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ORIGINAL ARTICLE

Long-term outcomes and survival analysis of cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy in patients with pseudomyxoma peritonei at a newly established peritoneal malignancy centre in Japan

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Abstract

Background: Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is established in the management of pseudomyxoma peritonei (PMP), selected cases of peritoneal mesothelioma, and resectable colorectal or ovarian peritoneal metastases in Western countries. However, the efficacy and feasibility of these techniques are not well established in the Asian population, and little has been reported on long-term survival outcomes for surgically resected PMP patients.

Materials and Methods: Retrospective analysis of a prospective database of short- and longer-term outcomes of consecutive patients who underwent CRS and HIPEC for PMP in a newly established peritoneal malignancy unit in Japan between 2010 and 2016.

Results: A total of 105 patients underwent CRS and HIPEC and 57 maximal tumor debulking (MTD) for pseudomyxoma peritonei. In the CRS group, the primary tumor was appendiceal in 94 patients (90%) followed by ovarian and colorectal. Major postoperative complications occurred in 22/105 patients (21%) with one in-hospital mortality (0.9%). The 5-year overall and disease-free survival rates for the CRS group were 74.2% and 50.1%, respectively. Multivariate analysis revealed unfavorable histology to be the significant predictor of reduced overall and disease-free survival. Completeness of cytoreduction, CA19-9, and CA125 were also associated with disease-free survival.

Conclusions: This is the first report on long-term outcomes and survival analysis of CRS and HIPEC for PMP in the Asian population. CRS and HIPEC can be conducted with reasonable safety and favorable survival in a new center. Complete tumor removal and histological type are the strongest prognostic factors for both overall and disease-free survival.

KEYWORDS
appendiceal tumor, cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, pseudomyxoma peritonei

1 | INTRODUCTION

Pseudomyxoma peritonei (PMP) is an uncommon malignancy with an estimated incidence of 2–3 per million per year.[1,2] PMP classically originates from a ruptured mucinous tumor of the appendix and is characterized by diffuse peritoneal spread with copious mucinous ascites.[3]

Cytoreductive surgery (CRS) combined with hyperthermic, intraoperative, intraperitoneal chemotherapy (HIPEC), first reported by Spratt et al.[4] and developed and popularized by Sugarbaker,[5] is now considered the optimal treatment and standard of care for selected patients with various peritoneal malignancies in Western countries.[6,7] CRS and HIPEC are performed with curative intent for patients with otherwise fatal outcomes and involve the removal of macroscopic tumor (cytoreductive surgery) with extensive stripping of the peritoneum and/or resection of involved non-vital organs, combined with HIPEC to address residual microscopic disease.[5] Although CRS and HIPEC are effective for selected patients with various peritoneal malignancies including colorectal peritoneal metastases,[6,8,9] peritoneal mesothelioma,[7] and ovarian cancer,[10] the best outcomes can be achieved in patients with PMP.[11,12]

Funding for CRS and HIPEC is not covered by national insurance in Japan despite widespread approval in western countries.[13] There has been persistent skepticism, particularly in the surgical and oncological community, about CRS and HIPEC, thus affecting government approval of these modalities. The main criticisms include lack of evidence, low cost-effectiveness, and surgical morbidity and mortality associated with these complex procedures. In the Japanese and Asian context, it seems important to provide clinical outcomes of CRS and HIPEC for PMP alone in the first instance. The techniques and outcomes in PMP will be the foundation on which clinical evidence is based for other peritoneal malignancies.

This paper aims to present data on short- and long-term outcomes of a consecutive series of patients who underwent CRS and HIPEC for PMP at a newly established peritoneal malignancy centre in Japan. To the best of our knowledge, this is the first robust report from Asia on the long-term outcomes with a multivariate analysis of a significant number of a consecutive series of patients with PMP.

2 | MATERIALS AND METHODS

2.1 | Study overview

This was a retrospective analysis of consecutive patients treated for PMP at a peritoneal malignancy service at the National Center for Global Health and Medicine (NCGM) between March 2010 and December 2016. The lead surgeon (HY) conducted a 2-year fellowship in an established peritoneal malignancy center before commencing the service in Tokyo with the involvement of a senior surgeon from the established center (BJM) in the initial cases.

