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ORIGINAL ARTICLE

Radiological Morphology of Colorectal Liver Metastases after Preoperative Chemotherapy Predicts Tumor Viability and Postoperative Outcomes

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Abstract
Introduction The computed tomography (CT) morphology after chemotherapy is reportedly correlated with the histopathologic response to chemotherapy and a better surgical outcome in patients with colorectal liver metastases (CLM). However, the true prognostic advantage of CT morphology remains uncertain.
Methods The prognostic advantage of CT morphology was validated in 86 patients who underwent surgical resection for CLM after undergoing a 5-fluorouracil-based chemotherapy regimen with or without bevacizumab.
Results An optimal morphologic response was observed in 18 (22.8 %) patients, and a strong correlation between the CT morphology and tumor viability was confirmed ($P<0.001$). A multivariate analysis revealed that bevacizumab (odds ratio [OR], 6.8; $P=0.03$) and chemotherapy cycles ≥6 (OR, 3.6; $P=0.04$) were associated with an optimal morphologic response. Overall survival (OS) and recurrence-free survival (RFS) were also predicted by CT morphology with a higher sensitivity. Particularly, a group 1 morphology was associated with a higher OS rate (3-year OS 100 %) and RFS rate (3-year RFS, 57.0 %), and a multivariate analysis confirmed that group 2 and group 3 tumor morphology was a significant predictive factor for tumor recurrence (hazard ratio [HR], 2.5; $P=0.03$ and HR, 3.2; $P<0.01$, respectively).
Conclusion The CT morphology of CLM predicts tumor viability and long-term surgical outcomes after chemotherapy.

Keywords Colorectal liver metastases · Chemotherapy · RECIST · Morphologic response · Pathologic response

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Introduction

With recent advancements in systemic therapies for colorectal cancer, various biologic agents have been introduced as well as effective cytotoxic chemotherapy regimens. Preoperative chemotherapy can downsize colorectal liver metastases (CLM) and increase their resectability[1,2] and may also be helpful in assessing oncological aggressiveness and the curability of tumors prior to surgical resection.[3,4] However, because of the unique anti-tumor mechanisms of individual biologic agents, conventional tumor size-based radiologic criteria, such as the Response Evaluation Criteria in Solid Tumors (RECIST), may not be sufficient to assess the response to chemotherapy, especially in patients treated with a regimen that includes bevacizumab.[5–7] In the era of modern

chemotherapy, it has been reported that pathologic response to chemotherapy, which is not always predictable with size-based response, can be a strong predictor of long-term survival after surgery.[8] Thus, a multifaceted approach in addition to the size-based conventional response may be needed in an assessment of response to chemotherapy.

The computed tomography (CT) morphologic response criteria were first reported in 2009 as a new surrogate marker for the pathologic response to chemotherapy in patients undergoing systemic therapies including bevacizumab for CLM[9] and were later validated in both surgically[10] and medically[11] treated populations. However, external validation with a sufficient number of patients has not yet been performed, and the reproducibility of the correlation between CT morphologic response and the pathologic response to chemotherapy has not been evaluated. In addition, given the fact that a clear correlation between the post-chemotherapy radiographic morphology and tumor viability has been confirmed in previous studies regardless of the pre-chemotherapy morphology of the tumor,[9,10] the conventional morphologic response criteria[9] might be simplified by excluding the pre-chemotherapy radiographic morphology of CLM.

The objectives of this study were to evaluate a simplified CT morphologic assessment of CLM with regard to its predictive value for pathologic response to chemotherapy and to validate the prognostic advantage of an optimal CT morphology after chemotherapy in patients undergoing the surgical resection of CLM.

