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Prognostic Impact of R0 Resection and Targeted Therapy for Colorectal Cancer with Synchronous Peritoneal Metastasis

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ABSTRACT

Background. The National Comprehensive Cancer Network guidelines recommend R0 resection and targeted therapy, a combination of cytotoxic and molecular targeted agents, such as bevacizumab, cetuximab, and panitumumab, for colorectal cancer with synchronous peritoneal metastasis (M1c). While these therapeutic strategies are drawing attention, their efficacy has not been fully examined.

Methods. The study population comprised 248 consecutive M1c patients who were treated at the National Cancer Center Hospital from 1997 to 2013. Multivariate analyses were performed to evaluate relationships between overall survival and R0 resection and targeted therapy using Cox proportional hazards regression models.

Results. The 3-year overall survival (3 yOS) was 19.5%, and median survival time (MST) was 16.2 months in 248 M1c patients. R0 resection was performed in 34 patients (14%), yielding a 3-year overall survival (OS) of 48.3% and median survival time (MST) of 29.9 months. Targeted therapy was performed in 54 patients (22%) at least once during the course of treatment, yielding a 3-yr OS of 38.2% and MST of 23.9 months. After adjusting for other key clinical factors, such as the number of organs involved with metastases, performance status, primary tumor site, and extent of peritoneal metastasis, both R0 resection and targeted therapy were independent factors associated with longer OS. Targeted therapy was associated with a significantly longer OS compared with multiple cytotoxic agent therapy [hazard ratio 0.65; 95% confidence interval (0.44–0.94); $p = 0.02$].

Conclusions. If achievable, R0 resection is a desirable therapeutic strategy for patients with M1c colorectal cancer. Moreover, targeted therapy might be the optimal chemotherapy in this patient population.

In the eighth edition of the tumor-node-metastasis classification published in 2017, colorectal cancer with peritoneal metastasis is newly categorized as M1c (i.e., metastasis to the peritoneum with or without other organ involvement) separately from M1a (metastasis to one organ) and M1b (metastasis to more than one organ), given the poor prognosis of peritoneal metastases compared with other metastatic diseases in visceral organs.[1,2] With regard to therapeutic strategies, the National Comprehensive Cancer Network (NCCN) guidelines for colon cancer recommend systemic chemotherapy as an exclusive treatment choice and do not recommend aggressive cytoreductive debulking and/or intraperitoneal chemotherapy outside the setting of a clinical trial.[3] In 2016, NCCN guidelines added the following footnote (page COL-8): "If R0 resection can be achieved, surgical resection of isolated peritoneal disease may be considered at experienced centers."[3] Hence, R0 resection (i.e., resection of only the diseased portion of the peritoneum), which differs from traditional cytoreductive surgery (i.e., resection of not only the diseased portion but also the entire peritoneum, i.e., peritonectomy) with hyperthermic intraperitoneal chemotherapy (HIPEC), was newly introduced as another treatment option for M1c colorectal cancer.[4,5] We recently reported the long-term outcomes of 78 M1c colorectal cancer patients who underwent R0 resection without aggressive cytoreductive

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surgery or HIPEC; median survival time (MST) was 33.4 months, and the 5-year overall survival (OS) was 28.7%. These findings suggested that R0 resection is an acceptable surgical treatment option in this patient population.[6]

The introduction of molecular targeted agents, such as vascular endothelial growth factor-targeted antibody (bevacizumab) and epidermal growth factor receptor-targeted antibodies (cetuximab, panitumumab), has improved OS of stage IV colorectal cancer patients. Median OS of patients diagnosed with unresectable stage IV colorectal cancer has improved, from approximately 1 year during the era of 5-fluorouracil (5FU) monotherapy to > 30 months with the integration of multiple cytotoxic agents and molecular targeted agents.[7] Combinations of cytotoxic agents and molecular target agents (i.e., targeted therapy) are now standard treatments for unresectable stage IV patients in various settings. A nationwide population-based study in the Netherlands showed that the addition of bevacizumab was associated with a longer OS in M1c patients.[8] Conversely, the Analysis and Research in Cancers of the Digestive System Database reported that patients with peritoneal-only involvement had worse survival than M1a patients and that these survival differences were more marked in patients who received systemic regimes, including targeted therapy compared with those who did not, suggesting that targeted agents are less effective for M1c than for M1a.[2] The effectiveness of targeted therapy in M1c patients has not been clarified.

