The various evaluation of liver function focused on the major hepatectomy: a narrative review

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Abstract: From long ago, hepatic fibrosis was known as the factor for unfavorable liver function. Most cases with hepatocellular carcinoma (HCC) have fibrosis to varying degrees among even the patients with Child-Pugh A. The severity of hepatic fibrosis is classified several stages, finally these resulted in the cirrhosis. Liver surgery for these patients showed a significantly increased mortality and morbidity. Besides, the patients with hepatic steatosis were increasing worldwide, these were 20% to 30% of peoples in the general population, meanwhile, 74% of obese peoples. Hepatic steatosis increases ischemia reperfusion injury and the risk of postoperative morbidity or mortality after liver surgery. Moreover, it was reported that the steatosis is correlated with liver functions, glucolipid metabolism and inflammation level among the patients with chronic hepatitis B. These pathological mechanism lead to impaired liver function. The complete resection of malignant hepatobiliary tumors is crucial for achieving long-term survival. Major hepatectomy is frequently required for complete resection, and main causes of unresectability is deficiency of remnant liver volume (RLV) or liver functional reserve (LFR). The complete resection of malignant hepatobiliary tumors is crucial for achieving long-term survival. Major hepatectomy is frequently required for complete resection, and main causes of unresectability is deficiency of RLV or LFR. Thus, while we perform major hepatectomy, the balance between the extent of hepatectomy considering the extent of tumor growth (tumor diameter, number, invasion into vessels) and LFR is especially important. This review article will highlight some of the current evaluations of LFR.

Keywords: Indocyanine green (ICG); technetium-99m galactosyl human serum albumin (99mTc-GSA); ALBI grade; EOB-MRI; hepatectomy

Introduction

From long ago, hepatic fibrosis was known as the factor for unfavorable liver function. Most cases with hepatocellular carcinoma (HCC) have fibrosis to varying degrees among even the patients with Child-Pugh A. The severity of hepatic fibrosis is classified several stages, finally these

resulted in the cirrhosis. These patients show macro- and microscopic changes of hepatic parenchyma and perfusion lead to a decrease in hepatocyte function and an increase in transhepatic perfusion resistance, causing portal hypertension. Strong fibrosis and portal hypertension causes bleeding from esophageal varices, hepatic encephalopathy, ascites, spontaneous bacterial peritonitis, thrombocyte count,

and splenomegaly (1). Liver surgery for these patients showed a significantly increased mortality and morbidity (1,2). Besides, the frequency of developing new HCC correlates with the degree of hepatic fibrosis among the patients with hepatitis C virus. These rates were 0.5% per year in patients with platelet counts of more than 150,000/µL, 2.6% per year in those of less than 100,000/µL (3,4).

Recently, the patients with hepatic steatosis were increasing worldwide, these were 20% to 30% of peoples in the general population, meanwhile, 74% of obese peoples (5,6). Hepatic steatosis could be caused by various reasons such as obesity, diabetes, pregnancy, hepatitis, and alcohol abuse (7,8). Hepatic steatosis is classified as mild (<30%), moderate (30–60%), or severe (>60%) grade according to the percentage of hepatocytes containing cytoplasmic fat droplets (9).

Hepatic steatosis augments oxidative stress, inflammation, the apoptosis and shows mitochondrial dysfunction or delayed hepatic regeneration after hepatectomy (10,11). Therefore, hepatic steatosis increases ischemia reperfusion injury and the risk of postoperative morbidity or mortality after liver surgery (11,12). Chen *et al.* reported that the steatosis is correlated with liver functions, glucolipid metabolism and inflammation level among the patients with chronic hepatitis B (13). These pathological mechanism lead to impaired liver function.

The complete resection of malignant hepatobiliary tumors is crucial for achieving long-term survival (14,15). Major hepatectomy is frequently required for complete resection, and main causes of unresectability is deficiency of remnant liver volume (RLV) or liver functional reserve (LFR).

Thus, while we perform major hepatectomy, the balance between the extent of hepatectomy considering the extent of tumor growth (tumor diameter, number, invasion into vessels) and LFR is especially important (16). In other words, hepatectomy should be performed without excess or deficiency within the safe limits of the resection volume determined by LFR. Therefore, accurate LFR assessment is essential for safe hepatectomy. The Child-Pugh classification has been widely used for a long time to evaluate liver function. However, it is widely known that the use of only the Child-Pugh classification is not sufficient as an evaluation method for performing hepatectomy.

