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REVIEW ARTICLE

Living donor liver transplantation

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Abstract
The introduction of living donor liver transplantation (LDLT) has been one of the most remarkable steps in the field of liver transplantation (LT). First introduced for children in 1989, its adoption for adults has followed only 10 years later. As the demand for LT continues to increase, LDLT provides life-saving therapy for many patients who would otherwise die awaiting a cadaveric organ. In recent years, LDLT has been shown to be a clinically safe addition to deceased donor liver transplantation (DDLT) and has been able to significantly extend the scarce donor pool. As long as the donor shortage continues to increase, LDLT will play an important role in the future of LT.

Introduction and historical notes

Today, liver transplantation (LT) represents the treatment of choice for end-stage liver disease and represents the culmination of a long history of innovations made by liver surgeons based on hemorrhage control, appreciating the occurrence of regeneration and understanding the liver anatomy [1]. Resective and transplant liver surgery influenced each other reciprocally during their historical evolution. On one hand, advances in liver transplantation surgery were based on the evolution of the surgical technique of liver resection. On the other hand, innovative concepts in oncologic liver surgery were developed in the light of new technical features used for liver transplantation.

Due to improved immunosuppressive regimens, tissue preservation, reduction of infectious disease, and better postoperative management, orthotopic LT has achieved patient and allograft survival rates that have expanded both the indications for transplantation and the number of potential recipients awaiting liver transplantation [2].

Despite supportive legislation, media network systems and attempts to raise public awareness, the actual donor numbers have remained relatively constant and do not meet the growing need for more organs (Figure 1). In 2004, for example, 2035 patients were listed for liver replacement, but only 1262 deceased donor livers became available in the Eurotransplant organization. At present, the combined mortality report for pediatric and adult patients on the waiting list ranges between 10% and 30% [3].

The disparity between organ demand and the cadaveric donor supply for children resulted initially in a pre-transplant mortality around 25% and was disproportionately high compared with adult patients [4]. The problem of size mismatch and the different epidemiology of pediatric donorship and terminally diseased children were responsible for that situation [5]. This stimulated the development of technical innovations, based on the segmental anatomy of the liver, which facilitated transplanting parts of large deceased donor livers into smaller recipients.

The first step in solving the size mismatch problem was the introduction of reduced-size liver transplantation (RSLT). The technique was originally described by Bismuth and Houssin [6] and consisted of performing a resection of the graft on the back table to reduce it to a size that fitted the small pediatric recipients [6–8]. This procedure was validated in the late 1980s [7,8] and later became standard practice worldwide, with 1-year survival rates of around 80% [7–9]. Although RSLT decreased the waiting list mortality of nearly 50% among children, it increased

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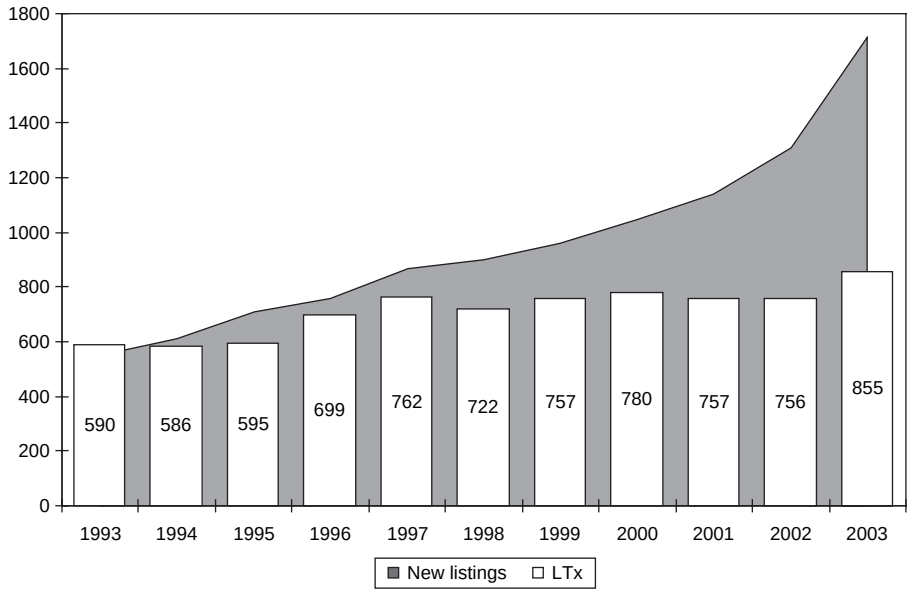

Figure 1. Progressive increase of the disparity between organ offer and demand in Europe (data from ELTR-Report 2004).

the number of adult patients on the waiting list, since the organs were withdrawn from the adult organ pool [10,11].

