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ORIGINAL ARTICLE – COLORECTAL CANCER

Prognostic Impact of Curative Resection for Peritoneal Recurrence of Colorectal Cancer

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ABSTRACT

Background. Peritoneal recurrence (PR) of colorectal cancer is a poor prognostic factor but may be treatable by curative resection. We investigated the efficacy of this treatment and identified risk factors for postoperative recurrence.

Methods. The subjects were patients who underwent radical surgery for colorectal cancer between January 2006 and March 2014. Those with PR were retrospectively reviewed. Prognostic factors for overall survival (OS) and risk factors for postoperative recurrence were identified.

Results. Among 2256 patients, 66 had PR (2.9%). Surgical resection of PR was performed in 41 patients. Curative resection was achieved macroscopically in 38 cases without diffuse metastases in the peritoneum distant from the primary tumor and with a peritoneal cancer index < 10. In multivariate analysis, curative resection was a significant prognostic factor [hazard ratio (HR) 0.198] for better 5-year OS compared with cases without curative resection (68.7% vs. 6.3%, $P < 0.001$). In 28 cases with concurrent metastasis, curative resection significantly improved 5-year OS compared with no curative resection (78.7% vs. 0%, $P = 0.008$). In the 38 patients with curative resection, the 3-year recurrence-free survival rate was 21.4%. In multivariate analysis, concurrent metastasis was a significant risk factor [HR 3.394] for postoperative recurrence, and cases with concurrent metastasis more frequently had recurrence within 2 years after curative resection.

Conclusions. Curative resection improved the prognosis in patients with limited and resectable PR of colorectal cancer with or without concurrent metastasis. However, recurrence after curative resection was common and concurrent metastasis was a risk factor for this recurrence.

Peritoneal metastasis of colorectal cancer may have a poorer prognosis than metastasis to other sites, and such metastasis is often treated palliatively.[1–3] Peritoneal recurrence (PR) is a rare recurrence pattern after potentially curative resection, with rates of 2–5% in previous reports.[2–6] Standard therapy for PR has not been established. Hyperthermic intraperitoneal chemotherapy (HIPEC) was thought to be effective for better prognosis. The multicenter phase III PRODIGE 7 trial has yet to be published but was presented in abstract form in 2018. This study did not show improved overall survival (OS) with HIPEC. In contrast, cytoreductive surgery gives satisfactory survival, and surgical resection for peritoneal metastasis also may be effective.[6] There are several reports on surgical resection of synchronous peritoneal metastasis but few on PR and none related to recurrence after curative resection for PR.[1,2,4,7,8]

Peritoneal metastasis often is accompanied by metastases to other organs, with rates of 30–60% for PR with concurrent metastasis.[2–4,9] Such cases often receive systemic chemotherapy or palliative treatment. However, it has been suggested that surgical resection may lead to a better prognosis if peritoneal and hematogenous metastases are completely resected.[10–13] In our department, we perform surgery for peritoneal metastasis with and without other organ metastases. In this study, we examined the

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efficacy of surgical resection for PR of colorectal cancer and identified risk factors for recurrence after curative resection of PR.

METHODS

Selection of Patients

Patients who underwent surgical resection for colorectal tumor at the National Cancer Center Hospital East between January 2006 and March 2014 were enrolled in the study. The exclusion criteria were patients with nonadenocarcinoma histologically and those who did not undergo radical surgery for stage 0–IV colorectal adenocarcinoma. Of the enrolled patients, those who developed PR were retrospectively reviewed, and the incidence and prognosis of PR were investigated. Clinical data were retrieved from medical records. Patient background factors, pathological findings for the primary tumor, patterns of peritoneal metastasis, and clinical outcomes were reviewed. The study protocol was approved by the National Cancer Center Institutional Review Board (2018-100). The requirement for acquisition of informed consent from patients was waived owing to the retrospective nature of this study. The study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments.

Definition, Diagnosis, and Assessment of Peritoneal Recurrence

Peritoneal recurrence included metachronous peritoneal metastasis (MPM) and peritoneal metastasis after synchronous peritoneal metastasis removal (PM-SPMR). Peritoneal recurrence was diagnosed on imaging, mainly with computed tomography (CT), and in some cases with fluorodeoxyglucose (FDG)-positron emission positron emission tomography (PET)/CT, which was performed for diagnostic support. Patients were classified using the Japanese classification of peritoneal metastasis, which is defined by the Japanese Society for Cancer of the Colon and Rectum (JSCCR) as follows: P1, metastasis localized to the peritoneum adjacent to the primary tumor; P2, metastasis limited to the peritoneum distant from the primary tumor; and P3, diffuse metastases in the peritoneum distant from the primary tumor.[10] Patients also were classified into three groups based on the Peritoneal Cancer Index (PCI): < 10, 10–20, and > 20.[11,12] The JSCCR classification and PCI were examined intraoperatively for cases that underwent surgery and evaluated radiologically for nonsurgical cases.

Surgical Resection of Peritoneal Recurrence

Surgical treatment was performed for metastatic lesions judged to be completely resectable, including peritoneal nodules and other organ metastases, or cases in which peritoneal nodule resection was required for symptom relief. Complete resection of peritoneal nodules macroscopically and other organ metastases (R0/1 resection) was defined as curative resection. Surgical resection of peritoneal nodules with a residual tumor macroscopically (R2 resection) was regarded as a case without curative resection.

