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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Dynamic Changes in Normal Liver Parenchymal Volume During Chemotherapy for Colorectal Cancer: Liver Atrophy as an Alternate Marker of Chemotherapy-Associated Liver Injury

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ABSTRACT

Background. The purpose of this study was to investigate the incidence, origin, and clinical significance of liver atrophy during chemotherapy for colorectal cancer.

Methods. This study included 103 patients who underwent chemotherapy before resection for colorectal liver metastases (training set) and 171 patients who underwent adjuvant or first-line chemotherapy without liver resection (validation set). A greater than 10% decrease (atrophy) or increase (hypertrophy) of the liver volume from the baseline was defined as a significant change.

Results. In the training set, the numbers of patients who developed atrophy, no change of volume, and hypertrophy of the liver after chemotherapy were 15 (14.6%), 73 (70.9%), and 15 (14.6%), respectively. Liver atrophy was associated with impaired hepatic function, and the postoperative morbidity rate and refractory ascites/pleural effusion were higher in the patients with liver atrophy than those without (60.0% vs. 31.8%, $P = 0.045$ and 46.7% vs. 8.0%, $P < 0.001$, respectively). Histopathological examination revealed a strong association between sinusoidal injury and liver atrophy ($P < 0.001$). The cumulative incidence of liver atrophy increased with increasing duration of chemotherapy, whereas the incidence of liver atrophy was less frequent in patients who had received bevacizumab than those who had not in both the training set (odds ratio [OR], 0.13; $P = 0.001$) and the validation set (OR, 0.31; $P = 0.007$).

Conclusions. Liver atrophy is associated with impaired hepatic functional reserve and observed at an increasing frequency as the duration of chemotherapy increases with frequent histopathological evidence of sinusoidal injury in the liver. Bevacizumab may protect against the development of liver atrophy.

For patients with stage IV colorectal cancer (CRC) with colorectal liver metastases (CLM), preoperative chemotherapy is increasingly used as a part of the multidisciplinary treatment approach.[1,2] While the perioperative mortality rate of hepatic resection has decreased, intensive chemotherapy before surgery remains the main cause of morbidity and mortality.[3–7] Although some types of liver injury are known to be strongly associated with specific chemotherapeutic agents, various macroscopic and

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microscopic pathological changes are observed in the liver in actual clinical settings,[5,8,9] and the overall picture of chemotherapy-induced liver injury remains unclear.

In the era of effective chemotherapy, more and more patients with CLM are becoming potential surgical candidates after intensive chemotherapy. With the elevated risk of liver injury after extensive chemotherapy, however, evaluation of the quality of the underlying liver and surgical decision-making based on dynamic volumetric data are becoming important.[10,11] After a recent report from a preliminary multicenter study of the potential clinical relevance of liver atrophy after chemotherapy for CLM,[12] similar observations have been confirmed by the other group.[13] Nevertheless, it remains unclear (1) whether this phenomenon also is observed in the cases without CLM, (2) whether the liver atrophy is associated with specific histopathological changes, and (3) whether some specific clinical factors are associated with the incidence of liver atrophy.

Given these unresolved clinical questions with regard to the occurrence of liver atrophy during chemotherapy for CRC, this study sought to investigate the actual incidence and clinicopathological features of liver atrophy during chemotherapy for CRC, both in a surgical cohort with CLM and a medical cohort with/without CLM.

METHODS

Study Population

The institutional review board of Toranomon Hospital approved this study protocol (No.1701). From a prospective database at Toranomon Hospital, 103 patients who underwent curative resection for CLM after chemotherapy between April 2008 and June 2018 were included as the training set for analysis. In addition, 100 patients with stage IIIB or stage IIIC CRC who received adjuvant chemotherapy after curative resection and 71 with unresectable stage IV CRC who received first-line chemotherapy were selected as the validation set. The details of patient selection are summarized in Supplemental Fig. 1.

