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REVIEW

Current trends in live liver donation

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Summary

The introduction of living donor liver transplantation (LDLT) has been one of the most remarkable steps in the field of liver transplantation (LT), able to significantly expand the scarce donor pool in countries in which the growing demands of organs are not met by the shortage of available cadaveric grafts. Although the benefits of this procedure are enormous, the physical and psychological sacrifice of the donors is immense, and the expectations for a good outcome for themselves, as well as for the recipients, are high. We report a current overview of the latest trends in live liver donation in its different aspects (i.e. donor's selection, evaluation, operation, morbidity, mortality, ethics and psychology). This review is based on our center's personal experience with almost 200 LDLTs and a detailed analysis of the international literature of the last 7 years about this topic. Knowing in detail how to approach to the different aspects of living liver donation may be helpful in further improve donor's safety and even recipient's outcome.

Introduction

The introduction of living donor liver transplantation (LDLT) has been one of the most remarkable steps in the field of liver transplantation (LT), able to significantly expand the scarce donor pool in countries in which the growing demands of organs are not met by the shortage of available cadaveric grafts.

Since 1989, more than 12 000 LDLTs have been performed worldwide [1,2; CM Lo, pers.comm., 2006; European Liver Transplant Registry 2005, www.eltr.org; United Network for Organ Sharing, www.unos.org].

The application of LDLT is associated with several theoretical advantages:

1 Transplantation can be performed on an elective basis before serious decompensation of the recipient (i.e. optimal timing; no waiting time).

2 Graft is of excellent condition (i.e. preselected organ quality) [3,4].

3 Ischemic time is short (i.e. complications because of preservation injuries are absent [5]).

4 Possibility of LT for recipients who might otherwise not be eligible for standard deceased donor LT (i.e. extended indications) [5,6].

The main drawback of this procedure is represented by the '200%' morbidity and mortality potential risk (100% donor and recipient's each). For this reason, during an international conference of transplant physicians, surgeons and allied health professionals held in Vancouver, Canada, in September 2005 [7]; the basic principles of live liver donation were defined as follows:

1 Live liver donation should only be performed if the risk to the donor is justified by the expectation of an acceptable outcome in the recipient.

2 The patient and graft survival of a live donor transplant should approximate the expected outcome for a recipient with the same disease etiology undergoing a deceased

donor transplant. Concerning a pediatric recipient of a live liver donor (mostly parental), the patient and graft survival should be superior to the outcome for a recipient of the same disease etiology undergoing a deceased donor transplant.

3 The indications for live donor LT should be the same as those established for deceased donor transplantation with the exception of institutionally approved protocol studies that consider live donor transplantation preferential to LT from a deceased donor.

4 Live donor LT should offer an overall advantage to the recipient when compared with waiting for an acceptable deceased donor organ to become available for transplantation. The decision to proceed with a live donor liver transplant should be made after a careful analysis of the recipient risk-to-benefit ratio as it relates to severity of liver failure, quality of life (QoL) and expected wait list time for a deceased donor.

In this paper, we report a current overview of the latest trends in live liver donation in its different aspects (i.e. donor selection, evaluation, operation, morbidity and mortality, and the underlying ethics and psychology). This review is based on our center's personal experience with almost 200 LDLTs and a detailed analysis of the international literature of the last 7 years about this topic.

Donor selection

The person who gives consent to be a live organ donor should be an adult who is competent, willing to donate, free from coercion, medically and psychosocially suitable, fully informed of the risks and benefits as a donor, and fully informed of the risks, benefits, and alternative treatment available to the recipient. The benefits to both donor and recipient must outweigh the risks associated with the donation and transplantation of the living donor organ [8].

The selection criteria are not uniform worldwide, mainly because of different political and cultural rules.

Donor age

Potential donors must be healthy volunteers between the ages of 18 and 55 years. For older donors, the donor's absolute age is less important than biological age. Older donors, however, do have an increased risk of occult medical problems. There is also the concern that livers from older donors will have diminished regenerative capacity, which can affect both recipient and donor outcomes [9].

For younger donors, most countries recognize 18 years as the minimum age for independent decision-making regarding the donation. In Korea, the legal age of consent for organ donation is 20 years, but it can be lowered to 16 years only when the recipient is the donor's parent. Especially for these adolescent donor candidates, intimate interviews and psychological evaluations are repeatedly performed as a surveillance mechanism to minimize the risk of coercive consent [10].

Donor–recipient relationship

Policies regarding the requisite relationship between donor and recipient vary widely around the world according to different political and cultural standards. In Germany, for example, a relationship with the recipient within the third degree of consanguinity or an intensive emotional relationship according to the German Transplant Law of 1997 is mandatory [11]. In the UK, only related donors (either genetically or by marriage) can donate [12].

In the US, initially, only relatives were allowed to be donors. More recently, donors have included friends, colleagues, and even people completely unknown to the recipient. It is preferable that donors be at least emotionally related to the recipient, although occasionally there are truly altruistic (i.e. anonymous, nondirected, or Good Samaritan) donors [9,13]. The Canadian law is even more liberal and states that living donation is permissible where there is informed consent by a competent adult with no restrictions pertaining to the relationship between the donor and the recipient [14].

In most Asian countries, there exists a similar policy to the American one. In Japan and Taiwan, the relation to the recipient is usually limited within the second to third degree of consanguinity [2]. Good Samaritan donors were usually used for left liver donation to avoid major donor risk [10]. Since 2003, the liver donor exchange program for adults, as in kidney transplantation, has started to overcome blood group mismatching [10].

ABO-compatibility

Identical or compatible ABO blood type is recommended; however, ABO incompatible blood type LDLT may be undertaken in special instances such as infants <1 year of age without the presence of isoagglutinins, and in emergency situations where no deceased donor allograft is available [7,10,15].

Recently, the Groups from Kyoto [16,17], Chicago [18] and Gent [19] (the only two reports from western countries in ALDLT!) demonstrated the feasibility also of adult to adult LDLT across ABO barriers by using different approaches and immunosuppressive protocols, which

have been performed at different moments of the entire procedure (see also Table 1).

Pre-operative
1 Apheresis of preformed hemo-agglutinins (anti-ABO IgM and IgG) to a level usually <1:16 with plasmapheresis [18,20] or antigen-specific immunoabsorption [19].
2 Intravenous Immune Globulin Infusion [18].
3 Immunosuppressive induction, e.g. IL2R-Abs [19], Ig-antilymphocite [18], cyclophsphamide [21,22], anti-CD20 MOAbs [16,22] and these last ones avoiding the splenectomy.

Intra-operative
1 Splenectomy [18,20].
2 Placement of intravascular devices (in the portal vein or hepatic artery system) for postoperative local prophylaxis of acute liver necrosis because of a 'single organ disseminated intravascular coagulation' triggered by humoral rejection [23].

