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Original

Prognostic Factors in Colorectal Cancer with Peritoneal Metastases

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Introduction: There are currently no curative treatments for peritoneal metastasis in colorectal cancer (CRC) patients, and determining effective therapeutic strategies represents a major challenge. The objective of this study was to elucidate potential prognostic factors by conducting a clinicopathological study in patients with peritoneal metastasis (PM). **Subjects and Methods:** Among the 2,605 patients who underwent initial CRC surgery in this department (April 1987 through December 2010), 104 patients underwent laparotomy, were diagnosed with PM, and were followed up; these patients were therefore included in our analysis. **Results:** The overall postoperative 2- and 5-year survival rates were 22.3% and 7.8%, respectively, and the median survival time (MST) was 353 days. According to the degree of PM, the 5-year survival rate was significantly longer in the P1 group than in the P2 and P3 groups ($p<0.01$). Prognosis was better in patients in the highly differentiated and moderately differentiated adenocarcinoma groups (according to pathological differentiation of CRC) ($p=0.018$), in those absence of hepatic metastasis ($p=0.018$), in those absence of distant metastasis ($p<0.01$), in those who underwent primary lesion resection ($p<0.01$), and in the curability B group ($p<0.01$). In multivariate analysis, the degree of PM (P1 vs P2, P3) (HR 2.11, 95% CI 1.26–3.54) and the presence of distant metastasis (HR 1.98, 95% CI 1.31–2.94) were found to be independent prognostic factors. When prognosis was analyzed according to the number of factors present, MST was 713 days, 386 days, and 135 days in patients with no, one, or two to three risk factors, respectively. Prognosis worsened as the number of risk factors increased. The correlation between efficacy of postoperative chemotherapy and the number of risk factors was also assessed, which showed that prognosis in patients who underwent postoperative chemotherapy was favorable regardless of the number of risk factors. Prognosis was poor in patients with PM severity of P2/3 and in those with distant metastasis. Moreover, survival time was prolonged by postoperative chemotherapy even in patients with multiple poor prognostic factors. **Conclusion:** The degree of PM and the presence of distant metastasis were identified as prognostic factors for CRC patients with PM. Survival time was prolonged by postoperative chemotherapy even in patients with multiple poor prognostic factors.

Key Words: peritoneal metastasis, prognostic factor, postoperative chemotherapy, colorectal cancer

Introduction

With recent advances in therapeutic methods, surgical therapy or systemic chemotherapy is now used as treatment for colorectal cancer (CRC) even in patients with distant or recurrent metastasis. In fact, good therapeutic outcomes after surgery have been reported in cases of hepatic and pulmonary metastases. Furthermore, with the recent developments in systemic chemotherapy, favorable effects on patient prognosis have been shown even in patients with unresectable tumors[1)2)].

Peritoneal metastasis (PM) is the second most common mode of progression after hematogenous metastasis and is a key factor influencing prognosis. Although resection has been reported to be efficacious for hepatic and pulmonary metastases[3)~8)], there are currently no curative therapeutic options for patients with PM, and determining effective therapeutic strategies remains a major challenge. Despite recent advancements in therapeutic meth-

ods, no dramatic improvements in the outcomes of patients with PM have been shown. However, combination systemic chemotherapy may prolong survival times even in cases of PM. The poor prognosis of CRC with PM has already been reported. However, the identification of prognostic factors is necessary to establish future therapeutic strategies for PM. Accordingly, the objective of this study was to elucidate potential prognostic factors for CRC patients with PM by conducting a clinicopathological study on PM cases encountered in our department.

Subjects and Methods

In the 24-year period from April 1987 through December 2010, 2,605 patients underwent initial CRC surgery in our department. Of these, 117 underwent laparotomy and were diagnosed with PM preoperatively or intraoperatively. Subjects with a history of therapy for other cancers within the previous 5 years were excluded from the study. Thus, 104 subjects (4.0%) in whom PM was histologically confirmed and whose prognosis could be followed were included in the present study. The study protocol was approved by the ethics committee of Tokyo Women's Medical University (approval no. 3,080).

According to the degree of PM, 44 cases were classified as P1 (42.3%), 27 as P2 (26.0%), and 33 as P3 (31.7%). With regard to the number of distant metastases other than peritoneal metastasis, 48 patients had no metastasis (46.2%), 28 had metastasis in one organ (26.9%), 7 had metastasis in two organs (6.7%), and 1 had metastasis in three organs (1.0%). Primary lesion resection was performed in 84 cases (80.8%) and curability B resection, in 51 cases (49.0%) (Table 1).

