Original Article

DOI: 10.5582/bst.2020.03303

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.

SUMMARY Blood loss is associated with the degree of damage in liver stiffness. Severe liver steatosis is a matter of concern in liver surgery, but does not correlate with liver stiffness. This study aimed to assess the relationship between blood perfusion of the liver and blood loss in liver pathologies. Data from elective liver resection for liver cancer were analyzed. All patients underwent preoperative assessments including perfusion CT. Patients were divided into 4 groups in accordance with the pathological background of liver parenchyma. Relationships between portal flow as assessed by perfusion CT and perioperative variables were compared. Factors correlating with blood loss were analyzed. In 166 patients, portal flow from perfusion CT correlated positively with platelet count and negatively with indocyanine green retention rate at 15 min. Background liver pathology was normal liver (NL) in 43 cases, chronic hepatitis (CH) in 56, liver cirrhosis (LC) in 42, and liver steatosis (LS) in 25. Rates of hepatitis viral infection and pathological hepatocellular carcinoma were more frequent in LC and CH groups than in the other groups ($p < 0.05$). LC and LS showed significantly worse liver function than the NL and CH groups. Portal flow from perfusion CT correlated positively with damage to liver parenchyma and negatively with blood loss at liver transection. Low portal flow on perfusion CT predicts blood loss during liver transection.

Keywords liver perfusion, blood loss, liver steatosis

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 obstacle 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 cm^2. 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/cm^2) 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/cm^2) 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 χ^2 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 $ICGR_{15}$ 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 $ICGR_{15}$ ($p < 0.001$).

3.3. Relationship between portal flow and preoperative liver functions

In terms of preoperative data, patients were divided into 3 categories by platelet count ($\leq 10^4/\mu L$, 10^4-$3 \times 10^4/\mu L$ and $> 3 \times 10^4/\mu L$) 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 $ICGR_{15}$: ≤ 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.

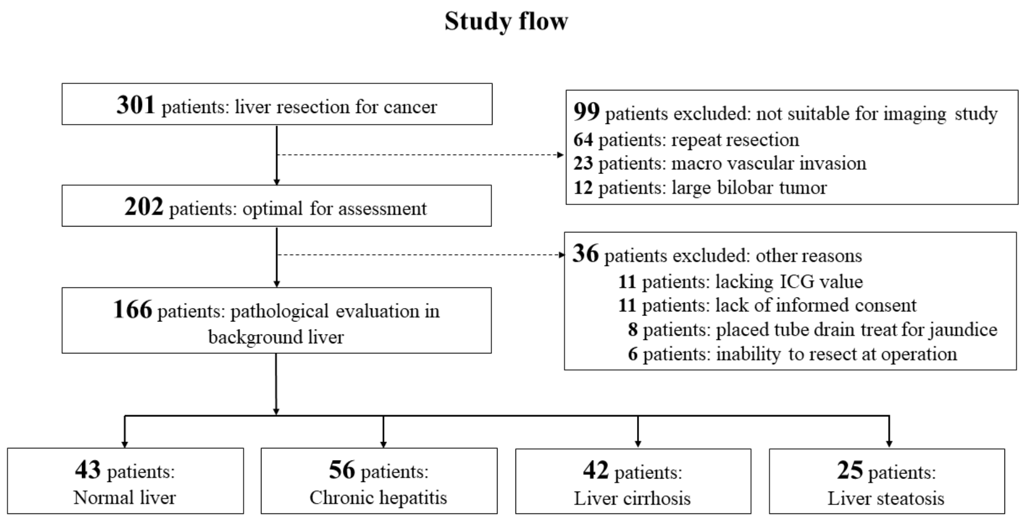

Figure 1. Study flow. Patients were divided into 4 groups based on the background liver. $ICGR_{15}$, indocyanine green retention rate at 15 min.