Imaging Analysis

The total liver volumes (TLV) before, during, and after chemotherapy were measured independently by two surgeons with experience of > 1000 three-dimensional (3D) volumetries (JS and YK). TLV was defined as the mean volume of the normal liver parenchyma excluding tumors measured by a 3D simulation software (SYNAPSE VINCENT®; Fujifilm, Tokyo, Japan). For the small number of cases (27/796 [3.3%] scans) for whom DICOM or computed tomographic data were not available for the 3D volumetry, the conventional manual tracing method was used to measure the TLV.[14] Changes in the spleen volume were also measured in the same fashion. The average CT numbers of the liver parenchyma were evaluated from five randomly selected regions of interest (ROIs) in each patient's scans. "Hypertrophy" and "atrophy" were defined as a 10% increase and decrease, respectively, of the TLV from the baseline, in accordance with a previous report.[12]

Pathological Analysis

In the training set, the histopathological changes in the normal liver parenchyma were re-reviewed by a pathologist with expertise in hepatobiliary histopathology (KK), who was blinded to the clinical data. Steatosis was graded according to the scoring system proposed by Kleiner et al.[15] Sinusoidal injury was graded according to the sinusoidal pathological score reported by Rubbia Brandt et al.[9]

Statistical Analysis

To ensure reliability of the data, a preliminary database was first reviewed by three external specialists blinded to the other part of clinical data [YM (hepatobiliary surgeon, volumetry section), WG (radiologist, imaging analysis section), and SY (medical oncologist, chemotherapy section)] before the complete database was established for the analyses in this study (*Step 1*). Then, by using the final database released to every collaborator at this point, preliminary statistical analysis was first performed by the principal investigators (JS and YK), and the reproducibility of these results was independently confirmed by the three reviewers (YM, WG, SY). The final results were approved by all the collaborators (*Step 2*).

Statistical analysis was performed using the IBM SPSS software (Ver 23.0 SPSS Inc., Chicago, IL). The median values (and ranges) of the continuous variables were compared using the Mann–Whitney U test. Categorical variables were compared using Pearson's Chi squared test or Fisher's exact test, as appropriate. P values < 0.05 were considered to indicate statistical significance. To identify factors associated with significant atrophy of the liver after chemotherapy, a multivariate analysis was performed using logistic regression with backward elimination. To prevent overfitting, only factors that showed a statistically significant association with tumor recurrence at $P < 0.1$ were included in the final model. The cumulative incidence of > 10% atrophy was evaluated by the Kaplan–Meier method and was compared using log-rank test.

RESULTS

Data Quality Control

In the review conducted by the external reviewers, a strong correlation ($r = 0.992$, $P < 0.0001$) was confirmed between the independent volumetric assessments of the two examiners (JS and YK) (Supplemental Fig. 2), and the imaging analyses and dose calculations also were confirmed as being appropriate.

Baseline Characteristics

The baseline characteristics of the study population are summarized in Table 1. The total number of chemotherapy cycles was higher, and irinotecan or biologic agents were used less frequently in the validation than in the training cohort. Comparison of the changes in the TLV, CT number, spleen volume, and platelet count after chemotherapy, which are presented as the respective post-/pre-chemotherapy ratio, revealed a 3% decrease of the median TLV, no significant change in CT number, 10% increase of the median spleen volume, and approximately 30% reduction of the platelet count in each group after chemotherapy. There were no significant differences in the changes in these variables between the training set and the validation set.

Changes in Volume of Normal Liver Parenchyma After Chemotherapy and Correlations with Clinical Variables

Stratification of the patients of the training set according to changes of the TLV after chemotherapy (Supplemental Fig. 3) revealed that liver atrophy, no change of the TLV, and liver hypertrophy were observed in 15 (14.6%), 73 (70.9%), and 15 (14.6%) patients, respectively. The indocyanine green retention rate at 15 min (ICG-R15) was significantly worse in the patients with liver atrophy (19.1%; 95% confidence interval [CI], 9.2–28.2%) than in those with no change of the TLV (11.0%; 95% CI, 7.0–16.0%) or liver hypertrophy after chemotherapy (12.0%; 95% CI, 8.6–18.5%) ($P = 0.025$). The post-/pre-chemotherapy ratio of the CT number tended to be smaller in the patients with liver hypertrophy after chemotherapy than in those with no change of the TLV or liver atrophy (0.95 vs. 1.01, $P = 0.072$). A mild negative correlation was observed between the post-/pre-chemotherapy TLV and the post-/pre-chemotherapy CT number (Supplemental Fig. 4). There was no correlation between the degree of changes in the TLV and that in the spleen volume ($r = 0.13$, $P = 0.174$).