Patient prognosis was retrospectively analyzed according to age; gender; and clinicopathological features such as lesion site, depth of tumor invasion, pathological differentiation of CRC, lymph node metastasis, presence of other distant metastases (e.g., in the liver, lung, bone, and brain), degree of PM, whether the primary lesion was resected, and curability. A history of chemotherapy was defined as systemic chemotherapy, administered orally or intravenously, as well as hepatic arterial infusion, for

Table 1 Characteristics of 104 patients with peritoneal metastasis of colorectal cancer

Factor	No. of patients (n = 104)	(%)
Preoperation factor		
Age (Median ± SD)	62.4 ± 12.0	
Sex		
Male	55	(52.9)
Female	49	(47.1)
Site of colorecatal cancer		
Colon	88	(84.6)
Rectum	16	(15.4)
Operation factor		
Depth invasion from patholigical findings*		
T1	0	
T2	2	(1.9)
T3	64	(61.5)
T4	18	(17.4)
unknown	20	(19.2)
Pathological differentiation of colorectal cancer**		
well	17	(16.4)
mod	51	(49)
por	9	(8.7)
muc	7	(6.7)
unknown	20	(19.2)
Lymphnode metastasis***		
N0	14	(13.5)
N1	27	(26)
N2	23	(22.1)
N3	8	(7.7)
M1	12	(11.5)
unknown	20	(19.2)
Hepatic metastasis****		
H0	67	(64.4)
H1	6	(5.7)
H2	7	(6.7)
H3	24	(23.1)
Degree of peritoneal metastasis*****		
P1	44	(42.3)
P2	27	(26)
P3	33	(31.7)
Number of the distant metastasis		
0	48	(46.2)
1	28	(26.9)
2	7	(6.7)
3	1	(1.0)
unknown	20	(19.2)
Resection of the primary tumor		
yes	84	(80.8)
no	20	(19.2)
Postoperation factor		
Curability		
curB	51	(49)
curC	53	(51)
Postoperative chemotherapy		
yes	62	(59.6)
no	30	(28.9)
unknown	12	

*T1: Tumor invades submucosa, T2: Tumor invades muscularis propria, T3: Tumor invades through the musclaris propria into the subserosa, or into non-peritonealized pericolic or perirectal tissues, T4: Tumor directly invades other organs or structures, and/or perforates visceral peritoneum.
**well: well differentiated adenocarcinoma, mod: moderately differentiated adenocarcinoma, por: poorly differentiated adenocarcinoma, muc: mucinous adenocarcinoma.
***N0: no lymph node metastasis, N1: metastasis to group 1, N2: metastasis to group 2, N3: metastasis to group 3, N4: metastasis to group 4.
****H0: no liver metastasis, H1: metastasis limited to one lobe, H2: some metastasis to both lobes (four lesions or less), H3: numerous metastasis to both lobes (five lesions or more).
*****P0: no peritoneal metastasis, P1: metastasis only to adjacent peritoneum, witch are removal by a combined resection, P2: a few metastasis to distant peritoneum, P3: numerous metastasis to distant peritoneum, CurB: no residual tumors but not evaluable as "curability a", CurC: definite residual tumors.

at least 2 months. All descriptions of the clinicopathological features conform to the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus, 7th edition[9].

JMP ver 11 software (SAS Co., Ltd., USA) was used for all data analyses. For statistical analyses, one-way analysis of variance was used for continuous variables, and the χ^2 test was used for categorical variables. The cumulative survival rate was calculated using the Kaplan–Meier method, and the log-rank test was used to test for significance. Multivariate analysis was performed using the Cox proportional hazard model, with $p < 0.05$ considered statistically significant.

Results

The overall 2- and 5-year postoperative survival rate in patients with PM among the 104 subjects were 22.1% and 7.7%, respectively, and the median survival time (MST) was 353 days (11.6 months) (Fig. 1a). When analyzed according to the degree of PM, the 5-year survival rate was significantly longer in the P1 group (15.9%) than in the P2 (3.7%) and P3 (0%) groups combined ($p < 0.01$) (Fig. 1b).

