

How Much Remnant Is Enough in Liver Resection?

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Key Words

Liver resection • Liver failure • Liver volume

Abstract

Background: Liver resection represents the first choice of treatment for primary and secondary liver malignancies, offering the patient the best chance of long-term survival. The extensive use of major hepatectomy increases the risk of post-hepatectomy liver failure (PHLF), which is associated with a high frequency of postoperative complications, mortality and increased length of hospital stay. **Aims:** The aim of this review is to investigate the different risk factors related to the occurrence of PHLF and to identify the limits for a safe liver resection in patients with normal liver and injured liver (cirrhosis, cholestasis, steatosis and post-chemotherapy liver injury). **Methods:** A literature search was undertaken in PubMed and related search engines, looking for articles relating to hepatic failure following hepatectomy in normal liver or injured liver. **Results:** In spite of improvements in surgical and postoperative management, the parameters determining how much liver can be resected are still largely undefined. A number of preoperative, intraoperative and postoperative factors all contribute to the likelihood of liver failure after surgery. The safe limits for liver resection can be estimated from the data of the literature for patients with normal liver and for those with different types of liver injury.

Conclusions: Preoperative assessment that includes evaluation of liver volume and function of the remnant liver is a mandatory prerequisite before major hepatectomy. The critical residual liver volume for patients able to predict PHLF is mainly related to the presence of pre-existing liver disease and liver function. Among patients with normal liver, the limit for safe resection ranges from 20 to 30% future remnant liver of total liver volume. In patients with injured liver (cirrhosis, cholestasis or steatosis), preoperative assessment of the risk of PHLF should include future remnant liver volumetry and accurate liver function evaluation, including different dynamic liver function tests.

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Introduction

Liver resection represents the first choice of treatment for primary and secondary liver malignancies, giving the patient the best chance of long-term survival [1–3]. Advances in hepatic surgical technique, perioperative care and improvements in patient selection criteria were able to increase the number of patients who could undergo major or extended hepatectomy with curative intent [4, 5]. In a recent review of 1,803 consecutive patients over a 10-year period, a decrease in postoperative mortality to 1.3% was seen, despite an increase in major procedures

Table 1. Definition criteria of PHLF applied in the literature

First author	Year	Bilirubin	Postoperative time	PT	Encephalopathy	Ascites
Imamura [12]	2003	>5 mg/dl	>3 days	index <50%	-	-
Vauthey [21]	2004	>10 mg/dl	-	INR >2.0	-	-
Kubo [22]	2004	>5 mg/dl	>5 days	-	-	+
Balzan [13]	2005	>50 μ mol/l	5 days	index <50%	-	-
Chen [23]	2006	>2.9 mg/dl	-	index <50%	+	-
Menon [24]	2006	>30 μ mol/l	-	>18 s	+	-
Capussotti [25]	2006	>5 mg/dl	>3 days	index <50%	-	-
Ohwada [26]	2006	>5 mg/dl	>5 days	-	+	+
Mullen [16]	2007	>7 mg/dl	-	INR >2.0	-	-
Pawlik [27]	2007	>6 mg/dl	-	-	-	-
Ribero [28]	2007	>10 mg/dl	-	-	+	+
Figuera [29]	2007	>50 μ mol/l	5 days	index <50%	+	-
Adam [30]	2007	>50 μ mol/l	-	index <50%	-	-
Nagino [31]	2007	>10 mg/dl	2 weeks	-	-	-
Hemming [32]	2008	>7 mg/dl	-	INR >2.0	+	+
Fukumori [33]	2011	>5 mg/dl	1-7 days	-	+	+

Bilirubin 30 μ mol/l = 1.7 mg/dl, 50 μ mol/l = 2.9 mg/dl; PT index <50% = INR >1.7, PT >18 s = INR >1.6.

[6]. With such extensive resections of hepatic parenchyma, the risk of post-hepatectomy liver failure (PHLF) is increased, and it is associated with a high frequency of postoperative complications, mortality and an increased length of hospital stay [7].

The occurrence of PHLF after major liver resection ranges from 0 to 32% in different case series in the literature. Jarnagin et al. [6] reported a frequency of PHLF of 5% in a group of patients mainly without chronic liver disease, whereas the occurrence of PHLF can reach 20% in patients with chronic liver disease or cirrhosis [8, 9].

PHLF is closely related to the volume and function of the remnant liver, and these two variables are the major determinants of the adequacy of future remnant liver (FRL) after resection [10]. In patients with normal liver, smaller FRL volume can be adequate for a rapid recovery after resection. In contrast, in diseased livers (chronic hepatitis, cirrhosis, cholestasis, steatosis and postchemotherapy liver disease), larger remnant liver is necessary to avoid a PHLF.

Definition of PHLF

PHLF is defined as failure of one or more synthetic and excretory functions that include hyperbilirubinemia, hypoalbuminemia, prolonged prothrombin time (PT),

elevated serum lactate and different grades of hepatic encephalopathy [6, 11-13]. The incidence of PHLF is extremely variable in the literature, between 1.2 and 32%, partly as a result of differences in the studied patient populations, performed procedures and the lack of a standardized and universally accepted definition [4, 14-16]. In the past decade, mortality after hepatectomy ranged from 0 to 5%, and although the cause of death is multifactorial, PHLF remains the predominant cause of hepatectomy-related mortality [6, 17-20].

Among the several definitions of PHLF (table 1), the most widely used in clinical practice is the following one: combination of prolonged PT and serum total bilirubin associated with hepatic encephalopathy and/or ascites during postoperative period. One of the more frequently definition utilized in clinical practice is the 50-50 criteria characterized by the combination of PT index <50% (equal to international normalized ratio - INR >1.7) and serum total bilirubin >50 μ mol/l (equal to >2.9 mg/dl) on the 5th postoperative day. When this criterion is fulfilled, patients had a 59% risk of mortality compared with 1.2% when they were not met (sensitivity 69.6% and specificity 98.5%) [13]. A recent study on 1,059 patients was designed to provide a standard definition of PHLF in subjects with normal preoperative liver function. These authors found that a peak serum bilirubin concentration >7 mg/dl predicted strongly hepatectomy-related death

Table 2. Consensus definition and severity grading of PHLF by the ISGLS [35, 36]

Definition:

Postoperatively acquired deterioration in the ability of the liver to maintain its synthetic, excretory, and detoxifying functions, characterized by an increased INR (or need of clotting factors to maintain normal INR) and hyperbilirubinemia on or after postoperative day 5

Grade	Mortality	
A	0%	PHLF resulting in abnormal laboratory parameters but requiring no change in the clinical management of the patient
B	12%	PHLF resulting in a deviation from the regular clinical management but manageable without invasive treatment (<i>fresh frozen plasma, albumin, daily diuretics, noninvasive ventilation</i>)
C	54%	PHLF resulting in a deviation from the regular clinical management and requiring invasive treatment (<i>vasoactive drugs, glucose infusion, hemodialysis, intubation and mechanical ventilation, extracorporeal liver support, rescue hepatectomy, transplantation</i>)

Table 3. Risk factors for PHLF

Patient related	Age Diabetes mellitus Obesity (BMI)
Liver related	Cholestasis Steatosis/cirrhosis CALI
Surgery related	Hypotension Massive bleeding Liver ischemia Remnant liver volume Infection/sepsis Portal hypertension

and worse postoperative outcomes (sensitivity 93.3% and specificity 94.3%), patients with bilirubin peak >7 mg/dl showed a more than 30% chance of dying from liver failure [16]. Schindl et al. [34] proposed a classification for the severity of PHLF; their score included four parameters (total serum bilirubin, PT, serum lactate concentration, and grade of encephalopathy) and classified PHLF into four grades of severity. The authors found that 72.7% of patients with severe hepatic dysfunction developed in-

fectious complications compared to 18.2% in patients without severe hepatic dysfunction.