Statistical Analysis

Categorical variables were compared by Fisher exact test. Prognostic factors for OS and risk factors for recurrence after curative resection were identified using univariate and multivariate analysis with a Cox proportional hazards regression model. Multivariate analysis was performed using a stepwise procedure with covariates with $P < 0.05$ in univariate analysis. Overall survival and recurrence-free survival (RFS) were estimated using the Kaplan–Meier method, and differences between survival curves were evaluated by log-rank test. $P < 0.05$ was considered to be significant. All statistical analyses and graphing were performed using EZR ver. 1.41 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a modified version of R commander designed for statistical functions that are frequently used in biostatistics, and a graphical user interface for R ver. 3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria).[13]

RESULTS

Patients Characteristics and Treatment for Peritoneal Recurrence

In our department, 2587 patients underwent surgical resection of a colorectal tumor between January 2006 and March 2014, of whom 84 with nonadenocarcinoma histologically and 247 who did not undergo radical surgery for stage 0–IV colorectal adenocarcinoma were excluded. Of the other 2256 patients, 55 of 2229 without SPM at the time of radical surgery for primary tumor developed MPM (2.5%), and 11 of 27 with SPM at the time of radical surgery for primary tumor developed PM-SPMR (40.7%). Thus, 66 cases with PR were included in the study (Fig. 1). The characteristics of these cases are shown in Table 1. The primary tumor was located in the right colon, left colon, and rectum in 24, 31, and 11 cases, respectively. The median time to PR from primary tumor resection was 16.5 months. FDG-PET/CT was performed as diagnostic

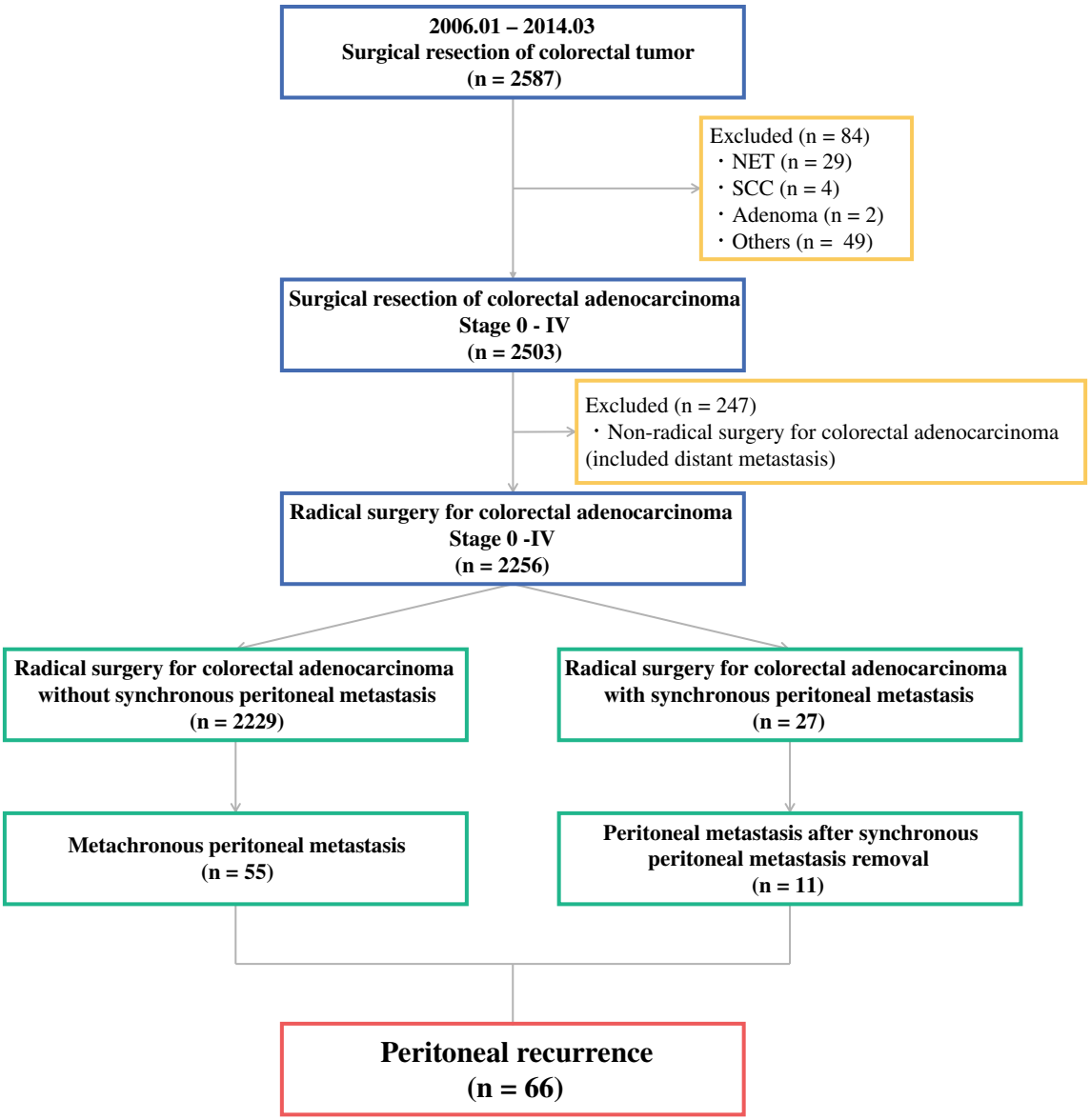

FIG. 1 Flow chart of included and excluded patients. *NET* neuroendocrine tumor; *SCC* squamous cell carcinoma

