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ORIGINAL REPORT

Early- and Long-Term Outcome Data of Patients With Pseudomyxoma Peritonei From Appendiceal Origin Treated by a Strategy of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

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ABSTRACT

Purpose
Pseudomyxoma peritonei (PMP) originating from an appendiceal mucinous neoplasm remains a biologically heterogeneous disease. The purpose of our study was to evaluate outcome and long-term survival after cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) consolidated through an international registry study.

Patients and Methods
A retrospective multi-institutional registry was established through collaborative efforts of participating units affiliated with the Peritoneal Surface Oncology Group International.

Results
Two thousand two hundred ninety-eight patients from 16 specialized units underwent CRS for PMP. Treatment-related mortality was 2% and major operative complications occurred in 24% of patients. The median survival rate was 196 months (16.3 years) and the median progression-free survival rate was 98 months (8.2 years), with 10- and 15-year survival rates of 63% and 59%, respectively. Multivariate analysis identified prior chemotherapy treatment ($P < .001$), peritoneal mucinous carcinomatosis (PMCA) histopathologic subtype ($P < .001$), major postoperative complications ($P = .008$), high peritoneal cancer index ($P = .013$), debulking surgery (completeness of cytoreduction [CCR], 2 or 3; $P < .001$), and not using HIPEC ($P = .030$) as independent predictors for a poorer progression-free survival. Older age ($P = .006$), major postoperative complications ($P < .001$), debulking surgery (CCR 2 or 3; $P < .001$), prior chemotherapy treatment ($P = .001$), and PMCA histopathologic subtype ($P < .001$) were independent predictors of a poorer overall survival.

Conclusion
The combined modality strategy for PMP may be performed safely with acceptable morbidity and mortality in a specialized unit setting with 63% of patients surviving beyond 10 years. Minimizing nondefinitive operative and systemic chemotherapy treatments before definitive cytoreduction may facilitate the feasibility and improve the outcome of this therapy to achieve long-term survival. Optimal cytoreduction achieves the best outcomes.

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INTRODUCTION

Epithelial appendiceal neoplasms account for 1% of colorectal cancer.[1,2] In its early stages, the diagnosis may be made incidentally at the time of appendectomy, occurring in less than 1% of appendectomies.[3] Advanced disease is often a result of tumor perforation and seeding of tumor cells within the peritoneal cavity leading to the clinical syndrome of pseudomyxoma peritonei (PMP). In the past, management of this disease involved repeated drainage of mucinous ascites or surgical debulking through removal of the primary tumor and omental mass. In an article from the Mayo clinic, Gough et al[4] reported that 34% of patients with limited low-grade appendiceal pseudomyxoma could become free of disease via debulking surgery, with an estimated 10-year survival rate of 32%. In another article from the

same institution,[5] patients with appendiceal adenocarcinoma who underwent surgery were reported to have a 5-year survival rate of 6%.

In the 1990s, a new therapeutic strategy combining macroscopic tumor removal through cytoreduction and locoregional chemotherapy was described.[6] This combined-modality therapy has been evaluated in four randomized trials of peritoneal metastases from colorectal cancer,[7,8] gastric cancer,[9] and sarcomatosis.[10] An expert consensus panel discussion at the Fifth International Workshop on Peritoneal Surface Malignancy in Milan, Italy (December 4-6, 2006) concluded that there was a survival benefit of the procedure compared with historical controls.[11] Owing to the rarity of this disease, our study aims to consolidate the current results of the strategy of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for appendiceal pseudomyxoma peritonei.