In 2011, the International Study Group of Liver Surgery (ISGLS) defined PHLF as increased INR and hyperbilirubinemia on or after the 5th postoperative day and provide a grade of severity depending on the impact on patient's clinical management [35]. PHLF grade A represents a postoperative deterioration that does not require a change in the patient's clinical management. Patients are diagnosed with grade B PHLF if there is a deviation from the regular postoperative clinical pathway but they can be managed without invasive treatment. Patients who develop PHLF requiring an invasive procedure are classified as having grade C PHLF (table 2).

This classification was applied retrospectively to a group of 576 patients who underwent hepatectomy. A total of 65 patients (11%) fulfilled the ISGLS criteria for PHLF. Grade A PHLF was diagnosed in 5 patients (8%), grade B in 47 patients (72%) and grade C in 13 patients (20%). The perioperative mortality of patients with PHLF grade A, B, and C was 0, 12 and 54%, respectively [36].

Pathogenesis

After liver resection, functional liver mass is lost, and in the remaining hepatocytes both regeneration and death occur. The ability of the liver remnant to overcome the effect of hepatectomy depends on its capacity to limit hepatocyte death, to preserve or recover an adequate synthetic function and to enhance its regenerative power [37].

Factors that limit the regeneration can be divided into patient related, liver related, and surgery related (table 3).

Patient-Related Factors

The role of age in the onset of PHLF is controversial. Nanashima et al. [38] showed that incidence of PHLF is not affected by age even though systemic complications are increased in elderly patients (≥ 70 years; 15 vs. 3%; $p < 0.05$). According to some authors, advanced age (≥ 70 years) increased the risk of postoperative morbidity and mortality with odds ratios of 1.02 (95% CI 1.01–1.03; $p < 0.01$) and 1.05 (95% CI 1.02–1.09; $p < 0.01$), respectively [13, 16]. Iakova et al. [39] studying gene expression and transcription factors involved in liver regeneration demonstrated that aging reduces hepatocyte proliferative capacity.

Likewise, diabetes is associated with greater risk of PHLF-related postoperative mortality. Little et al. [40] re-

ported a postoperative mortality rate in diabetic and non-diabetic patients of 8 and 2%, respectively ($p < 0.02$), with an 80% of PHLF-related death.

Overweight (BMI 25.0–29.9) and obesity (BMI ≥ 30.0) are significant predictors of adverse postoperative course with an increased morbidity rate after hepatic resection of 31–75 and 42–80%, respectively [41, 42].

Liver-Related Factors

Pre-existing cirrhosis, cholestasis, steatosis and chemotherapy-associated liver injury (CALI) are the most important preoperative conditions that affect regeneration and increase the risk of PHLF [43–45].

Cirrhosis

Cirrhotic livers demonstrate lower levels of hepatocyte growth factor and other transcription factors leading to a reduction of DNA synthesis and lower volumes of regenerated liver [46]. Moreover, cirrhotic livers show an increased risk of ischemia-reperfusion injury and fibrosis leading to regional ischemia contributes to impaired growth and regeneration [47]. In the 1980s, the operative mortality of major hepatectomy among cirrhotic patients was as high as 32%; more recent studies in the 2000s revealed a mortality rate of 5–6.5% [48–50]. More recently, some authors reported mortality near 0% also in cirrhotic livers [51]. The morbidity and mortality after hepatectomy in liver cirrhosis is higher in CHILD B/C stage patients (60 and 20%, respectively) [4, 52].

Cholestasis

Hepatectomy in the presence of cholestasis has been found to significantly inhibit liver regeneration by depressing the expression of proliferative genes and transcription factors involved in hepatocyte proliferation (C/EPB and cyclin E) compared with group control without cholestasis ($p < 0.01$) [53]. Some authors report that dilatation of the biliary tract, compressing vascular elements of the hepatic hilum, leads to a reduction in portal venous flow, accompanied by an increase in hepatic arterial flow [54]. This reduction in portal venous flow is further exacerbated by hepatectomy, which may contribute to impaired regeneration [55].

Cholestatic patients who undergo hepatic resection have an increased risk of postoperative complications compared to patients without cholestasis; the reported morbidity in the literature is 50 versus 15%, PHLF is 5–17 versus 0–3% and mortality 5–13 versus 0–6%, respectively [56, 57].

Steatosis and CALI

Steatosis of the liver is an increasingly common finding either due to lifestyle-related factors or as a complication of neoadjuvant chemotherapy (CALI) [58, 59]. Steatosis and steatohepatitis are associated with delay in regeneration, increased susceptibility to ischemia-reperfusion injury and increased risk of bleeding following hepatectomy. Experimental studies in rats demonstrated that steatosis induces impaired regeneration during the first days after surgery with a regenerated liver mass reduced by 60% when compared with non steatotic livers [45]. In clinical studies steatosis was associated with an increased rate of morbidity and mortality after hepatectomy, compared to patients with normal liver (43 vs. 26 and 9 vs. 2%, respectively) [60–62].

Surgery-Related Factors

Massive Bleeding and Transfusion

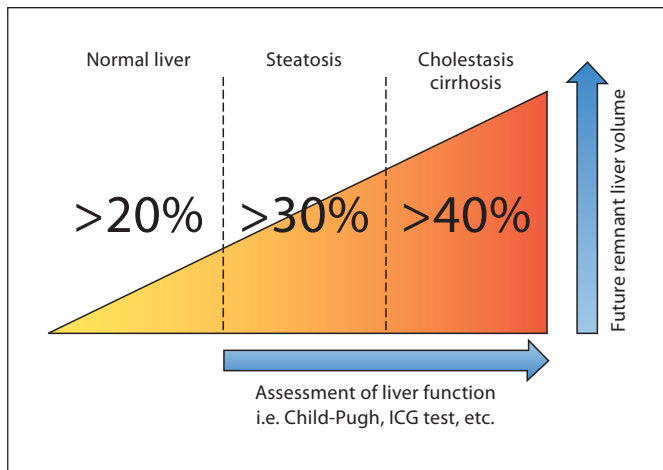
Massive bleeding (>1,000–1,250 ml) and need for blood transfusion, which can occur during hepatectomy, predispose the patient to PHLF, and increase morbidity (37–43 vs. 22–30%) and mortality rate (7.5–9 vs. 0–3%) [6, 12, 17, 63].

