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REVIEW ARTICLE

Issues to be considered to address the future liver remnant prior to major hepatectomy

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Abstract

An accurate preoperative evaluation of the hepatic function and application of portal vein embolization in selected patients have helped improve the safety of major hepatectomy. In planning major hepatectomy, however, several issues remain to be addressed. The first is which cut-off values for serum total bilirubin level and prothrombin time should be used to define post-hepatectomy liver failure. Other issues include what minimum future liver remnant (FLR) volume is required; whether the total liver volume measured using computed tomography or the standard liver volume calculated based on the body surface area should be used to assess the adequacy of the FLR volume; whether there is a discrepancy between the FLR volume and function during the recovery period after portal vein embolization or hepatectomy; and how best the function of a specific FLR can be assessed. Various studies concerning these issues have been reported with controversial results. We should also be aware that different strategies and management are required for different types of liver damage, such as cirrhosis in hepatocellular carcinoma, cholangitis in biliary tract cancer, and chemotherapy-induced hepatic injury.

Keywords Major hepatectomy · Future liver remnant · Portal vein embolization · Post-hepatectomy liver failure

Introduction

Major hepatectomy has become a common procedure in patients with large hepatocellular carcinoma (HCC) or cholangiocarcinoma. Over the past decade, in parallel with improvements in systemic chemotherapy for liver tumors, the indications for major hepatectomy have expanded to include metastases in the liver, especially colorectal liver metastases (CRLM). At the same time, the safety of hepatectomy has improved owing to the appropriate preoperative assessment of the liver function and advances in surgical techniques, leading to decreased intraoperative blood loss.

The risk of post-hepatectomy liver failure (PHLF) has fallen over the past decade, but remains high for several types of procedures; a nationwide survey of board-certified training institutions by the Japanese Society of Hepato-Biliary-Pancreatic Surgery showed 90-day mortality rates of 10.3% after left trisectionectomy and 6.7% after hepatopancreatectomy [1]. One of the most extensive types of hepatectomy, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) [2], which was initially introduced to induce rapid hypertrophy of the future liver remnant (FLR) before second-stage major hepatectomy [3], was still associated with a mortality rate of over 5% in the latest series [4].

Numerous recent studies have reported on strategies for safe major hepatectomy. A historical landmark was the introduction of portal vein embolization (PVE) in the mid-1980s to induce hypertrophy of the FLR [5–7]. The introduction of the Makuuchi criteria, which are based on the indocyanine green retention rate at 15 min (ICG-R15) [8], in the mid-1990s facilitated the preoperative assessment of the liver function. Since the 1990s, various methods have been proposed to accelerate FLR hypertrophy and evaluate the function of the FLR before surgery. However, several issues remain unresolved or controversial in the preoperative planning for major hepatectomy, as summarized in Fig. 1 and reviewed in this article.

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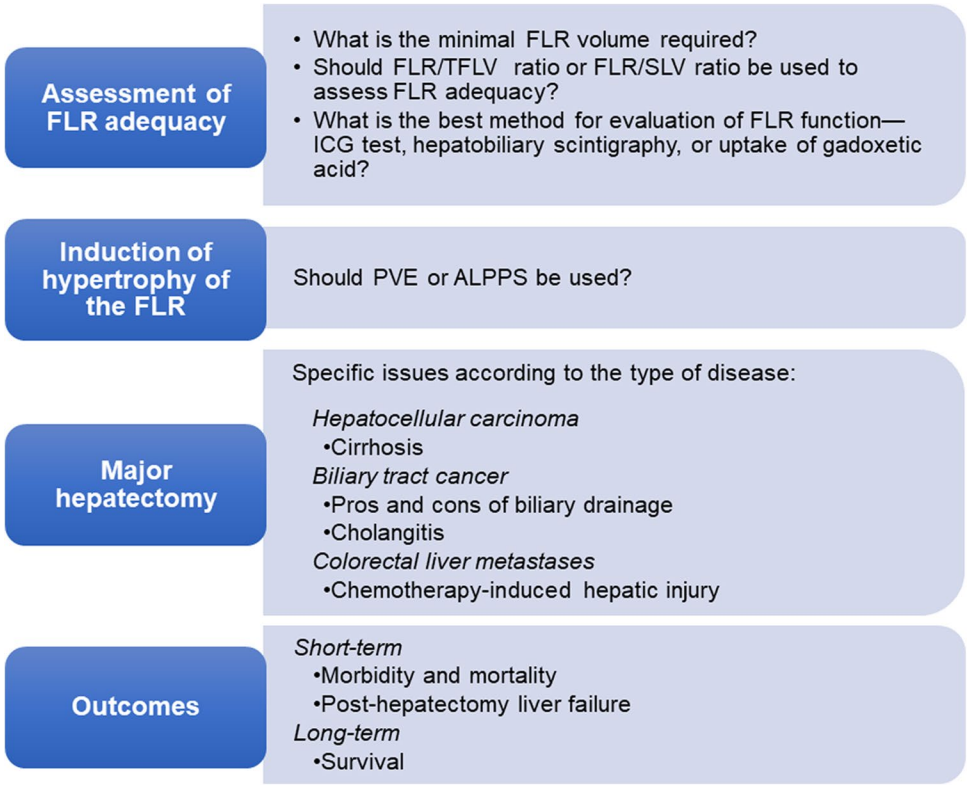