Clinicopathological features and prognosis

The 5-year survival rate was found to be significantly better in patients with well and moderately differentiated adenocarcinoma (vs poorly differentiated adenocarcinoma and mucinous adenocarcinoma), absence of hepatic metastasis, degree of PM, and absence of distant metastasis; in patients who underwent primary lesion resection; and in patients classified as curability B (vs curability C). However, the 2-year survival rate did not differ significantly according to sex, tumor site, depth of tumor invasion, or degree of lymph node metastasis (Table 2).

Multivariate analysis of prognostic factors

Multivariate analysis was performed using the four variables for which a significant difference was found in univariate analysis: pathological differentiation of CRC (well and differentiated vs poorly differentiated, mucinous), PM (P1 vs P2, P3), presence of distant metastasis, and curability (curability B vs C). Of these, PM and the presence of distant metastasis were found to be independent prognostic factors (Table 3). However, primary lesion resection was excluded from the analysis of 5-year survival rate because all patients in the non-resected group died within 2 years of the operation.

Prognosis was analyzed according to the number of preoperative and surgical risk factors (PM of P2/3 and distant metastasis other than peritoneal metastasis). PM (P1 vs P2, P3) (hazard ratio 2.11, 95% confidence interval 1.26–3.54) and the presence of distant metastasis (hazard ratio 1.98, 95% confidence interval 1.31–2.94) were found to be independent prognostic factors. The MST was 713 days in the group with no risk factors, 386 days in the group with one risk factor, and 135 days in the group with three risk factors. A significant difference was observed in the 5-year survival rate between the group with one or more risk factor (0%) and in the group with no risk factor (20.8%) (risk 0 vs 1; $p = 0.0008$, risk 1 vs 2; $p = 0.0007$, risk 0 vs 2; $p < 0.0001$; Fig. 2).

To examine whether the efficacy of postoperative chemotherapy varies among patients with different numbers of risk factors, prognosis was stratified by the use of chemotherapy and outcomes, and was compared between groups. The overall survival time was not significantly different between patients with and without chemotherapy in the group with no risk factors (Fig. 3a, $p = 0.0513$). However, overall survival was prolonged in patients who underwent postoperative chemotherapy in the groups with one or two risk factors (Fig. 3b, 3c).

Discussion

PM is associated with poor prognosis, and although various therapeutic methods have been evaluated, there is currently no standard treatment. Good outcomes have been reported for peritoneal resection and hyperthermic intraperitoneal chemotherapy or early postoperative intraperitoneal chemotherapy in addition to preoperative and postoperative chemotherapy. However, these procedures are currently performed at few facilities, owing to the complexity of the procedures and the relatively high risk of complications[10)~14)].

In addition, the use of combination systemic chemotherapy has been explored in patients with PM. Although PM is associated with poor prognosis,

