



Analysis of the characteristics and outcomes of patients with pseudomyxoma peritonei of appendiceal origin treated with curative-intent surgery

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ABSTRACT

Background: There are no previous studies on pseudomyxoma peritonei regarding the details of surgical procedures included in cytoreductive surgery and quantitative evaluation for peritoneal metastases by region in the abdominal cavity. This study aimed to describe the characteristics and procedural details involved in cytoreductive surgery, and survival outcomes of patients with pseudomyxoma peritonei originating from appendiceal mucinous neoplasm, and identify differences in the difficulty of cytoreductive surgery based on tumor location. **Methods:** Patient characteristics and survival outcomes were studied through a retrospective review. The complete cytoreduction rate (i), the 5-year survival rate for patients with complete cytoreduction (ii), and an index as a complement ($i \times ii \times 100$) were described for patients who had tumors larger than 50 mm in one of the 13 regions of the abdominal cavity.

Results: A total of 989 patients were treated with curative-intent cytoreductive surgery. The median peritoneal cancer index was 18 (interquartile range, 6–29), with complete cytoreduction achieved in 702 patients (71%); the major complication rate was 17%. The median overall survival was 92.9 months, compared to 53.8 months for patients who underwent total gastrectomy and 30.4 months for those who underwent total colectomy. In the 13 abdominal regions, the index scores indicating cytoreduction difficulty were categorized into three risk groups: upper and mid-abdominal (>20), lateral abdominal (10–20), and small bowel (<10).

Conclusions: Cytoreductive surgery offered favorable survival outcomes, even in cases involving total gastrectomy. The difficulty of achieving complete cytoreduction varied across abdominal regions and was classified into three levels.

1. Introduction

Pseudomyxoma peritonei (PMP) is a clinical condition characterized by the accumulation of mucin within the peritoneal cavity, generally originating from appendiceal tumors [1–3]. The incidence of PMP is estimated to be one to three cases per million people per year [4]. Due to its rarity, there have been no randomized controlled trials for its treatment [1]. In the past, surgical debulking or repeated drainage of mucinous ascites was the only option for treating PMP [5,6]. Unlike other malignant tumors, PMP is localized to the peritoneal cavity for

long periods and organ invasion is limited [7–9]. Therefore, aggressive local treatment is considered effective, and in recent years, a combination of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has been considered as a standard treatment, with a 10-year overall survival rate of 50–60% [10–14].

In Japan, aggressive surgery as a cancer treatment is performed more frequently than in other countries [15–20]. Examples include para-aortic nodal dissection and bursectomy for gastric cancer, extended lymphadenectomy for pancreatic cancer, and lateral pelvic node dissection for rectal cancer [15–20]. In addition, there are aggressive

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surgeries for PMP at some medical centers in Japan [21]. There is a consensus that CRS combined with HIPEC improves the prognosis of patients with PMP; however, the optimal degree of invasiveness involving organ resection remains unknown. Specialized strategies must be formulated for PMP in general and for huge PMP in specific [22].

The peritoneal cancer index (PCI) is widely recognized as an indicator of the extent of peritoneal disease, including PMP [13,23]. However, in PMP patients, there is no cutoff value of the PCI to indicate whether complete cytoreduction is feasible [24]. Even with a maximum PCI score of 39, there are cases wherein complete cytoreduction is possible [25]. The PCI is a score that assesses the overall intra-abdominal disease burden and cannot represent the difficulty of surgery in an abdominal region. Tumors located in some regions are considered more difficult (or easier) to remove than those located in other regions; however, the difficulty by region has not been quantitatively evaluated.

Large-scale studies on PMP have only been reported in Europe [13,14,26], and it is worthwhile to conduct this study using data from Japan, where different treatment strategies are employed. This study aimed to assess the prognostic implications and survival outcomes of patients with PMP treated with curative-intent surgery and describe the patient characteristics and outcomes of the surgical procedure (e.g., total gastrectomy and total colectomy) included in CRS. In addition, this study aimed to verify differences in the difficulty of CRS by region in the abdominal cavity.

2. Materials and methods

2.1. Study design and participants

This retrospective review study used the institutional databases of patients with PMP at two Japanese centers (Kishiwada Tokushukai Hospital and Omi Medical Center) from January 2006 to December 2019. This study was approved by the Institutional Review Boards of Kyoto University (approval number R2363) and the above two institutions and was conducted in accordance with the Declaration of Helsinki. We adopted the opt-out method owing to the observational nature of this retrospective study, and the patients were exempted from providing informed consent.

Patients with pathologically confirmed PMP originating from an appendiceal mucinous neoplasm who underwent curative-intent surgery were included in the study, whereas patients with PMP of a non-appendiceal origin treated only with chemotherapy and/or palliative care were excluded. Patients who underwent palliative surgery were also excluded.