While R0 resection and targeted therapy have become the focus of attention as therapeutic strategies for M1c, few studies have examined their efficacy. Therefore, the present study was designed to evaluate the prognostic impact of R0 resection and targeted therapy in patients with M1c colorectal cancer, specifically with respect to OS. During the study period, targeted molecular agents (bevacizumab, cetuximab, and panitumumab) were introduced in Japan for use in systemic chemotherapy for stage IV colorectal cancer. Thus, the first half of our patients received no targeted therapy but underwent 5FU monotherapy or multiple cytotoxic agent therapy. This heterogeneity makes it possible to investigate the efficacy of targeted therapy in our cohort. Multivariate analyses were performed to adjust for other key clinical factors: performance status, number of organs involved with metastases, primary tumor site, and extent of peritoneal metastasis, which have been shown to be prognostic factors for stage IV colorectal cancer.[2,9–11]

METHODS

Study Population

Subjects were patients with M1c colorectal adenocarcinoma who were treated at the National Cancer Center Hospital from January 1997 to December 2013. Synchronous peritoneal metastases were diagnosed by the presence of peritoneal tumors, which were resected and histologically proven to be peritoneal metastases of colorectal cancer, or by computed tomography images with multiple peritoneal nodules. Patients who received best supportive care only and those undergoing cytotoxic chemotherapy for other concomitant advanced cancer were excluded. Initial treatment decisions were typically made by a multidisciplinary team, including colorectal surgeons, medical oncologists, hepatobiliary surgeons, thoracic surgeons, and radiologists, taking into consideration disease severity and patient condition including comorbidities. Because targeted molecular agents were introduced in Japan for use in systemic chemotherapy for stage IV colorectal cancer during the study period (after 2007), the first half of the patients received no targeted therapy but underwent 5FU monotherapy or multiple cytotoxic agent therapy. This retrospective study was approved by the Institutional Review Board (IRB) of the National Cancer Center Hospital (IRB code: 2015-320).

Data Collection

The following parameters were retrospectively assessed using medical records: age, sex, type of surgery (R0 resection: primary tumor resection and metastasectomy, including dissection of the diseased portion of the peritoneum such that no macroscopic tumors remained; palliative primary tumor resection: primary tumor resection without metastasectomy; and nonresection: diverting stoma construction without resection of primary tumor, bypass surgery, or probe laparotomy), type of systemic chemotherapy (5FU monotherapy; multiple cytotoxic agent therapy, i.e., multiple cytotoxic agent therapy without molecular targeted agents, e.g., 5FU plus oxaliplatin and 5FU plus irinotecan; and targeted therapy, i.e., combination of cytotoxic agents with at least one molecular targeted agent, i.e., bevacizumab, cetuximab, or panitumumab), number of organs involved with metastases, ECOG performance status (PS), primary tumor site (right side: cecum, hepatic flexure, and transverse colon; left side: splenic flexure, sigmoid, rectosigmoid junction, and rectum), and extent of peritoneal metastasis (a few: peritoneal metastasis only to the adjacent peritoneum (P1) or a few metastases to the distant peritoneum (P2); diffuse: diffuse metastases to the distant peritoneum (P3), as defined by the

Japan Society for Cancer of the Colon and Rectum (JSCCR) in the Japanese classification of colorectal carcinoma).[12] A PCI score of P1 seems to range from 1 to 6.[13,14] A PCI score of P2 seems to range from 4 to 20, and a PCI score of P3 seems to be higher than 10.[13,14]

Statistical Analysis

Pearson's Chi square test for categorical variables and the Wilcoxon rank-sum test for continuous variables were performed to compare various factors in both groups. OS was defined as the interval between the date of stage IV colorectal cancer diagnosis and the date of death from all causes and censored for survivors at the date of data cutoff (July 2017). The Kaplan–Meier method was used to estimate OS. Differences in survival were assessed with the log-rank test. Multivariate Cox proportional hazards regression models were used to evaluate the prognostic impact of R0 resection and targeted therapy on OS, by adjusting for four key clinical factors (i.e., number of organs involved with metastases, performance status, primary tumor site, and extent of peritoneal metastasis). Results are presented as hazard ratios (HRs) and 95% confidence intervals (CIs).