This study was approved by the local ethics committee of the NCGM (Approval no: NCGM-G-001435-04) and conducted according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients prior to surgery. All the data regarding patient demographics, clinico-pathological variables, operative outcomes, and oncological outcomes were collected and extracted from an anonymized computer database.

2.2 | Preoperative workup

All patients who were referred to the NCGM for treatment of PMP underwent computed tomography (CT) of the chest, abdomen, and pelvis to assess disease extent and spread. Serum tumor markers including carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), and carbohydrate antigen 125 (CA125) were also routinely obtained. All patients were discussed in a multidisciplinary team meeting and assessed regarding the feasibility of surgery. Surgery was recommended if (1) complete tumor removal was thought to be feasible based on preoperative images or (2) the patient had major symptoms from abdominal distension and/or abdominal mass. Exclusion criteria for CRS and HIPEC included age above 80 years, poor performance status, and significant medical comorbidities. All patients who underwent surgery for PMP were included in the analysis.

2.3 | Surgery

On laparotomy, the extent of disease spread was recorded using the Peritoneal Cancer Index (PCI).[14] PCI was originally designed to assess the extent of disease spread and for prognostication in patients with carcinomatosis, where the score ranging from 0 to 39 is given as the sum of lesion score from 0 to 3 in each of 13 regions. More recently PCI has been utilized in patients with PMP as a useful score for outlining the extent of disease but does not correlate with resectability or prognosis as PCI does in other malignancies such as colorectal or gastric peritoneal metastases.

If significant involvement of (a) the small bowel and its mesentery and/or (b) the hepatoduodenal ligament was noted, then major tumor debulking (MTD) was performed with a view to alleviating symptoms, mostly in the form of greater omentectomy with extended right hemicolectomy or subtotal colectomy with an end ileostomy.

Otherwise, if the patient's physiology was suitable, CRS and HIPEC were performed. Right and left parietal peritonectomies were routinely performed to gain access to the retroperitoneum and to locate the ureters and major lower limb vessels. Peritonectomy was continued by stripping the urinary bladder of its peritoneum and, if the rectum and/or sigmoid were heavily infiltrated by disease, a rectal resection was also performed. In women, the uterus and both ovaries, if not previously excised, were generally removed via total abdominal hysterectomy and bilateral salpingo-oophorectomy. The greater and lesser omentum and falciform ligament were resected. The appendix was removed either via appendicectomy, caecectomy, or ileocaecal resection as required. The liver was mobilized to facilitate right diaphragmatic peritonectomy and the hepatoduodenal ligament was stripped of its peritoneum. The gallbladder, left diaphragmatic peritoneum, and right and left liver capsule were removed if necessary. When performing the diaphragmatic peritonectomy, the inferior phrenic artery was routinely ligated to reduce the risk of postoperative bleeding. Further visceral resections, depending on the disease extent, included splenectomy combined with left diaphragmatic peritonectomy and distal or total gastrectomy.

The presence of residual disease was recorded using the Completeness of Cytoreduction (CC) score as follows: CC-0, no residual tumor; CC-1, residual tumor up to 2.5 mm; CC-2, residual tumor nodules up to 25 mm; and CC-3, residual tumor greater than 25 mm.[15] Patients were defined as having undergone complete cytoreductive surgery (CCRS) if either CC-0 or CC-1 was achieved.

Following CCRS, mitomycin C perfusion was administered at a dose of 10 mg/m^2, heated to 42–43°C, for 1 h using the open coliseum technique.

Postoperative morbidity and mortality were recorded and graded into five categories based on the treatment or intervention that was required to correct the adverse events according to the Clavien–Dindo classification.[16]

2.4 | Histopathology

Histological classification of the resected specimen was conducted according to the consensus of the Peritoneal Surface Oncology Group International[17] and the specimens were categorized into four groups: (a) acellular mucin, (b) low-grade, (c) high-grade, and (d) high-grade with signet ring cells. In our study, we adopted a binary categorization defining “acellular mucin” and “low grade” as favorable histology whilst “high-grade” and “high-grade with signet ring cells” as unfavorable histology.

