features, which might contribute to their better survival.[26] The sex difference in survival was significant in the univariate analysis, but not in the multivariate analysis, in this study.

Lymph node metastasis is uncommon in patients with DMPM, but it is associated with extremely poor prognosis.[22] In this registry, 25 patients had positive lymph nodes identified during surgical exploration; the median survival of these patients was 20 months versus 56 months for patients without positive lymph nodes. Yan et al[22] reported that seven patients had positive lymph nodes. The median survival of these patients was 6 months, and the 1- and 2-year survival rates were 43% and 0%, respectively. Ninety-three patients had absence of lymph node involvement; the median survival of these patients was 59 months, and 5- and 7-year survival rates were 50% and 43%, respectively.[22] The crucial importance of lymph node metastasis should encourage surgeons to vigorously search for abnormal nodes when they perform CRS. Any enlarged or firm lymph nodes should be submitted for pathologic evaluation separately from the rest of the specimens. It should become current surgical practice to sample all suspicious lymph nodes in patients with DMPM to better determine prognosis and to provide more knowledge in the management of these patients.

Nearly all peritonectomy centers agree that adequate cytoreduction is one of the most significant prognostic factors for long-term survival.[14-22] Adequate cytoreduction is related to the pretreatment tumor load and the surgeon's technical ability to eradicate gross disease. Unlike pseudomyxoma peritonei, DMPM generally does not spare the peritoneal surfaces of the small intestine, which limits the ability to achieve CC. Clear resection margins are difficult to obtain. The recognition that surgery alone may not provide adequate local disease control has provided the rationale for combining CRS with HIPEC. CRS aims to remove all peritoneal tumors together with complete lysis of adhesions between the bowel loops, which would create an optimal situation for adjuvant intraperitoneal chemotherapy. Chemotherapy is administered intraoperatively to allow direct

chemotherapy and tumor-cell contact and to minimize systemic toxicity.[27] Hyperthermia has had direct cytotoxic effects in both temperature and time-dependent manners.[28] Heat increases the depth of penetration of chemotherapy[29] and synergizes the cytotoxic drugs selected for intraperitoneal use at the time of surgery.[30]

Although CRS combined with HIPEC has showed promising results, a prospective comparison of HIPEC versus no HIPEC is not available. Also, no definitive information concerning optimal choice of chemotherapy agents in HIPEC exists. The difficulties of performing such trials in a rare disease like DMPM should be acknowledged. For practical purposes, this multi-institutional database collected a minimum data set for all patients undergoing the combined treatment between 1989 and 2009. The standardized, quantitative, prognostic indicators, such as CC score and PCI, were published in 1996. We acknowledge that there were missing data, which might impact on the prognostic significance of the results. The main limitation of this study is that the data were nonrandomized; thus, unknown confounders that could influence outcome may exist. It is possible that the improved survival in this study compared with historical controls reflected a lead-time bias, in which patients underwent surgery earlier in their natural courses of disease. This could be related to modern diagnostic technologies and increased awareness of surgical treatment options, which would prompt referral to appropriate centers. Nevertheless, the results of this study should encourage early diagnosis and active treatment of DMPM. Although multivariate analysis has identified four prognostic factors that might have contributed to the improved survival results, the true significance of each factor is difficult to assess when interrelated factors are entered into the analysis. One must bear in mind the limitation of this methodology when interpreting the results. To prove the relevance of HIPEC, additional evaluation in a prospective manner is required. The main value of this experience is to provide a benchmark against which the results of future clinical trials can be judged. Meanwhile, in the absence of level-1 clinical evidence, those entrusted with the care of patients with peritoneal mesothelioma inevitably will be challenged with difficult decisions to share with their patients as together they seek balance between risk and benefit.

This disease, which previously was considered a preterminal condition, now can be treated with CRS and HIPEC at experienced centers to provide a benefit in terms of long-term survival. With a greater proportion of patients undergoing a well-defined treatment plan, more in-depth knowledge can be gained in the diagnosis, radiology, and histopathology of this rare disease. The roles of novel systemic chemotherapy,[31] immunotherapy, and targeted treatments in patients with DMPM remain to be evaluated, and integration into the combined therapy has yet to be determined.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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