All patients were preoperatively assessed to evaluate their eligibility for CRS/HIPEC treatment, which was determined based on the consensus of a multidisciplinary team. The surgical strategy, CRS, involves peritonectomy procedures and some visceral resections, as described by Sugarbaker [27]. The following surgical procedures were performed: partial gastrectomy, gastrectomy other than total gastrectomy; pancreatectomy, distal pancreatectomy; and liver hilum dissection, cytoreduction of tumors >50 mm in the liver hilum region. At the completion of CRS, patients underwent HIPEC, except for those who had poor general conditions after CRS due to high surgical stress, such as prolonged operative time and massive bleeding. HIPEC was administered with the open coliseum technique for 30–60 min at a target temperature of 42.5–43.5 °C in 3–5 L of saline. The most commonly administered HIPEC regimen was oxaliplatin 200 mg/m² or a combination of mitomycin C 15 mg/m² and cisplatin 60 mg/m². The perioperative chemotherapy regimen was decided based on the consensus of a multidisciplinary team.

2.2. Data collection

Our analysis included data regarding clinical and oncological

characteristics. Tumors were classified histopathologically as low- or high-grade according to the World Health Organization criteria. Moreover, the prior surgical score, which measures the extent of surgery prior to CRS and HIPEC, was assessed. Prior surgical score-0 indicated no surgery or only biopsy, prior surgical score-1 indicated surgery in one abdominal region, prior surgical score-2 indicated surgery in two to five regions, and prior surgical score-3 indicated surgery in more than five regions [28]. The PCI was calculated intraoperatively and consisted of a lesion size score (0–3) in the 13 abdominopelvic regions, resulting in a total index of 0–39 [23]. The lesion size score was determined as follows: lesion size –0, no tumor; lesion size-1, tumor nodules <5 mm; lesion size-2, tumor nodules 5–50 mm; and lesion size-3, tumor nodules >50 mm. The quality of CRS was assessed according to the completeness of cytoreduction (CC) score as follows: CC-0, no macroscopic residual tumor; CC-1, residual tumors measuring 0–2.5 mm; CC-2, residual tumors measuring 2.5–25 mm; and CC-3, residual tumors measuring >25 mm [23]. CC-0 and CC-1 indicated a complete CRS, whereas CC-2 and CC-3 indicated an incomplete CRS or debulking surgery. Major postoperative complications after 30 days postoperatively were defined as grade III–V according to the Clavien–Dindo classification [29]. Postoperative mortality was defined as death within 30 days after surgery.

To evaluate the difficulty of complete cytoreduction for each abdominal region, the CC-0/1 and 5-year survival rates were described for patients who had tumors >50 mm in one of the 13 regions of the abdominal cavity (a PCI score of 3 in a region). Additionally, an index as a complement to the CC-0/1 rate was calculated. This index was defined as the percentage of patients who achieved CC-0/1 with tumors >50 mm in one of the 13 regions multiplied by the 5-year survival rate for these patients × 100.

2.3. Statistical analysis

We analyzed the data of patients who underwent CRS from January 1, 2006, to December 31, 2019. Quantitative values are expressed as median (interquartile range [IQR]), while categorical data are reported as frequencies and percentages. Continuous variables were compared using the Mann–Whitney test and categorical variables were compared using Fisher's exact test or the chi-square test. The overall survival was measured from the first surgery until death, regardless of the cause. Moreover, recurrence-free survival was calculated from the first surgery to recurrence or death from any cause. Recurrence was defined as the presence of tumor nodules in radiological findings or their pathological evidence by cytology or histology. Data for patients without any recurrence-free survival event were censored at the last follow-up. Patients in this cohort were followed-up until December 31, 2020. The overall survival and recurrence-free survival curves were plotted using the Kaplan–Meier method and compared with the log rank test. Univariable and multivariable Cox regression analyses were performed to assess the impact of potential prognostic indicators on overall survival. Based on prior research and clinical consideration, variables likely to be associated with the outcome were included in the multivariable model analysis. The results are reported as hazard ratios (HR) or odds ratios (OR) with 95% confidence intervals (CI). All statistical analyses were conducted using JMP statistical software version 15 (SAS Institute, Cary, NC, USA) or IBM SPSS statistics version 29.0 (IBM, Armonk, New York, USA), and a two-tailed *P* value < 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

Between January 2006 and December 2019, 1329 patients were diagnosed with PMP. In total, 340 patients were excluded for the following reasons: 129 received only chemotherapy and/or palliative therapy, 118 had a non-appendiceal primary tumor, 71 underwent

palliative surgery, and 22 had missing critical variables data (Supplementary Fig. 1).

