"State of the art" in liver resection and living donor liver transplantation: a worldwide survey of 100 liver centers

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Abstract: BACKGROUND: New strategies have been developed to expand indications for liver surgery. The objective was to evaluate the current practice worldwide regarding critical liver mass and manipulation of the liver volume. METHODS: A survey was sent to 133 liver centers worldwide, which focused on (a) critical liver volume, (b) preoperative manipulation of the liver mass, and (c) use of liver biopsy and metabolic tests. RESULTS: The overall response rate to the survey was 75%. Half of the centers performed more than 100 resections per year; 86% had an associated liver transplant program. The minimal remnant liver volume for resection was 25% (15-40%) in cases of normal liver parenchyma and 50% (25-90%) in the presence of underlying cirrhosis. The minimal remnant liver volume for living donors was 40% (30-50%), whereas the accepted graft body weight ratio was 0.8 (0.6-1.2). Portal vein occlusion to manipulate the liver volume before resection was performed in 89% of the centers. CONCLUSIONS: Limits of liver volume and the current practice of liver manipulation before resection were comparable among different centers and continents. The minimal remnant liver volume in normal liver was 25%, and more than 80% of the centers performed portal vein occlusion.

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Abbreviations

ICG	Indocyanine green
PVE	Portal vein embolization
PVL	Portal vein ligation
SFSS	Small-for-size syndrome
GBWR	Graft body weight ratio
TACE	Transarterialchemoembolization
MRLV	Minimal remnant liver volume
LDLT	Living donor livertransplantation
DDLT	Diseased donor liver transplantation

Introduction

Resection of hepatic tumors is being performed with increasing frequency worldwide. Novel developments for the treatment of liver tumors during the past two decades have been based on improvements in several areas, including perioperative management [1–3], novel imaging modalities (particularly positron emission tomography [4, 5]), as well as better understanding on the mechanisms of liver regeneration [6–8], resulting in the possibility to manipulate the liver mass before surgery [9]. Moreover, risk factors for postoperative liver failure, such as liver steatosis or preoperative chemotherapy, have been better defined [9, 10].

Regeneration of liver volume, based on the replication and increase of size of different types of hepatic cells, can be initiated by partial hepatectomy [6–8] or by selective occlusion of the portal branches [9, 11]. Based on this

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knowledge, safer strategies, such as unilateral portal vein embolization or ligation, have been developed to increase the volume and related function of the potential remnant liver. In this context, two-stage hepatectomy for initially unresectable tumors may extend the indications for liver surgery [12–14].

Regarding liver transplantation, partial liver grafts (split-liver transplant and living donor liver transplantation) [9] are now established techniques. The use of so-called marginal (or extended criteria) organs [15] represents another strategy to expand the pool of organs. This survey was designed to gain insight into current practices in liver surgery among liver surgery specialists worldwide regarding preoperative assessment of the liver function, manipulation of liver volume, as well as critical size of liver volume in liver resection, and orthotopic liver transplantation (OLT).

Methods

Directors or codirectors of 133 hepato-pancreato-biliary (HPB) and liver transplant centers worldwide (North America, South America, Asia, Europe, Australia/New Zealand, and Africa) were invited to participate in the survey. Many HPB surgeons were personally contacted to complete the questionnaire during the meetings of the European Surgical Association (ESA) and the International Hepato-Pancreato-Biliary Association (IHPBA). The survey was additionally forwarded to leading HPB surgeons at other centers worldwide known through personal networks. Reminder emails were sent as many as three times every 4 weeks. The survey was closed on September 2007.

This HPB surgery and liver transplantation questionnaire consisted of three main topics to assess current practices in liver surgery and OLT: (a) critical liver volume in liver resection and living donor liver transplantation (LDLT), (b) manipulation of liver mass before surgery, and (c) use of liver biopsy and metabolic tests to assess liver function before surgery. Although the names of the surgeons and the centers were mentioned in the questionnaire, data were reported anonymously (Fig. 1). Results are expressed in percentages, medians, and ranges.