In Japan, the Makuuchi criteria are widely used. Patients with uncontrollable ascites and patients with serum bilirubin levels of 2.0 mg/dL or more are not indicated for hepatectomy. The surgical procedure is determined according to the indocyanine green (ICG) retention at 15 min (ICGR15) in patients who have a serum total bilirubin level (T-bil) of less than 2.0 mg/dL. These criteria allow right lobectomy or trisegmentectomy for patients whose ICGR15 is less than 10%. In 1995, Miyagawa *et al.* reported that the hospital and operative mortality rates were 2.3% and 0.6%, the morbidity rate was 37.2%, respectively, among 172 cases (17). Our criteria also specify that patients with uncontrollable ascites and patients with serum bilirubin levels of 2.0 mg/dL or more are not indicated for hepatectomy, and the surgical procedure is determined according to the ICGR15. However, we determine the liver resection volume according to the ICGR15 and the effective liver resection rates (ELRRs) and future remnant liver volume (FRLV) by CT volumetry. ELRR is defined as (resection volume – tumor volume)/(whole liver volume – tumor volume) ×100%. We perform hemi- or extended lobectomy for patients whose ICGR15 is 15% or less. However, our criteria involve ELRR of 60% or less and FRLV of 400 mL or more. If the cases in which ELRR is more than 60% or FRLV is less than 400 mL, we consider portal vein embolization (PVE). Kamiyama *et al.* reported that the morbidity rate was 15.6%, and the mortality rates were 0.1% among 172 cases in 2010 (18).

In this way, accurate evaluation methods of LFR is fundamental and crucial for liver surgery. Here, we reviewed the current evaluation methods for LFR. We present the follow article in accordance with the Narrative Review Checklist (available at http://dx.doi.org/10.21037/dmr-20-73).

The evaluation methods for LFR

ICG

ICG is a drug that is approved by the Food and Drug Administration. The ICG test is generally used as a liver function assay. ICG that is injected into the peripheral vein accumulates in the liver (19). OATP1B3 in hepatocytes and Na+ taurocholate cotransporting polypeptide (NTCP) located in the sinusoidal membrane have been demonstrated to transport ICG (20). Then, ICG is excreted into the biliary system via multidrug resistance-associated protein 2 (MRP2), which is an ATP-dependent export pump (21). ICG is used to evaluate kinetics and is widely used to evaluate hepatic functional reserve. These measurements include ICGR15, ICG elimination rate constant (ICGK), and maximal removal rate of ICG (ICGRmax); among them, ICGR15 is typically used to evaluate LFR in Japan.

Figure 1 Small HCC in left lateral lobe; high fluorescence signal. HCC, hepatocellular carcinoma.
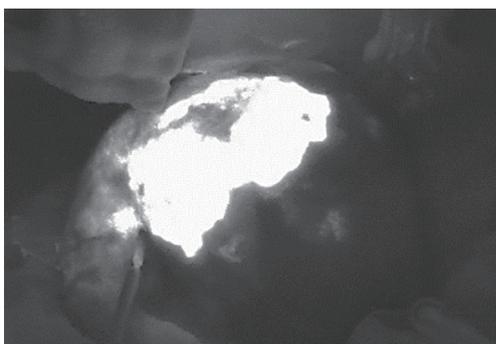

Figure 2 High fluorescence signal shows segment VIII.

This method is relatively safe and economical; however, it is not suitable for patients who have jaundice or a portosystemic shunt and those whose blood collection times are not strict (22). In addition, some patients show allergies to ICG.

Recently, ICG has been applied not only for the evaluation of LFR but also for navigation surgery. ICG combines with serum proteins and produces a fluorescence signal under excitation at 760–820 nm (23). For the application of the liver surgery, several studies have been reported such as the detection of HCC (*Figure 1*) or metastases derived from colorectal carcinoma (24,25), tattooing of the liver segment (26) (*Figure 2*), detection of biliary leakage (27), and evaluation of hepatic congested areas (28) and vascular flow (29) after liver transplantation.

Technetium-99m galactosyl human serum albumin (99mTc-GSA) scintigraphy

99mTc-GSA scintigraphy is well known as a modality for the assessment of LFR. The asialoglycoprotein receptor is only expressed on the sinusoidal surfaces of hepatocytes. 99mTc-GSA binds to the asialoglycoprotein receptor (30). The number of asialoglycoprotein receptors decreases in injured livers (31). Therefore, 99mTc-GSA scintigraphy is used for the assessment of LFR. Clinically, after 99mTc-GSA injection, the accumulation in the heart at 3 min (H3), the accumulation in the heart at 15 min (H15), and the accumulation in the liver at 15 min (L15) are measured. Parameters such as the hepatic uptake ratio to the liver plus heart at 15 min (LHL15; L15/L15+H15) and the blood pool clearance index (HH15; H15/H3) are used. This modality is not influenced by vascular shunt or jaundice (32).

