Analysis of Response Evaluation Criteria in Solid Tumors reduction ratio of primary chemotherapy in unresectable advanced or recurrent colorectal cancer

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Received September 13, 2018; Accepted June 14, 2019

DOI: 10.3892/mco.2019.1894

Abstract. Response Evaluation Criteria in Solid Tumors (RECIST) is used to assess the objective response of solid tumors to treatment. However, it remains unclear to what extent the response rate assessed by RECIST reflects a reduction of tumor size in multiple organs in patients with unresectable advanced or recurrent colorectal cancer (CRC) with multiple organ metastases. It is also unclear whether the management of liver metastases with systemic chemotherapy in CRC patients with multiple organ metastases improves their prognosis, although surgical resection has been shown to be the most effective treatment approach to CRC cases with liver metastases. A total of 38 CRC patients who underwent systemic chemotherapy in Kyushu Medical Center Hospital between January 2013 and April 2016 were examined. The patients had measurable lesions in multiple organs, including the liver, and did not undergo curative surgery for metastatic lesions after initiation of chemotherapy. The association between the total reduction ratio (TRR) of all lesions and liver lesion reduction ratio (LRR) was retrospectively analyzed. A total of 18 patients (47%) had H3 liver metastases, and the median liver lesion occupancy rate in the sum of the measured lesions with RECIST was 76%. TRR and LRR were strongly correlated, regardless of the volume of the liver metastases. Although a TRR of >30% was significantly associated with improved overall survival (OS), this improvement was not observed in patients with H3 liver metastases. TRR was correlated with LRR and was associated with a better OS. CRC patients with both multiple organ and H3 liver metastases exhibited poor survival, even with a high reduction ratio by chemotherapy.

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Key words: colorectal cancer, liver metastases, multiple organ metastases, Response Evaluation Criteria In Solid Tumors, liver resection

Introduction

Colorectal cancer (CRC) is the third most common malignancy and the fourth leading cause of cancer-related mortality worldwide (1,2). The improvement in treatments for unresectable advanced or metastatic CRC (mCRC) has markedly changed its prognosis over the past few decades (3-13), and the median overall survival (OS) and progression-free survival (PFS) are currently approaching 30 and 10 months, respectively (14,15). Although PFS has been recognized as a surrogate parameter for OS, the possible effect of post-progression treatments on OS is often considered. A randomized phase 3 trial (First-Line Treatment For Patients With Metastatic Colorectal Cancer-3) examining first-line chemotherapy for mCRC demonstrated that the depth of response (DpR) was correlated with survival time (16). Thus, DpR may also be considered as a surrogate endpoint for OS (4,16,17).

Controlling liver metastases is an important factor for improving OS in CRC patients with limited liver metastases, as several studies have demonstrated that the resection of liver metastases led to a better prognosis compared with hepatectomy after chemotherapy (18-22). In addition, adequate control of extrahepatic lesions is not necessarily associated with favorable survival when liver metastases persist (23). Furthermore, regardless of recurrence in the liver or extrahepatic organs following hepatectomy, hepatectomized patients had a significantly better prognosis compared with patients not undergoing resection (22,24-27). The Japanese Society for Cancer of the Colon and Rectum 2014 guidelines for the treatment of CRC recommend surgical resection of liver metastases when the liver lesions become resectable following