In the cohort of 989 patients, 653 (66%) patients were women, 66 (6.7%) had lymph node involvement, 410 (41%) had high-grade histopathology, the median age was 57 years (IQR, 46–67), and the median PCI was 18 (IQR, 6–29). CC-0/1 was achieved in 702 (71%) patients, 616 of whom underwent HIPEC (Table 1). For the HIPEC regimen, mitomycin C plus cisplatin was used in 438 patients, oxaliplatin in 153 patients, and others in 25 patients (Supplementary Table 1). The median operation time and estimated blood loss were 269 min (IQR, 180–340 min) and 1600 mL (IQR, 680–2600 mL), respectively. Furthermore, 413 (42%) patients received preoperative chemotherapy and 175 (18%) received postoperative chemotherapy (Table 1).

3.2. Postoperative complications

The major complication (Clavien–Dindo classification $\geq$ III) rate was 17% (167/989), and the minor complication rate was 24% (234/989). The most common major complications were intra-abdominal infections (Supplementary Table 2). The postoperative mortality rate was 1.5% (15/989) (Table 1).

3.3. Survival outcomes

Among the entire cohort of patients, 369 (37%) died, 417 (42%) were alive, and 203 (21%) were lost to follow-up, during a median

Table 1
Patient characteristics.

Characteristics	Patients (n = 989)
Age, years, median (IQR)	57 (46–67)
Sex, female, no. (%)	653 (66%)
Prior surgical score, no. (%)	
0	432 (44%)
1	330 (33%)
2	206 (21%)
3	12 (1.2%)
Missing	9 (0.9%)
CEA, ng/mL, median (IQR)	8.1 (2.8–34.8)
CA19-9, U/mL, median (IQR)	26.1 (8.7–109.0)
Lymph node involvement, no. (%)	
Yes	66 (6.7%)
No	912 (92%)
Missing	11 (1.1%)
Histopathology, no. (%)	
Low-grade	576 (58%)
High-grade	410 (41%)
Missing	3 (0.3%)
PCI (0–39), median (IQR)	18 (6–29)
Completeness of cytoreduction, no. (%)	
Complete cytoreduction	CC-0 464 (47%)
	CC-1 238 (24%)
Incomplete cytoreduction	CC-2 61 (6.2%)
	CC-3 226 (23%)
Operation time, min, median (IQR)	269 (180–340)
Estimated blood loss, mL, median (IQR)	1600 (680–2600)
Postoperative complication, no. (%)	
Major	167 (17%)
Minor	234 (24%)
Postoperative mortality, no. (%)	15 (1.5%)
HIPEC, no. (%)	
Yes	616 (62%)
No	373 (38%)
Preoperative chemotherapy, no. (%)	
Yes	413 (42%)
No	576 (58%)
Postoperative chemotherapy, no. (%)	
Yes	175 (18%)
No	814 (82%)

Abbreviations. CC, completeness of cytoreductive score; HIPEC, hyperthermic intraperitoneal chemotherapy; IQR, interquartile range; PCI, peritoneal cancer index; PMP, pseudomyxoma peritonei.

follow-up time of 32.0 months (IQR, 12.5–70.4). Moreover, 557 (56%) patients had recurrences.

The median overall survival was 92.9 months (95% CI, 84.5–108.5) (Supplementary Figs. 2–A), while the 5- and 10-year overall survival rates were 61% and 41%, respectively. Moreover, the median recurrence-free survival was 26.1 months (95% CI, 20.4–33.3) (Supplementary Figs. 2–B).

The factors associated with overall survival are shown in Table 2. In the univariable analysis, age $\geq$ 70 years, lymph-node metastases positive, high-grade histopathology, higher PCI, CC-2/3, no use of HIPEC, use of preoperative chemotherapy, use of postoperative chemotherapy, major postoperative complication, estimated blood loss $\geq$ 1500 mL, and operation time $\geq$ 270 min were associated with worse overall survival. In multivariable analysis, based on findings from previous studies and clinical decisions, the following variables were selected: age, prior surgical score, lymph node involvement, histopathology, PCI, CC, HIPEC, preoperative chemotherapy, postoperative chemotherapy, postoperative complication, estimated blood loss, and operation time. Independent prognostic factors associated with poorer overall survival were as follows: age $\geq$ 70 years old (HR, 1.48; 95% CI, 1.12–1.96), lymph node metastases positive (HR, 1.74; 95% CI, 1.20–2.52), high-grade histopathology (HR, 2.65; 95% CI, 2.11–3.33), higher PCI (HR, 1.50; 95% CI, 1.02–2.20 [PCI, 11–20]; HR, 3.07; 95% CI, 2.07–4.56 [PCI, 21–30]; HR, 3.07; 95% CI, 2.01–4.70 [PCI, 31–39]), CC-2/3 (HR, 1.97; 95% CI, 1.48–2.61) (Fig. 1A), use of preoperative chemotherapy (HR, 1.50; 95% CI, 1.20–1.89) (Supplementary Figs. 3–A), and major postoperative complications (HR, 1.90; 95% CI, 1.48–2.44). Furthermore, the use of HIPEC was associated with improved overall survival in the multivariable analysis (HR, 0.69; 95% CI, 0.55–0.87) (Supplementary Figs. 3–B).

