

Original Research Article

## Comparison of Cytoreductive Surgery and Resection of Isolated Peritoneal Metastases in Patients with Peritoneal Metastases from Colorectal Cancer: A Retrospective Study

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### Abstract

**Objectives:** This study aimed to compare the short and long-term outcomes of cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy and resection of isolated peritoneal metastases in patients with peritoneal metastases from colorectal cancer in Japan.

**Methods:** We included patients who had undergone surgery for peritoneal metastases from colorectal cancer between 2013 and 2019. Data were retrieved from a prospectively maintained multi-institutional database and retrospective chart review. Patients were classified into cytoreductive surgery and resection of isolated peritoneal metastases groups based on the surgery they had undergone.

**Results:** A total of 413 patients were eligible for analysis (257 and 156 patients in the cytoreductive surgery and resection of isolated peritoneal metastases groups, respectively). There was no significant difference in overall survival (hazard ratio and 95% confidence intervals, 1.27 [0.81, 2.00]). Six cases (2.3%) of postoperative mortality were observed in the cytoreductive surgery group, whereas none were observed in the resection of the isolated peritoneal metastases group. Cases of postoperative complications were significantly higher in the cytoreductive surgery group (risk ratio 2.02 [1.18, 2.48]) than those in the resection of isolated peritoneal metastases group. Among patients with a high peritoneal cancer index (6 points or higher), the complete resection rate was 115/157 (73%) and 15/44 (34%) in the cytoreductive surgery and the resection of isolated peritoneal metastases groups, respectively.

**Conclusions:** Cytoreductive surgery was not superior in providing long-term survival benefits for colorectal cancer peritoneal metastases; however, cytoreductive surgery provided a higher complete resection rate even in patients with a high peritoneal cancer index (6 points or higher).

### Keywords

colorectal cancer, cytoreductive surgery, peritoneum, metastases

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## Introduction

In 2020, colorectal cancer (CRC) was the third most common cancer and the number of CRC-related deaths was the second highest among patients with cancer globally[1]. Approximately 7% of patients undergoing primary surgery for CRC had peritoneal metastases (PM) at the time of primary surgery and 4-19% of the patients had PM during follow-up after the curative surgery[2]. Patients with PM have a poorer prognosis than those with other distant metastases and it is a major obstacle in the treatment of CRC[3,4].

Palliative treatment such as systemic chemotherapy and palliative surgery is the main treatment strategy for CRC with peritoneal metastases (CRC-PM)[5]. However, cytoreductive surgery (CRS), including Sugarbaker's peritonectomy and hyperthermic intraperitoneal chemotherapy (HIPEC) has been adopted for potentially resectable CRC-PM in the past several decades[6,7]. One randomized controlled trial and several observational studies reported the efficacy of this combination therapy; patients receiving the combination therapy have longer overall survival (OS) and disease-free survival period than those receiving only systemic chemotherapy[8-13]. Owing to the developments in chemotherapy for CRC in recent years, the OS of CRC patients with unresectable metastases has improved; however, the patient selection for CRS and HIPEC (CRS-HIPEC) remains unclear in the current scenario.

Although CRS-HIPEC was first reported in studies in Western countries and performed on a large scale globally in CRC-PM patients, this combination therapy is not commonly performed in some Asian countries[14,15]. In Japan, primary and metastatic tumor resection including resection of isolated peritoneal metastases (RIPM; surgery without peritonectomy) is performed when the PM is easily resectable[16]. This treatment strategy works well when R0 resection (macroscopically no residual tumor and pathologically negative resection margin) is achieved[17,18].

Patients with unresectable CRC-PM are generally not indicated for surgery. However, they are indicated for systemic chemotherapy. Palliative surgery such as colostomy and bypass may be performed if symptoms occur because of the primary tumor, e.g., bowel obstruction[16,19,20].

The prognosis of patients who underwent CRS-HIPEC or RIPM is reported to be better than those of patients with CRC-PM who underwent only systemic chemotherapy. Moreover, no study has presented a comparison of the treatment outcomes of CRS-HIPEC and RIPM. There are no clear guidelines on the specific procedures that are suitable for patients with CRC-PM; consequently, the indication for these surgeries depends on the preference and experience of surgeons. Therefore, this retrospective study aimed to compare the short and long-term outcomes of CRS-HIPEC and RIPM performed in Japan and clarify the effectiveness of

the CRS-HIPEC in CRC-PM patients.

