Original Research Article

Factors Affecting the Prognosis after Primary Tumor Resection for Patients with Metastatic Colorectal Cancer with Synchronous Peritoneal Metastasis: A Multi-center, Prospective, Observational Study

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Abstract

Objectives: To clarify the risk factors affecting prognosis after primary tumor resection (PTR) in patients with metastatic colorectal cancer with synchronous peritoneal metastasis (mCRC-SPM).

Methods: Patients were enrolled prospectively in the JSCCR project "Grading of Peritoneal Seeding in Colorectal Cancer." Factors that may influence overall survival—age, sex, location of the primary tumor, lymph node metastasis, presence of liver metastasis, degree of peritoneal metastasis, peritoneal cancer index (PCI), cancer cure, and postoperative chemotherapy—in the PTR group were examined using multivariate analysis.

Results: Of the 133 enrolled patients with mCRC-SPM, 112 patients underwent PTR. Among them, 26 (23.2%) had mCRC-SPM of grade P1, 47 (42.0%) of P2, and 39 (34.8%) of P3. The median PCI was 4 (range, 1-28); no surgery-related deaths occurred. Postoperative complications of Clavien-Dindo classification ≥grade 2 were observed in 20 (17.9%) patients. R0 surgery became more difficult as the degree of dissemination increased, and the PTR group had a significantly better prognosis than the non-PTR group. In the multivariate analysis, age ≥75 years, rectal cancer, presence of liver metastasis, higher PCI, non-curative resection, and non-treatment with systemic chemotherapy were associated with poor prognosis in patients after PTR.

Conclusions: In patients with mCRC-SPM, postoperative complications are infrequent for P1 with localized peritoneal dissemination, and PTR may be considered as aggressive treatment. Factors including age ≥75 years, rectal cancer, presence of liver metastasis, increased PCI, non-curative resection, and non-treatment with systemic chemotherapy are associated with a reduced survival benefit from PTR.

Keywords

colorectal cancer, primary tumor resection, prognosis, synchronous peritoneal metastasis

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Introduction

The incidence of colorectal cancer (CRC) is increasing annually in both men and women in Japan, where it is one of the major causes of death, similar to that in other countries[1]. Approximately 20% of patients with CRC are diagnosed with metastatic CRC (mCRC) at the time of initial diagnosis. In most patients, CRC metastasizes to the liver and lungs, but the frequency of synchronous peritoneal metastasis (SPM) is as low as 5%[2].

According to the NCCN guidelines[3], systemic chemotherapy is recommended as the initial treatment for mCRC with SPM (mCRC-SPM), and primary tumor resection (PTR) is considered when cancer-related symptoms are present. Recent randomized controlled studies demonstrated that PTR for mCRC had a negative impact on survival benefit, which supports the recommendation of the NCCN guidelines[4,5].

However, these randomized control studies included a small mCRC-SPM population of only 5%-7%. Recently, some studies have reported a survival benefit of PTR for asymptomatic mCRC[6,7]. Therefore, in this study, we aimed to clarify the risk factors affecting the prognosis after PTR in patients with mCRC-SPM, with the goal of achieving a survival benefit for patients with mCRC-SPM who are considered to have a poor prognosis.

Methods

This study was approved by the Japanese Society for Colorectal Cancer Research (JSCCR) Ethics Review Committee and the Ethics Committee of the Toho University Omori Medical Center (M16190). The details of the study were disclosed on the website of the Toho University Omori Medical Center, and the opportunity to refuse participation in the study was guaranteed by an opt-out method.