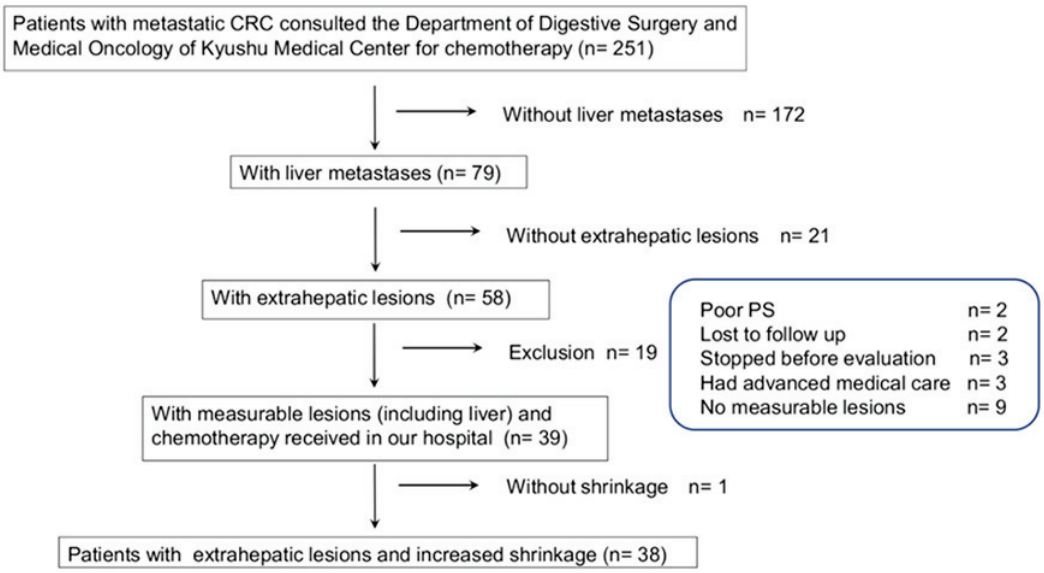

Figure 1. Flowchart of the study population selection process. CRC, colorectal cancer; PS, performance status.

systemic chemotherapy (28-32). However, it remains unknown whether it is also meaningful to control liver metastases by chemotherapy in CRC patients with metastases to multiple organs.

The Response Evaluation Criteria In Solid Tumors (RECIST) has been adopted as a widely accepted method for assessing the objective response of solid tumors to treatment (18). In RECIST version 1.0, the definition of response is a 30% decrease in the sum of diameters of measurable lesions in up to five organs (18). The number of lesions required to assess tumor burden for response determination was reduced from a maximum of 10 to 5 in the 2009 revision of RECIST guidelines (18), based on evidence that 5 measurable lesions was the minimum number of target lesions that did not cause meaningful changes in the reduction ratio (RR) (33). This revision may provide convenient and reproducible lesion measurements in clinical trials. Assessing the echange in tumor burden is crucial for evaluating tumor response, as both objective tumor response and PFS time are used as endpoints in clinical trials; these parameters are also key to assessing the effectiveness and appropriate selection of treatment in clinical practice. There are no data that analyze the RR for each metastatic organ. Particularly in mCRC, liver metastases are subdivided as H1-H3 according to tumor volume; however, it remains unknown how the degree of shrinkage differs for each case with various tumor volumes of liver metastases.

The aim of the present study was to investigate CRC cases with multiple organ metastases, including the liver, in order to analyze how the TRR is correlated with the LRR and to evaluate whether tumor reduction and the control of liver metastases with systemic chemotherapy can improve patient prognosis.

Patients and methods

Patients and definition of response. This was a retrospective study on the primary systemic chemotherapy of CRC patients with multiple metastases to the liver and other organs. Between April 2013 and April 2016, we screened 251 patients with CRC who received consult for the purpose of chemotherapy at the Department of Gastrointestinal Surgery and the Department of Medical Oncology of Kyushu Medical Center Hospital. Among those, 172 patients without liver metastases, 21 patients without extrahepatic lesions and 9 patients without measurable lesions in the liver and extrahepatic organs were excluded. Other patients who were excluded from the analyses were as follows: 2 patients who were unsuitable for chemotherapy due to poor performance status (PS), 2 patients who were lost to follow-up, 3 patients who did not receive chemotherapy prior to the evaluation, 3 patients whose insurance did not cover combined advanced healthcare services, and 1 patient who did not achieve tumor reduction by chemotherapy, as the present study evaluated RR. Finally, 38 patients who had measurable lesions in both the liver and extrahepatic organs, and who were able to continue chemotherapy at our hospital, were analyzed (Fig. 1). Clinical information, including age, sex, Eastern Cooperative Oncology Group PS, *RAS* mutation status, chemotherapy regimen, primary tumor site, H stage of liver metastases, tumor RR, treatment duration of primary chemotherapy and survival time, was obtained from medical records. H stage was determined by the number of liver metastases and size of the largest liver metastatic lesion: H1; ≤4 lesions, and lesions ≤5 cm in diameter, H2; ≥5 lesions, or lesions ≥5 cm in diameter, and H3; ≥5 lesions, and lesions ≥5 cm in diameter (17,34). The study protocol was approved by the ethics committee of Kyushu Medical Center Hospital.