Postoperative
1 Standard IS (CNI + MMF + steroids) ±IL2R-Abs [19] or Ig-antilymphocite [18].
2 Local intravascular infusion of PGE1, methyllprednisolone and gabexate mesylate: intra-portal [20] or intra-arterial [16,22].
3 Apheresis.
This different strategies allowed different centers to reach good patients' survival rates ranging from 60% [20] to 80% [18].

Medical suitability

Donors should be free of any medical disorder that significantly increases the perioperative risk or contraindicates donation (Table 2). For example, donor candidates who have diabetes, hypertension, or any other significant medical diseases are absolutely excluded from right lobe donation at most centers [10].

General surgical experience indicates that a high body mass index (BMI) (>30 kg/m^2) may increase the risk of surgical complications. In some centers, like ours, a BMI >30 represents an absolute contraindication to live liver donation [4,24] and in others, it does not [7].

Free voluntarism/free of coercion

The transplant community is in full agreement that live donor participation must be free of coercion. The extent to which events are or are not coercive is less clear. Examples of indirect coercion may include (i) social pressure by the intended recipient or family, (ii) economic pressure (e.g. payment), (iii) deteriorating health of the recipient and urgency of the needed intervention, (iv) cultural factors, (v) psychopathological factors, and (vi) the process of informed consent [25].

Forsberg *et al.* [26] recently analyzed the essence of living parental liver donation and found that there was total agreement among the donors that it is impossible to discuss living parental liver donation as a free choice. The parent–infant relationship was considered to be so inherently coercive that there was no other option than to accept the possibility to donate. The donors emphasized their moral responsibility as parents and the impossibility of living with the guilt of refusing to donate. Based on this knowledge, the question arises as to whether it is relevant to discuss living parental liver donation as a choice.

Similarly, Ross *et al.* [27]) argued that family members have a certain moral obligation to serve as organ donors. This expectation is based on the principle that intimate relationships generate moral obligations within families. Furthermore, intimacy implies the sharing of common interests and needs. Therefore, Ross *et al.* believe that if the donation of an organ meets the needs of one who is a next of kin, there can be a moral obligation for interfamilial donation, even if it entails some risk to the donor.

Table 1. Different approaches to ABO-incompatible living donor liver transplantation in different centers.

Author group	Pre-op. HA-apheresis	Splenectomy	Post-op. local	Post-op. systemic	Post-op. HA-apheresis
Egawa [23]	PP	Yes	PVIT (MP, PGE1, GM)	Steroids Tac MMF	PP
Tanabe [24] (Tokyo)	PP	Yes	PVIT (MP, PGE1, GM)	Steroids Tac CP/AZT	PP
Kozaki [25] Yoshizawa [19] (Kyoto)	PP + anti-CD20 MOAbs	No	HAIT (MP, PGE1)	Steroids Tac MMF	PP
Testa [21] (Chicago)	PP + anti-CD20 MoAbs	Yes	No	Steroids Tac MMF thymo	PP
Troisi [22] (Gent)	ASI	No	No	Steroids Tac MMF IL2RAb	ASI

ASI, antigen specific immunoabsorption; AZT, azathioprine; CP, cyclo-phosphamide; GM, gabexate mesilate; HA, hemagglutinin; HAIT, hepatic artery infusion therapy; IL2RAb, interleukine-2 receptor antibodies; MMF, mycophenolate mofetil; MP, methylprednisolone; PP, plasmapheresis; PVIT, portal vein infusion therapy; PGE1, prostaglandin E1; Tac, tacrolimus.

Table 2. Medical contraindications to living liver donation.

Parameter		Notes
Age	>60	Biological age should be considered
Body mass index	>30	Possible re-evaluation after diet
Alcohol	Abuse/dependence	
Pregnancy	+	
Cardio-vascular	Coronaropathy	And history of MI
	Severe arterial hypertension	
	Chronic heart failure	
	Valvulopathy	Hemodynamic significant
Respiratory	COPD	High grade ones
	Pulmonary hypertension	
Coagulopathy	Protein S or C deficiency	
	Factor V mutation	
	Activated protein C resistance	
	Hemophilia	
Oncological	All kind of malignancies	Liver adenoma should be included
Infective	HBV	HBV-Ag positivity
	HCV	positivity
	EBV	IgM positivity
	CMV	IgM positivity
	HSV	IgM positivity
	HIV	positivity
	Any active infectious disease	
Neurological	Epilepsy	
	Demielinating diseases	
Gastro-intestinal	M. Crohn and UC	
	Pancreatitis	Acute and chronic
Hepatological	NAFLD	Macrosteatosis >10%
	Hepatitis	Postinfective and not, acute and chronic
	Fibrosis	
	Metabolic liver disease	e.g. Alagille-Sy, urea-cycle defect, α1-antitrypsin deficit, Wilson disease
	Hepatolithiasis	
	Status posthepatectomy	
	Big-size benign tumors	
Renal	Chronic renal failure	
Endocrine	Diabetes mellitus Type I	
	Hypo- or hyperthyroidism	Therapy refractory
	Hypo- or hypersurrenalism	
Immunological	Autoimmune systemic diseases	

COPD, chronic obstructive pulmonary disease; EBV, Epstein–Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; HIV, human immunodeficiency virus; MI, myocardial infarction; NAFLD, nonalcohol associated fat liver degeneration; UC, ulcerous colitis.

Donor evaluation

The main goal of the evaluation process is to assure the safety of the donor and to provide grafts of better quality for the recipients. All efforts should be made to develop an effective screening protocol for the evaluation of donors with the aim of saving time and resources for an LT program.

The sequence of the examinations performed during the evaluation procedure is typically based on a progression from least to most invasive, but the key factor is also to determine which examinations identify a higher proportion of unsuitable candidates. Consequently, a person with no real chance of donation could be excluded as soon as possible during the selection process, saving considerable time and expenses for the LDLT program.

At this regard, different multistep and -disciplinary evaluation protocols have been proposed. Table 3 shows our standardized evaluation protocol at the University of Essen [4,24].

Blood tests

Blood tests results that confirm donor infection with HIV, HCV or HBV (HBsAg+) are a contraindication for living liver donation. The HBc-Ab positivity does not

Table 3. Evaluation protocol for potential living liver donors at the University Hospital of Essen, Germany [7,27].