In this study, patients were prospectively enrolled in the JSCCR project "Grading of Peritoneal Seeding in Colorectal Cancer," and prognostic information was collected during March 2020. The inclusion criteria were as follows: 1) primary CRC, 2) histologically identified adenocarcinoma, 3) peritoneal metastasis identified before and during surgery, 4) no history of multiple malignancies within 5 years, 5) age over 20 years, and 6) agreement to participate in the study. The degree of peritoneal metastasis was determined according to the ninth edition of the Japanese Classification of Colorectal Cancer[8]: P1, metastasis localized to the adjacent peritoneum; P2, limited metastasis to the distant peritoneum; and P3, diffuse metastasis to the distant peritoneum. We also used the peritoneal cancer index (PCI), a frequently
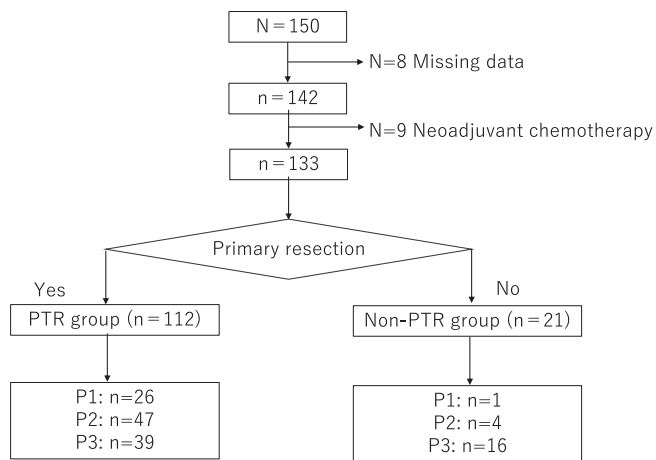
Figure 1. Flow diagram of the patient selection process.

used method[9], to classify the degree of peritoneal metastasis into 39 phases (13 regions and 4 lesion sizes). The following factors influencing overall survival (OS) in the PTR group were examined using multivariate analysis: age (<75 years vs. ≥75 years), sex, location of the primary tumor (colon vs. rectum), lymph node metastasis (N0+1 vs. N2), presence of liver metastasis, degree of peritoneal metastasis (P1+2 vs. P3), PCI, cancer cure (R0 vs. R1+2), and postoperative chemotherapy.

Statistical analysis

Comparisons between the two groups were performed using the chi-square (χ^2) or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. Survival was analyzed using the Kaplan-Meier method, and significant differences were determined using the log-rank test. The Cox proportional hazards model was used to examine the factors predictive of a poor prognosis. Tests of significance were two-sided, and p values <0.05 were considered statistically significant. All data were entered into a computer database and analyzed using EZR version 1.55, which is a modified version of the R commander, designed to add statistical functions frequently used in biostatistics[10].

Results

1. Patient characteristics

Between October 2012 and December 2016, 150 patients with mCRC-SPM from 28 centers were prospectively enrolled in the JSCCR project "Grading of Peritoneal Seeding in Colorectal Cancer" study. Among them, 133 patients were included in the present study after excluding 8 patients with missing data and 9 who received preoperative chemotherapy. Of the included patients, 112 patients were in the PTR group, and 21 were in the non-PTR group (Figure 1). Overall, 75 patients were males and 58 were females, with a median age of 66.0 years (range, 30-89). The median body mass index was 20.8 kg/m^2 (range, 14.9-40.5). Among the 133 patients, 26 (19.5%) had rectal cancer, and the remaining 107 (80.5%) had colon cancer. Among the preoperative tumor markers, the carcinoembryonic antigen level was abnormal in 101 (75.9%) patients and the carbohydrate antigen 19-9 level in 71 (53.4%) patients. Distant metastases other than peritoneal metastases were found preoperatively in 67 (50.4%) patients. In addition to SPM, 46 (34.6%) patients had one-organ metastases, 25 (18.8%) had two-organ metastases, and 5 (3.8%) had three or more organ metastases. A total of 112 (84.2%) patients underwent PTR, with no significant differences in preoperative background factors between the PTR and non-PTR groups (Table 1).

2. Surgical outcomes

The surgical outcomes of the PTR group are shown in Table 1. Among the patients, 26 (23.2%) had SPM of grade P 1, 47 (42.0%) of P2, and 39 (34.8%) of P3. The median PCI was 4 (range, 1-28). R0 resection was possible in 29 of 112 (25.9%) patients.

No surgery-related deaths occurred. Postoperative complications of Clavien-Dindo classification grade 2 or higher were observed in 20 (17.9%) patients, and serious complications of grade 3 or higher were observed in 8 (7.1%) patients.

According to peritoneal dissemination grade, postoperative complications occurred in four (15.4%) patients in the P 1, seven (14.9%) in the P2, and nine (23.1%) in the P3 groups. Severe postoperative complications (grade 3 or higher) occurred in one P1 (3.8%), four P2 (8.5%), and three P3 (7.7%) patients. Compared with P1 patients, P2 and P3 patients had higher incidences of postoperative complications, but the difference was not statistically significant.