The short-term surgical outcomes and histopathological changes observed in the normal liver parenchyma are summarized in Table 2. Patients with liver atrophy after chemotherapy showed a higher incidence of postoperative morbidity compared with those with no change of the TLV or liver hypertrophy. Although there was no case of death in the present study population, postoperative hepatic insufficiency was observed in one patient in the atrophy group (6.7% vs. 0%, $P = 0.146$), and the incidence of refractory ascites or pleural effusion after surgery was significantly higher in the group with liver atrophy after chemotherapy (46.7% vs. 8.0%, $P < 0.001$). The results of histopathological evaluations showed that the incidence of sinusoidal injury was significantly higher in the group that showed liver atrophy after chemotherapy (moderate to severe grade, 66.7% vs. 14.8%; $P < 0.001$).

In the validation set, the numbers of patients showing liver atrophy, no change of the TLV, liver hypertrophy were 49 (28.7%), 98 (57.3%), and 24 (14.0%), respectively. A mild negative correlation was confirmed between the post-/pre-chemotherapy TLV and the post-/pre-chemotherapy CT number (Supplemental Fig. 4). There was no correlation between the degree of change in the TLV and that in the spleen volume ($r = 0.12$, $P = 0.13$). Although the incidence of grade 3 or greater adverse events during chemotherapy was similar between the patients who showed liver atrophy and those without atrophy after chemotherapy (14.3% vs. 13.0%, $P = 0.815$), hepatic dysfunction (i.e., elevation of the transaminase levels greater than double the upper limit of the normal range) was observed at a higher frequency (30.4% vs. 6.1%, $P < 0.0001$) and suspension or discontinuation of chemotherapy due to hepatic dysfunction was required more frequently (12.5% vs. 3.5%, $P = 0.041$) in the patients with liver atrophy after chemotherapy.

Kinetic Changes of Normal Liver Volume and Predictive Factors

Figure 1 shows the kinetic changes of the normal liver parenchymal volume during chemotherapy. When the population was stratified according to the use of bevacizumab, liver atrophy, as well as the incidence of sinusoidal injury, was observed at a lower frequency in the cases treated with bevacizumab in the training set. Moderate (grade 2) to severe (grade 3) sinusoidal injury was observed in 15.1% of patients who received bevacizumab, whereas 40.0% of patients who were not treated with bevacizumab were found to have grade 2 or greater sinusoidal injury at histopathological examination ($P = 0.006$). Although the histopathological changes were not assessed in the validation cohort, a similar tendency in terms of the volume change was confirmed in the cases

