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Original Article

Comparison of Survival Outcomes Using Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Colon versus Rectal Cancer with Peritoneal Carcinomatosis in an Asian Medical Center

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Abstract

Background: The use of hyperthermic intraperitoneal chemotherapy (HIPEC) for colorectal cancer (CRC) with peritoneal carcinomatosis (PC) is still very controversial. The National Comprehensive Cancer Network guideline only recommends cytoreductive surgery (CRS) combined with HIPEC for colon cancer with PC for patients with limited metastases and can be removed with surgery. The short-term and long-term outcomes between colon versus rectal origin in this setting remain unclear. The present study compared our experience in the management of colon versus rectal cancer with PC through CRS-HIPEC and investigated whether the feasibility of extending the indication to the PC of rectal origin. **Materials and Methods:** The data of 78 and 10 patients with PC of colon and rectal origin, respectively, were collected from a prospectively maintained database of patients receiving CRS-HIPEC for peritoneal surface malignancy at any period during 2002–2018. CRS followed by HIPEC with mitomycin-C or 5-fluorouracil plus oxaliplatin was administered at 42° for 60 min. In addition, adjuvant chemotherapy was administered postoperatively. Data on sex, age, prior surgical score, preoperative or postoperative peritoneal cancer index (PCI), completeness of cytoreduction (CC) score, blood loss, operation time, transfusion unit, and hospital stay were recorded. Survival was compared between the colon and rectal groups. **Results:** The average patient was 56.4 years old, and 44 were men and 44 were women. The mean preoperative and postoperative PCI scores were 15.6 and 6.6, respectively. A complete CC score of 0-1 was achieved in 507 (56.9%) patients. The median overall survival durations were 34.0 ± 7.8 and 20.8 ± 13.2 months in the colon and rectal groups, respectively ($P = 0.367$). The 1-, 2-, 3-, 4-, and 5-year survival rates in the colon and rectal groups were 79% and 68%, 63% and 68%, 50% and 51%, 44% and 10%, and 44% and 0%, respectively. In multivariate analysis, the location of the primary tumor did not affect survival ($P = 0.597$; 95% confidence interval [CI] = 0.237–2.291); however, the postoperative PCI strongly predicted long-term survival ($P = 0.001$; 95% CI = 3.715–255.547). **Conclusion:** The management of CRC with PC remains challenging.

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CRS-HIPEC can provide similar survival benefits when applied to PC of rectal origin than when applied to PC of colon origin. The usage of mitomycin-C for HIPEC yields to a comparable survival benefit and a safe therapeutic option. However, the indication should be only extended to highly selective patients considering the possibility of adequate cytoreduction and performed in experienced centers.

Keywords: Colon cancer, cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, peritoneal carcinomatosis, rectal cancer

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and a leading cause of cancer-related deaths globally.[1] Approximately 10% to 15% of patients with CRC present with peritoneal carcinomatosis (PC) during the initial diagnosis, and 20% to 25% of patients develop PC with disease progression.[2] PC is considered a terminal disease and has poor prognosis with a median survival duration of 6–9 months if left untreated.[3] Current systemic therapy can increase the survival duration to 16.3 months in patients with unresectable CRC with PC.[4] Since the mid-1990s, cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have been applied with curative intent for PC originating from intraabdominal organs. Several studies have reported that the application of CRS-HIPEC could increase the overall survival (OS) duration to 12–63 months.[5-7]

The National Comprehensive Cancer Network guideline recommends CRS-HIPEC to be performed in long-established centers for selected patients with colon cancer who have limited PC and achievable R0 resection[8] but not for patients with rectal cancer. Studies have classified PC resulting from colon and rectal primary cancers together as "colorectal cancer" when examining the efficiency of CRS-HIPEC. Some studies have indicated that PC is a homogenous disease, whereas others have observed poor survival in patients with rectal cancer. Thus, the outcome comparison for CRS-HIPEC in rectal cancer with PC remains unclear.

The present study examined the survival benefits of CRS-HIPEC in patients with rectal cancer with PC and compared the prognosis of patients with different primary origins of colon and rectal cancer. In addition, this study determined prognostic factors for treating PC originating from CRC.

Materials and Methods

Study design

The data of 88 patients with CRC with PC were drawn from a prospectively maintained database of patients receiving CRS and HIPEC for peritoneal surface malignancy at the Comprehensive Care Center for Patients with Peritoneal Metastasis of (Wan Fang) Hospital at any period between January 2002 and December 2018; the data were collected and reviewed retrospectively. The institutional review board of this hospital (TMU-JIRB-C) approved this study (Number: N201807067). Informed consent was obtained from all patients enrolled in this study.