The treatment duration of primary chemotherapy was defined as the time from the first day of chemotherapy to the day on which the regimen was changed, or to the date of death from any cause. OS was defined as the time from the first day of chemotherapy to the last day on which the patient was confirmed to be alive, or to the date of death from any cause. For the total lesion reduction ratio (TRR), the selection of measurable lesions and calculation of the RR were conducted according to the RECIST. To evaluate the liver lesions, measurable lesions were selected (up to two lesions in each

Table I. Clinical characteristics of enrolled patients (n=38).

Characteristics	Number (%)
Age, years	
<65	18 (47)
≥65	20 (53)
Mean 66.2, median 65	
Sex	
Male	18 (47)
Female	20 (53)
ECOG-PS	
0	18 (47)
1	17 (45)
2	3 (8)
Primary tumor site	
Ascending colon	10 (26)
Transverse colon	5 (13)
Descending colon	1 (3)
Sigmoid colon	13 (34)
Rectum	9 (24)
H stage	
H1	9 (24)
H2	11 (29)
H3	18 (47)
RAS	
Wild-type	22 (58)
Mutation	12 (32)
Unknown	4
Resection of primary site	
Resection	18 (47)
No resection	20 (53)
Liver resection	
Resection	22 (58)
No resection	16 (42)
Targeted agents	
Bevacizumab	29 (76)
Anti-EGFR antibody	0
None	9 (24)
Chemotherapy	
Two-drug combination	33 (86)
Single-agent	5 (14)
Extrahepatic measurable lesions	
Lung	11
Peritoneum	5
Lymph nodes	23
Other	4
Median liver occupancy	76% (16-94%)
Median OS (days)	665 (95% CI: 507.9-822)

organ) according to the RECIST, the sum of the major diameters of the hepatic and extrahepatic lesions (short diameter for lymph nodes) was measured, and the reduction ratio at the

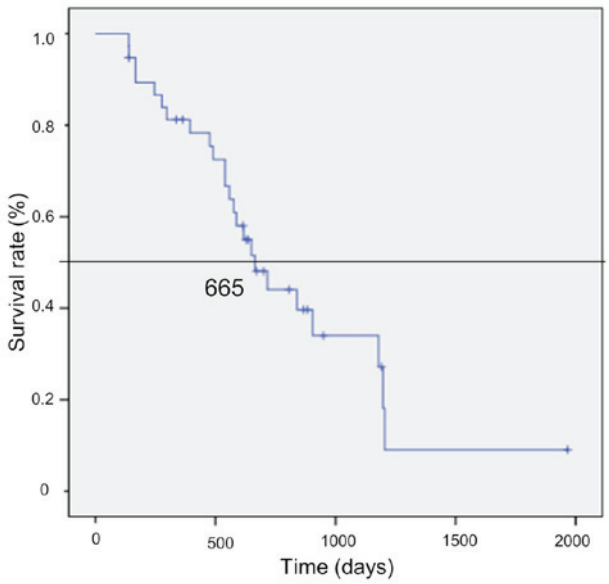

Figure 2. Overall survival of all 38 patients. The median survival time was 22.3 months (95% confidence interval: 16.9-27.4 months).

time of maximum reduction against pretreatment was calculated. The reduction ratio of all lesions assessed by RECIST was expressed as the TRR and the reduction ratio of only liver lesions was expressed as the liver lesion reduction ratio (LRR). Patients who developed a recurrence following hepatectomy are included in this study. In our hospital, the indications of hepatectomy for each case in which the surgeons consider it technically feasible to resect both the primary tumor and liver metastases, and which can withstand surgery and the disease state is stable, are discussed in a multidisciplinary joint conference.

Statistical analysis. Pearson's correlations were applied to determine the association between TRR and LRR. Partial correlation analysis was used to assess this association controlling for H stage. Univariate and multivariate analyses of factors associated with OS were calculated with Cox regression survival analysis. OS and duration of primary chemotherapy were calculated with the Kaplan-Meier method, and differences between survival curves were analyzed by the log-rank test. A difference was considered statistically significant when the two-sided P-value was <0.05. Patient categorical variables and characteristics between H1/2 and H3 liver metastases were compared using the Fisher's exact test and Student's t-test, respectively.