support in 47 cases, of which 40 showed accumulation of FDG. The JSCCR classification and PCI were examined intraoperatively in 46 patients who underwent laparotomy or laparoscopy. In the other 20 patients, these parameters were determined by imaging. PR was in classes P1, P2, and P3 in 20, 27, and 19 cases, respectively and PCI was < 10, 10–20, and > 20 in 55, 5, and 6 cases, respectively. Of all 66 cases, 38 had peritoneum metastasis only, and 28 had concurrent metastases at other sites, including 15 cases at one site and 13 at two or more sites.

Surgical treatment was performed in 41 cases, including 18 with surgical resection only and 23 with surgical resection and chemotherapy. No patients received HIPEC. Chemotherapy after PR was administered in 42 cases, including 19 patients treated with systemic chemotherapy alone. Six patients received best supportive care. These 25 patients did not undergo surgical treatment because of multiple extensive metastases at the peritoneum or other sites that were not amenable for surgical resection, a poor general condition, or rejection of surgery by the patient.

Surgical Outcomes

Six patients underwent resection of a peritoneal nodule only, and 35 patients underwent extended surgical resection, including adjacent organs. Ten patients received chemotherapy before surgical resection of a peritoneal nodule. The median operative time was 266.5 (range 69–579) min, and median blood loss was 705 (range 10–7024) ml. Seven patients developed postoperative

TABLE 1 Patient characteristics

Characteristics (n = 66)	n	%
Age (years), median (range)	66 (28–82)	
Sex		
Male	36	54.5
Female	30	45.5
Location of primary tumor		
Right colon	24	36.4
Left colon	31	47.0
Rectum	11	16.7
Time to peritoneal recurrence (months), median (range)	16.5 (1.9–139.5)	
JSCCR classification of peritoneal metastasis		
P1	20	30.3
P2	27	40.9
P3	19	28.8
Number of peritoneal nodule		
1	33	50.0
2–4	15	22.7
≥ 5	18	27.3
Size of peritoneal nodule		
< 10 mm	12	18.2
10 mm $\leq$, < 20 mm	18	27.3
≥ 20 mm	36	54.5
Peritoneal cancer index		
< 10	55	83.3
10–20	5	7.6
> 20	6	9.1
Concurrent metastasis[a]	28	42.4
One site	15	22.7
More than two sites	13	19.7
Liver	12	18.2
Distant lymph nodes	10	15.2
Ovary	6	9.1
Lung	4	6.1
Anastomosis site	3	4.6
Abdominal wall	3	4.6
Bone	2	3.0
Small intestine	1	1.5
Spleen	1	1.5
Adrenal gland	1	1.5
Surgical resection of peritoneal nodule	41	62.1
Curative resection (R0/1)	38	57.6
No curative resection (R2)	3	4.5
Chemotherapy[a]	42	63.6
Preoperative chemotherapy	10	15.2
Postoperative chemotherapy after curative resection	17	25.8

JSCCR Japanese Society for Cancer of the Colon and Rectum

[a]There is some duplication

complications of greater than Clavien–Dindo grade III.[14] However, no reoperation was required, and there was no mortality. The median postoperative hospital stay was 13 (range 5–20) days. Of the 41 patients treated with surgical resection, 32 had R0 and 6 had R1 curative resection, whereas 3 had R2 resection. Of 28 patients with concurrent metastases, 12 had curative resection, including other sites of metastases. Curative resection of peritoneal nodules and concurrent metastasis was performed simultaneously for eight of these patients and metachronously for four patients. After achieving curative resection, 17 patients received postoperative chemotherapy.

Survival

The 5-year OS rate was 43.3%, and the median survival period after diagnosis of PR was 50.2 months (Fig. 2a). In univariate analysis, time to PR, JSCCR classification, number of peritoneal nodules, PCI > 20, and curative resection were identified as possible prognostic factors. Subsequent multivariate analysis showed that curative resection was a significant independent prognostic factor (Table 2). Five-year OS was significantly better in cases with curative resection than in those without curative resection (68.7% vs. 6.3%, $P < 0.001$) (Fig. 2b). Age < 70 years and time to PR > 1 year were significantly more frequent in cases with curative resection, and there were no

