TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

REVIEW

Is there an advantage of living over deceased donation in liver transplantation?

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Keywords
deceased donors, live donors, liver clinical, outcome.

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Conflict of Interest
The authors declare no conflict of interest.

Received: 11 January 2012
Revision requested: 9 February 2012
Accepted: 20 July 2012
Published online: 2 September 2012

doi:10.1111/j.1432-2277.2012.01550.x

Summary

Living donor liver transplantation (LDLT) is a well-established strategy to decrease the mortality in the waiting list and recent studies have demonstrated its value even in patients with low MELD score. However, LDLT is still under a high level of scrutiny because of its technical complexity and ethical challenges as demonstrated by a decline in the number of procedures performed in the last decade in Western Countries. Many aspects make LDLT different from deceased donor liver transplantation, including timing of transplantation, procedure-related complications as well as immunological factors that may affect graft outcomes. Our review suggests that in selected cases, LDLT offers significant advantages over deceased donor liver transplantation and should be used more liberally.

Introduction

In the last decade, the discrepancy between organ supply and demand has reached its highest level, resulting in increased waiting times and higher death rates [1,2]. The transplant community has responded to this organ shortage by adopting several strategies, including the use of extended criteria donors and the use of partial grafts. Of the available strategies, living donor liver transplantation (LDLT) has the highest potential for expansion. Unlike living donor kidney transplantation, however, where the advantages of living donor over deceased donor grafts have been demonstrated at a relatively low risk for the donor, LDLT is still under a high level of scrutiny [3,4].

The aim of this manuscript was to review these differences and provide the reader with an up-to-date comparison between living and deceased donor liver transplantation in the modern era.

Materials and methods

A National Library of Medicine (Pubmed) search of the English language literature was performed using the following queries ''living donor liver transplantation'' and ''deceased donor liver transplantation'' or ''cadaveric liver transplantation'' or ''Orthotopic Liver Transplantation (OLT).'' Additional search words were later used for specific topics (e.g., ''intention-to-treat analysis'', ''timing'', ''Hepatitis C'', ''Hepatocellular Carcinoma'', ''rejection'' etc.). Manuscripts were included if directly addressed the subject of this review and offered differing points of view or additional explanations.

The review was structured to address the most important factors and differences involved in both living and cadaveric donation; (i) implications of ''early'' or ''timely'' transplantation, (ii) procedure-related morbidities and mortalities, (iii) the impact of the type of graft on disease processes.

Living over deceased donor: the importance of a timely transplant

More than 10 years after the introduction of LDLT in the clinical arena, there is still uncertainty regarding what population of adult candidates benefits the most from LDLT. The allocation of living donors to recipients with a MELD <15 is of particular importance in the US, where this score often determines whether or not the patient will receive a cadaveric organ in a timely fashion.

One of the first UNOS LDLT case-control outcome studies [5] showed that LDLT patients have similar survival rates in comparison with a matched population that received deceased donor liver transplantation (DDLT). One-year graft survival, however, was significantly lower (~15%) in the LDLT group, indicating that a significant number of patients underwent salvage retransplantation. An early report from the A2ALL study group [6], an NIH-funded consortium of nine transplant programs in the United States, first introduced the concept of intention-to-treat analysis as a tool to assess the potential benefit of a timely transplant. The consortium, with this study, challenged the well-accepted concept of no-net survival benefit of liver transplantation for MELD scores below 15 [7]. Of the transplant candidates with a MELD score <15 at the time of presentation ($n = 453$), 224 (49%) received LDLT, whereas 123 (27%) received DDLT and 106 (24%) did not receive a transplant. Interestingly, in the latter group, 49 (46%) died on the waitlist without receiving a transplant of any type. Overall, LDLT recipients had 56% lower mortality (HR = 0.44, 95% confidence interval 0.32–0.60; $P < 0.0001$). Similar results were confirmed for MELD scores of 6–10, 11–14, 15–19, and 20+ with a nearly constant survival advantage for LDLT across categories [8]. One potential limitation of this study is the introduction of selection bias, whereby candidates with low MELD scores in which LDLT was entertained could represent a group of individuals with a perceived increased risk of mortality beyond that associated solely with their MELD score. The authors concluded that, whereas the study continued to demonstrate the survival benefit of LDLT, a randomized controlled study is needed to confirm this data on a much larger scale.