2.5 | Follow-up

All patients were followed up at the NCGM, or locally, with 3-monthly serum tumor marker assessment of CEA, CA19-9, and CA125 and with 6-monthly CT scans. Diagnosis of recurrence is not always straightforward, and, in this study, recurrence was diagnosed when either the level of at least one of the tumor markers rose steadily and/or the CT imaging showed progression of abnormalities over time irrespective of the amount of fluid visualized on CT.

2.6 | Statistics

Statistical analysis was performed using STATA version 15 (StataCorp, College Station, Texas). Numerical values are expressed as median and range unless otherwise specified. Chi-squared test or Fisher's exact test was used to compare categorical variables and Mann–Whitney *U* test was used to compare continuous variables. Kaplan–Meier survival analysis was used to calculate overall and disease-free survival. Death from any cause was counted as an event in the overall and disease-free survival analyses. Survival curves were compared using the log-rank test and multivariate analysis was conducted to identify significant risk factors for survival using the Cox proportional hazards model. All variables that were significant ($p < 0.05$) were included in the multi-variate analysis and step-wise regression analysis was conducted. *p*-Value of less than 0.05 was regarded as statistically significant.

3 | RESULTS

3.1 | Patients

During the study period (2010–2016), 285 patients with PMP were referred to the NCGM and 171 underwent a laparotomy. Of these, 105/171 (61%) underwent complete CRS and HIPEC (CCRS) with curative intent (CC-0 or CC-1), 57 underwent MTD (CC-2 or CC-3), six underwent exploratory laparotomy only, two had a loop ileostomy, and one underwent intestinal bypass surgery. The reasons for not achieving complete cytoreduction in MTD cases were predominantly anatomical in 46 patients (small bowel involvement in 27, gross involvement of the hepatoduodenal ligament in 27, with some overlap), physiological (age and/or comorbidities) in nine, and iatrogenic in two (one major bleeding from the inferior vena cava and one uncontrollable bleeding from intraoperative coagulopathy).

Table 1 shows the demographics of the 162 patients who underwent major resectional surgery in the form of either CCRS ($n = 105$) or MTD ($n = 57$). The median age of CCRS group was 59 years (range, 24–80), significantly younger than MTD group. Two-thirds of the CCRS group were women whilst men were predominant in the MTD group. Amongst the CCRS group, 94/105 cases (90%) were appendiceal in origin, with six originating from the ovary and with five miscellaneous primaries, predominantly colorectal cancer (two descending colon, one ascending colon, one sigmoid colon, and one intestinal duplication).

TABLE 1 Patient demographics and perioperative outcomes.

Characteristics	CCRS ($n=105$)	MTD ($n=57$)	p Value
Age (years)	59 (24–80)	69 (35–84)	0.002
Sex			
Male	36	32	<0.001
Female	69	25	
Body mass index (kg/m^2)[a]	23 (14–35)	22 (16–35)	0.660
ASA-PS			
1	24	7	0.012
2	73	37	
3	8	13	
Primary site			
Appendix	94	55	0.296
Ovary	6	1	
Others	5	1	
Preoperative tumor markers			
CEA (ng/mL)	13.9 (1.0–4396.2)	52.5 (2.4–4908.0)	0.060
CA19-9 (U/mL)	14.3 (0.4–8935.7)	64.1 (0.4–9191.0)	0.030
CA125 (U/mL)	33.2 (6.6–278.1)	69.9 (8.0–617.9)	<0.001
PCI	28 (3–39)	35 (24–39)	<0.001
CC score			
0	68	0	-
1	37	0	
2	0	4	
3	0	53	
Operation time (h)	11.5 (6–18)	5.5 (3–17)	<0.001
Blood loss (mL)	924 (30–26 050)	400 (10–7014)	0.067
Length of intubation (days)	2 (0–10)	1 (0–10)	<0.001
Length of ICU stay (days)	6 (2–40)	3 (0–10)	<0.001
Length of hospital stay (days)	26 (10–188)	20 (9–98)	0.041
Postoperative complications (CD)			
None	41	39	0.021
Grade I/II	42	15	
Grade III (IIIa/IIIb)	17 (16/1)	2 (2/0)	
Grade IV (IVa/IVb)	4 (3/1)	1 (1/0)	
Grade V (mortality)	1	0	
Histological grade			
Acellular mucin	19	1	0.008
Low-grade	41	19	
High-grade	31	25	
High-grade + signet ring cells	14	12	

Note: Continuous variables are expressed as median (range).