Results

Participating centers

One hundred directors or codirectors from four continents replied to the questionnaire, yielding a high response rate of 75%. The geographic distribution is shown in Fig. 2. Sixty-three European centers were approached, 36 from North America, 20 from Asia, 7 from South America, 5 from Australia-New Zealand, and 2 from Africa. Almost half of the responders were from Europe ($n = 48$), a relevant number of replies were from North America ($n = 27$) and Asia ($n = 17$), whereas a minority were from Australia/New Zealand ($n = 4$) and South America ($n = 4$). No replies were received from Africa. The highest response rate was in Asia (85%; Fig. 2).

Half of the centers (51%) performed more than 100 liver resections per year, whereas one-third (32%) performed between 50 and 100 liver resections annually. The remaining 17% ($n = 17$) of the centers performed up to 50 liver resections per year (Fig. 2).

Eighty-six percent of the 100 HPB centers also performed OLT, and most of them (72 centers, 83%) also performed LDLT. The majority of centers performed more than 50 OLT per year (61.5%; Fig. 3).

Critical remnant liver mass after liver resection or LDLT

In normal livers, the median of the minimal remnant volume accepted after resections was 25% of the total liver volume (15–40%), whereas in cirrhotic patients the minimal remnant liver volume was 50% (25–90%; Table 1).

Regarding LDLT, the minimal remnant donor volume was 40% (range 30–50%) of the total liver volume. The minimal Body Graft Weight Ratio (BGWR) for recipients of LDLT was 0.8 (range 0.6–1.2). Values differentiated per continent are disclosed in Table 1.

Portal vein occlusion

Preoperative manipulation of liver mass, usually by unilobar portal vein occlusion though portal vein embolization or portal vein ligation was performed selectively in 89% ($n = 89$) of the centers, but with an average frequency of less than 1 in 10 patients (range 1–70%). The main reason was a predicted small remnant liver (72 centers; 80.8%). Other indications were major resections in cirrhotic or steatotic livers (11.2%) or cholangiocarcinoma patients (6.7%) regardless of the volume. Sixty-eight centers exclusively performed portal vein embolization. Seven centers sometimes combined portal vein embolization with transarterial chemoembolization, and nine centers also performed portal vein ligation (Table 2).

Preoperative liver and tumor biopsy

Seventy-three of 100 centers (73%) used liver biopsy of the nontumoral parenchyma before resection, but most of them applied this strategy selectively (93.1%; $n = 68$). The most

Name: _____ **Country/City:** _____

1. How many hepatectomies does your institution perform each year?
   □≤10 □10-25 □25-50 □50-100 □more than 100

2. What is the minimal remnant liver volume that you would accept for liver resection?
   Normal liver: ___% of total liver volume
   Cirrhotic liver: ___%of total liver volume

3. Do you use portal vein embolization (PVE) or other strategies to manipulate the liver mass before liver resection?
   □ No
   □ Yes, PVE
   □ Yes, other (Please specify: _____)

4. In which situations do you use PVE?
   _____

5. If you use PVE, in how many percent of your liver resections do you use PVE (estimation).
   ___% of liver resections

6. Do you use liver biopsies before liver resection?
   □ Never
   □ Routinely
   □ Selectively (Please specify indications: _____)

7. Do use metabolic tests (ICG, etc.) to assess liver function before major hepatecomy?
   □ No
   □ Yes (Please specify which test: _____)

8. If you use metabolic tests, what is your policy to use them?
   □ Never
   □ Routinely in each patients before major hepatectomy
   □ Only in cirrhotic and/or steatotic livers
   Other indications (Please specify: _____)

9. How many liver transplantations does your institution perform each year?
   □≤10 □10-25 □25-50 □50-100 □more than 100

10. What is the minimal remnant donor liver volume that you would accept in living donor liver transplantation?
    ___% of total liver volume

11. What is the minimal viable graft volume that you would accept for recipients in living donor liver transplantation?
    ___% of graft/ body volume

Fig. 1 International questionnaire on manipulating the liver mass

common reason for liver biopsy was the assessment of underlying liver disease in patients suffering from hepatocellular carcinoma; this was performed routinely in five centers (6.8%) and selectively in 80% of the centers.