This problem was addressed by split liver transplantation (SLT), in which a deceased donor liver is divided into two parts for two recipients. The technique was first described by Pichlmayr in 1988 [12,13]. It allowed the preparation of two split grafts by dividing all vascular and biliary structures and parenchyma for the benefit of two recipients, one receiving a right lobe graft and the other receiving a left lobe (segments 2–4) or left lateral one (segments 2–3).

The first series of SLT was reported by Broelsch and co-workers at the University of Chicago [14], and in the early 1990s, the technique was definitely validated by other groups [10,11,15].

The results turned out not to be as expected, but revealed the 'Achilles' heel' of the procedure: the cut edge of segment 4 and the biliary system. Hence, in the presence of a poorly functioning graft, both recipients were in jeopardy and the re-transplantation rate increased [16]. The bottom line was no real increase in donor organ availability for both pediatric and adult recipients. In addition, for the adults, a new phenomenon was discovered: the small for size graft syndrome, which prevented expansion of the procedure of hemiliver transplant between two adults [17].

The big hope for SLT temporarily vanished until the increasing pressure on transplant surgeons prompted them to change the extracorporeal split procedures of preserved organs into harvesting the donor organs in situ or by sophisticated ex situ procedures, avoiding the likelihood of a non-viable transplant. The hazards and the risks of a split harvest induced a drastic reduction of the split procedure to $<20\%$ of all donors. In addition, the logistics of sharing were another hampering factor in its broader application. Currently, most centers perform SLT under their own responsibility and within their own region to avoid long distance shipping and extended cold ischemia time. Unfortunately, the wider application of the split technique is still hindered by the lack of experience and unwillingness of some centers to split every suitable donor liver, making this procedure account for $<20\%$ of all LT performed [18,19].

Notwithstanding, SLT partially increased the donor pool and had an important impact on the waiting list and on the outcome of pediatric liver transplantation [20–24].

Facing the downsides of the RSLT and SLT series and the growing need for liver grafts, the development of segmental LT from a living donor was a natural consequence. In 1989, Raia et al. reported the first two transplantations using grafts taken from living donors, but both recipients died of medical complications [25]. The first successful living donor liver transplantation (LDLT) from a mother to her son was reported by Strong et al. with a graft survival of 14 months and no donor morbidity [26]. Simultaneously, Broelsch et al.'s group in Chicago established a living related liver program in a systematic fashion and they were able to demonstrate that survival of LDLT was comparable to that of deceased donor liver transplantation (DDLT) [17]. Equivalent results were obtained by the group of Tanaka et al. in Kyoto soon afterward, proving the clinical effectiveness of LDLT in children [27]. The procedure was gradually adopted more widely, especially in Asian countries, where cadaveric donors were scarce. In 1994, Yamaoka et al. first reported the use of a right lobe for transplantation, and Marcos et al. demonstrated in

their series of 30 patients that right lobe LDLT can be performed with minimal risk to the donor and recipient [28,29]. Up to now, almost 3500 adult-to-child and 2500 adult-to-adult LDLTs have been performed worldwide (Figure 2).

LDLT emerged as the only innovation 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.

The application of LDLT is associated with several theoretical advantages: (1) the transplantation can be performed on an elective basis before serious decompensation of the recipient; (2) grafts are in excellent condition and complications due to preservation injury are absent; and (3) the possibility of LT for recipients who might otherwise not be eligible for standard DDLT still exists. The drawback of this procedure is represented by the potential risk of death or serious complications to the donor and a series of still unsolved technical, physiological, and ethical questions.

The donor

Donor's evaluation

LDLT is based on two main principles: (1) donor morbidity and mortality must be kept to a minimum; and (2) graft and recipient survival should be as high as in full size DDLT.

In this regard, careful evaluation and selection of the donor minimizes the risk to the donor and maximizes the benefit to the recipient [30–32].

All potential donors therefore undergo a strict multi-step evaluation protocol, which normally includes exhaustive medical and psychological evaluations of the donor, as well as a precise anatomical study of the liver [33,34]. The published donor evaluation protocols are very similar [27,28,35]. Our multi-step evaluation protocol is reported in Table I [36,37].

