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Cytoreductive Surgery and Hyperthermic Intra-peritoneal Chemotherapy (HIPEC) in the Treatment of *Pseudomyxoma peritonei*: Ten Years Experience in a Single Center

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Abstract. *Background: Pseudomyxoma peritonei (PMP) is a rare and fatal disease for which no standard treatment has been established. Encouraging results have been recently reported with the combination of cytoreductive surgery (CRS) and hyperthermic intra-peritoneal chemotherapy (HIPEC). Patients and Methods: Seventy-five patients with PMP underwent CRS and closed abdomen HIPEC with mytomicin-C and cis-platinum over 10 years at a single institution. Potential clinicopathological prognostic variables were tested using multivariate analysis. Results: Optimal cytoreduction (residual tumor nodules ≤2.5 mm) was performed in 72 patients (96%). Operative mortality was 1%. Five-year overall (OS) and progression-free (PFS) survival were 78.3% and 31.1% in the overall series, respectively. Optimal CRS, no previous systemic chemotherapy and low histological aggressiveness were independent predictors of better OS and PFS using multivariate analysis. Conclusion: Favourable outcome after CRS and HIPEC can be expected in patients affected by PMP variants with low histological aggressiveness, undergoing optimal surgical cytoreduction and with no pre-operative systemic chemotherapy.*

Pseudomyxoma peritonei (PMP) is a rare disease entity characterized by peritoneal dissemination of mucinous tumour implants and abundant mucinous ascites originating from benign or low malignant appendiceal epithelial neoplasms (1).

PMP usually shows a protracted clinical course, being traditionally managed by repeated surgical debulking until no further benefit can be achieved. Both systemic and intra-peritoneal CT are only palliative. Long-term prognosis is poor and death ultimately occurs as a consequence of intra-abdominal disease progression (1).

Better knowledge of natural history and the recent evolution of loco-regional therapies has led to a new combined approach to peritoneal malignancies. It combines aggressive cytoreductive surgery (CRS), aiming at complete tumor removal, along with loco-regional heated chemotherapy to treat microscopic residual disease, namely hyperthermic intra-peritoneal chemotherapy (HIPEC) (2). Ongoing experience suggests a survival benefit for selected patients with PMP as several phase I and II prospective trials have registered 5-year overall survival of 75 to 97% (2-6).

The preliminary results of the first 33 patients with PMP treated in our institution with CRS and HIPEC were previously reported (6). The aim of the present study was to provide a detailed analysis of a ten-year case series with longer follow-up, paying special attention to prognostic clinicopathological variables.

Patients and Methods

All the patients included in the present study were treated according to a protocol approved by the Institutional Ethics Committee with written informed consent. Diagnosis of PMP was made or confirmed in our Pathology Department for each patient.

The details of the operative technique adopted in our center were previously described (6). Briefly, one to six of the following procedures were performed to remove all the visible disease: i) right parietal peritonectomy, right hemy-colectomy, greater omentectomy; ii) pelvic peritonectomy, sigmoid colectomy, hystero-annessectomy; iii) antrectomy, cholecystectomy, lesser omentectomy, hepatic hilum dissection; iv) right sub-diaphragmatic peritonectomy, Glisson's capsule dissection; v) left sub-diaphragmatic peritonectomy, splenectomy, left parietal peritonectomy; vi) other intestinal and/or abdominal mass resections.

HIPEC was performed according to the closed abdomen technique for 60 min, at a temperature of 42.5°C, with cis-platinum