Table 1. Patient characteristics by back ground pathological liver parenchyma

	Normal liver (*n* = 43)	Chronic hepatitis (*n* = 56)	Liver cirrohsis (*n* = 42)	Liver steatosis (*n* = 25)	*p*-value
Gender (male, %)	27 (62.8)	44 (78.6)	29 (69.1)	19 (76.0)	0.340
Age (years)	66 (40-83)	69 (40-83)	68 (46-79)	67 (47-78)	0.870
Body mass index	22.3 (16.1-31.1)	23.6 (16.8-30.2)	23.4 (17.8-33.3)	24.3 (17.7-31.0)	0.621
Tumor diameter (mm)	30 (12-115)	25 (14-130)	26 (10-137)	28 (10-133)	0.416
Number of tumor	1 (1-11)	1 (1-5)	1 (1-3)	1 (1-3)	0.841
Hepatocellular carcinoma (%)	15 (34.9)	44 (78.6)	38 (90.0)	9 (36.0)	< 0.001
Colorectal metastasis	19 (44.2)	11 (19.6)	3 (7.1)	16 (64.0)	< 0.001
Gallbladder cancer	8 (18.6)	1 (1.8)	0	0	
Others	1 (2.3)	0	1 (2.4)	0	
Hepatitis viral infection (%)	9 (20.9)	21 (37.5)	23 (54.8)	3 (1.2)	< 0.001
History of chemotherapy	4 (9.3)	1 (1.8)	0	16 (64.0)	< 0.001
Aspartate aminotransferase (IU/L)	28 (14-93)	34.5 (13-118)	53 (21-205)	32 (14-222)	0.284
Alanine aminotransferase (IU/L)	20 (8-201)	32.7 (10-158)	47.5 (16-106)	29 (8-315)	0.128
Albumin (g/dL)	4.2 (2.9-4.9)	4.0 (3.1-4.8)	3.6 (2.7-4.4)	4.0 (3.3-4.8)	0.113
Bilirubin (mg/dL)	0.54 (0.26-1.59)	0.63 (0.23-1.87)	0.82 (0.27-1.96)	0.24 (0.24-1.74)	0.167
Prothrombin activity (%)	100 (47-100)	97.5 (38-100)	92.5 (63-100)	99 (36-100)	0.501
Platelet count (10^4/μL)	20.5 (10.9-44.3)	15.7 (4.3-74.2)	9.9 (4.0-19.5)	20.0 (7.3-39.5)	< 0.001
ICG-R15* (%)	8.1 (2.9-19.4)	3.3 (12.7-44.9)	17.8 (7.4-54.5)	11.7 (3.5-37.7)	< 0.001

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

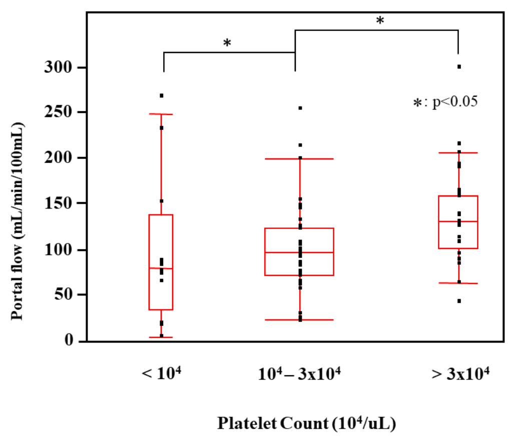

Figure 2. Relationship between portal flow and platelet count. Significant differences are apparent between portal flow and platelet count in each category ($p < 0.05$), and platelet count correlates positively with portal flow ($p < 0.05$).

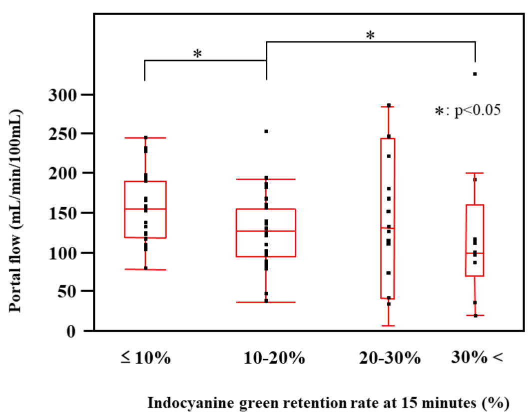

Figure 3. Relationship between portal flow and $ICGR_{15}$. Significant differences are observed between portal flow and $ICGR_{15}$ for each group ($p < 0.05$) and $ICGR_{15}$ correlates positively with portal flow ($p < 0.05$).

Table 2. Operation related variables by back ground pathological liver parenchyma

	Normal liver (n = 43)	Chronic hepatitis (n = 56)	Liver cirrohsis (n = 42)	Liver steatosis (n = 25)	p-value
Operation time (min)	316 (125-672)	321 (150-720)	368 (130-609)	358 (199-577)	0.675
Hepatic ischemia time (min)	121 (46-238)	119 (15-223)	111 (45-163)	127 (15-199)	0.511
Blood loss (mL)	193 (20-2398)	237.5 (15-4491)	404 (30-2158)	387 (54-1494)	0.041
Transection area (cm^2)	56.2 (4.7-219.8)	57.7 (7.3-225.1)	49.4 (7.2-242.1)	50.8 (4.7-152.8)	0.923
Complications (≥ Grade IIIb*) (%)	2 (4.7)	4 (7.1)	4 (9.5)	2 (8.3)	0.104
Mortality (%)	0 (0)	1 (0)	0 (0)	1 (0)	1.000

Data are expressed as median (range), *; Clavien-Dindo classification.