3. Pathological outcomes

The pathological outcomes in the PTR group are shown in Table 2. The histological types were as follows: 89 (79.5%) well or moderately differentiated adenocarcinomas, 12 (10.7%) poorly differentiated adenocarcinomas, and 11 (9.8%) others. Regarding the depth of invasion, 9 (8.0%) had T3, and 103 (92.0%) had T4 invasions. Regarding lymph node metastasis, 85 (75.9%) were positive for metastasis, and 27 (24.1%) were negative. In 29 mCRC-SPM patients with R0 resection, 2 had distant metastases other than peritoneal metastasis. Although one of these patients had liver metastases and the other had distant lymph node metastasis, the metastases were resected in both cases. According to peritoneal dissemination grade, R0 surgery was performed in 14 (53.8%) patients in the P1 group, 14 (29.8%) in the P2, and one (2.6%) in the P3 group, indicating that R 0 surgery was more difficult as the degree of dissemination

Table 1. Patient characteristics

	Total (N=133)	(%)	PTR (N=112)	(%)	Non-PTR (N=21)	(%)	p-value
Age*	66 (30-89)		66.5 (37-89)		65 (30-87)		0.961
Sex, n (%)							
Male	75	(56.4)	63	(56.3)	12	(57.1)	>0.99
Female	58	(43.6)	49	(43.8)	9	(42.9)	
BMI*	20.8 (14.9-40.5)		20.7 (14.9-35.6)		21.2 (16.3-40.5)		0.216
Location of primary tumor, n (%)							
Right colon	68	(51.1)	58	(51.8)	10	(47.6)	
Left colon	39	(29.3)	32	(28.6)	7	(33.3)	0.949
Rectum (including rectosigmoid colon)	26	(19.5)	22	(19.6)	4	(19.0)	
CEA*	21.8 (0.7-15000)		19.45 (0.7-15000)		24.5 (3.7-5444)		0.513
Normal	32	(24.1)	29	(25.9)	3	(14.3)	0.404
Abnormal	101	(75.9)	83	(74.1)	18	(85.7)	
CA19-9*	49.0 (0.4-22599)		47.5 (0.4-20119)		73.0 (1.6-22599)		0.839
Normal	62	(46.6)	53	(47.3)	9	(42.9)	0.812
Abnormal	71	(53.4)	59	(52.7)	12	(57.1)	
Distant metastases other than peritoneal metastasis, n (%)							
Negative	66	(49.6)	51	(45.5)	15	(71.4)	0.229
Positve	67	(50.4)	61	(54.5)	6	(28.6)	
1 organ	46	(34.6)	34	(30.4)	12	(57.1)	
2 organ	25	(18.8)	23	(20.5)	2	(9.5)	0.181
≥3 organs	5	(3.8)	4	(3.6)	1	(4.8)	
Peritoneal seeding grade, n (%)							
P1	27	(20.3)	26	(23.2)	1	(4.8)	
P2	51	(38.3)	47	(42.0)	4	(19)	0.002
P3	55	(41.4)	39	(34.8)	16	(76.2)	
PCI*	4 (1-29)		4 (1-28)		13 (2-29)		<0.001
Mortality, n (%)			0	(0)			
Postoperative complications, n (%)							
>Grade 2			20	(17.9)			
P1			4	(15.4)			
P2			7	(14.9)			0.601#
P3			9	(23.1)			
>Grade 3			8	(7.1)			
P1			1	(3.8)			
P2			4	(8.5)			0.808#
P3			3	(7.7)			
Postoperative chemotherapy, n (%)							
Yes	110	(82.7)	93	(83.0)	17	(81.0)	0.234
No	23	(17.3)	19	(17.0)	4	(19.0)	

*median (range), BMI: body mass index, Right colon: velmiformis, cecum, ascending colon and transverse colon, Left colon: descending colon and sigmoid colon, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, PCI: peritoneal cancer index

#: P1 versus P2+3

increased (Table 2).