Data are presented as numbers of patients, ratios (%), or HR and 95% CI as indicated. $p < 0.05$ was considered statistically significant. All statistical analyses were performed using the JMP12 software program (SAS Institute Japan Ltd., Tokyo, Japan).

RESULTS

Characteristics of the Study Cohort

Figure 1 shows the flowchart of patient selection. Between 1997 and 2013, a total of 1067 patients with stage IV CRC were referred to the National Cancer Center. Of these, 262 (24.6% of all stage IV patients) had synchronous peritoneal metastasis (M1c). Because our analysis focused on therapeutic strategies for M1c, we excluded 12 patients who only received best supportive care, and 2 patients who were undergoing chemotherapy for other concomitant advanced cancer. The final study population thus comprised 248 consecutive patients who underwent resection surgery and/or chemotherapy.

Patient characteristics are shown in Table 1. Because almost two-thirds of the entire cohort (63%) had not only peritoneal metastases but also nonperitoneal distant metastases, an aggressive surgical approach was not typically adopted. Thirty-four patients underwent R0 resection, 134 underwent palliative primary tumor resection, and 80 underwent systemic chemotherapy immediately after diagnosis (nonresection). For systemic chemotherapy, 51 patients received 5FU monotherapy, 116 received multiple cytotoxic agent therapy, and 54 received systemic regimes including targeted therapy. Twenty-seven patients who underwent surgery did not receive any chemotherapy. None of the patients in our series received HIPEC.

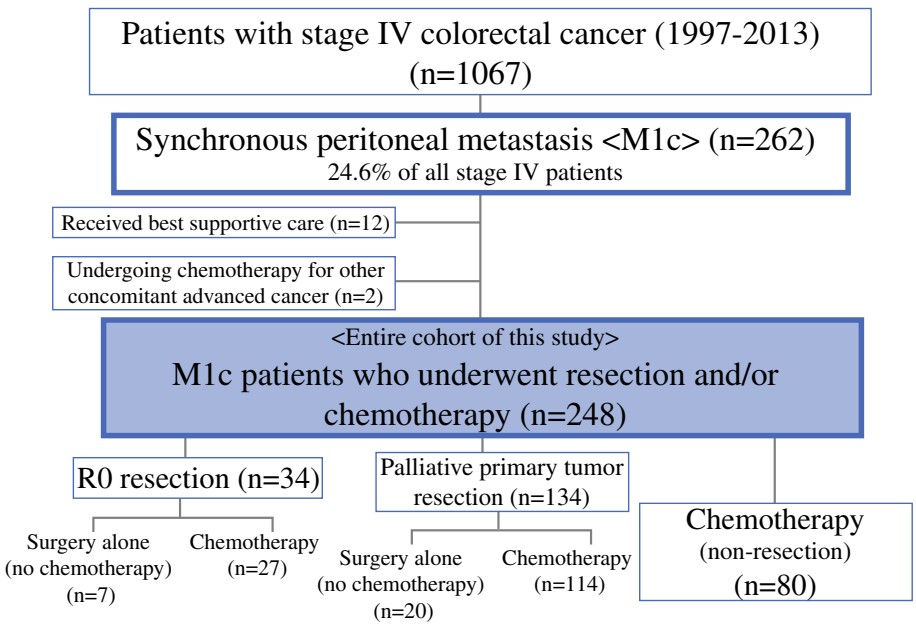

FIG. 1 Study cohort. After excluding patients who received best supportive care only ($n = 12$) and those undergoing chemotherapy for other concomitant advanced cancer ($n = 2$) from the initial 262 colorectal cancer patients with synchronous peritoneal metastasis (M1c), the final study population consisted of 248 patients