Fig. 1 Summary of the issues to be addressed when planning major hepatectomy. *FLR* future liver remnant, *TFLV* total functional liver volume, *SLV* standard liver volume, *ICG* indocyanine green, *PVE* portal vein embolization, *ALPPS* associating liver partition and portal vein ligation for staged hepatectomy

How should PHLF be defined?

A number of definitions of PHLF have been proposed. Most of them focus on the serum total bilirubin level and prothrombin time. Among the most commonly cited definitions are prothrombin time < 50% and serum bilirubin level > 50 μmol/L ("50–50 criteria") on the fifth postoperative day, proposed by Balzan et al. [9], and peak postoperative bilirubin level > 7.0 mg/dL (120 μmol/L), proposed by Mullen et al. [10]. Both criteria were shown to predict postoperative liver-related death. However, the bilirubin level > 7.0 mg/dL (120 μmol/L) criterion is simpler, and its use as an index of PHLF seems more feasible because this criterion predicted liver failure-related death with a sensitivity of 93.3% and specificity of 94.3%, while the 50–50 criteria predicted in-hospital death, including mortality not related to liver failure, with a sensitivity of 69.6% and specificity of 98.5% [9, 10].

Many studies have evaluated the preoperative factors that predicted PHLF based on the above definitions. The factors reported to predict PHLF included low immediate postoperative platelet count in patients with HCC or preoperative cholangitis in patients with hilar cholangiocarcinoma [11, 12]. When discussing these studies, it should be noted that not all patients with preoperative factors predictive of PHLF died after hepatectomy. Whether or not hepatectomy should be considered contraindicated in all patients with preoperative factors predictive of PHLF is another question.

The International Study Group of Liver Surgery (ISGLS) proposed a grading system for PHLF (Table 1) based on the literature and expert consensus [13], and this can be applied widely in clinical settings. Although the ISGLS definition of PHLF is based on the postoperative bilirubin level and prothrombin time, the ISGLS grading of severity of PHLF is based on the degree of deviation from normal clinical management. In clinical practice, it is reasonable for grade B and C PHLF to generally be considered clinically relevant PHLF and differentiated from grade A PHLF.

Is pre- or post-operative platelet count helpful as a simple index to predict PHLF?

Several studies have reported that a preoperative platelet count below $10–15 \times 10^4$/μL was associated with PHLF or mortality [14–21]. The aspartate aminotransferase (AST)/platelet count ratio index (APRI = AST level [/upper normal limit]/platelet counts [10^9/L] × 100) initially proposed by Wai et al. as a simple but highly reliable predictor of significant fibrosis and cirrhosis in patients with treatment-naïve chronic hepatitis C [22] and recommended as the preferred noninvasive test for assessing the presence of cirrhosis

Table 1 Definition and grading of PHLF proposed by the International Study Group of Liver Surgery [13] (cited with permission)

Definition of PHLF	• Increased* INR and concomitant hyperbilirubinemia on or after postoperative day 5 or • Need for clotting factors to maintain normal INR and concomitant hyperbilirubinemia on or after postoperative day 5 or • In patients with increased INR or bilirubin concentration preoperatively, increased INR and increased serum bilirubin concentration on or after postoperative day 5 compared with the values of the previous day	
Grade	A	Abnormal laboratory parameters, but requiring no change in clinical management
	B	Resulting in a deviation from the regular clinical management, but manageable without invasive treatment, e.g., administration of FFP, albumin, daily diuretics, or noninvasive ventilation
	C	Resulting in a deviation from the regular clinical management and requiring invasive treatment, e.g., hemodialysis, mechanical ventilation, extracorporeal liver support, rescue hepatectomy, transplant, or circulatory support

PHLF post-hepatectomy liver failure, *INR* international normalized ratio of prothrombin time, *FFP* fresh-frozen plasma