Methods

Study Population

By searching two sets of prospectively collected databases between January 2008 and June 2014, we identified 400 patients who underwent surgical resection for CLM at The University of Tokyo Hospital (n=242) and at Toranomon Hospital (n=158). Of these, 128 (32 %) patients underwent fluorouracil-based preoperative chemotherapy with or without bevacizumab for primarily unresectable or oncologically not preferable lesions for upfront surgery. To evaluate the pure oncological effects of the preoperative chemotherapy regimens, 32 patients who underwent 2 or more lines of regimens including the use of anti-epidermal growth factor receptor (EGFR) antibodies and those who failed to receive a curative surgical resection (R2 resection) (n=10) were excluded. The remaining 86 patients who achieved macroscopically curative hepatic resections (R0 or R1 resection) after preoperative systemic therapies were studied in detail. All the analyses in the current study were performed in accordance with the ethical guidelines for clinical studies at each of the institutions and were approved by the institutional review boards of these hospitals.

Imaging Analysis

Enhanced CT scans were performed using a multi-detector row CT, and the images were independently re-reviewed by two radiologists (WG and NO) who were blinded to the clinical data. As defined in the previous studies, the morphology of CLM was characterized according to the following criteria: group 1, homogenous and hypoattenuating with a thin, sharply defined tumor-liver interface; group 3, heterogeneous attenuation with a thick, poorly defined tumor-liver surface; and group 2, all morphologies not meeting the criteria for group 1 or group 3 (Fig. 1).[9] An optimal morphologic response to chemotherapy was defined as a change in morphology from group 3 or 2 to group 1. A change in morphology from group 3 to group 2 and the absence of remarkable changes in morphology were defined as suboptimal morphologic responses.[10] In patients with multiple tumors, the morphologic response was assigned based on the response observed for both of the lesions for patients with 2 nodules or at least 3 lesions including the largest lesion for patients with ≥3 nodules. Interobserver agreement was evaluated based on the initial image reading results of the two radiologists. In the cases of inconsistency, the final morphology was determined by discussion. The response to chemotherapy was also determined according to the RECIST version 1.1.[12]

Pathologic Analysis

All the pathologic specimens were reviewed by a pathologist (HA) who was blinded to the clinical data. The pathologic response to chemotherapy was semiquantitatively assessed using hematoxylin-eosin-stained sections by estimating the proportion of residual cancer cells in relation to the total tumor area as previously reported.[8] Tumor viability was categorized according to 5 % groupings.

Statistical Analysis

Continuous variables were compared using the Mann-Whitney U test, and categorical variables were compared using the chi-squared test or the Fisher exact test, where appropriate. Interobserver agreements in image reading were evaluated using the kappa value. The overall survival (OS) period and the recurrence-free survival (RFS) period were determined from the date of hepatic resection until the date of death or the initial tumor recurrence, respectively. All the cases without specific prognostic events were censored at the date of the last follow-up examination. The survival curves were generated using the Kaplan-Meier method and were compared using a log-rank test. To identify the prognostic risk