## Methods

### Patients

This retrospective, multi-institutional, observational study was conducted at 14 Japanese institutions, including Omi Medical Center, Kishiwada Tokushukai Hospital, Kyoto University, and 11 hospitals of the Kyoto University Surgeons Association. Medical records of patients who underwent surgery for CRC-PM between 2013 and 2019 were reviewed. The exclusion criteria were as follows: non-histologically diagnosed PM, cases of emergency surgery, non-peritoneal unresectable metastases, patients not scheduled for resection, or patients treated by ileostomy, colostomy, or enterostomy.

The study protocol was in accordance with the Declaration of Helsinki and was reviewed and approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee (R2363) and the ethics review board of each institution. The need for informed consent was waived using the opt-out method since this was a retrospective observational study. This manuscript adhered the STROBE recommendation for observational studies.

### Perioperative management

#### *CRS with peritonectomy and HIPEC (the CRS group)*

Cytoreduction surgery including the Sugarbaker technique was performed to resect all the visible PM[6]. The surgery was usually performed by laparotomy as peritonectomy with several organ resections (such that gastrectomy, colectomy, proctectomy, ovariectomy, hysterectomy, splenectomy, cholecystectomy, and small bowel resection were performed during the same procedure as needed). In addition, partial resection of the peritoneum, greater omentum, and lesser omentum was performed when necessary[21]. Resectable distant metastases other than PM were resected during the same or different surgery. HIPEC was performed using 4 L of saline solution when sufficient cytoreduction was achieved[22]. The intra-abdominal temperature was maintained at 42.5-43.5°C for the duration of the HIPEC procedure (30-60 min). Therapeutic agents used in this procedure were 5-fluorouracil (5-FU), oxaliplatin, mitomycin C, and cisplatin alone or a combination of these drugs, selected according to patient tolerance and preoperative treatment.

#### *RIPM (the RIPM group)*

The operative approach (open, laparoscopic, and robotic surgery) was selected according to institutional preference. The primary metastatic tumor was resected according to the guidelines of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) (Tokyo, Japan) for treating CRC[16]. Localized macroscopically detected PM that could be re-

sected without significant invasiveness were dissected by excision of the small range of isolated PM only. Therefore, neither CRS with peritonectomy procedures nor HIPEC was performed.

#### *Perioperative chemotherapy*

A systemic chemotherapy regimen was selected according to institution policy. Chemotherapy for stage IV CRC was performed according to the JSCCR guidelines for the treatment of CRC. 5-FU, oxaliplatin, irinotecan, and molecular target agents were administered as needed during the perioperative period[16].

#### *Data collection*

Patients' demographic data, perioperative chemotherapy, tumor histology, operative information, and survival information were obtained by a prospectively maintained multi-institutional database and chart review. Peritoneal cancer index (PCI) was calculated as previously described by Jacquet et al[23]. This index is widely used for quantitative assessment of both distribution and size of PM. For calculating the PCI, the whole abdomen was partitioned into 13 regions; each region was scored according to the lesion size (LS: 0 to 3). LS-0 indicated no PM in that region, LS-1 indicated a small lesion size <0.5 cm, LS-2 describes a lesion sized between 0.5 and 5 cm, and LS-3 indicated a lesion size >5 cm. Therefore, the range that PCI could be between 0 and 39. The residual PM was evaluated using the completeness of cytoreduction (CCR) score[24]. A score of CCR-0 indicates no visible PM, CCR-1 indicates that the PM is <0.25 cm, CCR-2 indicates that PM is between 0.25 and 2.5 cm, and CCR-3 indicates that the PM diameter is >2.5 cm.

These scores were calculated and classified retrospectively based on the description in the surgical record. If there were no records in the chart, the region invaded by PM was determined by reviewing surgical records and the LS was determined from the description of the nodule size. When the surgical record indicated the presence of PM in any region, but their size was unknown, LS in that region was regarded as 2. Then, PCI was calculated based on this estimated region and LS.

#### *Outcomes*

The primary outcome in this study was OS calculated as the time between the initial treatment of PM and the time of death for any reason. Patients were deemed censored when they were alive at the time of the last follow-up. Secondary outcomes were postoperative in-hospital mortality, complications, and complete resection rate. Postoperative in-hospital mortality was defined as death due to any cause without discharge. Postoperative complications were staged according to the Clavien-Dindo classification of surgical complications. Patients who scored grade III or higher were judged to have postoperative complication[25]. The incidence of postopera-

tive complications was the proportion of patients with at least one or more complications. Intra-abdominal abscess, fistula, anastomotic leakage, postoperative bleeding, and small bowel obstruction/ileus were described separately. Patients who achieved CCR-0,1 after the surgery were considered to have achieved complete resection.

