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The Prognostic Significance of a Histological Response to Preoperative Chemotherapy in Patients With Synchronous Colorectal Liver Metastases

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Objective: Preoperative chemotherapy (PC) for colorectal liver metastasis (CRLM) is widely used to improve prognosis, but its clinical benefit has not been fully established. This study aimed to assess the effectiveness of PC for synchronous CRLM and the correlation between the histologic response to PC and survival.

Summary of Background Data: We enrolled 69 patients who underwent initial hepatectomy for synchronous CRLM between 2004 and 2018 at Gifu University Hospital.

Methods: We retrospectively analyzed the clinicopathologic factors and outcomes of 69 patients who underwent hepatectomy after receiving PC (PC group: n = 43) or who underwent upfront hepatectomy (non-PC group: n = 26). In the PC group, the patients were divided into the Grade 1 (n = 27) and Grade 2/3 (n = 16) groups according to their histologic responses to PC.

Results: The median survival and 5-year overall survival (OS) rates were 80.9 months and 61.5%, respectively, in the PC group and 71.7 months and 61.5%, respectively, in the non-PC group ($P = 0.867$). Regarding recurrence-free survival (RFS) and remnant liver-RFS, there were no significant differences between the 2 groups ($P = 0.087$ and 0.291). However, in a subgroup analysis, the median 5-year OS, RFS, and remnant liver-RFS were significantly longer in the Grade 2/3 than Grade 1 group ($P = 0.008$, $P = 0.002$, and $P < 0.001$, respectively).

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Conclusions: Some patients benefit from PC, and the histologic response to PC had prognostic significance for patients with synchronous CRLM.

Key words: Colorectal cancer – Liver metastasis – Chemotherapy – Hepatectomy – Neoadjuvant chemotherapy

Liver metastasis is the most common distant metastasis of colorectal cancer (CRC), and approximately 15% to 25% of patients have synchronous colorectal liver metastases (CRLM) at initial treatment.[1,2] CRLM is resectable in 15% of patients,[3,4] and hepatectomy is considered the optimal, potentially curative treatment for CRLM, with a reported 5-year postoperative survival rate of 45% to 61%[5,6]; however, the rates of postoperative recurrence and remnant liver recurrence are both approximately 60% to 70%,[7,8] and the outcomes of hepatectomy are not fully satisfactory.

On the other hand, chemotherapy with combinations of 5-fluorouracil/leucovorin with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) plus molecular targeted therapy have improved tumor responses and median survival times up to more than 30 months for unresectable CRLM.[9] Perioperative chemotherapy including preoperative chemotherapy (PC) for CRLM is widely used to improve prognosis.[10] Although the histologic and radiologic responses to PC have been reported to be useful predictors of outcomes,[11,12] the clinical benefit of PC has not been fully established. Some studies also reported a difference in prognosis between patients with synchronous and metachronous CRLM[13] and between patients with intrahepatic and extrahepatic metastasis.[14] Therefore, we focused on synchronous CRLM, and the aims of this study were the following: (1) to assess the effectiveness of PC for synchronous colorectal liver-limited metastases, and (2) to analyze the correlation between histologic response to PC and postoperative survival.

Materials and Methods

Patients

Between June 2004 and December 2018, 168 consecutive patients underwent initial hepatectomy for CRLM at Gifu University Hospital in Gifu City, Japan. The exclusion criteria were as follows: (1) any other distant metastasis or peritoneal dissemination at the first treatment for CRLM, (2) R1/2 resection for primary tumor resection, and (3) R2 hepatectomy for CRLM. After excluding 45 patients who met the exclusion criteria, we excluded 54 patients with metachronous CRLM from the remaining 123 patients. This study thus included 69 patients with synchronous CRLM, and patients were divided into the PC group (n = 43) and upfront hepatectomy without PC (non-PC group, n = 26). Overall survival (OS), recurrence-free survival (RFS), and remnant liver-RFS were compared between the PC and non-PC groups. In the PC group, according to the histologic criteria for response to chemotherapy, survival outcomes were also compared between 16 patients who responded to PC (Grade 2/3), and 27 patients who did not (Grade 1) (Fig. 1).

All patients were fully informed of the study design according to the Ethics Committees of Gifu University Hospital (Approval number 2020–231; February 8, 2021), and informed consent was obtained from all patients by the opt-out method, in accordance with the guidelines of the Japanese Ministry of Health, Labor and Welfare (Tokyo, Japan).

Pathological assessment of CRLM

The pathologic liver resection specimens were fixed in formalin, embedded in paraffin, and stained with hematoxylin-eosin. All specimens were sectioned into 5-mm-thick slices. The slice revisions were performed by experienced pathologists. Pathologic response was evaluated based on the histologic criteria for the assessment of response to chemotherapy in the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma: the 3rd English Edition,[15] and classified into 5 subgroups, as follows. Grade 0 (no effect) was categorized as no tumor cell necrosis or degeneration in response to treatment. Grade 1a (minimal effect) was categorized as tumor cell necrosis or degeneration in less than one-third of the entire lesion. Grade 1b (mild effect) was categorized as tumor cell necrosis or degeneration in more than one-third but less than two-thirds of the entire lesion. Grade 2 (moderate effect) was categorized as prominent tumor cell necrosis, degeneration, lytic change, and/or disappearance present in more than two-thirds of the entire lesion, but remaining viable tumor cells.