The donors are generally, genetically or strongly emotionally, related to the recipient. Exclusion criteria for donors are: age under 18 years, obesity (BMI >30 mg/m^2), and significant medical co-morbidities [37].

The study of vascular and biliary anatomy of the liver can be performed in different ways (e.g. angiography, angio-CT, magnet resonance imaging, etc.). Based on our own experience, we prefer the 'all-in-one' CT procedure [38–40]. Data obtained by an all-in-one CT scan are further analyzed with HepaVision software (MeVis, Bremen, Germany) for a 3-D reconstruction of vascular functional liver anatomy (Figure 3). This new technology offers the following advantages: (1) 3-D reconstruction of the vascular and biliary anatomy; (2) automatic calculation of the liver volumetry, as well as the territorial volumes; (3) 3-D display of the individual territorial liver mapping; (4) risk analysis of the hepatic vein dominance relationship; and (5) virtual simulation of the liver partition [41,42].

The study of liver volume, generally performed by means of CT, represents another key point of the evaluation protocol of the donor. It must be accurate, as much as possible, in order to not only guarantee enough graft volume to the recipient but mainly to assure enough residual liver volume to the donor. In general, a graft volume body weight ratio (GVBWR) of 0.8 [43] or 40% of the recipient's standard liver volume [32,44] is recommended as a minimum cut-off for the recipient, even though successful transplantations have been reported with GVBWR <0.7 [45,46]. The Kyoto group showed a statistically significant correlation between complication, graft loss, and a GVBWR of <0.8 [47]. Similarly, the ratio between residual liver volume and the donor's weight should also be no less than 0.8.

The role of liver biopsy (LB) in donor selection remains controversial, since the procedure is associated with additional potential risks for the donor. We believe that LB in donor selection for right adult LDLT is mandatory, once the initial donor screening and non-invasive evaluation is complete [36].

During the psychological evaluation, donors are assessed for altruism and possible coercion [48]. In our protocol, in the case of adult LDLT, the psychological evaluation is held twice, first for the donor alone and second together with the recipient.

From April 1998 to May 2005, we evaluated 895 potential donors for 433 adult patients and 86 potential donors for 57 pediatric recipients. Almost 85% of evaluated potential donors were excluded. In the adult group, 773 (86%) donors were rejected, leaving only 122 suitable donors. For pediatric patients, 62 of 86 (72%) donors were rejected. In the adult group, 28% of donors were excluded owing

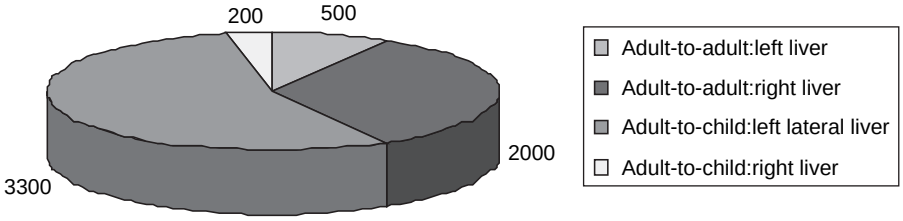

Figure 2. LDLTs performed worldwide from 1989 up to 2004 (almost 6000 LDLTs within 15 years).

Table I. Evaluation protocol for potential living liver donors at the University of Essen, Germany [38].

Step 1	Clinical evaluation: history and physical examination Lab tests: blood group, hematological tests, chemistry, coagulation profile, C-reactive protein, pregnancy test Serology: hepatitis A, B, C; HIV, CMV, HSV, EBV First informed consent
Step 2	Imaging studies: 'all-in-one' CT scan First psychological evaluation
Step 3	Special studies: ECG, chest X-ray, pulmonary function test, echocardiography, stress test Laboratory: thyroid function test (TSH, T3, T4), immunoglobulins IgA, IgG, IgM, iron, transferrin, ferritin, α-1-antitrypsin, ceruloplasmin, tumor markers (CEA, AFP, CA 19-9), factors V, VII, VIII, protein C and S, APCR, and urine sediment First autologous blood donation Selected consultations
Step 4	Second psychological evaluation (donor and recipient) Histology: liver biopsy Hepatologist consultation Second autologous blood donation
Step 5	Anesthesiological consultation Ethics board evaluation Final informed consent

HIV, human immunodeficiency virus; CMV, cytomegalovirus; HSV, herpes simplex virus; EBV, Epstein–Barr virus; CT, computed tomography, ECG, electrocardiography; TSH, thyroid-stimulating hormone; T3, triiodothyronine, T4, thyroxine; CEA, carcinoembryonic antigen; AFP, alpha-fetoprotein; APCR, activated protein C resistance.

to reasons related to the recipient. In 37% of cases in the pediatric group, the evaluation process of the donor was stopped, because the recipient underwent a DDLT. Only 14% of potential donors in our series were considered suitable candidates for donation, and all efforts should be made to create more effective screening evaluation protocols.

