Predictive value of perfusion CT for blood loss in liver resection

Shintaro Yamazaki, Tadatoshi Takayama*, Yusuke Mitsuka, Nao Yoshida, Atsuko Hosaka, Takaharu Kawai, Hayato Abe, Tokio Higaki

Department of Digestive Surgery, Nihon University School of Medicine, Tokyo, Japan.

1. Introduction

The liver shows unique blood flow characteristics, with two sets of inflow vessels (hepatic artery and portal artery flows) and one set of outflow vessels (hepatic veins). The amount of blood flow changes depending on the background liver parenchyma damage, such as cirrhosis, liver fibrosis, chemotherapy-associated steatohepatitis (CASH) and obstructive jaundice (1-3). However, the hemodynamics of the diseased liver are complex and not yet fully understood.

Measurement of liver stiffness by MRI or ultrasonography is a convenient, less-stressful method to assess damage to the background liver parenchyma (4,5). During liver resection, a correlation has been confirmed between blood loss and liver stiffness and a significant relationship is known to exist between intraoperative blood loss and morbidity (6-8). Evaluation of the background liver damage is thus key to avoiding severe complications.

With colorectal metastasis, perioperative chemotherapy is a common strategy that sometimes results in severe liver steatosis (9,10). CASH involves secondary damage to the liver parenchyma from chemotherapy and represents a risk for liver resection (10,11). Differing from liver cirrhosis, the parenchyma of a liver showing severe steatosis is soft and fragile, making liver stiffness hard to assess by conventional testing (4-8). Perfusion CT enables estimation of blood flow and volume in independent vessels and the mean transit time of blood (2,3,12). This may contribute to a better understanding of the etiology of liver damage. The aim of this study was thus to clarify whether parameters from perfusion CT correlate with liver function and can predict blood loss during liver transection.

2. Materials and Methods

2.1. Study design

Between April 2012 and December 2013, perioperative data including perfusion CT were collected from patients who underwent hepatic resection for liver cancer. First, preoperative data concerning liver function (indocyanine green retention rate at 15 min (ICGR_{15}) and platelet count) were evaluated for correlations with parameters from perfusion CT. Portal blood flow from perfusion CT was assessed on the basis of the histological difference.
of the background liver parenchyma. Finally, the relationship between portal flow from perfusion CT and intraoperative blood loss was analyzed. Written informed consent for clinical analysis was obtained from each patient. This clinical study was approved by the institutional review board of the Nihon University Itabashi Hospital (IRB. RK200114-10).

2.2. Perfusion CT analysis

A 320-detector row CT system (Aquilion One; Toshiba Medical Systems, Tochigi, Japan) was used for perfusion CT. Scan area of the perfusion CT was the whole liver, spleen and pancreas. To minimize respiratory-induced motion of the liver, each patient maintained natural breathing, but a crumpled towel was fixed to the subcostal abdominal wall using an elastic binder during scanning. Circular regions of interest (ROIs) were placed in the aorta, portal vein, right and left lobes of the liver, spleen and pancreas. The median value from five ROIs in the liver parenchyma was used as the representative value for the liver. The size of each ROI was ≥ 1.0 cm². Body Registration software (Toshiba Medical System, Tochigi, Japan) was used to automatically correct for the spatially inconsistent positions of each organ. Perfusion parameters (portal flow, arterial flow, perfusion index) were calculated on a pixel-by-pixel basis using the maximum slope model (Body Perfusion; Toshiba Medical System), with results expressed in units of milliliters per 100 milliliters per minute.

2.3. Blood loss measurement

The amount of blood loss was independently measured during liver transection. Blood loss per transection area of the liver (mL/cm²) was estimated based on the shape of the transection plane, as traced onto a piece of paper that was digitally photographed (Adobe Photoshop Elements® 14 software; Adobe System, San Jose, CA). Blood loss per transection area (mL/cm²) was calculated as blood loss divided by transection area.

2.4. Pathological evaluation

Patients were divided into four categories on the basis of the background liver parenchyma: normal liver (NL), chronic hepatitis (CH), liver cirrhosis (LC) and severe liver steatosis (LS), respectively. The New Inuyama classification was used to assess degree of fibrosis in the liver (grade 0-4) and inflammation (grade 0-3) by two independent pathologists (13). To assess the degree of liver steatosis, the Brunt scoring system (fat deposits in < 33%, 33-66%, or > 66% of hepatocytes) was used (14). Complications were defined according to the Clavien-Dindo classification and severe grade was defined as grade III or above (15).

2.5. Statistical analysis

Data are expressed as medians and ranges or as absolute values and percentages. Student's t-test, the χ² test, and Fisher's exact test were used, as appropriate. For multiple comparisons between different groups, the Bonferroni test was used. Values of p < 0.05 were considered indicative of statistical significance. Cutoff values and correlation coefficients for each variable were obtained from a receiver operating characteristic (ROC) curve. All analyses were performed using JMP version 13.2 statistical software (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patients

Data from 301 patients who underwent hepatic resection for liver cancer between April 2012 and December 2013 were included. Of these, 99 patients were excluded because of unsuitability for imaging studies; repeat resection (n = 64), macrovascular invasion (n = 23) and large tumor > 10 cm in diameter or > 5 cm for bilobar tumors (n = 12). Among them, 36 patients were excluded because of other reasons; lack of or abnormal ICGR₃¢ data (n = 11), lack of informed consent obtained from patients (n = 11), placement of a drainage tube to treat obstructive jaundice (n = 8), and an inability to resect the tumor (n = 6). (Figure 1).