Abbreviations: ASA-PS, American Society of Anesthesiologists physical status; CC, completeness of cytoreduction; CCRS, complete cytoreductive surgery; CD, Clavien–Dindo; ICU, intensive care unit; MTD, major tumor debulking; PCI, peritoneal cancer index.

[a]This includes ascites.

3.2 | Operative and perioperative outcomes

In the 105 patients who underwent CCRS, low anterior resection was required in 63 and right hemicolectomy or total colectomy in 98. Hysterectomy ± oophorectomy was performed in all 55 females excluding 14 patients who had had previous hysterectomy. Splenectomy was required in 85 patients and total or distal gastrectomy in nine.

Perioperative findings and outcomes are also shown in Table 1. The median PCI in the CCRS group was 28, significantly lower than in the MTD group. CC-0 was achieved in 68 patients and CC-1 in

37 patients. Major postoperative complications (Clavien–Dindo Grade III/IV/V) occurred in 22 patients (21%) in the CCRS group. Four patients developed Grade IV events including respiratory failure and intra-abdominal hemorrhage. The most common Grade III events were intra-abdominal hemorrhage and pancreatic fistula, all of which were successfully controlled with interventional radiology. No patients returned to theater. There was no 30-day postoperative mortality; however, one patient died suddenly on day 42 when the discharge plan was in place after a slow but steady postoperative recovery. This was thought to be likely to be due to a known ischaemic heart condition, but post-mortem examination was refused.

3.3 | Oncological outcomes

Histological examination of the resected specimens revealed 19 patients with "acellular mucin", 41 patients with "low-grade", 31 patients with "high-grade", and 14 patients with "high-grade with signet-ring cells" in the CCRS group which showed less aggressive histology compared with the MTD group (Table 1).

The median follow-up period for the 105 patients who had CCRS was 60 (1–137) months. None of the CCRS group were lost to follow but 2/57 who had MTD could not be contacted at the time of manuscript preparation.

The 5-year overall survival rate for the CCRS group was 74.2% compared with 25.2% for the MTD group ($p < 0.001$) (Figure 1A).

Of the 105 patients in the CCRS group, 44 (42%) were diagnosed with recurrence at a median of 18 (3–60) months after surgery. All but three patients had peritoneal recurrence; one had liver metastasis at 4 months postoperatively and two had pleural recurrence. The 5-year disease-free survival rate was 50.1% for the 105 patients who had CCRS (Figure 1B).

Univariate analysis revealed female sex, elevated CEA, elevated CA19-9, elevated CA125, CC-1 and unfavorable histology to be significant adverse prognostic factors for overall survival (Table 2). On multivariate analysis, histological type was identified as the only significant independent predictor of overall survival (hazard ratio, 4.23).

When univariate analysis was conducted for disease-free survival, elevated CEA, elevated CA19-9, elevated CA125, greater PCI, CC-1, longer operation time and unfavorable histology were significantly associated with poorer disease-free survival (Table 3). Multivariate analysis revealed histological type to be the strongest predictor of disease-free survival (hazard ratio, 4.66) followed by CA125 (hazard ratio, 2.30), CA19-9 (hazard ratio, 2.08), and CC-score (hazard ratio, 1.95).

Figure 2 shows survival according to histology for patients who underwent CRS and HIPEC. The 5-year overall and disease-free survival rates for 60 patients with favorable histology were 88.4% and 73%, which were significantly better than 55.3% and 21% for 45 patients with unfavorable histology ($p < 0.001$).

4 | DISCUSSION

In the current study we reviewed the short- and medium- to long-term outcomes of the initial consecutive series of patients with PMP in a newly established peritoneal malignancy unit in Japan. We also conducted multivariate survival analysis to identify significant prognostic factors. Complete tumor removal by CRS and HIPEC was achieved in 105 patients with 21% major morbidity and 0.9% mortality. The 5-year overall and disease-free survival rates for the 105 patients who had CRS and HIPEC were 74.2% and 50.1% and unfavorable histology was shown to be the strongest prognostic factor for reduced overall and disease-free survival on multivariate analysis.