TABLE 1 Baseline characteristics

	Training set (n = 103)	Validation set (n = 171)	P
Age (year)[a]	61 (31–84)	64 (32–86)	0.320
Sex			
Male	62 (60.2)	41 (39.8)	0.348
Female	93 (54.4)	78 (45.6)	
Body surface area (m^2)[a]	1.62 (1.25–2.08)	1.59 (1.17–2.13)	0.461
Primary sideness (left/right)	81/22	121/50	0.151
RAS mutational status (wild/mutant)[b]	32/52	39/59	0.815
Presence of liver metastases	103 (100)	28 (16.4)	< 0.001
Chemotherapy			
Total cycles[a]	4 (1–24)	8 (1–46)	< 0.001
Oxaliplatin	87 (84.5)	129 (75.4)	0.076
Irinotecan	20 (19.4)	17 (9.9)	0.026
Bavacizumab	73 (70.9)	55 (32.2)	< 0.001
Anti-EGFR antibodies	18 (17.5)	4 (2.3)	< 0.001
Cumulative dose of oxaliplatin (mg/m^2)[a]	340 (0–1690)	612 (0–7434)	< 0.001
Cumulative dose of irinotecan (mg/m^2)[a]	0 (0–2100)	0 (0–6300)	0.050
Cumulative dose intensity of 5-fluorouracil, capecitabine, or tegaful (%)[a]	400 (80–2400)	700 (100–4600)	< 0.001
Total liver volume (mL)			
Pre-chemotherapy[a]	1159 (751–1956)	1164 (723–2555)	0.625
Post-chemotherapy[a]	1170 (698–1840)	1128 (688–2434)	0.412
Ratio (post vs. pre)[a]	0.97 (0.69–1.30)	0.97 (0.70–1.65)	0.589
CT number (HU)			
Pre-chemotherapy[a]	59.9 (42.0–73.8)	58.6 (14.6–77.6)	0.456
Post-chemotherapy[a]	59.0 (22.2–74.8)	60.3 (− 5.5–78.0)	0.812
Ratio (post vs. pre)[a]	1.00 (0.41–1.38)	1.00 (− 0.13–1.57)	0.826
Spleen volume (mL)			
Pre-chemotherapy[a]	97 (4–313)	90 (16–240)	0.258
Post-chemotherapy[a]	107 (6–394)	104 (31–546)	0.480
Ratio (post vs. pre)[a]	1.08 (0.52–2.56)	1.13 (0.46–3.18)	0.567
Platelet count (10^4/mm^3)			
Pre-chemotherapy[a]	23.9 (10.8–63.9)	25.9 (9.6–51.3)	0.142
Post-chemotherapy[a]	17.4 (4.9–41.4)	18.5 (5.9–38.4)	0.238
Ratio (post vs. pre)[a]	0.68 (0.14–2.02)	0.76 (0.18–1.82)	0.736

Values are number or patients (percentage) unless otherwise indicated

[a]Median (range)

[b]Excluding unknown cases

treated with bevacizumab. As clearly confirmed in Fig. 2, the incidence of atrophy increased as the number of chemotherapy cycles increased, and there was a significant difference in the cumulative incidence of liver atrophy between patients treated and not treated with bevacizumab in both the training set and the validation set.

Multivariate logistic regression analysis identified use of bevacizumab as a significant independent factor that protected against liver atrophy during chemotherapy; the cumulative dose of oxaliplatin + 100 mg/m^2 also was associated with a 1.27-fold higher risk of liver atrophy in the training set (Table 3).

Liver Atrophy as a Marker of Liver Dysfunction

In the cases that showed shrinkage of the TLV from the baseline in the training set (n = 63), a mild correlation was confirmed between the degree of shrinkage and the ICG-R15 (r = − 0.351, P = 0.007) (Supplemental Fig. 5). According to the results of linear regression analysis, a

TABLE 2 Short-term surgical outcomes and pathological changes in liver parenchyma in the training cohort

	> 10% atrophy (n = 15)	No shrinkage (n = 88)	P
Major hepatectomy	7 (46.7)	31 (35.2)	0.402
Operation time (min), median (range)	218 (115–361)	219 (88–541)	0.950
Blood loss (mL), median (range)	420 (145–1483)	535 (0–2875)	0.634
Postoperative peak bilirubin level (mg/mL), median (range)	1.3 (0.8–23.8)	1.5 (0.6–5.5)	0.500
Any complication	9 (60.0)	28 (31.8)	0.045
Major complication	4 (26.7)	15 (17.1)	0.470
Refractory ascites/pleural effusion	7 (46.7)	7 (8.0)	< 0.001
Hepatic insufficiency	1 (6.7)	0 (0)	0.146
Length of hospital stay (d)	14 (7–36)	14 (5–67)	0.857
Steatosis[a]			0.989
None	6 (40.0)	39 (44.3)	
Mild	4 (26.7)	23 (26.1)	
Moderate	2 (13.3)	14 (15.9)	
Severe/NASH	3 (20.0)	12 (13.6)	
Sinusoidal injury[b]			< 0.001
None	2 (13.3)	66 (75.0)	
Grade 1	3 (20.0)	9 (10.2)	
Grade 2	5 (33.3)	10 (11.4)	
Grade 3	5 (33.3)	3 (3.4)	
Fibrosis[c]			0.876
F0	9 (60.0)	47 (53.4)	
F1	6 (40.0)	28 (31.8)	
F2	0 (0)	9 (10.2)	
F3	0 (0)	4 (4.5)	

Values are number or patients (percentage) unless otherwise indicated

NASH nonalcoholic steatohepatitis

[a]Scoring system by Kleiner et al.[15]

[b]Grading system by Rubbia-Brandt et al.[9]

[c]Based on the classification by Desmet et al.[24]

10% decrease of the liver volume was associated with an increase of the ICG-R15 value by 13.9% (ICG-k value of 0.131).