*According to the normal cut-off levels defined by the local laboratory

in the Asian-Pacific Association for the Study of the Liver consensus guidelines [23] has also been reported as a useful predictor of PHLF [24–26]. Ichikawa et al. [24] and Mai et al. [26], respectively, reported AST [IU/L]/platelet count [10^4/μL] > 10 and APRI > 0.55 as predictors of PHLF. Most of these studies evaluated patients with HCC, and one by Ratti et al. evaluated patients with CRLM treated with preoperative chemotherapy (mainly an oxaliplatin-based regimen). The association of thrombocytopenia with PHLF in these patients seems reasonable, as thrombocytopenia indicates portal hypertension that occurs either as a result of liver cirrhosis [27] or oxaliplatin-induced sinusoidal injury [28, 29]. In contrast, in the series by Golriz et al. [20], the most frequent liver disease was cholangiocarcinoma, and HCC accounted only for 15% of the total patients. Other studies showed that an immediate postoperative low platelet count < 10×10^4/μL or postoperative > 40% decrease in the platelet count predicted PHLF or mortality [11, 30, 31]. Margonis et al. evaluated the volume regeneration of remnant liver 2 months after major hepatectomy in 99 patients, and a postoperative platelet count < 15×10^4/μL was associated with a significant reduction in FLR hypertrophy [32]. These findings suggest that platelets may play a role in aiding liver regeneration, and several proteins, such as vascular endothelial grow factor or thrombospondin-1 secreted from platelet α-granules, have been suggested to modulate liver regeneration [33], although the mechanism remains unclear.

What is the minimal safe FLR volume?

Results of systemic volumetry to determine the volume of liver to be resected were first reported in 1997 by Kubota et al. [34], who showed that resection of up to 60% of the nontumorous liver parenchyma could be tolerated in patients with an ICG-R15 of < 10%, and resection of up to 50% of the nontumorous liver parenchyma could be tolerated in patients with an ICG-R15 of 10–20%. Notably, however, there were no deaths in their series, indicating that their criteria of 50% or 60% resection did not reflect the upper limit of safe hepatectomy. Resection of up to 80–90% of the liver was described in 2 case reports published in the 1960s and 1980s [35, 36], but the FLR volume in these reports was only estimated by the surgeons, without an exact volumetric measurement.

Nagasue et al., who were the first to study the regeneration of the FLR using computed tomography (CT), estimated that extended right lobectomy resected 80% of the whole liver [37]. Supporting this estimate, Abdalla et al., in a volumetric study of 102 patients without any hepatobiliary disease, showed that the left liver (segments II, III, and IV) could be very small; in their series, the left liver volume accounted for ≤ 25% of the total liver volume (TLV) in more than 10% of patients [38].

Currently, the consensus regarding the minimal safe FLR volume in patients with a normal liver is approximately 25–30% of the total functional liver volume (TFLV), where the TFLV is the volume of the liver minus the volume occupied by tumor [39–41]. At present the University of Texas MD Anderson Cancer Center's criteria for the standardized liver volume (SLV) of ≥ 20% is the minimal acceptable FLR volume for a safe resection in a normal liver [42].

Should the FLR/TFLV ratio or FLR/SLV ratio be used to assess FLR adequacy?

Another important issue in preoperative planning for major hepatectomy is whether the FLR volume ratio should be estimated using the TFLV or the SLV. While the TFLV is

measured directly by CT, the SLV is calculated using the body surface area. Generally, the ratio of the FLR volume to the TFLV is calculated using the formula FLR volume [ml]/(TLV [ml]—tumor volume [ml]). This formula is based on the assumption that the hepatic parenchyma excluding the tumor constitutes the TFLV. This method has been criticized, however, because it may be inaccurate in patients with multiple tumors, may underestimate tumor volume in patients with lesions beyond the resolution of imaging, and may underestimate the liver volume under conditions of compromise due to cholestasis in patients with bile duct tumors [43].

In recipients of liver transplants, not TLV but SLV is routinely used to estimate the required graft volume because the liver function of these patients is deteriorated and their liver is usually atrophic or abnormally enlarged. Yamashita et al. recently showed that hepatic atrophy of ≥ 10% after chemotherapy was a predictor of hepatic insufficiency after resection of CRLM [44]. Their results suggested the risk of overestimation of the FLR ratio based on TFLV, especially in patients who receive extensive preoperative chemotherapy for CRLM. Use of the FLR/TFLV ratio after PVE may also produce inaccurate estimates of FLR adequacy if PVE results in greater atrophy of the liver to be resected than hypertrophy of the FLR.