STEP 1	Clinical evaluation: history and physical examination
	Lab-tests: blood group, hemabiological tests, chemistry, coagulation profile, C-reactive protein, and pregnancy test
	Serology hepatitis A, B, and C; H1V. CMV. HSV. EBV
	First informed consent
STEP 2	Imaging studies: all-In-one computed tomography scan
	Liver biopsy
	First psychological evaluation
STEP 3	Special studies: ECG-chest X-ray, pulmonary function tests, echocardiography, stress test
	Laboratory: thyroid function tests (TSH, T3, T4), Immunoglobulins IgA, IgG, IgM, iron, transferrin, ferritin, α-1-antitrypain, ceruloplasmin, tumor markers (CEA, AFP, Cal 9-9), factors V, VII and VIII, protein C and S, APCR, and urine sediment
	First autologous blood donation
	Selected consultations
STEP 4	Second psychological evaluation (donor and recipient together)
	Hepatologist consultations
	Second autologous blood donation
STEP 5	HLA tryping.cross-match
	Anesthesiological consultation
	Ethics board evaluation
	Final informed consent

HIV, human immunodeficiency virus; CMV, cytomegalovirus; HSV, herpes simplex virus; EBV, Epstein–Barr virus; EOG, electrocardiogram; TSH, thyroid-stimulating hormone; T3, trilodothyronin; T4, thyroxin; CEA, carcinoembryonic antigen; AFP, alpha-fetoprotein; APCR, activated protein C resistance; HLA, human leukocyte antigens.

represent a contraindication to donation for a recipient affected by HBV-cirrhosis. Notwithstanding, testing for serum HBV DNA is recommended in donors with detectable anti-HBc with or without anti-HBs. [7,24].

Laboratory testing for a pre-existing hypercoaguable condition should be performed especially if the potential donor has a history of venous thrombosis [7,24].

Imaging

Imaging studies should be performed only after the basic evaluation has been completed. Appropriate radiological imaging should be obtained preoperatively to assess liver volume, vascular and biliary anatomy as well to plan the 'road map' for liver resection.

Volumetric imaging

The study of liver volume, generally performed by means of computed tomography (CT), represents another key point of the evaluation protocol of the donor. It must be as accurate as possible in order to not only guarantee enough graft volume to the recipient but also, more importantly, to assure enough residual liver volume to the donor.

Volumetric imaging analysis may overestimate the actual liver volume by as much as 10%. In this regard, Itamoto *et al.* [28] showed that estimated graft volume tended to be overestimated compared with graft weight determined after graft procurement. The main cause of the overestimation may be related to the difference between the vital liver filled with blood *in vivo* and the graft that is in a state of collapse *ex vivo*.

Donor safety requires a calculated remnant liver of at least 30% of the original liver volume with complete venous drainage. The Vancouver Forum participants concluded that in the interest of recipient safety an estimated graft liver volume to recipient body weight ratio (GWBWR) of >0.8% should be achieved [7,10].

Vascular anatomy

The complex vascular anatomy of the liver and the high prevalence of vascular variants reinforce the need for accurate preoperative vascular imaging. In early experiences with LDLT, all donors were subjected to invasive testing, including hepatic angiography with its correlated risks [29]. Currently, less invasive and equally reliable methods like multislice CT-angiography [30] or magnetic resonance (MR)-angiography [31] are preferred.

Biliary anatomy

Biliary tract complications, including bile leakage and bile duct stricture, are the most frequent cause of morbidity following the donor hepatectomy [28]. Therefore, precise identification of biliary duct variants in the donor before the operation is critical for the successful and safe performance of both the donor hepatectomy as well as the biliary reconstruction in the recipient. Biliary anatomy may be assessed either pre- or intra-operatively based upon the judgment of the surgical team.

Endoscopic retrograde cholangiopancreatography
Endoscopic retrograde cholangiopancreatography is invasive and is associated with a considerable number of complications (e.g. iatrogenic pancreatitis), thus potentially subjecting the voluntary donors to a higher risk than with CT cholangiography. This method has been mostly abandoned by LDLT-Centers.

CT-cholangiography
Computed tomography cholangiography enabled Itamoto *et al.* [28] to identify clearly not only different biliary tract variants, but also small biliary branches from the caudate lobe to the right hepatic ducts or the confluence in the majority of donors. Moreover, preoperative CT cholangiography combined with intra-operative cholangiography enabled the authors to divide the right hepatic duct at a more optimal site. Consequently, preoperative CT cholangiography and intra-operative cholangiography resulted in a low biliary complication rate (1.9%) in their program [28]. Similarly, Wang *et al.* [32] from San Francisco observed that in 24 subjects who underwent right lobe retrieval, biliary tract anatomy determined at CT cholangiography was concordant with findings at surgery in 23 (96%). The pre-operative CT cholangiography was reliable enough that only three of 24 subjects required conventional intra-operative cholangiography [12%] compared with all donors who needed intra-operative biliary imaging before the introduction of CT cholangiography (23 of 23 subjects; $P < 0.0001$).

Magnetic resonance cholangiography
The value of magnetic resonance cholangiography (MRC) is recently getting more and more relevance. In this regard, Kim *et al.* prospectively studied the accuracy of MRC in assessing the biliary anatomy with intra-operative confirmation in a cohort of 30 ALDLT donors who underwent right hepatectomy. Surprisingly, the sensitivity, specificity, positive predictive, and negative predictive values of MRC in detecting aberrant biliary anatomy were 92%, 100%, 100%, and 94%, respectively. Therefore, the authors concluded that preoperative MRC accurately depicts biliary anatomy in potential adult-to-adult LDLT donors and may guide the intra-operative management of the biliary tract [33].

Similar results sustaining the reliability of MRC have been observed by the group from Barcelona [34].

Intra-operative cholangiography
Although biliary variants can be readily depicted by means of intra-operative cholangiography, this procedure results in time delays and does not permit the surgeon to adjust the surgical strategy freely. Notwithstanding, this is, at present, the most performed biliary imaging procedure for living donors worldwide.

'All in one' procedures
To simplify and shorten such time-consuming and costly procedures, reports in the literature support the use of multidetector CT as a comprehensive evaluation tool, combining the advantages of minimal invasiveness with simultaneous assessment of the hepatic parenchymal morphology and detailed analysis of the vascular and biliary anatomy. At our center, a total of 250 potential living liver donors underwent a three-phase, dual-enhancement multidetector CT scan as an all-inclusive approach to evaluate in a single diagnostic study, the biliary, vascular, and parenchymal morphology of the liver [35,36]. Preoperative findings were correlated with intra-operative findings (available in 62 subjects). Underlying biliary and vascular anatomy was displayed at least to the second intrahepatic branch in all but seven patients. Detected anatomic variants involved the biliary (38.8%), arterial (40.0%), portal venous (21.4%), and hepatic venous (43.5%) systems. Correlation with intra-operative findings was excellent. The preoperatively determined anatomic pattern was confirmed intra-operatively in 57 (92%) of the 62 donors; in the other five subjects, either a right or a left hepatic branch was missed. All initially missed branches could be retrospectively detected on the CT image, which suggests that the reviewers' sensitization for the presence of hepatic arterial variants might be a more limiting factor than the achievable image quality [36]. This technology should reduce the need for multimodality donor evaluation protocols. At University Hospital Essen, this protocol currently represents the standard procedure and almost completely eliminates the need for further examinations to determine the candidate's anatomy.