TABLE 1 Patient characteristics

Category	Number (%)
Sex	
Male	134 (54%)
Female	114 (46%)
Age	
< 65	156 (63%)
≥ 65	92 (37%)
Performance status	
PS0, PS1	233 (94%)
≥ PS2	15 (6%)
Number of organs involved with metastases	
1 (peritoneal-only)	91 (37%)
≥ 2	157 (63%)
Primary tumor site	
Right side	109 (44%)
Left side	139 (56%)
Extent of peritoneal metastasis	
A few (P1, P2)	135 (54%)
Diffuse (P3)	113 (46%)
Type of surgery	
Non-resection	80 (32%)
Palliative primary tumor resection	134 (54%)
R0 resection	34 (14%)
Type of chemotherapy	
None	27 (11%)
5FU monotherapy	51 (20%)
Multiple cytotoxic agent therapy	116 (47%)
Targeted therapy	54 (22%)

P1 metastasis only to the adjacent peritoneum, *P2* a few metastases to the distant peritoneum, *P3* diffuse metastases to the distant peritoneum, as defined according to the Japanese classification of colorectal carcinoma, the Japan Society for Cancer of the Colon and Rectum

Long-term Outcomes of M1c Patients

The 3- and 5-year OS rates were 19.5 and 11.0%, respectively, with a median follow-up time for survivors of 40 (range 2–158) months. Median survival time (MST) was 16.2 months. Notably, 13 patients survived for more than 5 years (Fig. 2).

Figure 3A shows OS curves for M1c patients stratified into three groups by type of surgery. Patients who underwent R0 resection (3-year OS: 48.3%, MST: 29.9 months) had better OS than those who underwent palliative primary tumor resection (3-year OS: 19.1%, MST: 16.1 months). Patients who did not undergo resection (3-year OS: 6.9%, MST: 11.2 months) had worse OS than those who underwent palliative primary tumor resection.

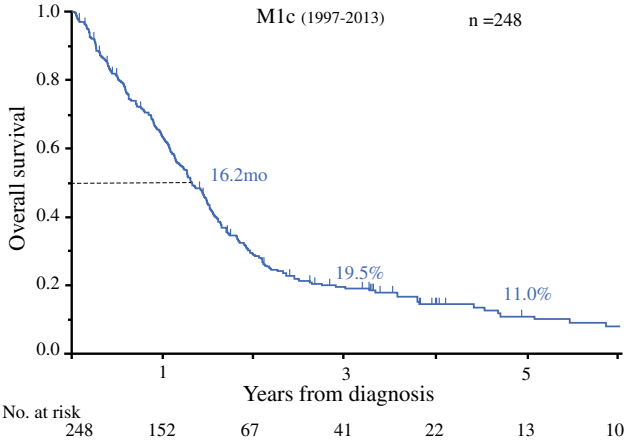

FIG. 2 Overall survival curve for colorectal cancer patients with synchronous peritoneal metastasis (M1c) (n = 248)

Figure 3b shows OS curves for M1c patients stratified into four groups by type of chemotherapy. Patients who received 5FU monotherapy (3-year OS: 20.2%, MST: 8.7 months) had similar OS compared with those who did not receive any chemotherapy (3-year OS: 14.8%, MST: 7.1 months). Compared with these patients, patients who received multiple cytotoxic agent therapy (3-year OS: 16.4%, MST: 16.5 months) showed better OS, and moreover, patients who received systemic regimes, including targeted therapy (3-year OS: 38.2%, MST: 23.9 months) showed much better OS.

Factors affecting Prognosis of M1c

According to univariate analysis, good performance status (PS0 or PS1) ($p < 0.0001$), involvement of only one organ (peritoneal only) ($p < 0.0001$), primary tumor site (left side) ($p = 0.045$), and peritoneal metastasis (a few) ($p < 0.0001$) were significantly associated with better OS, whereas sex and age were not associated with prognosis (Table 2).

