Comparative Study - Retrospective Cohort

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Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus R0 resection for resectable colorectal cancer with peritoneal metastases and low peritoneal cancer index scores: a collaborative observational study from Korea and Japan

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Background: The benefits of hyperthermic intraperitoneal chemotherapy (HIPEC) after cytoreductive surgery (CRS) for colorectal cancer with peritoneal metastasis (CPM) remain controversial. R0 resection without peritoneal stripping might be as effective as CRS plus HIPEC. The authors aimed to compare the long-term oncological outcomes of patients with CPM and peritoneal cancer index (PCI) scores less than or equal to 6 who underwent R0 resection in Japan with those who underwent CRS plus HIPEC in Korea.

Materials and methods: This international, retrospective cohort study was conducted in Korea and Japan using a prospectively collected clinical database. Patients who underwent surgery from July 2014 to December 2021 for CPM with a PCI score of less than or equal to 6 and completeness of the cytoreduction score-0 were included. The primary outcome was relapse-free survival (RFS), and the secondary outcomes were overall survival, peritoneal RFS (PRFS), and postoperative outcomes.

Results: The 3-year RFS was significantly longer in the CRS + HIPEC group than in the R0 resection group: 35.9% versus 6.9% ($P < 0.001$); 31.0% versus 6.7% ($P = 0.040$) after propensity score matching. The median PRFS was significantly longer in the CRS + HIPEC group than in the R0 resection group: 24.5 months versus 17.2 months ($P = 0.017$). The 3-year overall survival and postoperative complications did not significantly differ between the two groups.

Conclusions: RFS and PRFS rates were significantly prolonged after CRS plus HIPEC, whereas postoperative complications and length of hospital stay were not increased. Therefore, curative CRS plus HIPEC may be considered a treatment strategy for selected patients with resectable CPM and low PCI scores.

Keywords: colorectal cancer, peritoneal metastasis, hyperthermic intraperitoneal chemotherapy, cytoreductive surgery, R0 resection

Introduction

Colorectal cancer with peritoneal metastasis (CPM) accounts for ~10% of colorectal cancer (CRC) cases[1]. According to the National Comprehensive Cancer Network (NCCN) guidelines, although the primary treatment for CPM is systemic chemotherapy, surgical resection including cytoreductive surgery (CRS) for the isolated peritoneal disease, may be considered at experienced centres. The additional benefit of hyperthermic intraperitoneal chemotherapy (HIPEC) following CRS for CPM remains debatable[2,3]. The French PRODIGE 7 randomized controlled trial (RCT) failed to demonstrate any evidence of an overall survival (OS) benefit associated with CRS plus HIPEC compared with CRS alone[4]. However, as the PRODIGE 7 RCT investigated only one specific HIPEC protocol and regimen, it could not fully disprove the rationale

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behind CRS plus HIPEC[2]. Hence, several international guidelines continue to recommend CRS plus HIPEC for selected patients with resectable CPM[5].

Since 2014, CRS followed by HIPEC has been performed in South Korea to treat patients with CPM[6–10]. Although CRS with HIPEC is only performed at select specialized centres in Korea, it can be regarded as a treatment option for patients with stage IV CRC. Complete cytoreduction of gross metastatic sites and HIPEC with direct chemotherapeutic agents to treat microscopic metastatic lesions in the abdominal cavity are expected to prolong patient survival. In contrast, treatment strategies other than CRS plus HIPEC have been adopted in Japan[11,12]. According to the Japanese Society for Cancer of the Colon and Rectum guidelines for treating CRC, R0 resection, which is distinguished from aggressive cytoreductive debulking surgery or peritoneal stripping surgery, is a desirable treatment option if metastases are confined to the adjacent peritoneum, as well as in cases where a few easily resectable peritoneal metastases are present in the distant peritoneum[11,12]. The 5-year OS after R0 resection for CPM is ~30% in Japanese patients[13,14].

In a previous study that investigated the factors affecting the completeness of cytoreduction (CC) scores, a low peritoneal carcinomatosis index (PCI) score (≤ 6) was an independent factor affecting CC-0 in patients with CPM[15]. However, since treatment strategies for CPM vary across countries, international collaborative research is essential for comparing treatment outcomes. Korea and Japan have similar patient characteristics and healthcare systems, making them suitable for comparison. Accordingly, we aimed to compare the long-term oncological outcomes and clinical manifestations of patients with CPM and PCI scores less than or equal to 6 who underwent R0 resections in Japan with those who underwent CRS plus HIPEC in Korea.

