Factors affecting R0 resection of colorectal cancer with synchronous peritoneal metastases: a multicenter prospective observational study by the Japanese Society for Cancer of the Colon and Rectum

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Abstract

Background In Japan, R0 resection has been recommended for colorectal cancer patients with peritoneal metastases confined to the adjacent peritoneum and those with a few metastases to the distant peritoneum. R0 resection for M1c disease has drawn attention in Western countries and is currently considered an acceptable therapeutic option in the US National Comprehensive Cancer Network guidelines. However, clinical factors that affect the choice of R0 resection are unknown.
Methods This multicenter, prospective, observational study was conducted by the Japanese Society for Cancer of the Colon and Rectum. Colorectal cancer patients with synchronous peritoneal metastases were enrolled at 28 institutions in Japan from October 2012 to December 2016. To determine factors affecting R0 resection and R1 resection with intended R0 resection, stepwise logistic regression analyses were performed on clinical factors including age, sex, performance status (PS), body mass index, peritoneal cancer index (PCI) score, presence of ascites, presence of distant metastases, and primary tumor site.
Results R0/R1 resection was performed in 36 (31/5; 25%) of 146 patients. No distant metastases [odds ratio (OR) 52.9; 95% confidence interval (CI) 13.3–210.1; $p < 0.0001$], low PCI score (1–6) (OR 20.0; 95% CI 4.8–83.4; $p < 0.0001$), and high PS (0) (OR 2.40; 95% CI 0.66–8.68; $p = 0.18$) were independent factors affecting R0/R1 resection. PCI score and PS were also independent factors affecting R0/R1 resection in M1c patients without non-peritoneal distant metastases ($n = 59$).
Conclusion Distant metastases, PCI score, and PS are three factors which affect R0 resection for M1c disease.

Keywords Peritoneal metastasis · Colorectal cancer · R0 resection · Peritoneal cancer index score

Abbreviations

AUC	Area under the curve
CI	Confidence interval
CRC	Colorectal cancer
HIPEC	Hyperthermic intraperitoneal chemotherapy
NCCN	National Comprehensive Cancer Network
OR	Odds ratio
OS	Overall survival
PCI	Peritoneal cancer index
PS	Performance status
ROC	Receiver operating characteristic
TNM classification	Tumor-node-metastasis classification

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Introduction

The 8th edition of the TNM Classification of Malignant Tumors published in 2017 categorizes colorectal cancer (CRC) with peritoneal metastases as M1c, separately from M1a (metastases to one organ) and M1b (metastases to more than one organ), given the poor prognosis of peritoneal metastases compared to other metastatic diseases in visceral organs [1, 2]. With regard to therapeutic strategies, systemic chemotherapy, but not aggressive cytoreductive debulking and/or intraperitoneal chemotherapy outside the setting of a clinical trial, had been recommended as the exclusive

treatment choice by the National Comprehensive Cancer Network (NCCN) guidelines for colon cancer up until 2016 [3]. R0 resection (i.e., resection of only the diseased portion of the peritoneum), which differs from complete cytoreductive surgery, was added in 2016 as another treatment option for M1c CRC: "If R0 resection can be achieved, surgical resection of isolated peritoneal disease may be considered at experienced centers" [4–6]. This footnote was modified in 2017, as follows: "Complete cytoreductive surgery and/ or intraperitoneal chemotherapy can be considered in experienced centers for select patients with limited peritoneal metastases for whom R0 resection can be achieved" [4]. Accordingly, the current NCCN guidelines recommend R0 resection, complete cytoreductive surgery and/or hyperthermic intraperitoneal chemotherapy (HIPEC) in addition to systemic chemotherapy for patients with M1c CRC with limited peritoneal metastases [7].

Japan has long adopted unique therapeutic strategies that differ from those of Western countries for treating M1c CRC [8, 9]. According to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines for the treatment of CRC, R0 resection is a desirable treatment option if metastases are confined to the adjacent peritoneum, and in cases where a few easily resectable peritoneal metastases are present in the distant peritoneum [8, 10, 11]. A study conducted in 2014 using a database of a nationwide multicenter registry developed by the JSCCR, which covers approximately 10% of all patients with CRC in Japan, reported that none of the M1c patients received HIPEC [12, 13]. In Japan, the 5-year overall survival (OS) of patients with M1c CRC after R0 resection without HIPEC is roughly 30% [14, 15].