PATIENTS AND METHODS

Patient Population

The Peritoneal Surface Oncology Group International registry study on PMP was commissioned during the Seventh International Workshop on Peritoneal Surface Malignancy in Uppsala, Sweden (September 8-10, 2010). The participating institutions were from North America (n = 3), Australia (n = 1), and Europe (n = 12). Patients were treated between February 1993 and April 2011. Inclusion criteria were histologically confirmed PMP from an appendiceal mucinous neoplasm with histopathologic subtype classified by either Ronnett's criteria[12] or Bradley's criteria.[13] Ronnett's criteria comprise three groups; diffuse peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis (PMCA), or hybrid tumors. Bradley's classification is binary and comprises DPAM and hybrid tumors in one group, classified as low-grade tumors, and PMCA in the other group, classified as high-grade tumors or adenocarcinoma. Exclusion criteria include colorectal malignancies, patients with extra-abdominal metastases, patients deemed medically unfit to undergo radical surgery based on preoperative medical assessment, and those patients whose disease was considered technically unresectable at the multidisciplinary team meeting. The generic surgical approach involves peritonectomy procedures and visceral resections called CRS as described by Sugarbaker.[14] Hyperthermic intraperitoneal chemotherapy (HIPEC) was administered at the completion of cytoreduction using an open coliseum or closed technique depending on the individual unit's preference, with the chemoperfusate heated to achieve a temperature ranging between 40°C to 42°C. HIPEC with 10 to 12.5 mg/m^2 mitomycin C is delivered over a 90-minute period and 460 mg/m^2 oxaliplatin over a 30-minute period. After surgery, early postoperative intraperitoneal chemotherapy (EPIC) comprising 650 mg/m^2 flurouracil is administered intraperitoneally on days one to five at room temperature. In addition to HIPEC, EPIC is delivered in seven centers to patients who were deemed clinically stable after surgery without any evidence of early postoperative complications.

Data Collection

The institutional review boards at the respective centers approved the conduct of this registry study. Prior surgical score (PSS) ranged from 0 to 3. PSS-0 was the rating for no surgery or biopsy, PSS-1 for surgery in one abdominal region only, PSS-2 for surgery in two to five regions, and PSS-3 for surgery in more than five regions. The peritoneal cancer index (PCI) was determined intraoperatively and comprised a score of 0 to 3 in 13 abdominopelvic regions to a computed index ranging from 1 to 39.[15] Residual disease following CRS was scored according to the completeness of cytoreduction (CCR) score.[15] CCR0 indicates that no macroscopic residual cancer remained; CCR1 indicates that no nodule larger than 2.5 mm in diameter remained; CCR2 indicates that nodules between 2.5 mm and 2.5 cm in diameter remained; and CCR3 indicates that nodules larger than 2.5 cm in diameter remained. In general, CCR2 and 3 are incomplete cytoreduction and would be considered as a debulking surgery with gross residual tumor. The participating specialized units were classified arbitrarily as well established (≥ 10 years' experience) and emerging (< 10 years' experience). It must be acknowledged that our study is specific to PMP only and that units, although classified as emerging based on the numbers enrolled onto the registry, may also have substantial experience in CRS for other peritoneal malignancies. Postoperative complications were graded as follows: grade 0 refers to no complications, grade 1 refers to self-resolving complications, grade 2 refers to complications requiring medical treatment, grade 3 refers to complications requiring interventional radiology or minimally invasive procedurally treatment, grade 4 refers to complications requiring a return to the operating room for management, and grade 5 refers to a 30-day stay in hospital or mortality.

Statistical Analysis

Demographic and clinical treatment variables were examined for association with major postoperative complications (grades 3 to 5) using univariate and multivariate logistic regression models. The calculation of survival rates was specified from the date of cytoreduction and performed using the Kaplan-Meier method. Prognostic factors were examined using univariate and multivariate Cox proportional hazards regression models. Patients with missing values and postoperative mortalities were not included for survival analysis. Patients who underwent debulking surgery (CCR2/3) were considered to have immediate progression. The date of death was used for patients for whom the date of recurrence was not known. A total of 2,322 patients were entered onto the registry, however, follow-up and missing data led to the exclusion of 23 patients (1%), resulting in 2,298 patients for analysis. The data collected were analyzed using SPSS for Windows version 15.0 (SPSS, Munich, Germany). $P < .05$ was considered statistically significant.

RESULTS

Two thousand two hundred ninety-eight patients treated with CRS for appendiceal pseudomyxoma peritonei between February 1993 and April 2011 constituted the study population. Eight units recorded ≥ 100 patients each, ranging from 124 to 542 patients, accounting for a total of 2,117 patients. The remaining eight units recorded fewer than 100 patients each, ranging from 10 to 56 patients per unit to make up the remaining 181patients of the study.