4. OS curves of patients in the PTR and non-PTR groups

According to the peritoneal seeding grade, the P3 group had a significantly worse prognosis than the P1 group (p= 0.039; Figure 2). The OS of the PTR (n=112) and non-PTR (n = 21) groups was compared. The median survival time in the non-PTR group was 6 months (range, 4-12), whereas it was 26 months (range, 2-31) in the PTR group. A statistically significant difference was observed between the two groups (p<0.001; Figure 3A). We also compared OS between the PTR and non-PTR groups in P1+P2 patients (n= 78) and P3 patients (n=55). Even when restricted to the P3 group, the median survival time in the non-PTR group was 6 months (range, 3-11), whereas in the PTR group, it was 16 months (range, 9-30). A statistically significant difference

Table 2. Pathological outcomes

	PTR (N=112)	(%)
Histological type of primary tumor, n (%)		
Well or mod	89	(79.5)
Por	12	(10.7)
Others	11	(9.8)
T-category, n (%)		
T3	9	(8.0)
T4a	79	(70.5)
T4b	24	(21.4)
N-category, n (%)		
N0	27	(24.1)
N1a	17	(15.2)
N1b	22	(19.6)
N2a	24	(21.4)
N2b	22	(19.6)
Curability, n (%)		
R0	29	(25.9)
R1	4	(3.6)
R2	79	(70.5)
R0, n (%)		
P1	14	(53.8)
P2	14	(29.8)
P3	1	(2.6)

Well or mod: well or moderately differentiated adenocarcinoma, Por: poorly differentiated adenocaecinoma

was observed between the two groups (p=0.012), thereby suggesting that PTR has a survival benefit for patients with advanced mCRC-SPM, such as P3 (Figure 3B, C).

5. Prognostic factors in patients who underwent PTR

Results of univariate analysis of prognostic factors for the 112 patients with SPM are shown in Table 3. Age ≥75 years, presence or absence of lymph node metastasis, presence or absence of liver metastasis, degree of peritoneal metastasis (P classification and PCI), cancer residuals, and postoperative chemotherapy were statistically significantly associated with OS. In the multivariate analysis, poor OS was statistically related to age ≥75 years, rectal cancer, presence of liver metastasis, higher PCI, non-curative resection, and no postoperative chemotherapy (Table 4). Two multivariate analyses were performed in this study. In one, we controlled for P classification, and in the other we controlled for PCI, because they are potentially confounding factors.

6. Postoperative complications and prognosis

Postoperative complications of Clavien-Dindo classification grade 2 or higher were observed in 20 (17.9%) patients and grade 3 or higher in 8 (7.1%) patients. However, no statistically significant difference was observed between the grade of postoperative complications and OS (Figure 4). Additionally, no statistically significant differences were observed between the grades of postoperative complications
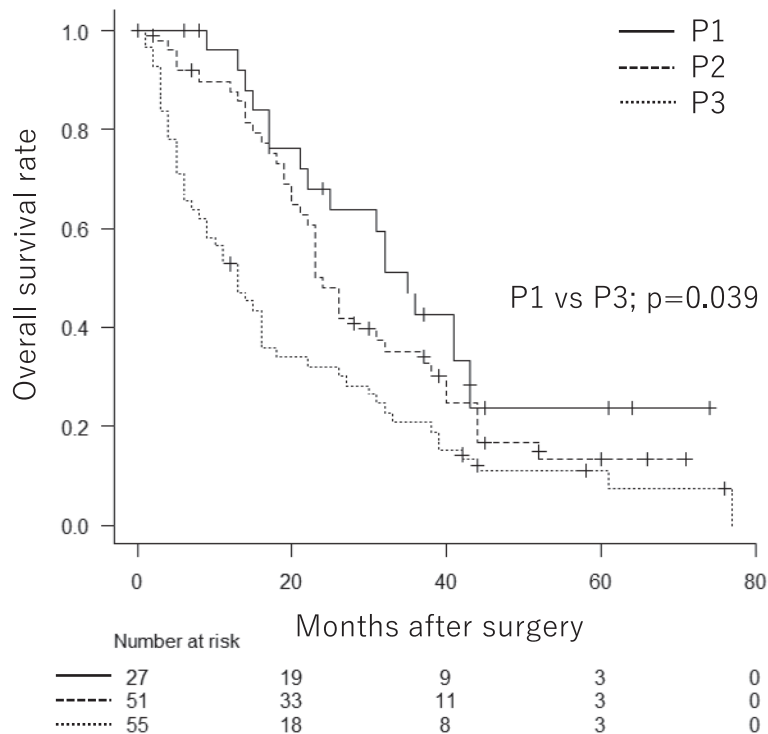