HIGHLIGHTS

- The benefits of hyperthermic intraperitoneal chemotherapy (HIPEC) after cytoreductive surgery for colorectal cancer with limited peritoneal metastases remain controversial.
- Colorectal cancer patients with peritoneal metastases and a peritoneal cancer index less than 6 treated with cytoreductive surgery followed by HIPEC showed improved 3-year relapse-free survival than patients who underwent R0 resections only.
- The 3-year overall survival and postoperative complications did not show a significant difference between cytoreductive surgeries with HIPEC and R0 resections.
- In patients with colorectal cancer with limited peritoneal seeding, cytoreductive surgery plus HIPEC can be considered to achieve curative treatment with local control.

Methods

Study design

This international, two-centre, retrospective cohort study was conducted in South Korea and Japan using data from prospectively collected clinical databases. Informed consent was obtained from all the participants using the opt-out option. The study protocol was approved by the ethics committees of each institution, and conformed to the provisions of the Declaration of Helsinki in 1964 (as revised in Brazil in 2013). The study was conducted from July 2014 to December 2021. This study is reported according to the Strengthening the Reporting of Cohort Studies in Surgery (STROCSS) guidelines[16].

Patient selection

Patients with a PCI score of less than or equal to 6 and CC-0, who underwent surgery between July 2014 and December 2021 for both synchronous and metachronous CPM, were included in this study. Patients with appendiceal cancer were excluded. The treatment strategy for CPM involved CRS plus HIPEC in South Korea, whereas R0 resection was performed in Japan. CPM was diagnosed preoperatively via abdominopelvic computed tomography (CT), PET CT, or diagnostic laparoscopy. The diagnosis was confirmed postoperatively via histopathological inspection of the resected specimens. PCI scoring was performed in 13 abdominopelvic regions based on the findings of diagnostic laparoscopies and preoperative CT and PET-CT scans in cases of surgery alone; however, final scores were determined based on findings of thorough abdominal exploration during surgery, including the omentum, adnexa, small bowel, etc. CPM previously or simultaneously diagnosed at the time of primary resection was defined as synchronous metastasis, while CPM recurring after primary resection was defined as metachronous metastasis. Each region was graded using the following scale: 0 points, absence of tumour; 1 point, tumour less than to 0.5 cm; 2 points, tumour from 0.5–5 cm; and 3 points, tumour greater than 5 cm[17]. CC was assessed based on the extent of the remnant tumour: CC-0, complete removal of the visible tumour; CC-1, remnant tumour less than 0.25 cm; CC-2, residual tumour between 0.25 and 2.5 cm; and CC-3, visible tumour greater than 2.5 cm in diameter[18]. CC-0 corresponds to R0/R1 according to the Japanese guidelines. The indications for preoperative and adjuvant chemotherapy were determined at the discretion of the multidisciplinary team. They were based on a comprehensive assessment of the extent of CPM, general condition of the patients, and expected adverse events following chemotherapy.

Procedures of CRS plus HIPEC in South Korea

The CRS and HIPEC procedures have been described previously[6]. The CRS procedure involved the resection of metastatic lesions and primary cancer via peritonectomy. Parietal peritonectomy and visceral resections were performed according to the Sugarbaker techniques[19,20]. Anterior peritonectomy, upper quadrant peritonectomy, pelvic peritonectomy, subphrenic peritonectomy, and omental bursectomy were selectively performed, depending on the site of peritoneal metastasis. HIPEC involved circulating a mixture of 35 mg/m^2 mitomycin-C (MMC) and 3 l hypertonic solution (Physioneal, 1.5% Peritoneal Dialysis Solution, Baxter Healthcare Ltd.). MMC was administered at 17.5 mg/m^2 initially for 30 min, and at 8.8 mg/m^2 for 60 min. The mixed solution was circulated for 800–1000 ml/min in a HIPEC pump (the Belmont Hyperthermic Pump) to maintain its temperature at 42–43°C for 90 min. The inflow and outflow temperatures of the HIPEC solution, as well as the body temperature of the patient, were recorded every 5 min.

Surgical procedure of R0 resection in Japan

Surgical procedures for R0 resection of CPM have been described previously[14,21]. For synchronous CPM, all macroscopically detectable CPM were dissected at the time of the initial primary tumour resection, along with the regional lymph nodes. In contrast, only the macroscopically detectable diseased portion of the peritoneum was dissected in cases with metachronous CPM. Consequently, no macroscopic tumours remained in either synchronous or metachronous CPM cases. However, the surgical concept behind R0 resections differs from that behind CRS, which involves the dissection of the diseased portion along with the adjacent peritoneum. Although CRS for CPM also does not necessarily mandate stripping of the entire peritoneum[22], it differs from R0 resections in that its definition does not include the concept of peritoneal stripping at all.