Previous larger studies comprising more than 100 patients who underwent complete CRS for PMP are listed in Table 4, illustrating the perioperative outcome and survival in each series.[18–24]

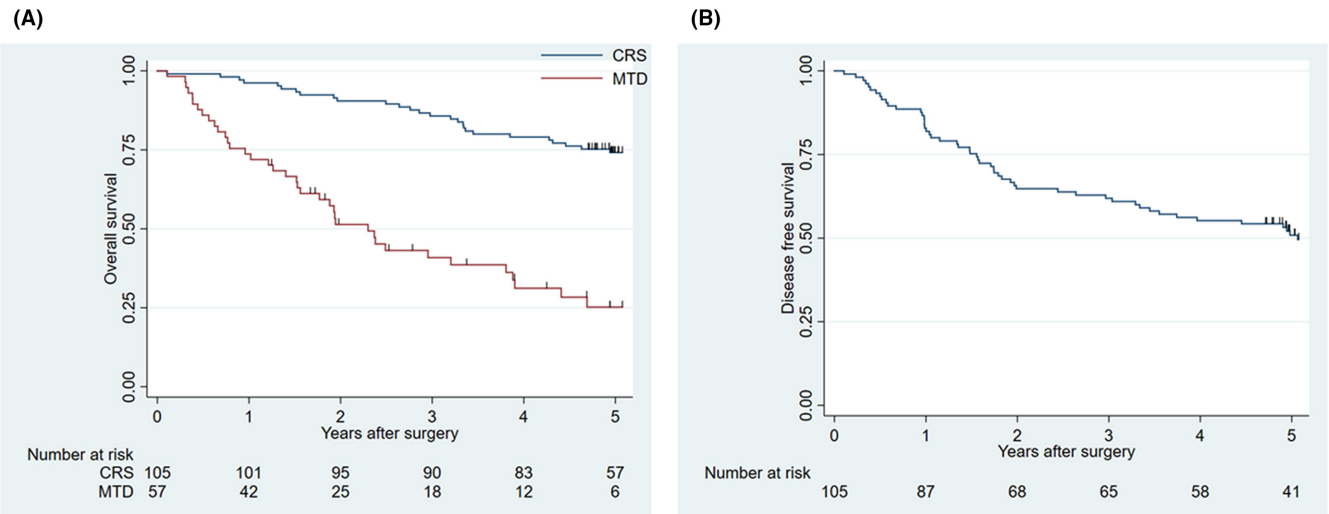

FIGURE 1 (A) Overall survival curves for the patients who underwent CRS and HIPEC versus MTD. (B) Disease-free survival curve for the patients who underwent CRS and HIPEC.

TABLE 2 Univariate and multivariate analyses of factors affecting overall survival in patients who underwent CRS and HIPEC.

		Univariate analysis			Multivariate analysis		
Variables	No. of patients	5-year overall survival	95% CI	*p* Value	HR	95% CI	*p* Value
Age, years				0.281			
<60	59	79.4	66.7–87.8				
≥60	46	67.3	51.9–78.9				
Sex				0.047			
Male	36	86.1	69.8–94.0				
Female	69	68.0	55.5–77.6				
BMI				0.632			
<25	85	73.9	63.1–82.0				
≥25	17	70.6	43.1–86.6				
ASA-PS				0.844			
1	24	82.6	60.0–93.1				
≥2	81	71.6	60.4–80.1				
Primary site				0.412			
Appendix	94	73.3	63.0–81.1				
Others	11	81.8	44.7–95.1				
CEA				0.016			
<5	32	93.8	77.3–98.4				
≥5	73	65.6	53.4–75.3				
CA19-9				0.012			
<37	66	84.9	73.7–91.5				
≥37	39	56.0	39.1–70.0				
CA125				0.019			
<35	54	83.3	70.4–91.0		Reference		
≥35	49	63.1	48.0–74.9		1.93	0.91–4.01	0.086
PCI				0.055			
<25	36	82.8	65.6–91.9				
≥25	49	69.6	57.2–79.0				
CC score				0.016			
CC-0	68	79.1	67.3–87.1		Reference		
CC-1	37	64.9	47.3–77.9		1.88	0.92–3.85	0.082
Operation time				0.207			
<720	59	77.6	64.5–86.4				
≥720	46	69.6	54.1–80.7				
Postoperative ICU stay				0.211			
<7	85	77.4	67.0–85.0				
≥7	20	60.0	35.7–77.6				
Postoperative hospital stay				0.484			
<28	62	77.2	64.5–85.8				
≥28	43	69.8	53.7–81.2				
Morbidity (C-D Grade)				0.555			
0/I/II	83	75.7	64.9–83.6				
III/IV/V	22	68.2	44.6–83.4				
Histology				0.000			
Favorable	60	88.3	77.1–94.3		Reference		
Unfavorable	45	55.4	39.7–68.5		4.23	1.92–9.33	0.000