To investigate the prognostic impact of R0 resection and targeted therapy, multivariate analyses were performed using Cox proportional hazards regression models to adjust for the above-mentioned four key clinical factors. R0 resection was associated with a significantly longer OS compared with nonresection [HR 0.28; 95% CI (0.14–0.54); $p < 0.0001$] and palliative primary tumor resection [HR 0.47; 95% CI (0.27–0.79); $p = 0.004$; Table 2). Targeted therapy also was associated with a significantly longer OS compared with 5FU monotherapy [HR 0.32; 95% CI (0.20–0.50); $p < 0.0001$] and multiple cytotoxic agent therapy [HR 0.65; 95% CI (0.44–0.94); $p = 0.02$; Table 2]. Moreover, both R0 resection and targeted therapy were found to be independent factors associated with better prognosis, after adjusting for the four

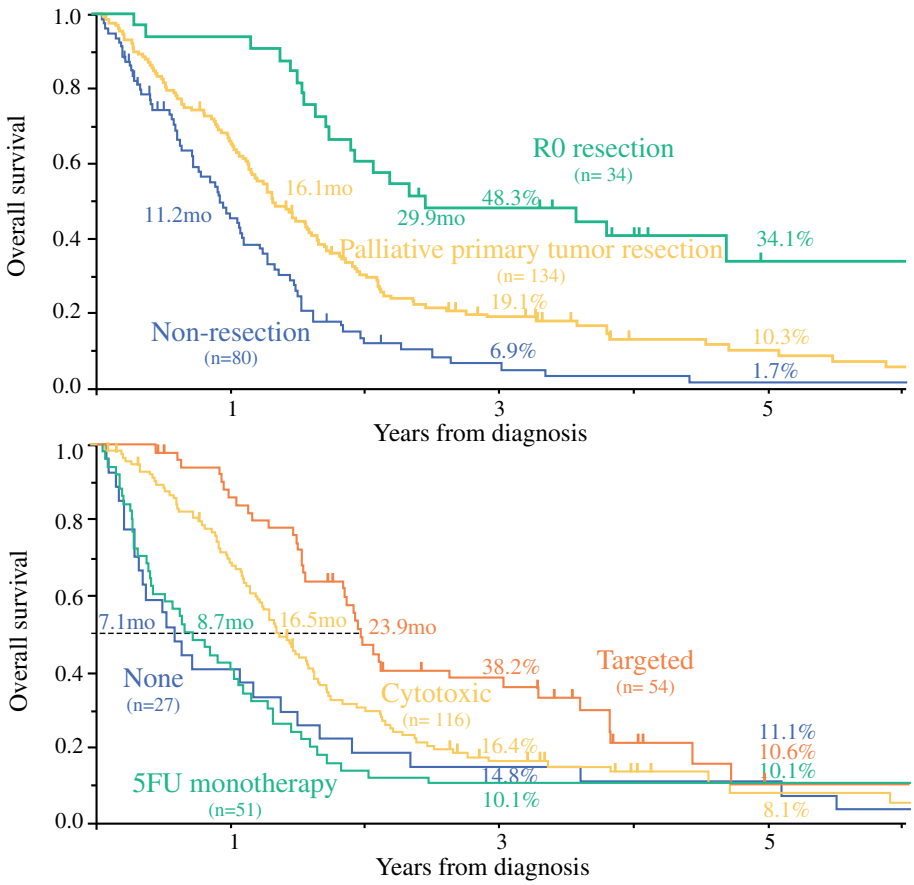

FIG. 3 Overall survival curves for M1c patients stratified into three groups according to the type of surgery (R0 resection, palliative primary tumor resection, and nonresection) (**a**), and for M1c patients stratified into four groups according to the type of chemotherapy (none, 5FU monotherapy, multiple cytotoxic agent therapy, and systemic regimens including targeted therapy) (**b**)

key clinical factors (i.e., number of organs involved with metastases, performance status, primary tumor site, and extent of peritoneal metastasis; Table 2).