Ischemia-Reperfusion Injury

Hepatic ischemia-reperfusion injury is a condition that may occur during hepatectomy in the case of massive bleeding and subsequent hypotension or hepatic in- or outflow occlusion [64]. Hepatic ischemia and reperfusion activate a complex cascade that triggers an inflammatory reaction mediated by cytokines (IL-6, TNF- α) and cells (Kupffer cells, neutrophils). Although this process is primarily intended to maintain homeostasis, uncontrolled activation may become destructive inducing necrosis and apoptosis of hepatocytes [65]. To reduce the hepatic tissue damage induced by vascular occlusion, different techniques have been developed. Pringle clamping can be employed in the intermittent cycle, with a period of ischemia followed by up to 30 min of reperfusion [66]. Ischemic preconditioning, 5–10 min of vascular occlusion followed by 5–10 min of reperfusion before starting liver resection, has been shown to decrease the severity of liver necrosis, exhibit an antiapoptotic effect, preserve liver microcirculation, and improve survival rates following hepatectomy [67–70].

Portal Vein Hypertension

Following hepatectomy, the loss of liver functional mass and vascular capacity result in a marked increase in hepatic artery resistance and an increase in portal vein



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Fig. 1. Limit for safe hepatic resection.

pressure [71]. Excessive portal vein pressure may result in microcirculatory collapse, sinusoidal endothelial damage, Kupffer cell injury and subsequent lack of hepatocyte regeneration up to liver atrophy [72].

In an experimental study of animals submitted to massive liver resection in which postreperfusion portal vein flow was 4 and 2 times the flow at baseline, the 5-day survival was 29 and 100%. The authors concluded that excessive portal hyperperfusion can lead to impairment of regeneration [73].

Sepsis

Sepsis represents an important risk factor for PHLF affecting postoperative course. In fact, sepsis affects postoperative liver function and regeneration in a number of different ways. Sepsis is an important cause of postoperative hypotension, and in this manner may prolong hepatic ischemia following surgery [74]. In addition, sepsis adversely affect Kupffer cell function, may increase the concentration of liver-toxic cytokines, and endotoxins released by bacteria have a direct inhibitory action on hepatocyte proliferation [75–78].

Small-for-Size Syndrome

Small-for-size syndrome (SFSS), formulated at the beginning for the liver transplantation surgery but also applicable in extended hepatectomy, is a clinical syndrome which occurs in the presence of a reduced mass of liver insufficient to maintain normal liver function, characterized by postoperative liver dysfunction with hyperbilirubinemia, prolonged PT, portal hypertension, and ascites

[79–81]. Inadequate functional liver mass, excessive portal perfusion and exposure to gut-derived endotoxin are implicated in the pathogenesis of SFSS [82].

Limits for Safe Liver Resection

The safe limits for liver resection are still a debated issue in the literature. The minimal volume of remnant liver depends on factors related to liver function and the presence of underlining liver disease. The preoperative evaluation of the safety of liver resection is based on the volume of FRL and liver function (fig. 1).

Liver Volumetry

The FRL volume in major hepatic resection is a critical factor for predicting postoperative outcome. With the introduction of CT, measurement of liver volume can now be accurately estimated and the volume of FRL established before surgical resection. FRL is usually expressed as the ratio of FRL volume and total functioning liver volume [total liver volume (TLV) – tumor volume] [83, 84].

Assessment of future liver volume with imaging techniques is necessary because a significant inter-patient variation exists in segmental liver volume. In most patients, right liver represents >50% of the TLV with a wide range of variation, 45–80%. Also the volume of the left liver is variable: 15–45% of TLV [85].

Different techniques of estimation of TLV have been introduced, and the two most frequently utilized in the literature are the 3-D volume CT calculation and the calculation of standardized liver volume utilizing body surface area or body weight. In the first technique, the use of cross-imaging techniques can precisely determine the volume of liver tumors and liver mass [86]. The actual liver volume can be calculated with CT or MRI imaging techniques, on each slice both TLV and FRL are outlined, and the sum of the slices are calculated with integrated software [87]. Tumor volumes are considered nonfunctional liver parenchyma and subtracted from TLV [84, 88]. This technique demonstrated its accuracy in estimating total and remnant liver volume before resection [89].

In patients with multiple tumors, measurement of individual volumes cumulates the error variability associated with each measurement, and lesions beyond resolution of imaging or areas of non-functioning liver for dilatation of bile ducts or vascular obstruction can result in inaccurate estimation of TLV [90].

The second method is defined as standardized method of liver volume calculation. This method utilizes CT

measurement of FRL (this part of the liver is not diseased, and CT measurement should be more precise), but TLV is calculated based on body surface area or body weight. Different formulas to calculate TLV had been proposed and validated in the literature, and recent meta-analysis demonstrated that the most precise method is related to body surface area. This method provides a uniform comparison between patients that is based on a single formula estimating normal functional TLV for all patients. However, this method has several limitations; all formulas are based on a population with normal livers and no data of standardized volumes in diseased livers are available in the literature.

Liver Function Tests

Precise assessment of liver function is one of the most important factors before hepatectomy. Unfortunately, how to assess and quantify liver function during the preoperative staging remains controversial because no single biological marker or score is able to accurately predict the postoperative outcome.

Liver function tests can be divided into three types: conventional liver function tests, scoring systems that integrate clinical and laboratory values and quantitative liver function tests that evaluate the metabolism or the clearance of different substrates (table 4).

The conventional liver function test includes laboratory parameters that represent different synthetic and excretory functions of the liver. Although these parameters are fundamentals of preoperative liver function evaluation, none of these factors provide adequate evaluation of liver function.

Among different scoring systems to evaluate preoperative liver function, Child-Pugh and MELD (model for end-stage liver disease) score are the most utilized in clinical practice.

Many qualitative tests have been proposed using different substrates (table 4); in spite the fact that they demonstrated to precisely evaluate liver function, they are rarely applied in clinical practice due to the complexity of tests.

Between the proposed tests to anticipate the postoperative residual liver function, indocyanine green (ICG) clearance is considered as the most powerful predictive test of operative mortality after hepatectomy compared to other tests [91, 92]. The 15 min retention rate (ICG-15 R15) is the most frequently used parameter in decision-making protocol before hepatectomy. The application of this test has been significantly increased in clinical practice in Western countries since the introduction of pulsed

Table 4. Liver function tests

Conventional tests	Alanine transaminase – aspartate transaminase Gamma glutamyl transpeptidase Alkaline phosphatase Albumin Bilirubin (total and conjugated) Coagulation test (INR) Serum glucose Lactate dehydrogenase Platelet count
Scoring systems	Child-Turcotte-Pugh Model for end-stage liver disease Model for end-stage liver disease-Na
Qualitative tests	Quantification uptake: 99-m TC-GSA scintigraphy Quantification clearance: ICG test Quantification metabolism: aminopyrine breath test, MEGX, galactose elimination, LiMAX

spectrophotometry using an optical sensor [93]. There is no clear consensus on the cutoff value of ICG retention with a predictive value of postoperative hepatic insufficiency, but it is believed that ICG-15 equal or more than 14% is indicative of inadequate clearance with limited hepatic reserve. Fan et al. [48] reported that 101 patients underwent major hepatic resection with a mortality of 13.8%; an ICG R15 value of 14% was the cutoff point for patient short-term survival according to discriminant analysis. Lau et al. [94] reported a mortality of 11% in 127 patients submitted to liver resection. In their study, ICG R15 was the only test that could discriminate between survivors and non-survivors.