Abbreviations: ASA-PS, American Society of Anesthesiologists physical status; BMI, body mass index; CC, completeness of cytoreduction; C-D, Clavien–Dindo classification; CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; PCI, peritoneal cancer index.

TABLE 3 Univariate and multivariate analyses of factors affecting disease-free survival in patients who underwent CRS and HIPEC.

		Univariate analysis			Multivariate analysis		
Variables	No. of patients	5-year disease-free survival	95% CI	*p* Value	HR	95% CI	*p* Value
Age, years				0.216			
<60	59	46.6	33.3–58.8				
≥60	46	56.5	41.1–69.4				
Sex				0.084			
Male	36	63.2	45.0–76.8				
Female	69	44.4	32.4–55.8				
BMI				0.799			
<25	85	51.3	40.2–61.4				
≥25	17	45.4	20.9–67.1				
ASA-PS				0.946			
1	24	49.4	28.1–67.3				
≥2	81	51.4	39.9–61.7				
Primary site				0.744			
Appendix	94	51.8	41.2–61.4				
Others	11	43.6	14.7–69.8				
CEA				0.006			
<5	32	71.1	51.5–83.8				
≥5	73	42.1	30.7–53.2				
CA19-9				0.000			
<37	66	66.4	53.6–76.5		Reference		
≥37	39	25.1	12.7–39.5		2.08	1.15–3.75	0.015
CA125				0.002			
<35	54	66.7	52.4–77.5		Reference		
≥35	49	36.1	22.9–49.5		2.30	1.27–4.13	0.006
PCI				0.007			
<25	36	69.4	51.7–81.8				
≥25	49	41.3	29.5–52.7				
CC score				0.002			
CC-0	68	59.6	46.8–70.3		Reference		
CC-1	37	34.9	20.2–50.1		1.95	1.10–3.47	0.021
Operation time				0.018			
<720	59	60.1	46.2–71.5				
≥720	46	39.0	25.1–52.7				
Postoperative ICU stay				0.809			
<7	85	51.1	39.9–61.2				
≥7	20	50.0	27.1–69.2				
Postoperative hospital stay				0.179			
<28	62	55.7	42.3–67.2				
≥28	43	44.2	29.2–58.2				
Morbidity (C-D Grade)				0.512			
0/I/II	83	51.3	40.0–61.5				
III/IV/V	22	50.0	28.2–68.4				
Histology				0.000			
Favorable	60	72.7	59.3–82.4		Reference		
Unfavorable	45	21.4	10.6–34.6		4.66	2.42–8.95	0.000

Abbreviations: ASA-PS, American Society of Anesthesiologists physical status; BMI, body mass index; CC, completeness of cytoreduction; C-D, Clavien–Dindo classification; CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; PCI, peritoneal cancer index.

