Research Article

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Hepatic atrophy following preoperative chemotherapy predicts hepatic insufficiency after resection of colorectal liver metastases

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Background & Aims: For patients with colorectal liver metastases (CLM) undergoing major hepatectomy, extensive preoperative chemotherapy has been associated with increased morbidity and mortality. The impact of extensive chemotherapy on total liver volume (TLV) change is unclear. The aims of the current study were twofold: (1) to determine the change of TLV following preoperative chemotherapy in patients undergoing resection for CLM and (2) to investigate the correlations among TLV change, postoperative hepatic insufficiency (PHI), and death from liver failure.

Methods: Clinicopathological features of patients with CLM who underwent preoperative chemotherapy and curative resection were reviewed (2008–2015). TLV change (degree of atrophy) was defined as the percentage difference of TLV (estimated by manual volumetry)/standardized liver volume (SLV) ratio: ([Pre-chemotherapy TLV] − [Post-chemotherapy TLV]) × 100 ÷ SLV (%). Receiver operating characteristic (ROC) analysis was performed to decide the accurate cut-off value of degree of atrophy to predict PHI. The Cox proportional hazard model was performed to identify the predictors of severe degree of atrophy and PHI.

Results: The study cohort consisted of 459 patients, of which 154 patients (34%) underwent extensive preoperative chemotherapy (≥7 cycles). ROC analysis identified the degree of atrophy ≥10% as an accurate cut-off to predict PHI, which was significantly correlated with ≥7 cycles of preoperative chemotherapy. Four factors independently predicted PHI: standardized future liver remnant ≤30% (odds ratio [OR] 4.03, $p = 0.019$), high aspartate aminotransferase-to-platelet ratio index (OR 5.27, $p = 0.028$), degree of atrophy ≥10% (OR 43.5, $p < 0.001$), and major hepatic resection (OR 5.78, $p = 0.005$). Degree of atrophy ≥10% was associated with increased mortality from liver failure (0% [0/374] *vs.* 15% [13/85], $p < 0.001$).

Conclusion: Extensive preoperative chemotherapy induced significant atrophic change of TLV. Degree of atrophy ≥10% is an independent predictor of PHI and death in patients with CLM undergoing preoperative chemotherapy and resection.

Lay summary: Extensive preoperative chemotherapy for patients with colorectal liver metastases (CLM) could induce hepatic atrophy. A higher degree of atrophy is an independent predictor of postoperative hepatic insufficiency and death in patients with CLM undergoing preoperative chemotherapy and resection.

Keywords: Total liver volume; Preoperative chemotherapy; Postoperative hepatic insufficiency; Colorectal liver metastases.

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Introduction

For patients with colorectal liver metastases (CLM), the introduction of effective systemic therapy and an increase in the utilization of extensive hepatectomy have led to significant improvements in long-term survival during the past decades.[1] However, while the perioperative mortality rate for hepatic resection is well below 5%, extensive preoperative chemotherapy remains a leading cause of morbidity and mortality.[2–9]

In the context of effective portal vein embolization, the impact of extensive chemotherapy on the degree of hypertrophy of future liver remnant after portal vein embolization remains controversial.[10,11] One study indicated patients with liver malignancy receiving chemotherapy prior to portal vein embolization had significantly less hypertrophy compared to patients not receiving chemotherapy.[10] Another report indicated that in patients with CLM, FOLFOX treatment was correlated with the development of hepatocyte atrophy in association with sinusoidal dilatation.[12] Meanwhile, there has been no report on the possible association between total liver volume (TLV) atrophy following preoperative chemotherapy and postoperative hepatic insufficiency (PHI).

The aims of the current study were twofold: (1) to determine the change of TLV following preoperative chemotherapy in

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patients undergoing resection for CLM and (2) to investigate the correlations among TLV change, PHI, and death from liver failure.

Materials and methods

Study population

Institutional Review Board approval was obtained for this retrospective study (PA14-0515). A prospectively complied hepatobiliary database of the Department of Surgical Oncology was reviewed, and 794 consecutive patients were identified who underwent curative resection for CLM between January 2008 and December 2015. The following exclusion criteria were then applied: (1) absence of preoperative chemotherapy, (2) previous liver treatment, (3) portal vein embolization, (4) two staged hepatectomy, (5) concomitant ablation, and (6) presence of extrahepatic disease (Fig. 1). From the remaining patients, we selected patients with available peri-chemotherapy abdominal enhanced computed tomography (CT) images (n = 459) for inclusion.

The following data were recorded from the electronic medical record: sex, age, pre-hepatic-resection chemotherapy characteristics (number of cycles and regimens used), pre-hepatic-resection laboratory examinations (serum aspartate aminotransferase, platelet count, and aspartate aminotransferase-to-platelet ratio index [APRI]),[13–15] perioperative outcomes (blood loss, blood transfusion, operative time, and surgical procedure [major resection was defined as hepatic resection including 3 or more liver segments]), CLM characteristics (synchronous *vs.* metachronous, largest metastasis, tumor number, tumor-free margin [R1 defined as tumor-free margin <1 mm]),[16] and non-tumoral liver pathology.[17–19]