ICG and bilirubin bind to the same carrier in the transport phase in hepatocytes determining a competitive inhibition. In the patients with obstructive jaundice, hyperbilirubinemia is independent of the reserve of hepatic function, and ICG retention is therefore not valid. In these cases, 99-m TC-GSA (diethylenetriamine-pentaacetic acid with galactosyl human serum albumin) scintigraphy is proposed to assume the role of a quantitative test of hepatic function [51]. Scintigraphy with 99-m TC-GSA is a dynamic technique that provides information on the density of specific receptors on the plasma membrane of hepatocytes, and this density reflects directly the functioning of the hepatic mass.

It has been described that the scintigraphy receptor amount of the remnant liver (R0-remnant) and the maximal removal rate of asialoglycoprotein in the remnant

liver (GSA-RL) represent the functional reserve after hepatectomy and can predict postoperative liver failure [95]. Kokudo et al. [96] reported a close relationship between the amount of the receptors in the remnant liver (R0-remnant) and postoperative liver failure. The morbidity rate in patients with remnant receptors of less than 0.05 μmol was 100%, and the rate decreased in inverse proportion to the remnant receptor amount.

How Much Remnant in Normal Liver?

The critical residual liver volume for patients without underlying liver disease able to predict postoperative severe hepatic dysfunction had been investigated in the literature, generally the accepted limit for safe resection ranging from 20 to 30% according to different authors [5, 7, 90, 97, 98]. Vauthey et al. [90] described a minimum safe FRL volume of 25% in patients who underwent extended right hepatectomy. The authors described the occurrence of major postoperative complications in 3 of 5 patients with standardized FLR volumes of $\leq 25\%$ compared with no major complications in the remaining 10 of the resected group with an FLR of $>25\%$ ($p = 0.02$). Shoup et al. [7] reported that patients without liver disease undergoing right trisectionectomy with less than 25% of liver remaining demonstrated a 90% incidence of hepatic dysfunction. None of the patients undergoing trisectionectomy with more than 25% of liver remaining showed postoperative hepatic dysfunction.

More recently, Abdalla et al. [5] showed that postoperative complication occurred in 50% of patients who underwent to extended right hepatectomy with FRL volume $\leq 20\%$ versus only 13% for patients with an FRL volume $>20\%$. This smaller cutoff value for safe resection in patients without liver disease was confirmed by two large follow-up studies [28, 98]. In particular Kishi et al. [98] analyzed 301 patients who underwent extended right hepatectomy. The authors analyzed the occurrence of liver insufficiency and death from liver failure based on FRL volume of ≤ 20 , 20.1–30.0, and $>30.0\%$ of TLV in a cohort of 301 patients. The authors identified a significant increase in the frequency of liver insufficiency and death from liver failure in patients with FRL volume $\leq 20\%$ of TLV (34 and 11%, respectively), compared with patients with FLR of 20–30% of TLV (10 and 3%, respectively; $p > 0.001$ and $p = 0.038$).

This minimum safe limit for liver resection with normal liver ($>20\%$ of TLV) was published in 2006 in the consensus statement following consensus conference on the resectability of liver metastases [97].

How Much Remnant in Chronic Liver Disease and Cirrhosis?

The safe limit for liver resection in chronic liver disease and cirrhosis is not well established in the literature. In these patients, the safe limits for liver resection are determined by FRL volume and liver function. The safety of surgical resection is greatly determined by the degree of liver dysfunction due to the underlying liver disease [84, 99].

Shirabe et al. [99] analyzed 80 patients with chronic liver disease who underwent major liver resection. In this study, the authors analyzed the factors related to death from liver failure, and identified that all the 7 deaths from liver failure occurred in patients with an FRL volume of less than 250 ml/m². The authors concluded that the expected remnant liver volume appears to be a good predictor for postoperative liver failure in patients who undergo a right lobectomy of the liver for HCC. An expected liver volume of 250 ml/m² seems to be a safe limit for such liver resections.

Other experiences in the literature emphasized the role of liver volume associated with the degree of liver dysfunction. Some authors proposed a different surgical approach depending on ICG R15, ranging from simple enucleation to major hepatectomy [51, 100]. The authors proposed a decision tree for selection of operative procedure in patients with impaired functional reserve. With this approach, Imamura et al. [51] reported one single death in over 1,400 liver resections during a 10-year period. More recently, the relationship between the ratio of remnant liver volume and the preoperative ICG15 value has been demonstrated in patients with postoperative liver dysfunction [101]. Chen et al. [23] identified a linear relationship between remnant liver volume and ICG R15 test for patients with higher risk of postoperative liver failure. Using this strategy, they observed that 83% of patients without liver dysfunction fall above the regression line. With this formula to calculate the resection ratio prior to hepatectomy using individual ICG R15 retention rates, they reported a sensitivity of 83% and specificity of 92% for occurrence of postoperative liver failure. Yamanaka et al. [102] proposed a predictive score for postoperative mortality incorporating the resection rate, the ICG R15 and age of patients. The authors observed a mortality of 33% in HCC patients with high risk score, whereas mortality was 7.3% for patients with low risk score.

How Much Remnant in Cholestatic Liver?

Despite advances in perioperative management and operative techniques, postoperative complications re-

main a major problem of liver resection in patients with jaundice or cholestasis. Moreover, patients with cholangiocarcinoma, who are frequently associated with jaundice and cholestasis, are more frequently submitted to extensive liver resection in order to achieve radical resection. Takahashi et al. [103] reported that the functional reserve of a liver in a patient with obstructive jaundice who was relieved of the jaundice by biliary drainage is significantly worst compared to the normal liver, and it is second only to that in those with liver cirrhosis.

The limits for a safe resection in patients with obstructive jaundice after preoperative biliary drainage are not well established in the literature. Ferrero et al. [104] in a group of 47 patients with preoperative jaundice observed a frequency of postoperative liver dysfunction of 40% for patients with an FRL volume between 30 and 35% compared to 0% in the normal liver group. The authors reported that the critical FRL volume to avoid postoperative liver dysfunction for these was 35% of TLV [104]. Suda et al. [105] reported that the mean extent of remnant liver volume in patients who developed postoperative hyperbilirubinemia was 42 and 35% for those with subsequent fatal outcome. The authors concluded that the extent of liver that can be safely resected is limited in the case of cholestatic liver, even after this condition has been relieved, and, when the estimated RLV/ELV ratio is lower than 40%, which is the critical point for postoperative liver dysfunction.