Patient Characteristics

The patient characteristics are presented in Table 1. There were 993 female patients (43%) and 1,305 male patients (57%), and the median age was 53 years (mean, 53; standard deviation, 12; range, 18 to 86). From the time of diagnosis of appendiceal PMP, patients were referred to specialized units at a median of 6 months (range, 0 to 332). Patients were referred at diagnosis (37% within 6 months of diagnosis) or after undergoing an operation (n = 997; 43%) with limited resectional surgery (PSS, 0 to 2; n = 1,170; 51%). Three hundred seventy-seven patients (16%) received systemic chemotherapy treatment before cytoreduction.

Characteristics of Surgical Treatment

At laparotomy, the median PCI was 20 (mean, 20; standard deviation, 11; range 0 to 39). Optimal cytoreduction (CCR0/1) was achieved in 1,904 patients (83%) of which 1,165 patients (51%) had a complete cytoreduction (CCR0). HIPEC was delivered intraoperatively in 2,054 patients (89%) of which mitomycin C–based HIPEC was the most common chemotherapeutic agent, used in 1,784 patients (77%). The intraperitoneal chemotherapy regimens of HIPEC and EPIC were delivered in 668 patients (29%), HIPEC alone in 1,382 patients (60%), and EPIC alone in 44 patients (2%). The median duration of the operative procedure was 9 hours (range, 2 to 24 hours).

Table 1. Characteristics of 2,298 Patients With Appendiceal Pseudomyxoma Peritonei Treated With Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

Characteristic	No. of Patients	%
Age, years		
< 53	931	41
≥ 53	957	42
Unknown	410	17
Sex		
Male	1,305	57
Female	993	43
Time from diagnosis to cytoreduction, months		
0 to 6	857	37
7 to 23	412	18
≥ 24	306	13
Unknown	723	32
Prior surgical score		
0 to 2	1,170	51
3	319	14
Unknown	809	35
No. of prior operations		
0 to 1	997	43
≥ 2	165	7
Unknown	1,136	49
Prior chemotherapy		
No	963	42
Yes	377	16
Unknown	958	42
Histopathologic subtype		
DPAM	1,419	62
Hybrid	140	6
PMCA	700	30
Unknown	39	2
Lymph node metastasis		
No	2,050	89
Yes	138	6
Unknown	110	5
Peritoneal cancer index		
0 to 10	354	15
11 to 20	442	19
21 to 30	401	18
31 to 39	303	13
Unknown	798	35
CCR		
CCR 0	1,165	51
CCR 1	739	32
CCR 2 or 3	387	17
Unknown	7	0
Intraperitoneal chemotherapy regimen		
HIPEC and EPIC	668	29
HIPEC alone	1,382	60
EPIC alone	44	2
None	203	9
Unknown	1	0
Type of HIPEC		
MMC	1,784	77
Oxaliplatin	258	11
Others	12	1
None	242	11
Unknown	2	0
Major postoperative complications		
No (grade 0 to 2)	1,751	76
Yes (grade 3 to 5)	547	24
Specialized units' expertise		
Emerging	181	8
Established	2,117	92

(continued in next column)

(continued from previous column)

Table 1. Characteristics of 2,298 Patients With Appendiceal Pseudomyxoma Peritonei Treated With Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (continued)

Abbreviations: CCR, completeness of cytoreduction; DPAM, diffuse peritoneal adenomucinosis tumors; EPIC, early postoperative intraperitoneal chemotherapy; HIPEC, hyperthermic intraperitoneal chemotherapy; MMC, mitomycin C; PMCA, peritoneal mucinous carcinomatosis tumors.