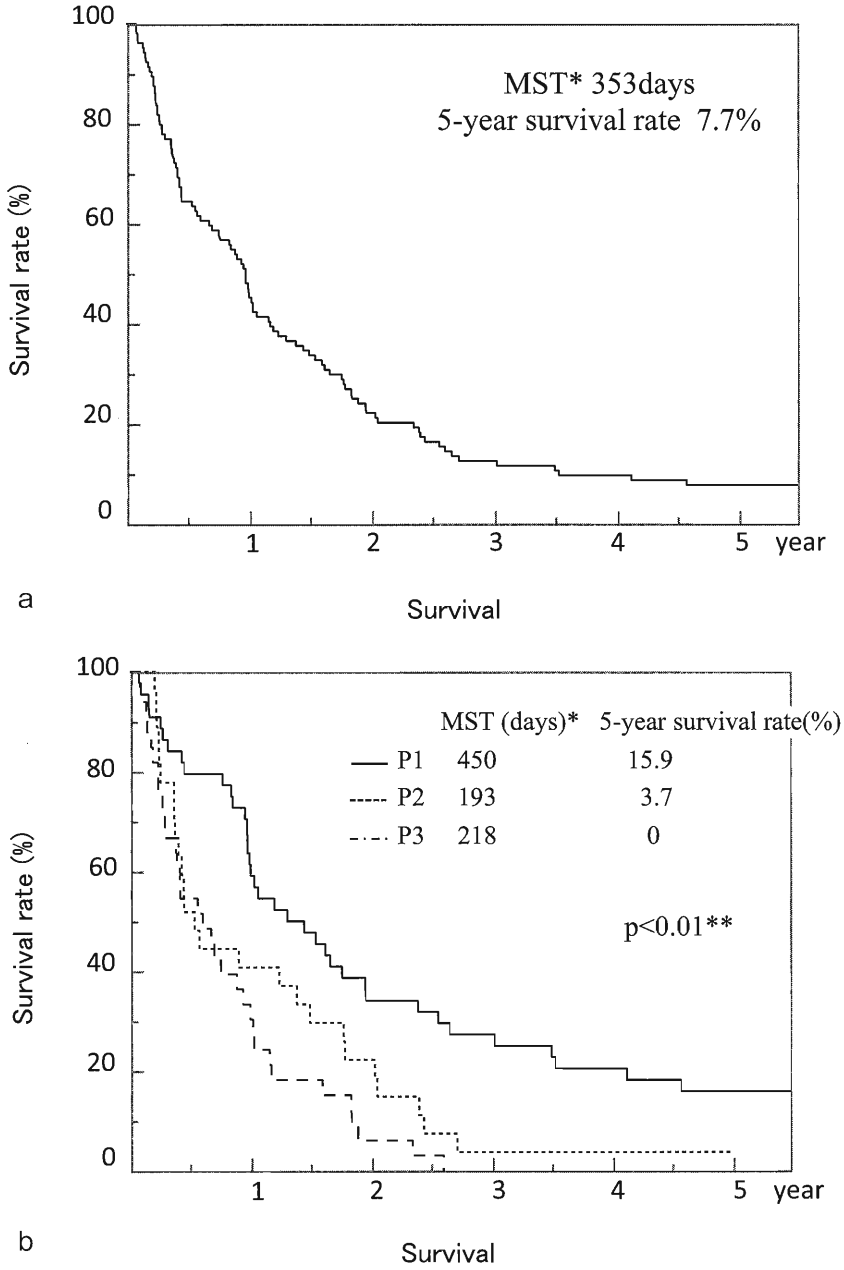

Fig. 1 Overall survival in 104 patients with peritoneal metastasis from colorectal cancer
a: Overall survival in all cases.
b: Overall survival according to the degree of peritoneal metastasis.
*MST: mean survival time.
**P1 vs P2, P3.

identifying other prognostic factors is important to improve the therapeutic outcomes of this malignancy. For this reason, in this study, we studied the clinicopathological features and their prognostic value in CRC patients with PM.

Of the 2,605 patients who underwent CRC surgery, 117 had PM. The incidence of CRC with PM was previously reported to be 4–6%, which is relatively low compared to the incidence of hepatic metastasis (9.2–11%)[15]. In the present study, the incidence was found to be 4.5%, which is similar to the values in previous reports.

The overall 2- and 5-year survival rates in all PM cases in this study were 22.1% and 7.7%, respectively, and the MST was 353 days, indicating poor prognosis of patients with PM; these findings are similar to the results of previous studies on the prognosis of CRC patients with PM[16)17)]. The 5-year

Table 2 Univariate analysis of the clinicopathological factors and treatment-related factors in 104 patients with peritoneal metastasis of colorectal cancer

Factor	2-year overall survival rate (%)	5-year overall survival rate (%)	MST (days)	p
Sex				
Male	21.6	1.8	309	0.17
Female	25.0	1.4	353	
Site of colorectal cancer				
Colon	22.1	7.9	193	0.63
Rectum	25.0	6.2	203	
Depth invasion from patholigical findings				
T2, 3≥	31.8	10.6	346	1.17
T4	11.1	5.5	273	
Pathological differentiation of colorectal cancer				
wel, mod*	32.6	11.6	474	0.018
por, muc**	6.7	0	304	
Lymphnode metastasis				
−	35.7	7.1	546	0.67
+	25.7	10.0	374	
Hepatic metastasis				
−	31.3	11.9	450	0.018
+	5.4	0	139	
Degree of peritoneal metastasis***				
P1	36.4	15.9	353	<0.01
P2	22.2	3.7	131	
P3	6.1	0	104	
Distant metastasis (M)				
−	36.6	12.2	589	<0.01
+	6.4	0	161	
Resection of the primary tumor				
yes	27.4	9.5	404	<0.01
no	0	0	111	
Curability				
CurB	37.3	13.7	604	<0.01
CurC	5.7	1.9	155	

*Well or moderate differentiated adenocarcinoma. **Poorly differentiated or mucinous adenocarcinoma. ***General rules for Clinical and Pathological Studies on Cancer of the colon, rectum and anus (The 7th edition).