Currently, R0 resection of peritoneal metastases from CRC is considered an acceptable therapeutic option for select patients in Japan as well as Western countries. However, no study has fully examined the indications for R0 resection. Accordingly, this study aimed to determine factors affecting R0 resection in patients with M1c CRC. To this end, we analyzed prospectively collected, nationwide data in Japan by stepwise logistic regression analysis.

Patients and methods

Study population

This multicenter, prospective, observational study targeting patients with CRC with synchronous peritoneal metastases was conducted by the JSCCR. Patients were enrolled at 28 institutions in Japan from October 2012 to December 2016 (see Acknowledgements). Eligibility criteria were histologically confirmed colorectal adenocarcinoma and age ≥ 20 years. Peritoneal metastases were diagnosed intraoperatively by the presence of peritoneal tumors, with at

least one requiring resection, and histologically proven peritoneal metastases from CRC. Patients with synchronous or metachronous (within 5 years) malignancy other than carcinoma in situ were excluded. Those with appendiceal carcinomas (defined under a different category in the TNM classification 8th edition [2]), and those who underwent HIPEC, which is rarely performed in Japan [12, 13] and could affect decisions to perform R0 resection, were also excluded from analysis. Written informed consent was obtained from all patients before enrollment. Initial treatment decisions were made at each institution, typically by a multidisciplinary team including colorectal surgeons, medical oncologists, hepatobiliary surgeons, thoracic surgeons, and radiologists, taking into consideration disease severity and patient conditions including comorbidities.

This study was approved by the Institutional Review Board (IRB) of each institution (IRB code: 2013–191 in National Cancer Center Hospital). The study protocol was approved by the ethics committee of the JSCCR.

Data collection

The following parameters were assessed: sex, age, ECOG performance status (PS), body mass index, non-peritoneal distant metastasis (presence or absence), ascites (presence or absence), and primary tumor site (right-sided: cecum, ascending colon, and transverse colon; left-sided: descending colon, sigmoid colon, rectosigmoid junction, and rectum) [16]. Residual tumor status was classified according to the R classification of the TNM staging system, as follows: R0 (no residual tumor), R1 (microscopic residual tumor), and R2 (macroscopic residual tumor) [17]. Extent of peritoneal metastases was assessed according to the peritoneal cancer index (PCI) score, as well as the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma by the JSCCR ("P classification": P1, peritoneal metastasis only to the adjacent peritoneum; P2, a few metastases to the distant peritoneum; and P3, diffuse metastases to the distant peritoneum) [18].

R0 resection of peritoneal metastases from CRC without cytoreductive surgery or HIPEC

Surgical procedures for R0 resection of peritoneal metastases in Japan have been described previously [15, 19]. Briefly, prior to tumor resection, the entire abdominal region including the local region, pouch of Douglas, and liver surface is examined by visual inspection and/or palpation, since peritoneal metastases from CRC, especially small peritoneal metastases, are difficult to detect preoperatively and are often discovered during initial surgery. If P1 or P2 peritoneal metastases are identified, for which R0 resection could be achieved, all macroscopically detectable metastases

are dissected at the time of initial primary tumor resection, together with regional lymph nodes, such that no macroscopic tumors remain. In the present study, our patients only underwent dissection of the diseased portion of the peritoneum. R0 resection differs from complete cytoreductive surgery in that the latter involves dissection of not only the diseased portion but also the entire peritoneum. Whereas cytoreductive surgery for colorectal peritoneal disease does not necessarily mandate stripping of the entire peritoneum [20], the NCCN guidelines (2016 version) clearly distinguish R0 resection from cytoreductive surgery.