Donor's operation

Nowadays the donor's left lateral hemihepatectomy represents a standardized procedure [49]. In addition, the right hemihepatectomy is almost standardized worldwide [27,31,33,34,50–53], but some points of discussion are still open. One major point of debate is whether the middle hepatic vein (MHV) should be harvested or not in the case of right or left hemihepatectomy. Based on radiological studies on partition of the venous vascular anatomy of the liver [41,42], as well on our own surgical experience [53,54], we can state that the MHV can be harvested without causing any outflow decompensation in the residual liver [53,55–57]. Additionally, by performing a 'carving' resection along the MHV, a volume-sparing resection could be also performed [54].

It is well known that the division of the right hepatic duct is one of the most important steps in the donor hepatectomy, potentially influencing both the out-

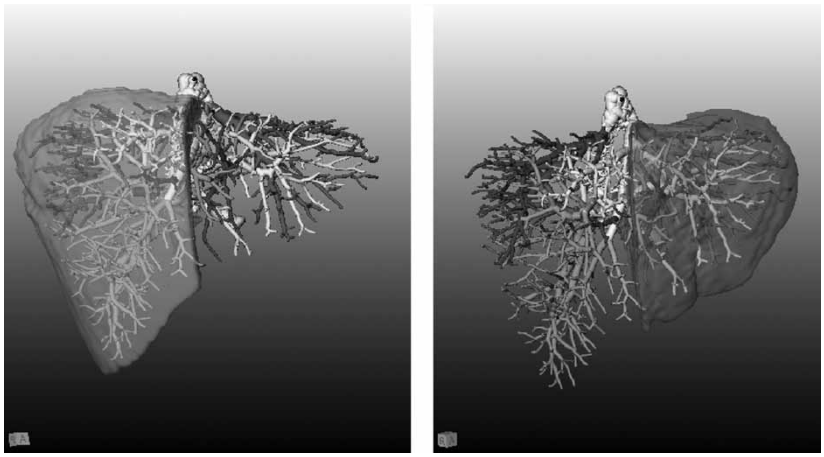

Figure 3. Three-dimensional reconstruction of vascular and biliary anatomy of a donor liver by means of MeVis-CT© [43,44].

come of the anastomosis in the recipient and the safety of the donor. Therefore, an intraoperative cholangiogram should be performed whenever the standard preoperative imaging protocols (i.e. MRI or CT) do not provide reliable information about the anatomy of the biliary tree. Based only on the 3-D pictures provided by the all-in-one CT, we could avoid an intraoperative cholangiogram in the last 67 cases, and no biliary complication in the donor was observed.

Additionally, the method and timing of biliary dissection should be mentioned. Although most centers perform the bile duct division at the end of the parenchymal transection, we are convinced that an early suprahilar bile duct division should be performed before the parenchymal transection [53]. The technique of hepatic duct probing and early division is safe, preserves the vascular supply of the hepatic duct, and allows an excellent yield of a single orifice for the recipient anastomosis. Moreover, it provides a precise definition of the anatomy of the hepatic duct confluence and facilitates one of the most challenging elements of the donor hepatectomy.

Careful preparation and blood-saving surgery will significantly lower the postoperative morbidity. We use a cell saver in every instance. The procedure is performed without hilar occlusion or by using only intermittent clamping. For the parenchymal transection, ultrasound or waterjet dissectors can be used in combination with electrocautery. After removal, the graft is flushed with either UW or HTK solution, although no difference between the two solutions has been reported [58]. We do not use a T-tube for biliary decompression of the donor's liver, although this is carried out in some centers [53].

