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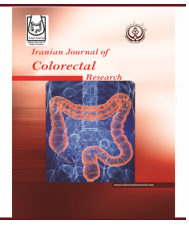

Indications for Cytoreductive Surgery Plus HIPEC in Patients with Colorectal Cancer and Peritoneal Metastasis

Yutaka Yonemura[1,2,3*], MD, PhD; Haruaki Ishibashi[2], MD; Akiyoshi Mizumoto[3], MD; Takuji Fujita[2], MD; Yang Liu[2], MD; Satoshi Wakama[2], MD; Syouzou Sako[2], MD; Nobuyuki Takao[3], MD; Toshiyuki Kitai[2], MD; Kanji Katayama[2], MD; Yasuyuki Kamada[2], MD; Keizou Taniguchi[4], MD; Daisuke Fujimoto[4], MD

[1]*Asian School of Peritoneal Surface Malignancy Treatment, Kyoto City, Kyoto Prefecture, Japan*
[2]*Department of Regional Cancer Therapy, Peritoneal Surface Malignancy Treatment Center, Kishiwada Tokushukai Hospital, Kishiwada City, Osaka Prefecture, Japan*
[3]*Department of Regional Cancer Therapy, Peritoneal Dissemination Center, Kusatsu General Hospital, Kusatsu City, Shiga Prefecture, Japan*
[4]*Department of Surgery, Mizonokuchi Hospital, Teikyo University, School of Medicine, Kawasaki, Kanagawa, Japan*

Corresponding authors:
Yutaka Yonemura, MD, PhD;
Representative of the Asian School of Peritoneal Surface Malignancy Treatment. Department of Regional Cancer Therapies, Peritoneal Surface Malignancy Treatment Center, Kishiwada Tokushukai Hospital, Osaka, Japan
Email: y.yonemura@coda.ocn.ne.jp

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Abstract

Background: Comprehensive treatment (COMPT) consisting of cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) improves survival in selected patients with peritoneal metastasis (PM) from colorectal cancer (CRC). The present study aimed to clarify clinicopathologic parameters that are indications for COMPT in CRC patients with PM.
Methods: Between 2006 and 2021, 447 patients were eligible for COMPT among 906 CRC patients with PM. Clinicopathologic parameters contributing to long-term survival and cure were analyzed.
Results: A log-rank test showed a significant survival difference for peritoneal cancer index (PCI) (≤12 vs. ≥13, P<0.0001), completeness of cytoreduction (CCR) score (CCR-0 vs. CCR-1, P<0.0001), small bowel (SB)-PCI (≤2 vs. ≥3), liver/lung metastasis (LLM) (negative vs. positive, P=0.002), histologic type (differentiated type vs. signet ring cell (SRC) subtype, P=0.008), number of involved peritoneal sectors (≤6 vs. ≥7), HIPEC (done vs. not done) and postoperative complication (grades 0–2 vs. grades 3–5, P<0.0001). Muti-variate analyses revealed that CCR score (CCR-0 vs. CCR-1, P<0.0001), SB-PCI score (≤2 vs. ≥3, P<0.005), LLM (negative vs. positive, P=0.002), and HIPEC (performed vs. not done) were independent prognostic factors. The incidence of postoperative grade 3–5 complications was 19.0% (85/447), and the mortality rate was 2.0% (9/447). One hundred seventy patients fulfilled the following clinicopathologic factors: PCI≤12, SB-PCI≤2, number of involved peritoneal sectors ≤6, no LLM, differentiated histologic type, and CCR-0. The median survival time of these patients was 5.5 years, and five and ten-year survival rates were 57.8% and 24.6%, respectively. Postoperative grade 3, 4, and 5 complications in these 170 patients occurred in 9 (5.3%), 15 (8.8%), and 1 (0.6%), respectively. Cured patients were defined as those alive without recurrence more than five years after CRS. All of the cured patients underwent CCR-0 resection. The PCI and SB-PCI of these 23 patients were ≤12 and ≤2, respectively.
Conclusion: Among CRC patients with PM, COMPT with CCR-0 resection is indicated for PCI ≤12, SB-PCI ≤2, number of involved peritoneal sectors ≤6, no LLM, and differentiated histologic type.

Keywords: Peritoneal metastasis, Colorectal cancer, Peritoneal cancer index, Peritonectomy

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Introduction

Colorectal cancer (CRC) is the second cause of death in cancer patients (1). Approximately 10% of patients die of peritoneal metastasis (PM) during treatment (2). CRC with PM (CRC-PM) has been considered a lethal condition (3, 4).