In the multivariable analysis, CC-0/1 was associated with overall survival (Supplementary Table 3 added in revision 1). At baseline, patients with CC-0/1 differed from patients with CC-2/3. Patients with CC-0/1 less frequently presented with age $\geq$ 70 years (13% versus 30%), high-grade histopathology (35% versus 56%), and estimated blood loss $\geq$ 1500 mL (47% versus 64%). Furthermore, patients in the CC-0/1 group more commonly had a PCI between 0 and 10 (49% versus 0.7%) and 11–20 (26% versus 9.1%), while they were less likely to have a PCI between 21 and 30 (19% versus 31%) and 31–39 (6.7% versus 60%). Moreover, HIPEC was more frequently administered to patients with CC-0/1 (67% versus 52%), whereas preoperative chemotherapy was less common in this group (39% versus 47%) (Supplementary Table 4 added in revision 2).

Of the 557 patients with recurrence, 200 underwent repeat surgeries, 52 of whom had two or more repeat surgeries (Supplementary Tables 5 and 6). Moreover, of the 270 patients with a recurrence after achieving CC-0/1 at the first surgery, 125 underwent repeat surgery. Among the 125 patients, the most common site of recurrence was the middle abdomen (72/125), followed by the lower abdomen (63/125) (Supplementary Table 7).

3.4. Characteristics and survival outcomes of patients for surgical procedures used

The characteristics and outcomes of the four procedures (total gastrectomy, total colectomy, pancreatectomy, and liver hilum dissection) are described in detail in Table 3 and Fig. 1B–E. A total of 117, 194, 33, and 177 patients underwent total gastrectomy, total colectomy, pancreatectomy, and liver hilum dissection, respectively. Moreover, the percentage of CC-0/1 achieved for total gastrectomy, total colectomy, pancreatectomy, and liver hilum dissection was 70%, 44%, 45%, and 100%, respectively. Additionally, the 5-year overall survival rates were 47%, 31%, 37%, and 59% for total gastrectomy, total colectomy, pancreatectomy, and liver hilum dissection, respectively.

Among patients who underwent CC-0/1, the 5-year survival rates for those who underwent total gastrectomy (n = 82), total colectomy n =

Table 2

Analysis of the association of overall survival with patient characteristics.

Variable	Category	Univariable			Multivariable		
		HR	95% CI	P-value	HR	95% CI	P-value
Age, years	<70	Ref			Ref		
	≥70	1.65	1.27–2.13	< 0.001	1.48	1.12–1.96	0.006
Sex	Female	Ref			—		
	Male	1.18	0.96–1.47	0.12	—		
Prior surgical score	0, 1	Ref			Ref		
	2, 3	1.09	0.85–1.38	0.49	1.15	0.90–1.48	0.26
Lymph node involvement	Negative	Ref			Ref		
	Positive	2.20	1.53–3.15	< 0.001	1.74	1.20–2.52	0.003
Histopathology	Low-grade	Ref			Ref		
	High-grade	3.57	2.87–4.42	< 0.001	2.65	2.11–3.33	< 0.001
PCI	0–10	Ref			Ref		
	11–20	2.08	1.44–2.97	< 0.001	1.50	1.02–2.20	0.037
	21–30	4.75	3.34–6.57	< 0.001	3.07	2.07–4.56	< 0.001
	31–39	7.59	5.55–10.38	< 0.001	3.07	2.01–4.70	< 0.001
Completeness of cytoreduction	CC-0/1	Ref			Ref		
	CC-2/3	4.28	3.46–5.30	< 0.001	1.97	1.48–2.61	< 0.001
HIPEC	No	Ref			Ref		
	Yes	0.66	0.53–0.81	< 0.001	0.69	0.55–0.87	0.001
Preoperative chemotherapy	No	Ref			Ref		
	Yes	2.17	1.76–2.66	< 0.001	1.50	1.20–1.88	< 0.001
Postoperative chemotherapy	No	Ref			Ref		
	Yes	1.83	1.47–2.28	< 0.001	0.96	0.75–1.22	0.73
Postoperative complication (CD)	0–2	Ref			Ref		
	3 ≤	2.36	1.86–2.99	< 0.001	1.90	1.48–2.44	< 0.001
Estimated blood loss, mL	<1500	Ref			Ref		
	≥1500	2.42	1.94–3.02	< 0.001	1.27	0.97–1.68	0.083
Operation time, min	<270	Ref			Ref		
	≥270	1.43	1.16–1.76	< 0.001	0.88	0.05–14.3	0.93

Abbreviations. CD, Clavien-Dindo classification; CI, confidence interval; HIPEC, hyperthermic intraperitoneal chemotherapy; HR, hazard ratio; PCI, peritoneal cancer index.

85), pancreatectomy (n = 15), and liver hilum dissection (n = 177) were 59%, 41%, 41%, and 59%, respectively (Supplementary Table 8 and Supplementary Fig. 4).