Grade 3 (marked effect) was categorized as necrosis and/or lytic change throughout the entire lesion and replaced by fibrosis with or without granulomatous change, and no viable tumor cells. In this analysis, no patient was Grade 0, and patients in the PC group were divided into 2 subgroups, Grade 1 (1a/1b) and Grade 2/3. For patients with multiple CRLMs, all resected lesions were evaluated using this same procedure. The pathologic characteristics of liver metastases were assessed based on patient-related analyses, and if the grades were different between metastases within a patient, the most advanced (lowest) grade was adopted.

Treatment strategies for CRLM

Since synchronous CRLM is considered a systemic disease, our treatment strategy is to resect the primary tumor, followed by hepatectomy for cases in which distant metastasis can be controlled. However, metastatic lesions affecting the superficial layer or limited to a single hepatic lobe and solitary lesions may be resected with the primary tumor synchronously.

We reported previously that the tumor shrinkage effect reaches a plateau in approximately 100 days based on the radiologic response of tumor shrinkage and drug-resistance mechanisms.[16,17] Based on this evidence, including the findings of the past trials,[18–20] following the approval of a multidisciplinary team, 6 cycles of oxaliplatin-based PC with molecular targeted drug therapy were administered to patients with borderline or unresectable CRLM that was in extensive contact with the root of the major hepatic veins or Glisson's capsules or who had insufficient residual liver volume. For patients with resectable CRLM, based on the results of the new EPOC trial,[21] 6 cycles of oxaliplatin-based PC without molecular targeted drug therapy were administered. In this study, the initial resectability rate was 100% in the non-PC group, compared with 79% in the PC group. For patients referred from other hospitals and patients with a complicated medical history, such as renal dysfunction, the regimen, duration, and timing of chemotherapy were decided at the discretion of the attending surgeon and medical oncologist in each case.

Hepatectomies for CRLM were nonanatomic hepatectomies with a single-stage strategy and were performed more than 4 weeks after the last cycle of oxaliplatin-based chemotherapy. Although hepatectomy is normally a nonanatomic procedure, anatomic hepatectomy may be performed for multiple liver metastases with consideration of the perfusion area and residual liver volume in relation to the vessels.

Preoperative chemotherapy

The following chemotherapy regimens were administered before hepatectomy: FOLFOX (n = 9); FOLFOX with bevacizumab (n = 9); FOLFOX with cetuximab (n = 8); FOLFOX with panitumumab (n = 5); capecitabine and oxaliplatin (CAPOX) with bevacizumab (n = 2); 5-fluorouracil/leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) with bevacizumab (n = 1); LV5FU2 with bevacizumab (n = 1); CAPOX (n = 1); and S-1 (n = 1). Some patients received 2 lines of chemotherapy: FOLFOX with panitumumab followed by LV5FU2 with bevacizumab (n = 1), FOLFOX with bevacizumab followed by CAPOX with bevacizumab (n = 1), S-1 with oxaliplatin (SOX) followed by FOLFOX with bevacizumab (n = 1), FOLFOX with bevacizumab followed by FOLFIRI (n = 1), FOLFOX followed by FOLFIRI (n = 1), and FOLFIRI followed by FOLFOX (n = 1), The median (range) duration and number of cycles of chemotherapy per patient were 3.5 (2–13) months and 6 (3–21), respectively.

Definitions

Liver metastases were classified into 3 subgroups, H1 to H3, based on the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma.[15] The H1 subgroup comprised patients with 1 to 4 metastatic tumors, all of which were $\leq$5 cm in maximum diameter. The H3 subgroup comprised patients with 5 or more metastatic tumors, at least 1 of which was >5 cm in maximum diameter. The H2 subgroup comprised patients who did not meet the criteria of either H1 or H3. Lymphatic and venous invasions were also classified based on the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma.[15] The radiological response of liver metastasis was assessed according to the revised Response Evaluation Criteria In Solid Tumors (RECIST), version 1.1.[22]

In this study, surgical margin status was defined by distance to the closest liver resection's surface, and surgical margin negative was defined as no microscopic evidence of the tumor in the liver resection margin with more than a 1-mm negative surgical margin. Postoperative complications were classified according to the Clavien-Dindo classification, with Grade 3a or worse defined as a major