The other critical factor for predicting postoperative liver failure is the degree of liver dysfunction due to the damage of chronic biliary obstruction. The most utilized preoperative liver test is ICG retention rate. Since such assessment is directly influenced by the severity of jaundice, due to excretory competition with bilirubin, its results are reliable only after effective biliary drainage and resolution of jaundice. Nagino et al. [106] proposed a score calculated by multiplying the proportion of the future liver remnant by the clearance of ICG (KICG). The author reported 240 consecutive patients who had undergone PVE and subsequent major hepatectomy for biliary cancer, in which a KICG of the future liver remnant of 0.05 was used as a cutoff value to determine eligibility for major hepatectomy for biliary cancer. In 28 patients whose KICG of the future liver remnant was less than 0.05, 8 (28.6%) patients died of postoperative complications, while in 165 patients whose KICG of the future liver remnant after PVE was greater than 0.05, 9 (5.5%) patients died ($p < 0.001$) [106].

How Much Remnant in Steatosis and Postchemotherapy Liver Disease (CALI)?

Steatosis of the liver is an increasingly common finding either due to lifestyle-related factors or as a common sequel to chemotherapy for colorectal liver metastases. Steatosis is related to a delay in regeneration, increased susceptibility to ischemia/reperfusion injury and increased risk of trauma and bleeding following hepatectomy [45, 60]. Recently, it was observed that liver hypertrophy in patients with steatosis was significantly lower than in patients without steatosis among patients who underwent hepatectomy. According to these results, steatosis, which frequently is induced by aggressive chemotherapy, may impede liver regeneration when one compares groups undergoing similar PVE or hepatectomy procedure [107].

The influence of steatosis and chemotherapy-induced steatosis in patients who undergo liver resection is still a matter of debate in the literature.

Some authors reported that liver resection for patients with steatosis is associated with an increased risk of perioperative mortality when compared to patients with normal livers (49 vs. 2%) [108]. Other studies in the literature failed to confirm a higher rate of postoperative mortality and morbidity in patients with steatosis. A recent meta-analysis revealed a significant association between degree of steatosis and increased risk of postoperative complications and mortality [109]. In this meta-analysis, the authors demonstrated that the presence of moderate steatosis (<30%) is associated with a significantly higher risk of complications compared to patients without any steatosis. This risk was even higher in patients with severe steatosis (>30%). The meta-analysis for mortality failed to confirm a higher risk for patients with moderate steatosis (<30%), whereas the risk of mortality for patients with more severe steatosis was significantly higher than in patients without any degree of steatosis.

Vauthey et al. [61] verified that patients with steatohepatitis had a postoperative 90-day mortality of 14.7% compared to 1.6% without this specific injury, while the presence of sinusoidal injury increased morbidity after major hepatectomy from 6.3 to 40.0% in a recent paper from Nakano et al. [62].

There are no accepted limits for safe resection in patients with severe steatosis or postchemotherapy liver disease. In the literature, the minimal safe volume for FRL is not well established; however, according to the data in the literature, the safe limits for patients with mild steatosis should be 30–35%, whereas for patients with severe steatosis the limit is 40%.

Conclusions

Major liver resection has now become the accepted gold standard of treatment for primary and secondary liver malignancies. With such extensive resections of hepatic parenchyma, the risk of PHLF is increased, and it is associated with postoperative complications, mortality and an increased length of hospital stay. The incidence of PHLF is extremely variable in the literature, between 1.2 and 32%, partly as a result of differences in the studied patient populations, performed procedures and the lack of a standardized and universally accepted definition. Among the different definitions of PHLF, the most widely used in clinical practice is as follows: combination of prolonged PT and serum total bilirubin associated with hepatic encephalopathy and/or ascites during postoperative period.

Different risk factors are related to the occurrence of PHLF; among patient-related factors, diabetes and overweight were related to higher frequency of PHLF. The presence of preexisting liver disease such as cirrhosis, cholestasis, steatosis and CALI had been involved with impaired liver regeneration and with the occurrence of postoperative complications.

Preoperative assessment that includes evaluation of liver volume and function of the remnant liver is a mandatory prerequisite before major hepatectomy. The critical residual liver volume for patients able to predict PHLF is mainly related to the presence of preexisting liver disease and liver function. Among patients with normal liver, the limit for safe resection ranges from 20 to 30% of TLV.

In patients with injured livers (cirrhosis, cholestasis or steatosis), preoperative assessment of the risk of PHLF should include FRL volumetry and accurate liver function evaluation, including different dynamic liver function tests. The critical FRL volume in these patients according to the data in the literature is 30–40%.

Finally, the carefully intraoperative management with reduced intraoperative blood loss and low ischemia-reperfusion injury can avoid additional liver damage.

Future perspectives in pharmacological perioperative protection of the liver, liver support with liver-assist device and perioperative enhancement of liver regeneration will improve postoperative outcome, decreasing the incidence of PHLF, in patients submitted to extended liver resection.

References

- 1 Poon RT, Fan ST, Lo CM, et al: Improving survival results after resection of hepatocellular carcinoma: a prospective study of 377 patients over 10 years. *Ann Surg* 2001;234:63–70.
- 2 Imamura H, Seyama Y, Kokudo N, et al: Single and multiple resections of multiple hepatic metastases of colorectal origin. *Surgery* 2004;135:508–517.
- 3 Choi SB, Kim KS, Choi JY, et al: The prognosis and survival outcome of intrahepatic cholangiocarcinoma following surgical resection: association of lymph node metastasis and lymph node dissection with survival. *Ann Surg Oncol* 2009;16:3048–3056.
- 4 Belghiti J, Hiramatsu K, Benoist S, Massault P, Sauvanet A, Farges O: Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. *J Am Coll Surg* 2000;191:38–46.
- 5 Abdalla EK, Barnett CC, Doherty D, Curley SA, Vauthey JN: Extended hepatectomy in patients with hepatobiliary malignancies with and without preoperative portal vein embolization. *Arch Surg* 2002;137:675–680, discussion 680–681.
- 6 Jarnagin WR, Gonen M, Fong Y, et al: Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. *Ann Surg* 2002;236:397–406, discussion 406–407.
- 7 Shoup M, Gonen M, D'Angelica M, et al: Volumetric analysis predicts hepatic dysfunction in patients undergoing major liver resection. *J Gastrointest Surg* 2003;7:325–330.
- 8 Tanabe G, Sakamoto M, Akazawa K, et al: Intraoperative risk factors associated with hepatic resection. *Br J Surg* 1995;82:1262–1265.
- 9 Hemming AW, Gallinger S, Greig PD, et al: The hippurate ratio as an indicator of functional hepatic reserve for resection of hepatocellular carcinoma in cirrhotic patients. *J Gastrointest Surg* 2001;5:316–321.
- 10 Yokoyama Y, Nishio H, Ebata T, Igami T, Sugawara G, Nagino M: Value of indocyanine green clearance of the future liver remnant in predicting outcome after resection for biliary cancer. *Br J Surg* 2010;97:1260–1268.
- 11 van den Broek MA, Olde Damink SW, Dejong CH, et al: Liver failure after partial hepatic resection: definition, pathophysiology, risk factors and treatment. *Liver Int* 2008;28:767–780.
- 12 Imamura H, Seyama Y, Kokudo N, et al: One thousand fifty-six hepatectomies without mortality in 8 years. *Arch Surg* 2003;138:1198–1206, discussion 1206.
- 13 Balzan S, Belghiti J, Farges O, et al: The '50-50 criteria' on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. *Ann Surg* 2005;242:824–828, discussion 828–829.
- 14 Farges O, Malassagne B, Flejou JF, Balzan S, Sauvanet A, Belghiti J: Risk of major liver resection in patients with underlying chronic liver disease: a reappraisal. *Ann Surg* 1999;229:210–215.
- 15 Cucchetti A, Ercolani G, Vivarelli M, et al: Impact of model for end-stage liver disease (MELD) score on prognosis after hepatectomy for hepatocellular carcinoma on cirrhosis. *Liver Transpl* 2006;12:966–971.
- 16 Mullen JT, Ribero D, Reddy SK, et al: Hepatic insufficiency and mortality in 1,059 non-cirrhotic patients undergoing major hepatectomy. *J Am Coll Surg* 2007;204:854–862, discussion 862–864.
- 17 Poon RT, Fan ST, Lo CM, et al: Improving perioperative outcome expands the role of hepatectomy in management of benign and malignant hepatobiliary diseases: analysis of 1,222 consecutive patients from a prospective database. *Ann Surg* 2004;240:698–708, discussion 708–710.
- 18 Kamiyama T, Nakanishi K, Yokoo H, et al: Perioperative management of hepatic resection toward zero mortality and morbidity: analysis of 793 consecutive cases in a single institution. *J Am Coll Surg* 2010;211:443–449.