Furthermore, the 5-year survival rates for patients who underwent partial gastrectomy (N = 90), low anterior resection (N = 358), small bowel resection (≥1 m) (N = 53), and diaphragm dissection (N = 347) were 53%, 47%, 44%, and 61%, respectively (Supplementary Table 9).

3.5. Evaluating the effectiveness of surgery

The incidence of tumors >50 mm for each region, the percentage of CC-0/1 achieved, and the 5-year survival rates are shown in Table 4. Regarding the CC-0/1 rate in the 13 abdominal regions, the values for regions 0, 1, 2, 3, and 6 were >35%, those for regions 4, 5, 7, and 8 were 15–35%, and those for regions 9, 10, 11, and 12 were <15% (Fig. 2A). Moreover, the 5-year survival rate for each CC-0/1 patient was more than 50% in 11 regions and 35–50% in 2 regions (regions 5 and 12) (Fig. 2B and Supplementary Fig. 5). The complementary indexes for regions 0, 1, 2, 3, and 6 were >20; those for regions 4, 5, 7, and 8 were 10–20; and those for regions 9, 10, 11, and 12 were <10 (Table 4 and Fig. 2C and D).

4. Discussion

This large-scale retrospective study investigated PMP originating from appendiceal mucinous neoplasms, with a focus on the details of the surgery. The treatment approach for malignant diseases differs between Asia (particularly Japan) and the West. Japan has a history of aggressive surgeries for abdominal cancer [15–20], and extended surgery has also been performed for PMP in some institutions [21]. Therefore, it is valuable for a large study regarding PMP to be reported from Japan.

PMP has the oncological characteristic of remaining within the abdominal cavity with a low frequency of invasion into the lymph nodes, liver, and other distant organs [7–9]. This unique oncological feature

allows aggressive locoregional treatment [1,13]. In our study, the overall survival of patients who achieved CC-0/1 was significantly better than that of patients with CC-2/3 (Fig. 1A), which is similar to the results of previous studies [13,26,30,31]. Undoubtedly, tumor removal has a positive impact on patient prognosis. However, unlimited multi-visceral resection for achieving CC-0/1 is detrimental to patients with PMP because the survival outcomes and patients' quality of life might be significantly impaired after massive organ removal. CRS includes a variety of surgical techniques, such as peritonectomy and/or resection of various organs, and its degree of invasiveness varies considerably [28]. Therefore, describing patient characteristics and outcomes by surgical procedure in CRS will be helpful in the selection of treatment for future patients with PMP. In this study, the most notable results were obtained in patients who underwent total gastrectomy or total colectomy. The extent of the invasiveness of organ resection that is acceptable for performing CRS remains unclear. In our study, patients treated with total gastrectomy had a 5-year survival rate of 47%, while patients who underwent total colectomy had a 5-year survival rate of 31% (Fig. 1B and C and Table 3). The percentage of CC-0/1 in patients with total gastrectomy was larger than that in patients with total colectomy (70% vs. 44%); therefore, we limited our analysis to cases with CC-0/1 and calculated the overall survival of patients with total gastrectomy and total colectomy. When patients were restricted to CC-0/1, the 5-year survival rates for patients with total gastrectomy and total colectomy were 59% and 41%, respectively (Supplementary Table 6). Cases requiring total gastrectomy for PMP in CRS have generally been considered unresectable [1,22]. The two overall survival values obtained in this study cannot be simply compared due to selection bias; however, our results could be a basis for performing total gastrectomy in CRS for PMP.

An equally interesting result of this study concerns liver hilum dissection. While a previous study reported that bloodless glissonectomy can be performed using the blunt-finger technique and bipolar scissors [32], massive involvement of the liver hilum region in most patients has