Table 1 Patient characteristics

Characteristic	Non-PC group (n = 26)	PC group (n = 43)	*P*
Age	62.5 [38–83]	65 [38–81]	0.73
Sex, male, n (%)	19 (73)	29 (67)	0.79
BMI at hepatectomy	21.2 [17.6–27.5]	22.6 [17.5–31.6]	0.34
Primary tumor characteristics, n (%)			
Right-side colon (Tumor location)	4 (15)	8 (19)	0.99
Differentiated adenocarcinoma (Histology)	26 (100)	40 (95)	0.52
T4a/b (depth of tumor invasion)	11 (42)	19 (45)	1
Lymph node metastasis	22 (85)	34 (81)	0.76
Severe lymphatic invasion (Ly1c)	5 (19)	5 (12)	0.49
Severe venous invasion (V1c)	9 (35)	15 (37)	1
RAS mutation	1 (20)[a]	11 (37)[b]	0.64
Liver metastasis characteristics (at pretreament)			
Number of liver metastases	1 [1–6]	4 [1–65]	0.14
Liver metastasis (H1/H2/H3)	3/3/2020	17 / 23 / 3	0
Bipolar liver metastasis, n (%)	8 (31)	27 (63)	0.02
Resectable/Unresectable	26 / 0	34 / 9	0.03
Maximum tumor size (mm)	24 [7–84]	26 [3–167]	0.39
Clinical response of PC (CR/PR/SD/PD)	-	1/28/12/1[c]	

BMI, body mass index; CR, complete response; PC, preoperative chemotherapy; PD, progressive disease; PR, partial response; SD, stable disease.

[a]Not available for 21 patients.

[b]Not available for 13 patients.

[c]Not available for 1 patient.

complication. All complications that developed within 90 days after hepatectomy were included.

OS was defined as the interval between the date of the first treatment and the date of death from any cause or the last follow-up day. RFS and remnant liver-RFS were defined as the interval between the date of the initial hepatectomy for CRLM and the date of diagnosis of recurrence (RFS) or remnant liver after initial hepatectomy (remnant liver-RFS).

Statistical analysis

Categorial variables were expressed as proportions, and numerical variables were expressed as median and range. All *P* values were 2 sided, and *P* values of 0.05 or less were considered statistically significant. Univariate analysis results were compared with the Student's *t*-test, χ^2 test, Mann-Whitney *U* test, or Fisher's exact test, as appropriate. Categorical variables were compared with the χ^2 test, and continuous variables with the independent sample Student's *t*-test. Survival curves were calculated with the Kaplan-Meier method and compared with the log-rank test (univariate analysis) or Cox proportional hazards regression (multivariate analysis). All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphic user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.[23]

Results

Patient characteristics

Between June 2004 and December 2018, 69 patients with synchronous CRLM underwent initial hepatectomy for CRLM at Gifu University Hospital in Gifu City, Japan. Patient characteristics are shown in Table 1. There was no difference between the PC and non-PC groups in the side, histologic type, tumor depth of T4, lymph node metastasis, and severe lymphatic and venous vessel invasion of the primary tumor. There were more patients with H1 liver metastasis (77% versus 40%) and resectable metastasis (100% versus 79%) in the non-PC than PC group. More patients in the non-PC group underwent synchronous resection with the primary tumor and received adjuvant chemotherapy after initial hepatectomy (Table 2).

PC responses

According to the RECIST 1.1 criteria, 1 patient (2%) achieved a complete response (CR), 28 patients

Table 2 Preoperative laboratory data and surgical outcomes

	Non-PC Group (n = 26)	PC Group (n = 43)	*P*
At pretreatment			
CEA (ng/mL)	7.9 [1.8–1026]	33.3 [1.2–1803]	0.06
CA19–9 (U/mL)	29.6 [2.0–1880]	23.7 [0.1–6727]	0.51
At hepatectomy			
CEA (ng/mL)	7.9 [1.6–1530]	3.8 [1.1–2416]	0.12
CA19–9 (U/mL)	29.6 [2.0–3190]	16.6 [0.1–2204]	0.32
Modified Glasgow Prognostic Score 0/1/2	19/4/1[a]	33/9/0[b]	0.41
CRP/albumin ratio	0.029 [0.005–0.60]	0.022 [0.005–1.39]	0.89
Prognostic Nutritional Index	48.8 [37.8–56.9]	47.7 [37.0–63.6]	0.36
Neutrophil/Lymphocyte Ratio	2.37 [0.87–6.88]	1.98 [0.96–6.87]	0.36
Platelet/Lymphocyte Ratio	162 [60–435]	156 [52–373]	0.41
Lymphocyte/Monocyte Ratio	3.8 [1.9–10.4]	4.2 [1.3–10.0]	0.65
Operative factors			
Synchronous resection with primary tumor, n (%)	21 (81)	3 (7)	< 0.001
Operative procedure (anatomic hepatectomy), n (%)	8 (31)	21 (49)	0.22
Operative time (min)	421 [201–562]	303 [126–658]	< 0.001
Amount of bleeding (mL)	800 [70–2595]	380 [65–3080]	0.02
Transfusions, n (%)	7 (27)	2 (5)	0.02
With ablation (MCT, RFA), n (%)	3 (12)	5 (12)	1
Surgical margin positive status (<1 mm), n (%)	6 (23)	13 (30)	0.71
Postoperative factors, n (%)			
Postoperative complication (Clavien-Dindo ≥ 3a)	8 (31)	8 (19)	0.39
Mortality	0	0	
Adjuvant chemotherapy after hepatectomy	21 (81)	22 (51)	0.02
Re-hepatectomy after recurrence	6 (38)	9 (29)	0.79
Metastasectomy after recurrence (including re-hepatectomy)	10 (63)	12 (43)	0.35

CEA, carcinoembryonic antigen; CRP, C-reactive protein; MCT, microwave coagulation therapy; PC, preoperative chemotherapy; RFA, radiofrequency ablation therapy.