Standard treatments for CRC patients with PM include systemic chemotherapy and palliative surgery (5). However, these treatments cannot cure CRC-PM, and the median survival time after systemic chemotherapy alone is just 12.7 months. In the late 1990s, the Peritoneal Surface Malignancy Group International (PSOGI) proposed a novel comprehensive treatment that combined cytoreductive surgery (CRS) and perioperative chemotherapy (POC). This comprehensive treatment aims to cure patients with PM by combining CRS, which removes macroscopic tumors, with POC to eradicate remaining residual micrometastases. Combining CRS with intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) is useful for resectable CRC-PM (6-10). One randomized controlled trial showed the efficacy of this comprehensive treatment, reporting longer overall survival (OS) and disease-free survival times than those in patients receiving ordinary surgical treatment and systemic chemotherapy (11). Postoperative mortality and morbidity after comprehensive treatment have been reported to be higher than standard surgical treatment (12-16).

The present study aimed to clarify those clinicopathologic parameters that constitute indications to perform the comprehensive treatment to achieve greater long-term survival and low postoperative mortality and morbidity in patients with CRC-PM.

Patients and Methods

This retrospective study was conducted at three Japanese institutions, Kishiwada Tokushukai Hospital, Ohmi General Hospital, and Teikyou University Hospital. Medical records of patients who underwent surgery for CRC-PM between 2006 and 2021 were reviewed.

The study protocol was reviewed and approved by the Medical Ethics Committee of Kishiwada Tokushukai Hospital and Ohmi General Hospital (Protocol number; H19-2) and the ethics review board of each institution. Informed consent was obtained from all patients who received treatment.

During the study interval periods, 906 CRC-PM patients were treated with modern systemic chemotherapy, i.e., FOLFOX, FOLFIRI, SOX, IRIS, or CAPOX with or without bevacizumab or panitumumab. During systemic chemotherapy, 447 patients were selected as eligible to undergo complete cytoreduction using diagnostic imaging modalities. Cytoreduction was performed to resect all visible PM.[17,18] The surgery was usually performed as laparotomy with peritonectomy and resection of the colon, ovary, uterus, spleen, gallbladder, and small bowel with its mesentery, if involved. The falciform ligament, greater omentum, and lesser omentum were always removed. In addition, resection of the parietal peritoneum, pelvic peritoneum, and diaphragmatic peritoneum was performed when necessary based on oncological assessment (17, 18). The final aim was to remove all macroscopic PMs and achieve complete cytoreduction (CCR-0).

The peritoneal surface is divided into 13 sectors according to Sugarbaker et al. (6), and the PMs were removed in sectors. However, sectors without macroscopic tumors were preserved (17, 18). Just after CRS, HIPEC was performed using 4 L of saline heated at 42.5–43.5 °C for the duration of the HIPEC procedure (40 min). Therapeutic agents used in this procedure were oxaliplatin 300 mg/person in the perfusate, with 500 mg of 5-fluorouracil (5-FU) and 50 mg of Isovorin® injected systemically before HIPEC. The thermal dose was calculated according to Separeto and Dewey (19) and HIPEC was terminated when the thermal dose reached 40 min.

Data Collection

The demographic data, perioperative chemotherapy, tumor histology, operative information, and survival information of patients were obtained from a prospectively maintained multi-institutional database and also by chart review. The peritoneal cancer index (PCI) was calculated as described by Jacquet et al (20). Residual PM was evaluated using the completeness of cytoreduction (CCR) score (20). A score of CCR-0 indicates no visible PM, while CCR-1 indicates the presence of residual macroscopic tumors.

Outcomes

The primary outcome in this study was overall survival (OS), calculated as the time between the date of CRS and the date of death. 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 and within one month after CRS. Postoperative complications were staged according to the Clavien–Dindo classification; patients with grade III or higher were judged to have a postoperative complication (21).

Statistical Analysis

Patient 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.

The chi-squared test or Fisher's exact test and the student t-test were used to compare groups. Kaplan-Meier survival curves were constructed for both groups, and the OS was compared using the

log-rank test. Univariable and multivariable Cox regression analyses were performed to calculate the hazard ratios (HRs) and 95% CI. 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).

Patient Background

Among the 447 patients, who were eligible for CRS, 332 (74.2%) patients underwent CCR-0 resection. The patients' background data are summarized in Table 1, which shows CCR-0 rates according to the clinicopathologic parameters. Synchronous and metachronous PM were present in 225 (50.3%) and 222 (49.7%) patients, respectively. CCR-0 resection rates were not significantly different by age (<65 vs. ≥65), gender (male vs. female), onset (synchronous vs. metachronous), tumor location (right side vs. left side), lymph node metastasis (pN0 vs., pN1,2,3), or the performance of preoperative chemotherapy (none vs. performed). In contrast, the CCR-0 resection rate in patients with a non-signet ring cell (SRC) subtype was 83.0% (283/361)—significantly higher than that (65.1%; 56/86) of those with the SRC subtype (P<0.05). Additionally, in patients with synchronous involvement of liver or lung metastasis (LLM) or previous resection of LLM, the rate was significantly lower (78.3%, 278/355) than in those without synchronous LLM (66.3%, 61/92) (P<0.05).