#### *Statistical analysis*

Patients' characteristics and operative findings were compared between the groups. In addition, the OS was compared between patients who achieved complete resection and those who did not achieve complete resection. Complete resection rate was evaluated separately based on the PCI. Additional subgroup analysis was performed to patients with a low PCI (PCI < 6) to reduce the differences between the groups.

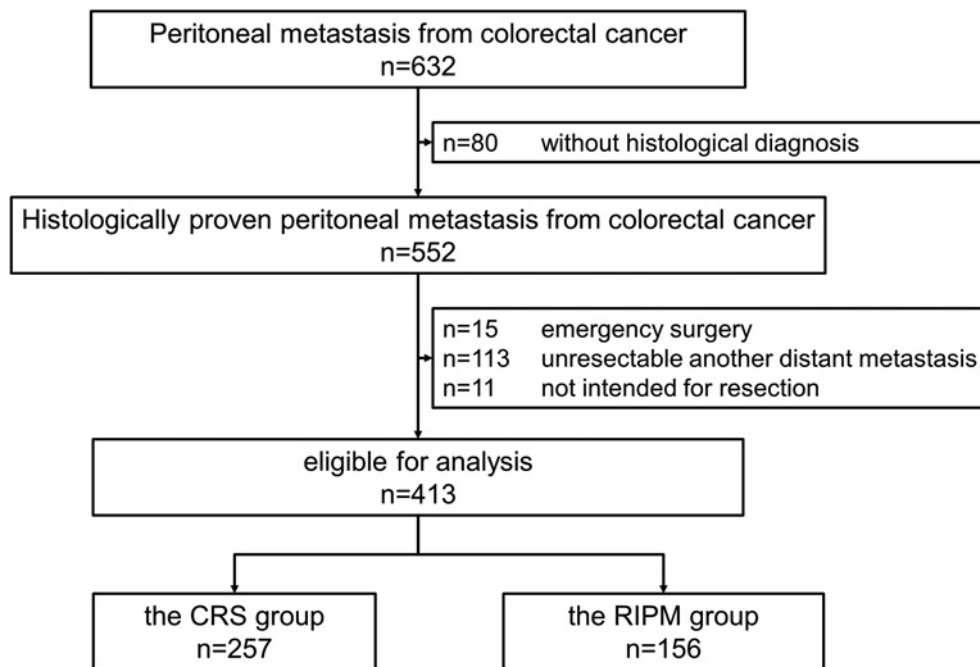
Numbers (percentage) have been used to describe categorical variables and mean (standard deviation) or median (interquartile range) have been used to describe continuous variables as appropriate. Chi-square test or Fisher's exact test was used to compare the groups: the risk difference (RD), risk ratio (RR), and 95% confidence interval (CI) for postoperative complications were calculated. Fisher's exact test was used when the cells in the contingency table include a number less than five. Multivariable generalized linear models using a binomial distribution with a log link were employed to estimate adjusted RR and 95% CI for postoperative complications. Kaplan-Meier survival curves were constructed for both groups and the OS was compared using the log-rank test between them. Univariable and multivariable Cox regression analyses were performed to calculate the hazard ratio (HR) and 95% CI.

Multivariable analysis was conducted by adjusting the clinically relevant variables, such as age ( $\geq 65 / < 65$ ), onset of PM (synchronous/metachronous), tumor location (colon/rectum), lymph nodes metastases (yes/no), other distant metastases (yes/no), PCI score ( $\leq 2 / 3$  to  $5 / 6$  to  $13 / \geq 14$ ) and preoperative chemotherapy (yes/no). We excluded the data of patients whose data for these variables were missing or incomplete. A two-sided *P*-value of <0.05 was set for statistical significance. All statistical tests were performed on STATA ver. 16.1 (STATA Corp, College Station, TX, USA).

## **Results**

#### *Patient background*

A total of 632 patients with CRC-PM were included from 14 institutions. Among them, 80 and 139 were excluded who had no histological diagnosis of PM, and those who underwent emergency surgery, after applying the exclusion criteria. Among the 413 eligible patients, CRS with peritonectomy was performed in 257 patients (CRS group), and



**Figure 1.** Flowchart of the study participants. CRS, cytoreductive surgery

RIPM without peritonectomy was performed in 156 patients (RIPM group) (Figure 1).

Patients' background data are summarized in Table 1. The CRS group had younger patients (median and range: 56 [11-88] and 70 [13-91] years in the CRS and RIPM groups, respectively), who tended to have metachronous PM and liver metastases and received preoperative chemotherapy than patients in the RIPM group. Systemic chemotherapy agents commonly consisted of 5-FU and oxaliplatin, followed by molecular-targeted agents.