Statistical analysis

Pearson's Chi-square test for categorical variables, and the Wilcoxon rank-sum test for continuous variables were performed to compare factors between the R0/R1 resection and R2 resection groups. Stepwise logistic regression analyses were performed to identify factors affecting R0/R1 resection among various clinical factors including sex, age, PS, body mass index, PCI score, distant metastases, primary tumor site, and ascites. A p value threshold model in both the forward and backward directions was used as the stopping rule. The maximum p value was set at 0.20 for an effect to be entered into the model during a forward step, and the minimum p value was set at 0.20 for an effect to be removed from the model during a backward step. A receiver operating characteristic (ROC) curve was constructed to evaluate the performance of the multivariate model. Odds ratios (ORs)

and 95% confidence intervals (CIs) were calculated for significant predictors of R0 resection.

Data are presented as numbers of patients, ratios (%), or ORs with 95% CIs, as indicated. All statistical analyses were performed using the JMP14 program (SAS Institute Japan, Ltd., Tokyo, Japan).

Results

Characteristics of the study cohort

Figure 1 shows the CONSORT flow diagram for patients included in this study. Between October 2012 and December 2016, a total of 150 patients were enrolled at 28 institutions in Japan. Of these, two patients with appendiceal carcinomas and two who underwent HIPEC were excluded. The final study population thus comprised 146 patients with M1c CRC. Patient characteristics are summarized in Table 1. The presence of non-peritoneal distant metastases was noted in 87 (60%) patients; 59 (40%) had no non-peritoneal distant metastases. R0 resection and R1 resection were performed in 31 (21%) and five (3%) patients, respectively, and R2 resection was performed in 110 (75%). With respect to patients who underwent R1 resection, the primary intention was to perform R0 resection (i.e., R1 resection was indicated after initial surgery). Accordingly, those who underwent R0/R1 resection were combined in subsequent analyses (a total of 36 patients, 25%).

Fig. 1 The present study cohort. After excluding two patients with appendiceal carcinoma and two who underwent hyperthermic intraperitoneal chemotherapy, the final study population consisted of 146 colorectal cancer patients with synchronous peritoneal metastasis (M1c)
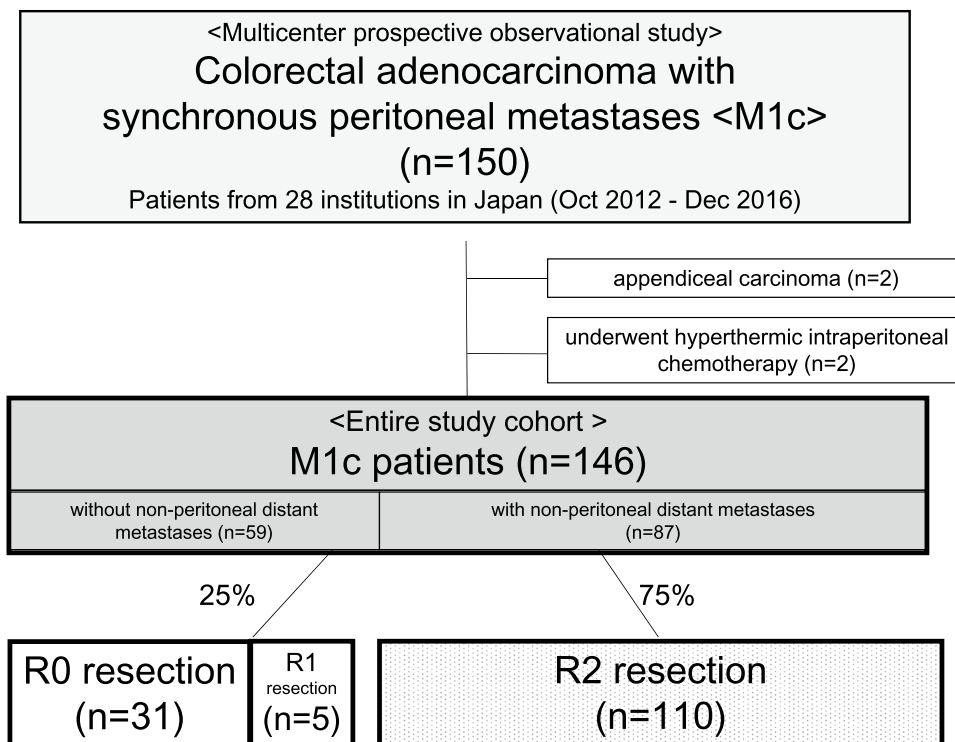
Table 1 Patient characteristics