Regarding PCI scores and CCR-0 ratios, the CCR-0 ratio in patients with PCI≤12 was 94.4% (251/266), and that in patients with PCI≥13 was 48.6% (88/181, P<0.0001). The small bowel PCI (SB-PCI) refers to the sum of the lesion size scores in the upper jejunum, lower jejunum, upper ileum, and lower ileum, ranging from 0 to 12. The CCR-0 rate of patients with SB-PCI≤2 (90.8%, 246/271) was significantly higher than that (52.8%, 93/176) of patients with SB-PCI≥3 (P<0.0001). Regarding the number of macroscopically involved peritoneal sectors, the CCR-0 rate (92.2%, 249/279) in patients with a value of ≤6 was significantly higher than that (48.6%, 86/177) in patients with a value of ≥7 (P<0.0001).

As shown in Table 2, salpingo-oophorectomy was performed in 182 female patients, and CCR-0 resection was performed in 157 (86.3%) patients. Resection of the small bowel and its mesentery

Table 1: Clinicopathological parameters and completeness of cytoreduction

Factors		CCR-0 n (%)	CCR-1 n	Total	P value
Age	<65	250 (75.3%)	82	332	>0.05
	≥65	89 (77.4%)	26	115	
Gender	Male	147 (73,1%)	54	201	>0.05
	Female	192 (78.0%)	54	246	
Onset	Synchronous	163 (72.3%)	62	225	>0.05
	Metachronous	176 (79.2%)	46	222	
Histology	Non-signet ring cell subtype	283 (83.0%)	78	361	0.015
	Signet ring cell (SRC)	56 (65.1%)	30	86	
Location	Right side	158 (72.8%)	59	217	>0.05
	Left side	181 (78.6%)	49	230	
Lymph node metastasis	Negative	114 (78.0%)	32	146	>0.05
	Positive (N 1-3)	225 (74.8%)	76	301	
	N3	36 (81.8%)	8	44	
Distant metastasis	Non	278 (78.3%)	77	355	0.016
	Liver or lung	61 (66.3%)	31	92	
	Liver alone	41	25	66	
	Lung alone	20	6	26	
Preoperative chemotherapy	None	31 (88.6%)	4	35	>0.05
	Performed	308 (74.8%)	104	412	
PCI	≤6	168 (94.4%)	10	178	<0.0001
	7~12	83 (94.3%)	5	88	
	13~18	42 (72,4%)	16	58	
	19~24	32 (64.5%)	18	50	
	≥25	14 (18.5%)	59	73	
Small bowel PCI	≤2	246 (90.8%)	25	271	<0.0001
	3-12	93 (52.8%)	83	176	
No. of involved peritoneal sectors	≤3	177 (94.1%)	11	188	<0.0001
	4-6	74 (90.2%)	8	82	
	7-9	51 (83.6%)	10	61	
	10-13	37 (31.9%)	79	116	
Total		339	108	447	

CCR-0: complete cytoreduction, CCR-1: incomplete cytoreduction, PCI: peritoneal cancer index. P values are based on the chi-squared test or Fisher's exact test

Table 2: Data associated with cytoreductive surgery, mean±SD or n (%)

		CCR-0	CCR-1	P value
No. of removed peritoneal sectors	5.8±2.4	6.5±3.0	3.7±3.7	0.0024
No. of removed organs	3.7±2.1	4.0±1.9	2.7±2.4	0.0001
Hysterectomy		150 (44.2%)	21 (11.1%)	
Salpingo-oophorectomy		157 (46.3%)	25 (23.1%)	
Small bowel		189 (55.8%)	64 (59.3%)	
Resection of small bowel mesentery		181 (53.4%)	54 (50%)	
Left diaphragmatic peritonectomy		111 (32.7%)	26 (24.1%)	
Right diaphragmatic peritonectomy		140 (41.3%)	27 (25%)	
Pelvic peritonectomy		283 (83.5%)	44 (40.7%)	
Resection of colon-rectum	Total colectomy	29 (8.6%)	18 (16.7%)	
	Transverse colectomy	5 (1.5%)	0 (0%)	
	Rectal resection	90 (26.5%)	2 (1.9%)	
	Sigmoidectimy	4 (1.2%)	1 (0.9%)	
	Right hemicolectomy + rectal resection	94 (27.7%)	18 (16.7%)	
	Right hemicolectomy	19 (5.6%)	15 (13.9%)	
	Left hemicolectomy + rectal resection	10 (2.9%)	3 (2.8%)	
	Wedge resection	1 (0.3%)	0 (0%)	
No. of removed peritoneal sectors	1~3	69 (20.4%)	63 (58.3%)	
	4~6	74 (21.8%)	17 (15.7%)	
	7~9	152 (44.8%)	18 (16.7%)	
	10~13	44 (13.0%)	10 (9.3%)	
Bleeding volume		1377±972	1443±1298	>0.05
Operation time		277±140	233±94	>0.05
Blood transfusion (units of red blood cells)		5.6±14.6	4.7±5.3	>0.05
Blood transfusion (fresh frozen plasma)		8.6±25.2	7.2±5.8S	>0.05
		339	108	Total; 447