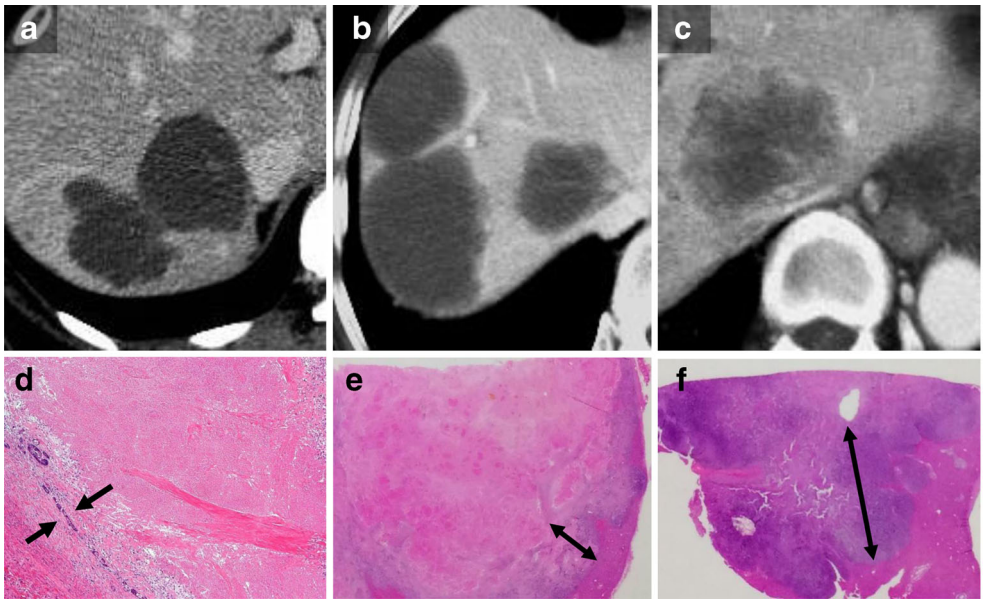

Fig. 1 Correlation between CT morphology after chemotherapy and tumor thickness at the tumor-liver interface. **a** Group 1 CT morphology; **b** group 2 CT morphology; **c** group 3 CT morphology; **d** typical tumor thickness at the tumor-liver interface in group 1 morphology (*arrows*); **e** tumor-liver interface in group 2 morphology (*double-ended arrow*); **f** thick tumor-liver interface in group 3 morphology (*double-ended arrow*)

factors, a multivariate regression analysis was performed using the Cox proportional hazard model with backward elimination for variables with $P<0.2$ in the univariate analysis. To identify factors associated with an optimal morphologic response, a multivariate analysis was performed using the logistic regression model for clinical variables with $P<0.2$ in the univariate analysis. Statistical analyses were performed using JMP (version 11.0; SAS Institute Inc., USA). All the statistical tests were two-sided, and significance was set at $P<0.05$.

Results

Patient Characteristics

Fifty-nine (69 %) patients underwent hepatic resection at The University of Tokyo Hospital, and 27 (31 %) patients underwent resection at Toranomon Hospital. This cohort included 49 men and 37 women with a median age of 61.5 years (range, 28 to 83 years). Fifty-eight (67 %) patients had a primary tumor in the colon, and the others had tumors in the rectum. Sixty-three (73 %) patients had lymph node metastases at the time of the primary tumor resection. Thirty-nine (45 %) patients had 41 extrahepatic lesions at the time of hepatic resection in following locations: lung ($n=21$), distant lymph nodes ($n=12$), peritoneum ($n=4$), adrenal gland ($n=1$), spleen ($n=1$), ovary ($n=1$), and local residual disease at the vaginal wall ($n=1$). Of the 39 patients, 19 were resected simultaneously and 14 patients were resected subsequently for lung metastases with median interval of 4 months from the date of liver resection after an additional chemotherapy. The remaining 6 patients had small lung metastases presenting complete response to chemotherapy and were closely followed up with no evidence of recurrence during the study period. Thirty-one (36 %) patients had a disease free interval of less than 6 months after the resection of the primary tumor. Sixty-five (76 %) patients had multiple liver metastases at the time of the hepatic resection. All the patients received fluorouracil-based chemotherapy as follows: oxaliplatin ($n=63$, 73 %), irinotecan ($n=12$, 14 %), and oxaliplatin+irinotecan ($n=11$, 13 %). Bevacizumab was added in 65 (76 %) patients. The median number of chemotherapy cycles before hepatic resection was 6 cycles (range, 1 to 30 cycles). Microscopically negative surgical margins (R0 resection) were obtained in 57 (66 %) patients, while the other cases exhibited very narrow surgical margins (<1 mm) (R1 resection). There were no patients who underwent staged surgery, ablation therapies, or the other anti-cancer treatment.

Correlation Between CT Morphologic Response and RECIST

Of the 86 patients, 18 (23 %) patients presented with a group 1 CT morphology after chemotherapy and were classified as having had an optimal morphologic response according to the morphologic response criteria and 26 (32 %) patients with a group 2 morphology and 36 (46 %) patients with a group 3 morphology after chemotherapy were classified as having had a suboptimal response. According to RECIST, 40 (51 %) patients had a partial response (PR), 30 (38 %) patients had stable disease (SD) and 9 (11 %) patients had progressive disease (PD). An optimal morphologic response was observed in 11 (28 %) of the 40 patients who were classified as having had a PR according to RECIST and in 7 (18 %) of the 39 patients who were classified as having had an SD or PD. No significant correlation was observed between the CT

morphologic response and the size response described by RECIST (P=0.42). A very high interobserver agreement between two independent radiologists was confirmed for the tumor morphology evaluations (κ=0.99).