[a]Not available for 2 patients.

[b]Not available for 1 patient.

(67%) achieved partial responses (PR), 12 (29%) showed stable disease (SD), 1 (2%) showed disease progression (PD), and 1 patient was unable to be evaluated because of a lack of images.

Long-term survival

The median (range) follow-up period was 57 (8–193) months. The median survival and 5-year OS rates in the PC and non-PC groups were 80.9 months and 61.5%, respectively, in the PC group and 71.7 months and 61.5%, respectively, in the non-PC group ($P = 0.867$; Fig. 2A). Univariate regression analysis identified severe lymphatic invasion in the primary tumor ($P = 0.002$), H2/3 liver metastasis at pretreatment ($P = 0.029$), and surgical margin positive status ($P = 0.004$) as positively associated with poor prognosis, whereas PC was not associated with prognosis ($P = 0.867$; Table 3). Multivariate analysis revealed that severe lymphatic invasion in the primary tumor (hazard ratio 4.185, $P = 0.005$) was an independent factor predicting poor OS.

As shown in Fig. 2, there were no significant differences between the PC and non-PC groups in RFS and remnant liver-RFS. The 5-year RFS rates in the PC and non-PC groups were 32.4% and 21.7%, respectively ($P = 0.087$; Fig. 2B). The 5-year remnant liver-RFS rates in the PC and non-PC groups were 44.0% and 36.3%, respectively ($P = 0.291$; Fig. 2C). Multivariate analysis revealed that tumor invasion to the serosa or adjacent structures (T4a/b) of the primary tumor (hazard ratio 1.897, $P = 0.034$) and surgical margin positive status (hazard ratio 2.453, $P = 0.006$) were associated with a high rate of recurrence. Multivariate analysis also revealed that a positive surgical margin (hazard ratio 2.597, $P = 0.008$) was associated with a high rate of remnant liver recurrence.

Analysis of OS, RFS, and remnant liver-RFS according to histologic response to chemotherapy in the PC group

We divided the PC group into 2 groups, the Grade 1 (n = 27) and Grade 2/3 (n = 16) groups, and compared their OS, RFS, and remnant liver-RFS.

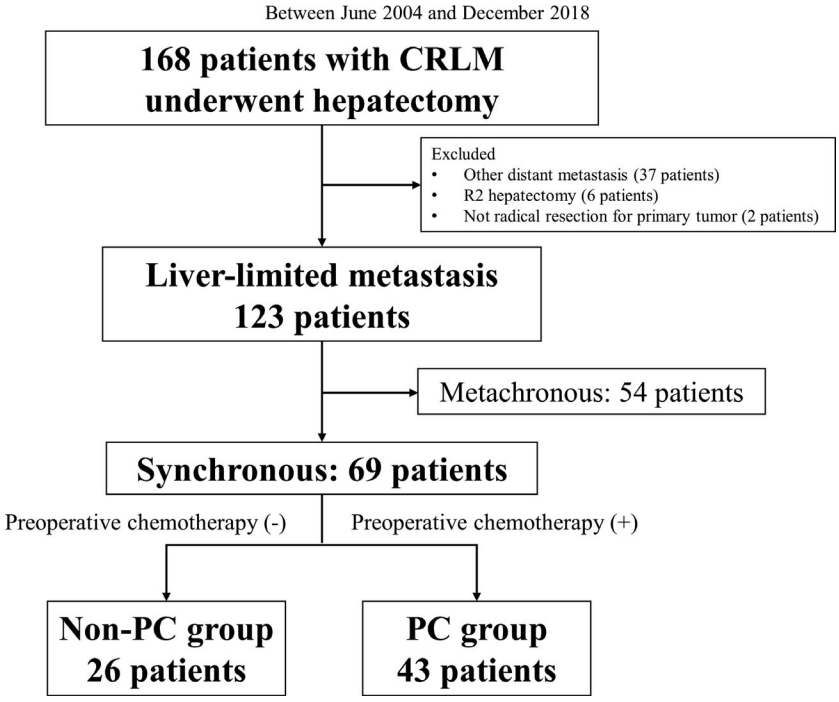

Fig. 1 Flowchart of the patient selection process.

There was no significant difference in the characteristics of the primary tumor and liver metastasis between the Grade 1 and Grade 2/3 groups (Table 4). Regarding the PC regimen, the anti–epidermal growth factor receptor (EGFR) (cetuximab/panitumumab) regimen tended to be more commonly administered in the Grade 2/3 group ($P = 0.09$). In the Grade 2/3 group, the carcinoembryonic antigen (CEA) value at hepatectomy was lower than in the Grade 1 group ($P = 0.004$). Regarding radiological response (PR/CR) based on RECIST image evaluation and surgical margin, the Grade 2/3 group tended to have more CR/PR (88%) and less surgical margin positive status (13%). The median 5-year OS in the Grade 2/3 group (70 months, 86.7%) was significantly longer than that in the Grade 1 group (58 months, 45.9%, $P = 0.008$; Fig. 3A). Moreover, the median 5-year RFS in the Grade 1 and 2/3 groups was significantly different, at 6.7 months and 45 months, respectively ($P = 0.002$; Fig. 3B). In addition, the median 5-year remnant liver-RFS was significantly longer in the Grade 2/3 group (65 months) than in the Grade 1 group (8 months, $P < 0.001$; Fig. 3C).