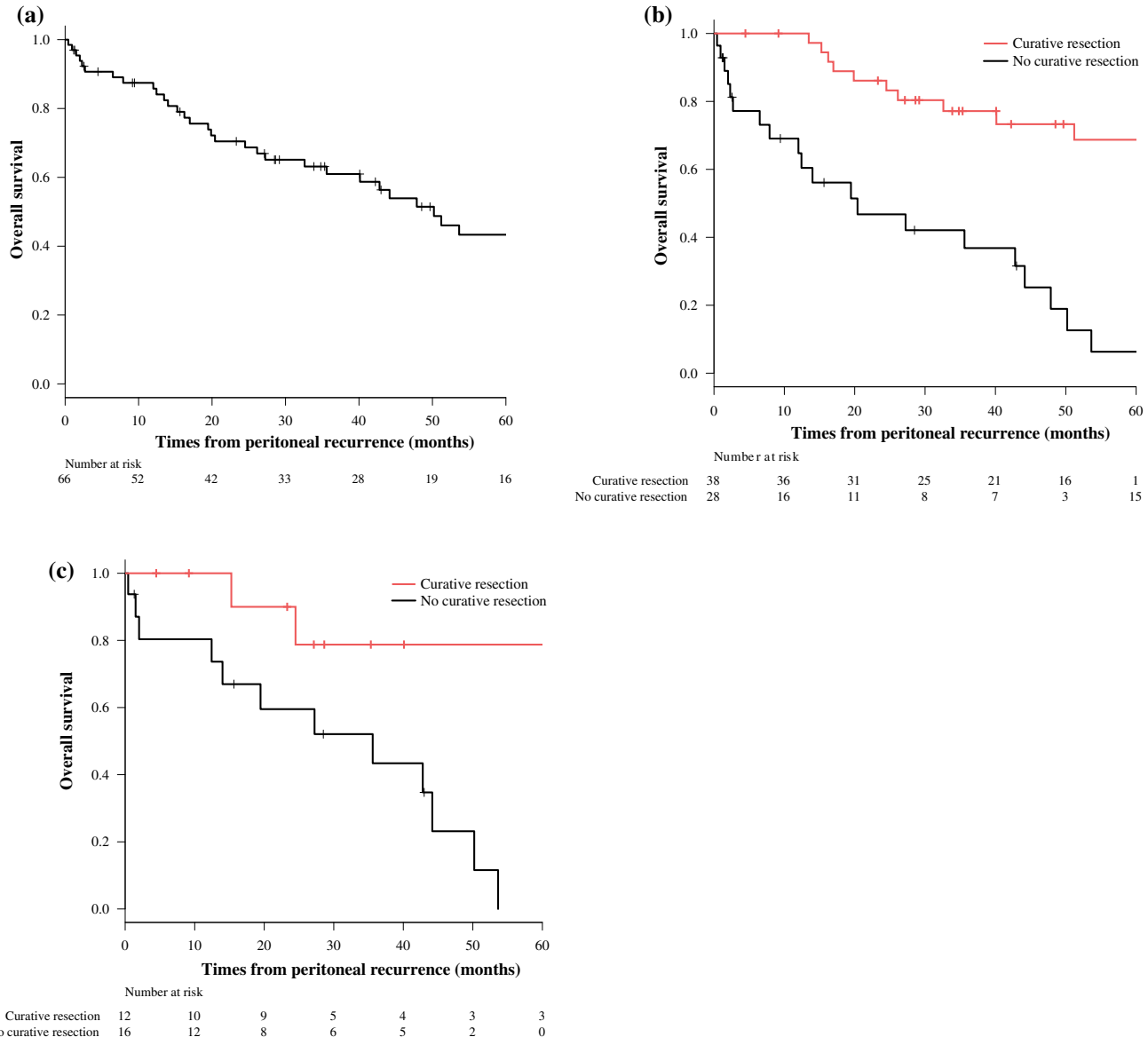

FIG. 2 Kaplan–Meier curves for overall survival. **a** All patients. **b** All patients classified into groups with and without curative resection. **c** Patients with concurrent metastasis classified into groups with and without curative resection

TABLE 2 Prognostic factors for overall survival in univariate and multivariate analyses

Prognostic factors (n = 66)	n	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P value	HR (95% CI)	P value
Age					
≥ 70 years	23	1.259 (0.628–2.523)	0.516	–	
< 70 years	43	Reference			
Sex					
Male	36	1.371 (0.685–2.741)	0.373	–	
Female	30	Reference			
Primary tumor location					
Right colon	24	1.432 (0.498–4.119)	0.505	–	
Left colon	31	0.964 (0.350–2.655)	0.943		
Rectum	11	Reference			
Peritoneal recurrence					
PM-SPMR	11	1.986 (0.917–4.301)	0.082	–	
MPM	55	Reference			
Time to peritoneal recurrence					
≤ 1 year	17	2.112 (1.055–4.230)	0.035	1.399 (0.579–3.380)	0.455
> 1 year	49	Reference		Reference	
JSCCR classification of peritoneal metastasis					
P3	19	8.734 (3.120–24.45)	< 0.001	3.562 (0.830–15.29)	0.087
P2	27	2.718 (1.043–7.083)	0.041	2.040 (0.729–5.710)	0.175
P1	20	Reference		Reference	
Number of peritoneal nodule					
Solitary	33	0.327 (0.160–0.668)	0.002	1.013 (0.341–3.005)	0.982
Multiple	33	Reference		Reference	
Size of peritoenal nodule					
≥ 20 mm	36	1.467 (0.710–3.032)	0.301	–	
< 20 mm	30	Reference			
Peritoneal cancer index					
> 20	6	6.592 (2.417–17.98)	< 0.001	2.634 (0.923–7.513)	0.070
10–20	5	0.931 (0.124–7.017)	0.945	0.369 (0.048–2.854)	0.340
< 10	55	Reference		Reference	
Concurrent metastasis					
Yes	28	1.778 (0.899–3.518)	0.098	–	
No	38	Reference			
Curative resection					
Yes	38	0.198 (0.094–0.416)	< 0.001	0.198 (0.094–0.416)	< 0.001
No	28	Reference		Reference	
Chemotherapy					
Yes	42	1.067 (0.526–2.162)	0.858	–	
No	24	Reference			