DISCUSSION

In the present study, our patients (n = 248) had a 3-year OS of 19.5%, 5-year OS of 11.0%, and MST of 16.2 months, suggesting that patients with M1c colorectal cancer have a significantly shorter OS compared with those with metastases to other sites. We revealed both R0 resection and targeted therapy to be independent factors associated with longer OS in patients with M1c colorectal cancer, after adjusting for the four key clinical factors: performance status, primary tumor site, number of organs involved with metastases, and extent of peritoneal metastasis. For patients with metastatic colorectal cancer, well-known prognostic factors included performance status, primary tumor site, and number of organs involved with metastases.[2,9,10] Extent of peritoneal metastasis is widely known as a prognostic factor for M1c colorectal cancer.[11] Consistent with these reports, good performance status, tumor location on the left side, peritoneal-only metastasis, and a few peritoneal metastases were all associated with better prognosis in the present study. The results of our multivariate analyses suggest that resection of visible peritoneal metastases should be recommended as a therapeutic strategy for M1c colorectal cancer if R0 resection appears achievable, and systemic regimes, including targeted therapy, should be considered as the optimal chemotherapy.

Japan has adopted unique therapeutic strategies to address peritoneal metastasis of colorectal cancer, which differ from those of Western countries.[15] Specifically, R0 resection is performed when peritoneal metastasis extends only to the adjacent peritoneum (P1) and is considered if there are a few easily resectable peritoneal metastases to the distant peritoneum (P2).[15] Although R0 resection can be achieved only in selected patients due to diffuse peritoneal metastasis and/or synchronous hematogenous metastasis, the Study Group for Peritoneal Metastasis from Colorectal Cancer by the JSCCR reported that 224 (18%) of 1217 consecutive M1c patients underwent R0 resection between 1991 and 2007.[16] Similarly, R0 resection was achieved in 14% of all M1c patients in the present cohort. Moreover, none of our M1c patients received HIPEC, which is consistent with data from a nationwide multicenter registry of the JSCCR covering approximately 10% of all patients with colorectal cancer in Japan.[17,18] With these strategies, Japan has achieved a 5-year OS of roughly

TABLE 2 Univariate and multivariate analyses of factors affecting survival in colorectal cancer patients with synchronous peritoneal metastasis (M1c)

Variable	Category	Median overall survival (months)	Univariate analysis *p* value	Multivariate analysis		
				Hazard ratio	95% CI	*p* value
Sex	Male	16.5 (14.4–18.8)	0.807			
	Female	15.9 (12.5–19.1)				
Age	< 65	15.6 (13.3–19.0)	0.448			
	≥ 65	16.5 (13.5–18.6)				
Performance status	PS0, PS1	17.5 (15.1–18.9)	< 0.0001	Reference		
	≥ PS2	4.5 (2.1–6.1)		2.66	1.38–4.87	0.004
Number of organs involved with metastases	1 (peritoneal-only)	20.7 (18.4–25.1)	< 0.0001	Reference		
	≥ 2	13.7 (12.1–15.9)		1.90	1.38–2.66	< 0.0001
Primary tumor site	Right side	15.0 (11.8–17.5)	0.045	Reference		
	Left side	18.5 (14.6–20.9)		0.73	0.55–0.97	0.032
Extent of peritoneal metastasis	A few (P1, P2)	19.5 (16.6–23.5)	< 0.0001	Reference		
	Diffuse (P3)	12.4 (9.8–18.3)		1.49	1.05–2.11	0.026
Type of surgery	Non-resection	11.2 (8.8–13.3)	< 0.0001	Reference		
	Palliative primary tumor resection	16.1 (13.9–19.3)		0.59	0.41–0.84	0.004
	R0 resection	29.9 (21.0–82.5)		0.28	0.14–0.51	< 0.0001
Type of chemotherapy	None	7.7 (3.4–16.7)	< 0.0001	2.45	1.46–3.99	0.001
	5FU monotherapy	8.7 (4.9–12.8)		2.04	1.39–2.95	0.0003
	Multiple cytotoxic agent therapy	16.5 (14.6–19.1)		Reference		
	Targeted therapy	23.9 (18.8–36.7)		0.65	0.44–0.94	0.023

Data are presented as median (95%CI) or hazard ratio (95%CI)

30% after R0 resection in patients with M1c colorectal cancer without performing aggressive cytoreductive surgery or HIPEC.[6,16] On the other hand, the median 5-year survival in previous studies for patients undergoing cytoreductive surgery with HIPEC was reported to be an average of 30 months for those with limited peritoneal metastases, and one study reported the 5-year OS rate as 29.7% for colon cancer and 37.9% for rectal cancer.[19–21] Based on these results, R0 resection seems an acceptable surgical treatment option in this particular patient population.