Discussion

The present retrospective study demonstrated that PC in patients with synchronous CRLM did not prolong OS and RFS. The results of this study are in accordance with those of recent studies. Following the phase III trial of the European Organization for Research and Treatment of Cancer Intergroup (EORTC) trial 40983,[24] the Guidelines of the National Comprehensive Cancer Network[25] and the European Society for Medical Oncology (ESMO)[26] recommended perioperative adjuvant chemotherapy for CRLM. However, there was no significant difference in survival in the intention-to-treat analysis of EORTC trial 40983, and it was later reported that OS in a preoperative FOLFOX group was not better than in a surgery-alone group (hazard ratio 0.87, 95% CI 0.66–1.14, $P = 0.303$) at a subsequent 5-year follow-up. A systematic review also reported similar survival outcomes of PC.[27] The ESMO guidelines, revised in 2016, recommended surgery alone and postoperative chemotherapy in addition to perioperative chemotherapy for technically resectable CRLM.[9] As most studies were retrospective and included some biases, the debate as to whether PC or surgery alone is best is still ongoing. Only 1 prospective study is currently in progress,[28] and the results of this study are awaited.

PC for CRLM is expected to have an effect of securing a cancer-free surgical margin due to tumor shrinkage (improvement of R0 resection rate), early treatment and suppression of micrometastases, and determination of the response to chemotherapy. Based on the findings of the present study, these