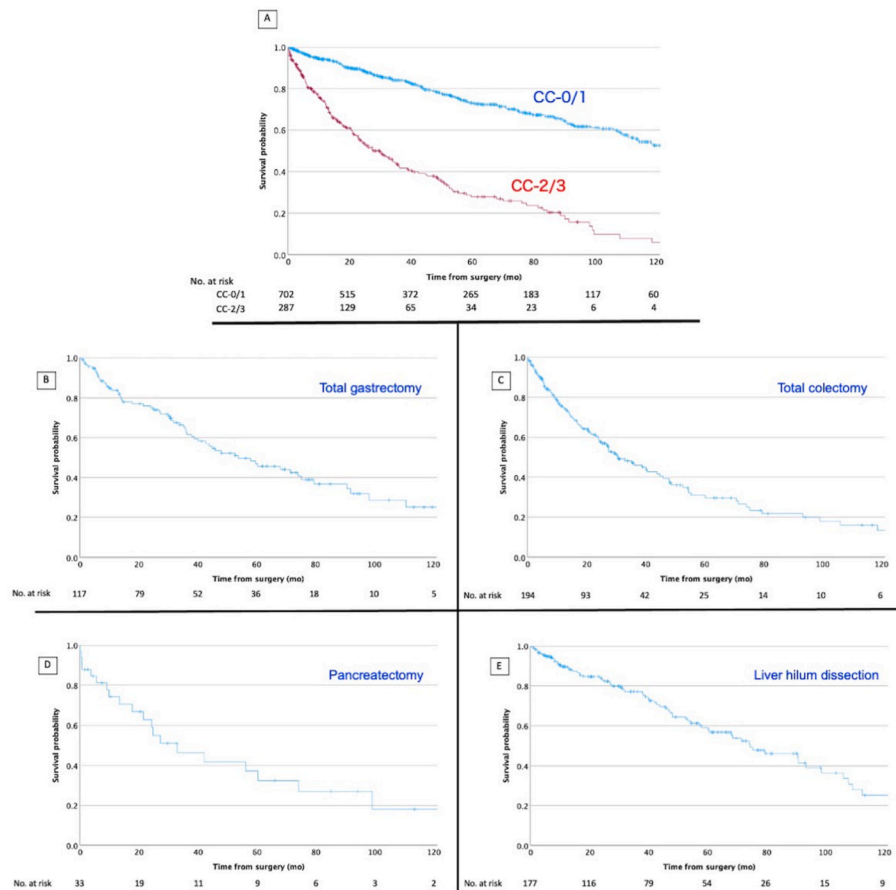


Fig. 1. Title: Kaplan-Meier analysis of overall survival in patients with pseudomyxoma peritonei according to the completeness of cytoreduction and surgical procedure

A: CC-0/1 and CC-2/3

B: Total gastrectomy

C: Total colectomy

D: Pancreatectomy

E: Liver hilum dissection

Abbreviations: CC, completeness of cytoreduction.

Table 3

Characteristics and survival outcomes by surgical procedure.

	Total gastrectomy (n = 117)	Total colectomy (n = 193)	Pancreatectomy (n = 33)	Liver hilum dissection (n = 177)
Age, median (IQR), y	56 (45–66)	58 (45–66)	61 (45–66)	56 (46–66)
Sex (female), no. (%)	50 (43%)	95 (49%)	14 (42%)	116 (66%)
Prior Surgical Score (≥ 2), no. (%)	15 (13%)	40 (21%)	3 (9.1%)	25 (14%)
Lymph node involvement (yes), no. (%)	5 (4.3%)	9 (4.7%)	3 (9.1%)	9 (5.1%)
Histopathology (high-grade), no. (%)	60 (51%)	112 (58%)	20 (61%)	76 (43%)
PCI (0–39), median (IQR)	31 (25–35)	31 (27–35)	31 (27–37)	26 (22–30)
Completeness of cytoreduction (CC 0/1), no. (%)	82 (70%)	85 (44%)	15 (45%)	177 (100%)
Operation time, median (IQR), min	351 (300–398)	314 (260–368)	357 (302–412)	336 (285–387)
Estimated blood loss, median (IQR), mL	3300 (2260–5270)	2670 (1833–3925)	3740 (2405–6263)	2510 (1710–3730)
Major postoperative complication (yes), no. (%)	32 (27%)	51 (26%)	12 (36%)	48 (27%)
HIPEC (yes), no. (%)	73 (62%)	119 (62%)	18 (55%)	121 (68%)
Preoperative chemotherapy (yes), no. (%)	72 (62%)	120 (62%)	21 (64%)	87 (49%)
Postoperative chemotherapy (yes), no. (%)	27 (23%)	41 (21%)	7 (21%)	32 (18%)
Repeat surgery after recurrence (yes), no. (%)	31 (27%)	47 (24%)	9 (27%)	43 (24%)
Survival outcomes				
median OS, mo.	53.8	30.4	32.9	74.4
3-y OS rate	64%	47%	46%	77%
5-y OS rate	47%	31%	37%	59%

Abbreviations. CC, completeness of cytoreduction; HIPEC, hyperthermic intraperitoneal chemotherapy; IQR, interquartile range; OS, overall survival; PCI, peritoneal cancer index.

Table 4
Categorization of the difficulty of complete cytoreduction for each abdominal region.