Liver volumetry and degree of atrophy

All patients in the current cohort underwent multidetector row enhanced CT, 4, 16, or 64 slices (Light-Speed; GE Healthcare, Piscataway, NJ), using a triphasic liver protocol or single-phase technique at 2.5–5 mm thick slices. Future liver remnant (FLR) volume (cc) was estimated according to our previously reported method[20] before preoperative chemotherapy. Standardized liver volume (SLV) was calculated using the following formula:[21]

$$\text{SLV (cc)} = -794.41 + 1267.28 \times \text{body surface area } (\text{m}^2).$$

Standardized FLR (sFLR) (%) was defined as the ratio of the estimated FLR volume to the baseline SLV.[6] Ratio of estimated FLR to body weight was expressed as a percentage of the body weight.[22] TLV was determined as whole-liver volume minus tumor volume, which was calculated by loading the CT images onto an Advantage Workstation 4.1 (GE Medical Systems, Milwaukee, WI).[23] The accuracy of the TLV measurements based on the use of modern CT techniques has been demonstrated in studies indicating an association between TLV as measured by CT and the actual TLV measurements at autopsy with low interobserver variability (<1%).[21,24] Degree of TLV atrophy by preoperative chemotherapy was defined as the percentage difference of TLV/SLV ratio:

$$([\text{Pre-chemotherapy TLV}] - [\text{Post-chemotherapy TLV}]) \times 100 \div \text{SLV } (\%).$$

Perioperative management

During preoperative chemotherapy, restaging was performed, and CLM were deemed resectable when a hepatic resection was predicted to achieve a negative margin while preserving sFLR >20–30%, sparing 2 continuous hepatic segments, and maintaining vascular inflow/outflow and biliary drainage.[25] Second-line chemotherapy was considered for patients with progression of disease or suboptimal tumor response after first-line chemotherapy.[26,27] Postoperative chemotherapy was administered to complete a total of 12 cycles, including cycles administered preoperatively.

Definition of outcomes

Postoperative complications were classified using standard criteria, and major complications were defined as grade IIIa or higher complications.[28] PHI was defined as a postoperative peak total bilirubin level in serum greater than 7 mg/dl.[29,30] Death from liver failure was calculated at 90 days after surgical resection.

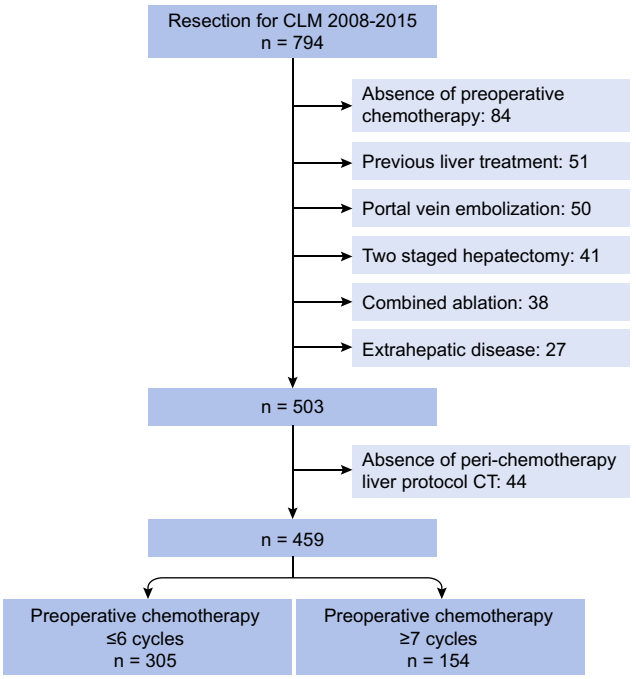

Fig. 1. Patient selection.

Statistical analyses

Continuous variables were compared using the Wilcoxon rank-sum test, and categorical variables were compared using the χ^2 test. The performance of degree of atrophy in predicting PHI was assessed using receiver operating characteristics (ROC) analysis. The accuracy in discriminating patients with and without PHI was assessed by calculating the area under the curve (AUC). Using the best cut-off value determined by the ROC analysis, PHI and 90-day mortality from liver failure were compared among patients. For evaluation of risk factors of severe degree of atrophy after preoperative chemotherapy, univariable and multivariable analyses were performed by logistic regression analysis. For the evaluation of risk factors of PHI, univariable and multivariable analyses were performed by logistic regression analysis. On univariable and multivariable analyses for risk factors of severe degree of atrophy and PHI, either sFLR or ratio of estimated FLR to body weight was employed as one traditional criterion since those 2 parameters should be highly confounded. Variables with p <0.1 in univariable analysis were entered into each multivariable analysis. p <0.05 was considered statistically significant in all analyses. Statistical analysis was performed with JMP software (version 12.1.0; SAS Institute Inc, Cary, NC).

For further details regarding the materials used, please refer to the CTAT table.

Results

Patient characteristics according to the extent of preoperative chemotherapy

Of the 459 patients, 305 (66%) had ≤6 cycles of preoperative chemotherapy and 154 (34%) had ≥7 cycles of preoperative chemotherapy (Fig. 1).[6] Clinicopathologic and operative data for the ≤6 and ≥7 cycles of preoperative chemotherapy groups are summarized in Table 1, and further details about postoperative complications are provided in Table S1.

Compared to the ≤6 cycles group, the ≥7 cycles group had higher APRI, higher degree of atrophy, larger tumor size, more frequent blood transfusion, sinusoidal injury,[19] and PHI. There were no significant differences between the two groups with

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