Outcomes

The primary outcome was relapse-free survival (RFS), which was defined as the time from surgery for CPM to the first peritoneal or distant relapse or death from any cause. Secondary outcomes were OS (defined as the interval between surgery for CPM and death from any cause), peritoneal RFS (PRFS; the interval between surgery for CPM and the first peritoneal relapse or death from any cause), and postoperative outcomes.

Statistical analysis

Numerical data are presented as medians (ranges). They were compared using the Mann–Whitney U test. Categorical data are presented as numbers (percentages). They were compared using Fisher's exact test. Survival outcomes are presented as rates (%) with 95% 95% CI. Survival curves were estimated using the Kaplan–Meier method. The differences in RFS, OS, and PRFS between the CRS + HIPEC and R0 resection groups were evaluated using the log-rank test. All *P* values were two-sided, and a *P* value of 0.05 or less was considered statistically significant. Propensity score matching (PSM) was performed for both groups in a 1:1 ratio. Age, American Society of Anesthesiologists physical status (ASA-PS), histopathological type, emergence time (synchronous or metachronous), PCI score, preoperative chemotherapy within 6 months before the surgery, and adjuvant chemotherapy were included as covariates for PSM. Statistical analyses were performed using SAS (version 9.4; SAS Institute), R statistics 4.2.2 (http://www.r-project.org), and EZR[23], a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria [version 2.13.0]), as required.

Results

Patient characteristics

The patient characteristics of the entire cohort are presented in Table 1. In total, 166 patients met the inclusion criteria. Based on the emergence time of CPM, 47 of the 166 patients (28%) had synchronous CPM, and the remaining 119 (72%) had metachronous CPM. The median PCI score was 3. Preoperative, HIPEC, and adjuvant chemotherapy were administered to 47%, 65%, and 66% of the patients, respectively.

The CRS + HIPEC and R0 resection groups included 108 and 58 patients, respectively. The CRS + HIPEC group had a significantly younger age, higher body surface area, and lower CA19-9 values. Furthermore, the proportion of patients with ASA-PS of 3–4 (32% versus 5%) and those who were administered adjuvant chemotherapy (79% versus 43%) was significantly higher in the

Table 1

Patient characteristics of the entire cohort.

	Entire cohort (*N* = 166)	CRS + HIPEC (*N* = 108)	R0 resection (*N* = 58)	*P*
Sex, *N* (%)				
Female	98 (59)	58 (54)	40 (69)	0.069
Male	68 (41)	50 (46)	18 (31)	
Age (years)	59 [17–82]	56 [17–79][a]	65 [30–82][a]	< 0.001
BMI (kg/m^2)	23.3 [14.9–37.1][a]	23.3 [16.6–37.1][a]	22.5 [14.9–32.8][a]	0.422
BSA (m^2)	1.60 [1.28–2.36][a]	1.63 [1.33–2.36][a]	1.59 [1.28–2.03][a]	0.036
ASA-PS, *N* (%)				
1–2	127 (77)	72 (67)	55 (95)	< 0.001
3–4	39 (23)	36 (33)	3 (5)	
CEA (ng/ml)	4.3 [0.5–386.9][a]	4.2 [0.5–386.9][a]	4.3 [1.2–375.5][a]	0.656
CA19-9 (U/ml)	12.2 [0.6–2686.3][a]	10.2 [0.8–2686.3][a]	16.2 [0.6–483.6][a]	0.002
Primary tumour location, N (%)				
Right-sided	65 (39)	38 (35)	27 (47)	0.183
Left-sided	101 (61)	70 (65)	31 (53)	
Histopathological type, N (%)				
Well differentiated	12 (7)	7 (6)	5 (9)	0.936
Moderately differentiated	128 (77)	84 (78)	44 (76)	
Poorly differentiated	10 (6)	7 (6)	3 (5)	
Mucinous	16 (10)	10 (9)	6 (10)	
Emergence time, *N* (%)				
Synchronous	47 (28)	36 (33)	11 (19)	0.070
Metachronous	119 (72)	72 (67)	47 (81)	
PCI score	3 [1–6][a]	3 [1–6][a]	4 [2–6][a]	0.082
Preoperative chemotherapy (≤ 6 months), *N* (%)	78 (47)	54 (50)	24 (41)	0.329
Surgical approach, N (%)				
Open	145 (87)	108 (100)	37 (64)	—
Laparoscope	21 (13)	0	21 (36)	
Adjuvant chemotherapy, *N* (%)	110 (66)	85 (79)	25 (43)	< 0.001

[a]Median [range].