Operative Complications of Cytoreduction

The postoperative mortality rate was 2% (43 of 2,298 patients). Major operative complications (grades 3, 4, or 5) occurred in 547 patients (24%), of which 283 patients (12%) had grade 3 and 221 patients (10%) had grade 4 complications. Factors associated with major operative complications include sex (female, 22%; male, 26%; $P = .015$), prior surgical score (PSS 0 to 2, 28%; PSS 3, 36%; $P = .004$), number of prior operations (0 to 1, 31%; ≥ 2, 46%; $P < .001$), PCI (≤ 20, 22%; > 20, 39%; $P \leq .001$), and the unit's level of expertise (established unit, 23%; emerging unit, 35%; $P < .001$). Logistic regression analysis identified three independent factors associated with major operative complications: prior surgical score of 3 (odds ratio [OR], 1.24; 95% CI, 1.1 to 1.5; $P = .006$), at least two prior operations (OR, 1.60; 95% CI, 1.1 to 2.4; $P = .019$), and PCI more than 20 (OR, 2.54; 95% CI, 1.9 to 3.4; $P < .001$).

Survival Outcomes

The median follow-up period was 36 months (range, 1 to 220) from the date of cytoreductive surgery. The median survival rate was 196 months (16.3 years) and the median progression-free survival rate was 98 months (8.2 years). The overall 3-, 5-, 10-, and 15-year survival rates were 80%, 74%, 63%, and 59%, respectively (Fig 1).

Prognostic factors associated with overall survival are presented in Table 2. When the variables were examined in univariate analysis with progression-free survival, the following factors were associated with progression-free survival: sex ($P < .001$), prior surgical score ($P < .001$), number of prior operations ($P < .001$), prior chemotherapy treatment ($P < .001$), time interval from diagnosis to cytoreduction ($P < .001$), tumor histopathology ($P < .001$), lymph node metastasis ($P < .001$), PCI ($P < .001$), CCR ($P < .001$), use of HIPEC ($P < .001$), use of EPIC ($P < .001$), and major postoperative complications ($P < .001$).

A multivariate analysis (Appendix Table A1; online only) with a Cox regression model was performed to determine independent predictors of progression-free survival. Prior chemotherapy treatment (hazard ratio [HR], 1.91; $P < .001$), PMCA histopathologic subtype (HR, 1.9; $P < .001$), major postoperative complications (grade 3 to 5; HR, 1.36; $P = .008$), higher peritoneal cancer index (HR, 1.38; $P = .013$), and debulking surgery (CCR2/3; HR, 2.11; $P < .001$) predicted for a poorer progression-free survival rate. The use of HIPEC (HR, 0.65; $P = .030$) was associated with favorable progression-free survival. Older age (age ≥ 53 years; HR, 1.53;

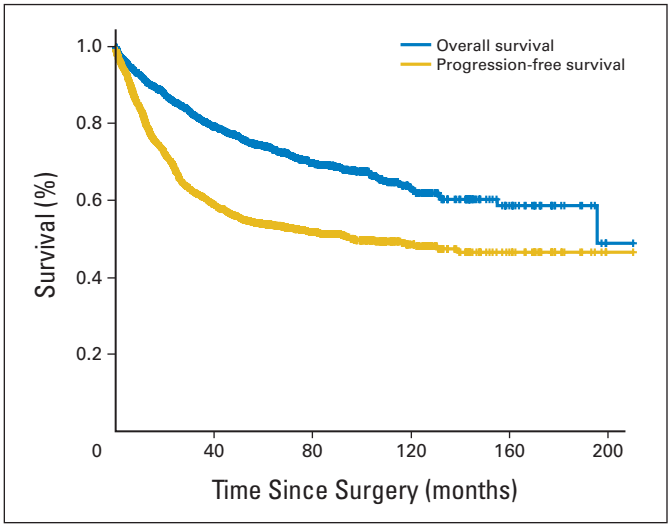

Fig 1. Overall survival and progression-free survival rates of 2,298 patients with appendiceal pseudomyxoma treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

$P = .006$), major postoperative complications (HR, 1.82; $P < .001$), debulking surgery (CCR2/3; HR, 2.09; $P < .001$), prior chemotherapy treatment (HR, 1.7; $P = .001$), and PMCA histopathologic subtype (HR, 1.69; $P < .001$) were independent predictors of poorer overall survival (Figs 2 and 3).

Subgroup Analysis of Overall Survival by Histopathologic Subtype

For this analysis, 1,559 patients with DPAM and hybrid tumors were classified as having low-grade appendiceal pseudomyxoma and 700 patients with PMCA were classified as having high-grade disease or appendiceal adenocarcinoma.