Cytoreductive surgery-hyperthermic intraperitoneal chemotherapy

CRS and HIPEC were performed according to the standard protocols of our institution. For the operation, a generous midline incision was made from the subxiphoid to the pubic symphysis. After considerable lysis of adhesions resulting from previous surgical procedures, the dissemination status of the intraabdominal malignancy was evaluated to calculate the peritoneal cancer index (PCI) score per the principles outlined by Sugarbaker.[9,10] The PCI index is calculated by assigning each of the 13 abdominal regions (0–12) a score ranging from 0 (no tumor observed) to 3 (a tumor of >5 cm in size or confluence). The total PCI index score is calculated by adding the scores of all 13 regions and can thus range from 0 to 39. CRS combined with peritonectomy was performed to remove all macroscopically visible tumors and all intraabdominal organs affected by the malignancy. For diffuse dissemination in the small bowel wall, segmental resection up to the maximal length possible without compromising a patient's quality of life was performed. For small mesentery carcinomatosis, resection of the mesentery surface through electric cauterization or ablation was conducted using an argon beam coagulator. HIPEC was performed for 60 min using the closed technique along with 6 L of saline, and intraperitoneal chemotherapeutic drugs were administered at 42°C during the whole procedure. Mitomycin-C (20 mg/m^2) was used as the chemotherapeutic drug for HIPEC. The extent of CRS was determined by calculating postoperative completeness of cytoreduction (CC) scores according to criteria described by Sugarbaker: CC scores of 0, 1, 2, and 3 indicate no residual tumor and <2.5 mm, 2.5–25 mm, and >25 m of the residual tumor, respectively.[10] After CRS-HIPEC, all patients were closely monitored in intensive care units. Postoperative morbidity and mortality were graded according to the Clavien–Dindo classification system.[11] Adjuvant chemotherapy was performed in selected patients with satisfactory performance status. All patients were routinely followed up in outpatient clinics.

Statistical analysis

Survival after CRS-HIPEC was recorded, with the endpoint being the latest follow-up or patient death. The survival duration was estimated using the Kaplan–Meier method and compared among subgroups. The log-rank test was employed to identify significant differences. Cox proportional hazards regression was used to examine both univariate and multivariate associations between predictors and OS after CRS-HIPEC. Data were analyzed using SPSS version 20.0 (SPSS, IBM Analytics, USA). $P < 0.05$ indicated statistical significance.

Results

Patient demographics

Between January 2002 and December 2018, a total of 88 patients with CRC with PC or locally advanced stage underwent CRS and HIPEC in Wan Fang Hospital, Taiwan. Among these 88 patients, 78 and 10 were included in the colon and rectal groups, respectively. The average age of patients was 56.4 years. Among the 88 patients, 44 were men and 44 were women [Table 1]. The preoperative Eastern Cooperative Oncology Group (ECOG) performance status score was <2, which was suitable for the indication of CRS-HIPEC. Furthermore, 11 (14%) patients in the colon group and 1 (10%) patient in the rectal group had Stage III disease and received HIPEC for prophylactic intent to prevent further progression to PC. No significant differences were observed in the distribution of age, sex, body mass index, ECOG status, and stage between the 2 groups.

The prior surgical score (PSS) is calculated to estimate the extent of surgery by quantitating surgical dissection within 9 abdominopelvic regions. Patients who have not undergone surgery or have received only biopsy or laparoscopy are assigned a score of 0 (PSS-0). Patients who have undergone surgery in 1, 2–5, and >5 abdominopelvic regions are assigned scores of 1 (PSS-1), 2 (PSS-2), and 3 (PSS-3), respectively.[10] In the colon group, 17 (21.8%) patients had PSS-2 whereas no patient had PSS-3. In the rectal group, 3 (30%) patients had PSS-2 and 1 (10%) patient had PSS-3 ($P = 0.026$). Patients in the rectal group appeared to have undergone more extensive procedures previously [Table 1].