HR hazard ratio, *CI* confidence interval, *PM-SPMR* peritoneal metastasis after synchronous peritoneal metastasis removal, *MPM* metachronous peritoneal metastasis, *JSCCR* Japanese Society for Cancer of the Colon and Rectum

P3 and PCI > 10 cases with curative resection. Concurrent metastasis also was significantly less frequent in cases with curative resection (Table 3). However, among patients with concurrent metastasis, 5-year OS was significantly better in those with curative resection than in those without curative resection (78.7% vs. 0%, P = 0.008) (Fig. 2c).

TABLE 3 Comparison between cases with and without curative resection

Characteristics (n = 66)	No curative resection (n = 28)	Curative resection (n = 38)	P value
Age			
≥ 70 years	14 (50%)	9 (23.7%)	0.037
< 70 years	14 (50%)	29 (76.3%)	
Sex			
Male	16 (57.1%)	20 (52.6%)	0.805
Female	12 (42.9%)	18 (47.4%)	
Primary tumor location			
Right colon	11 (39.3%)	13 (34.2%)	0.845
Left colon	12 (42.9%)	19 (50%)	
Rectum	5 (17.9%)	6 (15.8%)	
Peritoneal recurrence			
PM-SPMR	7 (25%)	4 (10.5%)	0.182
MPM	21 (75%)	34 (89.5%)	
Time to peritoneal recurrence			
≤ 1 year	12 (42.9%)	5 (13.2%)	0.010
> 1 year	16 (57.1%)	33 (86.8%)	
JSCCR classification of peritoneal metastasis			
P1	2 (7.1%)	18 (47.4%)	< 0.001
P2	7 (25%)	20 (52.6%)	
P3	19 (67.9%)	0 (0%)	
Number of peritoneal nodule			
1	3 (10.7%)	30 (78.9%)	< 0.001
2–4	8 (28.6%)	7 (18.4%)	
≥ 5	17 (60.7%)	1 (2.6%)	
Size of peritoneal nodule			
< 10 mm	7 (25%)	5 (13.2%)	0.524
10 mm ≤, < 20 mm	7 (25%)	11 (28.9%)	
≥ 20 mm	14 (50%)	22 (57.9%)	
Peritoneal cancer index			
< 10	17 (60.7%)	38 (100%)	< 0.001
10–20	5 (17.9%)	0 (0%)	
> 20	6 (21.4%)	0 (0%)	
Concurrent metastasis[a]			
All	16 (57.1%)	12 (31.6%)	0.047
One site	8 (28.6%)	7 (18.4%)	
More than two sites	8 (28.6%)	5 (13.2%)	
Liver	7 (25%)	5 (13.2%)	
Distant lymph nodes	7 (25%)	3 (7.9%)	
Ovary	1 (3.6%)	5 (13.2%)	
Lung	4 (14.3%)	0 (0%)	
Anastomosis site	2 (7.1%)	1 (2.6%)	
Abdominal wall	2 (7.1%)	1 (2.6%)	
Bone	2 (7.1%)	0 (0%)	
Small intestine	0 (0%)	1 (2.6%)	
Spleen	0 (0%)	1 (2.6%)	
Adrenal gland	0 (0%)	1 (2.6%)	

PM-SPMR peritoneal metastasis after synchronous peritoneal metastasis removal, *MPM* metachronous peritoneal metastasis, *JSCCR* Japanese Society for Cancer of the Colon and Rectum

[a]There is some duplication

Recurrence after Curative Resection

After curative resection, 28 cases developed recurrences. The site was the peritoneum only in 11 cases, hematogenous or lymphatic metastases only in 5 cases, and both sites in 12 cases. In 38 patients who underwent curative resection, the 3-year RFS rate was 21.4%, and the median RFS time was 12.8 months (Fig. 3a). In univariate and multivariate analyses, concurrent metastasis was an independent risk factor for recurrence after curative resection (Table 4). Cases with concurrent metastasis recurred more frequently within 2 years after curative resection (2-year RFS: 0% vs. 39.1%, $P = 0.002$) (Fig. 3b).

DISCUSSION

In this study, we investigated the efficacy of surgical resection of PR of colorectal cancer and identified risk factors for recurrence after curative resection of PR. Patients who underwent curative resection for limited PR had a significantly better prognosis. However, recurrence was common after curative resection, particularly for patients with concurrent metastasis. Peritoneal metastasis is a well-known poor prognostic factor in several cancers, and in colorectal cancer, Franko et al. found that the prognosis of cases with peritoneal metastasis was significantly worse than that of cases with liver or lung metastasis.[9] In this study, PR was defined as MPM and PM-SPMR. The prognosis of cases with metachronous metastasis is generally found to be more favorable than for those with synchronous metastasis.[15,16] However, patients with MPM have as poor a prognosis as patients with SPM.[17–19] PR is less commonly reported compared with lung or liver metastases, and the rate of PR ranges from 2 to 5%.[2–5] There have been few reports on PR and surgical resection of PR, but resectable PR was not uncommon in this study. To the best of our knowledge, there have been no reports on recurrence after curative resection.