### Operative findings

The surgical findings are shown in Table 2. In the CRS group, the procedure most performed was pelvic peritonectomy, followed by left/right hemidiaphragm, and abdominal wall peritonectomy. According to resected organs, large and small bowel resection, hysterectomy, and ovariectomy were performed more frequently in the CRS group than in the RIPM group. Only open procedures were performed in the CRS group, however, minimally invasive surgery such as laparoscopy and robotic surgery were selected in more than half of the RIPM group. The operative time was longer, and the amount of operative bleeding was higher in the CRS group than in the RIPM group. More patients had a high PCI score (6 points or higher) in the CRS group. Complete resection was achieved for 202/252 (80%) of the CRS group and 113/155 (73%) of the RIPM group. HIPEC was performed in 190/257 patients (74%) in the CRS group.

Postoperative mortality and complications are summarized in Table 3. Six (2.3%) postoperative mortalities were ob-

served in the CRS group whereas none were observed in the RIPM group (RD: 2.3%, 95% CI: 0.49% to 4.2%,  $P=0.09$ ). The incidence of postoperative grade III or worse overall complication was 50 (19.5%) in the CRS group and 15 (9.6%) in the RIPM group (RD: 9.8%, 95% CI: 3.1% to 16.5%, RR: 2.02, 95% CI: 1.18 to 3.48,  $P=0.008$ ). Of these complications, intra-abdominal abscess and anastomotic leakage are relatively common in the CRS group. In multivariable analysis, the postoperative complication was not significantly different between the groups (adjusted RR: 1.42, 95% CI: 0.62 to 3.25,  $P=0.41$ ).

### Survival analysis compared between the CRS and RIPM groups

The survival curves of 407 patients were analyzed after excluding patients with missing data. The Median follow-up time was 26.4 months in this cohort. Moreover, 216/407 patients (53.1%) in this entire cohort died: 128/251 (51.0%) and 88/156 (56.4%) in the CRS and RIPM groups. Compared with the CRS group vs the RIPM group, the median OS was 42.3 vs 35.0 months (HR: 0.91, 95% CI: 0.69 to 1.19,  $P=0.48$ ) (Table 4, Figure 2). Furthermore, the OS was not significantly different between both the groups after adjustment of clinically relevant covariates (adjusted HR: 1.27, 95% CI: 0.81 to 2.00,  $P=0.29$ ) (Table 4).

### Patients who achieved CCR-0,1 and CCR-2,3

Figure 3 shows the Kaplan-Meier curves for patients who accomplished complete resection (CCR-0,1) and those who did not (CCR-2,3). The OS of patients who accomplished

**Table 1.** Patient Characteristics.

Factor	No./Total No. (%)		P value
	CRS (n=257)	RIPM (n=156)	
Age			<0.001
<65	183/256 (71%)	40/156 (26%)	
≥65	73/256 (29%)	116/156 (74%)	
Sex			0.09
Male	118 (46%)	85 (54%)	
Female	139 (54%)	71 (46%)	
Onset			<0.001
Synchronous	130/246 (53%)	128/156 (82%)	
Metachronous	116/246 (47%)	28/156 (18%)	
Tumor histology			0.01
tub	168/255 (66%)	121/156 (78%)	
por/sig/muc/others	87/255 (34%)	35/156 (22%)	
Tumor location			<0.001
Colon	242 (94%)	127 (81%)	
Rectum	15 (6%)	29 (19%)	
lymph nodes metastases	178/245 (73%)	115/156 (74%)	0.82
ascites	77 (30%)	62 (40%)	0.04
CEA median, (IQR) [No.], mg/dl	6.9 (3.0, 30.1) [243]	7.0 (3.1, 15.0) [155]	0.41
CA19-9 median, (IQR) [No.], mg/dl	19.8 (8.6, 79.0) [242]	22.7 (8.5, 68.6) [155]	0.99
Distant metastases			
Liver	56 (22%)	16 (10%)	0.003
Lung	3 (1.2%)	2 (1.3%)	1.00
Others	3 (1.2%)	12 (8%)	0.002
Preoperative chemotherapy	223 (87%)	21 (13%)	<0.001
Postoperative chemotherapy	143/256 (56%)	109/155 (70%)	0.004
Systemic chemotherapy agents			
Fluorouracil	230/257 (89%)	116/155 (75%)	<0.001
Oxaliplatin	157/257 (61%)	78/155 (50%)	0.03
Irinotecan	109/257 (42%)	25/155 (16%)	<0.001
Molecular-targeted agent	123/257 (48%)	61/155 (39%)	0.09
Immune checkpoint inhibitor	2/257 (0.8%)	0/155 (0%)	0.53