Preoperative metabolic liver tests

Metabolic tests before major liver resections were performed in 38 centers (38%). Nearly half of these centers (18 centers; 47.4%) performed them routinely, whereas the other half (20 centers; 52.6%) used them selectively. When selectively used, the assessment of liver function in diseased organs (e.g., steatosis or cirrhosis) was the main indication ($n = 20$; 100%). The most commonly used metabolic liver tests were the indocyanine green (ICG) test ($n = 29$; 76.3%) and the amino-breath test ($n = 4$; 10.5%). Regarding continental distribution of the use of preoperative metabolic tests, Asia ranked first (76% of the centers) followed by Europe (43%), Australia (20%), and North America (11%). Metabolic liver tests were not used in the four South American centers surveyed (Table 3a–c).

Discussion

This survey provides comprehensive insight into the modern practice of liver surgery in specialized centers. One hundred centers, mainly high-volume HPB and liver

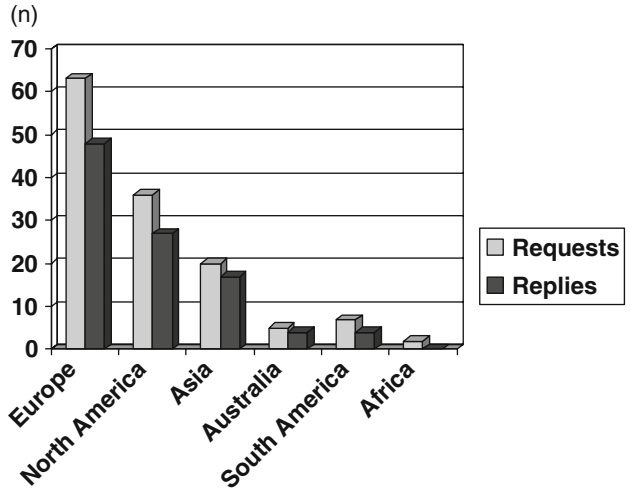

Fig. 2 Survey requests and replies according to continents

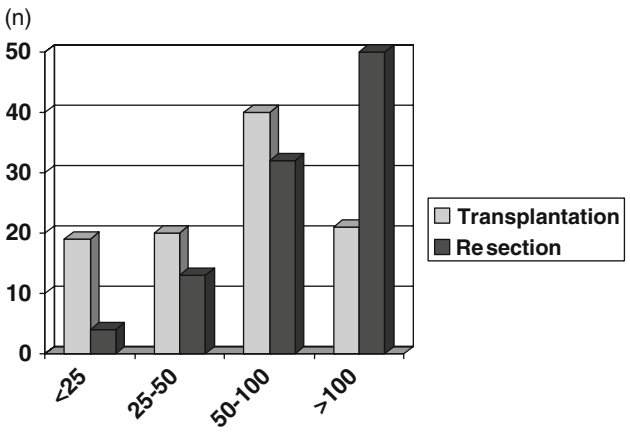

Fig. 3 Number of cases per center

transplantation centers, throughout the world were evaluated. The critical size of remnant liver after resection was 25% in the presence of normal liver parenchyma and 50% in cirrhotic patients. Eighty-nine percent of the liver centers used preoperative strategies to manipulate the liver mass, most frequently portal vein occlusion.