Thus far, only a few studies have compared postoperative outcomes between the two methods of FLR evaluation. Ribero et al. compared the FLR/TFLV and FLR/SLV ratios in 243 patients who underwent major hepatectomy [45]. They reported that TFLV was lower than the SLV in 60% of the patients. In addition, the incidence of PHLF, defined as peak postoperative serum total bilirubin level > 7.0 mg/dL (120 µmol/L), was significantly higher in the patients who underwent hepatectomy without PVE based on a safe FLR/TFLV ratio but deficient FLR/SLV ratio than in the patients who underwent hepatectomy without PVE based on safe FLR/SLV and FLR/TLV ratios (6/27 [22.2%] vs. 8/162 [4.9%], $p = 0.001$), although the mortality rates in the two groups were similar [45]. Similarly, Kim et al. evaluated the outcomes of right hepatectomy in 74 patients and showed that the incidence of PHLF was significantly higher in the patients with an FLR/SLV ratio < 30% than in patients with an FLR/SLV ratio ≥ 30%, but PHLF ratio did not markedly differ between patients with an FLR/SLV ratio < 40% versus ≥ 40% or the patients with an FLR/TFLV ratio < 40% versus ≥ 40% [46]. These two studies suggested that an evaluation by the FLR/SLV ratio would be more appropriate for predicting the risk of PHLF. In both of these studies, however, the number of patients with a safe FLR/SLV ratio but an insufficient FLR/TFLV ratio was small (5 of 243 patients in the Ribero et al. series, 1 of 74 patients in the Kim et al. series).

Several formulae to calculate the SLV have been reported based on different patient cohorts. Olthof et al. compared the TLV with the SLV calculated according to 16 different formulae for 529 patients in the ALPPS registry, 85% of them Caucasian, and showed that the majority of the formulae produced SLV values substantially higher than the measured TLV [47]. Therefore, whether or not the SLV estimated from the body surface area more appropriately reflects the total liver function than the TLV measured on CT or if a higher value of SLV than TLV results in expanding the indication of PVE to reduce the risk of PHLF remains unclear.

What is the best method for the preoperative assessment of the FLR function?

ICG retention rate

The combination of the FLR/TFLV ratio and ICG-R15 value is commonly used to predict the risk of PHLF, especially in Asian countries. The Makuuchi criteria [8] regulate the degree of hepatic resection based on the ICG-R15 value, and the utility of these criteria were recently validated with a Japanese national clinical database showing a higher incidence of postoperative Clavien–Dindo grade > III morbidities in the patients exceeding the criteria [48].

The ICG-R15 value, however, reflects the function of the TFLV but not that of the FLR, and whether or not a gain of FLR volume as a result of PVE is a true reflection of an improved FLR function remains unclear. Several studies have suggested that the FLR function increases before hypertrophy of volume is apparent on CT [49, 50]. Uesaka et al. measured the biliary ICG concentration from multiple biliary drainage tubes placed for draining the entire liver in 8 patients who underwent right PVE and reported that the ratio of ICG excretion in the FLR to ICG excretion in the whole liver increased 20% on average after PVE, while the FLR/TFLV ratio increased only 8% on average [49].

Pattern of FLR volume regeneration

A number of studies have evaluated the relationship between volume regeneration of the FLR and functional recovery of the FLR. Studies evaluating chronological changes in the remnant liver volume after donor hepatectomy for living donor liver transplant showed a rapid volume increase in the early (within 3 months) postoperative period despite functional recovery taking up to one year for normalization [51, 52]. Maeda et al. recently evaluated the volume change following PVE and also 7 days after extended hepatectomy in 289 patients with perihilar cholangiocarcinoma [53]. They showed a significant negative correlation between the kinetic

growth rate (kGR), defined as the change in the FLR/SLV ratio [%] divided by the interval [weeks] [54] after PVE and kGR after hepatectomy. This result makes sense from the viewpoint that remarkable FLR hypertrophy occurred before rather than after surgery and was associated with a reduced incidence of PHLF. These authors also showed that there was no association between the kGR after either PVE or hepatectomy and the incidence of hepatic insufficiency. They concluded that there was a discrepancy between the recovery of the FLR volume and the recovery of the FLR function in the early phase of liver regeneration [53]. Because most patients in their series had hilar cholangiocarcinoma, other factors, such as perioperative cholangitis, might have affected the incidence of PHLF.