CCR-0: complete cytoreduction, CCR-1: incomplete cytoreduction, SD: standard deviation, n: number. P values are based on the chi-squared test, Fisher's exact test, or student t-test

Table 3: Survival after cytoreductive surgery related to clinicopathologic data

Clinicopathologic parameters		No. of cases	MST (Years)	5-YSR	10-YSR	P value X^2
Peritoneal cancer index (PCI)	≤12	251	2.87	30.3%	16.4%	<0.0001
	≥13	196	0.899	7.1%	1.9%	88.8
Completeness of cytoreduction (CCR) score	CCR-0	338	3.92	34.1%	16.1%	<0.0001
	CCR-1	109	0.67	6.3%	0%	79.8
Small bowel PCI	≤2	268	2.93	31.8%	16.5%	<0.0001
	≥3	179	0.89	5.9%	1.6%	88.8
With liver/lung metastasis	No	352	2.06	24.4%	8.5%	0.002
	Positive	95	1.71	8.1%	NR	9.19
Histologic type	Non-signet ring cell subtype	359	2.07	23,4%	12.0%	0.008
	Signet ring cell subtype	88	1.40	12.5%	4.2%	6.99
No. of involved peritoneal sectors	≤6	275	2.85	30.10%	16.40%	<0.0001
	≥7	172	0.87	6.50%	1.70%	85.7
Postoperative complications	Grades 0-2	360	2.13	22.50%	12.10%	<0.0001
	Grades 3-5	87	1.15	14.40%	4.30%	15.21

MST: median survival time; 5-YSR: five-year survival rate, 10-YSR: ten-year survival rate

was performed in 189 (42.3%) and 181 (40.5%) patients, respectively. Left and right diaphragmatic peritonectomy was done in 137 (30.6%) and 167 (37.4%) patients, respectively. Pelvic peritonectomy was performed in 327 (73.2%) and colorectal resection in 309 (69.1%) patients. The number of removed peritoneal sectors was 5.8±2.4, and the values in those with CCR-0 and CCR-1 resection were 6.5±3.0 and 3.7±3.7, respectively (P=0.0024). The number of organ resections was 3.7±2.1; this value in the CCR-0 and CCR-1 groups was 4.0±1.9 and 2.7±2.4, respectively (P<0.0001). There was no significant difference in bleeding volume, operation time, and blood transfusion volume between the CCR-0 and CCR-1 groups.

Table 3 shows postoperative survivals according to the clinicopathologic prognostic factors. There was no survival difference in gender (male vs. female),

lymph node metastasis (pN0 vs. pN+), tumor location (right side vs. left side), neoadjuvant chemotherapy (none vs. performed), onset (synchronous vs. metachronous), CEA-, CA19-, or CA125-tumor marker levels (within normal vs. higher than normal), and age (<65 vs. ≥65 years). In contrast, a log-rank test showed significant survival difference for PCI (≤12 vs. ≥13), CCR score (CCR-0 vs. CCR-1), SB-PCI (≤2 vs. ≥3), LLM (negative vs. positive), histologic type (non-SRC subtype vs. SRC subtype), number of involved peritoneal sectors (≤6 vs. ≥7), HIPEC (performed or not) (Figure 1), and postoperative complications (grades 0–2 vs. 3–5). Figure 1 shows the survival curves for HIPEC and non-HIPEC.IPEC patients.

Muti-variate analyses revealed that CCR score (CCR-0 vs. CCR-1), SB-PCI score (≤2 vs. ≥3), LLM (negative vs. positive), and HIPEC (performed or not) were independent prognostic factors (Table 4).

Postoperative mortality and complications are summarized in Table 5. The incidence of postoperative grade 3–5 complications was 19.0% (85/447), and the mortality rate was 2.0% (9/447). Of the grade 5 complications, multiple organ failure and pulmonary embolism developed in three and two patients, respectively. Four patients died of pneumonia, necrosis of a lower extremity, cardiac tamponade, or

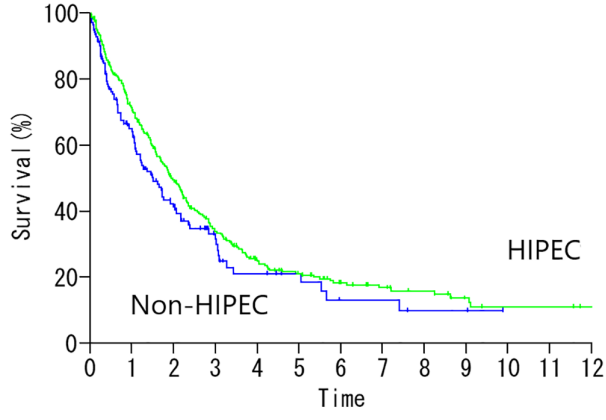

Figure 1: Survival of patients over time (years) treated with cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) (N=299; green line) and CRS without HIPEC (N=148; blue line). Log-rank test, P=0.043.