Variables	Entire cohort $n = 146$ (%)	R0/R1 resection $n = 36$ (%)	R2 resection $n = 110$ (%)	p value
Sex				
Male	82 (56)	16 (44)	66 (60)	0.104
Female	64 (44)	20 (56)	44 (40)	
Age				
< 65	63 (43)	19 (53)	44 (40)	0.181
≥ 65	83 (57)	17 (47)	66 (60)	
Performance status				
PS 0	96 (66)	29 (81)	67 (61)	0.079
PS 1	38 (26)	5 (14)	33 (30)	
PS 2	12 (8)	2 (6)	10 (9)	
Body mass index (kg/m^2)				
< 25	129 (88)	31 (86)	98 (89)	0.634
≥ 25	17 (12)	5 (14)	12 (11)	
Primary tumor site				
Right-sided	75 (51)	20 (56)	55 (50)	0.562
Left-sided	71 (49)	16 (44)	55 (50)	
Ascites				
Absent	61 (42)	21 (58)	40 (36)	0.021
Present	85 (58)	15 (42)	70 (64)	
Cytology of ascites or lavage cytology				
Negative	32 (40)	11 (69)	21 (32)	0.008
Positive	49 (60)	5 (31)	44 (68)	
Non-peritoneal distant metastases				
Absent	59 (40)	33 (92)	26 (24)	< 0.001
Present	87 (60)	3 (8)	84 (76)	
CEA				
≤ 5	34 (23)	20 (56)	14 (13)	< 0.001
> 5	111 (77)	16 (44)	95 (87)	
CA19-9				
≤ 37	66 (46)	23 (66)	43 (39)	0.007
> 37	78 (54)	12 (34)	66 (61)	
PCI score				
1–6	88 (60)	33 (92)	55 (50)	< 0.001
≥ 7	58 (40)	3 (8)	55 (50)	
Japanese P classification				
P1	30 (21)	19 (53)	11 (10)	< 0.001
P2	56 (38)	16 (44)	40 (36)	
P3	60 (41)	1 (3)	59 (54)	

PCI peritoneal cancer index

Data not available: cytology of ascites or lavage cytology $n = 64$, CEA $n = 1$, CA19-9 $n = 2$

Between the R0/R1 resection and R2 resection groups, no significant differences were observed in terms of sex, age, PS, body mass index, and primary tumor site ($p = 0.104$, $p = 0.181$, $p = 0.079$, $p = 0.634$, and $p = 0.562$, respectively) (Table 1). However, significant differences were observed in the presence of ascites ($p = 0.021$), positive rate of cytology

of ascites or lavage cytology ($p = 0.008$), presence of distant metastases ($p < 0.001$), CEA ($p < 0.001$), and CA19-9 ($p = 0.007$) between the two groups. Moreover, significant group-dependent differences were observed in the extent of peritoneal metastases according to PCI scores (1–6 vs. ≥ 7; $p < 0.001$) and the Japanese P classification ($p < 0.001$).

R0/R1 resection was performed in three of 87 patients with distant metastases (one with liver metastases and two with distant lymph node metastases), three of 58 patients with PCI score ≥ 7, and two of 12 patients with PS 2.

Factors affecting R0 resection in M1c patients

Stepwise logistic regression analyses revealed the presence of distant metastases, PCI score, and PS to be independent factors affecting R0 resection (Table 2). On the other hand, sex, age, body mass index, presence of ascites, and primary tumor site did not affect R0 resection. Multivariate logistic regression analysis was performed to calculate ORs for the three significant predictors of R0 resection, as follows: distant metastases (absence *vs.* presence), OR = 52.9 (95% CI 13.3–210.1; $p < 0.001$); PCI score (1–6 vs. ≥ 7), OR = 20.0 (95% CI 4.8–83.4; $p < 0.001$); and PS (0 vs. 1, 2), OR = 2.40 (95% CI 0.66–8.68; $p = 0.181$). The area under the ROC curve (AUC) of this multivariate model was 0.9237.