Watanabe et al. evaluated the factors that affected hypertrophy of the FLR after PVE and showed that an initial FLR volume ≥ 35% of the TLV, alkaline phosphatase level ≥ 450 IU/dL, and cholinesterase level < 220 ng/dL were independent predictors of insufficient FLR hypertrophy (< 25% increase) [55]. An inverse correlation between the FLR volume and hypertrophic rate was reported in a series of donor hepatectomies that showed faster regeneration after right hepatectomy than after left hepatectomy [52] as well as in an experimental study of the ALPPS model in rats [56]. The ALPPS study also showed that a small FLR volume was associated with increased severity of sinusoidal injury and elevated activation of hepatic progenitor cells after ALPPS. These findings suggested discrepancy between functional recovery and volume regeneration of FLR.

Specific imaging methods proposed to evaluate the FLR function

For the preoperative evaluation of the FLR function, several methods have been reported (Table 2).

Two methods are based on CT. Nagino et al. evaluated the change in the FLR volume and plasma disappearance rate of ICG (kICG) in patients who underwent extended hepatectomy following PVE for biliary cancer; the study included 176 survivors and 17 patients who died due to postoperative complications. The authors showed that FLR hypertrophy did not distinguish between survivors and non-survivors, but the kICG after PVE did, so they proposed a kICG of the FLR ≥ 0.05, with the kICG of the FLR defined by the formula kICG × FLR [ml]/TLV [ml], as a criterion for safe hepatectomy [57]. This cut-off value was validated in their later series [58, 59]. Shindoh et al. proposed evaluating the FLR function using the kGR, defined as the increase in the FLR volume from baseline divided by the length of time in weeks after PVE, and this was shown to be a better predictor of postoperative morbidity and mortality than the preoperative FLR/SLV ratio or FLR hypertrophy rate in a large series of patients [54]. However, in another series, kGR did not correlate with outcomes after ALPPS [60]. In fact, the high incidence of morbidity and mortality suggested that no volumetric measurement predicted outcomes after ALPPS.

Scintigraphy using technetium 99m (^{99m}Tc)-labeled galactosyl human serum albumin (GSA), which is mainly available in Japan, was developed on the basis that GSA receptors are expressed exclusively on functional hepatocytes involved in the clearance of glycoproteins containing terminal galactose residues from the circulation [61]. In Europe, however, ^{99m}Tc-labeled mebrofenin hepatobiliary scintigraphy is more popular than ^{99m}Tc-labeled GSA

Table 2 Methods proposed for evaluating the function of the FLR

Imaging modality	Index	Definition	Authors	Year
CT	kICG-F	kICG × FLR volume [ml]/TLV [ml]	Nagino et al. [57]	2006
	Kinetic growth rate	Degree of FLR hypertrophy [%]/duration after PVE [weeks]	Shindoh et al. [54]	2013
Scintigraphy	GSA-Rmax in FLR	Maximal removal rate of ^{99m}Tc-GSA in the FLR measured from SPECT images	Kwon et al. [63]	2006
	^{99m}Tc-GSA liver uptake ratio	Liver radioactivity/injected radioactivity) in the FLR measured in SPECT and CT fusion images	Iimuro et al. [64]	2010
	FLR function by HBS	^{99m}Tc-labeled mebrofenin uptake in FLR from dynamic HBS images	de Graaf et al. [65]	2010
MRI	Remnant hepatocellular uptake index	FLR volume [liters] × [(L_{20}/S_{20}) − 1]	Kim et al. [69]	2018
	Increase of signal intensity of FLR	$(SI_{HB} - SI_{unenhanced})/SI_{unenhanced}$	Asenbaum et al. [70]	2018

FLR future liver remnant, *kICG* plasma disappearance rate of indocyanine green, *TLV* total liver volume, *PVE* portal vein embolization, *Tc* Technetium, *GSA* galactosyl human serum albumin, *SPECT* single-photon emission computed tomography, *HBS* hepatobiliary scintigraphy, *L20* the mean signal intensity in the FLR on hepatobiliary phase images, S_{20} the mean signal intensity in the spleen on hepatobiliary phase images, SI_{HB} the signal intensity in the hepatobiliary phase, $SI_{unenhanced}$ the signal intensity on unenhanced scan

hepatobiliary scintigraphy. Mebrofenin enters hepatocytes and is excreted into the bile canaliculi unmetabolized; therefore, ^{99m}Tc-labeled mebrofenin hepatobiliary scintigraphy measures the kinetic process of the uptake and excretion by hepatocytes [62]. Measuring the uptake rate of these substances using single-photon emission computed tomography permits the estimation of the function of specific regions of the liver, and several studies have shown that the FLR function measured using hepatobiliary scintigraphy was more accurate than the FLR volume for predicting PHLF [63–66]. Scintigraphy is more expensive than CT, and methods to measure the uptake rate are rather complicated. In addition, the possibility of underestimating the left lobe function and overestimating the right lobe function was reported [67, 68].