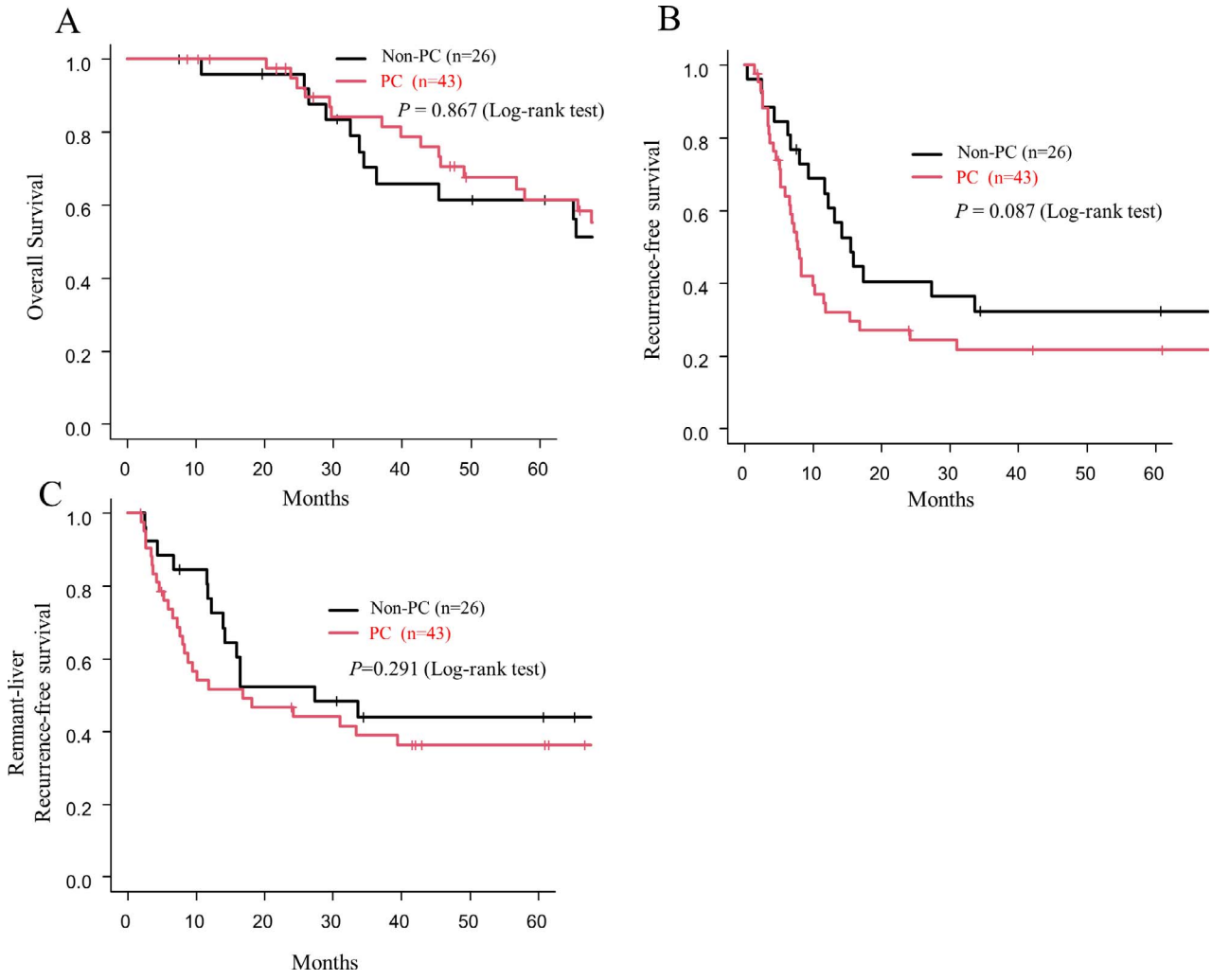

Fig. 2 Long-term survival in the non-PC and PC groups. (A) OS. (B) RFS. (C) Remnant liver- RFS. OS was calculated from the date of the first treatment for CRLM. RFS and remnant liver-RFS were calculated from the date of the initial hepatectomy.

expected effects of PC are limited, because there were no differences in survival and cancer-free surgical margin rate if chemotherapy was or was not administered before hepatectomy; therefore, PC should not be administered routinely to all patients with CRLM. However, in the subgroup analysis based on the histologic response to PC, the Grade 2/3 group (responders) achieved a higher cancer-free surgical margin rate, and prolonged OS, RFS, and remnant liver-RFS than the Grade 1 group (nonresponders). This means that some patients derive a survival benefit from PC, and there is a prognostic significance of the histologic response to PC in patients with synchronous CRLM. Similar to this result, many studies recently reported that responders to PC had a better prognosis after hepatectomy than nonresponders.[29–31]

Tanaka *et al*[32] reported that 23 patients with 81 CRLMs presented with a complete pathologic response (Grade 3) to PC, and patients with at least 1 metastasis confirmed to achieve a complete pathologic response had a better survival than those with no complete pathologic response. However, in this study, OS in 7 patients (16%) with at least 1 metastasis confirmed to achieve a complete pathologic response (Grade 3) was not significantly longer than in those with no complete pathologic response ($P = 0.113$). We speculate that the variations in CRLMs and their influences on survival are a possible reason for this. In this study, 2 patients with a Grade 3 response (29%) and 6 patients (16%) with multiple CRLMs had different grades of metastases within a patient. Cai *et al*[33] recently reported that tumor heterogeneity, manifesting as

Table 3 Univariate and multivariate analysis of clinicopathological variables for OS, RFS, and remnant liver-RFS

	OS				RFS				Remnant liver-RFS			
	Univariate	Multivariate analysis			Univariate	Multivariate analysis			Univariate	Multivariate analysis		
Variable	*P*	Hazard ratio	95% CI	*P*	*P*	Hazard ratio	95% CI	*P*	*P*	Hazard ratio	95% CI	*P*
Age (≥65)	0.92				0.13				0.15			
Sex (male)	0.6				0.08				0.46			
Right-side colon cancer	0.2				0.43				0.47			
T4a/b of primary tumor	0.14				0.021	1.897	1.051–3.423	0.03	0.29			
Lymph node metastasis of primary tumor	0.69				0.56				0.44			
Ly1c of primary tumor	0.002	4.185	1.538–11.39	0.01	0.048			0.26	0.58			
V1c of primary tumor	0.99				0.24				0.15			
RAS mutation	0.83				0.13				0.46			
H2/3 liver metastasis (Tumor number ≥5 or Maximum size >50 mm)	0.029			0.06	0.003			0.06	0.003			0.07
CEA at hepatectomy (≥5)	0.47				0.15				0.048			0.12
CA19–9 at hepatectomy (≥37)	0.99				0.75				0.1			
Preoperative chemotherapy	0.87				0.09				0.29			
Synchronous resection with primary tumor	0.56				0.63				0.91			
Transfusions	0.53				0.66				0.42			
With ablation (MCT, RFA) at hepatectomy	0.3				0.57				0.36			
Surgical margin positive status (<1 mm)	0.004			0.11	< 0.001	2.453	1.299–4.630	0.01	< 0.001	2.597	1.283–5.255	0.01
Postoperative complication (≥3a)	0.34				0.63				0.14			
Adjuvant chemotherapy after hepatectomy	0.44				0.45				0.75			

CEA, carcinoembryonic antigen; MCT, microwave coagulation therapy; OS, overall survival; RFA, radiofrequency ablation therapy; RFS, recurrence-free survival.