Factors affecting R0 resection in M1c patients without non-peritoneal distant metastases

Since the presence of distant metastases was found to be a very strong factor affecting R0 resection, we next analyzed factors affecting R0 resection in M1c patients without non-peritoneal distant metastases ($n = 59$). Stepwise logistic regression analyses revealed PCI score and PS to be independent factors affecting R0 resection (Table 3). Multivariate logistic regression analysis was performed to calculate ORs for the two significant predictors of R0 resection, as follows: PCI score (1–6 vs. ≥ 7), OR = 19.1 (95% CI 4.4–82.9; $p < 0.001$); and PS (0 vs. 1, 2), OR = 2.89 (95% CI 0.68–12.2; $p = 0.150$) (Table 3). The AUC of this multivariate model was 0.8147.

Discussion

This multicenter, prospective, observational study targeting CRC patients with synchronous peritoneal metastases revealed a general consensus in Japan that no distant metastases, a low PCI score (1–6), and high PS (0) are good indications for R0 resection in M1c patients. Moreover, among M1c patients without non-peritoneal distant metastases, both PCI score and PS were found to be factors affecting R0 resection. In other words, the presence/absence of distant

Table 2 Univariate and multivariate logistic regression analyses of various clinical factors associated with R0/R1 resection

Variable	Objective variable	Control	Univariate analysis			Multivariate analysis		
			OR	95% CI	p value	OR	95% CI	p value
Presence of distant metastases	Absent	Present	35.5	10.1–125.4	<0.001	52.9	13.3–210.1	<0.001
PCI score	1–6	≥7	11.0	3.18–38.0	<0.001	20.0	4.78–83.4	<0.001
Performance status	PS 0	PS 1, PS 2	2.66	1.07–6.60	0.035	2.40	0.66–8.68	0.181
Age	<65	≥65	1.68	0.79–3.58	0.181			
Sex	Female	Male	1.88	0.88–4.00	0.105			
Body mass index	≥25	<25	1.32	0.43–4.03	0.629			
Primary tumor site	Right-sided	Left-sided	1.25	0.59–2.66	0.563			
Ascites	Absent	Present	2.45	1.14–5.28	0.022			

Data are presented as odds ratios (95% CIs)

CI confidence interval

Table 3 Univariate and multivariate logistic regression analyses of various clinical factors associated with R0/R1 resection among patients without non-peritoneal distant metastases

Variable	Objective variable	Control	Univariate analysis			Multivariate analysis		
			OR	95% CI	p value	OR	95% CI	p value
PCI score	1–6	≥7	18.9	4.49–79.4	<0.001	19.1	4.39–82.9	<0.001
Performance status	PS 0	PS 1, PS 2	2.81	0.86–9.21	0.088	2.89	0.68–12.2	0.150
Age	<65	≥65	1.70	0.60–4.83	0.319			
Sex	Female	Male	1.64	0.58–4.61	0.352			
Body mass index	≥25	<25	0.55	0.11–2.71	0.463			
Primary tumor site	Right-sided	Left-sided	1.06	0.38–2.97	0.908			
Ascites	Absent	Present	1.40	0.50–3.93	0.523			

Data are presented as odds ratios (95% CIs)

CI confidence interval

metastases, PCI score, and PS significantly affect decisions to perform R0 resection in Japan. The number of organs involved [1], extent of peritoneal metastases [21], and PS [22] are well-known prognostic factors in M1c CRC. Thus, it seems natural for Japanese surgeons to perform R0 resection in M1c patients with favorable prognostic factors who were expected to survival for a long time. On the other hand, while primary tumor site, age, and presence of ascites are also prognostic factors in M1 CRC [16, 22, 23], these factors were not identified as factors affecting R0 resection in the present study. Furthermore, sex and body mass index did not affect R0 resection. While therapeutic strategies for M1c CRC differ between Japan and Western countries [8], these results from Japan seem instinctively acceptable also in Western countries.