A comparison between the performance of 'all-in-one' magnetic resonance imaging (MRI) and 'all-in-one' multidetector computed tomography showed that both techniques are efficient to evaluate potential living liver donors' anatomy in a single diagnostic step, but the main advantage of CT lies in the ability to accurately assess the biliary anatomy [35]. The same conclusion was reached by Yeh *et al.* [37] who compared conventional MR, MRC and multidetector CT with intra-operative findings. These authors also confirmed that CT cholangiography enables significantly better biliary tract visualization than conventional or excretory MR cholangiography – either alone or in combination.

With CT imaging, however, there are concerns, including the inherent radiation exposure and the necessity to administer large volumes of potentially nephrotoxic contrast agents, accompanied by a considerable risk of adverse reactions. It is therefore an ethical obligation to

fully inform the subjects and to perform the examination with the highest possible level of care. Based upon available studies, though, it seems that the inherent risks associated with CT imaging are justified by CT's ability to provide accurate, detailed images in a single diagnostic study.

Operation planning

In addition to the 2-D images provided by these studies, software approved by the US Food and Drug Administration is now available, which allows 3-D reconstructions and modelling for planning liver surgery (MeVis Liver-Analyzer and Liver-Viewer, Bremen, Germany). Data obtained by an 'all-in-one' CT-scan [35] are further analyzed with the software HepaVision (MeVis, Bremen, Germany) for a 3-D reconstruction of vascular functional liver anatomy. This new technology offers the following advantages: (i) 3-D reconstruction of the vascular anatomy, which can define vascular territories supplied or drained by the hepatic venous, portal venous, and hepatic arterial branches; (ii) 3-D reconstruction of biliary anatomy; (iii) automatic calculation of the liver volumetry, as well as the territorial volumes; (iv) 3-D display of the individual territorial liver mapping; (v) risk analysis of the hepatic vein dominance relationship; and (vi) virtual simulation of the liver partition allowing pre-operative mapping of the plane of resection [38–41].

Liver biopsy

The role of liver biopsy (LB) in donor selection remains controversial, as the procedure is associated with additional potential risks for the donor.

The Vancouver Forum participants [7] suggested that a donor LB should be performed if blood specimen liver tests are abnormal and if steatosis or other abnormalities are noted on imaging studies. The LB may be considered if the BMI is >30 or in potential donors genetically related to an intended recipient with autoimmune hepatitis, primary sclerosing cholangitis or primary biliary cirrhosis [7]. Additionally, the histological findings that should preclude living liver donation were also clearly defined during the Forum. They include (i) portal or sinusoidal fibrosis (ii) nonalcoholic steatohepatitis, (iii) Steatosis >20% (only for right liver) and (iv) portal inflammation or necrotic-inflammatory changes [7].

In our center, 31 (21%) out of 144 candidates who underwent LB had a positive finding at histological examination that induced their exclusion from donation. Of the 31 excluded candidates, 21 (67%) had liver steatosis of varying kind and grade (10–80%) and 10 (33%) had a nonsteatotic hepatopathy (non-A-D hepatitis in six cases, diffuse granulomatosis in 2, schistosomiasis in 1, fibrosis in 1) [4].

Based on these findings, we believe that not invasive screening modalities can be unreliable, and therefore (on the contrary of Vancouver Forum participants) we are convinced that preoperative LB in the donor selection for adult LDLT should be always performed, once the initial donor screening and noninvasive evaluation is complete in order to detect not only the presence and extent of hepatic steatosis, but also any underlying and often unexpected histological liver damage, which would adversely affect the recipient allograft and donor remnant.

In fact, an accurate quantification of hepatic fat as a contraindication to donation cannot be afforded by BMI and imaging studies alone. The use of the BMI as a predictor of hepatic steatosis, and thus the need for a donor LB is not absolute. Rinella *et al.* [42] reported that hepatic steatosis increases linearly with the BMI. They suggested that individuals with a BMI >28 should undergo LB, whereas those with a BMI <25 and the absence of risk factors do not need one. Remarkably, Ryan *et al.* [43] observed that 73% of potential donors with a BMI >25 had <10% hepatic steatosis. Therefore, the indication for LB was extended to all patients with high BMI, permitting additional candidates to be considered as potential donors.

Recently, Park *et al.* [44] demonstrated that unenhanced CT can accurately depict moderate-to-severe (i.e. ≥30%) macro-vesicular steatosis, thereby avoiding a biopsy in potential living liver donors demonstrating an unacceptable degree of steatosis for transplantation by imaging. Biopsy will still be needed in donors with macro-vesicular steatosis of <30% by unenhanced CT to rule out occult chronic liver disease and more severe steatosis not detected at CT [45]. Iwasaki *et al.* [46] proposed the liver-to-spleen CT attenuation values ratio (L/S ratio) on noncontrast-CT as an reliable index of hepatic steatosis in comparison with other parameters including BMI.

In our experience, we excluded patients with BMI >30 *a priori* not only because of the higher risk of liver steatosis, but also mainly because of BMI >30 also correlates with a high rate of perioperative complications (i.e. lung embolism and wound healing problems). Surprisingly, we also found that some potential donors with normal BMI had a high percentage of liver steatosis.

Because of the reversibility of liver steatosis, dieting is recommended in patients with initially prohibitive hepatic steatosis. A repeat LB should be obtained after weight reduction [7,13,50,51].

Psychology

During the psychological evaluation, donors are assessed for altruism and possible coercion [49].

Forsberg *et al.* [26] investigated the expressed deeper emotions and the experiences of parents who donated a part of their liver to their own child. Based upon the results, the authors were able to generate precise recommendations for the formation of guidelines for living parental liver donation.

Similarly, our group has provided important guidelines for psychosomatic evaluation of potential donors for adult LDLT [49]. Our psychosomatic evaluation consists of following relevant aspects: (i) psychological stability of the potential donor and (ii) verification of informed consent (iii) competence to consent and (iv) absence of coercion. The evaluation has been performed in two steps: firstly, verification of informed consent and assessment of mental stability (i.e. previous psychiatric disorders, social functioning and healthy behavior, psychological coping, analysis of mood); secondly, evaluation of psychodynamics of the relationship between donor and recipient (sufficient autonomy of both, realistic outcome expectations) and the ability of each to anticipate the transplantation procedure (psychological preparation for LDLT e.g. shift in attention from donor to recipient, coping with pain, emotional care for both) [50]. In our preliminary experience, 12% of potential donors who underwent a psychosomatic evaluation were excluded as a result.

It is imperative for healthcare professionals to understand the decision-making process from the donors' perspective in order to develop a more reliable process of informed consent and to provide a more efficient psychosocial support system once the donor makes a decision. Having a precise and formal psychosocial assessment, protocol aids the transplant team in supporting the donor's decision before and after donation [51].

The decision-making process of adult-to-adult LDLT involves several psychosocial factors. Compared with adult-to-child LDLT, in which a patient's parents often make an immediate decision to save their child, decision-making in adult-to-adult LDLT often evokes familial conflict and struggle as potential donors must be often chosen among themselves who will give to a sibling or parent.