Table 1: Demographics of patients with colon and rectal cancer with peritoneal carcinomatosis treated with cytoreductive surgery – hyperthermic intraperitoneal chemotherapy

Variables	All patients ($n=88$)	Colon group ($n=78$)	Rectum group ($n=10$)	*P*
Age (years±SE)	56.4±1.3	56.5±1.5	55.7±2.9	0.117
Gender				
Male	44 (50)	38 (48.7)	6 (60)	0.369
Female	44 (50)	40 (51.3)	4 (40)	
BMI	23.2±0.4	23.1±0.4	23.7±0.9	0.729
ECOG				
0	1 (1.1)	1 (1.3)	0	0.569
1	80 (90.9)	70 (89.7)	10 (100)	
2	7 (8.0)	7 (9.0)	0	
ASA score				
1	1 (1.1)	1 (1.3)	0	0.153
2	66 (75.0)	56 (71.8)	10 (100)	
3	21 (23.9)	21 (26.9)	0	
Stage				
III	12 (13.6)	11 (14.1)	1 (10)	0.590
IV	76 (86.4)	67 (85.9)	9 (90)	
PSS score				
0	9 (10.2)	9 (11.5)	0	**0.026**
1	58 (65.9)	52 (66.7)	6 (60)	
2	20 (22.9)	17 (21.8)	3 (30)	
3	1 (1.1)	0	1 (10)	

Data are expressed as, *n* (%) unless otherwise specified. Bold values indicate difference between groups being significant. SE: Standard error, BMI: Body mass index, ECOG: Eastern Cooperative Oncology Group (performance status), ASA: American society of anesthesiology, PSS: Prior surgical score

Perioperative characteristics

With regard to cancer type, most of the patients had adenocarcinoma [83 patients, 94%; Table 2]. Furthermore, 66% of the patients received chemotherapy before CRS-HIPEC, and 83% of the patients underwent adjuvant chemotherapy after surgery. The recurrence rate during follow-up after CRS-HIPEC did not significantly differ between the colon and rectal groups (16.7% vs. 30%; $P = 0.261$). Carcinoembryonic antigen and cancer antigen 19-9 levels were both elevated, whereas the average cancer antigen 125 level increased only in the colon group but not significantly so. The preoperative and postoperative mean PCIs were 15.2 and 6.4 in the colon group, respectively, and 18.4 and 8.0 in the rectal group, respectively [$P = 0.683$; Table 3]. The CC score was 0 or 1 for 45 (57.7%) patients in the colon group and 5 (50%) patients in the rectal group ($P = 0.558$). The morbidity rate was 21.6%. Among the study patients, 15.9% of them had Clavien–Dindo classification scores of 3 or 4, which include 5 (5.7%) patients with anastomosis leakage, 6 (6.8%) with wound dehiscence, 1 (1.1%) with lung infection, 1 (1.1%) with paralytic ileus, and 1 (1.1%) with stroke. Peritonectomy was performed in 64% patients if suitable. No significant differences in operation time, transfusion rate, blood loss, and length of stay were observed between these 2 groups.

Survival rate comparison

The 1-, 2-, 3-, 4-, and 5-year survival rates in the colon and rectal groups were 79% and 68%, 63% and 68%, 50% and 51%, 44% and 10%, and 44% and 0%, respectively [Table 4]. The median survival duration was 34 months in the colon group and 28 months in the rectal group [$P = 0.367$; Figure 1]. Although the rectal group tended to have poor survival, this tendency was not statistically significant.

Prognostic factor analysis

In a multivariate analysis, the location of primary tumors did not affect survival [$P = 0.597$, 95% confidence interval (CI) = 0.237–2.291; Table 5]. Meanwhile, preoperative PCI, undergoing or not undergoing peritonectomy and chemotherapy, and blood loss did not affect survival. By contrast, we revealed that "postoperative" PCI strongly predicted long-term survival ($P = 0.001$, 95% CI = 3.715–255.547), especially for a postoperative PCI score of >20. Simultaneously, difficult complete cytoreduction and extensive surgical procedure with a long operation duration served as another prognostic factor. In the subgroups with postoperative PCI scores of 1–10, 11–19, and 20–39, the median survival duration was 43.7, 20.3, and 8.5 months, respectively [$P = 0.001$; Figure 2]. The Kaplan–Meier survival

Table 2: Perioperative characteristics in patients with colon and rectal peritoneal carcinomatosis treated with cytoreductive surgery – hyperthermic intraperitoneal chemotherapy