ASA-PS, American Society of Anesthesiologists-physical status; BSA, body surface area; CA, cancer antigen; CEA, carcinoembryonic antigen; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; PCI, peritoneal carcinomatosis index.

Table 2

Postoperative outcomes.

	CRS + HIPEC (*N* = 108)	R0 resection (*N* = 58)	*P*
Operation time (min)	385 [201–900][a]	285 [81–678][a]	< 0.001
Blood loss (ml)	500 [0–5200][a]	180 [2–3171][a]	0.003
Blood transfusion, *N* (%)	15 (14)	8 (14)	1.000
Morbidity (≥ CD Grade III), *N* (%)	8 (7)	5 (9)	0.770
Reoperation, *N* (%)	3 (3)	0	0.552
Mortality, *N* (%)	0	0	—
Length of hospital stay (day)	14 [7–104][a]	13 [5–47][a]	0.344

[a]Median [range].

CD, Clavien–Dindo classification; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy.

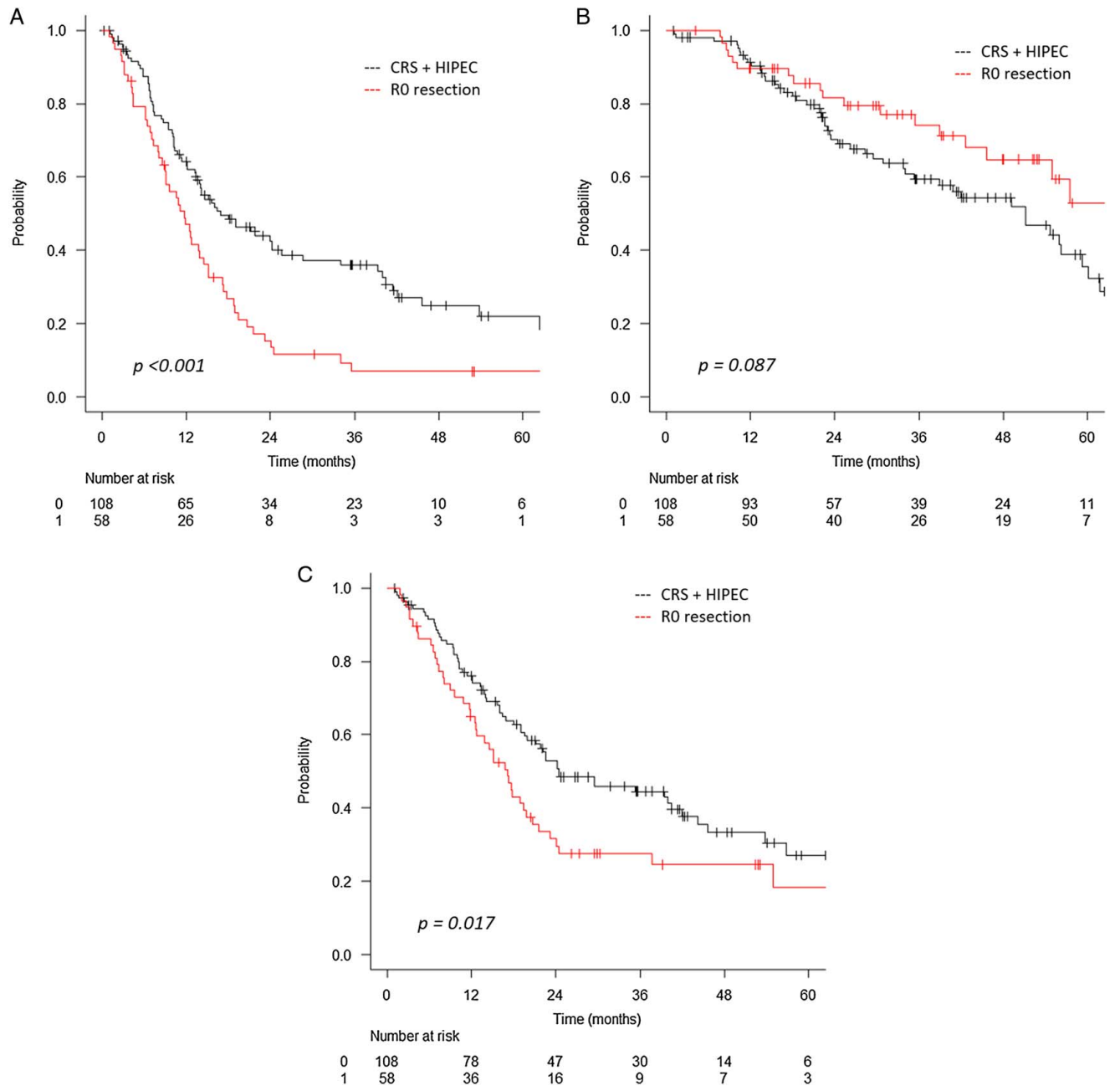

Figure 1. Kaplan–Meier curves for survival outcome. (A) Relapse-free survival. (B) Overall survival. (C) Peritoneal relapse-free survival. CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy.