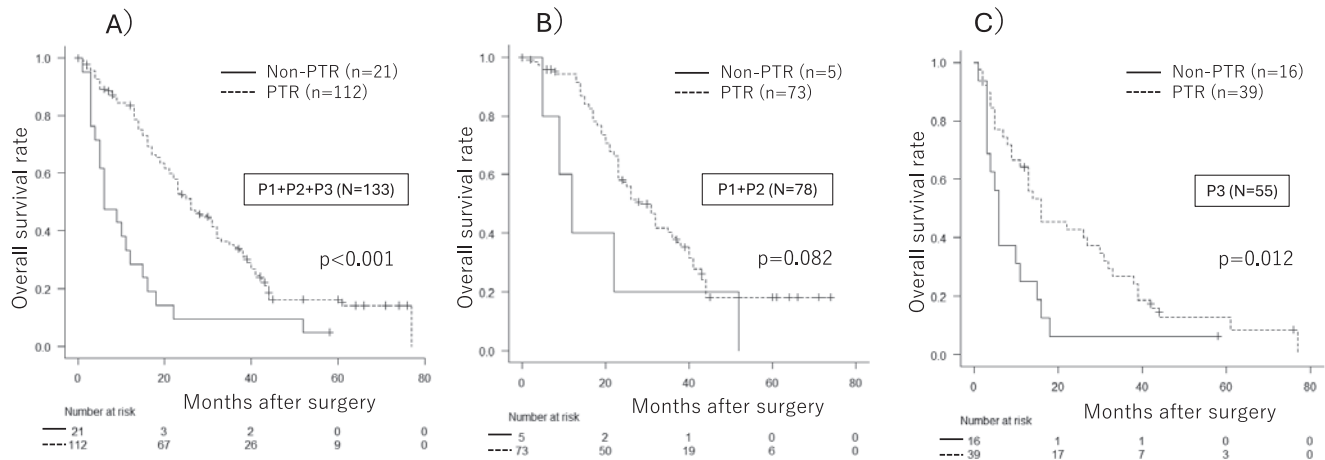**Figure 2.** Overall survival curves of patients according to the peritoneal seeding grade.

Figure 3. Overall survival curves of patients in the primary tumor resection (PTR) and non-PTR groups.
A) P1+P2+P3 cases (n =133).
B) P1+2 cases (n=78).
C) P3 cases (n=55).

Table 3. Univariate analysis of survival

Variables	p-value
Age: <75/≥75 years	0.001
Sex	0.183
BMI: <20/≥20 kg/m^2	0.167
Location of primary tumor: right/left	0.240
Location of primary tumor: colon/rectum	0.051
Tumor markers: normal/abnormal	0.104
CEA	0.078
CA19-9	0.608
Histological type: well or moderately differentiated/other	0.440
pT3/pT4	0.293
pN0+pN1/pN2	0.014
Distant metastasis: yes/no	0.079
Liver metastasis: yes/no	0.003
Lung metastasis: yes/no	0.939
Distant metastasis: 0,1,2,3,4	<0.001
Peritoneal metastasis: P1+P2/P3	0.024
PCI	0.049
Residual tumor: R0/R1+R2	0.002
Postoperative chemotherapy: yes/no	0.001
Postoperative complications: yes/no	0.301

BMI: body mass index, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, PCI: peritoneal cancer index

and OS in P1 (n=26) and P2+3 patients (n=86) (Figure 5).

Discussion

SPM is generally less frequent than liver or lung metastases in mCRC. In addition, SPM is often difficult to diagnose preoperatively and is frequently detected during laparotomy. Many surgeons have performed PTR for mCRC-SPM in the hope of benefiting from postoperative adjuvant chemotherapy, despite the difficulty of achieving R0 resection. This is because PTR relieves cancer-related symptoms such as bloody stools and impaired stool evacuation. However, the occurrence of mortality and morbidity due to PTR for mCRC is not infrequent, and complications can delay the introduction of anticancer therapy and significantly affect patients' quality of life and remaining life expectancy.

The survival benefit of PTR for mCRC is still being debated[4,11,12]. Recently, two randomized controlled trials, in which the population of mCRC-SPM was only 5%-7%, reported that PTR for stage IV CRC was not associated with prolonged OS.