Variables	All patients (*n*=88)	Colon group (*n*=78)	Rectum group (*n*=10)	*P*
Pathologic type				
Adenocarcinoma	83 (94.3)	74 (94.9)	9 (90)	0.461
Mucinous adeno	5 (5.7)	4 (5.1)	1 (10)	
Neoadjuvant chemotherapy	58 (66)	51 (65.4)	7 (70)	0.538
EPIC	21 (25)	19 (24.4)	2 (20)	0.557
Adjuvant chemotherapy	73 (83.0)	66 (84.6)	7 (70)	0.227
Recurrence				
No	72 (81.8)	65 (83.3)	7 (70)	0.261
Yes	16 (18.2)	13 (16.7)	3 (30)	
Laboratory data				
CEA (ng/mL)	35.7±8.3	39.3±9.4	11.7±7.8	0.110
CA199 (U/mL)	243.0±61.1	257.5±68.9	150.7±103.5	0.425
CA125 (U/mL)	89.0±33.6	99.1±37.4	8.1±0.99	0.306
CRP (mg/dL)	2.1±0.6	2.0±0.6	3.4±3.2	0.079

EPIC: Early postoperative intraperitoneal chemotherapy, CEA: Carcinoembryonic antigen, CRP: C-reactive protein

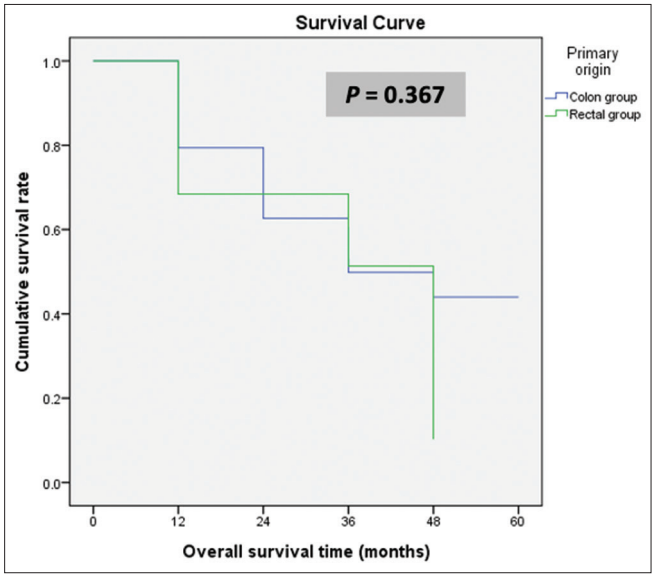

Figure 1: Kaplan–Meier survival curves based on colon versus rectal origins of peritoneal carcinomatosis

curve indicated that the remnant cancer burden was a strong predictive factor for outcomes.

Discussion

PC is considered to less frequently originate from rectal cancer than from colon cancer because of the difference in terms of extraperitoneal and intraperitoneal locations.[12] In our series of patients with CRC with PC receiving CRS-HIPEC, only 11.4% of PC were of rectal origin. Because of this discrepancy in the case number, most studies have used the umbrella category of CRC. Whether colon and rectal primary cancers sharing a similar disease entity have similar outcomes and biological behaviors should be considered when making treatment-related decisions. The surgical complication rate was higher and the survival rate was lower in patients with rectal cancer.[13] Therefore, PC originating from colon versus rectal primary cancer might be distinct diseases. However, findings from comparisons of the survival rate between PC from colon origin and PC of rectal origin are contradictory and controversial.

Table 3: Clinical and operative outcomes in patients with colon and rectal peritoneal carcinomatosis treated with cytoreductive surgery – hyperthermic intraperitoneal chemotherapy

Variables	All patients (*n*=88)	Colon group (*n*=78)	Rectum group (*n*=10)	*P*
PCI score				
Preoperative PCI	15.6 (0-39)	15.2 (0-39)	18.4 (0-39)	0.683
Postoperative PCI	6.6 (0-39)	6.4 (0-39)	8.0 (0-39)	0.899
CC score				
0	40 (45.5)	35 (44.9)	5 (50)	0.558
1	10 (11.4)	10 (12.8)	0	
2	17 (19.3)	14 (17.9)	3 (30)	
3	21 (23.9)	19 (24.4)	2 (20)	
Morbidity	19 (21.6)	16 (20.5)	3 (30)	0.369
Clavien–Dindo class				
0	67 (76.1)	61 (78.2)	6 (60)	0.343
1-2	7 (8.0)	6 (7.7)	1 (10)	
3	8 (9.1)	7 (9.0)	1 (10)	
4	6 (6.8)	4 (5.1)	2 (20)	
Peritonectomy	56 (63.6)	51 (65.4)	5 (50)	0.269
Ostomy	12 (13.6)	10 (12.8)	2 (20)	0.410
Operation time (min)	516±21	513±23	534±60	0.992
Transfusion (unit)				
PRBC	3.8±0.4	3.8±3.5	4.1±6.4	0.335
FFP	3.0±0.5	3.0±4.2	2.8±6.3	0.526
Blood loss (ml)	577±73	540±66	846±364	0.126
Length of stay (days)	13±1	14±1	11±2	0.440