Cytoreductive surgery with HIPEC contributes to improved OS of patients with peritoneal metastasis.[20–23] However, in the UNICANCER phase III trial, addition of HIPEC did not improve OS, whereas curative resection (complete or near-complete peritoneal nodule resection) gave satisfactory survival with median OS of 41.2 months and median RFS of 11.1 months.[6] Furthermore, high morbidity and mortality occur after HIPEC.[24] In Japanese studies, the significance of macroscopic resection of SPM without HIPEC has been shown, but macroscopic resection of PR has not been examined.[1,25,26] Nagata et al. reported that surgical resection of PR had a positive effect on prognosis, but the procedure used for peritoneal nodule resection was relatively palliative.[4] Our study clearly shows the prognostic significance of curative resection of PR without HIPEC.

In our department, we perform surgery for limited and resectable peritoneal metastasis. We plan curative resection if it is judged that complete resection can be achieved for a P1 or P2 recurrence, including other organ metastases. In previous reports, the surgical resection rate of PR has ranged from 9 to 34%.[2,4] In this study, surgical resection was performed in 41 of 66 cases (62.1%). This higher rate is due to performance of surgery for cases requiring

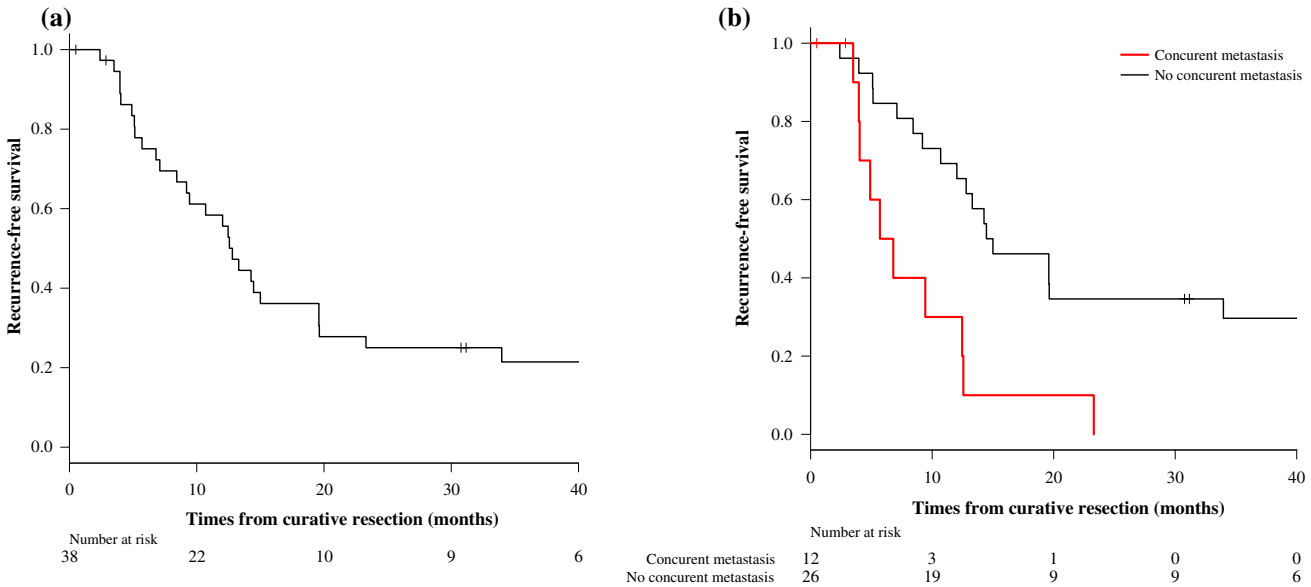

FIG. 3 Kaplan–Meier curves for recurrence-free survival after curative resection. **a** Patients after curative resection. **b** Patients after curative resection classified into groups with and without concurrent metastasis

TABLE 4 Risk factors for recurrence after curative resection in univariate and multivariate analyses

Risk factors (n = 38)	n	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P value	HR (95% CI)	P value
Age					
≥ 70 years	9	0.458 (0.173–1.215)	0.117	–	
< 70 years	29	Reference			
Sex					
Male	20	1.299 (0.617–2.734)	0.491	–	
Female	18	Reference			
Primary tumor location					
Right colon	13	2.469 (0.765–7.964)	0.130	–	
Left colon	19	1.195 (0.392–3.639)	0.754		
Rectum	6	Reference			
Peritoneal recurrence					
PM-SPMR	4	1.122 (0.337–3.733)	0.852	–	
MPM	34	Reference			
Time to peritoneal recurrence					
≤ 1 year	5	0.321 (0.075–1.365)	0.124	–	
> 1 year	33	Reference			
JSCCR classification of peritoneal metastasis					
P2	20	2.373 (1.096–5.138)	0.028	1.601 (0.634–4.044)	0.319
P1	18	Reference		Reference	
Number of peritoneal nodule					
Solitary	30	0.990 (0.419–2.338)	0.982	–	
Multiple	8	Reference			
Size of peritoenal nodule					
≥ 20 mm	22	1.474 (0.674–3.222)	0.331	–	
< 20 mm	16	Reference			
Concurrent metastasis					
Yes	12	3.394 (1.506–7.651)	0.003	3.394 (1.506–7.651)	0.003
No	26	Reference		Reference	
Preoperative chemotherapy					
Yes	9	0.872 (0.352–2.161)	0.767	–	
No	29	Reference			
Postperative chemotherapy					
Yes	17	1.500 (0.713–3.156)	0.286	–	
No	21	Reference			