Results

Patient characteristics. The clinical characteristics of the 38 patients who were finally enrolled in this study are listed in Table I. The study population included 18 (47%) men. The median age at diagnosis was 65 years (range, 44-84 years). The majority of the patients had a PS of 0 or 1, but the PS of 3 patients was 2 (8%). The primary sites were as follows: 10 cases in the ascending colon (26%), 5 in the transverse colon (13%), 1 in the descending colon (3%), 13 in the sigmoid colon (34%), and 9 in the rectum (24%). The *RAS* status

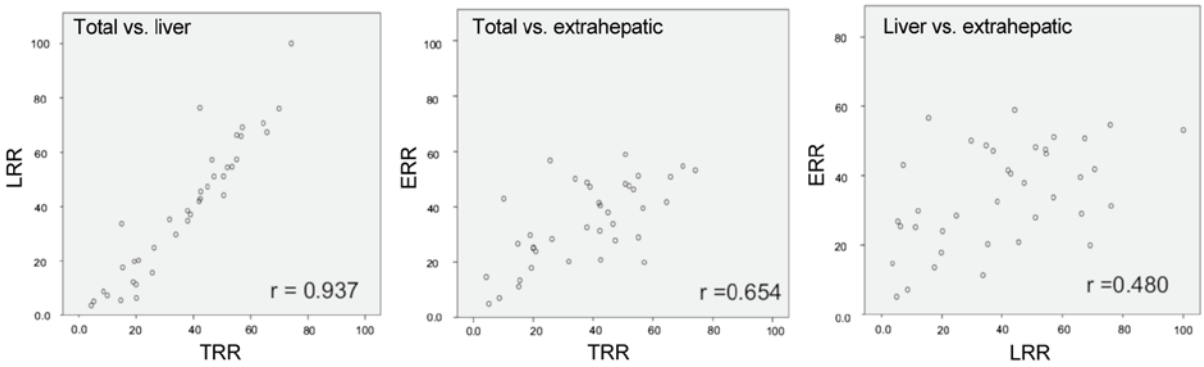

Figure 3. Correlation between total lesion reduction ratio (TRR) and liver lesion reduction ratio (LRR) in all and each H stage of liver metastases (H1/2: n=20, H3: n=18). The mean of the TRR was 37% (95% CI: 31-43), and of the LRR 39% (95% CI: 31-47). TRR and LRR were strongly correlated in any H stage. ERR, extrahepatic lesions reduction ratio.

was wild-type in 22 patients (29%), and 4 patients were not investigated. Regarding the H stage of liver metastases, 9 patients (24%) were H1, 11 (27%) were H2, and 18 (47%) were H3. Measurable lesions other than those in the liver included lesions in the lung, lymph nodes, peritoneum, ovary, and soft tissue. The median of the maximum diameter of liver lesions was 81.2 mm (range, 8.39-228.7 mm), and the median liver occupancy rate in all measurable lesions of each of the 38 patients was 76% (range, 16-94%). Among these patients, 18 underwent resection of the primary site before primary chemotherapy, 11 underwent resection to manage their symptoms, and the remaining 7 underwent radical surgery; 22 of the 38 patients developed recurrence after hepatectomy. A two-drug combination chemotherapy was administered to 33 (86%) patients, and 29 (76%) were administered bevacizumab, a molecular-targeted agent. Five patients (14%) received monotherapy. The median survival time of the 38 patients was 665 days [95% confidence interval (CI): 548-767] (Fig. 2).

Association between TRR and LRR. The mean of the TRR was 37% (95% CI: 31-43), and the mean of the LRR was 39% (95% CI: 31-47). TRR and LRR were strongly correlated (r=0.937, P<0.0001) in any H stage (H1/H2: r=0.911, H3: r=0.915; Fig. 3). The results of univariate and multivariate analyses for predictors of OS are summarized in Table II. On univariate analysis, *RAS* wild-type status, >30% of TRR and >30% of LRR were associated with a better OS. On multivariate analysis, *RAS* wild-type status [hazard ratio (HR)=0.281, P=0.016] and >30% TRR (HR=0.23, P=0.006) were independent predictors of better OS.

