REVIEW ARTICLE

Chances and Risks in Living Donor Liver Transplantation

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SUMMARY

Introduction: Liver transplantation is the first-line therapy in treatment of end-stage liver diseases. Due to the mismatch of available donor organs and growing waiting lists in Germany, live donation is of great interest.

Methods: Selective literature review.

Results and discussion: Pediatric living donor liver transplantation almost eliminated waiting list mortality in children and achieved excellent short and long term survival. The situation in adult-to-adult living donor liver transplantation is different, due to the need for extensive donor resection and smaller graft volume for the recipient. Careful donor evaluation and defined selection criteria are essential to minimize the donor's risk and to achieve results comparable to whole organ transplantation. Living donor liver transplantation offers the recipient certain advantages such as superior graft quality, but the procedure should be reserved for selected patients. Donor safety is the highest priority in this procedure. Living donor transplantation should remain in the hands of experienced centers.

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Key words: liver transplantation, organ shortage, living donor liver transplantation, evaluation of living donors, recipient outcome

Since the performance of the first successful liver transplantation by T. E. Starzl in Pittsburgh in 1963, more than 80 000 patients have received liver transplants at more than 250 transplantation centers around the world (1). In Germany, 11 949 liver transplantations had been performed by 2005 (2). The number of procedures performed in Germany has remained stable since 1996 at around 795 per year (range, 699 to 976), but the number of patients accepted onto the organ waiting list each year has markedly increased, particularly over the last five years (*figure 1*). The discrepancy between the supply and the demand for transplanted organs has markedly prolonged individual waiting times and elevated the frequency of death on the waiting list from 10% to 20% (3, e1). Roughly 1100 post-mortem organs would have to be available per year to keep this situation from arising (2). The stagnating or declining supply of post-mortem organs – which is due to multiple factors, including the medicolegal situation in Germany and a less than fully exploited potential for organ donation – heightens the need for alternative procedures, such as split-liver transplantation and living donor liver transplantation. In split-liver transplantation, two functional liver halves are obtained from a single brain-dead donor in the existing pool; living donor transplantation, in contrast, is a way to enlarge the pool of donors. In 2005, 8% of the liver transplantations in Germany were performed with organs from living donors (2). In this review article, based on a selective survey of the literature, we will discuss the present value and future possibilities of this method of transplantation in the light of its historical development and the current scientific data.

Development

The stage was set for living donor liver transplantation by Couinaud's systematic description of the segmental anatomy of the liver (e2). After initial successes in the transplantation of organs of reduced size and in split-liver transplantation, the first two cases of transplantation of left lateral hepatic segments from living donors into recipient children were described in 1988, one in Brazil and the other in Australia (4, 5). Broelsch published the first series of 20 living donor liver transplantations in Chicago in 1989 and then introduced this method to Europe at the University Hospital of Hamburg in 1991. The rapid further development of

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New patients on the liver transplantation waiting list and liver transplantations in Germany from 1996 to 2005. The gap between the number of patients awaiting transplantation and the actual number of procedures performed remains, despite a slow trend toward an increase in the number of transplantations. From: www.dso.de, with the kind permission of the German Organ Transplantation Foundation (Deutsche Stiftung Organtransplantation, DSO).

the technique and increasing experience with it led to excellent results, with patient survival rates above 90% for pediatric living donor liver transplantation (e3); thus, living donor liver transplantation, in combination with split-liver transplantation, practically eliminated the problem of death on the waiting list for children in need of a transplant (6, 7). Living donor liver transplantation into adults could only be performed successfully once the technique of transplantation of the right hepatic lobe had been developed, because adults require a much larger amount of liver tissue. It has by now become an established form of treatment at specialized transplantation centers (3, 8). Often, as much as 70% of the total hepatic volume of the donor must be resected for living donor liver transplantation into an adult; thus, both the donor and the recipient must undergo a careful medical and psychological evaluation before the procedure is performed.