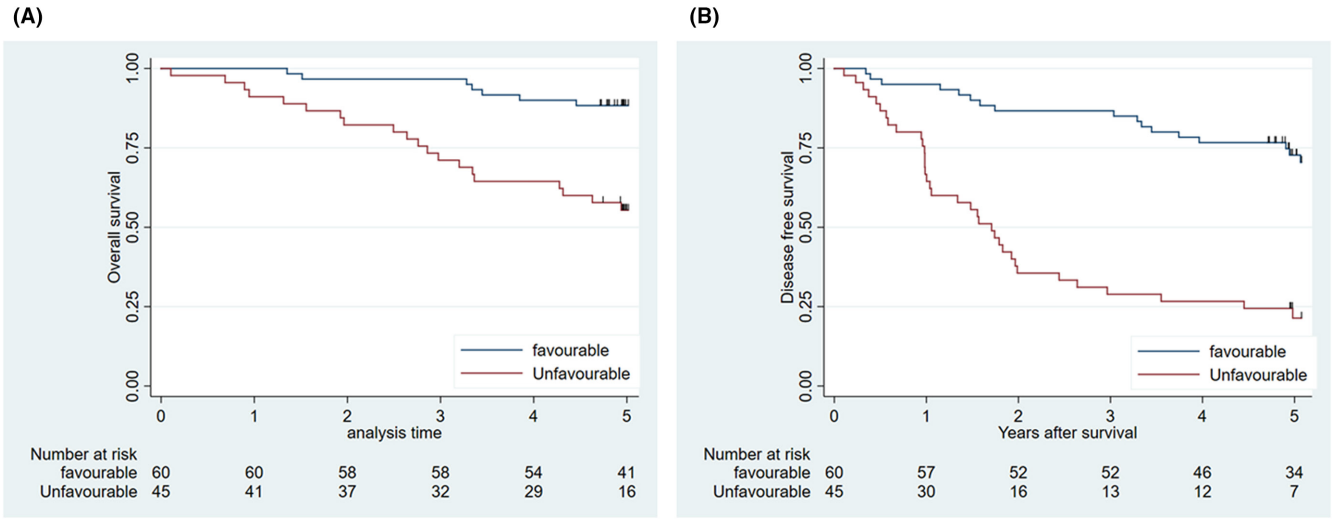

FIGURE 2 Overall (A) and disease-free (B) survival according to histology (favorable vs. unfavorable) in 105 patients who underwent complete CRS and HIPEC.

Our perioperative outcomes compared favorably to those of previous reports, with a major morbidity rate of 21% and 0.9% mortality. Intra-abdominal hemorrhage was one of the most serious, and common, complications and all the events were successfully controlled by interventional radiology and blood transfusion and no return to theater was required. Pseudoaneurysm, created by high-power diathermy at the time of peritonectomy, might be a possible cause in some cases, suggesting the need for caution during surgery. During the series, we commenced the routine multiple ligations of the inferior phrenic artery when stripping the hemidiaphragm and the incidence of significant postoperative hemorrhage was subsequently reduced (data not shown). The other major morbidity was respiratory failure which may have been mitigated if the patients had been fitter. In order to address this, we have initiated a prehabilitation programme where patients are optimized physiologically and nutritionally as early as possible in their journey.

Complete cytoreduction was achieved in 61% of all patients who underwent laparotomy for PMP. The most common reason for not achieving complete cytoreduction was small bowel (and mesenteric) involvement and gross involvement of the hepatoduodenal ligament. A more aggressive approach where the hepatoduodenal ligament are dissected in combination with gastrectomy might facilitate higher rates of complete cytoreduction.[25] This needs to be addressed in future studies in the context of the longer-term oncological outcomes and quality of life from post-gastrectomy syndromes.

The median follow-up period of this study was 60 months which was significantly longer than most previous studies. Even longer follow-up would be preferable in view of generally less aggressive biology of PMP.

With regards to oncological outcomes, the overall survival of the patients who underwent CRS and HIPEC was comparable to that in previous reports, although the disease-free survival was less favorable (Table 4). Possible explanations for this would include (a) longer follow-up period, (b) more stringent criteria for surgery, (c) more extensive follow-up and more lenient criteria for diagnosing recurrence, (d) larger proportion of high-grade histology and (e) more deaths from non-PMP causes. We have adopted an expectant non-operative management where possible if the primary has been removed and the remaining disease is minimal. Low-grade histology accounted for 57% of the complete CRS group in our study compared with 68%–82% in other reports. In the current experience, we experienced death from other causes without evidence of PMP recurrence in eight out of 33 who died during follow-up.

It is noteworthy that, despite being a palliative procedure, MTD offered the 5-year overall survival as high as 25% with minimal morbidity and no mortality. However, MTD is still a major undertaking with a median of 5.5-hours operating time and requires moderate ITU and a long hospital stay. Great care should be taken in selecting and optimizing the patients as those who undergo MTD are often physically and nutritionally compromised as a result of extensive abdominal distension and muscle wasting.