Association between reduction ratio and OS. Patients with >30% TRR had a significantly better OS compared with those with <30% (1,179 vs. 540 days, respectively; HR=0.245, 95% CI: 0.101-0.597, P=0.001) (Fig. 4). Patients with >30% LRR also had a significantly better OS compared with those with <30% (1,179 vs. 540 days, respectively; HR=0.27, 95% CI: 0.111-0.656, P=0.002) (Fig. 5). However, in patients with H3 liver metastases, no significant statistical differences in OS were observed between these two groups of patients upon analysis for each H stage of liver metastasis (H1/2, HR=0.225, 95% CI: 0.064-0.791; H3, HR=0.339, 95% CI: 0.094-1.224) (Fig. 6). The treatment duration of primary chemotherapy in patients

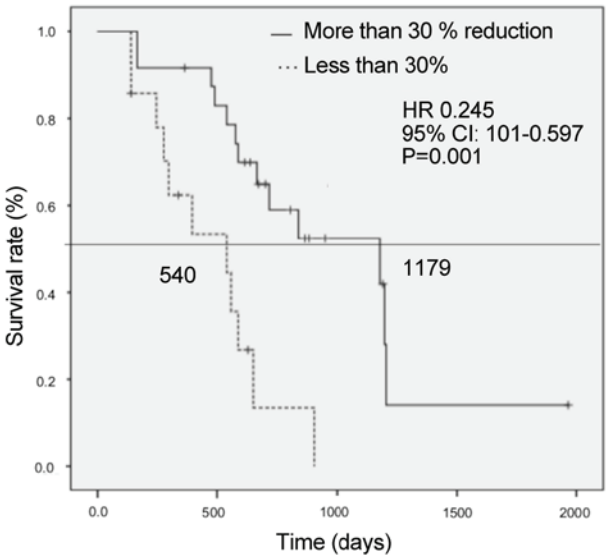

Figure 4. Overall survival (OS) in >30% and <30% total lesion reduction ratio (TRR). Patients with >30% TRR had a significantly better OS compared with those with TRR <30%. HR, hazard ratio; CI, confidence interval.

with H1/2 liver metastases was significantly longer compared with that in patients with H3 (389 vs. 250 days, respectively; HR=0.472, 95% CI: 0.339-0.969, P=0.036) (Fig. 7). In comparison to the characteristics of patients with H1/2 and H3 liver metastases immediately prior to chemotherapy, the maximum diameter of liver metastases, number of liver metastases, and levels of serum carcinoembryonic antigen, serum cancer antigen 19-9, aspartate transaminase, lactate dehydrogenase, alkaline phosphatase and γ-glutamyl transpeptidase, were higher in H3 patients. On the other hand, the serum albumin levels were higher in H1/2 patients. Furthermore, more patients with *RAS* mutations were H3 (Table III).

Discussion

To the best of our knowledge, this was the first study to investigate the correlation between RECIST RR and the LRR in mCRC patients, and to analyze the association between tumor reduction of liver metastases and prognosis. A strong correlation between TRR and LRR in any H stage was

Table II. Univariate and multivariate analyses for predictors of overall survival.

	Univariate	Multivariate		
Variables	P-value	HR	95% CI	P-value
Age, years				
≥65 vs. <65	0.517			
Sex				
Male vs. female	0.517			
ECOG PS score				
0-1 vs. 2-4	0.333			
Liver metastases time				
Synchronous vs. metachronous	0.451			
Resection of primary site				
Resection vs. no resection	0.265			
H stage of liver metastases				
H1 or 2 vs. H3	0.118			
RAS status				
Wild-type vs. mutation	0.041	0.016	0.281	0.100-0.786
CEA level				
High vs. normal	0.539			
CA19-9 level				
High vs. normal	0.246			
RECIST RR				
≥30 vs. <30%	0.002	0.006	0.238	0.086-0.657
Liver RR				
≥30 vs. <30%	0.004	(0.024)	(0.35)	(0.141-0.871)
RR other than liver				
≥30 vs. <30%	0.012			
No. of liver metastases				
≥5 vs. <5	0.327			
Primary site				
Right vs. left colon	0.848			
Albumin level				
Low vs. normal	0.855			
Targeted agents				
Yes vs. no	0.158			

HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; CEA, carcinoembryonic antigen; CA, carbohydrate antigen; RECIST, Response Evaluation Criteria in Solid Tumors; RR, reduction ratio.

observed. In mCRC cases with liver metastases, regardless of the tumor volume of the liver (H stage), the TRR reflected the LRR (Fig. 3). As 70-87% of patients with unresectable or recurrent CRC harbored liver metastases (32,33,35-38), the RR reported in clinical trials for unresectable or recurrent CRC mostly reflected the LRR.