Correlation Between CT Morphology After Chemotherapy and Tumor Viability

As shown in Fig. 1, the viable tumor thickness at the periphery of a tumor in a pathologic specimen tended to be relatively thin when a better CT morphology was obtained after chemotherapy. The proportion of residual cancer cells in relation to the total tumor area (viability of tumor) was better stratified using the CT morphology, rather than RECIST (Fig. 2). The median viability of the tumor was 10 % (interquartile range [IQR], 8–20 %) in group 1, 35 % (IQR, 10–80 %) in group 2, and 70 % (IQR, 40–80 %) in group 3, respectively (P<0.001).

Predictors for an Optimal Morphologic Response After Preoperative Chemotherapy

To identify the factors associated with an optimal morphologic response, 12 possible confounders were assessed in a multivariate logistic regression to predict group 1 morphology after preoperative chemotherapy as presented in Table 1. Of the 12 factors, bevacizumab (odds ratio [OR], 6.80; 95 % CI, 1.18–129; P=0.03) and number of chemotherapy cycles equal to or greater than 6 (OR, 3.57; 95 % CI, 1.08–14.3; P=0.04) were positively correlated with an optimal morphologic response.

Long-Term Outcomes After Curative Resection of CLM

After a median follow-up period of 42.4 months (range, 2–85 months), 60 (70 %) patients experienced disease recurrence and 23 (27 %) deaths were recorded. The long-term outcomes of the patients stratified according to the response to preoperative chemotherapy are presented in Fig. 3. When stratified according to the CT morphology of CLM after chemotherapy, group 1 had better long-term outcomes in terms of both OS and RFS than either group 2 or group 3 (Fig. 3a, c), regardless of the median number of tumor nodules (4 nodules [IQR 2–6] in group 1 vs. 2 nodules [IQR 1–6] in group 2 or group 3). A group 2 morphology resulted in a slightly better RFS rate than a group 3 morphology. However, no difference in the OS rates was observed between groups 2 and 3 (Fig. 3c). On the other hand, when the study cohort was stratified according to the size response as determined using RECIST, patients with a PR or SD had a better OS rate than those with PD (Fig. 3b). However, no difference in the RFS rate was observed when examined according to the RECIST responses (Fig. 3d).

Prognostic Factors After Curative Resection for CLM

Because no deaths were recorded among the patients who presented with an optimal post-chemotherapy morphologic response (i.e., group 1 morphology) after a median follow-up period of 42.4 months, the prognostic advantage of a group 1 morphology was assessed using a multivariate analysis for tumor recurrence. First, we have assessed the effects of 14 potential confounders on the recurrence-free survival rate using univariate analyses as presented in Table 2. In a subsequent multivariate analysis, R1 resection (HR, 2.37; 95 % CI, 1.37–4.06; P<0.01), a group 3 CT morphology (HR, 3.24; 95 % CI, 1.50–8.07; P<0.01), and a group 2 CT morphology (HR, 2.47; 95 % CI, 1.08–6.63; P=0.03) after chemotherapy were identified as independent risk factors for tumor recurrence.

All the patients who presented optimal morphologic response survived at the time of current analysis (3-year OS, 100 %) regardless of the margin status with median follow-up period of 28 months for R0 resection and 37 months for R1 resection, while R1 resection was associated with poor survival for the group presenting suboptimal morphologic response