Univariate analysis of each tumor histopathologic subtype (low-grade appendiceal pseudomyxoma and appendiceal adenocarcinoma) is presented in Table 4. On multivariate analysis, older age (age $\geq$ 53 years; HR, 1.73; 95% CI, 1.1 to 2.8; $P = .024$), time from diagnosis to cytoreduction (HR, 1.42; 95% CI, 1.0 to 2.0; $P = .037$), major postoperative complications (HR, 2.67; 95% CI, 1.6 to 4.4; $P < .001$), and debulking surgery (HR, 2.87; 95% CI, 1.5 to 5.4; $P = .001$) were independently associated with poorer overall survival for patients with low-grade appendiceal pseudomyxoma. For patients with appendiceal adenocarcinoma, prior chemotherapy (HR, 1.75; 95% CI, 1.2 to 2.6; $P = .006$), higher PCI (HR, 1.38; 95% CI, 1.1 to 1.7; $P = .005$), and debulking surgery (HR, 3.20; 95% CI, 1.9 to 5.5; $P < .001$) were identified as independent predictors of poorer overall survival on multivariate analysis.

DISCUSSION

The combined modality strategy combining surgical cytoreduction and intraperitoneal chemotherapy was first introduced by Spratt et al[16] in the 1980s to treat peritoneal dissemination of cancer. It adopts a logical and rational approach to address the mechanism of peritoneal metastasis in a disease process such as pseudomyxoma peritonei. This treatment has superseded traditional debulking surgery in the

Table 2. Univariate Analysis of Overall Survival After Cytoreductive Surgery Plus Hyperthermic Intraperitoneal Chemotherapy in Patients With Appendiceal Pseudomyxoma

Variable	No. of Patients	Survival Data (%) 5-Year	10-Year	Log-Rank *P*
Age, years				.016
< 53	931	73	56	
≥ 53	957	68	55	
Sex				<.001
Male	1,305	70	55	
Female	993	77	68	
Time from diagnosis to cytoreduction, months				<.001
0 to 6	857	72	59	
7 to 23	412	66	50	
≥ 24	306	60	41	
Prior surgical score				.002
0 to 2	1,170	77	66	
3	319	67	57	
No. of prior operations				<.001
0 to 1	997	71	59	
≥ 2	165	59	20	
Prior chemotherapy				<.001
No	963	77	62	
Yes	377	52	34	
Histopathologic subtype				<.001
DPAM	1,419	81	70	
Hybrid	140	78	63	
PMCA	700	59	49	
Lymph node metastasis				<.001
No	2,050	76	64	
Yes	138	44	32	
Peritoneal cancer index				<.001
0 to 10	354	88	81	
11 to 20	442	83	75	
21 to 30	401	72	55	
31 to 39	303	64	56	
CCR				<.001
CCR 0	1,165	85	75	
CCR 1	739	80	69	
CCR 2 or 3	387	24	7	
HIPEC				<.001
No	242	40	27	
Yes	2,054	78	68	
Type of HIPEC				.218
MMC	1,784	78	66	
Oxaliplatin	258	82	78	
EPIC				<.001
No	1,580	69	57	
Yes	712	84	73	
Major postoperative complications				<.001
No (grade 0 to 2)	1,751	78	67	
Yes (grade 3 to 5)	547	63	48	
Specialized units' expertise				.091
Emerging	181	65	40	
Established	2,117	75	64	

Abbreviations: CCR, completeness of cytoreduction; DPAM, diffuse peritoneal adenomucinosis tumors; EPIC, early postoperative intraperitoneal chemotherapy; HIPEC, hyperthermic intraperitoneal chemotherapy; MMC, mitomycin C; PMCA, peritoneal mucinous carcinomatosis tumors.