Conversely, a systematic review by Anwar et al.[13] concluded that PTR has a survival benefit and should be considered based on the performance status (PS) and tumor status rather than the presence or absence of symptoms. In a meta-analysis by Simillis et al.[14], PTR improved the prognosis in the absence of increased complications. In a retrospective study of 6,708 young patients with CRC, aged 18-45 years, Arhin et al.[15] reported that surgical treatment of primary sites and metastases significantly improved prognosis. Recently, Rovers et al.[6] and Rijken et al.[7] reported that PTR for mCRC-SPM was associated with an improved prognosis.
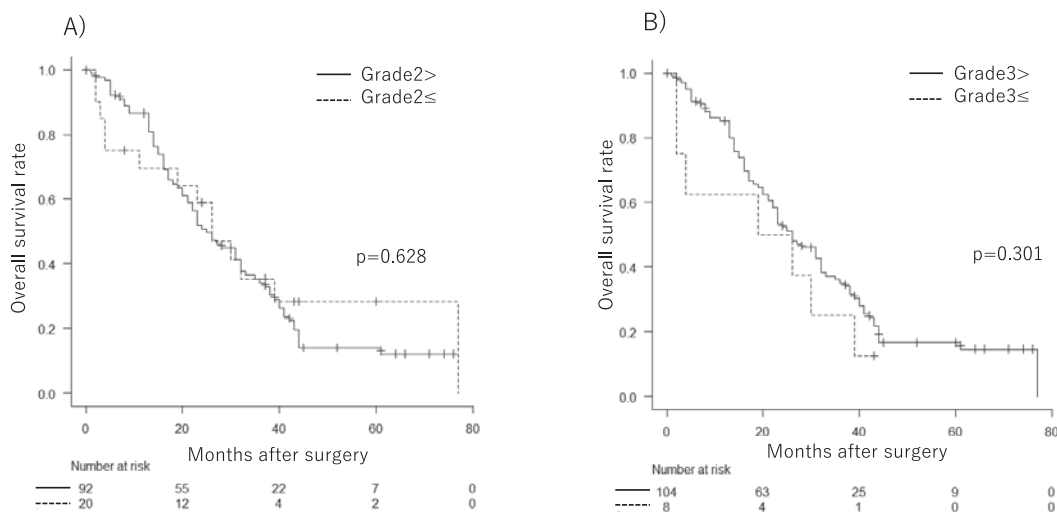
In this study, despite the 25.9% R0 resection rate, the median OS was 26 months in the PTR group, which was significantly better than the 6 months in the non-PTR group, suggesting a possible survival benefit of PTR in patients with mCRC-SPM regardless of R0 resection. This is because the survival time is longer than the reported median survival time (5-15 months)[16,17] of patients with mCRC treated with palliative systematic therapy to date. However,

Table 4. Multivariate analysis of survival

Variables	Univariate	Multiple		
	p-value	Hazard ratio	95% CI	p-value
Age: <75/≥75 years	0.001	2.32	1.347-3.996	0.024
Sex	0.183	1.071	0.671-1.709	0.775
Location of primary tumor: colon/rectum	0.051	0.3912	0.225-0.680	0.001
pN0+pN1/pN2	0.014	1.203	0.710-2.039	0.492
Liver metastasis: yes/no	0.003	1.603	0.958-2.680	0.072
Peritoneal metastasis: P1+P2/P3	0.024	1.394	0.841-2.312	0.198
Residual tumor: R0/R1+R2	0.002	1.539	1.033-2.292	0.034
Postoperative chemotherapy: yes/no	0.001	0.2342	0.113-0.486	<0.001

Variables	Univariate	Multiple		
	p-value	Hazard ratio	95% CI	p-value
Age: <75/≥75 years	0.001	2.301	1.336-3.963	0.003
Sex	0.183	1.161	0.725-1.860	0.534
Location of primary tumor: colon/rectum	0.051	0.3677	0.211-0.640	0.004
pN0+pN1/pN2	0.014	1.152	0.677-1.960	0.602
Liver metastasis: yes/no	0.003	1.897	1.108-3.248	0.020
PCI	0.049	1.053	1.014-1.094	0.008
Residual tumor: R0/R1+R2	0.002	1.348	0.900-2.019	0.147
Postoperative chemotherapy: yes/no	0.001	0.2609	0.125-0.544	<0.001