IQR indicates interquartile range; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; CRS, cytoreductive surgery; RIPM, resection of isolated peritoneal metastases

complete resection was significantly better than those who did not (median OS 46.1 vs 21.4 months, HR 0.37, 95% CI: 0.27 to 0.50,  $P < 0.001$ ). Among the patients with a low PCI (<6), more than 80% achieved complete resection in both the CRS and RIPM groups (87/93, 94% vs 97/110, 88%). Among the patients with a high PCI (6 points or higher), 15/44 (34%) achieved complete resection in the RIPM group although 115/157 (73%) of the patients achieved complete resection in the CRS group (Table 5).

#### **Subgroup analysis in patients with a low PCI (PCI < 6)**

The patient characteristics and operative findings were summarized in the Supplementary Table 1, 2. The CRS group had more young patients, metachronous disease, liver metastasis and preoperative chemotherapy. Most patients in the CRS group underwent pelvic peritonectomy (68/94,

72%). More organs were resected and operative bleeding was significantly higher in the CRS group.

The incidence of postoperative grade III or worse overall complication was 17 (18.1%) in the CRS group and 10 (9.1%) in the RIPM group (RD: 9.0%, 95% CI: -0.46% to 18.4%, RR: 1.99, 95% CI: 0.96 to 4.13,  $P = 0.059$ ) (Supplementary Table 3). Compared with the CRS group vs the RIPM group, the median OS was 65.5 vs 40.6 months (HR: 0.54, 95% CI: 0.35 to 0.83,  $P = 0.005$ ) (Supplementary Figure). However, There was no significant difference between the two groups in multivariable analysis (HR 1.06, 95%CI: 0.50 to 2.25,  $P = 0.87$ ) (Supplementary Table 4).

## **Discussion**

In this retrospective study, there was no significant differ-

**Table 2.** Operative Findings.

Factor	No./Total No. (%)		P value
	CRS (n=257)	RIPM (n=156)	
Simultaneous resection of primary tumor	127/246 (52%)	129/156 (83%)	<0.001
Peritonectomy procedure			
Abdominal wall peritonectomy	65 (25%)	0 (0%)	<0.001
left/right hemidiaphragm peritonectomy	104 (40%)	0 (0%)	<0.001
Pelvic peritonectomy	198 (77%)	0 (0%)	<0.001
Number of resected organs, median (IQR) [No.]	2 (1, 4) [257]	1 (1, 1) [156]	<0.001
Resected organs			
Colon/Rectum			<0.001
no resection	64 (25%)	23 (15%)	
partial resection	158 (61%)	130 (83%)	
total resection	35 (14%)	3 (2%)	
Small bowel	137 (53%)	13 (8%)	<0.001
Uterus	102/139 (73%)	6/71 (8%)	<0.001
Ovary	110/139 (79%)	19/71 (27%)	<0.001
Stomach	16 (6%)	3 (2%)	0.05
Bladder	6 (2%)	2 (1%)	0.72
Liver	45 (18%)	6 (4%)	<0.001
Paraaortic lymph node	1 (0.4%)	3 (2%)	0.15
Kidney	1 (0.4%)	2 (1%)	0.56
Gallbladder	12 (5%)	5 (3%)	0.47
Colostomy/Ileostomy	118 (46%)	23 (15%)	
Approach			
Open	257 (100%)	66 (42%)	<0.001
Laparoscopy/Robot	0 (0%)	90 (58%)	<0.001
Operative time, mean (SD) [No.], min	305.3 (111.8) [170]	261.9 (113.6) [156]	<0.001
Operative bleeding, median (IQR) [No.], ml	1236.5 (697.5, 1860) [188]	63.5 (8.5, 230) [156]	<0.001
Peritoneal cancer index			<0.001
≤2	47/253 (19%)	73/154 (47%)	
3 to 5	47/253 (19%)	37/154 (24%)	
6 to 13	77/253 (30%)	25/154 (16%)	
14≤	82/253 (32%)	19/154 (12%)	
Completeness of cytoreduction score			0.09
0,1	202/252 (80%)	113/155 (73%)	
2,3	50/252 (20%)	42/155 (27%)	
Hyperthermic intraperitoneal chemotherapy	190 (74%)	0 (0%)	<0.001

IQR indicates interquartile range; SD, standard deviation, CRS, cytoreductive surgery; RIPM, resection of isolated peritoneal metastases

ence in postoperative complications between the CRS and the RIPM groups in multivariable analysis. The OS of patients who underwent CRS-HIPEC was not shown to be superior to that of patients who underwent RIPM for CRC-PM. Complete resection was associated with a longer OS in patients with CRC-PM, and most patients undergoing CRS-HIPEC achieved complete resection despite having a higher PCI than those undergoing RIPM.