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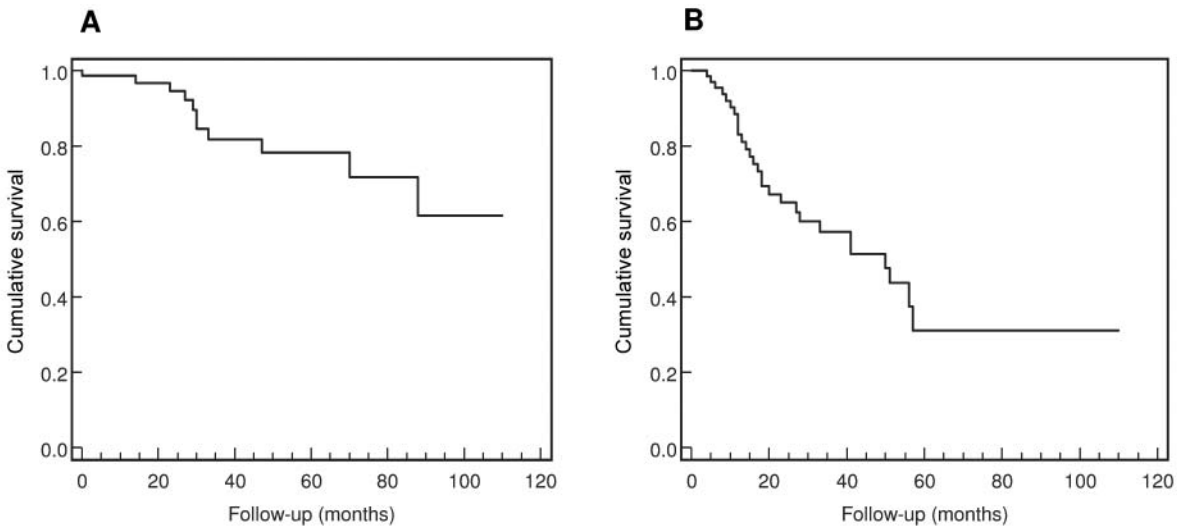

Figure 1. *Overall (A) and progression-free (B) survival in the overall series of 75 patients with pseudomyxoma peritonei.*

(25 ml/mq/L) plus mitomycin-C (3.3 mg/mq/L). Perfusate volume was 4-6 L and average flow 700 mL/min.

Histological aggressiveness was classified into disseminated peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis (PMCA) and peritoneal mucinous carcinomatosis with intermediate or discordant features (PMCA-ID) according to Ronnett *et al.* (7).

The extent of previous surgical procedures was rated according to the Prior Surgical Score (PSS): 0=only biopsy; 1=one abdominopelvic region dissected; 2=2-5 regions dissected; 3=>5 regions dissected (2). Pre-operative patient performance status was classified according to the Eastern Cooperative Oncology Group (ECOG) score (8). The extent of peritoneal involvement was scored at surgical exploration according to the Peritoneal Cancer Index (PCI) (9). The completeness of cytoreduction (CC) was classified at the end of the surgical phase, according to Sugarbaker: 0=no residual disease; 1=residual disease ≤2.5mm; 2=residual disease >2.5 mm ≤2.5 cm; 3=residual disease >2.5 cm (10).

Overall (OS) and progression-free survival (PFS) were calculated from surgery to the time of death or post-operative disease progression, according to the Kaplan-Meier method (11). Patients with an uneventful post-operative course were censored at last follow-up visit. The log-rank test was used to assess the significance of the survival distribution. On the basis of univariate analysis, significant variables were included in a Cox proportional hazard model for multivariate analysis (12). A p-value <0.05 was considered significant.

Results

From June 1996 to June 2006, 75 patients underwent CRS and HIPEC. Thirty-four were males and 41 females. Median age was 57 (range 24-76). ECOG performance status was 0 in 55 patients, 1 in 19 and 2 in 1. PSS was 0 in 18 patients, 1 in 9, 2 in 37 and 3 in 11. Twenty patients underwent systemic CT before admission to our center.

The average number of peritonectomy procedures was 5.1 (range 2-6). Seventy-two (96%) patients underwent optimal cytoreduction (CC-0 in 52 and CC-1 in 20). Two patients were scored as CC-2; 1 as CC-3. Sixty-two patients were diagnosed with DPAM, 13 with PMCA; no PMCA-ID was observed. One patient died 21 days after the procedure due to duodenal perforation and bleeding. Major complications requiring re-operation, ICU admission or interventional radiology occurred in 10 patients (13.3%).

Median follow-up was 37 months (range 1-110 months). Five-year OS and PFS were 78.3% and 31.1% in the overall series, respectively (see Figure 1). PMP relapsed in 28 patients after a median of 16 months (range 4-57 months), involving the abdomen in 21 patients, the pleural cavity in 4 and both in 3. Eight patients died after a median of 30 months (range 14-88 months). Results from univariate and multivariate analysis are displayed in Table I: DPAM histological variant, no previous systemic CT and optimal (CC-0/1) surgical cytoreduction were independent prognostic factors for both OS and PFS.