Data are expressed as mean (range). Data are expressed as, *n* (%) unless otherwise specified. Data are expressed as mean±SE. SE: Standard error, PCI: Peritoneal cancer index, CC: Completeness of cytoreduction, PRBC: Packed red blood cell, FFP: Frozen fresh plasma

Tonello examined 36 patients with colorectal PC (31 patients in the colon group and 5 in the rectal group) and reported differences in prognosis between the 2 groups, with median survival durations of 47.8 and 22.0 months in the colon and rectal groups, respectively (P = 0.008).[14] The 3- and 5-year survival rates were 74% and 50% in the colon group, respectively, and 20% and 0% in the rectal group, respectively. Rodrigo Gomes da Silva reported that the median survival duration was 17 months for 6 patients with rectal cancer who underwent complete cytoreduction and 35 months for 64 patients with colon cancer who underwent complete cytoreduction (P = 0.126).[15] Similarly, Verwaal indicated that

Table 4: Survival data of patients with colon and rectal peritoneal carcinomatosis treated with cytoreductive surgery – hyperthermic intraperitoneal chemotherapy

Variables	All patients	Colon group	Rectum group	*P*
Status on study				
Survive	55 (62.5)	51 (65.4)	4 (40)	0.114
Expire	33 (37.5)	27 (34.6)	6 (60)	
Overall survival rate (years) (%)				
1	78	79	68	0.367
2	64	63	68	
3	0	0	1	
4	36	44	10	
5	36	44	0	
Median survival time (months)	34.0±6.6	34.0±7.8	28.0±13.2	0.367

Data are expressed as, *n* (%) unless otherwise specified. Data are expressed as mean±SD. SD: Standard deviation

Table 5: Multivariate cox regression analysis of prognostic factors for overall survival

Variables	Hazard ratio	*P*	95% CI
Group			
Rectum group	0.736	0.597	0.237-2.291
Colon group	1	-	
Preoperative PCI			
20-39	3.246	0.141	0.676-15.577
11-19	2.534	0.209	0.594-10.815
1-0	1	-	-
Postoperative PCI			
20-39	30.811	**0.001**	**3.715-255.547**
11-19	2.609	0.135	0.743-9.168
1-10	1	-	-
Peritonectomy			
No	2.237	0.259	0.553-9.057
Yes	1	-	-
Operation time (min)			
>480	5.765	**0.049**	**1.005-33.062**
≤480	1	-	-
Blood loss (ml)			
>500	2.134	0.133	0.794-5.735
≤500	1	-	-
Adjuvant chemotherapy			
No	2.790	0.108	0.797-9.765
Yes	1	-	-

Bold values indicate difference between groups being significant. PCI: Peritoneal cancer index, CI: Confidence interval

the location of the primary tumor in the rectum (HR = 3.14; 95% CI = 1.11-8.91; *P* = 0.069) was associated with a shorter survival duration.[16] The median survival duration was 21.6 months in the colon group and 16 months in the rectal group. By contrast, Simkens analyzed his series of 58 patients for colon PC and 29 patients for rectal PC and reported that the disease-free survival durations were 13.5 and 13.6 months in the rectal and colon groups, respectively (*P* = 0.621).[17] The 2- and 5-year OS rates were 54% and 32% in patients with rectal cancer, respectively, and 61% and 24% in patients with colon cancer, respectively (*P* = 0.987). Votanopoulos reported that the median survival durations were 14.6 and 17.3 months in 13 patients with rectal cancer and 204 patients with colon cancer, respectively, whereas the 3-year survival rates were 28.2% and 25.1%, respectively (*P* = 0.644).[18] They observed no difference in the survival rates between patients with colon PC and those with rectal PC who received CRS-HIPEC.