To the best of our knowledge, there are no reports comparing CRS-HIPEC and RIPM to date; therefore, this is the first report presenting this comparison. Good long-term survival (median 12-63 months) has been reported in a systematic review of CRS-HIPEC for CRC-PM[26]. In this study,

the effectiveness of CRS-HIPEC was not shown in comparison to RIPM, which may be because a relatively good OS was observed in patients undergoing RIPM in Japan. Moreover, in the latest RCT, which assessed the therapeutic effect of HIPEC when added to CRS in patients with CRC-PM, the long-term survival in the CRS alone group was better than expected[27]. These results suggest that complete resection of the PM may contribute to better long-term survival than previously expected, supporting the statement in NCCN guideline that “if R0 resection can be achieved, surgical resection of isolated peritoneal metastases may be considered at experienced centers.”[19] In this study, all the patients in the CRS group underwent an open procedure, however, 58%

**Table 3.** Postoperative Complications, Uni- and Multi-Variable Regression Analysis.

	CRS (n=257)	RIPM (n=156)	Univariable			Multivariable	
			RD (95% CI)	RR (95% CI)	P value	adjusted RR (95% CI)	P value
Postoperative in-hospital mortality	6 (2.3%)	0 (0%)	2.3% (0.49%, 4.2%)	-	0.09		
Postoperative complication (CD grade $\geq$ III)	50 (19.5%)	15 (9.6%)	9.8% (3.1%, 16.5%)	2.02 (1.18, 3.48)	0.008	1.42 (0.62, 3.25)	0.41
intra-abdominal abscess	15 (5.8%)	3 (1.9%)					
fistula	3 (1.2%)	0 (0%)					
anastomotic leakage	15 (5.8%)	3 (1.9%)					
postoperative bleeding	5 (1.9%)	2 (1.3%)					
small bowel obstruction/ileus	2 (0.8%)	4 (2.6%)					
others	11 (4.3%)	6 (3.8%)					

The incidence of postoperative complications was the proportion of patients with at least one or more complications.

Multivariable analysis was adjusted by age ( $\geq 65$ / $<65$ ), onset of PM (synchronous/metachronous), tumor location (colon/rectum), lymph node metastases (yes/no), other distant metastases (yes/no), PCI score ( $\leq 2$  / 3 to 5 / 6 to 13 / 14 $\leq$ ) and preoperative chemotherapy (yes/no)

CD indicates Clavien-Dindo; CRS, cytoreductive surgery; RIPM, resection of isolated peritoneal metastases; RD, risk difference; RR, risk ratio; CI, confidence interval; PM, peritoneal metastases; PCI, peritoneal cancer index

**Table 4.** Overall Survival, Uni- and Multivariable Cox Regression.

	Univariable			Multivariable		
	No. of events/No. at risk	HR (95% CI)	P value	No. of events/No. at risk	adjusted HR (95% CI)	P value
RIPM	88/156	Ref		88/154	Ref	
CRS	128/251	0.91 (0.69, 1.19)	0.48	116/233	1.27 (0.81, 2.00)	0.29

Multivariable analysis was adjusted by age ( $\geq 65$ / $<65$ ), onset of PM (synchronous/metachronous), tumor location (colon/rectum), lymph nodes metastases (yes/no), other distant metastases (yes/no), PCI score ( $\leq 2$  / 3 to 5 / 6 to 13 / 14 $\leq$ ) and preoperative chemotherapy (yes/no)

RIPM indicates resection of isolated peritoneal metastases; CRS, cytoreductive surgery