Donor morbidity and mortality

Morbidity. The most serious ethical concerns in LDLT focus on the risks to the donor and relate to the principle of 'do no harm'. There is an extensive literature focused on the incidence and type of complications after living liver donation, although a clear definition of what should be considered a 'complication' is lacking. Donor morbidity has been reported in numerous reports and ranges from 0% to 67%, with an overall crude complication rate of 31% [30,53,59–62]. Biliary complications including bile leaks and strictures were the most frequently reported morbidities, with a median of approximately 7%. Wound infections, pneumonia, abscess, small bowel obstruction, and incisional hernia occurred in 9–19% of all donors. Umeshita et al. reported 244 postoperative complications in 228 of 1853 donors, which amounts to an overall complication rate of 12% [63]. Right hepatectomies were associated with a greater morbidity risk than left-sided graft operation. As surgeons have become more familiar with the procedure, donor outcomes have improved significantly.

Mortality. Overall, there have been 12 donor deaths reported (10 early and 2 late). Seven of them donated a right graft, three a left graft [50,53,64–68]. Relating to the approximately 3800 left and 2200 right hepatectomies worldwide, the overall mortality risk is estimated to be 0.16% and 0.38%, respectively [51]. Causes of death in the adult-to-adult donations were sepsis in three, massive bleeding in one, pulmonary embolism in one, postoperative liver failure on the grounds of an unrecognized congenital lipodystrophy in one, and unknown in one patient. In the adult-to-child donations, causes of death included pulmonary embolism in one, anesthetic complications in one and multiple organ failure in one donor. Again, the right hepatectomy seems to be associated with a greater risk than the left lateral. Two additional donors themselves became candidates for liver transplantation, but died 3 and 10 years afterwards [30,50,51].

The LDLT recipient

Indications

The indications for LDLT are similar to standard LT in both adult and pediatric patients. Nonetheless, clinical experiences have shown that the willingness to donate increases as the clinical condition of the recipient worsens. Consequently, there is a trend to extend the indications for LDLT, especially in tumor patients (i.e. hepatocellular carcinoma (HCC) represents 10% of primary indications for standard LT and 23% for LDLT), with surprisingly good results.

Recipient's operation

Timing of the operation. Generally, the recipient's operation follows the donor's operation in a timely fashion, with the possibility of overlapping in the case of two teams of experienced transplant surgeons, with consequent reduction of the cold ischemic time for the graft. Notwithstanding, the clinical condition of the recipient and the indication for transplantation also dictate a change in the sequence of the surgeries. For example, in patients with advanced HCC, the exploration of the recipient should precede the donor's hepatectomy.

Technical aspects of recipient's hepatectomy. The retrohepatic inferior vena cava (IVC) should always be preserved and completely mobilized to guarantee an optimal IVC occlusion in case of complicated outflow reconstruction. A temporary porto-caval bypass can be used selectively in the case of patients with severe portal hypertension and previous abdominal surgery or a foreseeable long anhepatic period. The indications for systemic venovenous bypass (VVB) are still controversial [69]. In the case of planned duct–duct biliary anastomosis, the dissection of the bile duct should be extended deeply into the hilar plate [70,71].

The time of completion of the hepatectomy (removal of the recipient's own liver) depends on the availability of the graft and on the clinical and hemodynamic condition of the recipient.

Benching the graft

The benching of the right graft became more time-consuming and complicated with better understanding of the physiology of the venous outflow. The actual state of the art is to maximize the venous outflow by reconnecting all major veins, draining the graft in one single large conduit ('blanket' technique) (Figure 4) [54].

Implantation of the graft

Much emphasis should be placed on the hepatic outflow tract to prevent graft congestion, a key problem leading to early postoperative graft dysfunction. In consideration that the rapid regeneration of the graft could cause kinking, compression, or torsion of the outflow tracts, a wide cavotomy of subdiaphragmatic IVC joining the triangulation of the three hepatic veins became mandatory in right LDLT. The wide cavotomy (triangle-shaped), combined with a single large venous conduit, can protect the outflow even in the case of medial graft rotation.

The portal vein is generally anastomized to the main portal vein of the recipient. In the presence of multiple branches of the right portal vein, a single anastomosis using a common patch is preferred.

The graft hepatic artery is anastomosed to the proper, right or left, hepatic artery. The bile duct(s) are reconstructed by using a Roux-en-Y loop or are anastomosed in an end-to-end/end-to-side fashion with or without insertion of a T-tube [71,72].