3.2. Preoperative data by background liver parenchyma

After pathological evaluation of the resected specimen, patients were divided into four groups on the basis of the background liver parenchyma: NL group (n = 43); CH group (n = 56); LC group (n = 42); and LS group (n = 25) (Table 1). Regarding the analysis of raw data, significant differences were observed in the rate of hepatocellular carcinoma (p < 0.001) and hepatitis viral infection (p < 0.001). In terms of liver function, significant differences were observed in preoperative platelet count and ICGR₃¢ (p < 0.001).

3.3. Relationship between portal flow and preoperative liver functions

In terms of preoperative data, patients were divided into 3 categories by platelet count (≤ 10⁴/µL, 10⁴-3 × 10⁴/µL and > 3 × 10⁴/µL) and compared in terms of portal flow on perfusion CT (Figure 2). Significant differences were evident between groups and significant positive correlations were apparent between platelet count and portal flow. Patients were divided into 4 categories by ICGR₃¢: ≤ 10%; 10-20%; 20-30%; and > 30% (Figure 3). Significant differences were seen between groups and a significant negative correlation was identified between platelet count and portal flow.
Figure 1. Study flow. Patients were divided into 4 groups based on the background liver. ICGR_{15}, indocyanine green retention rate at 15 min.

Table 1. Patient characteristics by back ground pathological liver parenchyma

<table>
<thead>
<tr>
<th></th>
<th>Normal liver (n = 43)</th>
<th>Chronic hepatitis (n = 56)</th>
<th>Liver cirrhosis (n = 42)</th>
<th>Liver steatosis (n = 25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male, %)</td>
<td>27 (62.8)</td>
<td>44 (78.6)</td>
<td>29 (69.1)</td>
<td>19 (76.0)</td>
<td>0.340</td>
</tr>
<tr>
<td>Age (years)</td>
<td>66 (40-83)</td>
<td>69 (40-83)</td>
<td>68 (46-79)</td>
<td>67 (47-78)</td>
<td>0.870</td>
</tr>
<tr>
<td>Body mass index</td>
<td>22.3 (16.1-31.1)</td>
<td>23.6 (16.8-30.2)</td>
<td>23.4 (17.8-33.3)</td>
<td>24.3 (17.7-31.0)</td>
<td>0.621</td>
</tr>
<tr>
<td>Tumor diameter (mm)</td>
<td>30 (12-115)</td>
<td>25 (14-130)</td>
<td>26 (10-137)</td>
<td>28 (10-133)</td>
<td>0.416</td>
</tr>
<tr>
<td>Number of tumor</td>
<td>1 (1-11)</td>
<td>1 (1-5)</td>
<td>1 (1-3)</td>
<td>1 (1-3)</td>
<td>0.841</td>
</tr>
<tr>
<td>Hepatocellular carcinoma (%)</td>
<td>15 (34.9)</td>
<td>44 (78.6)</td>
<td>38 (90.0)</td>
<td>9 (36.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Colorectal metastasis</td>
<td>19 (44.2)</td>
<td>11 (19.6)</td>
<td>3 (7.1)</td>
<td>16 (64.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gallbladder cancer</td>
<td>8 (18.6)</td>
<td>1 (1.8)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>1 (2.3)</td>
<td>0</td>
<td>1 (2.4)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hepatitis viral infection (%)</td>
<td>9 (20.9)</td>
<td>21 (37.5)</td>
<td>23 (54.8)</td>
<td>3 (1.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>History of chemotherapy</td>
<td>4 (9.3)</td>
<td>1 (1.8)</td>
<td>0</td>
<td>16 (64.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Aspartate aminotransferase (IU/L)</td>
<td>28 (14-93)</td>
<td>34.5 (13-118)</td>
<td>53 (21-205)</td>
<td>32 (14-222)</td>
<td>0.284</td>
</tr>
<tr>
<td>Alanine aminotransferase (IU/L)</td>
<td>20 (8-201)</td>
<td>32.7 (10-158)</td>
<td>47.5 (16-106)</td>
<td>29 (8-315)</td>
<td>0.128</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.2 (2.9-4.9)</td>
<td>4.0 (3.1-4.8)</td>
<td>3.6 (2.7-4.4)</td>
<td>4.0 (3.4-8.8)</td>
<td>0.113</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>0.54 (0.26-1.59)</td>
<td>0.63 (0.23-1.87)</td>
<td>0.82 (0.27-1.96)</td>
<td>0.24 (0.24-1.74)</td>
<td>0.167</td>
</tr>
<tr>
<td>Prothrombin activity (%)</td>
<td>100 (47-100)</td>
<td>97.5 (38-100)</td>
<td>92.5 (63-100)</td>
<td>99 (36-100)</td>
<td>0.501</td>
</tr>
<tr>
<td>Platelet count (10^{12}/μL)</td>
<td>20.5 (10.9-44.3)</td>
<td>15.7 (4.3-74.2)</td>
<td>9.9 (4.0-19.5)</td>
<td>20.0 (7.3-39.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ICG-R15 (%)</td>
<td>8.1 (2.9-19.4)</td>
<td>3.3 (12.7-44.9)</td>
<td>17.8 (7.4-54.9)</td>
<td>11.7 (3.5-37.7)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Data are expressed as median (range), *; indocyanine green retention rate at 15 min.