Table 4: The results of multivariate Cox regression analysis

		X2	P value	Hazard ratio	CI
Peritoneal cancer index (PCI)	≤12	2.33	NS	1.52	0.89-2.59
	≥13				
CCR score	CCR-0	25.02	<0.0001	2.25	1.64-3.09
	CCR-1				
Nodal status	pN0	1.42	NS	1.16	0.91-1.48
	pN1,2,3				
Small bowel PCI	≤2	12.72	<0.005	1.84	1.32-2.59
	≥3				
With liver/lung metastasis	No	9.2	0.002	1.61	1.18-2.18
	Positive				
No. of involved peritoneal sectors	≤6	0.05	NS	0.94	0.55-2.62
	≥7				
HIPEC	Not performed	6.175	0.0129	0.72	0.55-0.93
	Performed				
Postoperative complications	Grades 0-2	3.14	NS	1.3	0.972-2.613
	Grades 3-5				
Histologic type	Differentiated	0.51	NS	1.11	0.82-1.51
	Signet ring cell				

CCR: completeness of cytoreduction; CCR-0: complete cytoreduction; CCR-1: incomplete cytoreduction; CI: confidence interval; HIPEC: hyperthermic intraperitoneal chemotherapy

Table 5: Postoperative complications (Fisher's exact test)

Clinicopathologic parameters		No. of cases	Grade 3	Grade4	Grade 5	P value
Peritoneal cancer index (PCI)	≤12	251	17 (6.8%)	20 (8.0%)	2 (0.8%)	X2=4.495
	≥13	196	23 (11.7%)	15 (7.7%)	7 (3.6%)	P=0.045
CCR score	CCR-0	338	28 (8.3%)	33 (9.8%)	3 (0.9%)	X2=0.019
	CCR-1	109	12 (11.0%)	2 (1.8%)	6 (5.5%)	P>0.05
Small bowel PCI	≤2	268	20 (7.5%)	21 (7.8%)	2 (0.7%	X2=2.88
	≥3	179	20 (11.2%)	14 (7.8%)	7 (4.1%)	P>0.05
With liver/lung metastasis	No	352	31 (8.9%)	30 (8.5%)	9 (2.6%)	X2=0.984
	Positive	95	9 (9.5%)	5 (5.3%)	0 (0.0%)	P>0.05
No. of involved peritoneal sectors	≤6	275	19 ‘ (6.9%)	23 (8.4%)	3 (1.1%)	X2=2.363
	≥7	172	21 (12.2%)	12 (6.9%)	6 (3.5%)	P>0.05

CCR: Completeness of cytoreduction; CCR-0: Complete cytoreduction, CCR-1: Incomplete cytoreduction

bleeding. The incidence of grade 3–5 complications in patients with PCI ≤12 was significantly lower than that of patients with PCI ≥13 (15.6% vs. 23.0%, P=0.045). However, there was no relationship between grade 3–5 complications and CCR, SB-PCI, LLM, or the number of involved peritoneal sectors.

There were 170 patients with the following clinicopathologic factors: PCI ≤12, SB-PCI ≤2, number of involved peritoneal sectors ≤6, no LLM, non-SRC histologic type, and CCR-0. The median survival time (MST) of these patients was 5.5 years, and five and ten-year survival rates were 57.8% and 24.6%, respectively (Figure 2). Additionally, postoperative grade 3, 4, and 5 complications occurred in 9 (5.3%), 15 (8.8%), and 1 (0.6%) of these patients, respectively. The single postoperative death was due to a pulmonary embolism.

Cured patients were defined as those alive without recurrence longer than five years after CRS (N=21) or resection of a recurrent metastasis (N=2) after CCR-0 resection during the initial peritonectomy (Tables 6, 7). All of the cured patients underwent CCR-0 resection. The PCI and SB-PCI of these 23 patients were ≤12 and ≤2, respectively. Those patients with 1, 2, 4, and 5 peritoneal sectors involved were numbered 13, 5, 3, and 1, respectively. Two patients showed positive peritoneal lavage cytology. Regarding histologic types, signet ring cell, mucinous, well-differentiated, and moderately differentiated carcinoma were seen in 1, 4, 8, and 11 patients, respectively. Positive cytology was found in two patients. NAC was given to 20 patients, but three did not receive NAC. Postoperative chemotherapy was administered in 17 patients. One patient was alive ten years after CRS alone.