Size mismatching of the graft

In case of marginal GVBWR (<0.8) and presence of portal hypertension (>20 mmHg), a small for size syndrome may develop in a short time. It is mainly caused by a hypertensive high portal flow, graft congestion, and consequent reduction of arterial flow, which can lead to enhanced hepatocyte injury with consequent graft dysfunction up to graft loss. In this regard, different surgical solutions with different results have been proposed and can be summarized in two groups: the outflow and the inflow schools. The first, mainly represented by our group and the group from Hong Kong, is mainly oriented in maximizing the venous outflow by harvesting the MHV and performing a wide singular venous conduit [52,54,55]. The other school of thought aims to reduce the portal flow, indirectly through the ligature of splenic artery [73], or directly by means of a meso-caval shunt [64,74] or hemiportocaval shunt [75].

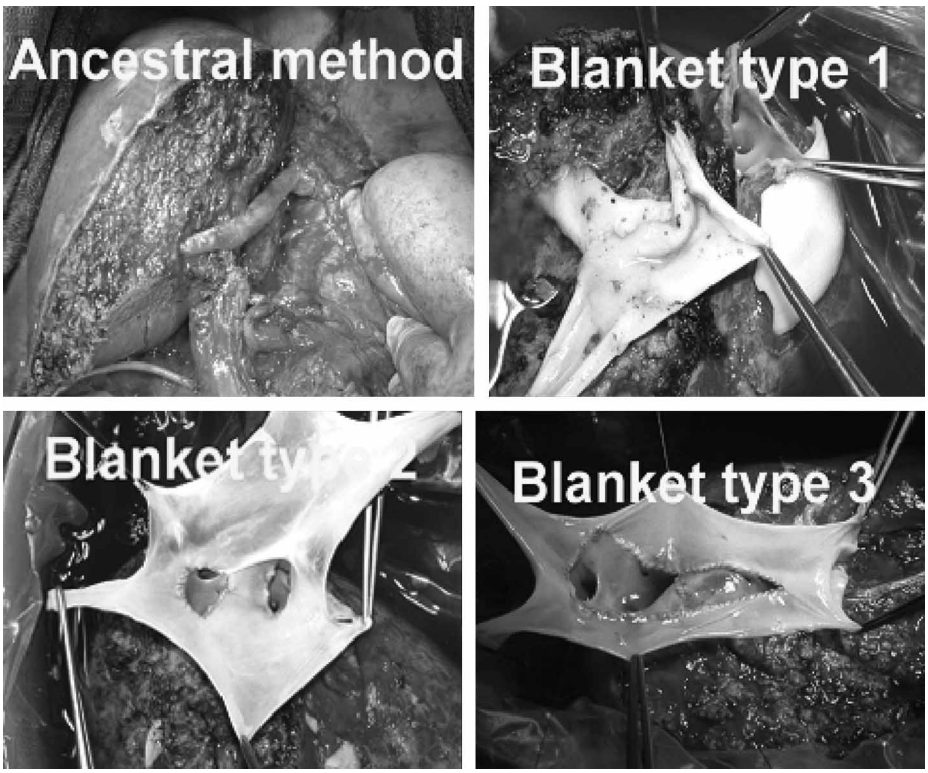

Figure 4. Historical evolution of reconstruction of venous outflow in right LDLT [56].

The actual trend is in reality a combination of the two schools according to individual patient's requirements, mainly based on intraoperative hemodynamic monitoring of portal and arterial flows and pressures.

While small for size grafts are a major problem in adult transplantation, large for size grafts occur predominantly in children and are associated with a higher incidence of graft loss due to vascular complications [76,77].

Recipient's results

Vascular complications

With the introduction of microsurgery, the incidence of hepatic arterial thrombosis was reduced dramatically. Two cumulative studies reported an incidence between 3% and 5%, respectively [43,78]. These results are far better than the 22% reported at the start of performing pediatric LDLT with the left lateral segment [79].

Portal vein thrombosis (PVT) is a rare event. The caliber and the short length of the vessel are the main reasons for the low incidence of thrombosis. Several reports have reported no PVT at all in adult LDLT, and in our program, we experienced only one case [34,51,80]. However, in left lateral LDLT, the incidence is between 5% and 8%, attributable mainly to the diameter disparity between the graft and recipient portal vein. In particular, children with biliary atresia, after undergoing a Kasai operation, show a narrow and sclerotic portal trunk [81].

Biliary complications

Biliary reconstruction remains the Achilles' heel in LDLT, with a reported complication rate between 6% and 35% [72,82,83], including leakage, stricture, or biliomas, eventually leading to graft loss. In $<50\%$, a single duct is obtained, and more often, two or more ducts are present. The small diameters of the bile ducts make the anastomosis very demanding and therefore at high risk for more complications.