- 19 Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M: Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. *Br J Cancer* 2006;94:982–999.
- 20 Detroz B, Sugarbaker PH, Knol JA, Petrelli N, Hughes KS: Causes of death in patients undergoing liver surgery. *Cancer Treat Res* 1994;69:241–257.
- 21 Vauthey JN, Pawlik TM, Abdalla EK, et al: Is extended hepatectomy for hepatobiliary malignancy justified? *Ann Surg* 2004;239:722–730, discussion 730–732.
- 22 Kubo S, Tanaka H, Shuto T, et al: Hepatic failure after liver resection in patients with cirrhosis (in Japanese). *Nihon Geka Gakkai Zasshi* 2004;105:669–673.
- 23 Chen XP, Zhang ZW, Zhang BX, et al: Modified technique of hepatic vascular exclusion: effect on blood loss during complex mesohepatectomy in hepatocellular carcinoma patients with cirrhosis. *Langenbecks Arch Surg* 2006;391:209–215.
- 24 Menon KV, Al-Mukhtar A, Aldouri A, Prasad RK, Lodge PA, Toogood GJ: Outcomes after major hepatectomy in elderly patients. *J Am Coll Surg* 2006;203:677–683.
- 25 Capussotti L, Muratore A, Ferrero A, Masuccio P, Ribero D, Polastri R: Randomized clinical trial of liver resection with and without hepatic pedicle clamping. *Br J Surg* 2006;93:685–689.
- 26 Ohwada S, Kawate S, Hamada K, et al: Perioperative real-time monitoring of indocyanine green clearance by pulse spectrophotometry predicts remnant liver functional reserve in resection of hepatocellular carcinoma. *Br J Surg* 2006;93:339–346.
- 27 Pawlik TM, Olino K, Gleisner AL, Torbenson M, Schulick R, Choti MA: Preoperative chemotherapy for colorectal liver metastases: impact on hepatic histology and postoperative outcome. *J Gastrointest Surg* 2007;11:860–868.
- 28 Ribero D, Abdalla EK, Madoff DC, Donadon M, Loyer EM, Vauthey JN: Portal vein embolization before major hepatectomy and its effects on regeneration, resectability and outcome. *Br J Surg* 2007;94:1386–1394.
- 29 Figueras J, Llado L, Miro M, et al: Application of fibrin glue sealant after hepatectomy does not seem justified: results of a randomized study in 300 patients. *Ann Surg* 2007;245:536–542.
- 30 Adam R, Aloia T, Levi F, et al: Hepatic resection after rescue cetuximab treatment for colorectal liver metastases previously refractory to conventional systemic therapy. *J Clin Oncol* 2007;25:4593–4602.
- 31 Nagino M, Nishio H, Ebata T, Yokoyama Y, Igami T, Nimura Y: Intrahepatic cholangiojejunostomy following hepatobiliary resection. *Br J Surg* 2007;94:70–77.
- 32 Hemming AW, Reed AI, Fujita S, Zendejas I, Howard RJ, Kim RD: Role for extending hepatic resection using an aggressive approach to liver surgery. *J Am Coll Surg* 2008;206:870–875, discussion 875–878.
- 33 Fukumori D, Kamiyama T, Nakanishi K, et al: Analysis of risk factors for hyperbilirubinemia occurring after hepatectomy. *J Hepatobiliary Pancreat Sci* 2011;18:724–730.
- 34 Schindl MJ, Redhead DN, Fearon KC, Garden OJ, Wigmore SJ: The value of residual liver volume as a predictor of hepatic dysfunction and infection after major liver resection. *Gut* 2005;54:289–296.
- 35 Rahbari NN, Garden OJ, Padbury R, et al: Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery* 2011;149:713–724.
- 36 Reissfelder C, Rahbari NN, Koch M, et al: Postoperative course and clinical significance of biochemical blood tests following hepatic resection. *Br J Surg* 2011;98:836–844.
- 37 Michalopoulos GK, DeFrances MC: Liver regeneration. *Science* 1997;276:60–66.
- 38 Nanashima A, Abo T, Nonaka T, et al: Prognosis of patients with hepatocellular carcinoma after hepatic resection: Are elderly patients suitable for surgery? *J Surg Oncol* 2011;104:284–291.
- 39 Iakova P, Awad SS, Timchenko NA: Aging reduces proliferative capacities of liver by switching pathways of C/EBPalpha growth arrest. *Cell* 2003;113:495–506.
- 40 Little SA, Jarnagin WR, DeMatteo RP, Blumgart LH, Fong Y: Diabetes is associated with increased perioperative mortality but equivalent long-term outcome after hepatic resection for colorectal cancer. *J Gastrointest Surg* 2002;6:88–94.
- 41 Balzan S, Nagarajan G, Farges O, et al: Safety of liver resections in obese and overweight patients. *World J Surg* 2010;34:2960–2968.
- 42 Cucchetti A, Cescon M, Ercolani G, Di Gioia P, Peri E, Pinna AD: Safety of hepatic resection in overweight and obese patients with cirrhosis. *Br J Surg* 2011;98:1147–1154.
- 43 Khuntikeo N, Pugkhem A, Bhudhisawasdi V, Uttaravichien T: Major hepatic resection for hilar cholangiocarcinoma without preoperative biliary drainage. *Asian Pac J Cancer Prev* 2008;9:83–85.
- 44 Takenaka K, Kanematsu T, Fukuzawa K, Sugimachi K: Can hepatic failure after surgery for hepatocellular carcinoma in cirrhotic patients be prevented? *World J Surg* 1990;14:123–127.
- 45 Selzner M, Clavien PA: Failure of regeneration of the steatotic rat liver: disruption at two different levels in the regeneration pathway. *Hepatology* 2000;31:35–42.
- 46 Tiberio GA, Tiberio L, Benetti A, et al: IL-6 promotes compensatory liver regeneration in cirrhotic rat after partial hepatectomy. *Cytokine* 2008;42:372–378.
- 47 Corpechot C, Barbu V, Wendum D, et al: Hepatocyte growth factor and c-Met inhibition by hepatic cell hypoxia: a potential mechanism for liver regeneration failure in experimental cirrhosis. *Am J Pathol* 2002;160:613–620.
- 48 Fan ST, Lai EC, Lo CM, Ng IO, Wong J: Hospital mortality of major hepatectomy for hepatocellular carcinoma associated with cirrhosis. *Arch Surg* 1995;130:198–203.
- 49 Tjandra JJ, Fan ST, Wong J: Peri-operative mortality in hepatic resection. *Aust N Z J Surg* 1991;61:201–206.
- 50 Poon RT, Fan ST, Lo CM, et al: Extended hepatic resection for hepatocellular carcinoma in patients with cirrhosis: is it justified? *Ann Surg* 2002;236:602–611.
- 51 Imamura H, Sano K, Sugawara Y, Kokudo N, Makuuchi M: Assessment of hepatic reserve for indication of hepatic resection: decision tree incorporating indocyanine green test. *J Hepatobiliary Pancreat Surg* 2005;12:16–22.
- 52 Capussotti L, Muratore A, Amisano M, Polastri R, Bouzari H, Massucco P: Liver resection for hepatocellular carcinoma on cirrhosis: analysis of mortality, morbidity and survival – a European single center experience. *Eur J Surg Oncol* 2005;31:986–993.
- 53 Nakano K, Chijiwa K, Tanaka M: Lower activity of CCAAT/enhancer-binding protein and expression of cyclin E, but not cyclin D1, activating protein-1 and p21(WAF1), after partial hepatectomy in obstructive jaundice. *Biochem Biophys Res Commun* 2001;280:640–645.
- 54 Kanda H, Nimura Y, Yasui A, et al: Hepatic blood flow after acute biliary obstruction and drainage in conscious dogs. *Hepatogastroenterology* 1996;43:235–240.
- 55 Baer HU, Guastella T, Wheatley AM, Zimmermann A, Blumgart LH: Acute effects of partial hepatectomy on liver blood flow in the jaundiced rat. *J Hepatol* 1993;19:377–382.
- 56 Cherqui D, Benoist S, Malassagne B, Humeres R, Rodriguez V, Fagniez PL: Major liver resection for carcinoma in jaundiced patients without preoperative biliary drainage. *Arch Surg* 2000;135:302–308.
- 57 Kennedy TJ, Yopp A, Qin Y, et al: Role of preoperative biliary drainage of liver remnant prior to extended liver resection for hilar cholangiocarcinoma. *HPB (Oxford)* 2009;11:445–451.
- 58 Brouquet A, Benoist S, Julie C, et al: Risk factors for chemotherapy-associated liver injuries: a multivariate analysis of a group of 146 patients with colorectal metastases. *Surgery* 2009;145:362–371.
- 59 Pessaux P, Chenard MP, Bachellier P, Jaeck D: Consequences of chemotherapy on resection of colorectal liver metastases. *J Visc Surg* 2010;147:e193–e201.