A simpler method of evaluating the FLR function is magnetic resonance imaging with intravenous injection of gadoxetic acid contrast medium, which is transported into hepatocytes. The increase in the signal intensity in the FLR in the hepatobiliary phase compared to the unenhanced phase might be an indicator of the FLR function that could predict the risk of PHLF [69, 70]. Graaf et al. proposed using the ^{99m}Tc-labeled mebrofenin uptake rate in the FLR [%/min] divided by the body surface area [m^2] ≤ 2.69%/min/m^2 as a predictor of PHLF [65]. This predictor was recently validated in a multi-institutional study from the ALPPS registry [71], showing that an uptake rate ≤ 2.7% min/m^2 and daily kGR ≤ 4.1% were independent predictors of ISGLS grade B/C PHLF.

Should PVE or ALPPS be used to induce hypertrophy of the FLR?

Another key question is whether PVE or ALPPS is superior for ensuring an adequate FLR for two-stage hepatectomy. Initially PVE was performed mostly in patients with hilar cholangiocarcinoma [5]. As the indications for hepatectomy for CRLM expanded to include even advanced bilobar disease, the use of major hepatectomy and, in parallel, the use of PVE increased remarkably [72, 73]. Furthermore, the development of chemotherapy contributed to the improvement of the prognosis after hepatectomy [74].

Jaeck et al. proposed two-stage hepatectomy for bilobar multiple CRLM, consisting of wedge resection of tumors in the FLR followed by PVE and second-stage major hepatectomy, in order to minimize the risk of both liver failure after major hepatectomy and rapid tumor growth after PVE [75]. In this series, the waiting periods between first hepatectomy and PVE and between PVE and second hepatectomy were 5–109 days and 4–6 weeks, respectively. Given these findings, ALPPS seems superior to PVE, as with ALPPS, FLR hypertrophy was confirmed after a median interval of 9 days (range 5–28) following right portal vein ligation and in situ hepatic parenchymal dissection in the first operation [3].

A randomized controlled trial from a Scandinavian group that compared resection rates between two-stage hepatectomy with PVE and ALPPS showed higher resection rates with ALPPS than PVE (44/48 [92%] vs. 28/49 [57%], $p < 0.0001$) [76]. In that series, the mean kGR [54] during the first 7 days was 12.3% in the PVE group and 35.4% in the ALPPS group [76]. Interestingly, such remarkable hypertrophy has also been shown even without actual liver parenchymal partition. Another randomized controlled trial compared PVE and liver partition with portal vein ligation using radiofrequency for virtual liver parenchymal partition (RALPP) [77] and showed a significantly more rapid increase in the FLR volume after the virtual liver parenchymal partition (mean increase of 80.7% after a median of 20 days after RALPP vs. 18.4% after a median of 35 days after PVE, $p < 0.001$) [78]. Other modified approaches with only partial parenchymal dissection or with tourniquet placement without splitting induced a 60–70% increase in the FLR volume in 7–14 days [79–81].

Although several experimental studies with animal models of ALPPS have suggested that cytokines might be associated with enhanced FLR hypertrophy [82–84], how much discrepancy exists between the recovery of the FLR volume and that of the FLR function after ALPPS has not been fully elucidated [85, 86].

Considering the rather high rate of complications of ALPPS, including biliary fistula after the first-stage operation and PHLF after second-stage hepatectomy, routine application of ALPPS for extensive disease is not yet warranted; PVE, a less-invasive method for inducing FLR hypertrophy, cannot be replaced with ALPPS. The use of spherical microspheres as embolization material or additional embolization of segment IV for extended right hepatectomy may enhance PVE-induced FLR hypertrophy [87]. The median hypertrophy rate of segments II and III after embolization of the right portal vein and segment IV branches exceeded 50% [88, 89]. The combination of PVE with transarterial chemoembolization is also effective, especially in patients with HCC [90, 91]. Furthermore, liver venous deprivation combining PVE with ipsilateral hepatic vein embolization, first reported by Nagino et al. [92] and recently increasingly frequently reported [93–95], shows promise. In these studies, although the interval until hepatectomy was 3 to 4 weeks, the degree of hypertrophy [96] or kGR was higher after liver venous deprivation than after PVE alone, and there were few procedure-related or postoperative severe complications. Rapid functional recovery was also confirmed using hepatobiliary scintigraphy [97]. LVD may therefore be a new and safe approach for optimizing liver regeneration before major hepatectomy [98].