Conceptual models can serve as a tool for healthcare professionals to understand a donor's preoperational experience as seen with living donor kidney transplantation [52]. However, these models cannot be applied directly to LDLT as the two procedures differ in the risk to the donor and the alternatives for the recipient. Living donor kidney transplantation is an attempt to improve the patient QoL while LDLT serves as a 'desperate remedy' [53]. On the opposite, the liver patient will die if a donor is not found within a short period of time [54].

Fujita *et al.* [55] defined a 5-step decision-making model of the psychological process that a potential donor experiences [(i) recognition, (ii) digestion, (iii) decision-making, (iv) reinforcement, and (v) resolution] leading up to donation in adult LDLT. The authors found that potential donors often moved from one phase to the next based on a feeling of 'having no choice'. This perception of 'having no choice' was usually predicated on one of four justifications: priority of the recipient's life above all else, an understanding that LDLT was the only option, a willingness to do anything for family, or a sense that the donor was the only eligible candidate. This study has several implications for clinical practice in LDLT. In our opinion, this study's framework serves as an essential tool for healthcare professionals to understand a donor's experience and, based on that understanding, to provide sufficient support to the donor.

Informed consent

Donors must be able to comprehend the risks of liver resection and should understand the possible benefits and outcomes for their intended recipient. This includes understanding of the etiology of their recipient's liver disease and the expected outcome with transplantation for that specific indication. There can be considerable disparity in expected outcome for patients with different disease processes. Many liver diseases that lead to transplantation are often recurrent (e.g. hepatitis B, hepatitis C, and hepatocellular carcinoma), and donors must be informed of these risks for their intended recipients so that they can be truly informed with regard to their own decision whether to donate [9].

There are different opinions about what should potential donors also be told [56]. The Ethics Group of the Vancouver Forum [57] deliberated that the potential donor should be informed about following aspects:

1 The risk of death, reported worldwide and at the center where the procedure is proposed.
2 Medical morbidities.
3 Changes in health and organ function.
4 Impact upon insurability/employability.
5 Potential effects on family and social life.
6 Psychological impact of donation and nondonation.
7 The responsibility of the individual and of the health and social systems in the management of discovered conditions (such as the discovery during the evaluation process of HIV, tuberculosis or other transmissible diseases).
8 Any specific recipient conditions which may impact upon the decision to donate; however, no information can be given to the potential donor until permission is obtained from the recipient.
9 Expected transplant outcomes (favorable and un-favorable) for the recipient.
10 Information on alternative types of treatments for the recipient, including deceased organ transplantation.

11 The limited information available on extra-renal live donation results in uncertainty about donor and recipient outcomes.
12 The request that the potential donor participate in long-term information gathering (registries) to increase the knowledge base.

The death of a right lobe liver donor in 2002 at New York's Mount Sinai Hospital [58] led the New York State Department of Health to formalize rules that supported state-of-the-art care of the donor. One requirement is that live-donor liver transplant programs must have a 'donor advocate team' consisting of an independent medical specialist, a social worker who works with donors but not with their intended recipients, and a transplantation psychiatrist. The donor advocate team shares in an assessment of donor suitability and advises the donor surgeon. If the donor surgeon overrides recommendations of the donor advocate team, the reason for doing so must be documented and is subject to future review [25,59].

Medical out

There should be a formal and deliberate 'time out' period between the completion of the donor's evaluation and the actual surgery, so the donor can reflect upon his or her decision and not get caught up in the urgency to transplant the recipient [9]. This time for reflection provides the donors maximal freedom of withdrawing themselves from the process of donation at any time [12].

Potential donors should be informed from the outset that they can back out at any time, right up to the moment they undergo anesthesia. They should be formally offered a 'medical out' – that is, a medical excuse so that the recipient may back out with dignity and without repercussions and without family members realizing the donor has decided to back out. It is important, however, not to fabricate any medical condition that might become a part of the donor's medical records [9].

If a potential donor is unsuitable for any reason, the transplant team offers to help the potential donor to convey this to significant others. Rather than giving reasons that are untrue, the team tells the recipient and/or any third parties that 'it was not appropriate to proceed' [12].

Donor operation

The left lateral segment donor hepatectomy currently represents an established and standardized procedure [60]. In addition, the right hemihepatectomy is almost standardized worldwide [30,61–65], but some points of discussion are still open.

Focusing on donor safety and looking for the ideal graft for the recipient, Hwang *et al.* [10] recently developed useful guidelines for permissible donor conditions and graft type selection (i.e. right, extended right, right posterior, left, and left lateral) based primarily on donor age, liver histology (grade of steatosis) and congestion-free remnant volume.

Timing

Generally, the recipient's operation follows the donor's in a timely fashion. When two teams of experienced transplant surgeons are available it is possible to overlap the two surgical procedures with consequent reduction of the cold ischemic time for the graft. Notwithstanding, the clinical conditions of the recipient and the indication for transplantation may also dictate a change in the sequence of the surgeries. As an example, in patients with advanced HCC, the exploration of the recipient to confirm the absence of extra-hepatic malignancy should precede the start of the donor's hepatectomy [66].

Approach to the bile duct

It is well known that the division of the right hepatic duct is one of the most important steps of the donor hepatectomy, potentially influencing both the outcome of the anastomosis in the recipient and the safety and long-term morbidity of the donor.

Whenever the standard preoperative imaging protocols (i.e. MRI or CT) do not provide reliable information about the anatomy of the biliary tree, an intra-operative cholangiogram must be performed. In our center, based only on the 3D pictures provided by the all-in-one-CT [35], we have avoided the need for intra-operative cholangiogram in the last 67 consecutive cases with no donor biliary complications (personal data).

Additionally, the technique and timing of biliary dissection should be mentioned. Although most centers performed the bile duct division at the end of parenchymal transection, we are of the opinion that an early suprahilar bile duct division should be performed before the parenchymal transection [65,70,71]. In our experience, this approach offers better visualization of the transection plane, prevents thermal injury to the duct and yields perfectly vascularized bile duct stumps for both the graft and the donor side.

Technique of parenchymal transection

For the parenchymal transection, ultrasound or water-jet dissectors are generally used in combination with electrocautery. Preferentially, the division is done without hilar occlusion or using only intermittent clamping [67].

In addition to conventional open operative techniques, some centers have begun to investigate minimally invasive approaches to the donor hepatectomy. Cherqui *et al.* [69] reported for the first time two laparoscopic left lateral lobe retrievals for pediatric LDLT. It was only an initial experience, but if the safety and feasibility of this procedure can be shown in larger series, laparoscopic donor left lobectomy could become a new option for pediatric LDLT.

Recently, Kurosaki *et al.* [70] reported the first results after video-assisted living donor hepatectomy through a 12-cm laparotomy. This technique appears to be as feasible as standard open donor hepatectomy, but with less pain and improved postoperative symptoms. However, as with other approaches to the donor surgery, a randomized study comparing both donor and recipient outcomes and long-term follow-up are needed to confirm the role of this procedure.