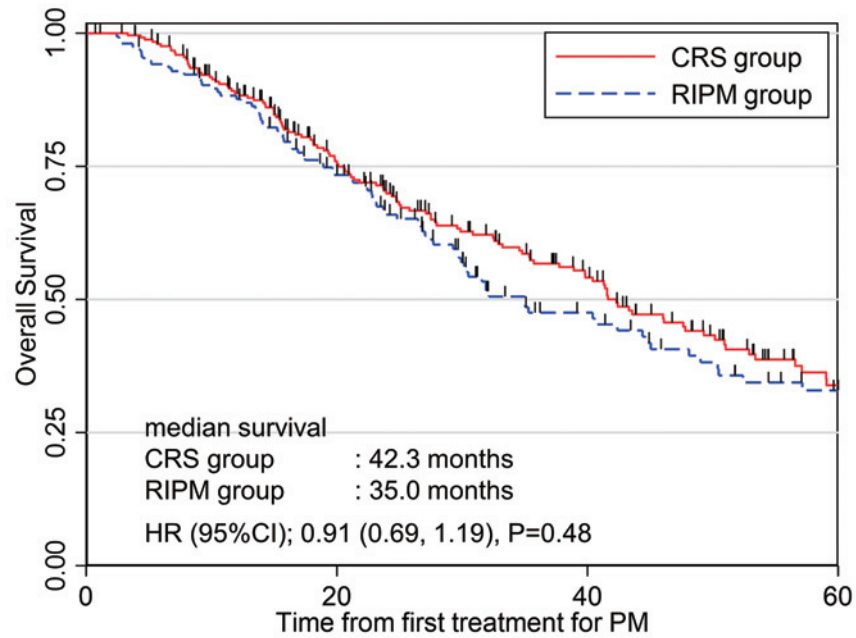
of the patients in the RIPM group underwent laparoscopic surgery. The prognosis of RIPM, including the laparoscopic approach, was relatively better in patients with low PCI. The result suggests that laparoscopic surgery may be indicated for patients with low PCI[28].

Patients who achieved CCR-0,1 or R0 were reported to have a better prognosis than those who did not, which is consistent with the results of this study[7,18]. Indeed, it seems that CRS is the only treatment currently available to achieve complete resection even in patients with advanced PM (who scored high PCI). In contrast, in patients with localized PM (who scored low PCI), complete resection was achieved by the RIPM. Therefore, the extent of PM and the appropriate boundaries for excision still need to be evaluated. Patients with advanced PM with high PCI likely received palliative surgery when they underwent RIPM surgery. Therefore, patients with a poor prognosis were excluded from this study, which raises a bias against patients who underwent CRS-HIPEC.

Regarding the short-term postoperative outcomes, Clavien-Dindo grade III or higher grade of complications in

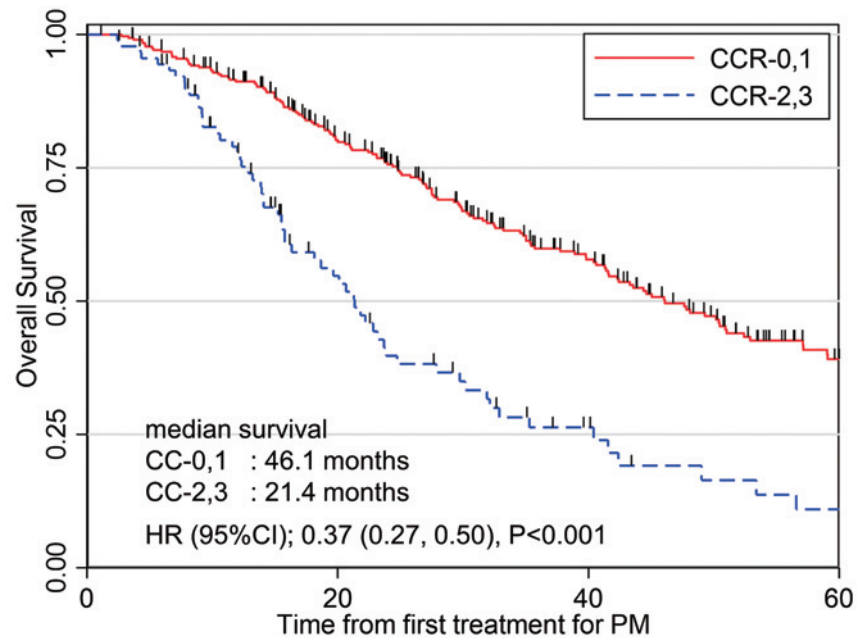
patients undergoing CRS-HIPEC was 19.5% in this study, which is comparable to that reported in a systematic review, reporting similar postoperative morbidity outcomes of CRS-HIPEC as that for other major abdominal surgery[29]. It might be considered that CRS-HIPEC was safely performed in specialized centers in Japan although postoperative in-hospital mortality of (2.3%) was observed. However, it should be noted that this study alone could not rule out that the incidence of postoperative in-hospital mortality and complications is higher in patients undergoing CRS-HIPEC than those undergoing RIPM.