- 60 Rao MS, Papreddy K, Abecassis M, Hashimoto T: Regeneration of liver with marked fatty change following partial hepatectomy in rats. *Dig Dis Sci* 2001;46:1821–1826.
- 61 Vauthey JN, Pawlik TM, Ribero D, et al: Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *J Clin Oncol* 2006;24:2065–2072.
- 62 Nakano H, Oussoultzoglou E, Rosso E, et al: Sinusoidal injury increases morbidity after major hepatectomy in patients with colorectal liver metastases receiving preoperative chemotherapy. *Ann Surg* 2008;247:118–124.
- 63 Silva MA, Muralidharan V, Mirza DF: The management of coagulopathy and blood loss in liver surgery. *Semin Hematol* 2004;41:132–139.
- 64 Jaeschke H: Molecular mechanisms of hepatic ischemia-reperfusion injury and preconditioning. *Am J Physiol Gastrointest Liver Physiol* 2003;284:G15–G26.
- 65 Moussa ME, Sarraf CE, Uemoto S, Sawada H, Habib NA: Effect of total hepatic vascular exclusion during liver resection on hepatic ultrastructure. *Liver Transpl Surg* 1996;2:461–467.
- 66 Clavien PA: Surgical techniques for liver resection. *J Gastrointest Surg* 2006;10:166–167.
- 67 Peralta C, Prats N, Xaus C, Gelpi E, Rosello-Catafau J: Protective effect of liver ischemic preconditioning on liver and lung injury induced by hepatic ischemia-reperfusion in the rat. *Hepatology* 1999;30:1481–1489.
- 68 Yadav SS, Sindram D, Perry DK, Clavien PA: Ischemic preconditioning protects the mouse liver by inhibition of apoptosis through a caspase-dependent pathway. *Hepatology* 1999;30:1223–1231.
- 69 Szijarto A, Hahn O, Lotz G, Schaff Z, Madarasz E, Kupcsulik PK: Effect of ischemic preconditioning on rat liver microcirculation monitored with laser Doppler flowmetry. *J Surg Res* 2006;131:150–157.
- 70 Gomez D, Homer-Vanniasinkam S, Graham AM, Prasad KR: Role of ischaemic preconditioning in liver regeneration following major liver resection and transplantation. *World J Gastroenterol* 2007;13:657–670.
- 71 Kin Y, Nimura Y, Hayakawa N, et al: Doppler analysis of hepatic blood flow predicts liver dysfunction after major hepatectomy. *World J Surg* 1994;18:143–149.
- 72 Niiya T, Murakami M, Aoki T, Murai N, Shimizu Y, Kusano M: Immediate increase of portal pressure, reflecting sinusoidal shear stress, induced liver regeneration after partial hepatectomy. *J Hepatobiliary Pancreat Surg* 1999;6:275–280.
- 73 Hessheimer AJ, Fondevila C, Taura P, et al: Decompression of the portal bed and twice-baseline portal inflow are necessary for the functional recovery of a ‘small-for-size’ graft. *Ann Surg* 2011;253:1201–1210.
- 74 Champion HR, Jones RT, Trump BF, et al: A clinicopathologic study of hepatic dysfunction following shock. *Surg Gynecol Obstet* 1976;142:657–663.
- 75 Selzner N, Selzner M, Odermatt B, Tian Y, Van Rooijen N, Clavien PA: ICAM-1 triggers liver regeneration through leukocyte recruitment and Kupffer cell-dependent release of TNF-alpha/IL-6 in mice. *Gastroenterology* 2003;124:692–700.
- 76 Gross K, Katz S, Dunn SP, Cikrit D, Rosenthal R, Grosfeld JL: Bacterial clearance in the intact and regenerating liver. *J Pediatr Surg* 1985;20:320–323.
- 77 Akita K, Okuno M, Enya M, et al: Impaired liver regeneration in mice by lipopolysaccharide via TNF-alpha/kallikrein-mediated activation of latent TGF-beta. *Gastroenterology* 2002;123:352–364.
- 78 Nolan JP: Endotoxin, reticuloendothelial function, and liver injury. *Hepatology* 1981;1:458–465.
- 79 Kiuchi T, Kasahara M, Uryuhara K, et al: Impact of graft size mismatching on graft prognosis in liver transplantation from living donors. *Transplantation* 1999;67:321–327.
- 80 Heaton N: Small-for-size liver syndrome after auxiliary and split liver transplantation: donor selection. *Liver Transpl* 2003;9:S26–S28.
- 81 Tucker ON, Heaton N: The ‘small for size’ liver syndrome. *Curr Opin Crit Care* 2005;11:150–155.
- 82 Emond JC, Renz JF, Ferrell LD, et al: Functional analysis of grafts from living donors. Implications for the treatment of older recipients. *Ann Surg* 1996;224:544–552, discussion 552–554.
- 83 Ogasawara K, Une Y, Nakajima Y, Uchino J: The significance of measuring liver volume using computed tomographic images before and after hepatectomy. *Surg Today* 1995;25:43–48.
- 84 Kubota K, Makuuchi M, Kusaka K, et al: Measurement of liver volume and hepatic functional reserve as a guide to decision-making in resectional surgery for hepatic tumors. *Hepatology* 1997;26:1176–1181.
- 85 Abdalla EK, Denys A, Chevalier P, Nemr RA, Vauthey JN: Total and segmental liver volume variations: implications for liver surgery. *Surgery* 2004;135:404–410.
- 86 Heymsfield SB, Fulenwider T, Nordlinger B, Barlow R, Sones P, Kutner M: Accurate measurement of liver, kidney, and spleen volume and mass by computerized axial tomography. *Ann Intern Med* 1979;90:185–187.
- 87 Kawasaki S, Makuuchi M, Matsunami H, et al: Preoperative measurement of segmental liver volume of donors for living related liver transplantation. *Hepatology* 1993;18:1115–1120.
- 88 Azoulay D, Castaing D, Smail A, et al: Resection of nonresectable liver metastases from colorectal cancer after percutaneous portal vein embolization. *Ann Surg* 2000;231:480–486.
- 89 Yamanaka J, Saito S, Fujimoto J: Impact of preoperative planning using virtual segmental volumetry on liver resection for hepatocellular carcinoma. *World J Surg* 2007;31:1249–1255.
- 90 Vauthey JN, Chaoui A, Do KA, et al: Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. *Surgery* 2000;127:512–519.
- 91 Nonami T, Nakao A, Kurokawa T, et al: Blood loss and ICG clearance as best prognostic markers of post-hepatectomy liver failure. *Hepatogastroenterology* 1999;46:1669–1672.
- 92 Hemming AW, Scudamore CH, Shackleton CR, Pudek M, Erb SR: Indocyanine green clearance as a predictor of successful hepatic resection in cirrhotic patients. *Am J Surg* 1992;163:515–518.
- 93 Okochi O, Kaneko T, Sugimoto H, Inoue S, Takeda S, Nakao A: ICG pulse spectrophotometry for perioperative liver function in hepatectomy. *J Surg Res* 2002;103:109–113.
- 94 Lau H, Man K, Fan ST, Yu WC, Lo CM, Wong J: Evaluation of preoperative hepatic function in patients with hepatocellular carcinoma undergoing hepatectomy. *Br J Surg* 1997;84:1255–1259.
- 95 Kwon AH, Matsui Y, Kaibori M, Ha-Kawa SK: Preoperative regional maximal removal rate of technetium-99m-galactosyl human serum albumin (GSA-Rmax) is useful for judging the safety of hepatic resection. *Surgery* 2006;140:379–386.
- 96 Kokudo N, Vera DR, Tada K, et al: Predictors of successful hepatic resection: prognostic usefulness of hepatic asialoglycoprotein receptor analysis. *World J Surg* 2002;26:1342–1347.
- 97 Abdalla EK, Adam R, Bilchik AJ, Jaeck D, Vauthey JN, Mahvi D: Improving resectability of hepatic colorectal metastases: expert consensus statement. *Ann Surg Oncol* 2006;13:1271–1280.
- 98 Kishi Y, Abdalla EK, Chun YS, et al: Three hundred and one consecutive extended right hepatectomies: evaluation of outcome based on systematic liver volumetry. *Ann Surg* 2009;250:540–548.
- 99 Shirabe K, Shimada M, Gion T, et al: Postoperative liver failure after major hepatic resection for hepatocellular carcinoma in the modern era with special reference to remnant liver volume. *J Am Coll Surg* 1999;188:304–309.
- 100 Miyagawa S, Makuuchi M, Kawasaki S, Kakazu T: Criteria for safe hepatic resection. *Am J Surg* 1995;169:589–594.
- 101 Lee CF, Yu MC, Kuo LM, et al: Using indocyanine green test to avoid post-hepatectomy liver dysfunction. *Chang Gung Med J* 2007;30:333–338.