Living over deceased donor: procedure-related complications

Recipient outcomes

Few reports systematically compare risk and severity of complication between living donor and DDLT [9,10]. In one report from the A2ALL study group [9], complications of 384 LDLT were compared with 216 DDLT over a period of 6 years. Complications that occurred at a higher rate ($P < 0.05$) after LDLT were mostly surgical and included: biliary leak (31.8% vs. 10.2%); unplanned re-exploration (26.2% vs. 17.1%); hepatic artery thrombosis (6.5% vs. 2.3%); and portal vein thrombosis (2.9% vs. 0.0%). There were more complications leading to retransplantation or death (Clavien grade 4) following LDLT relative to DDLT (15.9% vs. 9.3%, $P = 0.023$). In LDLT, cold ischemia time was found to be associated with a high risk of graft failure, although cold ischemia time was considerably lower than DDLT. Many complications occurred more commonly during early center experience; the odds of grade 4 complications were more than twofold higher when centers had performed <or = 20 LDLT (vs. >40). Interestingly, low graft to recipient body weight ratio (GRBWR) was not a significant predictor of bile leak, biliary stricture, or grade 4 complications. As expected, in the same study, LDLT recipients had significantly lower adjusted pretransplant hospital day and admission rates, but significantly higher post-transplant admission rates despite lower acuity of disease. It is likely that recent technical refinement (inflow modulation), better donor/recipient match selection, and improved preoperative imaging planning will continue to decrease complication rates in living donor recipients.

Donor outcomes

Although thousands of patients around the world have benefitted from LDLT, living liver donation is accompanied by a discrete, quantifiable morbidity, and mortality. The complication rate varies depending on the extent of the hepatectomy. Ringe and Strong [11] in 2008 reported one of the most comprehensive, verified, and updated review on living donor liver mortality. In their study, the authors concluded that the worldwide donor mortality rate can be estimated at 0.1–0.3%, possibly reaching 0.5% when using the right hemiliver. Interestingly, in only 36% of the cases, the information available in the literature was considered truly reliable, highlighting the need for a more structured reporting system, and transparency in the field. In a more recent analysis on right lobe liver donation, Abecassis *et al.* [12] reported a 39% overall morbidity. Regarding the severity of these complications, 2.8% of patients had Clavien grade 3 or 4 complications with the rest of the patients experiencing only minor complications (grade 1 and 2). Further analysis revealed that nearly 80% of these complications resolved by 3 months after presentation. Data on mortality are more difficult to assess, as deaths tend to be under reported in countries lacking a centralized data collection system. In a recent study on 4111 adults in the United States that had donated a portion of their liver over a period of 17 years (1994–2011), the risk of death was 1.7 per 1000 donors and the risk of catastrophic outcomes (including acute liver failure requiring transplantation) was 2.9 per 1000

donors. These rates vary slightly in different regions of the world (0.3 in Japan vs. 2.3 deaths per 1000 donors in Europe) [13,14].

Living over deceased donor: the impact of the type of graft on the disease process

Living donor liver transplantation is most commonly performed between individuals immunologically related. Such factor, theoretically, could interact with the underlying recipient's disease and affect the outcome of the transplanted graft. Moreover, the high regeneration rate that characterizes partial grafts in the early postoperative period could play an important role in patients' HCV and hepatocellular carcinoma (HCC) recurrence.