This retrospective study has some limitations. First, unknown and unmeasured confounding factors were excluded because this was a retrospective study, although the important factors for selecting treatment strategy (age, PCI, preoperative chemotherapy, and other distant metastases) were included in the multivariable model. Selection bias, which was disadvantageous for patients' outcomes undergoing CRS, seemed to affect the study results as patients with a poor prognosis who underwent only palliative surgery were excluded. Also, it might be difficult to simply compare the two



Number at risk				
CRS group	251	151	81	28
RIPM group	156	103	43	21

**Figure 2.** Kaplan–Meier curve for overall survival comparing the patients undergoing CRS–HIPEC (the CRS group) and the patients undergoing RIPM (the RIPM group). CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; RIPM, resection of isolated peritoneal metastases



Number at risk				
CCR-0,1	313	215	112	44
CCR-2,3	91	37	11	4

**Figure 3.** Kaplan–Meier curve for overall survival comparing the patients who achieved complete resection (CCR-0,1) and those who did not achieve (CCR-2,3), CCR, completeness of cytoreduction



**Table 5.** Number and Proportion of Patients Who Achieved Complete Resection.

PCI score	No./Total No. (%)		P value
	CRS	RIPM	
≤2	44/47 (94%)	67/73 (92%)	1.00
3 to 5	43/46 (93%)	30/37 (81%)	0.10
6 to 13	69/76 (91%)	12/25 (48%)	<0.001
14≤	46/81 (57%)	3/19 (16%)	0.002

PCI indicates peritoneal cancer index; CRS, cytoreductive surgery; RIPM, resection of isolated peritoneal metastases

surgical procedures as the indications for CRS are different in each institution. In addition, the younger patients tended to perform a more demolitive procedure (CRS), which is considered more effective to cure the peritoneal metastasis. To increase the validity of the comparison, we performed multivariable analyses, which included clinically important factors. Second, there were no data on chemotherapy after tumor recurrence or progression, which made it difficult to evaluate the effect of systemic chemotherapy after tumor recurrence and progression to OS. However, it might be considered that there is no significant difference in the systemic chemotherapy regimen regardless of which surgery is selected, as chemotherapy after recurrence or progression may be performed according to Japanese treatment guidelines for CRC. Third, the generalizability of these results for patients with CRC-PM is limited due to the single ethnicity in Japan, although the internal validity of this study may be higher than that of previous studies. This is because, in this study, the control group consisted of patients who underwent RIPM, in which the PM is resected, rather than patients who underwent systemic chemotherapy without the goal of tumor lesion resection including PM. However, it should be noticed that some operative reports in the RIPM group did not describe the size of the peritoneal metastasis, which leads to underestimation of PCI.

In conclusion, in patients with CRC-PM, CRS was not associated with a better prognosis compared to RIPM. Patients who achieved complete resection showed good long-term survival, suggesting that surgery aimed at complete resection should be performed in patients with potentially resectable CRC-PM. Patients with extended PM may require CRS to achieve complete resection, but patients with localized PM may be able to achieve complete resection with RIPM, which may be accompanied by fewer postoperative complications. Further research is needed to determine the appropriate resection procedure according to the extent of PM.

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#### Conflicts of Interest

Koya Hida has received a grant from Senko Medical Instrument Mfg. Co., Ltd. All the other authors have no conflict of interest to declare.

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#### Authors Contributions

Shinya Yoshida, Yasuyuki Kamada, Koya Hida, and Kazuyuki Okada contributed to the study design and conceptualization. Shinya Yoshida and Satoshi Morita conducted the statistical analysis. Koya Hida, Kazutaka Obama, Toshiyuki Kitai, and Yutaka Yonemura contributed to the interpretation of the results. All authors reviewed the draft of the manuscript and conducted critical scrutiny. All authors have approved the publication of the final version of the manuscript.

#### Approval by Institutional Review Board (IRB)

The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution in accordance with the Declaration of Helsinki. Kyoto University Graduate School and Faculty of Medicine Ethics Committee, Approval No. (R2363). The need for informed consent was waived using the opt-out method since this was a retrospective observational study.

#### Data Sharing and Accessibility

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

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### Supplementary Files

**Supplementary Table 1.** Patient characteristics in patients with a low PCI (PCI<6).

**Supplementary Table 2.** Operative findings in patients with a low PCI (PCI<6).

**Supplementary Table 3.** Postoperative complications, uni- and multi-variable regression analysis in patients with a low PCI (PCI<6).

**Supplementary Table 4.** Overall survival, uni- and multivariable cox regression in patients with a low PCI (PCI<6).

**Supplementary Figure.** Kaplan-Meier curve for overall survival comparing the patients with a low PCI (PCI<6) undergoing CRS-HIPEC (the CRS group) and the patients undergoing RIPM (the RIPM group). PCI, peri-

toneal cancer index; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; RIPM, resection of isolated peritoneal metastases.

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