What issues need to be considered in planning for major hepatectomy for different types of disease?

Major hepatectomy is indicated for various types of liver tumor, and the background liver damage and approach to surgery, especially whether or not the extrahepatic bile duct is resected, differ by type of disease. These factors influence the degree of liver regeneration. For example, several studies evaluating the liver function by ^{99m}Tc-mebrofenin hepatobiliary scintigraphy have shown that the liver function in patients with perihilar cholangiocarcinoma was similar to that in patients with HCC and worse than that in patients with benign liver tumor [99, 100]. Therefore, management should be tailored to the type of disease.

HCC

HCC generally develops in livers damaged by chronic hepatitis or cirrhosis. The ICG test has been a popular method of estimating the degree of liver damage, although it is mostly performed in Asian countries. In the Barcelona Clinic Liver Cancer staging system [101], which is mainly used in Europe, hepatectomy is not indicated in patients with HCC with portal hypertension, defined as a hepatic venous pressure gradient ≥ 10 mmHg [102]. This seems reasonable, as portal hypertension resulting in splenomegaly, thrombocytopenia, or varicose veins is more common in patients with HCC than in those with other hepatic tumors. However, routinely measuring the hepatic venous pressure is not practical. A platelet count-based index such as the APRI is a simple and feasible predictor of liver fibrosis [22], and its validity as a predictor of postoperative outcomes in patients with HCC has been reported [103, 104]. Another study by Navarro et al. showed that a platelet count $< 140 \times 10^9$/L and FLR/body weight ratio < 0.55% were independent predictors of clinically relevant PHLF in patients with HCC, but an ICR-R15 > 11% and FLR/TLV ratio < 35% were not [21].

Yamashita et al. compared the outcomes after PVE between patients with HCC, patients with biliary tract cancer, and patients with CRLM and showed that subsequent major hepatectomy was achieved most frequently in the patients with HCC (HCC, 64/70 [91%]; biliary tract cancer, 133/172 [77%]; CRLM, 59/77 [77%]; $p = 0.029$). However, while disease progression was the most frequent reason for deciding against hepatectomy in the patients with biliary tract cancer (79%) and CRLM (83%), it was cited as the reason for only 33% of dropout cases among patients with HCC [105]. These results suggest that the rather slow growth of HCC is associated with a long waiting period after PVE.

Chan et al. compared the outcomes of PVE and ALPPS in patients with HCC, most of whom had HCC related to hepatitis B virus infection. The rates of hypertrophy of the FLR and resectability were both significantly higher in the ALPPS group than in the PVE group, and the postoperative morbidity and mortality rates were similar in the PVE and ALPPS groups [4]. Notably, in their series, the median increment in the FLR volume after the first operation of ALPPS was 48%, which was smaller than the figures from other studies, mainly of patients with CRLM.

We should be aware that HCC is associated with a higher risk of insufficient hypertrophy after PVE than other types of cancer affecting the liver.

Biliary tract cancer

Major hepatectomy for biliary tract cancer is mainly indicated in patients with perihilar cholangiocarcinoma. Management of obstructive jaundice and cholangitis is required both before and after hepatectomy because the procedure usually is accompanied by extrahepatic bile duct resection (EBR). Takagi et al. showed that the regeneration rate of the FLR during the early postoperative period was lower after major hepatectomy with EBR than after major hepatectomy without EBR both in rat models [106] and in a study of 244 human patients [107]. These authors also showed that EBR was an independent predictor of PHLF among the patients who underwent right hepatectomy [107]. Although several studies have shown similar incidences of morbidity and mortality in patients who underwent major hepatectomy with and without preoperative biliary drainage for jaundice, the study populations of those reports were small (range 47–71), and the mortality rate tended to be higher among patients without biliary drainage than among those with drainage [108–111]. A European multi-institutional study of 366 patients who underwent right or left hepatectomy with EBR revealed that preoperative biliary drainage was associated with decreased mortality in the patients with right hepatectomy, but increased mortality in those with left hepatectomy [112]. Such paradoxical results might be explained by the findings that both preoperative jaundice and cholangitis as well as small FLR were predictors of PHLF [12, 113].