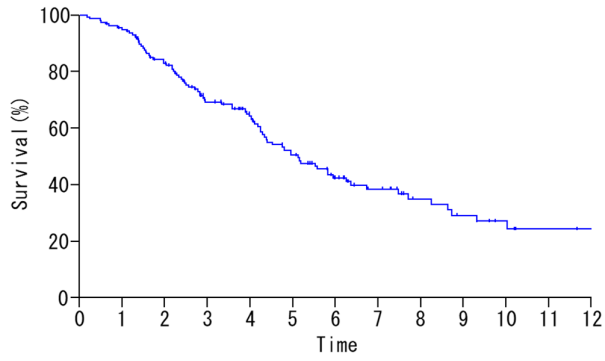

Figure 2: Survival over time (years) of 170 patients with peritoneal cancer index (PCI)≤12, small bowel-PCI≤2, number of metastatic sectors ≤6, non-signet ring cell subtype, and no liver/lung metastasis who underwent complete cytoreduction (CCR-0) resection (N=153). Thirty-eight patients survived longer than five years. Median survival time: 3.6 years; five-year survival rate: 57.8%; ten-year survival rate: 24.6%

Discussion

The current reference treatment for CRC-PM patients is CRS with HIPEC; although better survival results (9, 14, 15) have been achieved compared with systemic chemotherapy alone (4), its therapeutic efficacy remains under debate. Guidelines recommend that a multidisciplinary team in an experienced center should lead the management of CRC-PM, with consideration of CRS + HIPEC in selected patients (22).

Among several prognostic factors, CCR-0 resection, PCI- or SB-PCI below a threshold level, non-SRC histology type, and lower serum tumor marker levels have been reported as independent prognostic factors. As shown in the present study, the ten-year survival rate of 338 CCR-0 patients was 16.1%, but that of 109 CCR-1 patients was 0%, and multivariate analysis revealed that CCR-0 was the strongest and most important prognostic factor, in line with the literature (Table 4) (23, 24).

CCR-0 resection is conditioned on the PCI and SB-PCI, and PCI levels are closely associated with prognosis (14-16, 18). Freysness et al. reported that the only factor associated with OS on multivariate analysis was PCI, with a hazard ratio of 1.05 for every increment in the PCI score (25). A surgical PCI of >20 is often used to exclude patients from receiving CRS in CRC-PM. As shown in the present study, PCI≤12 allowed a significantly higher rate of CCR-0 resection and conferred a favorable prognosis as compared with PCI≥13. Additionally, diffuse involvement of the small bowel and its mesentery is the main factor leading to incomplete cytoreduction. Spiliotis J et al. studied the OS by stratifying SB-PCI into three groups (0–4, 5–8, and 9–10), and an SB-PCI of 0–4 was significantly associated with favorable OS after CCR-0 resection (24). We have already reported the significance of SB-PCI on postoperative survival, and the ten-year survival of patients with SB-PCI values of 0, 1, and 2 was 26.1, 19.5, and 6.2%, respectively (26). In contrast, that of patients with SB-PCI ≥3 was 0%. Multivariate analysis of the present study also revealed that SB-PCI ≤2 was an independent favorable prognostic factor. Accordingly, PMs on the small bowel should be removed completely when the SB-PCI is 1 or 2.

For the preoperative diagnosis of PCI, computed tomography (CT) and magnetic resonance imaging (MRI) have limitations in detecting small nodules ≤8 mm (27). Torkzad reported that CT and MRI have equal sensitivity and specificity in determining PCI when read by both experienced and inexperienced radiologists, and that CT gives better results when read by inexperienced radiologists compared to MRI (27). In contrast, the diagnostic accuracy of laparoscopy for PCI is excellent and superior to both CT and MRI. Laparoscopy is a proper selection tool in patients with peritoneal metastases. Sensitivity is high for detecting non-resectable patients, especially with extensive small bowel disease, but laparoscopy may underestimate the extent of PM (28, 29).

Treatment remains controversial in CRC-PM patients with either LLM or a previous history of complete resection of LLM. In general, LLM has been viewed as an exclusion criterion for CRS on the basis that such spread represents systemic disease.