CRS + HIPEC group. No significant differences were observed in other patient characteristics between the two groups.

Postoperative outcomes

The median operation time was 385 min in the CRS + HIPEC group and 285 min in the R0 resection group. Hence, it was significantly longer in the CRS + HIPEC group. The median blood loss was significantly higher in the CRS + HIPEC group than that in the R0 resection group (500 versus 180 ml). No significant differences in the proportion of blood transfusions, severe morbidity, reoperations, death, or postoperative hospital stay were observed between the two groups. The median length of postoperative hospital stay was 14 and 13 days in the CRS + HIPEC and R0 resection groups, respectively, with no significant differences observed between the two groups (Table 2).

Survival outcomes

The median follow-up period was 26.0 months for the CRS + HIPEC groups and 33.7 months for the R0 resection group. The Kaplan–Meier curves for RFS are demonstrated in Fig. 1A. In the CRS + HIPEC group, the 3-year RFS [95% CI] was 35.9% [26.1–45.8], and the median RFS was 16.9 months. In the R0

resection group, the 3-year RFS was 6.9% [2.0–16.3], and the median RFS was 11.8 months. Hence, the CRS + HIPEC group had a significantly longer RFS than the R0 group ($P < 0.001$). As shown in Fig. 1B, the 3-year OS of CRS + HIPEC group was 59.4% [48.1–69.0], and the median OS was 51.1 months. In the R0 resection group, the 3-year OS was 74.1% [59.2–84.3], and the median OS was 69.4 months. No significant difference in OS was observed between the two groups ($P = 0.087$). The Kaplan–Meier curves of PRFS are demonstrated in Fig. 1C. In the CRS + HIPEC group, the 3-year PRFS of CRS + HIPEC group was 44.5% [34.2–54.3], and the median PRFS was 24.5 months. In the R0 resection group, the 3-year PRFS [95% CI] was 27.6% [16.4–39.9], and the median PRFS was 17.2 months. The CRS + HIPEC group had a significantly longer PRFS than the R0 resection group ($P = 0.017$). The proportion of patients with peritoneal relapse events who underwent reoperations for recurrent CPM was 23% in the CRS + HIPEC group and 37% in the R0 resection group. Collectively, our results suggest a tendency for more reoperations for recurrent CPM in the R0 resection group.

Propensity score matching

The patient characteristics of each cohort selected after PSM are demonstrated in Table 3. The sample size included 41 patients in each group. Although a significant difference in CA19-9 levels remained between the two groups after PSM, differences in the other factors disappeared.

The Kaplan–Meier curves after PSM are presented in Fig. 2. In the CRS + HIPEC group, the 3-year RFS was 31.0% [16.5–46.7], and the median RFS was 15.6 months. In the R0 resection group, the 3-year RFS was 6.7% [1.30–18.6], and the median RFS was 12.6 months. Even after PSM, the CRS + HIPEC group had a significantly longer RFS than the R0 group ($P = 0.040$). The 3-year OS of CRS + HIPEC group was 59.4% [39.1–74.9], and the median OS was 51.1 months. In the R0 resection group, the 3-year OS was 80.5% [63.1–90.3], and the median OS was 69.4 months. After PSM, the R0 resection group had a significantly longer OS than the CRS + HIPEC group ($P = 0.031$). In the CRS + HIPEC group, the 3-year PRFS was 38.1% [22.1–53.9], and the median PRFS was 19.6 months. In the R0 resection group, the 3-year PRFS [95% CI] was 28.8% [15.7–43.3], and the median PRFS was 17.7 months. Although the CRS + HIPEC group tended to have a longer PRFS, this significant difference disappeared after PSM ($P = 0.303$).

Table 3

Patient characteristics of each cohort after propensity score matching.