Ethical aspects and legal principles

The risk to the healthy donor and his or her altruistic decision to undergo surgery for the benefit of the recipient are the central issues in the ethical debate that began even before living donor liver transplantation became a reality. Particularly when the intended recipient is an adult, the donor's voluntary consent must be carefully evaluated. When the intended recipient is a child, the donor is usually the mother or father; the situation and the family relationships are not comparable in the case of an adult recipient. An adult requiring a liver transplant, as part of the reaction to his or her own situation of dire need, may put the potential donor under pressure, either consciously or unconsciously. Furthermore, the risk to the donor is greater than when

a child is the intended recipient. For both of these reasons, the voluntary nature of the donor's informed consent must be critically assessed. Standardized testing and counseling by experienced psychologists are indispensable and of tremendous importance (*box*).

The living donor

The donor must be selected and carefully evaluated before living donor transplantation can proceed. The donor's safety has the highest priority in all pre-, intra-, and postoperative phases of the procedure. The donor must be informed of the typical risks of the operation and of the possibility of dying during or after the procedure. The donor may retract his or her consent at any moment up to the induction of general anesthesia.

Criteria and evaluation

At the University Hospital of Kiel, living donors of hepatic transplants must meet the following general requirements:

- Age 18 to 60 years
- A genetic or emotional relationship to the recipient
- A compatible blood type (exception: a very young recipient in whom isoagglutinin antibodies are not yet demonstrable)
- Body-mass index < 30 (if the BMI is 30 or above, the risk of thromboembolic complications is elevated) (e4)
- Absence of severe preexisting illnesses or prior major abdominal surgery
- Planned residual liver volume > 30% of the initial liver volume
- Fatty degeneration of the liver < 30% if the left lateral hepatic lobe is to be donated or < 10% if the right hepatic lobe is to be donated
- Absence of anatomical variations that would necessitate a reconstructive procedure in the donor.

The donor is evaluated according to the stepwise algorithm shown in *table 1*. Because, in general, only one out of three potential donors screened is actually a suitable donor (9), the more invasive diagnostic tests should be performed only at the end of the evaluation, when the likelihood that the potential donor will become an actual donor is greater. Important components of the evaluation include assessments of the general medical risk, of the size and functional capacity both of the planned residual liver in the donor and of the liver tissue to be transplanted, and of the donor's psychological state. Thrombophilia testing and the exclusion of known risk factors for thromboembolic events are important, because perioperative pulmonary embolism is a feared complication (10, e5).

Types of liver donation

The most important distinction is between donation for a child and donation for an adult. The left lateral hepatic lobe (segments II–III, about 20% of the total liver volume) is generally an adequate transplant for children weighing up to 25 kg. For children weighing more than 25 kg and smaller adults weighing less than

65 kg, the donor's left hepatic lobe (segments I–IV, about 40% of the total liver volume) is resected. This procedure is rarely performed. Adults weighing more than 65 kg generally need to receive the right hepatic lobe as a graft (segments V–VIII, about 60% of the total liver volume) (*figure 2*). In individual cases the choice of the graft can vary. Reports have been published of transplantation of the right lateral sector (segments VI and VII), of the extended right lobe (segments IV–VIII), and of the extended left lobe (segments II–V and VIII, with or without segment I) (e6). Monosegmental transplantation has also been performed in a small number of cases (e7, e8).

The most important considerations determining the choice of the hepatic lobe to be transplanted are, first, minimal risk to the donor, and second, the needs of the recipient. The amount of residual liver tissue that the donor still possesses after resection must suffice to prevent postoperative liver failure. There is no generally agreed-upon definition of the critical residual volume. In Kiel, we have taken 30% of the total liver volume as a threshold value, as suggested in ref. (11). The fat content of the liver must be subtracted from the total liver volume.

The volume of the transplant should be roughly 0.8% to 1% of the recipient's body weight (corresponding to 40% to 50% of the standard liver volume) in order to satisfy the metabolic requirements of adequate liver function in the recipient. In particular, for persons needing urgent liver transplantation, the amount of tissue transplanted should be more than 1% of the recipient's body weight, if possible. On the other hand, for patients undergoing elective liver transplantation under optimal conditions, the authors have been able to achieve satisfactory results with a volume of only 0.7% of body weight.