Region		Tumors >50 mm	CC-0/1			5-year OS rate		Index†		Category
		no.	no.	%‡	Range	CC-0/1§	CC-2/3	Value	Range	
0	Central	469	211	45%	>35%	62%	22%	27.9	>20	Group 1
1	Right upper	436	197	45%	>35%	62%	25%	27.8	>20	Group 1
2	Epigastrium	343	123	36%	>35%	57%	25%	20.4	>20	Group 1
3	Left upper	364	141	39%	>35%	60%	23%	23.2	>20	Group 1
4	Left flank	235	65	28%	15–35%	51%	20%	14.1	10–20	Group 2
5	Left lower	226	61	27%	15–35%	47%	19%	12.7	10–20	Group 2
6	Pelvis	442	204	46%	>35%	53%	24%	24.5	>20	Group 1
7	Right lower	248	78	31%	15–35%	53%	19%	16.6	10–20	Group 2
8	Right flank	240	67	28%	15–35%	51%	21%	14.3	10–20	Group 2
9	Upper jejunum	100	6	6.0%	<15%	63%	19%	3.8	<10	Group 3
10	Lower jejunum	97	5	5.2%	<15%	75%	20%	3.9	<10	Group 3
11	Upper ileum	118	12	10%	<15%	52%	20%	5.3	<10	Group 3
12	Lower ileum	134	16	12%	<15%	37%	24%	4.4	<10	Group 3

Abbreviations. CC, completeness of cytoreduction; OS, overall survival. †Index: ‡the percentage of CC-0/1 patients with tumors >50 mm in a region × §the 5-year OS rate for that patient × 100.

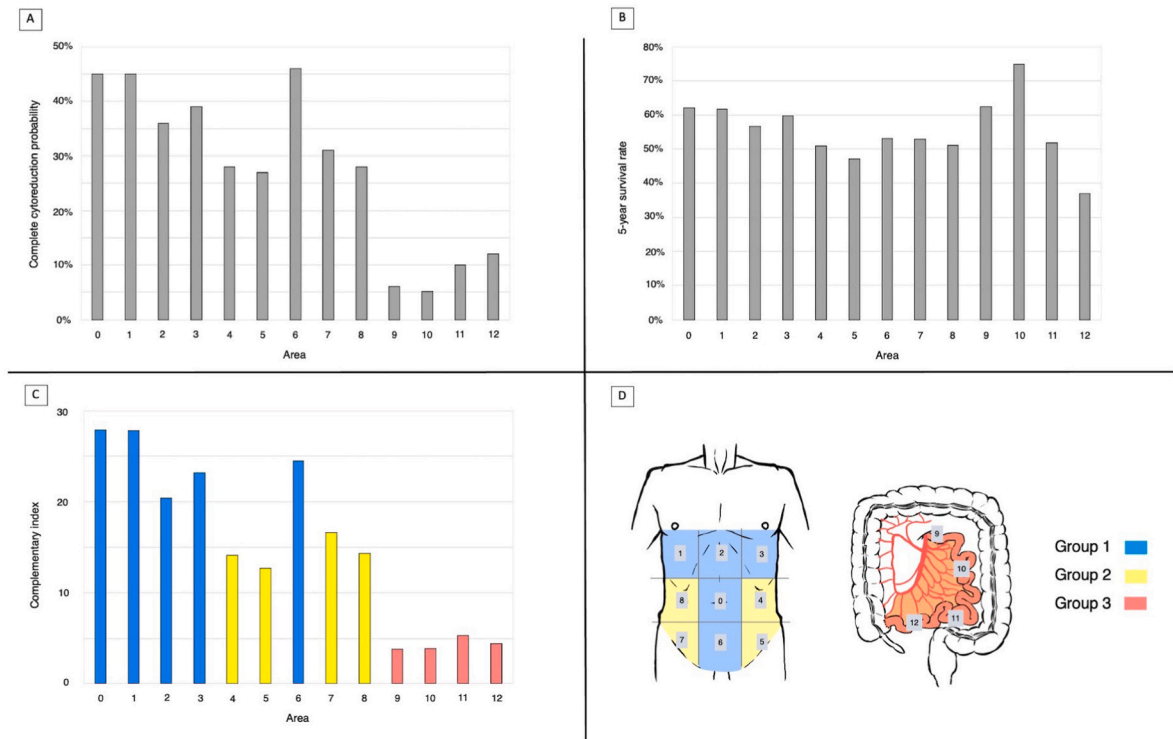


Fig. 2. Title: Categorization of the difficulty of complete cytoreduction for each abdominal region
A: Distribution of the CC-0/1 rate
B: Distribution of the 5-year survival rate for CC-0/1 patients
C: Distribution of the complementary index†
D: Illustrations of the categorization: group 1, CC-0/1 rate >35%; group 2, 15–35%; group 3, <15%
Abbreviations: CC, completeness of cytoreduction
†The percentage of CC-0/1 patients with tumors >50 mm in a region × the 5-year survival rate for that patient × 100.