Interestingly, 5FU monotherapy did not show any survival benefit over palliative primary tumor resection without chemotherapy [HR 0.83; 95% CI (0.50–1.41); $p = 0.49$] (data not shown). Multiple cytotoxic agent therapy had a significant survival benefit over 5FU monotherapy [HR 0.49; 95% CI (0.34–0.71); $p = 0.0003$], whereas targeted therapy had a significant survival benefit over multiple cytotoxic agent therapy [HR 0.65; 95% CI (0.44–0.94); $p = 0.02$; Table 2]. These results suggest that, for peritoneal metastases, systemic regimes, including targeted therapy, are the most effective, followed by multiple cytotoxic agent therapy, whereas 5FU monotherapy was less effective.

In this study, we stratified the entire cohort into three groups according to the type of surgery (i.e., R0 resection, palliative primary tumor resection, and nonresection). We distinguished between palliative primary tumor resection and nonresection for the following reason: for unresectable stage IV colorectal cancer, several studies using propensity analyses reported that palliative primary tumor resection was associated with longer OS.[22,23] Unlike other types of stage IV colorectal cancer, the survival benefit of palliative primary tumor resection has not been clarified for M1c. In the present multivariate analyses, palliative primary tumor resection showed a significant survival benefit over chemotherapy alone (nonresection) for unresectable M1c colorectal cancer [HR 0.59; 95% CI (0.41–0.84); $p = 0.004$; Table 2]. Thus, in this patient population, palliative primary tumor resection might be more beneficial than chemotherapy alone in terms of survival. Given the heterogeneity and potential selection bias between the two groups, further studies will be needed to confirm these results.

During the study period, recurrence after R0 resection ($n = 34$) was observed in 21 patients (62%), with the peritoneum as the most frequent recurrence site ($n = 10$). Hematogenous recurrence in the liver ($n = 9$), lungs ($n = 6$) as well as local recurrence ($n = 2$) also were observed (data not shown). Because of the high recurrence rate, adjuvant chemotherapy (i.e., chemotherapy just after resection) was performed for some of these patients. Of the 34 patients who underwent R0 resection, 14 patients (41%) received adjuvant chemotherapy (i.e., chemotherapy just after resection) for 6 months; 8 were treated with 5-FU monotherapy, 4 were treated with multiple cytotoxic agent therapy (5-FU plus oxaliplatin), and 2 were treated with systemic regimes, including targeted therapy (data not shown). Two patients who were treated with targeted therapy had several metastases to the distant peritoneum (P2), although macroscopic R0 resection was achieved. Whereas both anti-VEGF and anti-EGFR therapy drugs have failed in postresection setting in stage III disease, efficacy of these agents for M1c colorectal cancer in post R0 resection setting, not at the time of recurrence, remains unknown.[24–26]

There are some limitations to this study. First, because the study was retrospective in design, biases may exist. Second, although consecutive patients were enrolled, the study period was from 1997 to 2013. During this long period, treatment strategies, including chemotherapy, have changed significantly, as well as the perioperative awareness of peritoneal metastasis; therefore, our data may not be comparable to other studies with novel approaches. Third, the sample size was relatively small, which could affect the results. Nonetheless, the present findings warrant further consideration and validation in a larger patient series of colorectal cancer with synchronous peritoneal metastases.

In conclusion, our results suggest both R0 resection and targeted therapy are independent factors associated with better prognosis in patients with M1c colorectal cancer, after adjusting for four key clinical factors (i.e., number of organs involved with metastases, performance status, primary tumor site, and extent of peritoneal metastasis). Thus, resection of visible peritoneal metastases should be recommended as a therapeutic strategy for colorectal cancer with synchronous peritoneal metastasis, if R0 resection appears achievable, and systemic regimes, including targeted therapy should be considered as the optimal chemotherapy for M1c.

DISCLOSURE None to report.

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