Another available innovative method of liver transplantation is dual donation, i.e., the transplantation of liver grafts from two donors into a single recipient. The risk to each donor is minimized by the resection of a smaller amount of tissue to each, while the recipient receives an adequate volume of liver tissue. The combined risk to the entire family is thus kept low, even though two donors, instead of one, are exposed to an operative risk. This method is also highly technically demanding and logistically cumbersome. A clinical series of dual donations has already been carried out in Korea (12, e9), but only a few transplantation centers have been able to perform dual-donor transplantations successfully in the Western world (13). Dual-donation transplantation is currently performed only in selected cases in a few specialized centers.

Morbidity

The donor morbidity rates in 131 published studies vary all the way from 0% to 100% (9). This is clearly the result of varying classifications and definitions of complications. A standardized classification including all complications, not just surgical ones, would allow results to be meaningfully compared across centers

BOX

Legal principles of living donor liver transplantation

• § 8 of the German Law on Transplantation (TPG): Permissibility of Organ Removal

The removal of organs from a living person is permitted only if

1. the person in question is
 - a) of legal majority and competent to give informed consent,
 - b) has been . . . fully informed and has . . . consented to the procedure,
 - c) . . . is a suitable donor . . . who is not exposed to any risks to health beyond the operative risk itself, . . . and whose health is not otherwise seriously compromised in any way,
2. transplantation of the organ. . . is a suitable means of preserving the life of the recipient, . . . of curing a severe illness, . . . of preventing its progression, . . . or of palliating its symptoms,
3. a suitable organ . . . is not otherwise available . . . at the time of organ removal.

(1) The removal of organs . . . is . . . only permitted . . . for transplantation into a first- or second-degree relative, a spouse, a person to whom the donor is engaged to be married, or a person who evidently stands in an especially close personal relationship to the donor.

(2) The organ donor must be informed by a physician about the nature and scope of the procedure and its . . . immediate and late consequences . . . as well as about the probability of success of the proposed transplantation. This information must be provided . . . in the presence . . . of a second physician.

(3) Organ removal . . . may be performed only after the organ donor and the organ recipient have declared themselves willing to participate in medically recommended follow-up care after the procedure. A further precondition is that the committee in charge of such matters according to State law has officially determined whether there are any . . . reasons to suspect that the consent . . . may not have been given voluntarily, or that the organ has been the subject of forbidden trading in organs as specified in §17 . . .

and would enable the overall risk to donors to be properly assessed (14).

In general, donation of the right hepatic lobe seems to be fraught with greater morbidity than left lateral donation (15, e10), though the authors have found no significant difference in morbidity between these two types of transplants over the last five years at the University Hospital of Hamburg-Eppendorf. The overall morbidity in 64 left lateral donations was 12.5%, compared to 9.8% in 41 right lobe donations. When the living donation program was begun in this center in 1991, the morbidity of left lateral donation was 80%; when right lobe donation began to be performed in 1992, nearly all of the donors developed complications postoperatively. The entire, highly specialized, interdisciplinary team of the transplantation center traveled along a learning curve, so that, over the years, we were able to achieve the low morbidity rates that have been described (14).

Donors of the right hepatic lobe regularly go through a temporary phase of hepatic insufficiency

TABLE 1

Evaluation of the living donor for liver transplantation

Stage 1, ambulatory	Stage 2, in hospital		Stage 3, ambulatory
1 day	2–3 days	1–2 days	1 day
<p>First contact with patient and family; detailed information provided to prospective donor and recipient; psychological assessment¹, degree of relationship, age, body weight and height, medical history, physical examination, blood type</p> <p><i>Laboratory tests:</i> ESR, differential blood count, electrolytes, hepatic and renal function tests, amylase, lipase, glucose, protein electrophoresis, triglycerides, cholesterol, TSH, CRP, ferritin, transferrin with saturation, α1-antitrypsin, ANA, coagulation studies, urinalysis</p> <p><i>Serology:</i> HBV, HCV, HIV, CMV, EBV, HSV</p> <p><i>Thrombophilia studies:</i> Protein C, protein S, antithrombin III, factor V disorder mutation, prothrombin mutations, homocysteine, factor VIII, cardiolipin and antiphospholipid antibodies</p>	<p><i>Clinical evaluation:</i> ECG/stress-ECG, chest x-ray, echocardiography (age > 40), pulmonary function testing, Doppler ultrasonography of the carotid arteries (age > 40), abdominal ultrasonography, upper abdominal CT with volumetry of the two hepatic lobes, MRI + MRCP + angio-MR of the liver, liver biopsy (for right hepatic lobe donation)</p>	<p><i>Psychological assessment, then medical assessment:</i> Assessment by an independent physician, anesthesiological evaluation and patient information, then surgical evaluation and patient information in the presence of an independent physician</p>	<p>HBV vaccination, transplant coordination, final check for completeness, external ethics committee</p>