DISCUSSION

In this study, we analyzed the kinetic changes occurring in the normal liver parenchyma during/after chemotherapy for CRC. A careful review of the data demonstrated that significant atrophy of the liver, observed in association with prolonged chemotherapy, was associated with impaired hepatic functional reserve and an increased risk of postoperative morbidity and/or liver dysfunction during/after chemotherapy. The histopathological review indicated that sinusoidal injury in the liver parenchyma was associated strongly with atrophy of the liver. Furthermore, use of bevacizumab was associated with a decreased risk of liver atrophy during/after chemotherapy.

Changes of the TLV occurring after chemotherapy have been empirically known to hepatobiliary surgeons in clinical settings. However, Tani et al. were the first to report significant decrease of the TLV during/after chemotherapy for CLM, although the actual cause of the atrophy and reproducibility in cases without liver metastases remained unclear.[12] Because the quality of 3D volumetry is highly dependent on the examiners' skill and quality of CT scans, quality control of imaging analysis is mandatory for this kind of study. With the careful study design and analysis, a high-quality objective database could be obtained and this study yielded several novel findings.

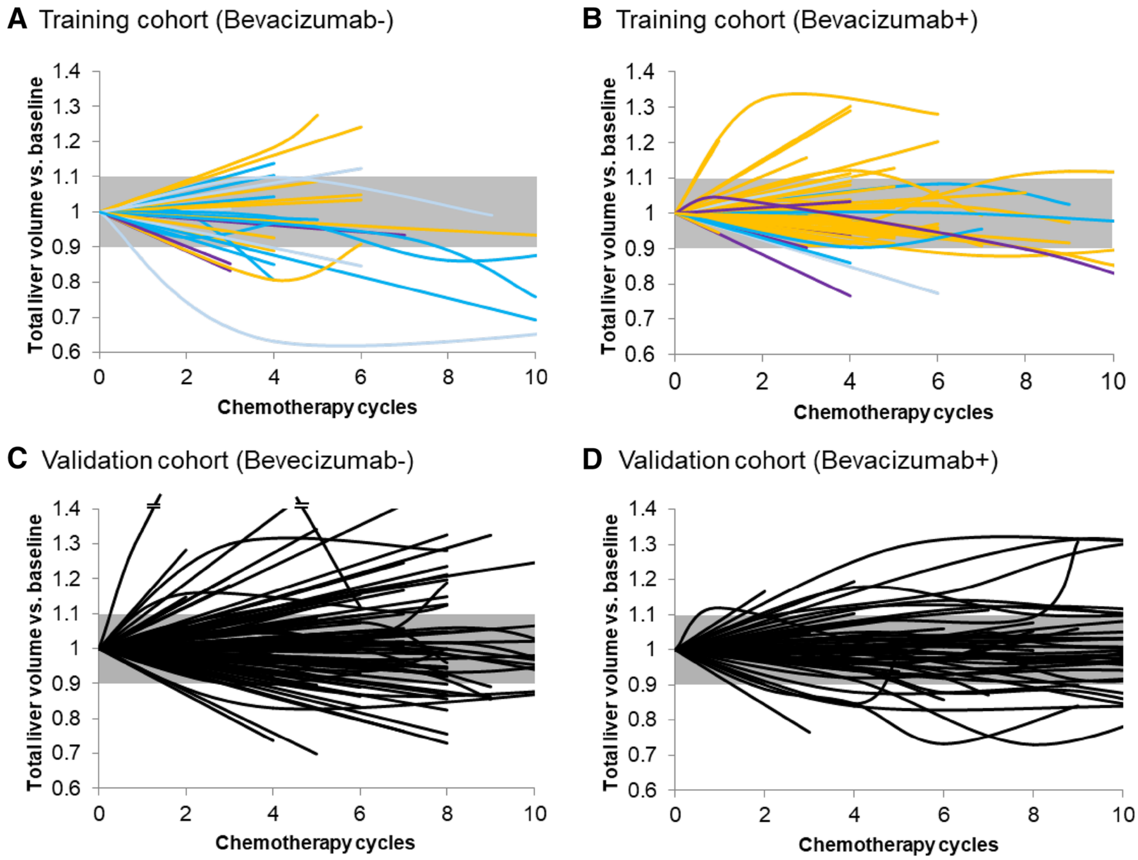

FIG. 1 Kinetic changes of the liver volume during/after chemotherapy for colorectal cancer. **a**, **b** Surgical population receiving preoperative chemotherapy. **c**, **d** Medical population receiving adjuvant chemotherapy after resection of primary lesions or first-line chemotherapy for unresectable stage IV disease. Each line indicates the kinetic changes of the liver volume in an individual patient. For the training cohort, the light blue line indicates grade 1 sinusoidal injury, the blue line indicates grade 2 sinusoidal injury, the purple line indicates grade 3 sinusoidal injury, and the yellow line indicates no sinusoidal injury

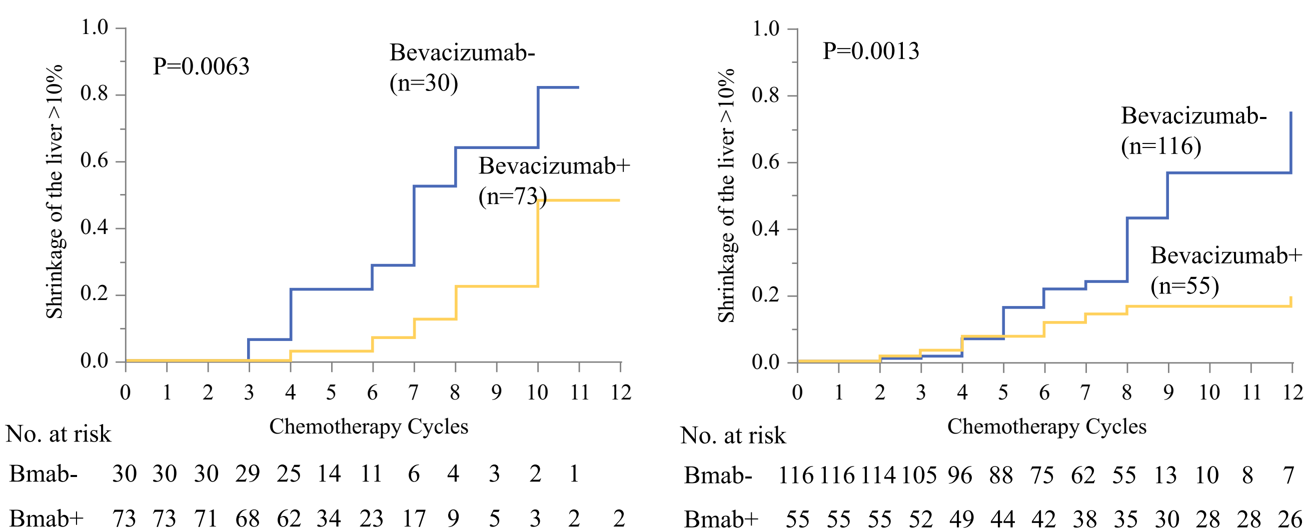

FIG. 2 Cumulative incidence of significant shrinkage of the liver (> 10% decrease of the liver volume) during/after chemotherapy for colorectal cancer classified by the use of bevacizumab

TABLE 3 Factors associated with > 10% atrophy of the liver

	*P**	Coefficients†	SE	Wald χ^2	OR	95% CI
Training cohort						
Bevacizumab	0.001	− 2.05	0.64	10.3	0.13	0.04–0.45
Cumulative dose of oxaliplatin + 100 mg/m^2	0.034	0.23	0.12	4.5	1.27	1.02–1.60
Validation cohort						
Bevacizumab	0.007	− 1.17	0.43	7.4	0.31	0.13–0.72