PCI: peritoneal cancer index

Figure 4. Overall survival curves of patients according to the postoperative complications.
A) Postoperative complication <grade 2 vs. ≥grade 2.
B) Postoperative complication <grade 3 vs. ≥grade 3.

in the subanalysis of SPM by grade, only P1 showed significant differences. Although no mortalities occurred, postoperative complications of grade 2 or higher were observed in 17.9% of all patients. Ahmed et al.[18] reported a mean 30-day postoperative mortality of 4.9% and morbidity of 25.9% in their review, higher than those in the present study. However, postoperative complications increased with the grade of dissemination, and the frequency of morbidity after PTR for

P1, P2, and P3 metastasis was 15.4%, 14.9%, and 23.1%, respectively. Although some studies, such as those by Zhou et al.[19] and Cascales-Campos et al.[20], have reported that high postoperative morbidity affects OS, in the present study, this was not the case. However, since morbidity likely plays a significant role in postoperative chemotherapy initiation and quality of life, whether to conduct PTR should ultimately be determined by considering the patient's PS and
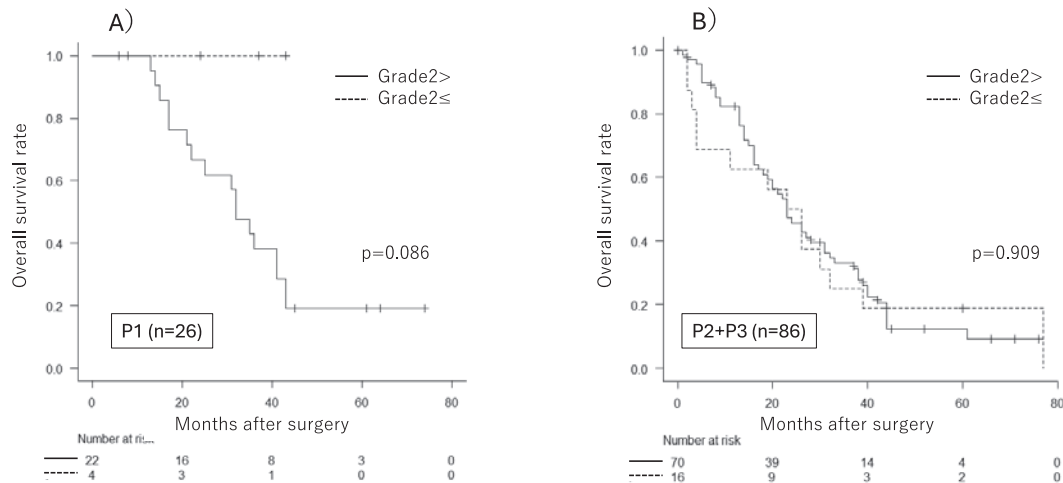
Figure 5. Overall survival curves of patients according to the peritoneal seeding grade and postoperative complications.
A) P1 cases (n = 26), postoperative complication ≥grade 2.
B) P2+3 cases (n = 86), postoperative complication ≥grade 2.

tumor burden.

In addition, surgeons need to be aware of the prognostic factors when making appropriate decisions to perform PTR. In this study, multivariate analysis was performed to examine the prognostic determinants of PTR, revealing age ≥75 years, rectal cancer, liver metastasis, a higher PCI, cancer residuals, and no postoperative chemotherapy as independent factors affecting OS after PTR for mCRC-SPM. Elderly individuals have poor PS and many comorbidities due to age-related declines in physiological function. The elderly may be limited by their physical vulnerability to standard treatment modalities such as surgery and anticancer therapy[20,21]. A multi-center study by Sarasqueta et al.[22] reported that age is an important factor in postoperative adjuvant therapy for advanced CRC. In this study, the exact reason could not be elucidated because the choice of surgical technique and anticancer drug treatment was determined by the physician in charge and the patient. However, the age cutoff of 75 years might have played a role in OS, as the rate of chemotherapy administration was significantly lower in those aged ≥75 years than in those aged <75 years (62.5% vs. 88.6%, p<0.001).CRC treatment has also made advances in the last two decades. In a report comparing the prognoses of colon and rectal cancers since 2000, Duraes et al.[23] found that colon cancer had a better prognosis than rectal cancer when adjusted for age, sex, the American Society of Anesthesiologists' classification, chemotherapy, and pathological progression. mCRC-SPM occurs more frequently in the colon than in the rectum[24-26]. Although the histological types of mucinous carcinoma and poorly differentiated adenocarcinoma resulted in poor OS in previous studies[27,28], no differences in histology were observed between the rectum and colon in the present study.