Hepatitis C virus

Hepatitis C virus (HCV)-related cirrhosis is the leading indication for liver transplantation in the USA and Western Europe [15]. Early outcome studies of HCV-infected LDLT recipients reported a poorer outcome than DDLT HCV+ recipients, raising concerns about the use of LDLT in this patient population [5,15–21]. Several hypotheses have been proposed to explain this early data. The rapid liver regeneration occurring in the early post-transplant period in recipients of living donor grafts may alter early virologic or immunologic events and thereby increase the risk of progressive liver disease [20,22–24]. In addition, live donor recipients are more likely than deceased donor recipients to share human leukocyte antigens and, although the relationship between human leukocyte antigens matching and risk of recurrent HCV is controversial, it represents another difference between LDLT recipients and DDLT recipients that may affect HCV disease recurrence [19,25]. At the present time, these proposed mechanisms for a different natural history of HCV infection in LDLT recipients remain speculative.

One of the first reports from University of Barcelona described 94 DDLT and 22 LDLT HCV-positive patients undergoing liver transplantation in which protocol liver biopsies were used to evaluate disease progression after transplantation. The authors reported that, at 2 years, LDLT recipients were at increased risk of developing severe recurrence, defined as biopsy-proven cirrhosis and/or occurrence of clinical decompensation (45% vs. 22%, $P = 0.019$). This outcome was observed in 45% of LDLT recipients compared with 22% of DDLT recipients at 2 years after transplantation ($P = 0.019$) [21]. In a retrospective analysis of HCV-infected patients in the A2ALL study who were transplanted between 1998 and 2003, cumulative unadjusted graft survival was found to be significantly inferior in LDLT ($P = 0.040$; log-rank test). Importantly, however, a closer analysis of the results showed that center experience with LDLT affected the results. When the first 20 LDLT recipients performed at each transplant center were excluded from the analysis, there was no difference in graft survival between the LDLT and DDLT groups ($P = 0.66$; log-rank test). This study is important because it suggested that ongoing complications resulting from early events can ultimately affect graft longevity.

As the original report from the University of Barcelona, several additional studies using protocol biopsies to assess disease severity, and two studies not using protocol biopsies, have been published. These studies found no difference between LDLT and DDLT in how quickly the HCV infection reoccurred, or in the severity of that recurrence, including the frequency of cholestatic hepatitis and rate of fibrosis progression. [26–33]. One recent retrospective study from the University of Toronto, using protocol biopsies, compared 46 LDLT and 155 DDLT recipients and found slower fibrosis progression in LDLT recipients than in DDLT recipients (DDLT 0.19 fibrosis stage/year vs. LDLT 0.11 fibrosis stage/year; $P < 0.05$) [33]. This study was the first one to describe a possibly beneficial impact of LDLT on HCV recurrence and the authors suggested this was likely attributable to younger donor age of LDLT recipients.

One potential advantage of LDLT is that allows the transplant team to choose the proper timing, a factor that can allow an attempt at pretransplant viral eradication. Liver transplant in a recipient negative for serum HCV RNA on therapy has a low chance of post-transplant recurrence (~10%) and could represent a cure for HCV infection [34]. Furthermore, LDLT has the ability to occur at lower MELD scores, when the chance of tolerating antiviral therapy is higher. The two studies confirming the importance of pretransplant HCV therapy as a mean to reduce post-transplant recurrent disease were from University of Colorado and Barcellona and were published in 2004 and 2005. Everson and his colleagues [35], reported results for 124 patients with decompensated HCV-related cirrhosis treated with interferon and ribavirin (RBV). The on-treatment virologic response rate was 46%, and the sustained virological response rate (SVR) was 24% (no detection of HCV RNA 6 months after completion of therapy). Recurrent HCV infection was prevented in all patients achieving SVR. Forns *et al.* [36] treated 30 patients for a median of 3 months; nine patients (30%) achieved an undetectable HCV RNA on treatment prior to transplantation, and HCV recurrence was prevented in two-thirds of these patients (six of nine). Several studies suggest the use of antiviral therapy in wait-listed patients with low MELD because of the high risk for decompensation during treatment and to the high treatment dropout rate in patients with advanced disease. A large multicenter study of pretransplant

treatment of patients with living donors and those with HCC is currently underway (A2ALL LADR study).