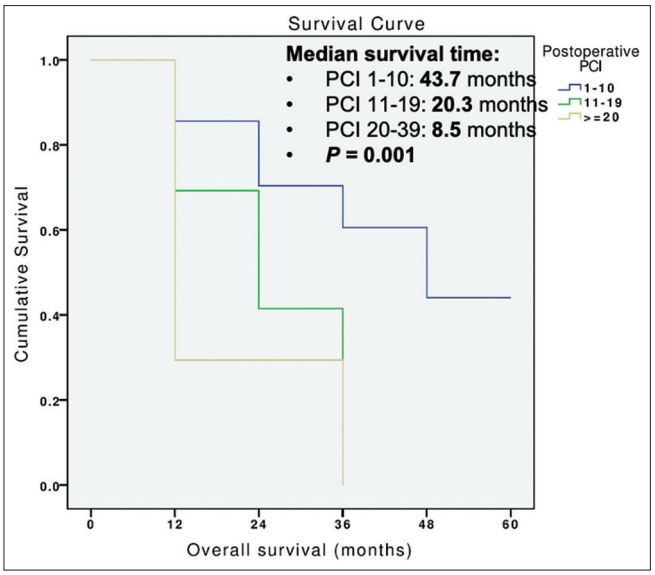

Figure 2: Kaplan–Meier survival curves based on postoperative peritoneal cancer index

In our series of 78 patients with colon PC and 10 patients with rectal PC, the median OS duration was 34 and 28 months, respectively (*P* = 0.367). Although a trend of poor survival was noted in patients with rectal PC, this trend was not statistically significant. Thus, CRS-HIPEC is suitable for patients with PC originating from the rectum and is as efficient as that in patients with PC originating from the colon. However, patient selection is still a crucial factor. In our prognostic analysis, we observed that postoperative PCI was a strong risk factor for survival benefit. The remnant cancer burden strongly predicted prognosis. Patients with a postoperative PCI score of >20, which indicates significant incomplete cytoreduction, might not be suitable for undergoing CRS-HIPEC, considering the high morbidity rate of the procedure itself. In addition, the CC score indicated no difference between the 2 origins of primary cancer. We suggest that the postoperative PCI, which demonstrates the remnant cancer burden in each abdominal region, serves as a more dedicated indicator for cytoreduction completion and a more accurate marker to predict prognosis.

Some studies have indicated preoperative PCI to be a prognostic factor; however, it was not a significant predictor in our series. Thus, the remnant cancer burden might be a more accurate prognostic factor than the extent of cytoreduction. To achieve complete cytoreduction, surgeons should improve the

surgical technique for extensive debulking resection and not rely on the effect of HIPEC alone for tumor eradication. In particular, a recent phase 3 trial, PRODIGE 7, reported that the addition of HIPEC with oxaliplatin after CRS did not improve survival.[19] The efficacy of adding HIPEC to treat patients with CRC with PC remains debatable. Some key points pertinent to this study were reported. For example, the choice of the HIPEC regimen including oxaliplatin (instead of mitomycin-C), which is the standard adjuvant chemotherapeutic agent, should be administered before any consideration of HIPEC to arrest disease progression in PC. The use of a short HIPEC duration of 30 min only for perfusion is uncommon in current practice and can result in an inadequate oncological effect. As indicated in a subgroup analysis, patients with a medium PCI score of 11–15 can still receive HIPEC to gain a survival benefit. The discussion of the limitation of PRODIGE 7 is beyond the scope of this study, and we emphasized the importance of CRS rather than HIPEC. Furthermore, we noticed that the Grade 3 or worse adverse events in the present study patients using mitomycin-C for HIPEC was 15.9%, compared the PRODIGE 7 study using oxaliplatin for HIPEC with 42%. This fact might indicate that mitomycin-C for HIPEC yields a comparable survival benefit and a safe therapeutic option.

This study has several limitations. First, because of the retrospective nature of this study and the small sample size, firm conclusions cannot be drawn. Additional prospective large cohort studies are necessary. Second, the data used in this study were obtained from a single specialized and long-established HIPEC center; thus, the application of the same regimen, procedure, and patient selection criteria may not lead to similar outcomes in other institutions. Some patients with Stage III received HIPEC as a preventive measure. However, the results remained similar when these patients were excluded.

Conclusion

The survival benefit of CRS-HIPEC was similar between patients with PC originating from the rectum and those with PC originating from the colon. Remnant cancer burden is a crucial prognostic indicator. When administering CRS-HIPEC in patients with rectal cancer with PC, clinicians should consider the possibility of complete cytoreduction to achieve a postoperative PCI score of <20. Maximal debulking is also the mainstay for better outcomes.

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Conflicts of interest

There are no conflicts of interest.

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