Liver metastasis is the most frequent metastasis in mCRC, and treatment for liver metastasis is associated with an improved prognosis in mCRC. The reported frequency of simultaneous liver metastases in CRC is approximately 15%; however, in this study, approximately 80% of the patients had liver metastases, which might have been extracted as an important prognostic factor affecting OS.

The PCI scores 13 regions in the abdominal cavity and is widely reported as an important prognostic factor[29,30]. A systematic review by Narasimhan et al.[31] also reported that a higher PCI was associated with poorer OS, along with incomplete cytoreduction and lymph node involvement. Although various reports on the PCI cutoff value have been published, Kobayashi et al.[32], in their study of 564 patients with mCRC-SPM, reported that a PCI cutoff value of 10 is reasonable. Nagata et al.[33] identified PCI >10 as a prognostic factor for iatrogenic peritoneal metastasis in colon cancer. However, we could not determine the appropriate cutoff value for PCI in this study. A higher PCI was identified as one of the risk factors affecting OS in this study. Regarding the fact that P1/P2+3 was not a significant risk factor despite PCI being one, we believe that this can be attributed to the detailed classification of the PCI. However, this classification is quite cumbersome and time-consuming, making it infeasible for clinical practice.

R0 resection is generally important for achieving good survival. A systematic review and meta-analysis of the treatment of mCRC-SPM by Wu et al.[34] noted that curative treatments improve 3- and 5-year outcomes, but are associated with morbidity, while Shida et al.[35] and Kobayashi et al.[36] reported the importance of R0 resection for mCRC-SPM.

In this study, R0 resection was performed in only 25.9%

of the patients, and postoperative complications of grade 2 or higher increased with increasing dissemination grade, regardless of curative or non-curative resection.

Systemic chemotherapy plays an important role in the treatment of mCRC-SPM to improve the prognosis, as indicated in the NCCN guidelines[3]. A median survival of 5-15 months has been achieved with systemic palliative therapy. With regard to chemotherapy, many reports indicate that adjuvant chemotherapy after R0 resection is an important factor in improving the prognosis in mCRC-SPM[28,37-39]. In addition, hyperthermic intraperitoneal chemotherapy (HIPEC) improved the prognosis after resection and cytoreduction surgery in a recent study, and it is becoming accepted as the standard of care for CRC with peritoneal dissemination[40,41].

Limitations

This study has certain limitations. Although this was a multi-center, prospective, observational study, we encountered several difficulties in examining the significance of PTR. First, the number of patients in the non-PTR group was not sufficient to clarify the significance of PTR. In addition, the non-PTR group had 16 (76.2%) more patients with P3, which might have caused the significant difference in OS between the PTR and non-PTR groups. Second, the treatment strategies for mCRC-SPM differed between institutions and surgeons, and the choice of procedure and postoperative treatment might have been subject to the individual discretion of each surgeon. Finally, although cytoreductive surgery with HIPEC is performed worldwide, only a few patients in this study underwent HIPEC; therefore, the significance of HIPEC in cytoreductive surgery was not examined.

Conclusion

PTR may be aggressively considered for patients with mCRC-SPM and localized peritoneal dissemination; however, age ≥75 years, rectal cancer, liver metastases, a higher PCI, non-curative resection, and non-treatment with systematic chemotherapy are factors leading to a reduced survival benefit from PTR.

Conflicts of Interest
There are no conflicts of interest.

Author Contributions
KF and SK conceived the idea of the study. SK collected and analyzed the data. SK wrote the manuscript text under supporting of KF.
Contributions to the submitted work from each author: data collection

Approval by the Institutional Review Board (IRB)
The study protocol was approved by the Institutional Review Board of the Toho University Omori Medical Center (M16190).

Disclaimer
Soichiro Ishihara is the Editor-in-Chief of Journal of the Anus, Rectum and Colon and on the journal's Editorial Board. Kimihiko Funahashi is one of the Associate Editors of Journal of the Anus, Rectum and Colon and on the journal's Editorial Board. They were not involved in the editorial evaluation or decision to accept this article for publication at all.

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