Aggressive histology was associated with significantly poorer survival compared with more favorable histology with the median disease-free interval of 12 months. This suggests the aggressive nature of the disease and, whilst simulating PMP, may be best described as mucinous adenocarcinoma. Nevertheless, almost all recurrences were in the peritoneal cavity, indicating the need for more effective intraoperative agents other than mitomycin C or for a tailor-made approach based on molecular profile and sensitivity to the drug used. It may be worthwhile to consider adding systemic chemotherapy peri-operatively in patients with unfavorable histology.

In the current study, multivariate analysis revealed favorable histology and optimal cytoreduction (CC-0 vs. CC-1) to be positively associated with both overall and disease-free survivals. Raised serum tumor markers, CA19-9 and CA125 in particular, were also independent prognostic factors for recurrence. The

TABLE 4 Short- and longer-term outcomes of CRS and HIPEC in previous reports and current study.

Author	Ref	Place	Publication year	Time of recruitment	Median follow-up period (months)	Number of patients who had CCRS	Mortality (in-hospital)	Morbidity (CD III/IV)	5-year overall survival	10-year overall survival	5-year disease-free survival	10-year disease-free survival
Sugarbaker	[18]	Washington DC USA	1999	1989–1999	37.6 (mean)	250	2.0%	27%	79.0%	-	62.0%	-
Elias	[19]	France Villejuif	2008	1994–2006	48	105	7.6%	60% (CD II–IV)	80.2%	-	68.4%	-
Andreasson	[20]	Uppsala Sweden	2012	1993–2008	40	110	1.0%	35%	74.0%	-	67.0%	-
Mizumoto	[21]	Kusatsu Japan	2012	2007–2011	-	147	3.8%	16%	-	-	-	-
Ansari	[22]	Basingstoke UK	2016	1994–2014	36	738	1.6%	15%	87.4%	70.3%	74.9%	63.5%
Narasimhan	[23]	Melbourne Australia	2019	2008–2017	37	155	0.5%	40%	90.0%	-	-	-
van Eden	[24]	Amsterdam Netherlands	2019	1996–2015	68	225	4.4%	37%	Acellular 93% DPAM 69.8% PMCA 55%	Acellular 93% DPAM 54.5% PMCA 36%	-	-
Yano		Tokyo Japan	2022	2010–2016	60	105	0.9%	21%	74.2%	-	50.1%	-

Abbreviations: CCRS, complete cytoreductive surgery; CRS, complete cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy.

majority of the previous studies conducted multivariate survival analysis on all the patients who underwent CRS and HIPEC including CC-2 or CC-3 cases, where, unsurprisingly, CC score constituted the strongest universal prognostic indicator. In addition to CC score, histology appears to remain the most significant independent prognostic factor for survival which is consistent across all studies. The largest series from Basingstoke, UK, showed elevated CEA and CA125 were associated with adverse overall survival whilst elevated CEA and CA19-9 with adverse disease-free survival.[22] Elias et al. reported CA19-9 and histology as significantly prognostic for disease-free survival.[19]

The limitations of this study include its retrospective nature, relatively small number of patients and single-center design. Despite these limitations, the findings have demonstrated the overall efficacy and safety of CRS and HIPEC for PMP in the Asian population. We strongly suggest that future studies should expand to incorporate multiple centres in Japan and in different Asian countries to share experience and knowledge and increase the number of patients with longer-term follow-up.

5 | CONCLUSION

CRS combined with HIPEC can be conducted with reasonable safety in a new center despite being highly aggressive and having prolonged procedures. Optimal outcomes are achieved by complete CRS and HIPEC and, if complete CRS is not achievable, MTD provides reasonable mid- to long-term survival in many. Future studies are warranted with a larger number of patients and with a longer follow-up to identify patients at greater risk of recurrence and to aid in selecting patients for more intensive treatment such as systemic chemotherapy and/or immunotherapy.

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CONFLICT OF INTEREST STATEMENT

The authors have no financial interest to disclose for this article.

ETHICS STATEMENT

Approval of the research protocol: This study was approved by the local ethics committee of the NCGM (Approval no: NCGM-G-001435-04) and conducted according to the principles of the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from all patients prior to surgery.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

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