- 102 Yamanaka N, Okamoto E, Oriyama T, et al: A prediction scoring system to select the surgical treatment of liver cancer. Further refinement based on 10 years of use. *Ann Surg* 1994;219:342–346.
- 103 Takahashi T, Togo S, Tanaka K, Endo I, Fujii Y, Shimada H: Safe and permissible limits of hepatectomy in obstructive jaundice patients. *World J Surg* 2004;28:475–481.
- 104 Ferrero A, Vigano L, Polastri R, et al: Post-operative liver dysfunction and future remnant liver: where is the limit? Results of a prospective study. *World J Surg* 2007;31:1643–1651.
- 105 Suda K, Ohtsuka M, Ambiru S, et al: Risk factors of liver dysfunction after extended hepatic resection in biliary tract malignancies. *Am J Surg* 2009;197:752–758.
- 106 Nagino M, Kamiya J, Nishio H, Ebata T, Arai T, Nimura Y: Two hundred forty consecutive portal vein embolizations before extended hepatectomy for biliary cancer: surgical outcome and long-term follow-up. *Ann Surg* 2006;243:364–372.
- 107 Tanaka K, Kumamoto T, Matsuyama R, Takeda K, Nagano Y, Endo I: Influence of chemotherapy on liver regeneration induced by portal vein embolization or first hepatectomy of a staged procedure for colorectal liver metastases. *J Gastrointest Surg* 2010;14:359–368.
- 108 Selzner M, Clavien PA: Fatty liver in liver transplantation and surgery. *Semin Liver Dis* 2001;21:105–113.
- 109 de Meijer VE, Kalish BT, Puder M, Ijzermans JN: Systematic review and meta-analysis of steatosis as a risk factor in major hepatic resection. *Br J Surg* 2010;97:1331–1339.