Table 3 Multivariate analysis of the prognostic factors in 104 patients with peritoneal metastasis of colorectal cancer

Factors	Hazards ratio	95% Confidence interval	p
Pathological differentiation (wel, mod*/por, muc**)	1.59	0.84-2.83	0.1522
Digree of peritoneal metastasis (P1/P2, 3)	2.11	1.26-3.54	0.0043
Distant metastasis (+/−)	1.98	1.13-2.94	0.0015
Curability (B/C)	1.37	0.77-2.40	0.2811

*Well or moderate differentiated adenocarcinoma.
**Poorly differentiated or mucinous adenocarcinoma.

survival rate according to the degree of PM was significantly longer in the P1 group (15.9%) than in the P2 (3.7%) or P3 (0%) groups. Of note, in the P1 group, it was not possible to determine whether resection had a positive effect because the PM lesions were resected in all cases.

On multivariate analysis with factors found significant in univariate analysis, the degree of PM (P1 vs P2, P3) and the presence of distant metastasis were found to be independent prognostic factors.

In this study, the 5-year survival rate of the 41 patients with PM alone was 12.2%, which was signifi-

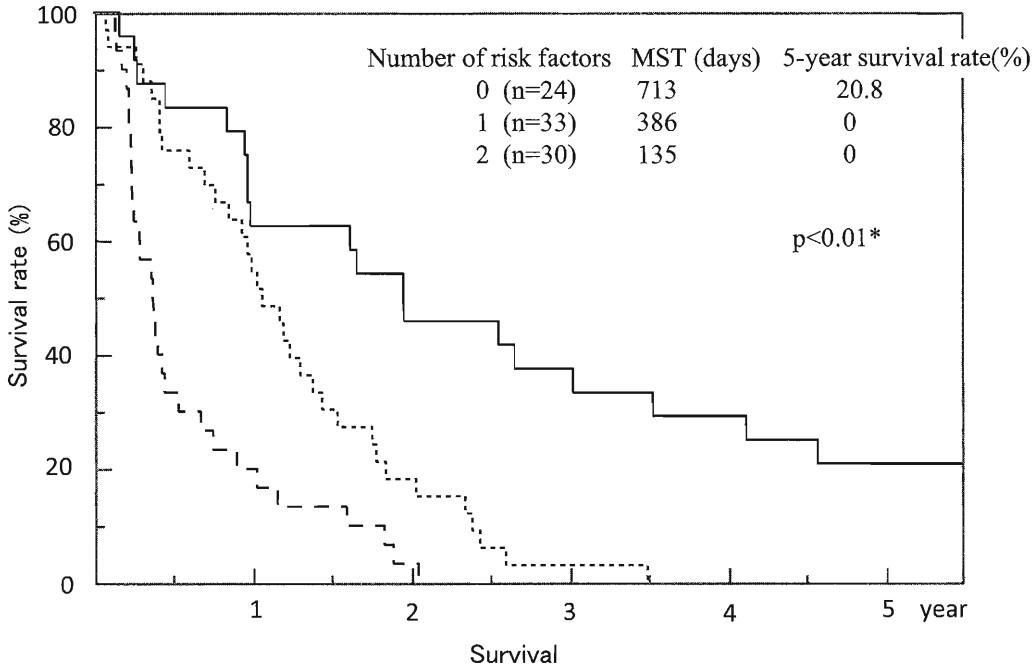

Fig. 2 Overall survival according to the number of the risk factors
*Number of risk factor 0 vs 1 $p<0.01$.
Number of risk factor 1 vs 2 $p<0.01$.
Number of risk factor 0 vs 2 $p<0.01$.

cantly better than that of patients with additional distant metastases other than PM. In the comparison of prognosis in each group stratified by the presence/absence of postoperative chemotherapy, which is a treatment factor, no significant differences were found in the group with no risk factors between patients who received and those who did not receive chemotherapy. In contrast, significant differences according to chemotherapy use were found in the groups with one or two risk factors. These results indicate that prognosis was poor in the groups with P2, P3, or distant metastasis. However, overall survival was prolonged by chemotherapy use, even in patients with distant metastases.