Table 6: Data of 23 cured patients

Onset	Post-operative years	Alive/ died	Age	LNM	PCI	No of re-moved sec-tors	Histo-logic type	No. of in-volved sec-tors	SB-PCI	CCR	Cytol-ogy	HIPEC	NAC	Ef-fect of NAC	POC
Recur-rence	8	Alive	33	0	1	9	Muc	1	1	0	1	1	FOLFOX	PD	FOLF-OX
Synchro-nous	8	Died of pancreas cancer	57	1	2	5	Tub2	1	0	0	1	1	XELOX	NC	XE-LOX
Recur-rence	5	Alive	44	1	2	5	Tub1	1	0	0	1	1	XELODA	NC	no
Synchro-nous	10	Alive	48	0	2	2	Tub1	1	0	0		0	No	NC	no
Recur-rence	10	Alive	58	1	8	8	Tub2	4	0	0		1	XELOX	NC	XE-LOXX
Recur-rence	12	Alive	45	1	3	2	Tub1	1	0	0		1	No	PR	no
Synchro-nous	9	Alive	69	0	12	2	Muc	5	0	0	5	1	CDDP IP	NC	S1
Recur-rence	10	Alive	67	1	4	3	Tub2	2	0	0	1	0	FOLFOX+ BEV	NC	no
Recur-rence	9	Alive	53	1	0	1	Tub1	1	0	0	5	1	CPT+ P-MAB	PR	P-MAB
Synchro-nous	6	Alive	35	0	1	7	Tub2	1	0	0	1	1	SOX	NC	S1
Synchro-nous	12	Alive	62	0	4	6	Tub2	4	2	0	1	2	FOLDIRIS1	NC	S1
Recur-rence	8	Alive	64	1	4	5	Tu1	2	0	0		6	IRIS	NC	S1
Recur-rence	6	Alive	39	3	4	2	Tub1	1	0	0		1	XELOX+ BEV	CR	no
Synchro-nous	14	Alive	37	0	1	7	Tub1	1	0	0	1	1	IRIS	NC	S1
Recur-rence	7	Alive	37	0	2	8	Muc	1	0	0	1	1	FOLFOX, FOLFIRI	NC	S1
Synchro-nous	6	Alive	33	0	1	4	Tub1	1	0	0	1	1	DCS IP	NC	S1
Synchro-nous	8	Alive	49	1	4	9	Tub2	2	0	0		6	XELOX+ BEV	NC	no
Recur-rence	14	Alive	72	1	8	9	Tub2	4	0	0	1	1	XELOX	NC	S1
Synchro-nous	12	Alive	37	1	2	9	Sig	1	0	0	1	6	SOX	NC	Xelox
Synchro-nous	9	Alive	59	1	3	2	Muc	1	0	0	1	1	TC	NC	S1
Recur-rence	7	Alive	65	1	3	7	Tub2	2	0	0	1	1	SOX	NC	IRIS
Recur-rence	7	Alive	66	4	4	1	Tub2	2	2	0	1	0	No	NC	S1
Recur-rence	8	Alive	72	1	2	4	Tub2	1	0	0	1	13	FOLFOX+ Bev	NC	Xelox

LNM: Lymph node metastasis, NAC: Neoadjuvant chemotherapy, POC: Postoperative chemotherapy, Muc: Mucinous, Tub1: Well-differentiated adenocarcinoma, Tub2: Moderately differentiated adenocarcinoma, Sig: Signet ring cell carcinoma, PCI: Peritoneal cancer index, SB: Small bowel, CCR: Completeness of cytoreduction, HIPEC: Hyperthermic intraperitoneal chemotherapy

Table 7: Clinicopathologic factors on comparison of recurrent and cured patients

	Location		PCI		Number of metastatic sectors		SB-PCI		Liver/lung metatsasis		Histologic type	
	Right side	Left side	≤12	≥13	≤6	≥7	≤2	≥3	Negative	Positive	Non-SRC	SRC
Recurrent cases (N=250)	107 (42.8%)	143	170	80	177 (70.8%)	73	163 (65.2%)	87	189 (75.6%)	61	40 (16.0%)	210
Cured patients (N=23)	11 (47.8%)	12	23	0	23 (100%)	0	23 (100%)	0	23 (100%)	0	1 (4.4%)	22
P value	NS		0.0002		0.0005		0.0001		NS		NS	

PCI: Peritoneal cancer index, SB: Small bowel, SRC: Signet ring cell, NS: Not significant

The presence of LLM associated with peritoneal carcinomatosis is associated with a poorer prognosis, with survival at five years of 13.95% (95% CI 2.9–33.6) vs. 43.87% (22.2–63.7) when no metastases were present (P=0.018) (30). However, iterative surgery for recurrent lesions after peritonectomy can provide long-term survival benefits to highly selected patients with acceptable mortality and morbidity (31). In the present study, the five-year survival rate of patients with LLM was 8.1%, significantly poorer than that of patients without LLM. However, two patients were still alive without recurrence over five years after the resection of recurrent lung metastasis. Accordingly, a solitary LLM should be removed even after CRS for PM.

Regarding the surgical procedure, almost all surgeons globally are performing CRS using peritonectomy techniques. Nagata H et al. reported survival after peritoneal nodule resection without peritonectomy and HIPEC for strictly selected patients (32). They found that median post-metachronous peritoneal metastasis survival was 29.6 months and that the three-year survival rate after local resection of metachronous peritoneal metastases was 75%. None of the patients underwent peritonectomy or HIPEC. These results may indicate that some CRC patients with PM have localized metastasis without micrometastases in other peritoneal sectors. Accordingly, patients with limited peritoneal disease can be cured by local excision of limited metastasis without HIPEC.

In the 2019 National Comprehensive Cancer Network guideline, CRS+HIPEC was recommended for treating PM from CRC. Since then, CRS+HIPEC has been performed regularly in at least 430 expert centers in 19 countries (22, 33). However, considering the absence of an overall survival benefit after adding HIPEC to CRS and more frequent postoperative late complications with this combination, data from PRODIGE 7 suggest that cytoreductive surgery alone should be the cornerstone of therapeutic strategies with curative intent for CRC-PM (34). After a presentation at the 2018 ASCO meeting, the national guideline consensus seemed to move away from using HIPEC in treating PM from CRC, resulting in the exclusion of HIPEC from national guidelines. However, HIPEC is still performed in 8 countries (33). In contrast, the present study clearly demonstrated a survival improvement with HIPEC (HR: 0.72).