The dilemma of the middle hepatic vein

The harvesting of the middle hepatic vein (MHV) with a right hepatectomy for LDLT allows an optimal venous drainage for the recipient but can also have adverse effects for the donor.

The group from Hong Kong introduced this concept and widely demonstrated the validity of the method, stating that the inclusion of the MHV in right-lobe LDLT is safe and is essential for optimal graft function and patient survival [71,72]. Subsequently, centers in Toronto [73] and Paris confirmed the feasibility and safety of this procedure [74].

Using an algorithm based on donor–recipient body weight ratio, right lobe-to-recipient standard liver volume estimate, and donor hepatic venous anatomy, de Villa *et al.* [75] were able to tailor the extent of the donor hepatectomy with or without the MHV with equally successful outcomes in both donors and recipients.

Our results confirm the findings of de Villa *et al.* In particular, based on the radiological studies about segmental partition, the venous vascular anatomy of the liver [38,39,41] and on our own surgical experience [62,76], we can state that the MHV can be harvested without causing impaired outflow in the residual liver [11,30,62,74]. Additionally, remnant liver volume could be spared by performing a 'carving' resection along the MHV [39,76,77].

Dual graft

Aimed to achieve maximal donor safety through minimal resection of liver mass, the group from Seoul introduced recently the technique of 'dual graft' adult-to-adult LDLT in which two left lateral lobe grafts are procured from two donors and implanted into one recipient [10,78,79]. When other than suboptimal donors are not available, the group allowed for the second donor to be a 'Good Samaritan' donor. The authors argue that, unlike a right liver harvest, left lobe and left lateral segment donation does not produce life-threatening complications. However, there still remains a compelling need to determine the real risk to these dual-graft donors [10]. Following the introduction of dual graft transplantation for adult recipients, the rejection rate of potential donors because of inadequate volume or excessive steatosis was reduced from 40% to <20% [10].

Drains

Because of the detailed pre-operative imaging of the biliary anatomy and meticulous surgical technique, abdominal drainage is no longer mandatory after donor hepatectomy in LDLT [80,81] (and personal data).

Furthermore, most LDLT-centers do not advocate the use of a T-tube for biliary decompression of the donor's liver [67].

Intra-operative anesthetic management

The main goal of intra-operative anesthetic management is to avoid heterologous blood transfusion in the donor.

Preoperative autologous blood donation is widely recommended for the live liver donor [82] although autologous blood transfusion may be associated with many of the same complications as transfusion of allogenic units, including the risk of bacterial infection, hemolysis, and volume overload [83].

Acute isovolemic hemodilution (AIH) entails the removal of whole blood from a patient immediately before surgery and simultaneous replacement with colloids to maintain isovolemia [82].

The intra-operative recovery of blood (cell salvage) involves the collection and reinfusion of autologous red cells lost by a patient during surgery.

Lutz *et al.* showed that by applying all three techniques (preoperative donation, AIH, cell salvage) only one of 44 donors required a heterologous blood transfusion. Additionally, maintaining a reasonably low central venous pressure (CVP) during parenchymal transection may be desirable to minimize intra-operative blood losses [84,85].

The combination of refined surgical technique and adoption of the above-mentioned anesthetic skills has significantly allowed our group to reduce the mean intra-operative blood loss during donor hepatectomy from 647 to 106 ml [67].

Postoperative management

All donors should be monitored in the ICU during the initial postoperative period, typically 1–2 days. An adequate postoperative analgesia (epidural, i.v.) should be routinely applied for at least 2–3 days after surgery [10]. Prophylactic management to avoid deep vein thrombosis should be employed routinely (i.e. heparin or low-molecular-weight heparin products, pneumatic cuffs, intermittent mechanical leg compression) [10,67,86].

Outcome

Donor morbidity

The most serious ethical concerns in LDLT focus on the risks to the donor and relate to the principle of 'do no harm'. Most live liver donations are uncomplicated or do not lead to permanent consequence. Notwithstanding, the true extent of morbidity among live liver donors remains poorly understood. For example, the estimated risk of mortality and morbidity currently associated with live donor right hepatectomy is 0.4% and 35%, respectively [7]. The development of standards for defining and reporting complications would foster a better understanding of the incidence and magnitude of such adverse events.

To this end, the Vancouver Forum liver work group [7] proposed following all aspects that define any complication occurring in a live liver donor. This includes (i) unexpected results of a procedure performed on the donor, (ii) a deviation from the ideal course, (iii) anything inducing changes in management of patients (diagnostic/therapeutic) and (iv) untoward events occurring during surgical performance or recovery from the procedure.

Evaluation-related morbidity

At the moment, there is a lack of knowledge about morbidity as a result of the donor evaluation. The few reported cases are secondary to complications after percutaneous LB (i.e. intrahepatic hematoma) [7,14] or aborted donor operation after intra-operative findings of liver anomalies (i.e. high grade steatosis) [11].

In our opinion [4], the benefit of avoiding an unnecessary operation or a poor outcome for the donor or recipient justifies the low risk of LB-related complications. Donors who are biopsied and do not donate as a result of the biopsy do benefit. Firstly, they are spared an unnecessary surgical exploration (or even a life-threatening liver resection in cases of critical remnant liver volume) and additionally, they are diagnosed with something (a hepatopathy) that would possibly never have been diagnosed otherwise and that can now be treated or followed.

Postoperative morbidity

The majority of complications after donor right hepatectomy occur in the perioperative period. There is an extensive literature focused on the incidence and type of complications after living liver donation. Morbidity rates in these reports range from 0% to 67% [10,12,90].

Typically reported complications include biliary leakage, fistula and strictures [9,11,88,89], gastric stasis/dyspepsia [89], wound infection [89], abdominal wall hernia [89], pleural effusion [89,90], pulmonary embolism [11,86,90,91], bleeding [92], psychosocial problems [93], postoperative liver dysfunction [14,92] and the donor's need for LT [88,94,95]. Recently, our group reported a rare complication which occurred in four donors who ended up with an *in situ* divided liver (hepar divisum) after the intra-operative death of the recipient of an intended right adult living donor LT [96].

The right hepatectomy has been associated with higher rate of complications in comparison with left and left lateral hepatectomies (ranging from 20% to 60%, overall approximately 35%) [88,89,97,98].

Data regarding the effect of era and center experience on postoperative donor's outcome are, until now, failing. As a result of ongoing improvement in surgical technique, donor selection, and postoperative care, Broering *et al.* [11] were able to reduce the perioperative morbidity significantly from 53.8% at the beginning of the program to 9.2% in the last period, despite introducing right lobe grafting in the interim.

Obviously, how 'morbidity' is defined influences how centers report their complications and calculate their incidence of morbidities. Several different classification systems for defining complications have been proposed:

1 Clavien's classification of operative morbidity according to severity of events [99,100] (Table 4) and recommended by the Vancouver Forum participants [7].