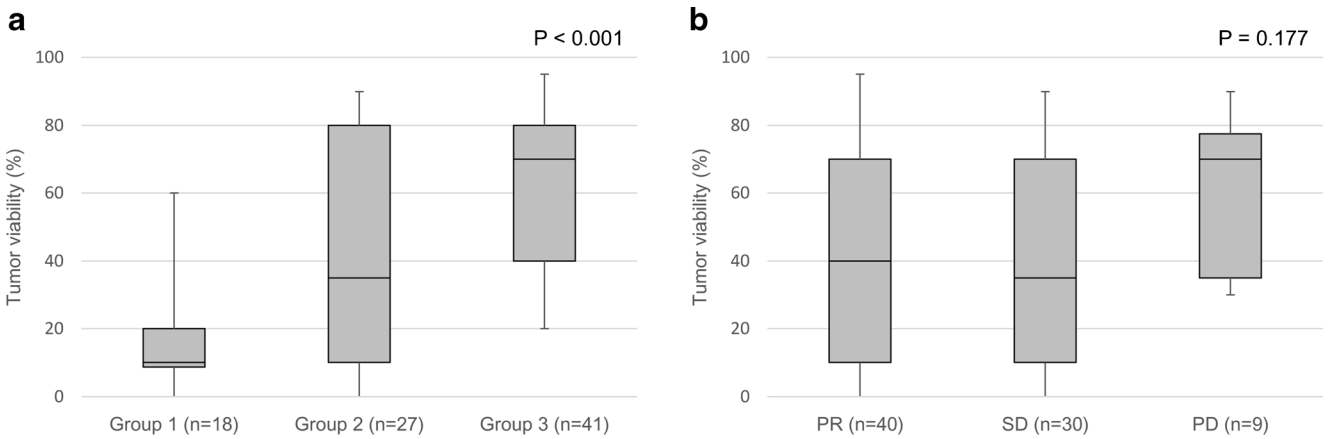

Fig. 2 Proportion of residual cancer cells in relation to the total tumor area stratified by the CT morphology (**a**) and RECIST (**b**). *PR* partial response, *SD* stable disease, *PD* progressive disease

Table 1 Univariate and multivariate analysis of predictors for optimal radiologic response

Variables	No. of patients	Patients with optimal response		Univariate analysis			Multivariate analysis		
		No.	%	*P*	OR	95 % CI	*P*	OR	95 % CI
Age, years									
>60	46	10	21.7	0.84	1.11	0.39–3.24			
≦60	40	8	20.0						
Sex									
Male	49	9	18.4	0.50	0.70	0.24–2.01			
Female	37	9	24.3						
Primary tumor									
Colon	58	14	24.1	0.28	1.91	0.60–7.31			
Rectum	28	4	14.3						
Extrahepatic disease									
Positive	39	10	25.6	0.33	1.68	0.59–4.92			
Negative	47	8	17.0						
Primary tumor nodal status									
Positive	63	11	17.5	0.11	0.39	0.13–1.24	0.23		
Negative	20	7	35.0						
No. of liver metastases									
Solitary	21	4	19.0	0.81	0.86	0.22–2.78			
Multiple	65	14	21.5						
Size of largest metastasis before chemotherapy, cm									
≦5	52	13	25.0	0.41	1.67	0.51–6.51			
>5	24	4	16.7						
No. of chemotherapy cycles before hepatectomy									
≧6	51	14	27.5	0.06	2.94	0.94–11.1	0.04	3.57	1.08–14.3
<6	35	4	11.4						
Fluorouracil-based chemotherapy regimen									
Oxaliplatin	63	11	17.5	0.46	0.56	0.14–2.88			
Irinotecan	12	4	33.3	0.75	1.33	0.22–8.71			
Oxaliplatin + irinitecan	11	3	27.3						
Bevacizumab									
Yes	65	17	26.2	0.02	7.08	1.31–132	0.03	6.80	1.18–129
No	21	1	4.8						
CT morphology before chemotherapy									
2	9	3	33.3	0.42	1.89	0.36–8.18			
3	67	14	20.9						
Institution									
The University of Tokyo Hospital	59	12	20.3	0.84	0.89	0.30–2.86			
Toranomon Hospital	27	6	22.2						

CT computed tomography, *OR* odds ratio, *95 % CI* 95 % confidence interval

(3-year OS, 77.7 % for R0 resection vs. 52.2 % for R1 resection; $P=0.025$).

Discussion

In this study, we analyzed the predictive value of CT morphology for assessing the tumor viability of CLM after chemotherapy and the prognostic advantage of an optimal morphologic response in patients undergoing hepatic resection for CLM. The CT morphology after chemotherapy showed a clear correlation with tumor viability and sensitively predicted surgical outcomes independent of tumor size or pre-chemotherapy CT morphology. Bevacizumab was identified as a strong predictor of a preferable morphologic change after chemotherapy.