This study have several limitations. Because this was a retrospective study spanning 24 years, chemotherapy regimens changed during the period, meaning that patients in this study received different treatments (Table 4). To simplify this heterogeneity, we classified patients who received chemotherapy as those who underwent anti-cancer drug therapy for at least 2 months. In addition, it was not possible to obtain performance status (PS) data in this study. In our department, chemotherapy is proactively performed in patients with PS0 or PS1, and electively performed in those with PS2. However, in principle, chemotherapy is considered unsuitable for patients with PS3[18]. Therefore, we cannot rule out the possibility that patients who received chemotherapy had a good PS. Nevertheless, chemotherapy may be effective in prolonging survival time in patients in whom chemotherapy is possible[19)20)], and although the study period was long and there was variability in the regimens used, we believe that our results indicate favorable prognosis in patients who receive proactive intervention with multimodal therapy[21)~23)]. Treatment regimens during the study period were broadly grouped into newly developed chemotherapy regimens, including FOLFOX and CapeOX, and conventional chemotherapy regimens. The lack of a significant difference in outcome data between groups may be due to the small number of patients who received the newly developed chemotherapy regimens. However, a slight increase in the MST was observed; therefore, it is possible that newly developed chemotherapy regimens improve prognosis. Furthermore, prognosis according to the anti-