¹ "psychological assessment" means evaluation of the prospective donor's motivation and his or her connection/relationship to the recipient, exclusion of emotional or financial pressure, and judgment whether the prospective donor is aware of the implications of donation and has the emotional means to deal with them.

Remark: The evaluation protocol for living donors varies slightly among transplantation centers depending on the local resources, expertise, and individual experience.

that is explicable as the result of the loss of a large amount of parenchyma (16) and is completely reversible. This phase manifests itself clinically in a short-term reduction of synthesis of hepatic products, resulting in a partial coagulopathy that may need to be treated with clotting-factor substitution. Hepatic regeneration, a major guarantor of the success of living donor liver transplantation, begins immediately. After one to two weeks, the regeneration process is largely completed; the ensuing remodeling phase takes place over a period of up to one year (17, e11, e12). Ultimately, approximately 90% of the preoperative hepatic volume is reached (e13).

The most common severe complications are problems affecting the biliary tree (leakage, strictures) and infection. Postoperative biliary leakage, in particular, occurs more frequently after right hepatic donation, because of the specific anatomical features and variations of the biliary system on the right side, as well as the considerably larger amount of tissue that is resected.

Mortality

Approximately 6000 living donor liver transplants (all types of donation included) have now been performed worldwide; ten early and three late fatal complications have been reported. Seven of the ten early deaths

occurred after right lobe donation and three of them after left lateral donation.

The mortality of left lateral donation is thus circa 0.09% (18), while that of right lobe donation is circa 0.4% to 0.5% (19). The overall mortality is 0.2% in relation to the total number of liver donations worldwide (9).

Death after liver donation was attributable to inappropriate selection of donors and, in cases of donation to adult recipients, the resection of excessive amounts of hepatic tissue. This underscores the need for careful preoperative evaluation of prospective donors.

The recipient

The recipient derives a number of advantages from living donor liver transplantation as opposed to the transplantation of a post-mortem organ. The published series of living donor transplantation have yielded good results that are comparable to those of whole organ hepatic transplantation. Nonetheless, living donor transplantation is still performed in only a fraction of the total number of transplantations performed annually in Germany and the USA.

Advantages

Living donor hepatic transplantation shortens the

recipient's waiting time, can be planned, and can be adapted to the individual situations of the donor and the recipient. The elective character of live donation enables optimal preparation of the recipient and can lower the mortality before transplantation in patients with progressive disease. Patients with cholestatic disease, most of whom must wait a very long time for their transplants, can also benefit from early transplantation from a living donor. Interdisciplinary management by experienced hepatologists is important so that living donor transplantation can be performed with optimal timing. Transplantation too early in the course of the recipient's disease should be avoided, because, in such cases, the risks of surgery outweigh the foreseeable benefit.

Moreover, liver tissue obtained from a living donor is of higher quality than liver tissue from a brain-dead donor (20). Hemodynamic fluctuations after brain death diminish perfusion in the distribution of the portal circulation and the microvascular circulation of the liver (e14). Organs from brain-dead donors have been found to have a higher frequency of inflammatory infiltrates (e15), and apoptosis has been seen at a higher rate in an animal model (e16). A further factor is the significantly longer cold ischemia time of the post-mortem organ; in live donation, this time can be kept very short, so that less cellular damage can be expected.

Criteria

The recipient should meet the following criteria:

- Up to 70 years of age
- A generally accepted indication for transplantation
- Absence of severe extrahepatic infection
- Absence of significant cardiopulmonary disease
- The weight of the liver tissue to be transplanted is at least 0.7% of the recipient's body weight.