Table 4 Patient characteristics between the Grade 1 and Grade 2/3 groups

	Grade 1 Group (n = 27)	Grade 2/3 Group (n = 16)	*P*
Age	63 [38–81]	66 [54–75]	0.36
Sex, male, n (%)	20 (74)	9 (56)	0.38
BMI at hepatectomy	22.6 [17.5–31.6]	21.9 [18.1–30.8]	0.71
Primary tumor characteristics, n (%)			
Right-side colon (Tumor location)	3 (11)	5 (31)	0.13
Differentiated adenocarcinoma (Histology)	25 (96)	15 (94)	1
T4a/b (Depth of tumor invasion)	15 (58)	4 (25)	0.08
Lymph node metastasis	20 (77)	14 (88)	0.69
Severe lymphatic invasion (Ly1c)	4 (16)	1 (6)	0.63
Severe venous invasion (V1c)	9 (36)	6 (38)	1
RAS mutation	8 (47)[a]	4 (27)[b]	0.5
H2/3 liver metastasis (Tumor number ≥5 or Maximum size >50 mm)	17 (63)	9 (56)	0.91
PC, n (%)			
Oxaliplatin	26 (96)	15 (94)	1
Irinotecan	4 (15)	0 (0)	0.28
Capecitabine	2 (7)	2 (13)	0.62
Bevacizumab	13 (48)	4 (25)	0.24
Cetuximab / Panitumumab	6 (22)	8 (50)	0.09
PC duration (mo)	3.5 [2–13]	3.5 [2–6]	0.88
Response rate (CR/PR) according to the RECIST image evaluation, n (%)	15 (58)[c]	14 (88)	0.08
CEA at hepatectomy (ng/mL)	6.1 [1.1–2416]	2.6 [1.1–18.7]	0
CA19–9 at hepatectomy (U/mL)	29.5 [0.1–2205]	12.6 [0.1–118]	0.19
Operative factors			
Operative time (min)	249 [126–658]	274 [180–394]	0.9
Amount of bleeding (mL)	380 [80–3080]	383 [65–770]	0.46
With ablation (MCT, RFA), n (%)	3 (12)	2 (13)	1
Surgical margin positive status (<1 mm), n (%)	11 (41)	2 (13)	0.09
Postoperative factors, n (%)			
Postoperative complication (Clavien-Dindo ≥ 3a)	5 (19)	3 (19)	1
Adjuvant chemotherapy after hepatectomy	12 (57)	10 (71)	0.62
Re-hepatectomy after recurrence	7 (30)	2 (22)	1
Metastasectomy after recurrence	8 (40)	4 (44)	1

BMI, body mass index; CEA, carcinoembryonic antigen; CR, complete response; MCT, microwave coagulation therapy; PC, preoperative chemotherapy; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; RFA, radiofrequency ablation.

[a]Not available for 21 patients.

[b]Not available for 10 patients.

[c]Not available for 1 patient.

differences in metastatic tumor burden and chemotherapy sensitivity, exists among liver metastases and results in pronounced discrepancies in grade scores in the same patient after PC.[11] They also reported that the worst metastasis (highest score of tumor regression grade) was considered as the reference in such cases. In this study, we used the same adoption method, and there was no significant difference in survival except for this study's classification that separated the Grade 1 and Grade 2/3 groups. Therefore, this study's histologic criteria according to the residual tumor amount are considered to be appropriate for prognosis prediction.

Some studies recently reported that the radiologic morphology of CRLM after PC also predicts postoperative outcomes.[12,34] In this study, there was a correlation between histologic response (Grade 2/3) and radiologic response (PR/CR), but there was no significant difference in survival between the PR/CR and SD/PD groups according to the revised RECIST image evaluation. For this reason, it is considered that the morphologic changes with bevacizumab were not sufficiently reflected in the RECIST image evaluation. Based on the findings of the present study, histologic assessment is considered to be superior to radiologic response for predicting prognosis.

We also showed that surgical margin positive status (< 1 mm) was associated with a high rate of remnant liver recurrence. However, contradictory