	CRS + HIPEC ($N = 41$)	R0 Resection ($N = 41$)	*P*
Sex, *N* (%)			
Female	21 (56)	28 (68)	0.176
Male	20 (44)	13 (32)	
Age (years)	59 [32–76][a]	60 [30–82][a]	0.774
BMI (kg/m^2)	23.3 [16.6–32.6][a]	23.5 [14.9–32.8][a]	0.959
BSA (m^2)	1.62 [1.33–2.05][a]	1.60 [1.29–2.03][a]	0.167
ASA-PS, *N* (%)			
1–2	39 (95)	38 (93)	1.000
3–4	2 (5)	3 (7)	
CEA (ng/ml)	4.7 [0.9–134.8][a]	4.3 [1.2–270.2][a]	0.835
CA19-9 (U/ml)	5.3 [0.8–114.3][a]	16.4 [1.2–338.0][a]	< 0.001
Primary tumor location, *N* (%)			
Right-sided	15 (37)	18 (44)	0.653
Left-sided	26 (63)	23 (56)	
Histopathological type, *N* (%)			
Well differentiated	1 (2)	4 (10)	0.547
Moderately differentiated	35 (85)	29 (71)	
Poorly differentiated	2 (5)	3 (7)	
Mucinous	3 (7)	5 (12)	
Emergence time, *N* (%)			
Synchronous	12 (29)	10 (24)	0.804
Metachronous	29 (71)	31 (76)	
PCI score	3 [1–6][a]	4 [2–6][a]	0.374
Preoperative chemotherapy ($\leq$ 6 months), *N* (%)	14 (34)	15 (37)	1.000
Surgical approach, *N* (%)			
Open	41 (100)	25 (61)	—
Laparoscope	0	16 (39)	
Adjuvant chemotherapy, *N* (%)	27 (66)	25 (61)	*0.819*

[a]Median [range].

ASA-PS, American Society of Anesthesiologists-physical status; BSA, body surface area; CA, cancer antigen; CEA, carcinoembryonic antigen; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; PCI, peritoneal carcinomatosis index.

Discussion

Our findings demonstrated that the RFS of patients with CPM who had a PCI score less than or equal to 6 and underwent curative CRS plus HIPEC was significantly longer than that of patients who underwent R0 resection. They also suggest that CRS plus HIPEC was an optimal treatment strategy for the limited cohort included in this study. In contrast, the OS was comparable for both groups, with favourable median OS of 51.1 and 69.4 months in the CRS + HIPEC and R0 resection groups, respectively. Hence, although concerns about the local control achieved with R0 resection without peritoneal stripping remain, both CRS plus HIPEC and R0 resection performed at experienced centres can be acceptable treatment strategies for selected patients with resectable CPM and low PCI scores in terms of prognosis.

The physiologic plasma-peritoneum barrier limits the uptake of effective concentrations of chemotherapeutic agents after systemic administration. It also prevents systemic drug uptake after HIPEC, thus facilitating prolonged exposure and higher drug concentration at the peritoneal surface than in the plasma. This pharmacokinetic advantage leads to a favourable locoregional therapeutic effect with limited systemic toxic effects[24,25]. Furthermore, owing to the high intraperitoneal concentrations of anticancer drugs, intraperitoneal chemotherapeutic agents can penetrate peritoneal tumour tissue to a penetration depth of a few millimetres[26]. These characteristics of intraperitoneal chemotherapy could be emphasized by the combination of peritoneal stripping surgery before HIPEC. Hence, this results in the prolonged RFS and PRFS observed in the CRS + HIPEC group in this study. In contrast, R0 resection, which is the standard treatment strategy for CPM in Japan, focuses only on the removal of macroscopically visible CPM without peritoneal stripping or HIPEC. The shorter RFS in the R0 resection group in this study could imply that invisible CPM might have been missed. However, our results, especially those observed after PSM, suggest that R0 resection, which involves tumour burden reduction, may contribute to OS prolongation in patients with CPM.