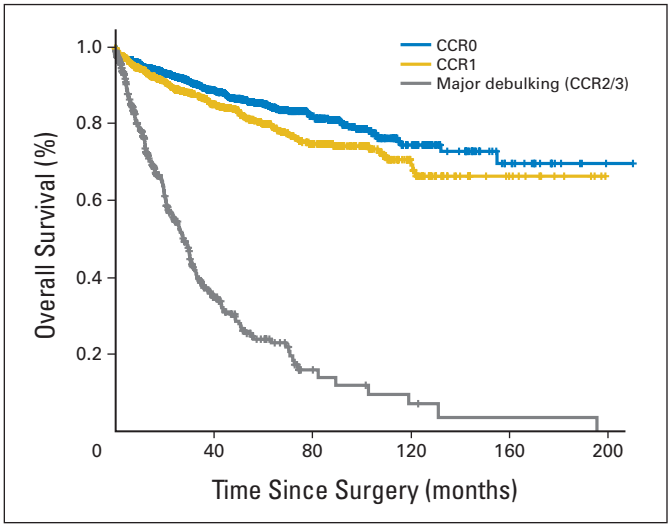

Fig 2. Prognostic impact of completeness of cytoreduction (CCR) in surgery on overall survival ($P < .001$).

management of this disease.[4,17] The early results indicate that long-term disease control and cure may potentially be achieved in a greater proportion of patients compared with debulking surgery.[18] Our retrospective, multi-institutional registry is the largest study of pseudomyxoma peritonei from appendiceal neoplasms and reports a median overall survival rate of 16.3 years with a 15-year survival rate of 59%. Importantly, the long median progression-free survival rate of 8.2 years demonstrates the efficacy of achieving disease control using this combined modality approach. A proportion of patients in this registry were previously reported in single institutional studies.[13,19-24]

From the analysis of the impact of clinical and treatment-related variables on outcomes, we demonstrate that for patients with an incomplete cytoreduction analogous to a debulking surgery (CCR2 or CCR3) in whom there is gross residual disease, the outcome is significantly poorer with a 5-year survival rate of 24% (in patients with CCR2 or CCR3) compared with 85% (CCR0 patients) and 80% (CCR1 patients). This difference remained significant when stratified by histopathologic subtype on multivariate analysis. The poor outcome of debulking surgery in both groups of patients provides compelling data to emphasize that a maximal cytoreduction may achieve long-term survival. Although in the article by Miner et al,[17] patients with incomplete cytoreduction achieved a median survival rate of 4.2 years, it is likely that this reflects a different patient mix, given that patients who are often referred to a cytoreductive surgical unit have failed previous surgical or medical therapy thus explaining the poorer outcome observed in patients who underwent incomplete cytoreduction in our study. Further, Miner et al[17] reported a median survival rate of 4 years and a 10-year survival rate of 10% for patients with appendiceal adenocarcinoma, of whom not all had a complete or optimal cytoreduction. This is in contrast with a 10-year survival rate of 49% reported in our registry study, in which the majority of patients had a complete (CCR0) or optimal (CCR1) cytoreduction. Comparing our results to those reported by Miner et al,[17] we show that combining cytoreduction and HIPEC may prove to be a treatment that delivers longer survival versus surgery alone. In particular, the multivariate analysis of progression-free survival demonstrates that HIPEC is associated with an improved rate of progression-free survival. However, when analyzed for overall survival, HIPEC was not shown to be a statistically significant independent factor. Therefore, the data suggest that HIPEC may improve disease control, however, optimal cytoreduction seems to be the strongest factor associated with long-term survival.

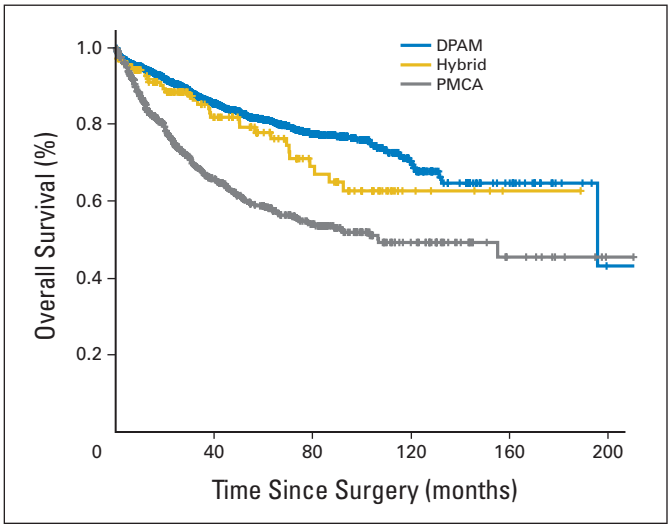

Fig 3. Prognostic impact of histopathologic subtype of appendiceal pseudomyxoma on overall survival ($P < .001$). DPAM, diffuse peritoneal adenomucinosis tumors; PMCA, peritoneal mucinous carcinomatosis tumors.