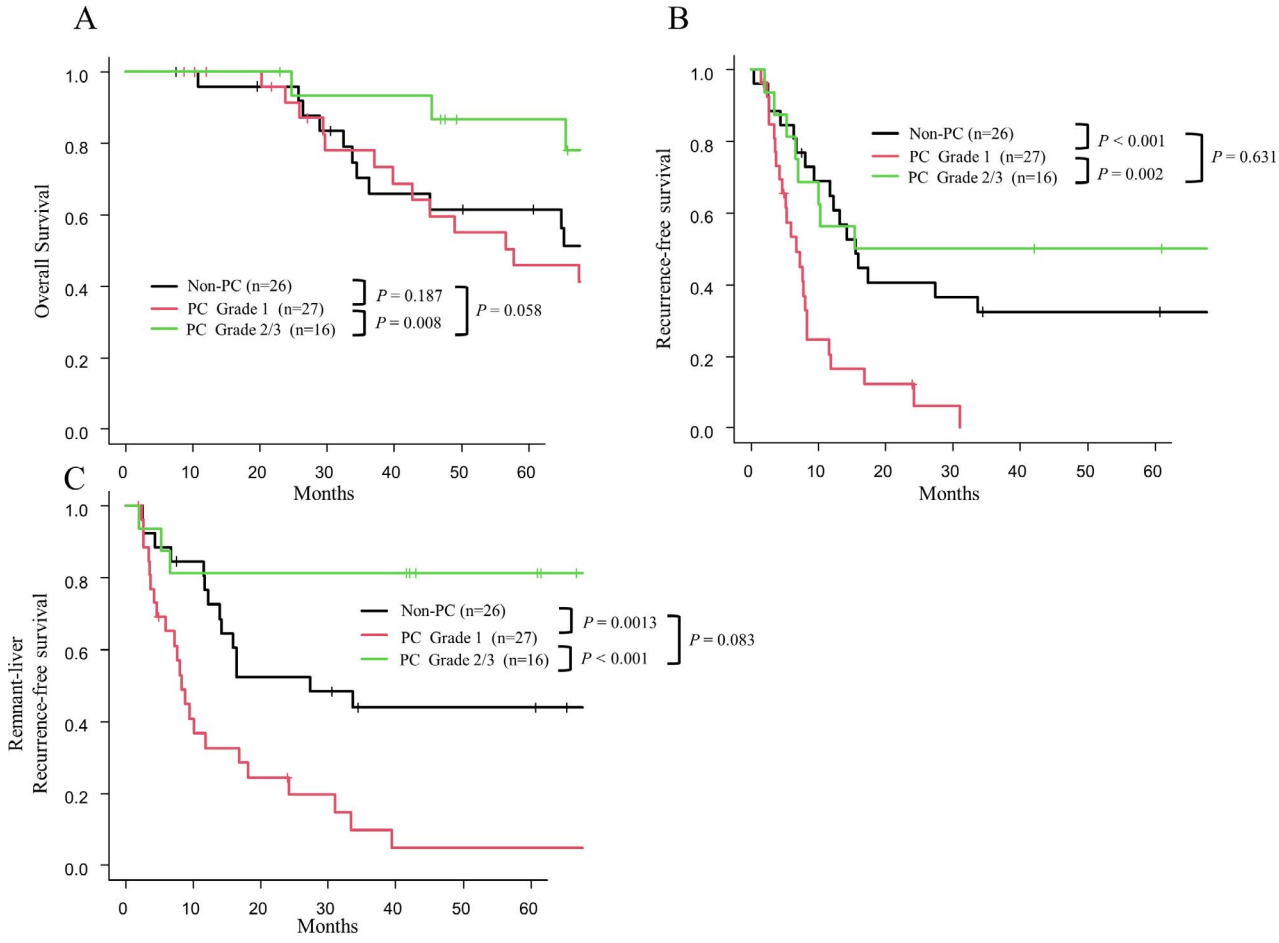

Fig. 3 Long-term survival in the non-PC, Grade 1 and Grade 2/3 groups. (A) OS. (B) RFS. (C) Remnant liver-RFS.

outcomes in the literature are reported, in which OS and disease-free survival (DFS) are similar for patients with surgical margin negative or positive status.[35] The most likely reason for this is difficulty of accurate assessment of the resection margin in hepatic surgery, and current techniques of gross evaluation after formalin fixation may bias actual measurement of the surgical margin.[36] Moreover, the friability of the liver itself can cause the liver to crack, making assessment of the true resection margin difficult. However, recent large meta-analyses have strongly suggested that a tumor-free surgical margin of more than 1 mm is sufficient for achieving long-term DFS in patients with CRLMs, and 31% of CRLMs had micrometastases that were located far from the metastatic tumor edge.[37–39] In our subgroup analysis of the PC group, surgical margin positive status (<1 mm) was associated with a high rate of remnant liver recurrence. Therefore, we suggest that a cancer-free surgical resection margin of more than 1 mm should be achieved in all patients with CRLM, irrespective of PC administration.

The present study had some limitations. First, because it was a single-center retrospective study, the number of patients was limited. Second, the greatest limitation is that the PC regimens were not uniform due to patient referrals from other hospitals and patient past medical histories. Moreover, the patients in the PC group had a more advanced stage of hepatic metastasis pretreatment. The initial resectability rate was 100% in the non-PC group, compared with 79% in the PC group. More patients in the non-PC group underwent synchronous resection of the primary tumor, possibly because of easier resectability. These differences in resectability characteristics may have also affected the survival results in the present study and could be a major source of bias in this study. Regarding the effect of PC, initially unresectable CRLM became resectable after PC in 7 patients. However, it is not clear how PC increases the actual resection rate, as we did not

know the exact total number of cases with initially unresectable CRLM.

To whom PC should be administered is unclear, but the Grade 2/3 group had a significantly lower CEA value after neoadjuvant chemotherapy than the Grade 1 group. The reduced CEA value after neoadjuvant chemotherapy may predict a good histologic response to PC. Neofytou *et al*[29] also reported that the CEA value following PC was correlated with prognosis. Recent studies reported an association of circulating tumor DNA (ctDNA) with recurrence in patients with CRC, and a strategy based on ctDNA detection was recommended.[40,41] We also reported previously that MYC upregulation is a useful biomarker for selecting anti-EGFR combination therapy in PC for CRLMs,[42] and evaluation of genomic information has become essential in planning CRC treatment.

Although the present study provides significant findings, a prospective study with uniform PC regimens and patient characteristics, including sufficient genomic information, is needed. In the near future, the development of individualized treatment strategies for CRLM based on evaluation of various types of genetic information is expected.

Conclusion

In conclusion, PC did not prolong survival in patients with synchronous liver-limited metastases. Therefore, PC should not be given routinely to all patients with synchronous CRLMs. However, some patients benefit from PC, and histologic response to PC had prognostic significance for patients with CRLMs. In the future, it is predicted that genomic identification for individualized treatment will guide the administration of PC for resectable CRLMs.

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