In the present study, R0/R1 resection was performed in almost one quarter of all M1c patients (24%), consistent with a previous report in Japan [15, 19, 24]. With respect to long-term outcomes of R0 resection, a previous study in Japan reported a median survival time of 33.4 months and 5-year overall survival (OS) of 28.7% in 78 M1c CRC patients who underwent R0 resection without aggressive cytoreductive surgery or HIPEC [15, 25]. R0 resection has been reported to be a significant independent factor associated with longer OS in M1c patients [19, 26]. Thus, although evidence is still limited, resection of visible peritoneal metastases could be a desirable therapeutic strategy for patients with M1c CRC, as recommended by the JSCCR guidelines for the treatment of CRC [8, 10, 11]. The advantage of R0 resection without aggressive cytoreductive surgery or HIPEC for M1c CRC is that it may help to avoid unnecessary side effects and the risks involved with resection of the entire peritoneum as well as the HIPEC. One disadvantage is that resection of only the peritoneal surfaces with macroscopic disease presents the risk of missing invisible peritoneal metastases. However, in such cases, systemic chemotherapy including target agents after surgery could help to either manage or eradicate invisible peritoneal metastases.

The PCI score is widely used throughout the world for evaluating peritoneal metastases. In Japan, the Japanese P classification developed by the JSCCR [18] is exclusively used, which defines metastases only to the adjacent

peritoneum as P1, a few metastases to the distant peritoneum as P2, and diffuse metastases to the distant peritoneum as P3. According to the Study Group for Peritoneal Metastasis from Colorectal Cancer by the JSCCR, many Japanese surgeons classify P1 as < 4 metastases, P2 as 4–10 metastases, and P3 as > 10 metastases [27]; that is, P2 is defined as ≤ 10 peritoneal metastases disseminated in two or more areas, and P3 as > 10 peritoneal metastases disseminated in more than three areas. Thus, PCI scores 1–6 correspond to P1, 4–20 to P2, and > 10 to P3 [15, 19, 27]. Indeed, in the present study, PCI scores for P1, P2, and P3 ranged from 1–5, 1–10, and 2–29, respectively (data not shown). P1 and P2 seemed to overlap in terms of PCI scores. In fact, of the 29 patients with a PCI score of 2, 12 were classified as P1, 16 as P2, and 1 as P3. Thus, the disparity between PCI score versus Japanese P classification is particularly noticeable in Japanese P2 patients. Although P1 is defined as metastasis only to the adjacent peritoneum and P2 is defined as metastasis to the distant peritoneum, each location has yet to be precisely defined. One previous paper about Japanese P classification proposed a new definition for P2 as 10 or fewer peritoneal metastases disseminated in two or more areas, or peritoneal metastases confined to one area but for which the size is > 20 mm [27]. Thus, to overcome the misclassifications between Japanese P classification versus the PCI score, enhancing the objectivity of the Japanese P classification, particularly that for 'P2', is needed.

This study has some limitations. First, the sample size was relatively small. Second, since Japanese surgeons who have been using the Japanese P classification are not familiar with the PCI score, there is a possibility of misclassification. The Japanese P classification is easy to use but is somewhat subjective. As mentioned above, the PCI score ranges for P1 and P2 as well as these for P2 and P3 seem to overlap. Thus, there is a need for Japanese surgeons to become more familiar with the PCI score in the future.

In conclusion, the present multicenter, prospective, observational study targeting CRC patients with synchronous peritoneal metastases revealed that resection of visible peritoneal metastases was performed in almost one quarter of patients in Japan. Distant metastases, PCI score, and PS are three factors that affect R0 resection for M1c disease. Moreover, there appears to be a consensus in Japan that no distant metastases, low PCI score (1–6), and high PS (0) are good indications for R0 resection. Since these three factors are well-known prognostic factors in M1c CRC, it seems natural for Japanese surgeons to perform R0 resection in M1c patients with favorable prognostic factors who are expected to survive for a long time. These results seem instinctively acceptable also in Western countries, even though therapeutic strategies for M1c CRC differ between Japan and Western countries.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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