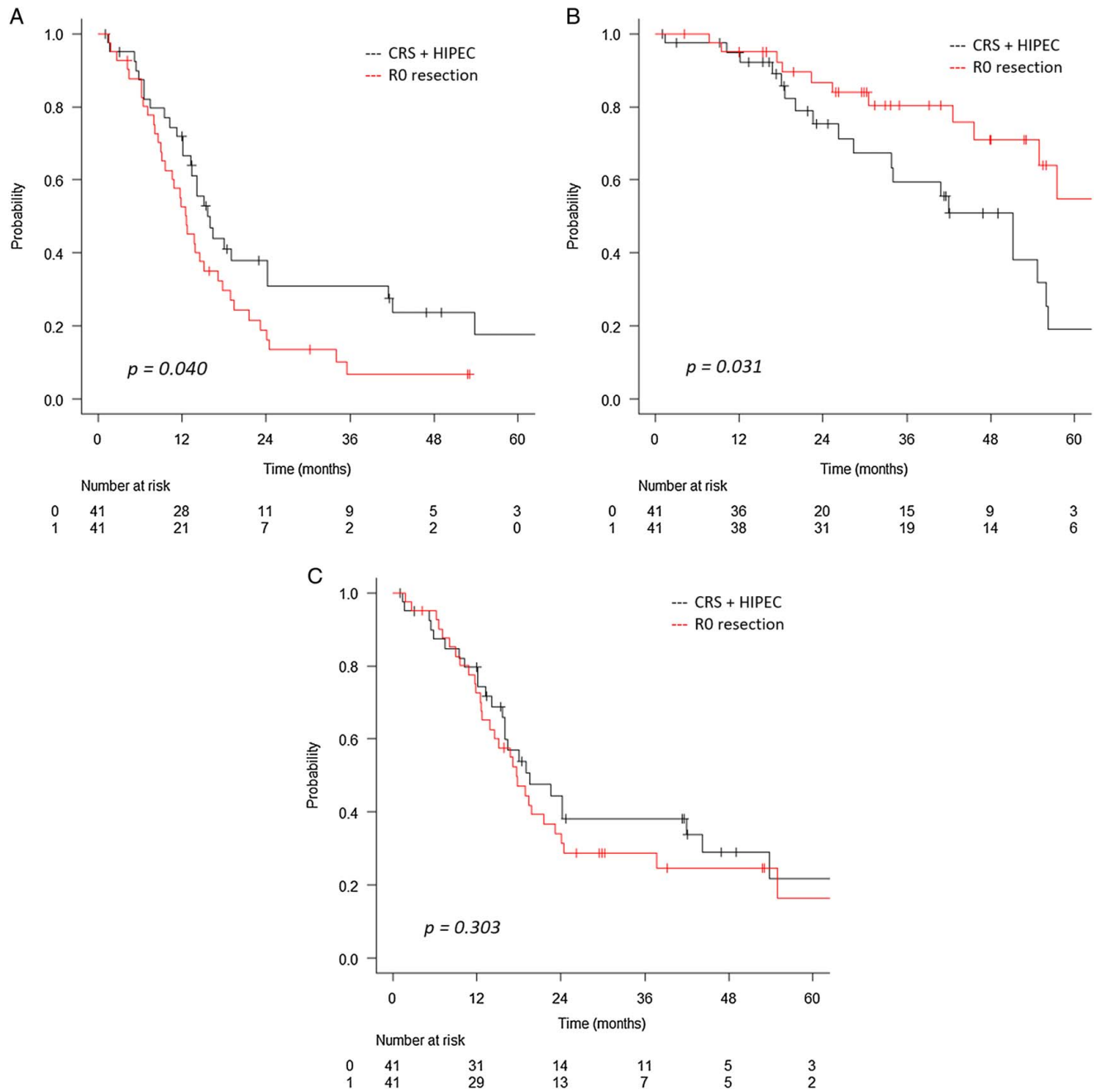

Figure 2. Survival outcome after propensity score matching. (A) Relapse-free survival. (B) Overall survival. (C) Peritoneal relapse-free survival. CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy.

The French PRODIGE 7 RCT failed to exhibit improvement in OS after adding HIPEC to CRS. It also did not demonstrate a significant difference in median RFS rates between the CRS plus HIPEC and CRS-only groups, which led to a strong argument against the efficacy of oxaliplatin-based HIPEC as a local treatment[4]. However, our findings confirmed that CRS plus MMC-based HIPEC could still be a promising treatment option for resectable CPM in patients with low PCI scores. It could lead to significantly better long-term outcomes, including local control. In a previous large retrospective study, no significant differences were observed in survival between patients who received oxaliplatin-based HIPEC and those who received MMC-based HIPEC in the entire cohort. However, MMC was associated with increased survival, specifically in patients with a low tumour burden[27]. These results are consistent with the favourable long-term outcomes of CRS plus MMC-based HIPEC observed in this study. A Spanish GECOP-MMC RCT investigating the additional survival benefits of MMC-based HIPEC for CRS is currently underway[28].