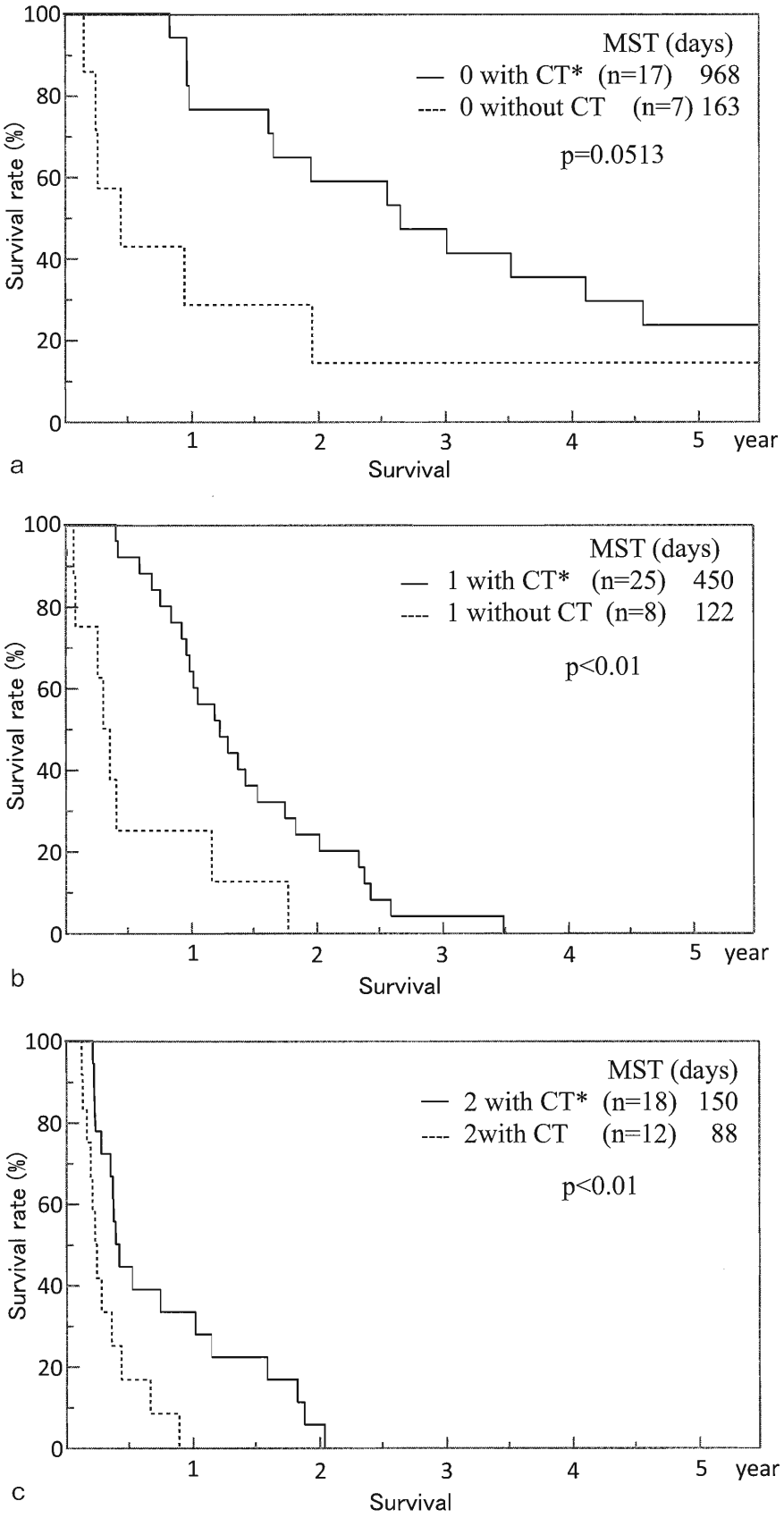

Fig. 3 Relation between the number of the risk factors and chemotherapy
a: Overall survival in patients with no risk factor.
b: Overall survival in patients with one risk factor.
c: Overall survival in patients with two risk factors.
*CT: chemotherapy following surgery.

Table 4 Variety of postoperative chemotherapy on 104 patients with peritoneal metastasis of colorectal cancer

Factor	Case (n = 104)
Cases with postoperative chemotherapy	60
Systemic chemotherapy	
5'-DUFR	9
S-1	9
LV/tegaful/uracil	19
5FU	3
5FU + CDDP	5
CDDP	1
FL	7
FOLFOX	4
CapeOX	1
Hepatic arterial infusinon chemotherapy for hepatic metastases	
5FU + MMC	1
5FU + CDDP	1
Cases without postoperative chemotherapy	32
Unknown	12

FL: fluorouracil and leucovorin, FOLFOX: infusional 5-fluorouracil + leucovorin + Oxaliplatin, CapeOX: capecitabine + Oxaliplatin.

cancer drug use should be studied prospectively, but this requires further data collection; we await such results on the long-term prognosis of these patients.

Although the primary lesion was resected in 84 (80.8%) of the 104 cases in this study, primary lesion resection could not be assessed as a prognostic factor because none of the patients who did not undergo resection survived to 2 years. A multicenter collaborative prospective study on the significance of primary lesion resection is in progress, and we are awaiting its results.

Conclusion

In the analysis of the prognosis of patients with PM, the degree of PM and presence of distant metastasis were found to be independent prognostic factors. In contrast, chemotherapy is an elective therapeutic factor. Therefore, it is important to adopt a therapeutic strategy that allows early introduction of chemotherapy. Increased efficacy of newly developed chemotherapy regimens with new anti-cancer drugs is expected in the future.

The authors indicated no conflicts of interest.

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大腸癌同時性腹膜転移症例における予後因子の検討

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〔緒言〕大腸癌における腹膜転移は，根治的治療法がなく有効な治療戦略を決定することは現在でも大きな課題である．本研究は自験例における腹膜転移症例の臨床病理学的検討を行い，予後規定因子を明らかにすることを目的とした．〔対象と方法〕当科で経験した初発大腸癌手術症例2,605例中（1987年4月～2010年12月），腹膜転移を認めた開腹手術症例で追跡調査が可能であった104例を対象とした．〔結果〕対象症例全体の術後2年生存率は22.1%，5年生存率は7.7%，生存期間の中央値（以下，MST）は353日であった．術前および手術因子では，P1がP2, P3に対し予後良好であった（$p<0.01$）．組織分類別では高分化および中分化腺癌（$p=0.018$），肝転移無（$p=0.018$），遠隔転移無（$p<0.01$），原発切除施行（$p<0.01$），根治度B群（$p<0.01$）において予後が良好であった．多変量解析で腹膜転移の程度（P1 vs P2, 3）（ハザード比2.11, 95%信頼区間1.26–3.54），遠隔転移の有無（ハザード比1.98, 95%信頼区間1.31–2.94）の2項目が独立した予後規定因子項目として抽出された．リスク因子別のMSTは各々，リスク因子0：713日，1：386日，2：135日でリスク因子が多いほど予後は不良であった．リスク因子数別に術後化学療法の効果を検証したところ，リスク因子数に関わらず化学療法施行症例の予後が良好であった．腹膜転移の程度がP2以上で，遠隔転移のある症例の予後が不良であることが判明した．さらに複数の予後不良因子を有する症例であっても術後化学療法を施行することで予後の延長が認められた．〔結論〕腹膜転移の程度，遠隔転移の有無が予後因子として抽出された．複数の予後不良因子を有する症例であっても術後化学療法を施行することで予後の延長が認められた．