2 Modified Clavien's classification adapted to the need of the living donor.

- **(a)** Chicago [101].
- **(b)** Hamburg [11].
- **(c)** Essen (Table 5).

3 Hong Kong classification [86].

The variability seen in issue highlights the need for a national/international registry to collect accurate and consistent data so that potential donors can give truly informed consent [9].

Mortality

Because there is no single worldwide registry for living liver donation, it is impossible to determine the true denominator (total living donations) for mortality risk

Table 4. Clavien and Dindo's classification of surgical complications [103].

Grade	Definitions
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and. physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient

Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks. CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

Table 5. Classification of complications (medical and psychiatric ones) in living liver donor at the University Hospital Essen, Germany.

(i) No complication
Regular course without interventions and no medication required except parenteral infusion, analgesics, antipyretics and antiemetics
(ii) Minor complications
(a) All events that if left untreated have a spontaneous resolution, alternatively requiring drug therapy or simple bedside procedures and resolve. (e.g. pleural effusion, neuromuscular syndrome, neurological complications, prolonged ileus, sepsis, urinary tract infection, cheloid, vascular complications, pneumonia, gynecological infection, glomerulonephritis)
(b) Psychiatric complaints not fulfilling a complete disturbance, for instance diffuse somatoform abdominal complaints, not requiring psychotherapy.
(iii) Major complications
(a) All nonlife threatening events requiring invasive procedures, re-operations, hospital stay longer than 30 days or re-hospitalization (e.g. subphrenic abscess, minor bille leak, moderate liver failure, incisional hernia, severe wound infection)
(b) Psychiatric complaints which fulfill ICD-10 diagnostic criteria and require an outpatient psychotherapeutic treatment.
(iv) Severe complications
(a) All life threatening events requiring invasive procedures, re-operations, hospital stay longer than 30 days or re-hospitalization (e.g. major bile leak, pancreatitis, mechanic ileus)
(b) Psychiatric complaints which fulfill ICD-10 diagnostic criteria and require a inpatient psychotherapeutic treatment.
(v) Chronic complications
(a) Complications leading to long term disability or in need of continuous medical treatment
(b) Psychiatric complications leading to long term disability or in need of psychotherapeutic medical treatment for a period longer than 6 months.
(vi) Death

calculations. Lacking an accurate calculation, transplant teams are left to estimate the mortality risk based on their own center's experience, UNOS mortality data, personal communications from their colleagues at other institutions, unpublished case reports at professional society meetings, the lay media, and/or journal articles [1,102]. These many data sources make risk calculation and consequent 'informed consent' difficult.

To date, more than 12 000 live donor hepatic resections have been performed worldwide (ELTR, UNOS, CM Lo, pers. comm., 2006: mortality approaches 0.5% for the right lobe donor in contrast to approximately 0.1% for left lobe donation). [7] The risk of death quoted by transplant center websites ranges from 0.2% to 2% [102].

Table 6 summarizes the worldwide reported donor's mortalities collected from the international literature and from recent reports at professional society meetings. To date, there have been 18 reported cases of early postoperative mortality directly related to the donor operation and five late deaths, although only one of these seems to be a result of a late postoperative complication.

Neuberger *et al.* [103] recently studied how the approach of adults towards living donor donation changed after being informed about mortality risks of the pro-

Table 6. Worldwide reported mortalities of living liver donors divided in early (postoperative) and late mortalities.

#	Reference	Location	Graft	Cause
	Early			
1	[94,133]	Hamburg (Germany)	Left lateral	Pulmonary embolism
2	[7,70]	Essen (Germany)	Right	Liver failure in unrecognized congenital lipodystrophy
3	[134]	Lyon (France)	Right	Multiple postoperative complications, sepsis and multiple organ failure
4	[135]	Texas (US)	Left	Anaphylactic shock
5	[136]	California (US)	Left	Pulmonary embolism
6	[137]	North Carolina (US)	Right	Sepsis
7	[138]	Brazil	Right	Subarachnoid hemorrage
8	[61]	New York (US)	Right	florid clostridial gastritis and toxin-mediated shock
9	[139]	Kyoto (Japan)	Right	Liver failure in fatty remnant liver
10	[1]	US	Right	Liver failure
11	[140]	Germany	Right	Massive bleeding
12	[90]	Korea	Right	Unknown
13	[CM Lo, pers. comm., 2006, 90]	Hong-Kong	Right	Air embolism during endoscopy because perforated duodenal ulcer in inferior vena cava
14	[90]	Argentina	Right	Unknown
15	[CM Lo, pers. comm., 2006]	Singapore	Unknown	Myocardial infarction
16	[CM Lo, pers. comm., 2006, 141]	India	Unknown	Liver failure secondary to small for size syndrome
17	[CM Lo, pers. comm., 2006]	India	Unknown	Unknown
18	[J Najarian, pers. comm., 2006, 143]	Egypt	Right	Sepsis after bile leak
	Late			
1	[1]	Unknown	Unknown	Acute Budd–Chiari secondary to torsion of remnant liver
2	[144]	Kyoto	Left lateral	Unknown (3 years later)
3	[92]	Japan	Unknown	Unknown (10 years later)
4	[145]	Los Angeles (US)	Right	Drug overdose (23 months later)
5	[14]	Hamburg (Germany)	Left lateral	Lou Gherig's disease (amytrophic lateral sclerosis) (3 years later)

cedure. The authors observed that approximately three-quarters of the study population of 1734 adults over 15 years of age were supportive of LDLT and more than half believed that a donor risk of mortality of 1:200 is acceptable.

Psychological outcome

The traditional endpoints of medical and surgical therapy (e.g. disease control, cure, and palliation) do not apply to living donors, as they are in perfect or nearly perfect health before the surgery. For donors, the benefit of donation is primarily psychological. Were it not for their selflessness, these donors would not be patients and would not be having major abdominal surgery. Their expectations, therefore, are considerably different from those of the typical patient with some form of medical pathology. This alone underscores the importance of comprehensive preoperative patient education and also of careful postoperative observation for depression or other psychiatric/psychological disorders.

Different studies have analyzed the changes in QoL after donation for LDLT [54,104–111]. In general, donors have an increased sense of self-esteem after donation and rarely regret their decision to donate. Some psychosomatic disorders have been reported, however, such as diffuse nonspecific abdominal symptoms and pain [87,104,110], sexual dysfunction [106], anxious depression and overall complaints [112].

A minority of donors exhibit an enhanced perception of distress and low self-esteem before and after surgery, which can easily be overlooked in the preoperative evaluation or during postoperative care [93,112,113]. Similarly, it has been reported that for some donors, the reported return to normalcy took a significant amount of time even when no serious medical complications were experienced [10,117].

Donors whose recipients do well clinically are themselves more likely to do well psychologically [107,115]. This suggests an inherent benefit for the donor by the simple act of donation. On the contrary, Post *et al.* [116] found no correlation between clinical outcome of the recipient and psychological outcome of the donor. Interestingly, while the health benefits of donation have not been studied in detail, there is evidence that altruism is associated with improvements in health and longevity [116].