been considered a contraindication for performing CRS [1,33,34]. Dissection of the hepatic pedicle region involves the risk of bleeding from the portal vein or hepatic artery and injury to the common bile duct. We performed liver hilum dissection in patients who were considered suitable to achieve complete CRS. The CC-0/1 rate of 100% among patients who underwent liver hilum dissection may have been influenced by selection bias. Additionally, the 5-year survival rate of patients who underwent liver hilum dissection was 59% (Fig. 1E and Table 3). The data presented here suggest that not all patients with massive involvement of the hepatic pedicle should be regarded as

unresectable. However, surgical skills and an understanding of surgical anatomy are essential for performing this surgical procedure. Similar to complete CRS, the degree of peritoneal disease is an important factor associated with PMP prognosis, which is commonly measured by the PCI. The PCI is a total score of peritoneal tumors for the entire abdominal cavity; therefore, it does not indicate the difficulty of cytoreduction at each region. However, some regions are easy to resect in peritoneal diseases, while others are difficult to resect. Therefore, we described the CC-0/1 rate and 5-year survival rate in cases of peritoneal diseases with tumors >50 mm (a PCI score of 3 in a region). The

presence of tumors >50 mm in a region is indicative of a massive tumor or widespread peritoneal disease [23], and therefore, complete resection of the region may be difficult. The index as a complement was additionally calculated as follows: the percentage of patients who achieved CC-0/1 with tumors >50 mm in a region multiplied by the 5-year survival rate for these patients $\times 100$. This indicator was added because the CC-0/1 rate is strongly influenced by patient selection. The surgeon's intraoperative decision to continue with the procedure, in addition to the surgeon's skills and extent of tumor dissemination in each region or the entire abdomen, are considered to affect the quality of CRS. If the surgeon allows high-invasiveness and performs the operation, the complete CRS rate will be higher. Consequently, both the CC-0/1 rate and the index were categorized into group 1 (regions 0, 1, 2, 3, and 6), group 2 (regions 4, 5, 7, and 8), and group 3 (regions 9, 10, 11, and 12) (Table 4 and Fig. 2). Most PMPs originate from appendiceal mucinous neoplasms and accumulate first in the greater omentum and dome-shaped regions, such as the diaphragm and pelvic regions [8,9]. These jelly-like tumors then metastasize to the parietal peritoneum other than the diaphragm and pelvic regions, and finally, to the organs and mesentery of the gastrointestinal tract. The categorization we showed here could reflect the sequence of peritoneal dissemination in PMP, suggesting that group 1 is in the early stage of disease progression, while group 3 is in the advanced stage. The results also suggest that achieving CC-0/1 while preserving organ function is difficult when there are large peritoneal tumors in the small intestinal region (group 3), as noted in previous literature [22]. The patient should not be treated at the risk of developing short bowel syndrome postoperatively. Additionally, if there are large tumors in the diaphragmatic and/or pelvic regions, a high probability of complete cytoreduction would be possible. The unique technique of peritoneal dissection in the diaphragmatic and pelvic region, which is rarely performed in general surgery, is considered worth the effort to acquire. The findings of the present study are particularly useful for institutions in the early stages of CRS implementation. It may be worthwhile to investigate whether tumors other than PMP show improved outcomes after surgical resection in the diaphragm and pelvic regions as opposed to those in the small bowel regions.

This study has several limitations. First, the unintentional selection bias cannot be excluded because it is a retrospective study. The choice of surgical procedure within CRS was largely influenced by the surgeons. The study outcomes may also be biased by the fact that the study was conducted solely at two institutions. Second, it is difficult to generalize this report from Japan, a country with a unique treatment strategy for malignant diseases, including PMP. Third, the CC-0/1 rate

and a complementary index of patients with tumors >50 mm in a region was analyzed, but we did not conduct a strict comparison of the survival outcomes between CC-0/1 patients and CC-2/3 patients. Therefore, future validation is needed. However, the findings of this study, especially regarding the details of the surgical procedures and the original index, are novel and may have implications for future PMP treatment.

5. Conclusion

We analyzed the characteristics and outcomes of patients with PMP of appendiceal origin. PMP patients treated with CRS showed good survival, including cases that underwent total gastrectomy. To our knowledge, this is the largest study to describe the details of the procedures included in CRS for PMP and quantitatively evaluate the difficulty of complete cytoreduction by region in the abdominal cavity. The CC-0/1 rate of patients with tumors >50 mm in a region was analyzed. Additionally, the value of the index, used as a complementary measure, was used to categorize these patients into three groups based on the tumor location: small bowel regions, lateral abdominal regions, and upper and mid-abdominal regions. These regions were ranked in order of surgical difficulty. If the metastases are located in a more difficult region, this study's results suggest that the prognosis is likely to be poor.

The data analyzed here provides new evidence for PMP and may be helpful when performing CRS. However, further studies focusing on details of the procedure in CRS and validating the indicators for other peritoneal metastases are important for future research.

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Data availability statement

The data supporting the findings of this study are available upon request from the corresponding author.

Author contributions

YK contributed to the conceptualization and design of the study, acquisition and analysis of data, and drafting of the manuscript. KH contributed to the design of the study and revision of the manuscript. YY, TK, and AM contributed to acquisition of data and revision of the manuscript. AN was responsible for analysis of data and revision of the manuscript. SY and YT contributed to the acquisition and analysis of data and drafting of the manuscript. KO was responsible for the conception of the study and revision of the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

None.

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Appendix A. Supplementary data

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