Despite the longer RFS associated with CRS plus HIPEC, the OS in this cohort was not statistically significant compared with R0 resection. Several potential explanations were considered for

the discrepancy between RFS and OS. First, the proportion of adjuvant chemotherapy administration was significantly lower in the R0 resection group (79% versus 43%), which could have led to early postoperative relapse and contributed to the extremely shorter RFS observed in the R0 resection group. However, since both groups were administered appropriate chemotherapy after the diagnosis of the relapse, this may not have led to a significant difference in OS. Second, the proportion of patients with an ASA-PS of 3-4 was significantly higher in the CRS + HIPEC group, which could have led to a shorter OS in the CRS + HIPEC group. However, this discrepancy between RFS and OS remained even after PSM, contrasting with the significantly longer OS observed in the R0 resection group. The proportion of reoperations for recurrent CPM was higher in the R0 resection group (23% versus 37%), which could have contributed to the longer OS in the R0 resection group. Reoperations for recurrent CPM may allow for the preservation of first-line or second-line potent chemotherapy regimens. Multimodal therapy, including surgery and chemotherapy, is essential to prolong OS in patients with CPM. Therefore, the relative ease of reoperation for recurrent CPM, that is, salvageability, may be one of the major advantages of R0 resection.

The proportion of Clavien–Dindo grade III or higher postoperative morbidity was only 7% (8 of 108) and 9% (5 of 58) in the CRS + HIPEC and R0 resection groups, respectively. The lower morbidities observed after R0 resection without peritoneal stripping were reasonable. However, the postoperative morbidities after CRS plus HIPEC in this study were also substantially lower compared with those reported in previous RCTs[4,29]. Although the operation time was significantly longer in the CRS + HIPEC group, it was comparable if the 90 min required for HIPEC was subtracted from the total time. Although the volume of blood loss was also significantly higher in the CRS + HIPEC group, the proportion of blood transfusions was the same between the two groups. Furthermore, the length of postoperative hospital stay was not significantly different between the two groups, with a median length of two weeks observed in both groups. The most substantial survival advantages are associated with HIPEC in patients with a PCI of 10–15[4,30,31]. However, with a focus on safety, patients with a PCI less than or equal to 6 may also be an optimal cohort for CRS plus HIPEC.

This study has several limitations. First, this was a retrospective cohort study, with a relatively small sample size. CRS + HIPEC and R0 resection were performed at different centres; therefore, the influence of selection bias and confounding factors could not be completely eliminated. After PSM, the proportion of patients who received adjuvant chemotherapy could be equalized, but not their regimens. Second, although we could collect mostly complete records with a few missing data, the median follow-up period was not as long as 30 months, which may have led to the lack of statistical power regarding OS rates. Third, data on RAS/BRAF mutations, circulating tumour DNA, or microsatellite instability could not be collected because analysis technology was not available during the early stages of the study period[32]. Fourth, although this was an international collaborative study, it only included two participating centres, which could lead to insufficient external validity. Although conducting international RCT on this topic may be difficult because treatment policies differ in various countries, a larger international prospective registry study must be conducted to validate our results.

Conclusions

In this study, we demonstrated that CRS plus HIPEC significantly prolonged RFS and PRFS compared with R0 resection without increasing postoperative complications and length of hospital stay. Therefore, curative CRS plus HIPEC performed at experienced centres could be the optimal treatment strategy for selected patients with resectable CPM and low PCI scores, especially in terms of achieving local control. In contrast, R0 resection is also acceptable owing to its combination of safety and prolonged OS, but is limited by the low PCI score requirement. Therefore, complete cytoreduction can prolong the OS of patients with CPM. Prospective case registrations and long-term follow-ups are required in the future.

Ethical approval

The study protocol was approved by the ethics committees of the National Cancer Center Hospital East, Chiba, Japan (registration number: 2022-318) and Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea (registration number: 3-2022-0483).

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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Author contribution

D.K. and E.J.P.: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, validation, visualization, writing—original draft, writing—review and editing. S.H.B.: methodology, resources, supervision. S.S.: data curation. Y.T. and M.I.: supervision.

Conflicts of interest disclosure

All authors declare no financial or non-financial competing interests related to this study.

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Guarantor

Eun Jung Park, Daichi Kitaguchi, and Masaaki Ito are guarantors.

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This paper is not commissioned, externally peer-reviewed.

Data statement

The data of this investigation are shared in Mendeley Data. Park, Eun Jung; Kitaguchi, Daichi (2023), "Cytoreductive Surgery plus Hyperthermic Intraperitoneal Chemotherapy versus R0 Resection for Resectable Colorectal Cancer with Peritoneal Metastases and Low Peritoneal Cancer Index Scores: A Collaborative Observational Study from Korea and Japan", Mendeley Data, V1, doi: 10.17632/zys6gdc2pg.1

Presentation

This study was invited to be presented as a podium presentation at the International Colorectal Research Summit 2023, Seoul, South Korea.

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