Since PRODIGE 7 data were presented, several interventions have been augmented, i.e., drugs used in HIPEC, duration of HIPEC, and thermal dose. Nearly all patients registered in PRODIGE 7 had already been treated with oxaliplatin-based systemic chemotherapy, as NAC and oxaliplatin were used during the HIPEC procedure. After neoadjuvant treatment using oxaliplatin, the sensitivity of CRC cells against oxaliplatin is known to decrease (33, 35). According to the PSOGI web-based survey, oxaliplatin+5FU+LV was used in 8/18 (44.4%) institutions in 2017, but Mitomycin C (MMC) is now mainly used in 12/18 (66.7%) institutions. Accordingly, a phase IV randomized clinical trial to evaluate the efficacy of HIPEC with high-dose MMC (35 mg/m^2) was started (36); 216 patients with PCI≤20 will be randomized intraoperatively to arm 1 (with HIPEC) or arm 2 (without HIPEC), with a primary endpoint of peritoneal recurrence-free survival at three years. Regarding the time and temperature during HIPEC, the cytotoxicity of chemotherapeutic agents in HIPEC depends on the exposure time and temperature (37, 38). HIPEC is performed for 60 to 90 min HIPEC at 15 (83.3%) of 18 expert institutions (33). The thirty minutes of HIPEC used in PRODIGE 7 may have been sub-optimal to achieve adequate oncological activity (37).

According to Separeto and Dewey, cells show irreversible changes when treated at a temperature above 43 °C and are killed exponentially in a time-dependent manner (19). The "thermal dose" is the cytotoxic unit for heat under objective evaluation. In the present study, the thermal dose during HIPEC was strictly controlled, and every case was treated with a thermal dose of 40 min. In PRODIGE 7, HIPEC was conducted at 43 °C for 30 min. This means a thermal dose of 30 min. However, the thermal dose was not described in PRODIGE 7. Additionally, HIPEC in PRODIGE 7 was performed using closed circulation in about half of the patients. With closed HIPEC, the temperature in every part of the peritoneal cavity cannot be equally raised at 43 °C. Accordingly, patients should be treated with the same thermal dose during HIPEC to obtain a

constant effect.

The SRC subtype of CRC is a rare subtype and occurs in 1% of all CRC patients. Patients with the SRC subtype have a poor prognosis because they tend to have PM and a low CCR-0 rate compared with other histologic types (39). The present study showed that the CCR-0 rate in patients with the SRC subtype was just 65.1% (56/86), and the five and ten-year survival rates were 12.5% and 4.2%, respectively. These results indicate that even patients with CRC and PM who have the SRC subtype may benefit from CRS and HIPEC, but developing more effective drugs for the SRC subtype is needed.

Regarding lymph node metastases, favorable long-term results are obtained in CRC-PM when there are negative lymph nodes at the time of the primary operation (38). In the present study, however, no significant post-CRS difference in survival was detected based on the presence or absence of lymph node metastasis at the first operation. The present study also showed no significant post-CRS survival difference with respect to age, gender, onset, location, or preoperative chemotherapy (Table 4).

Treating CRC-PM patients is complex and often requires high-risk surgical procedures with an extensive learning curve (16, 22, 40, 41). In the present study, grade 3–5 complications were found in 18.8% (84/447), and the mortality rate was 2.0% (9/447). Severe complications were significantly correlated with the PCL score (Table 5).

Accordingly, a strict selection of candidates is needed for CRS+HIPEC. If CCR-0 resection was performed in patients with PC I≤12, SB-PCI ≤2, ≤6 involved segments, and a histologic type other than the SRC subtype, selected by intraoperative findings, then the MST, five-year, and ten-year survival rates for these patient groups were 5.5 years, 57.8% and 24.6%, respectively (Figure 2). Additionally, postoperative grade 3, 4, and 5 complications occurred in 5.3%, 8.8%, and 0.6% of patients, respectively. Twenty-three cured patients had PCI≤12 and SB-PCI≤2.

Conclusion

Our findings suggest selection criteria for CRS+HIPEC that should be added to the global guidelines. Among CRC patients with PM, COMPT with CCR-0 resection is indicated for PCI≤12, SB-PCI≤2, ≤6 involved peritoneal sectors, no LLM, and differentiated histologic type.

Authors' Contribution

Writing: Yutaka Yonemura, Conceptualization: Haruaki Ishibashi, Akiyoshi, Mizumoto, Takuji Fujita, Format analysis: Yang Liu, Satoshi Wakama, Data analysis: Syouzou Sako, Nobuyuki Takao, Toshiyuki Kitai, Kanji Katayama, Yasuyuki Kamada, Keizou Taniguchi, Daisuke Fujimoto. All authors have read and agreed to the published version of the manuscript.

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Ethical Approval and Consent to Participate

The Ethics Committee of Kishiwada Tokushukai Hospital approved the study, based on the protocol: code H-19-2, titled "A study of comprehensive treatment for peritoneal metastasis." It was approved on October 15, 2007.

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