In the present study, no patients received anti-epidermal growth factor receptor (EGFR) antibody, and only bevacizumab was used as a molecular-targeted agent. It was reported that anti-EGFR antibody combination therapy exerted a higher tumor shrinkage effect compared with anti-vascular endothelial growth factor combination antibodies (35-37). These cases, even in patients with wild-type *RAS*, did not require an immediate reduction effect, but rather a sustained treatment strategy of sequential therapies.

Multivariate analysis revealed that >30% tumor reduction was correlated with a favorable prognosis. The OS was significantly better in patients with >30% reduction ratio in the log-rank test (Figs. 4 and 5), and DpR was suggested to improve the prognosis. However, in the analysis of the association between reduction of liver metastases and prognosis of each H stage, no statistically significant difference

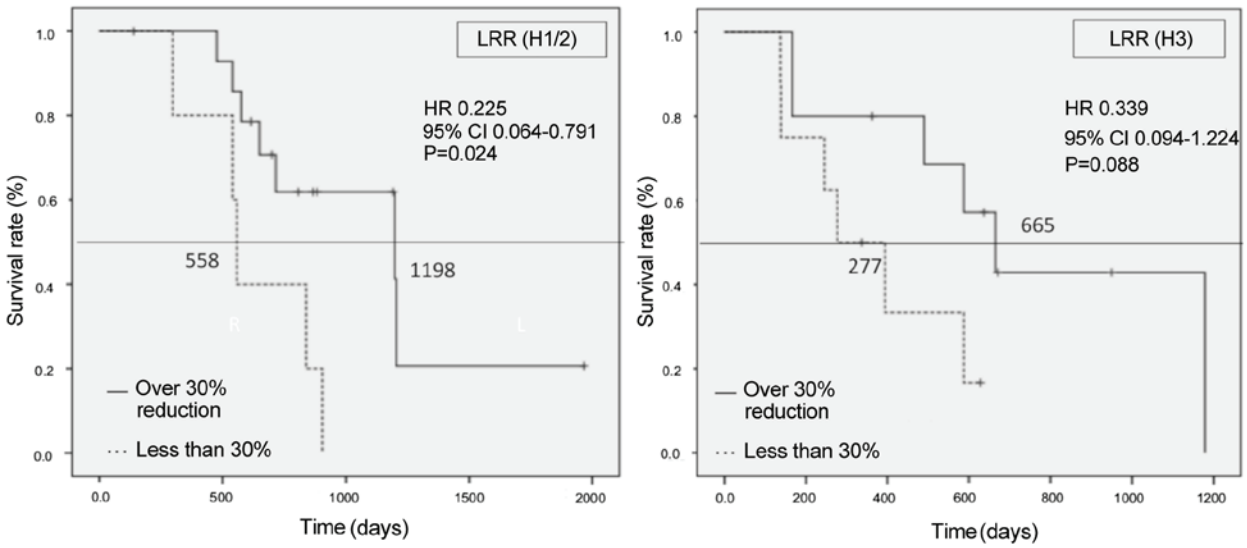

Figure 5. Overall survival (OS) in >30% and <30% liver lesion reduction ratio (LRR). Patients with >30% LRR also had a significantly better OS compared with those with LRR <30%. HR, hazard ratio; CI, confidence interval.