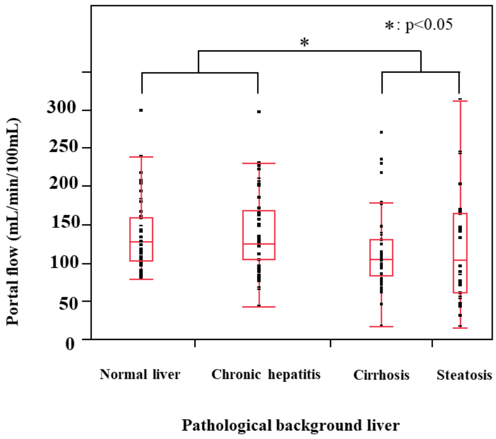

Figure 4. Trends in postoperative liver function. No significant difference in blood loss is evident between NL and CH or between CH and LS. A significant difference is observed between the former two groups and the latter two groups ($p < 0.05$).

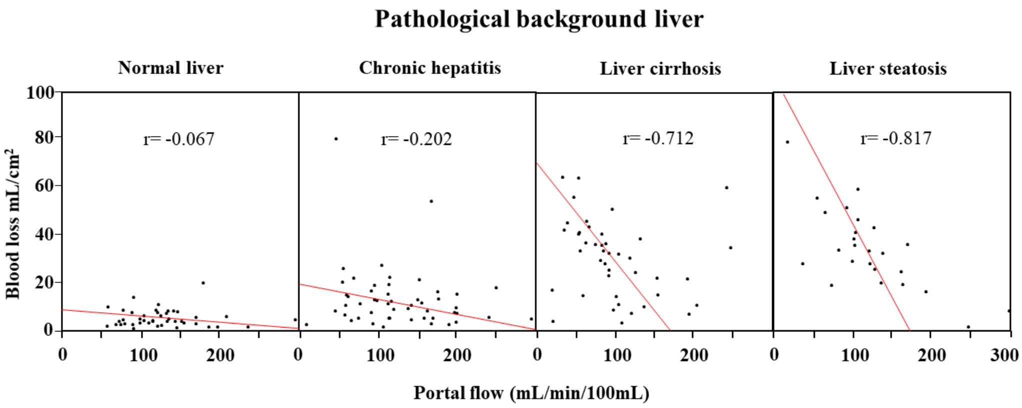

Figure 5. Recovery of parenchyma volume after liver resection. Very weak correlations are evident between portal blood flow and blood loss in NL (r = -0.067) and CH (r = -0202) groups. In contrast, strong correlations are observed in the LC (r = -0.712) and LS groups (r = -0.817).

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 and latter groups ($p < 0.05$) (Figure 4). Very weak correlations were apparent between portal blood flow and blood loss in the NL (r = -0.067) and CH (r = -0.202) groups. In contrast, strong correlations were observed in the LC (r = -0.712) and LS groups (r = -0.817) (Figure 5).

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 $ICGR_{15}$. 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

1. Rubbia-Brandt L, Audard V, Sartoretti P, Roth AD, Brezault C, Le Charpentier M, Dousset B, Morel P, Soubrane O, Chaussade S, Mentha G, Terris B. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. Ann Oncol. 2004; 15:460-466.
2. Ronot M, Asselah T, Paradis V, Michoux N, Dorvillius M, Baron G, Marcellin P, Van Beers BE, Vilgrain V. Liver fibrosis in chronic hepatitis C virus infection: differentiating minimal from intermediate fibrosis with perfusion CT. Radiology. 2010; 256:135-142.
3. Hashimoto K, Murakami T, Dono K, Hori M, Kim T, Kudo M, Marubashi S, Miyamoto A, Takeda Y, Nagano H, Umeshita K, Nakamura H, Monden M. Assessment of the severity of liver disease and fibrotic change: the usefulness of hepatic CT perfusion imaging. Oncol Rep. 2006; 16:677-683.
4. Zhao H, Chen J, Meixner DD, Xie H, Shamdasani V, Zhou S, Robert JL, Urban MW, Sanchez W, Callstrom MR, Ehman RL, Greenleaf JF, Chen S. Noninvasive assessment of liver fibrosis using ultrasound-based shear wave measurement and comparison to magnetic resonance elastography. J Ultrasound Med. 2014; 33:1597-1604.
5. Grgurevic I, Puljiz Z, Brnic D, Bokun T, Heinzl R, Lukic A, Luksic B, Kujundzic M, Brkljacic B. Liver and spleen stiffness and their ratio assessed by real-time two dimensional-shear wave elastography in patients with liver fibrosis and cirrhosis due to chronic viral hepatitis. Eur Radiol. 2015; 25:3214-3221.
6. Wong JS, Wong GL, Chan AW, Wong VW, Cheung YS, Chong CN, Wong J, Lee KF, Chan HL, Lai PB. Liver stiffness measurement by transient elastography as a predictor on posthepatectomy outcomes. Ann Surg. 2013; 257:922-928.
7. Sato N, Kenjo A, Kimura T, Okada R, Ishigame T, Kofunato Y, Shimura T, Abe K, Ohira H, Marubashi S. Prediction of major complications after hepatectomy using liver stiffness values determined by magnetic resonance elastography. Br J Surg. 2018; 105:1192-1199.
8. Hayato A, Midorikawa Y, Mitsuka Y, Aramaki O,