HR hazard ratio, *CI* confidence interval, *PM-SPMR* peritoneal metastasis after synchronous peritoneal metastasis removal, *MPM* metachronous peritoneal metastasis, *JSCCR* Japanese Society for Cancer of the Colon and Rectum

extended resection of adjacent organs. Curative resection was achieved in 38 of 41 cases (92.7%). Although surgery for PR seems to be highly invasive, the short-term outcomes in the postoperative course showed no complications needing reoperation and no deaths related to surgery. Consequently, curative resection led to remarkably positive outcomes in our cases.

Peritoneal metastasis often is accompanied by other organ metastases, with reported rates of concurrent metastasis with PR of 30–60%.[2–4,9] Concurrent metastasis also has been reported to be a poor prognostic factor.[4] In the present study, 28 cases (42.4%) had PR and simultaneous metastasis at another site. Such cases often receive systemic chemotherapy or palliative treatment, but the efficacy of surgical resection for cases with peritoneal and liver metastases has been shown.[27–30] In this study, five cases with peritoneal and liver metastases had a good prognosis after curative resection. Therefore, surgery should be considered if curative resection is possible for peritoneal metastasis and metastases at other sites.

There are no previous reports on recurrence after curative resection of PR from colorectal cancer. We found a recurrence rate of $> 70\%$ at 3 years after curative resection, which is particularly high. Despite the small number of cases, concurrent metastasis was identified as an independent risk factor, and most cases with this factor developed recurrence within 2 years. The recurrence site after curative resection was the peritoneum only in 11 cases, hematogenous or lymphatic metastases only in 12 cases, and both sites in 5 cases. The median RFS was about 12 months. Second-look surgery has been proposed for high risk patients with PR after resection of a primary tumor, and this strategy may be considered about 1 year after curative resection of PR.[31,32] There is no standard adjuvant therapy after curative resection of PR. In this study, 17 of 38 patients (44.7%) underwent chemotherapy after curative resection. The high number of recurrences outside the peritoneal site suggests that there may be merit to adjuvant chemotherapy after surgery.

This study has several limitations. First, it was a retrospective review at a single center. Second, although the number of radical surgeries for stage 0-IV colorectal adenocarcinoma was a sufficient sample size compared with previous reports, the number of PR cases was relatively small. Third, the PCI status without surgery seemed to be milder than in previous reports, which may be because PCI scores were evaluated radiologically and might be underestimated.[33] Also, PR might have been diagnosed at a relatively early stage, because we performed FDG-PET/CT for many patients. Fourth, most cases of PR in this study were solitary nodules or had a low PCI < 10. There is no method for distinguishing a solitary peritoneal nodule close to the primary tumor location (P1) from local recurrence. However, a solitary nodule located far from the primary tumor location (P2) should be regarded as PR. Fifth, standard chemotherapy regimens changed over the long study period. Therefore, chemotherapy for the subjects included various regimens.

CONCLUSIONS

Curative resection improved overall survival in patients with PR of colorectal cancer with or without concurrent metastasis. This treatment approach should be considered for cases with limited and resectable PR, even with concurrent metastasis. However, the recurrence rate after curative resection of PR was extremely high. Therefore, additional management and treatment for PR cases are needed, especially in those with concurrent metastasis.

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REFERENCES

1. Ozawa H, Kotake K, Kobayashi H, et al. Prognostic factors for peritoneal carcinomatosis originating from colorectal cancer: an analysis of 921 patients from a multi-institutional database. *Surg Today*. 2014;44:1643–50.
2. Quere P, Facy O, Manfredi S, et al. Epidemiology, management, and survival of peritoneal carcinomatosis from colorectal cancer: a population-based study. *Dis Colon Rectum.* 2015;58:743–52.
3. van Gestel YR, Thomassen I, Lemmens VE, et al. Metachronous peritoneal carcinomatosis after curative treatment of colorectal cancer. *Eur J Surg Oncol.* 2014;40:963–9.
4. Nagata H, Ishihara S, Hata K, et al. Survival and prognostic factors for metachronous peritoneal metastasis in patients with colon cancer. *Ann Surg Oncol.* 2017;24:1269–80.
5. Mayanagi S, Kashiwabara K, Honda M, et al. Risk factors for peritoneal recurrence in stage II to III colon cancer. *Dis Colon Rectum.* 2018;61:803–8.
6. Quenet F, Elias D, Roca L, et al. A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7. *J Clin Oncol.* 2018;36(18_suppl):LBA3503.
7. Klaver YL, Lemmens VE, de Hingh IH. Outcome of surgery for colorectal cancer in the presence of peritoneal carcinomatosis. *Eur J Surg Oncol.* 2013;39:734–41.
8. Sato H, Toyama K, Koide Y, et al. Prognoses and treatment strategies for synchronous peritoneal dissemination of colorectal carcinoma. *Surg Today.* 2016;46:860–71.
9. Franko J, Shi Q, Meyers JP, et al. Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the Analysis and Research in Cancers of the Digestive System (ARCAD) database. *Lancet Oncol.* 2016;17:1709–19.
10. Japanese Society for Cancer of the Colon and Rectum. Japanese classification of colorectal, appendiceal, and anal carcinoma, third English edition. Tokyo: Kanehara & Co., Ltd.; 2019.
11. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. *Cancer Treat Res.* 1996;82:359–74.
12. Chua TC, Morris DL, Esquivel J. Impact of the peritoneal surface disease severity score on survival in patients with colorectal cancer peritoneal carcinomatosis undergoing complete cytoreduction and hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol.* 2010;17:1330–6.
13. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant.* 2013;48:452–8.
14. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* 2004;240:205–13.