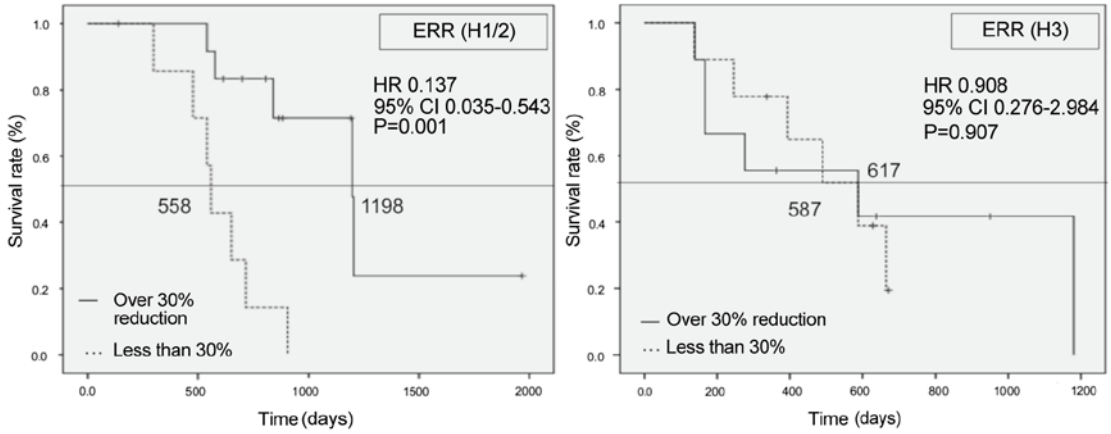

Figure 6. Overall survival (OS) in patients with >30% liver lesion reduction ratio (LRR) when stratified according to H stage. In patients with H3 liver metastases, no statistically significant differences in OS were observed between these two groups of patients upon analysis for each H stage of liver metastasis. HR, hazard ratio; CI, confidence interval; ERR, extrahepatic lesions reduction ratio.

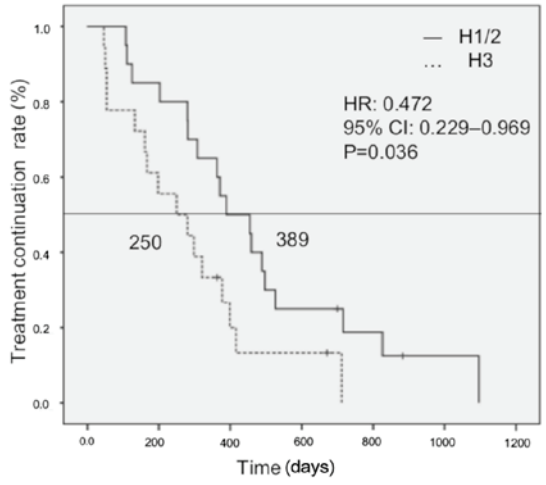

Figure 7. Primary treatment duration of patients with H1/2 and H3 liver metastases. The treatment duration of primary chemotherapy in patients with H1/2 liver metastases was significantly longer compared with that in patients with H3. HR, hazard ratio; CI, confidence interval.

was observed in patients with H3 liver metastases, even with >30% reduction of the lesions (Fig. 6). Although there may not be a significant difference due to the small number of cases, it is suggested there are some factors that affect the prognosis in addition to tumor reduction in the H3 group.

In the H3 group, the duration of primary chemotherapy was clearly shorter compared with the H1/2 group. Liver function prior to treatment of H3 patients was significantly worse compared with that of H1/2 patients (Table III), but there was no difference in the dose intensity and treatment intensity of chemotherapy. Considering the rapid regrowth of lesions and appearance of new lesions in the H3 group, the poor prognosis may be attributed to the biological characteristics of the tumor. An example is the *RAS* mutation. In this study, *RAS* mutation was a contributing factor to the poor prognosis on multivariate analysis (HR=3.5, P=0.02; Table II), and more patients in the H3 group tended to harbor *RAS* mutations, although the difference was not statistically significant. Several studies have

Table III. Comparison of characteristics between H1/2 and H3 liver metastases.