*Based on likelihood test adjusted for the other factors in the final model

†Estimated coefficient for the variable and the associated standard error

SE standard error; *OR* odds ratio; *CI* confidence interval

Multivariate logistic regression was applied with stepwise backward selection. Initially, all factors were included in the model. Then factors that showed no or limited statistically significant association ($P \geq 0.1$) with > 10% shrinkage of liver parenchyma adjusted for the remaining factors in the model were deleted from the model in stepwise fashion. The 8 factors tested were as follows: age, sex, size of liver lesion (training cohort) or presence of liver metastases (validation cohort), cumulative dose of oxaliplatin, cumulative dose of irinotecan, cumulative dose intensity of 5-fluorouracl/capecitabine/tegaful, bevacizumab, and anti-EGFR antibodies

First, there were various kinetic changes in the liver volume during chemotherapy (Fig. 1). The detrimental tendency toward decreased hepatic functional reserve in patients presenting with liver atrophy and toward increased steatosis in patients presenting with liver hypertrophy were compatible with the observations reported in a previous study.[12] Interestingly, a strong correlation was observed between sinusoidal injury in the normal liver parenchyma and the degree of liver atrophy (Table 2; Fig. 1), and the cumulative dose of oxaliplatin, which is a known risk factor for developing sinusoidal injury,[5,9] was found to be an independent predictor of liver atrophy in the training set (Table 3). Use of bevacizumab was associated with a significant reduction in the incidence of sinusoidal injury in the training set (15.1% vs. 40.0%, $P = 0.006$), in line with previous studies,[16–18] and the cumulative incidence of liver atrophy was significantly lower in the patients treated with bevacizumab (Fig. 2). A similar tendency was confirmed in the validation set. These findings suggest that bevacizumab may protect against liver atrophy, which is associated with impaired hepatic functional reserve and increased morbidity,[19] probably through prevention of sinusoidal injury.

Another noteworthy result was that the degree of atrophy of the liver appeared to be a useful predictor of the hepatic functional reserve. Although the correlation was mild, a tendency toward impaired ICG-R15 was confirmed with increasing degree of atrophy (Supplemental Fig. 5). Regression analysis revealed that a 10% decrease of the liver volume corresponded to a worsening of the ICG-R15 by 13.9%. These results suggest that major hepatectomy should be performed with caution in patients presenting with significant shrinkage of the liver after chemotherapy and portal vein embolization (PVE) should be considered when necessary.[2,13] Actually, although no postoperative mortality was recorded in the current population, one patient developed postoperative hepatic insufficiency and refractory ascites or pleural effusion was observed at a higher frequency in the cases with liver atrophy (Table 2). According to previous volumetric studies, the right hemiliver corresponds to a median liver volume of about 65%.[20,21] However, the estimated future liver remnant requirement for patients with an ICG-R15 value of 13.9% is 38.1%, based on the safety criteria of ICG-Krem ≥ 0.05.[22,23] Although the ICG test is not widely available in many countries, the preoperative size of the liver could be a marker to estimate the surgical risk; therefore, preoperative workup should include volumetry of the liver to determine the surgical risk and indications of PVE in heavily pretreated patients.

The limitations of the current analysis include its retrospective design and potential bias in the selected populations. However, the current analysis was performed based on a prospectively collected database, and the patients were treated similarly during the study period. Another limitation was that the patients in the validation cohort were derived from two patient groups undergoing chemotherapy without liver resection: stage IIIB/IIIC patients receiving adjuvant therapy and unresectable stage IV patients. More patients of the former group received oxaliplatin-based chemotherapy without biologic agents, and the latter group was intensively treated with bevacizumab in most cases. However, although the latter group received a greater number of cycles of cytotoxic agents and was accordingly at a higher risk of hepatic injury, the incidence of atrophy was lower, probably because of the higher frequency of use of bevacizumab. These findings strongly imply the protective effect of bevacizumab against the development of liver during chemotherapy and warrant an external validation study.

CONCLUSIONS

The current study confirms that the degree of liver atrophy during/after chemotherapy increases as the duration of chemotherapy for CRC increases. Patients who develop liver atrophy during/after chemotherapy show impaired hepatic functional reserve and are at a higher risk of postoperative morbidity and/or hepatic dysfunction during/after chemotherapy. Bevacizumab may decrease the risk of development of liver atrophy, probably through preventing sinusoidal injury.

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