However, 99mTc-GSA scintigraphy might underestimate left lobe function because of partial volume effects and tracer accumulation in the heart (33).

It was also reported that the maximum removal rate of 99mTc-GSA (Rmax) is useful (34). Furthermore, this modality is useful for estimating the LFR of not only the whole liver but also the future liver remnant by combination with CT volumetry (*Figure 3*). Recently, there have been many reports about 3D CT/99mTc-GSA scintigraphy fusion imaging, such as functional FRL rate (FRLR) (35,36). Usually, FRLR and functional FRLT are often correlated, but cases that have macroscopic vascular invasion or a history of preoperative treatment or cases in which the tumor volume is beyond 1,000 mL sometimes show a deviation between FRLR and functional FRLR. Especially in such cases, functional FRLR has very important significance (35).

ALBI grade

In 2015, Johnson *et al.* proposed ALBI grade as a novel method for evaluating LFR (37). They built a Cox regression model based on albumin and $\log_{10}$ bilirubin with the Japanese training set. The linear predictor = ($\log_{10}$ bilirubin × 0.66) + (albumin × –0.085), where bilirubin is in µmol/L and albumin is in g/L. Linear prediction is applied to the cut off values were as followings:

≤–2.60 for ALBI grade 1; more than –2.60 to ≤–1.39 for grade 2; and more than –1.39 for grade 3.

Fagenson *et al.* reported that the ALBI grade was a powerful predictor of post-hepatectomy liver failure (PHLF) and mortality compared with the Model for End-Stage Liver Disease (MELD) score by analyzing 13,783 patients (38). Their study showed that the odds ratios (ORs) for severe PHLF and mortality were 2.30 *vs.* 1.00 and 3.35 *vs.* 1.73,
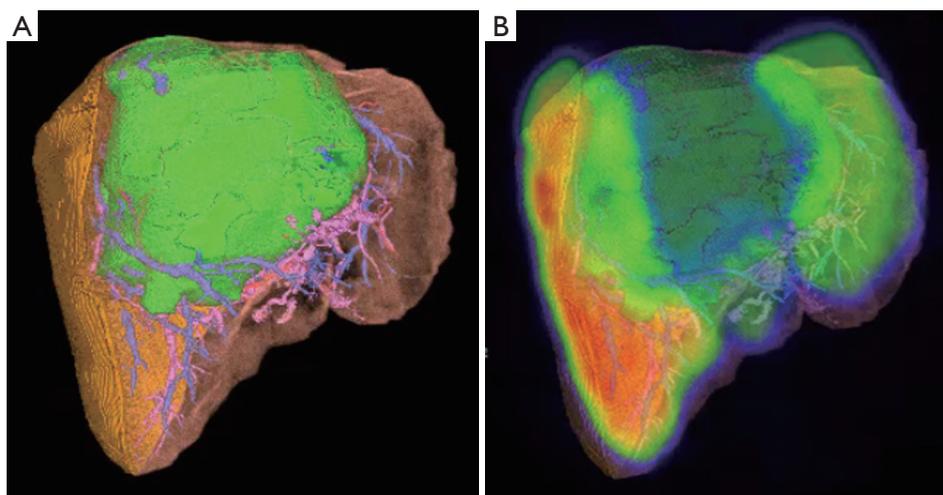
Figure 3 Preoperative 3D navigation. (A) CT-volumetry. (B) CT-volumetry/99mTc-GSA scintigraphy fusion imaging.

respectively (ALBI grade 2/3 *vs.* MELD ≥10). Wang *et al.* reported that the ALBI grade corelated PHLF in patients with HCC who were performed hepatectomy more strongly than the Child-Pugh classification, and not only the incidence but also the severity of PHLF increased with increasing ALBI grade (39). They claimed that patients with ALBI grade 3 seemed to be contraindicated for hepatectomy, those with ALBI grade 2 were not ideal candidates for major resection, and those with ALBI grade 1 were good candidates to perform hepatectomy.

It is known that the significant factors of survival for patients undergoing hepatectomy for liver tumors are both tumor factors and factors concerning liver function. Thus, the ALBI grade was also reported as a survival factor for patients with HCC or intrahepatic cholangiocarcinoma after hepatectomy (39,40). In addition, the ALBI grade at one year and five years after curative hepatectomy for HCC was reported as a long-term prognostic factor (41,42).