To achieve maximal cytoreduction requires technical expertise but may also be affected by patient factors. The results indicate that nondefinitive treatment with debulking operations is detrimental to outcome and also increases the rates of major postoperative complications. Prior debulking surgery results in the formation of intra-abdominal adhesions that makes subsequent cytoreduction technically challenging. Adhesion and scar tissues result in tumor entrapment that may result in a sanctuary site for disease progression. Chua et al[25] previously examined 83 consecutive patients with appendiceal pseudomyxoma who underwent cytoreductive surgery and intraperitoneal chemotherapy stratified by patients who were treated upfront primarily and those who were treated after prior debulking operations. They demonstrated that upfront treatment conferred a superior 5-year recurrence-free survival rate (77% *v* 37%; $P = .011$) and 10-year overall survival benefit (67% *v* 35%; $P = .054$).

In our study, the influence of the PCI remained a significant prognostic variable for both patients with low-grade appendiceal pseudomyxoma and appendiceal adenocarcinoma. For patients with appendiceal pseudomxyoma, though a high PCI is associated with poorer survival, it must be viewed in perspective, because even in patients with PCI ranging from 31 to 39, 5- and 10-year survival rates of 73% and 68%, respectively, may still be achieved. Likewise for patients with appendiceal adenocarcinoma, 5- and 10-year survival rates of 56% and 46%, respectively, may still be achieved despite high volume peritoneal disease. Therefore, patients with high volume disease from mucinous appendiceal neoplasms should still be referred to a specialized center for evaluation considering the potential survival benefit that may be achieved after cytoreduction. Further, the similar 5-year survival rate of 50% in the subset of patients with low-grade

Table 3. Univariate Analysis of Overall Survival After Cytoreductive Surgery Plus Hyperthermic Intraperitoneal Chemotherapy in Patients With Low-Grade Appendiceal Pseudomyxoma and Appendiceal Adenocarcinoma

Variable	Low-Grade Appendiceal Pseudomyxoma				Appendiceal Adenocarcinoma			
		Survival Data (%)				Survival Data (%)		
	No. of Patients	5-Year	10-Year	Log-Rank *P*	No. of Patients	5-Year	10-Year	Log-Rank *P*
Age, years				.010				.095
< 53	603	82	64		305	50	37	
≥ 53	701	76	64		240	45	31	
Sex				.001				.173
Male	633	78	59		340	55	48	
Female	926	83	75		360	62	51	
Time from diagnosis to cytoreduction, months				.001				.320
0 to 6	606	80	68		234	48	32	
7 to 23	288	75	59		119	45	30	
≥ 24	209	68	44		94	43	38	
Prior surgical score				.005				.043
0 to 2	747	84	72		407	64	54	
3	203	74	55		106	51	NR	
No. of prior operations				.027				.039
0 to 1	660	79	64		317	54	45	
≥ 2	79	71	19		78	42	20	
Prior chemotherapy				< .001				< .001
No	694	83	69		246	60	42	
Yes	168	70	48		193	31	18	
Lymph node metastasis				< .001				.026
No	1,475	81	69		556	62	52	
Yes	25	50	NR		112	43	35	
Peritoneal cancer index				< .001				.001
0 to 10	247	93	87		102	74	64	
11 to 20	293	90	79		138	70	64	
21 to 30	255	80	66		141	60	46	
31 to 39	161	73	68		137	56	46	
CCR				< .001				< .001
CCR 0	847	91	81		299	68	55	
CCR 1	470	85	73		264	72	62	
CCR 2 or 3	239	33	10		134	0	0	
HIPEC				< .001				< .001
No	159	50	33		73	18	10	
Yes	1,398	85	74		627	64	55	
Type of HIPEC				.154				.296
MMC	1,229	84	72		536	63	53	
Oxaliplatin	162	89	85		86	70	NR	
EPIC				< .001				< .001
No	1,060	76	63		486	53	45	
Yes	496	91	79		211	69	58	
Major postoperative complications				< .001				.304
No (grade 0 to 2)	1,270	84	73		452	59	48	
Yes (grade 3 to 5)	289	69	49		248	57	51	
Specialized units' expertise				.232				.299
Established	1,471	81	68		607	60	53	
Emerging	88	84	NR		93	50	17	