15. Tsai MS, Su YH, Ho MC, et al. Clinicopathological features and prognosis in resectable synchronous and metachronous colorectal liver metastasis. *Ann Surg Oncol.* 2007;14:786–94.
16. Kumar R, Price TJ, Beeke C, et al. Colorectal cancer survival: an analysis of patients with metastatic disease synchronous and metachronous with the primary tumor. *Clin Colorectal Cancer.* 2014;13:87–93.
17. Bloemendaal AL, Verwaal VJ, van Ruth S, et al. Conventional surgery and systemic chemotherapy for peritoneal carcinomatosis of colorectal origin: a prospective study. *Eur J Surg Oncol.* 2005;31:1145–51.
18. Pelz JO, Chua TC, Esquivel J, et al. Evaluation of best supportive care and systemic chemotherapy as treatment stratified according to the retrospective peritoneal surface disease severity score (PSDSS) for peritoneal carcinomatosis of colorectal origin. *BMC Cancer.* 2010;10:689.
19. Klaver YL, Leenders BJ, Creemers GJ, et al. Addition of biological therapies to palliative chemotherapy prolongs survival in patients with peritoneal carcinomatosis of colorectal origin. *Am J Clin Oncol.* 2013;36:157–61.
20. Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol.* 2003;21:3737–43.
21. Glehen O, Kwiatkowski F, Sugarbaker PH, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. *J Clin Oncol.* 2004;22:3284–92.
22. Elias D, Gilly F, Boutitie F, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. *J Clin Oncol.* 2010;28:63–8.
23. Prada-Villaverde A, Esquivel J, Lowy AM, et al. The American Society of Peritoneal Surface Malignancies evaluation of HIPEC with mitomycin C versus oxaliplatin in 539 patients with colon cancer undergoing a complete cytoreductive surgery. *J Surg Oncol.* 2014;110:779–85.
24. Koppe MJ, Boerman OC, Oyen WJ, et al. Peritoneal carcinomatosis of colorectal origin: incidence and current treatment strategies. *Ann Surg.* 2006;243:212–22.
25. Kobayashi H, Kotake K, Funahashi K, et al. Clinical benefit of surgery for stage IV colorectal cancer with synchronous peritoneal metastasis. *J Gastroenterol.* 2014;49:646–54.
26. Shida D, Tsukamoto S, Ochiai H, et al. Long-term outcomes after R0 resection of synchronous peritoneal metastasis from colorectal cancer without cytoreductive surgery or hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol.* 2018;25:173–8.
27. Carmignani CP, Ortega-Perez G, Sugarbaker PH. The management of synchronous peritoneal carcinomatosis and hematogenous metastasis from colorectal cancer. *Eur J Surg Oncol.* 2004;30:391–8.
28. Elias D, Liberale G, Vernerey D, et al. Hepatic and extrahepatic colorectal metastases: when resectable, their localization does not matter, but their total number has a prognostic effect. *Ann Surg Oncol.* 2005;12:900–9.
29. Maggiori L, Goéré D, Viana B, et al. Should patients with peritoneal carcinomatosis of colorectal origin with synchronous liver metastases be treated with a curative intent? A case-control study. *Ann Surg.* 2013;258:116–21.
30. Lorimier G, Linot B, Paillocher N, et al. Curative cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy in patients with peritoneal carcinomatosis and synchronous resectable liver metastases arising from colorectal cancer. *Eur J Surg Oncol.* 2017;43:150–8.
31. Sugarbaker PH. Second-look surgery for colorectal cancer: revised selection factors and new treatment options for greater success. *Int J Surg Oncol.* 2011. https://doi.org/10.1155/2011/915078.
32. Elias D, Honoré C, Dumont F, et al. Results of systematic second-look surgery plus HIPEC in asymptomatic patients presenting a high risk of developing colorectal peritoneal carcinomatosis. *Ann Surg.* 2011;254:289–93.
33. Koh JL, Yan TD, Glenn D, et al. Evaluation of preoperative computed tomography in estimating peritoneal cancer index in colorectal peritoneal carcinomatosis. *Ann Surg Oncol.* 2009;16:327–33.