Discussion

In spite of its slow intra-abdominal growth, PMP is regarded as a lethal condition. In the historical case series of the Mayo Clinic 10-year survival was 32% (13).

The combination of CRS and HIPEC has been recently advocated as the new standard care for PMP (1). Such an innovative approach involves complete tumor removal by mean of peritoneum stripping and visceral resections. Intra-operative heated loco-regional CT is combined with surgery to sterilize residual mucinous tumor nodules and to avoid entrapment of tumor cells in early post-operative scars (1-2).

Table I. *Univariate and multivariate analysis of factors influencing overall and progression-free survival in 75 patients with pseudomyxoma peritonei.*

		Overall survival			Progression-free survival		
	N°	Univariate *p*-value	Hazard ratio (95% CI)	Cox proportional *p*-value	Univariate *p*-value	Hazard ratio (95% CI)	Cox proportional *p*-value
Gender							
M	34	0.131			0.806		
F	41						
Age							
≤57 yrs	37	0.715			0.123		
>57 yrs	38						
Histological subtype							
DPAM	62	0.024	6.24	0.014	0.016	3.31	0.006
PMCA	13		(1.46-26.71)			(1.40-7.83)	
Previous systemic CT							
Yes	20	0.004	4.45	0.025	0.022	2.28	0.037
No	55		(1.21-16.32)			(1.05-4.94)	
Performance status							
0	55	0.373			0.640		
1-2	20						
Previous surgical score							
0-1	18	0.028			0.517		
2-3	55						
PCI							
≤25	14	0.917			0.961		
>25	61						
CC							
0-1	62	0.026	6.05	0.032	0.002	7.38	0.003
2-3	3		(1.17-31.24)			(1.96-27.85)	

DPAM: disseminated peritoneal adenomucinosis; PMCA: peritoneal mucinous carcinomatosis; CT: chemotherapy; PCI: peritoneal cancer index; CC: completeness of cytoreduction score; CI: confidence interval.

The procedure, however, is expensive in terms of financial resources, operative time and technological facilities. In the literature, morbidity and mortality rates are 12-55% and 0-12%, respectively. Bowel perforation and anastomotic leakage are the most common adverse events (1). The 30-day post-operative morbidity rate was 12% in a series of 205 patients treated in our institution for carcinomatoses of different origins. Nevertheless, only 2 patients (1%) died for treatment-related complications (14). In this context, the patient selection is of great importance to maximize the clinical results.

In the present study, potential clinicopathological prognostic factors were assessed by multivariate analysis in a relatively large case series uniformly managed by CRS and HIPEC. DPAM histological variant, no previous CT and optimal cytoreduction with residual tumor nodules ≤2.5 mm were recognized as independent determinants of favourable outcome.

To date, CRS and HIPEC have been evaluated for PMP in few centers (2-6). The largest series was reported by Sugarbaker, including 205 patients who underwent HIPEC with mitomycin-C and post-operative intraperitoneal 5-fluorouracil and 180 treated with early intraperitoneal CT (2). Completeness of cytoreduction, histopathology and PSS were related to survival at multivariate analysis.

It has been demonstrated that the penetration of hyperthermic chemotherapeutic agents into tumor tissue is limited to a few millimeters (1). Thus, it is not surprising that surgical cytoreduction leaving behind no or minimal residual disease is needed to completely eradicate PMP.

The dissemination pattern of PMP has been defined as a redistribution phenomenon, indicating that tumor cells with low biological aggressiveness distribute within the abdominal cavity following mucinous fluid flow. This results in tumor deposits at anatomic sites which can be easily cleared (6). Conversely, cells with moderate invasiveness are able to infiltrate mesentery or bowel surfaces hampering adequate cytoreduction.

The prognostic impact of previous CT could be explained by the fact that only patients whose disease was perceived as highly aggressive received such treatment. A selection bias could have occurred in that setting.

In conclusion, the combination of CRS and HIPEC confirmed its efficacy in the treatment of PMP. We propose histological aggressiveness, completeness of surgical cytoreduction and no pre-operative systemic chemotherapy as selection factors predicting clinical outcome.

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