Table 2 Preoperative portal vein occlusion (PVO)

	PVO	Frequency of PVO
Europe	47 (97)	10% (2–20%)
North America	23 (85)	5% (2–20%)
Asia	14 (82)	8% (1–70%)
Australia	2 (40)	10% (10–10%)
South America	3 (75)	10% (5–16%)
Overall	89 (89)	8% (1–70%)

Data expressed as numbers with percentages in parentheses and median with ranges in parentheses

Table 3 (a–c) Use of metabolic tests to assess liver function before liver surgery

	n	%
(a) Use of metabolic tests		
Europe	21	43
North America	3	11
Asia	13	76
Australia	1	20
South America	0	0
Overall	38	38
(b) Type of metabolic tests		
ICG	29	76.4
Breath tests	4	10.5
GSA scintigraphy	2	5
Other (no details)	3	7.9
(c) Indications of metabolic tests		
Routinely	18	47.4
Selectively	20	52.6

ICG indocyanine green

There is a worldwide trend to concentrate complex liver surgery in high-volume centers, because it is widely accepted that morbidity and mortality for major surgery correlate with the case-load of the hospital and the experience of the team [16, 17]. In complex HPB surgery as for other complex procedures, outcome improvements are not solely based on the experience of a surgeon but also on the

Table 1 Critical liver mass for liver resection and partial liver transplantation

	Normal liver (%)	Cirrhotic liver (%)	Donor volume in LRLT (%)	Graft-body-weight-ratio
Europe	28 (15–40)	50 (30–80)	35 (30–50)	0.8 (0.6–1.2)
North America	25 (15–30)	50 (25–90)	35 (30–45)	0.8 (0.8–1)
Asia	30 (20–40)	50 (30–80)	35 (30–45)	0.8 (0.6–0.8)
Australia	28 (25–30)	50 (40–50)	35	–
South America	28 (25–40)	45 (40–80)	38 (35–40)	0.8 (0.8–1.2)
Overall	25 (15–40)	50 (25–90)	40 (30–50)	0.8 (0.6–1.2)

Data are expressed as medians and ranges unless otherwise indicated

availability of facilities, such as anesthesia, intensive care unit, and nursing [18]. The critical number for liver resections per center is not completely standardized, whereas for pancreatic surgery (Whipple procedure), a high-volume center should perform more than 50 pancreatic resections per year [19]. In the current survey, the vast majority of participating centers (>80%) performed a high volume of more than 50 liver resections and more than 50 liver transplantations per year. Therefore, we would speculate that the results of this survey are highly representative regarding the current "state of the art" of liver surgery throughout the world.

Impaired liver function of the remaining liver is of major concern for the HPB surgeon, particularly in patients with some degree of underlying liver diseases. Today the standard to estimate the remnant volume is based on volumetric techniques using MR- or CT-data sets [20, 21]. Below a certain volume, a remnant liver cannot sustain metabolic, synthetic, and detoxifying functions. Symptoms, such as jaundice, coagulopathy, encephalopathy, ascites, as well as renal and pulmonary failure, have been termed the "small-for-size syndrome" [22, 23]. Although a number of risk factors for postoperative liver failure are known [9], critical remnant liver volumes in humans have not been evaluated on a scientific basis. Belghiti et al. reported an incidence of 9% of small remnant liver (defined as <30% of total liver volume) after major hepatectomies (≥3 segments) [24]. Liver cirrhosis is the best-studied underlying liver disease in patients undergoing resection, which is associated with lower tolerance of tissue loss, given its impaired function and decreased ability to regenerate [25]. Additional portal hypertension, associated with a compromised portal flow, correlates with a high risk of postoperative liver failure and death even after minor liver resection [26]. In the present study, the median of the minimal remnant volume after resection in normal liver was 25% (range 15–40%), whereas in cirrhotic patients the replies were much more inhomogeneous, ranging from 25 to 90% (median, 50%) without differences among continents and interestingly also without differences between centers with or without a transplantation program. These data are consistent with a recent review published by Clavien et al. [9].

Graft function in liver transplantation depends on several characteristics of the donor as well as of the recipient [27, 28]. Particularly in LDLT, volume of the graft liver and volume of the remnant liver of the donor are critical for success. Regarding the recipient, a minimal graft body weight ratio of 0.8 has been widely reported [9, 29, 30], which is consistent with the practice in most of the centers (Fig. 2).