The ALBI grade is needless for assessing empirical variables, i.e., hepatic encephalopathy and ascites such as Child-Pugh classification. However, the ALBI grade might not be as useful in patients who show obstructive jaundice due to tumor compressions of the bile duct or those with low serum albumin levels due to extrahepatic disease because the ALBI grade includes only two quantitative variables (39). Moreover, hepatectomy is usually performed for the patients with normal bilirubin levels. Accordingly, the advantage of the ALBI grade in surgical patients often might be based on the serum albumin level. Kokudo *et al.* proposed the albumin-indocyanine green evaluation

(ALICE) grading system, where the grades are determined based on a combination of albumin and ICGR15 (43). The linear predictor = $(\log_{10} \text{ICGR15} \times 0.663) - (\text{albumin} \times 0.0718)$, where ICGR15 is in % and albumin is in g/L. Linear prediction is applied to the cut off values were as followings: ≤–2.20 for ALICE grade 1; more than –2.20 to ≤ –1.39 for grade 2; and more than –1.39 for grade 3. ALICE grade 2 is divided into ALICE grades 2a (–2.20 to –1.88) and 2b (more than –1.88 to ≤–1.39). They reported the predictive power of the ALICE grade for long- and short-term outcomes, and there were no significant differences in the mortality rate or ascites in the ALICE grade 2a group (minor resection; 0.9%, 4.2%. major resection; 2.1%, 4.2%), while the ALICE grade 2b group had a significantly higher mortality rate and incidence of ascites (minor resection; 1.1%, 7.5%. major resection; 5.7%, 18.9%).

Gd-EOB-DTPA-MRI

Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced MRI (EOB-MRI) is frequently performed before hepatectomy. Gd-EOB-DTPA is a liver-specific paramagnetic gadolinium-based contrast agent used exclusively in MRI liver imaging. Gd-EOB-DTPA is a contrast agent transported into hepatocytes by OATP1B3 during the hepatobiliary phase (44,45). Gd-EOB-DTPA is also excreted into the biliary system via MRP2 or MRP3 (46). Therefore, EOB-MRI is useful for the detection of small liver tumors. Furthermore, the application of EOB-MRI for the evaluation of LFR has recently been reported.

The principles by which EOB-MRI can evaluate LFR are the same as those of ICG. Several parameters of EOB-MRI have been reported. The liver-to-spleen signal intensity ratio (LSR) is usually used (47,48). Other previous papers showed the change rates between the hepatic signal intensity at the hepatobiliary phase (SI_H) and those at the precontrast enhanced images (SI_p) (49) and the liver-to-erector spinae muscle (LMR) for standardization (50). These were well correlated with the ICG test, 99mTc-GSA scintigraphy, prothrombin time, serum albumin, total bilirubin, and liver fibrosis or steatosis (48,51,52). This modality could be used for the quantitative analysis of regional liver function, such as the subsegmental level (53), but it is not suitable for patients with obstructive jaundice (48).

Clinically, applications for evaluating the damage of territorial liver function after TACE (54), minimizing postoperative liver failure in patients with cirrhosis (55), and evaluating regional liver function after liver transplantation (50) have been reported.

LiMax test

The LiMax (liver maximum capacity) test was proposed by Stockmann *et al.* in 2009 (56). ^{13}C-labeled methacetin, which is radioactive product is used for this method. ^{13}C-labeled methacetin is exclusively metabolized by the hepatic cytochrome P450 1A2 enzyme, and then the non-radioactive product $^{13}CO_2$ is exhaled. After fasting, the baseline $^{13}CO_2/^{12}CO_2$ ratio in breath is evaluated by a specific analyzer, and the mean is used for the delta-over-baseline (DOB) calculation. The patients are performed bolus injection of 2 mg/kg ^{13}C-labeled methacetin solution, and then the breath analysis regarding $^{13}CO_2/^{12}CO_2$ ratio is performed automatically within 60 min. The LiMax value was calculated as follows: LiMax = $DOB_{max} \times 0.011237 \times$ the estimated CO_2 production rate [300 (mmol/h) body surface area] × the molar mass of 13C-methacetin/the body weight of the person (kg) (56). Normal range had been defined as >315 μg/kg/h [311–575] from previous tests on healthy volunteers (57). Lock *et al.* reported that LiMax test was useful for the patients with colorectal liver metastases who performed hepatectomy after chemotherapy in order to avoiding postoperative morbidity (58).

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Footnote

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