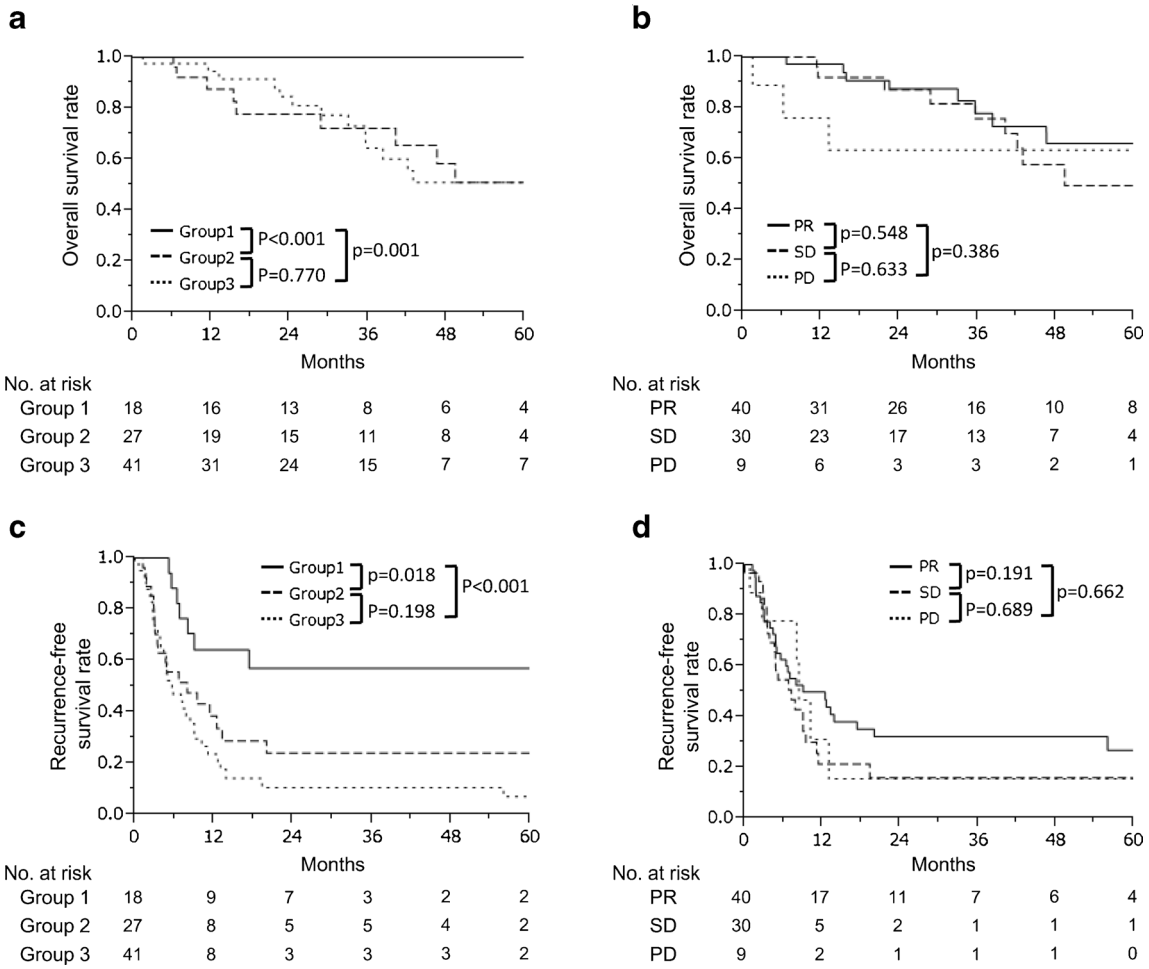

Fig. 3 Long-term outcomes after resection of colorectal liver metastases stratified by the CT morphology and RECIST. **a** Overall survival stratified by the CT morphology; **b** overall survival stratified by the RECIST; **c** recurrence-free survival stratified by the CT morphology; **d** recurrence-free survival stratified by the RECIST. *PR* partial response, *SD* stable disease, *PD* progressive disease