Initially, a hepatico-jejunostomy was used in LDLT, but recently, more and more duct-to-duct biliary reconstructions have been performed. However, long-term observation is necessary to confirm the reported advantages of this procedure.

Outcome

Over the past years, it has been shown that LDLT for children is superior to DDLT in terms of patient and graft survival [81]. Several centers reported a 1-year graft and patient survival beyond 90%, and a 3-year graft and patient survival of 78 vs 73%, respectively [84,85]. Furthermore, the pre-transplant mortality is significantly decreased. In fact, waiting list mortality reaches only 2% in centers that perform pediatric LDLT, but it is still 15% in programs that do not [83].

With a 5-year graft and patient survival between 72% and 97%, adult LDLT shows at least as good results as DDLT [33,53,86], although the 3-year graft survival is slightly lower compared with the standard DDLT (65% vs 68%, respectively). This is probably related to different indications – specifically, more viral cirrhosis, more cancers, and more advanced liver failures in adult-to-adult LDLT. Interestingly, patients with HCC, who otherwise would not qualify for a DDLT, have benefited from LDLT. Of 316 LDLTs performed for HCC, patient survival and disease-free survival at 3 years were 78.7% and 79.1%, when the Milan criteria were applied [87].

Extended indications

In consideration of actual donor scarcity, the indications are result-oriented in terms of best overall and disease-free survival. In this regard, some indications are considered not standard, or better defined as extended indications: (1) HCC beyond Milan criteria; (2) decompensated end-stage liver disease (UNOS 2A); and (3) hepatitis C (HCV) cirrhosis. For these reasons, these patients are going to be excluded from the waiting list for DDLT, and the only alternative that can be offered to them is LDLT.

HCC beyond Milan criteria

Until the start of the 1990s, the results of DDLT were very poor, as the main indication for LT was advanced HCC. As a result, HCC became a contraindication for DDLT until the introduction of the Milan criteria by Mazzaferro et al. in 1996 [88]: no extrahepatic metastases, no macroscopic vascular invasion, single tumor nodule ≤ 5 cm or ≤ 3 tumors ≤ 3 cm. Applying the Milan criteria, a 4-year survival of 83% and a disease-free survival at 4 years of 75% was reached [88]. Similar results were observed for LDLT in different centers. Unfortunately, the actual preoperative tumor screening and tumor staging are not always reliable; the consequence is that sometimes patients are over-staged before LT, with exclusion of a high number of patients who could benefit from LT. Additionally, probabilities of dropping out must be taken into account, because tumor progression during the waiting time ranges between 40% and 50% at 2 years after diagnosis. To escape the dilemma of limited organ availability, LDLT is a good alternative, offering a short waiting time with consequently less drop out and reduced mortality in the waiting list.

Additionally, more than 50% of patients in the published series of LDLT for HCC were beyond the Milan criteria. For these reasons, Yao et al. proposed expanding the Milan criteria in the case of LDLT: single nodule ≤ 6.5 cm or ≤ 3 nodules ≤ 4.5 cm.

The authors reported a 1- and 5-year survival of 90% and 75%, respectively [89].

Actually, it seems that the number of tumor nodules represents a less important factor than diameter, presence of vascular infiltration, and histological type associated with different grades of malignancy. Therefore, Lee et al. suggested extending the Milan criteria in selected cases with a higher number of tumor nodules, as long as the HCC were small without macrovascular invasion [90]. Recently, the size of the tumor has also been under discussion. Gondolesi et al. recently reported good results with LDLT for large HCCs [91,92]. Overall, in patients with HCC >5 cm ($n=12$), there were no statistically significant differences in survival or in freedom from recurrence between recipients of living donor and cadaveric grafts. LDLT allows timely transplantation in patients with early or large HCC.

In conclusion, although complicated factors, such as donor voluntarism and selection criteria, limit the role of LDLT for HCC, LDLT allows more patients to undergo early transplantation, which also results in a better outcome in cases beyond the Milan criteria. We need to decide rather, whether a patient with malignant disease should be offered a chance of life prolongation. Any other oncological treatment for a large unresectable HCC would experience unrestricted acceptance if providing the same efficiency as LT [93].