Figure 2. Relationship between portal flow and platelet count. Significant differences are apparent between portal flow and platelet count in each category (p < 0.05), and platelet count correlates positively with portal flow (p < 0.05).

Figure 3. Relationship between portal flow and ICG-R15. Significant differences are observed between portal flow and ICG-R15 for each group (p < 0.05) and ICG-R15 correlates positively with portal flow (p < 0.05).
3.4. Operation-related data by background liver parenchyma

Blood loss was significantly greater in the LC and LS groups than in the other two groups ($p = 0.041$) (Table 2). Operation time, hepatic ischemia time and transection area did not differ significantly between groups. No perioperative mortality was encountered and the rate of severe-grade complications did not differ between groups.

3.5. Correlation between portal flow and preoperative liver functions

No significant difference in blood loss was seen between NL and CH or between CH and LS. A significant difference was observed between the former two groups and the latter two groups ($p < 0.05$).

4. Discussion

This study showed that portal flow as measured by perfusion CT correlated significantly with ICGR$_{15}$.
and platelet count, which are known to reflect liver functional reserve. Portal flow correlates with the degree of damage to the liver parenchyma and to blood loss during liver transection. Perfusion CT provides information not only on tumor status, but also on portal flow, which is predictive of blood loss.

A significant correlation between complications and damage to the liver parenchyma is well known (7,8,16). A positive relationship existed between intraoperative blood loss and outcomes (17,18). Many techniques have been devised to improve blood loss, including Pringle's maneuver, the total blood flow occlusion technique, hanging maneuver, and use of energy devices during liver transection (19-21). As blood loss during liver transection depends on the damage of background liver parenchyma, assessment of the liver parenchyma plays a key role in avoiding severe complications (7,8,18). Thus, liver stiffness measurement represents a useful preoperative option (4-8). In this study, portal blood flow from perfusion CT correlated positively with platelet count and negatively with ICGR (4). Moreover, a significant correlation was observed between portal flow and blood loss per transection square. This means that blood loss depends on liver stiffness as shown in previous studies using different imaging modalities, such as MRI and ultrasound (4-8).

In imaging studies, CASH is expressed as severe steatosis with splenomegaly (22,23). This implies the presence of portal hypertension while the liver parenchyma is soft and fragile at liver transection. As the underlying etiologies remain poorly recognized, standardized methods are lacking to assess liver function in severe steatosis, including CASH. Interestingly, in the LS group, even though the stiffness of the liver parenchyma differed from that in liver cirrhosis, the relationship between portal flow and blood loss resembled that in the LC group. The pathological features of CASH are known to involve "sinusoidal obstruction syndrome", as blood congestion caused by injury to the peripheral sinusoids (1,9,10,22,23). Therefore, one speculation is that together with fat deposition inside hepatocytes, severe parenchymal congestion results in decreased portal flow. Increased blood loss during liver transection under conditions such as liver cirrhosis is easily understood. Further investigation by perfusion CT should clarify the hemodynamics of severe steatosis.

We used a uniform procedure at the time of operation, but this study did not eliminate the variable influence of surgical factors such as blood flow control and the difference in central venous pressure during liver transection resembling previous studies (4-8). Even though the total number of patients included in this study was larger than another study of perfusion CT, the number of participants in each group was still small because of the 4 different pathological groups. This was the main limitation of the present study, and we therefore aim to analyze a larger number of participants in the future. In addition, two different types of steatosis were included: CASH and obesity. Hemodynamics in those subsets of patients may differ, and larger numbers of patients are required to properly assess each category. In addition, data were lacking to compare the results of portal flow as determined ultrasonographically. Assessment of blood flow is not objective and easily changes between operators, and more objective assessment of blood flow requires estimation from perfusion CT. Further study is needed to compare blood flow data between ultrasound and perfusion CT to determine which modality is more convenient and correct in clinical use.

In conclusion, parameters of perfusion CT enable the assessment of hemodynamics in the diseased liver. Portal flow from perfusion CT is predictive of blood loss at liver transection, and thus appears useful for planning liver resection.

References

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*Address correspondence to:
Tadatoshi Takayama, Department of Digestive Surgery, Nihon University School of Medicine, 30-1 Oyaguchikami-machi, Itabashi-ku, Tokyo 173-8610, Japan.
E-mail: takayama.tadatoshi@nihon-u.ac.jp

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