The extent of resection seems to be also an important factor in the donor's psychological recovery [109].

A rare but psychologically stressful situation can occur with the intra-operative death of a recipient before the

implantation of the already harvested graft, thus, resulting in an 'orphan' graft [117]. In this situation, the donor would be emotionally and potentially physically devastated by having undergone the surgical procedure without a positive end result for the recipient. In the case of completion of the hepatectomy, the situation is further complicated by the ethical dilemma of either discarding the harvested liver or donating it to another recipient. Many donors are willing to take risks because they know they are helping a loved one with whom they have a close relationship. With the tragic death of the loved one prior to receiving the procured graft from the donor, the emotional gain for the donor disappears. At this point, the donor in theory gains nothing psychologically by having someone unknown received his or her liver. Therefore, if, at any point in time, the graft can be left safely in the donor, it should be unless it becomes a greater risk to the donor to leave it than to remove it. If it is felt that the graft should not be left in the donor because of prohibitive risk, the question becomes how to now allocate the graft to 'next-best' maximize the benefit for the donor [96].

Financial outcome

Nearly, all reports cite financial difficulties for the donor related to donation [7,11,107].

Trotter *et al.* [104] reported that donors can expect to experience significant financial burdens including a 3-month recovery period and out-of-pockets cost (including lost wages) averaging US$3660. Additionally, the donors' ability to obtain life insurance after donation may be compromised [118].

The participants of the Vancouver Forum [7] considered any outcome that penalizes living donors for the act of donation to be unacceptable and agreed that financial disincentives to donation and the donor's ability to obtain and maintain health and life insurance must continue to be examined by the transplant community [7].

Liver regeneration

Donor livers regenerated to about double the size of their remnant liver within several months, reaching a median 89% of the original liver size (from follow-up varying from 7 days to 12 months) [7,11] ([3]). Marcos *et al.* [64] assessed the regeneration prospectively by volumetric MRI in living right liver donors and showed that the regeneration occurs in the first week after resection. More recently, it was suggested that the functional recovery occurs much more gradually than the recovery of volume and liver biochemistries [3].

We studied 27 donors who underwent a right hepatectomy averaging 61% of the whole liver volume [3]. Mean residual volume increased by 88% within 10 days and thereafter did not show any significant variation. After 1 year, only 83% of the original volume was reached. We also found that it takes only 10 days to normalize liver biochemistries, while cholinesterase and albumin recovery requires over 90 days. More importantly, a direct measure of the cytosolic liver function obtained by galactose elimination capacity showed that functional recovery occurs much more gradually than the recovery of volume and liver biochemistries [3].

Ethics

Living donor LT has always been accompanied by ethical concerns, mainly related to the risk imposed on the donor [119]. Donating an organ to another human being always involves real personal sacrifice in the donor. It is this truly heroic act that raises unique ethical concerns for healthcare providers. The act of donation is truly altruistic, being the opportunity to save someone else's life as well as the chance to benefit society by increasing the donor pool [9].

In the selection of living donors, the guiding ethical principles include altruism, the absence of coercion or monetary reward, patient autonomy, beneficence, and nonmaleficence [12].

Over the past decade, it has been proven that LDLT significantly increases the donor pool and that the outcome for the recipient is equal or even superior to deceased donor liver transplantation (DDLT). In this sense, the risk benefit/ratio for the recipient is clearly in favor for LDLT [119]. Applying the principle of justice to LDLT is also complex, and nobody knows whether a procedure that violates the principle 'above all, do no harm' can be justified. Furthermore, ethical discussions regarding such questions as who should receive a living donor transplant are still ongoing. While some argue that stable patients with chronic liver disease benefit the most from LDLT before hepatic decompensation, others maintain that very ill patients are precisely the ones who should be offered LDLT [77,120]. An extension of this argument is concerned with patients that cannot currently be placed on the waiting list due to advanced cancer, but in whom LDLT offers the only effective oncological option. Disagreement still exists about LDLT for high urgency situation generally associated to suboptimal results even in DDLT. At this regard, several reports have shown that patients with fulminant hepatic failure (FHF) (whether idiopathic, drug or toxin-induced, or acute exacerbation of chronic liver disease) can be well served by LDLT [121–125].

The adoption of LDLT as an option for children suffering from FHF has met with some reluctance because of the potential pressure on the living donor imparted by

the imminence of the child's death. Nonetheless, resistance to LDLT in such cases has gradually diminished, because the procedure's life-saving potential has far outweighed any ethical dilemma and possible constraints resulting from the shortness of time for psychological evaluation of donor and family. Patients survival rates after LDLT for children with FHF varies between 59% and 73% in different series but with significant lower rates of grafts survival ranging between 50% and 60% being also in this case worse than those for children with other indications for LT [121–124,126], but still better than in case of DDLT for FHF [127]. The survival results appeared inferior when compared with adult patients who underwent LDLT for high-urgency situations. The reasons for the difference were unclear, but could be related to the difference in cause of the disease (e.g. long-lasting unknown hepatitis viral infection), pattern of postoperative complications, and incidence of rejection (i.e. refractory acute and ductopenic rejection) ([122]).

In our single center experience with almost 200 LDLTs, we performed this operation only in five children (none in adult patients) affected of FHF with 80% patient and graft's survival (pers. unpubl. data).

Although it was suggested that the results of emergency LDLT were inferior to those of elective transplantations, LDLT has emerged as a life-saving procedure in adult patients in high-urgency situations for LT. The issue of application of LDLT in high-urgency situations in adults was first addressed by Lo *et al.* [128] in 1999 reaching 85% survival rate. The main medical dilemma in this situation consists of the inverse relationship between the duration of donor evaluation and neurological consequences for the recipient [122]. An additional obstacle when adopting LDLT for adult patients with FHF is represented by estimating and obtaining an adequate-size liver graft able to maintain adequate initial postoperative liver function in an emergency case with severely damaged liver function, such as seen in FHF. At this regard Uemoto *et al.* suggest that the minimal Graft Recipient Weight Ratio for a successful LDLT for FHF might be 0.8 and that a relatively safe value would be 1.0 independently of the type of graft used, left [129] or right [121] one. Although left lobe liver grafts can be used successfully in adult-to-adult LDLT in high-urgency situations, there is a trend toward more frequent use of the larger mass provided by the right lobe of the liver. Notwithstanding, the benefits of right lobe LDLT have to be weighed against the risks for the donor undergoing major hepatectomy.

Conclusion

In the last decades, LDLT has emerged as a clinically safe addition to DDLT. Although the benefits of this procedure are enormous, the physical and psychological sacrifice of the donors is immense, and the expectations for a good outcome for themselves, as well as for the recipients, are high.

Knowing in detail how to approach to the different aspects of living liver donation may help us to further improve the donor's safety and even recipient's outcome.

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