Extended end-stage liver disease

LDLT for patients with decompensated end-stage liver disease (UNOS 2A, MELD >30) is controversial. Nevertheless, these patients are most in need of a timely liver transplant. In our series, patient and graft survival rates were only 43% [94]. Notwithstanding the high mortality rate, no donors had regrets about the procedure, and all donors stated that they would donate again if presented with the same decision. LDLT represents a timely and effective alternative to DDLT in the case of decompensated end-stage liver disease. Nonetheless, the ethical concerns regarding risks and benefits for both donor and recipient should be discussed.

HCV cirrhosis

Approximately 170 million people worldwide have been infected with HCV. By the year 2020, current estimates suggest that nearly 14 million people will have cirrhosis due to chronic HCV. HCV-related disease accounts for more than half of the indications for LT in most transplant programs. As waiting lists continue to expand, the time to transplantation is becoming increasingly prolonged. The current number of deaths on the waiting list is, at the moment, higher for patients with the diagnosis of chronic HCV infection than for other diagnoses. Liver cirrhosis, secondary to HCV, represents 30–50% of indications for LT in European and American countries.

Relapse of HCV occurs virologically in 100% of LT recipients. Histological recurrence occurs in approximately 50% of recipients, with ensuing graft failure in 10% of patients by the fifth postoperative year. Additionally, 8–31% of patients with post transplant HCV recurrence develop cirrhosis within 5–7 years, resulting in reduced long-term survival rates [95,96].

In contrast to whole DDLT, survival outcomes and effects of recurrence following adult LDLT for HCV are not yet defined. Preliminary reports showed an earlier severe recurrence within the first year after transplantation, with higher incidence of cholestatic hepatitis [97]. In this case, the advantages of early transplantation may be offset by the risk of graft failure imposed by early recurrent disease. Nevertheless, an emerging strategy for preventing recurrent HCV infection is pre-transplant treatment to achieve viral eradication (especially in patients with HCC and compensated cirrhosis with a good viral profile: non-genotype 1 or genotype 1 with low viral load) followed by timed LDLT [98,99]. If such strategies become successful, LDLT may exhibit an advantage over DDLT.

The extension of the indications for LDLT should be drawn carefully and individually based on both patient and donor safety. Nevertheless, LDLT opens new perspectives for patients with advanced HCC, decompensated end-stage liver disease, and HCV cirrhosis.

Ethical considerations

LDLT has always been accompanied by ethical concerns, mainly related to the risk imposed on the donor [100,101]. Over the past decade, it has been proven that LDLT significantly increases the donor pool and that the outcome is equal or even superior to DDLT. In this sense, the risk benefit/ratio for the recipient is clearly in favor of LDLT [102]. 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. Further, ongoing ethical discussions are concerned with questions such as who should receive a living donor transplant. While some argue that stable patients with chronic liver disease, before hepatic decompensation, benefit the most from LDLT, others maintain that very ill patients are precisely the ones who should be offered LDLT [103,104]. An extension of this argument is concerned with patients who cannot currently be placed on the waiting list due to advanced cancer, but in which LDLT offers the only effective option. Disagreement still exists about patients with acute hepatic failure, even though several reports have shown that patients with acute hepatic failure can be well served by LDLT [103,105].

However, who should donate then? LDLT is guided by two main principles: (1) donor morbidity and mortality must be kept to a minimum; and (2) graft and recipient survival should be as high as in full size LDLT. The exact risk to the living donor is not known. The evidence from several surveys and subjective assessments indicates that donor mortality is somewhere between 0.2 and 1% and morbidity as high as 60% [106]. Trotter reported that a complete recovery required more than 3 months in 75% of all donors [107]. Despite all this, recent studies have shown a significant benefit for the donor. Liver donors reported satisfaction and increased self-esteem. In a study by Karliova et al., 92% of all donors would decide to donate again [108]. A high degree of preoperative information enabled the donors to have a realistic view of the operation and its potential complications and explained the overall positive retrospective rating.

Clearly, donor safety is paramount in LDLT, and the risks and benefits to the donors will undoubtedly be debated by ethicists.

Conclusions

In the last decades, LDLT has emerged as a clinically safe addition to DDLT. The widespread adoption of LDLT has the potential to decrease waiting list mortality. The advantages of LDLT are obvious: (1) transplantation can be performed on an elective basis before serious decompensation of the recipient; and (2) complications due to organ preservation are minimized or completely absent, and grafts are generally in excellent condition. Although the benefits 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. Donor safety has an absolute priority, and only the assurance of a low morbidity and zero mortality can justify this procedure.

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