Higaki T, Matsumoto N, Moriyama M, Haradome H, Abe O, Sugitani M, Tsuji S, Takayama T. Predicting postoperative outcomes of liver resection by magnetic resonance elastography Surgery. 2017; 162:248-255.
9. Narita M, Oussoultzoglou E, Chenard MP, Fuchshuber P, Rather M, Rosso E, Addeo P, Jaeck D, Bachellier P. Liver injury due to chemotherapy-induced sinusoidal obstruction syndrome is associated with sinusoidal capillarization. Ann Surg Oncol. 2012; 19:2230-2237.
10. Zhao J, van Mierlo KMC, Gómez-Ramírez J, *et al.* Systematic review of the influence of chemotherapy-associated liver injury on outcome after partial hepatectomy for colorectal liver metastases. Br J Surg. 2017; 104:990-1002.
11. Wolf PS, Park JO, Bao F, Allen PJ, DeMatteo RP, Fong Y, Jarnagin WR, Kingham TP, Gönen M, Kemeny N, Shia J, D'Angelica MI. Preoperative chemotherapy and the risk of hepatotoxicity and morbidity after liver resection for metastatic colorectal cancer: a single institution experience. J Am Coll Surg. 2013; 216:41-49.
12. Shin J, Yoon H, Cha YJ, Han K, Lee MJ, Kim MJ, Shin HJ. Liver stiffness and perfusion changes for hepatic sinusoidal obstruction syndrome in rabbit model. World J Gastroenterol. 2020; 26:706-716.
13. Ichida F, Tsuji T, Omata M, Ichida T, Inoue K, Kamimura T, Yamada G, Hino K, Yokosuka O, Suzuki H. New Inuyama Classification for histological assessment of chronic hepatitis. Hepatol Commun 1996; 6:112-119.
14. Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA, Bacon BR. Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. Am J Gastroenterol. 1999; 94:2467-2474.
15. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004; 240:205-213.
16. Fung J, Poon RT, Yu WC, Chan SC, Chan AC, Chok KS, Cheung TT, Seto WK, Lo CM, Lai CL, Yuen MF. Use of liver stiffness measurement for liver resection surgery: correlation with indocyanine green clearance testing and post-operative outcome PLoS One 2013; 8:e72306.
17. Aramaki O, Takayama T, Higaki T, Nakayama H, Ohkubo T, Midorikawa Y, Moriguchi M, Matsuyama Y. Decreased blood loss reduces postoperative complications in resection for hepatocellular carcinoma. J Hepatobiliary Pancreat Sci. 2014; 21:585-591.
18. Kim MS, Lee JR. Assessment of liver stiffness measurement: novel intraoperative blood loss predictor? World J Surg. 2013; 37:185-191.
19. Kokudo N, Imamura H, Sano K, Zhang K, Hasegawa K, Sugawara Y, Makuuchi M. Ultrasonically assisted retrohepatic dissection for a liver hanging maneuver. Ann Surg. 2005; 242:651-654.
20. Rahbari NN, Koch M, Zimmermann JB, Elbers H, Bruckner T, Contin P, Reissfelder C, Schmidt T, Weigand MA, Martin E, Büchler MW, Weitz J. Infrahepatic inferior vena cava clamping for reduction of central venous pressure and blood loss during hepatic resection: a randomized controlled trial. Ann Surg. 2011; 253:1102-1110.
21. Ichida A, Hasegawa K, Takayama T, Kudo H, Sakamoto Y, Yamazaki S, Midorikawa Y, Higaki T, Matsuyama Y, Kokudo N. Randomized clinical trial comparing two vessel-sealing devices with crush clamping during liver transection. Br J Surg. 2016; 103:1795-1803.
22. Rubbia-Brandt L. Sinusoidal obstruction syndrome. Clin Liver Dis. 2010; 14:651-668.
23. Stevenson HL, Prats MM, Sasatomi E. Chemotherapy-induced sinusoidal injury (CSI) score: a novel histologic assessment of chemotherapy-related hepatic sinusoidal injury in patients with colorectal liver metastasis. BMC Cancer. 2017; 17:35.

Received August 8, 2020; Revised August 26, 2020; Accepted August 28, 2020.

**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

Released online in J-STAGE as advance publication September 6, 2020.