Regarding living donors, the current evaluation of the median remnant liver volume was 40% (range 30–50%), which is in accordance with published data [9, 31, 32]. According to Tan et al. a safe donation is not possible with a volume of <30% of the remnant liver [31]. Because the volume of segments V–VIII ranged between 50–80% of the liver volume in cadaveric studies, it is expected that at least 25% of potential donors will have a left liver volume <30% [32]. In this situation, if a left liver graft (segments I–IV) was not large enough and no cadaveric donor was available, the utilization of a right posterior graft (segments VI–VII) or a dual graft have been reported [30].

Several strategies have been developed to minimize the subsequent risk of liver failure after major liver resection. In 1990, Makuuchi et al. first described that selective occlusion of the right branch of the portal vein may improve outcome after major hepatectomy [33]. Selective interruption of the portal flow to a portion of the liver causes atrophy of the ipsilateral hemiliver and hypertrophy of the contralateral side and can be achieved by portal vein embolization or ligation. Both approaches of portal vein occlusion and ligation were usually performed to close the right portal vein in preparation for a right (removal of segments V–VIII) or an extended right hepatectomy (and removal of segment IV) [33–37]. The additional occlusion of the left medial branch (segment IV) may increase the regeneration of the left liver segments, particularly before extended right hepatectomy [37].

Selective portal vein occlusion has been recently integrated into several strategies for two-stage hepatectomy for advanced liver tumors [9, 14, 38, 39] to extend the limits of respectability, and therefore, provide a curative treatment option for many patients, otherwise considered unsuitable for a curative option. The maximal growth of liver volume is reached 2–4 weeks after portal vein occlusion [40] and normally affords an extended liver resection at this time. According to the present evaluation, the manipulation of the liver mass by selective portal vein occlusion is well implemented throughout the world in specialized centers (89% of liver centers); however, the mean frequency of application remains relatively low (8%, with a large range of 1–70%; Table 2). Small predicted remnant liver was the main indication to use selective portal vein occlusion.

The presence of underlying liver diseases increases the risk for postoperative liver failure after hepatectomy [9], although which degree of disease negatively impact on outcome remains largely unknown. Liver biopsy is still the standard modality for identifying liver pathologies, such as steatosis, fibrosis, cirrhosis, or hepatitis. Less invasive techniques, such as MR elastography [41] or ultrasound stiffness measurements [42], may provide valuable information in the future.

Metabolic tests allow analysis of different metabolic pathways by measuring the pharmaco-kinetics of an

exogenous substance eliminated by the liver to assess the preoperative liver function. Indiocyanine green test is the most commonly applied metabolic test; however, the rate of retention of indocyanine is influenced by several factors, especially the liver flow [36, 43]. The retention rate at 15 minutes and plasma disappearance rate are the standard values to predict liver function. Despite its theoretical advantages, the ICG test is not yet accepted worldwide. Although in western countries, the ICG test is not thought to be reliable, it is widely incorporated in the decision making in eastern countries. Preoperative quantitative liver-function tests were used in more than one-third (38%) of the centers participating in the present survey. In Asia, the rate of preoperative metabolic tests was significantly higher than in the other continents (76%). Particularly Americans have a completely different practice, with only 11% of the centers performing metabolic tests before surgery.

A limitation of the survey is a potential selection bias of included centers. It is in the nature of a survey that only a selection of population is approached and only part of the surveyed surgeons may reply. Leading surgeons in the field of liver surgery in all continents were contacted at two of the most important international congresses. The present evaluation included a high number of specialized centers with a high rate of replies (75%). Therefore, we speculate that this evaluation is well representative of the opinion and current practice in major HPB centers, although some continents has more representation in the survey. We are not aware of the availability of similar data.

Conclusions

This survey provides an overview of current practices in liver surgery and transplantation worldwide. A transplantation program is in place in almost all high-volume HPB centers. Selective portal vein occlusion is well implemented in most specialized centers throughout the world. Preoperative liver biopsy and functional liver tests are applied selectively by most surgeons, with remarkable differences between eastern and western countries. Although the mean critical liver mass for resections and LDLT is similar across the continents, the ranges are high and may require further evaluation and consensus on safety in liver surgery.

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