The evaluation of the recipient is no different than that which would precede the planned transplantation of a post-mortem organ. A prerequisite for living donor liver transplantation is that the recipient must be listed with Eurotransplant according to the standard procedure. If a post-mortem organ should become available while the living donor transplantation is still in the planning stage, then the post-mortem

FIGURE 2

Nomenclature of the hepatic segments and lobes. From: Rogiers, Bismuth, Busuttil, Bröring, Azoulay: Split liver transplantation. Heidelberg, Dr. Dietrich Steinkopff Verlag 2002, with kind permission from Steinkopff Verlag.

organ should be transplanted instead, so that the prospective living donor can be spared the risks of surgery.

Living donor liver transplantation should, ideally, be performed only as an elective procedure. Living donor liver transplantation as an emergency procedure, particularly in cases of acute hepatic failure, puts the living donor under incomparably greater pressure, which may render the free and altruistic nature of his or her consent questionable. Furthermore, recipients of emergency liver transplants (corresponding to a "model for end-stage liver disease" [MELD] score > 30 in the new allocation system) have been found less likely to survive after living donor transplantation than after transplantation of post-mortem organs (e17, e18, e19). One reason for this is the need for a greater hepatocyte mass because of these patients' critical general condition. The transplant should optimally weigh more than 1% of the recipient's body weight; this often cannot be achieved in living donor

TABLE 2

The benefits and risks of living donor liver transplantation

Benefits to donor	Risks to donor	Benefits to recipient	Risks to recipient
Survival of a near relative	Very low but nonzero risk of death during the procedure or afterward	Shorter waiting time with less risk of death on the waiting list	Specific complications of partial liver transplantation (more frequent biliary complications)
Psychological benefit: actively helping a person with whom one has a close relationship	Postoperative complications of the procedure	Optimal opportunity to plan the transplantation procedure	Guilt feelings in case the donor has a complication
No long-term morbidity	The recipient might still die or need another transplant after living donor liver transplantation	Optimal organ quality	

Cumulative patient survival (Kaplan-Meier plots) after 41 living donor transplantations of the right hepatic lobe and 207 transplantations of entire livers obtained from brain-dead donors at the University Hospital of Hamburg-Eppendorf, from January 2001 to June 2006

transplantation for an adult recipient. In Asian countries, where, for religious reasons, post-mortem organs are hardly ever transplanted, living donor transplantation is the standard procedure in acute hepatic failure. In contrast, a relatively large supply of post-mortem organs is available within the Eurotransplant area, so that these can be used in "high-urgency" situations in preference to live donation.

Risks

The adult recipient who receives a transplant of borderline volume is in danger of developing "small-for-size syndrome," which is characterized by hyperbilirubinemia, ascites, and diminished hepatic synthetic function. The most common postoperative complications other than this are infections and problems of surgical technique. Living donor liver transplantation is more demanding on the surgeon and should be performed in centers with adequate experience so that complication rates can be held low. In particular, the

rate of biliary complications after living donor transplantation is problematic if it is in the range of 24% to 60%, as has been reported in some series (3, 8, e20) (table 2).

Results

Living donor liver transplantation yields better results than the transplantation of post-mortem organs for child recipients (21); for adult recipients, too, the patient and transplant survival rates after living donor transplantation are comparable, or even superior, to those of post-mortem organ transplantation (22, 23, 24, 25, e21, e22). In Germany, the rate of adequate hepatic function after living donor transplantation is slightly higher than that after post-mortem organ transplantation. At the University Hospital of Hamburg-Eppendorf, the authors have obtained a five-year patient survival rate of 82.9% and a five-year transplant survival rate of 80.5% after 41 living donor liver transplantations. These survival rates are comparable to those of the 207 patients who underwent post-mortem organ transplantation in the same clinic during the same period: 82.1% patient survival and 72.9% transplant survival at five years. The difference between the living donor transplantation and post-mortem organ transplantation groups is not significant (figure 3a and b).

Overview

The good results of living donor liver transplantation, for both child and adult recipients, provide a strong motivation to offer this therapeutic alternative to suitable recipients and their families. Living donor liver transplantation should only be performed in centers with the appropriate degree of experience and expertise, so that the risks of the procedure, particularly to the donor, can be held to a minimum. Further research must be directed toward making the procedure even safer and even more effective for both the donor and the recipient.

Conflict of interest statement

The authors state that they have no conflict of interest as defined by the guidelines of the International Committee of Medical Journal Editors.

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