The CT morphologic response to chemotherapy has been reported to be a good indicator of prognosis before the resection of CLM, especially in patients undergoing chemotherapy that includes bevacizumab.[9,10] These unique radiographic changes were strongly correlated with the pathologic response to chemotherapy, which has been reported to be a strong predictor of long-term outcomes after the resection of CLM.[8,13] Several observational studies have confirmed that CT morphology may be superior to conventional size-based response criteria for patients receiving modern 5-fluorouracil-based chemotherapy and that it might be useful for stratifying histopathologic tumor viability regardless of tumor size.[10,11] However, because most of this evidence was obtained in studies conducted at a single institution and external validation has been insufficient, the true prognostic advantage of CT morphology remains uncertain.

The current study was conducted to validate the prognostic advantage of the CT morphologic response based on data from two high-volume hepatobiliary centers. Based on blinded evaluations of radiologic and pathologic findings, a strong correlation between the CT morphology after chemotherapy and tumor viability was confirmed, while the conventional size-based response criteria failed to adequately stratify tumor viability (Fig. 2). In addition, the use of bevacizumab (OR, 6.8) was identified as the strongest predictor of an optimal morphologic response in a multivariate analysis, consistent with the results of a previous report.[10]

The novelty of the current study was that the predictive value for tumor viability and the correlation with postoperative prognosis were confirmed for CT morphology determined after chemotherapy only, regardless of the pre-chemotherapy CT morphology or size-based response. In the current results, the one-point evaluation of CT morphology after chemotherapy strongly predicted the tumor viability and patient prognosis, with typical histopathologic changes in the tumor thickness at the tumor-normal interface[14,15] (Fig. 1). In addition, pre-chemotherapy CT morphology was not a predictor of an optimal response (Table 2). These results suggest that the CT morphology after chemotherapy itself can be used as an alternate prognostic indicator for the

Table 2 Univariate and multivariate analysis of predictors for tumor recurrence

Variables	No. of patients	3-year RFS (%)	Median RFS (months)	Univariate analysis			Multivariate analysis		
				P	HR	95 % CI	*P*	HR	95 % CI
Age, years									
>60	46	28.8	9.0	0.30	0.76	0.46–1.27			
≦60	40	20.6	6.7						
Primary tumor nodal status									
Positive	63	23.4	7.8	0.71	1.12	0.62–2.17			
Negative	20	31.9	7.9						
Extrahepatic disease									
Present	39	31.8	7.2	0.64	0.89	0.53–1.47			
Absent	47	19.3	8.0						
DFI, months									
<6	31	33.7	11.1	0.15	0.68	0.39–1.15	0.10		
≧6	55	19.6	6.7						
Preoperative chemotherapy regimen									
Oxaliplatin	63	22.9	7.2	0.94	1.03	0.48–2.69			
Irinotecan	12	35.8	13.0	0.43	0.41	0.20–2.02			
Oxaliplatin + irinitecan	11	25.0	6.8						
Bevacizumab									
No	21	16.9	8.4	0.62	1.16	0.63–2.01			
Yes	65	27.6	7.9						
No. of tumors									
Solitary	21	33.3	7.8	0.50	0.82	0.43–1.45			
Multiple	65	21.8	8.0						
Size of largest metastasis before chemotherapy, cm									
≦5	52	23.8	7.2	0.43	1.34	0.67–3.06			
>5	24	31.8	11.3						
No. of chemotherapy cycles before hepatectomy									
<6	35	27.9	9.0	0.56	0.86	0.51–1.44			
≧6	51	23.0	7.2						
Margin status									
R1 resection	29	13.1	3.4	<0.01	2.51	1.47–4.21	<0.01	2.37	1.37–4.06
R0 resection	57	31.2	11.1						
Adjuvant chemotherapy									
Yes	45	22.0	9.0	0.77	0.92	0.56–1.55			
No	41	26.5	7.8						
RECIST response[a]									
PD	9	15.6	8.4	0.66	1.22	0.46–2.78			
SD	30	16.1	7.2	0.19	1.46	0.82–2.59			
PR	40	32.3	9.0						
Morphology of CLM before surgery									
3	41	10.7	5.6	<0.01	3.86	1.80–9.55	<0.01	3.24	1.50–8.07
2	27	24.1	7.9	0.02	2.67	1.18–6.87	0.03	2.47	1.08–6.63
1	18	57.0	NE						
Institution									
The University of Tokyo Hospital	59	24.7	7.8	0.84	1.06	0.63–1.85			
Toranomon Hospital	27	25.5	9.0						