Ribero et al. reported that preoperative cholangitis was associated with an increased risk of hepatic insufficiency after major hepatectomy for hilar cholangiocarcinoma, especially in the patients with FLR < 30% [12]. They also showed that cholangitis occurred more frequently in the patients with biliary drainage than in those without. However, their results showed that preoperative total bilirubin level > 3 mg/dL was an independent predictor of hepatic insufficiency, suggesting the importance of managing jaundice with efforts to minimize biliary drainage–induced complications [12]. Watanabe et al. proposed an age ≥ 69 years old as another

risk factor for postoperative severe complications in patients with biliary tract cancer [114]. In this series, the rate of hypertrophy of the FLR after PVE was similar between the older and younger patients, and the incidences of postoperative hyperbilirubinemia and severe complications were higher in the elderly group only in the subgroup of patients with preoperative FLR/TLV ratio < 45%. Therefore, the authors proposed a minimum safe preoperative FLR/TLV ratio of 45% in patients ≥ 69 years old.

Colorectal liver metastases

Over the past few decades, hepatectomy has become a standard strategy for obtaining a long-term survival in patients with CRLM. Advances in chemotherapy, especially the introduction of drugs such as oxaliplatin, bevacizumab, and cetuximab, seem to have contributed to the increased chance of curability and a long-term survival [74].

As preoperative chemotherapy in patients with CRLM has become standard, especially in patients with extensive disease, chemotherapy-induced hepatic injury has been increasingly recognized. The most common manifestations are sinusoidal injury, mainly related to oxaliplatin, and steatosis, mainly related to irinotecan [115, 116]. Chemotherapy-induced hepatic injury has been reported to increase the risk of postoperative morbidity and mortality [117, 118]. Bevacizumab, a monoclonal antibody to vascular endothelial growth factor, has been shown to impair hepatic regeneration in murine models [119, 120], and 6 to 8 weeks, corresponding to approximately two half-lives, is usually recommended as an interval between bevacizumab and hepatectomy [121]. In contrast, the influence of bevacizumab on FLR regeneration after PVE or portal vein ligation in human studies has been controversial [122, 123]. More recent studies have shown no adverse influence of bevacizumab on FLR regeneration after hepatectomy [124] or even enhanced regeneration, especially with bevacizumab in combination with oxaliplatin [125]. In fact, it has been reported that bevacizumab may have the paradoxical effect of suppressing the induction of sinusoidal injury by oxaliplatin [126–128], and bevacizumab may inhibit splenomegaly and thrombocytopenia [29]. Importantly, not only specific drugs or regimens, but also their cumulative dose or duration of therapy are related to an increased risk of PHLF [128]. As mentioned in the section on the FLR/TFLV ratio versus the FLR/SLV ratio earlier in this article, hepatic atrophy after extensive chemotherapy may be useful as a simple predictor of PHLF [44].

Other concerns in preoperative planning for major hepatectomy for CRLM include whether or not chemotherapy-induced hepatic injury is reversible and whether or not tumor progression during the waiting period after PVE [129–131] affects the long-term outcomes. Takamoto et al. reported that ICG-R15 values recover after at least 2 weeks following the cessation of chemotherapy [132]. Omichi et al. reported that even in patients with hepatic atrophy after chemotherapy, the risk of PHLF was not elevated if sufficient FLR hypertrophy, with a kGR ≥ 2%/week, was achieved following PVE [133]. Regarding tumor progression after PVE, Simoneau et al. showed that the disease-free survival was worse in patients with tumor progression after PVE than in those with stable disease, but the overall survival was similar between the two groups. The authors also showed that tumor progression during chemotherapy was the only predictor of tumor progression after PVE in a multivariate analysis [134]. A recent prospective study and a recent propensity score-matched comparison study suggested that tumor progression after PVE did not affect the patients' survival [135, 136]. As mentioned above, ALPPS, which is still associated with a high incidence of morbidity, has not been established as a standard strategy, and PVE remains a safer strategy than ALPPS for increasing opportunities for extended hepatectomy in cases of advanced disease.

Conclusions

Advances in accurate methods of preoperatively evaluating the FLR function have improved the safety of major hepatectomy. Various techniques can induce FLR regeneration effectively while taking into account disease-specific comorbidities, such as cirrhosis in patients with HCC, cholangitis in patients with biliary tract cancer, and chemotherapy-induced hepatic injury in patients with CRLM. In this review, we mainly focused on preoperative factors. We should be aware, however, that intraoperative factors, such as an increased amount of blood loss or red blood cell transfusion, were also associated with PHLF [53, 137–139]. Control of blood loss was achieved through advances in surgical practices [140–142] and efforts to decrease central venous pressure during hepatectomy [143–145]. Novel techniques and advances are being evaluated, and these efforts are expected to further reduce the incidence of PHLF.

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Compliance with ethical standards

Conflict of interest Yoji Kishi and other co-authors have no conflicts of interest.

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