Abbreviations: CCR, completeness of cytoreduction; EPIC, early postoperative intraperitoneal chemotherapy; HIPEC, hyperthermic intraperitoneal chemotherapy; MMC, mitomycin C; NR, not reached.

histology but with positive lymph nodes compared with 43% in patients with appendiceal adenocarcinoma with positive lymph nodes may raise the need for disease reclassification.

The impact of prior chemotherapy as an independent predictor for poorer progression-free and overall survival rates may highlight a group of patients that had aggressive disease either with high volume tumor burden or PMCA histopathology that resulted in treatment with systemic chemotherapy before they were referred for cytoreduction. This was evident in the 377 patients who received preoperative chemotherapy; 51% had PMCA, 36% had DPAM, and 9% had hybrid disease. It is also likely that prior systemic chemotherapy may lead to the auto-selection of chemoresistant cellular clones. From the study reported by Shapiro et al,[26] who treated patients' appendiceal pseudomyxoma with systemic chemotherapy and selected a prespecified

subgroup of patients for cytoreductive surgery, the group that underwent surgery had a significantly improved survival. This reiterates that systemic chemotherapy is only indicated in the setting of unresectable disease or as an adjunct to cytoreductive surgery. In a recent prospective neoadjuvant chemotherapy protocol study, Sugarbaker et al[27] treated 34 consecutive appendiceal adenocarcinoma patients with neoadjuvant oxaliplatin and fluorouracil chemotherapy and observed that 65% of patients had stable disease on computed tomography imaging. However, intraoperatively, 50% of patients were judged to have disease progression with only 29% of patients having histologic response to chemotherapy. The discrepant results of patients whose disease progressed while on chemotherapy highlight the failure of current imaging modality to directly provide a mirror of the actual intra-abdominal peritoneal tumor volume that is determined intraoperatively.[28] Although the data may only be considered preliminary, it emphasizes the need for early definitive surgery before disease becomes unresectable.

In the French multicenter PMP registry study,[20] a center's experience was consistently shown to have an impact on treatment outcomes. In our study, the level of experience of a unit (stratified by fewer than or more than 10 years experience) did not significantly influence outcome. This may be in part because the participating units are established members of Peritoneal Surface Oncology Group International and the senior surgeons in the emerging units all had previously completed postfellowship training with other senior cytoreductive surgeons. This may explain the lower major postoperative complication rate of 24% compared with the rate of 40% observed in the French registry study of PMP[20] and a rate of 0% to 52% reported in a systematic review of the morbidity and mortality in the literature on cytoreductive surgery and intraperitoneal chemotherapy.[29] It must be emphasized that although the centers were categorized as established versus emerging, this definition constitutes only an individual center's experience with PMP. Several units that have been classified as emerging do, however, have significant experience with CRS for other peritoneal malignancies.

The role of EPIC appears to contribute favorably to overall survival. However, it is only used in some institutions because of its anticipated increase in length of hospital stay and potential complications. A collaborative multi-institutional trial[30] to compare the intensification of intraperitoneal chemotherapy treatment of both HIPEC and EPIC versus HIPEC alone after cytoreduction to explore the relative toxicity and survival outcome may be informative.

In summary, this is the largest multi-institutional registry study of cytoreductive surgery and HIPEC in patients with pseudomyxoma peritonei of appendiceal origin. Although the data are not randomized, our study provides compelling evidence for patients with mucinous appendiceal neoplasms to be managed with optimal cytoreductive surgery.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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