Characteristics	H1/H2 (n=20)	H3 (n=18)	P-value
PS score			0.594
0-1	19 (95)	16 (89)	
2	1 (5)	2 (11)	
Age, years			0.531
<65	10 (50)	7 (39)	
≥65	10 (50)	11 (61)	
Sex			0.351
Male	11 (55)	7 (39)	
Female	9 (45)	11 (61)	
Liver metastases			0.72
Synchronous	14 (70)	18 (100)	
Metachronous	6 (30)	0 (0)	
Targeted drug			0.13
Yes	13 (65)	16 (89)	
No	7 (35)	2 (11)	
Shrinkage			0.503
≥30%	14 (70)	10 (56)	
<30%	6 (30)	8 (44)	
Pathology			1.00
Tubular	6 (30)	6 (33)	
Others	14 (70)	12 (67)	
Primary site			0.468
Colon	16 (80)	12 (67)	
Rectum	4 (20)	6 (33)	
Resection of primary site			0.058
Resection	12 (60)	5 (28)	
No resection	8 (40)	13 (72)	
Number of liver metastases			0.025
≥6	8 (40)	14 (78)	
<6	12 (60)	4 (22)	
RAS status			0.089
Wild-type	14 (70)	7 (39)	
Mutation	5 (25)	10 (61)	
Unknown	1	1	
Maximum diameter of hepatic metastases (mm)	29.45 (8.39-54.79)	29.45 (8.39-54.79)	<0.001
CEA (ng/ml)	13.5 (6.2-1,314.5)	221.1 (4.3-1,471.1)	0.045
CA19-9 (U/ml)	12 (1-2,937)	873 (4.1-10,590)	0.0007
AST (U/ml)	20 (12-85)	39 (14-210)	0.011
ALT (U/ml)	19 (10-62)	25.5 (8-85)	0.41
LDH (U/ml)	225 (141-406)	415 (175-2,400)	0.0076
ALP (U/ml)	244 (141-815)	462 (7-1,291)	<0.001
γ-GTP (U/ml)	31 (13-255)	109.5 (24-495)	0.023
Serum albumin (g/dl)	3.7 (2.6-4.6)	3.2 (2.0-4.0)	0.012
Lymph node metastases			1.00
Yes	10 (50)	9 (50)	
No	10 (50)	9 (50)	

Data are presented as no. (%) or as median (range). PS, performance status; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; AST, aspartate transaminase; ALT, alanine transaminase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; γGTP, γ-glutamyltransferase.

reported that mutations in the *RAS* gene itself is a poor prognostic factor (38-42), and that prognosis following hepatectomy is poor in the *RAS* mutation group. Thus, mutations in the *RAS* gene may lead to an aggressive tumor phenotype (43-45). Although *BRAF* mutations were not examined in this study, further progress in gene research is expected to provide more detailed prognostic predictions and treatment strategies.

These results suggest that >30% reduction did not always improve the prognosis in CRC patients with H3 liver metastasis. For such cases, systemic chemotherapy alone may not improve the prognosis, and other treatment strategies may be required to control liver metastases, such as combination with local treatment, including debulking liver resection. There are some reports that liver metastasis control contributes to the improvement of survival. For example, Elias *et al* (24) reported that the prognosis was improved by curative resection of liver lesions, even if the patients had extrahepatic metastases, and Bokemeyer *et al* (41) reported that a good prognosis was obtained by combining resection with chemotherapy, even with R1 resection of liver metastases. However, Passot *et al* (40) reported that node-positive primary tumors, a tumor diameter of >3 cm, and >7 cycles of preoperative chemotherapy, were factors associated with worse OS for mCRC patients who had hepatectomy, and the more of these prognostic factors the patients had, the worse their OS, even if R0 hepatectomy was performed. Maughan *et al* (42) reported that the response to preoperative chemotherapy was likely to be a significant prognostic factor affecting survival time following curative hepatectomy. Therefore, it is hypothesized that the prognosis after hepatectomy may be associated with various factors, and further studies on the therapeutic indications for local control of liver metastases are needed.

There were certain limitations to the present study. First, this was a retrospective single-center study, and the number of cases was limited. Second, recurrence cases after hepatectomy are included, whereas time to relapse was not considered. Third, the treatment regimen was not uniform. Fourth, tumor reduction was evaluated only by the tumor diameter, and the possible reduction effect of changes such as tumor necrosis and lumen formation could not be evaluated in this manner.

It may be that larger tumors are less likely to exhibit shrinkage due to tumor necrosis and lumen formation; therapeutic effect evaluation may be difficult in these cases.

Taken together, the results of the present study demonstrated that the LRR was strongly reflected by the TRR in mCRC cases with liver metastases. The correlation of DpR with both TRR and LRR and prognosis was suggested; however, H3 patients did not achieve prolonged survival, even in DpR cases. Multidisciplinary treatments, including local therapy, may improve the prognosis of H3 patients. However, further studies with a larger number of cases are needed to draw more definitive conclusions.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

All the datasets generated and analyzed in the present study are included in this published manuscript.

Authors' contributions

SK and KU conceived the present study. SK designed the current study and performed the necessary calculations. SK, KU and MN verified the analytical methods used. EB and KU performed the experiments. All authors discussed the results and contributed to the final manuscript.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Kyushu Medical Center Hospital.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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