RFS recurrence-free survival, *HR* hazard ratio, *95 % CI* 95 % confidence interval, *DFI* disease-free interval, *PR* partial response, *SD* stable disease, *PD* progressive disease, *CLM* colorectal liver metastases, *NE* not estimated

[a] Response was not assessable in seven patients due to missing pre-chemotherapy CT

morphologic response criteria, which require two-point evaluations before and after chemotherapy.

Meanwhile, the current result may raise a question why RECIST did not correlate with survival outcomes. One possible explanation would be that the current population was enriched with patients receiving bevacizumab which is strongly associated with pathologic response.[15,16] Histopathologic change in tumor has been reported to be a strong aspect of response to chemotherapy predicting long-term surgical outcomes.[8,16,17] This unique histologic change occurs independently from size response as confirmed in this study (Fig. 2) and previous studies.[9,10] Although the size-based response to chemotherapy remains a standard indicator in surgical decision making for marginal resectable cases in actual clinical settings,[18] the current results suggested that the hiatopahologic change, which cannot be assessed by RECI ST, has strong correlation with surgical outcomes and, therefore, should be accounted when assessing response to preoperative chemotherapy for CLM. Given the fact that the group 1 CT morphology was correlated with very high recurrence-free survival rate and overall survival rate even in patients with extrahepatic diseases or histopathologically positive surgical margins (Fig. 3), CT morphology after chemotherapy can be used as a marker of oncological aggressiveness of tumor and surgical curability of CLM.

From a clinical standpoint, the current results have practical importance. First, because the preferable long-term outcomes observed in the group 1 CT morphology were not influenced by tumor size or the number of nodules, the information obtained from CT morphology after chemotherapy may help appropriate surgical decisions to be made, especially for patients with marginally resectable or initially unresectable multiple CLM. The encouraging results even after R1 resection may support the clinical significance of the optimal CT morphologic change in CLM. Second, because bevacizumab and an adequate number of chemotherapy cycles are associated with a preferable morphologic response, an improved response can be expected by adding bevacizumab or more than 6 cycles of chemotherapy when a patient presents with an inadequate response or no response to chemotherapy. Third, because an evaluation of CT morphology at only one time point was predictive of the pathologic response and patient outcome after surgery with a very high interobserver agreement for image reading, the CT morphology after chemotherapy might be a simple and reliable prognostic indicator for patients with CLM.

The limitations of the current study include its retrospective nature and the relatively limited number of subjects. However, the present analysis was based on a prospectively collected database, and similar outcomes of previous studies were also observed using blinded radiologic and pathologic evaluations. In addition, patients who received anti-EGFR antibodies were excluded from the present analysis, and prognostic contribution of CT morphology remains unclear among patients who are treated with anti-EGFR antibodies. Further investigations involving a sufficient number of patients, including those treated with cetuximab or panitumumab, are needed to clarify the most suitable method of evaluating the response to chemotherapy in the era of biologic agents.

Conclusions

In conclusion, CT morphology after preoperative chemotherapy is a strong predictor of tumor viability and patient prognosis after curative surgical resection for CLM irrespective of tumor size or pre-chemotherapy CT morphology. Post-chemotherapy CT morphology may provide useful information for making adequate surgical decisions for patients with CLM.

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Conflict of Interest Dr. Shindoh reports receiving lecture fee from Chugai Pharmaceutical Co., Ltd. The other authors have no conflicts of interest to disclose.

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