Hepatocellular carcinoma

Hepatocellular carcinoma is the third leading cause of cancer-related death worldwide [37]. Complete resection of the tumor is considered the mainstay of treatment. However, curative surgery is often precluded in many patients because of the presence of cirrhosis and multifocal disease. In this setting, liver transplantation represents the only chance of cure for both the cirrhosis and the tumor [38].

For strictly selective criteria, such as the Milan and UCSF criteria, the 5-year survival rate for patients who undergo transplantation for HCC is comparable to recipients transplanted for benign diseases [39,40]. The use of adult-to-adult LDLT has the theoretical advantage of shortening waiting time, therefore decreasing the dropout rate as well as the mortality on the waiting list [41,42].

On the other hand, potential risks associated with LDLT in the setting of HCC include: donor safety; ''fast-tracking'' to transplantation, in which, paradoxically, faster access to transplant may provide a higher risk of post-transplantation tumor recurrence [43, 44]; the risk of a less optimal cancer surgery owing to technical constraints; and the rapid regeneration that occurs in the immediate post-LDLT period, which could provide an ideal milieu for cancer progression [45,46].

In a very well-designed study by Azoulay *et al.* [47], an intention-to-treat analysis was conducted with recurrence rate representing the primary endpoint. The authors were able to show that LDLT and DDLT for patients who have liver cirrhosis with HCC have similar recurrence rates and survival outcomes. The dropout rate and waiting periods in the LDLT group were significantly lower compared with the DDLT group. There was also a trend toward longer time to recurrence in the LDLT group. Transplantation outside UCSF criteria, poorly differentiated tumors, and vascular invasion, emerged as independent predictive factors for recurrence in their study.

Various studies have reported conflicting results regarding the ideal selection criteria for LDLT in patients with HCC. There is no doubt that the Milan criteria adopted by UNOS as the standard criteria for selection of patients with HCC for DDLT is safe and applicable to LDLT as well [48,49].

In a study by the Mount Sinai group [38] one-third of patients receiving a living donor graft were beyond the Milan criteria, however, the incidence rates of recurrence, overall survival (OS), and disease-free survival (DFS) were similar to results after DDLT performed during the same period at their center. The Japanese Study Group on Organ Transplantation [50] showed that when the Milan criteria were exceeded, a 3-year OS and DFS, of 60% and 52.6%, respectively, was achieved in LDLT patients. Lo *et al.* [51] reported that transplanting patients beyond UCSF criteria was an independent positive predictive factor for recurrence.

Grant and colleagues [52] performed a literature search focused on comparisons of outcomes of LDLT and DDLT for HCC. The authors found that there is no high-quality data justifying or refuting the use of different criteria and based on the data available.

Most of the studies challenging the Milan Criteria come from Asian countries, where LDLT virtually represents the only hope for patients with unresectable HCC. Several major Universities in Japan (Tokyo, Kyoto and Kyushu) published their results [53–55] on patients who received a LDLT under extended selection criteria with acceptable outcomes. Particularly, the addition of preoperative tumor markers (able to correlate with microvascular invasion), such as the des-gamma-carboxy prothrombin (DCP) level along with tumor size and number, seems to be a promising step in the prediction of post- transplant tumor recurrence. In a recent study [53], the Kyushu criteria (DCP level <300 mAU/ml, tumor size <5 cm, any number) proved to be a very powerful predictive tool (outside the Milan criteria) for HCC recurrence in LDLT.

Currently, there is no consensus about an acceptable HCC recurrence risk or an acceptable donor risk. The number of patients meeting the proposed expanded criteria is generally small and most of the studies are retrospective in nature. Further trials will have to validate independently these findings. In the mean time, particularly in Western countries, a proposed benchmark of 50% 5-year survival [56] should be considered when transplanting patients with expanded criteria, to avoid significant harm to other transplant candidates without HCC [57] or challenging solid ethical principles [58].

Outcomes of LDLT for acute liver failure

There are more than 2000 cases per year of acute liver failure (ALF) in the United States [59,60]. As the rapid evolution of ALF and the shortage of deceased donor livers, many patients with ALF die waiting for a DDLT. LDLT has the potential to reduce waiting time and provide more optimal timing of surgery compared with DDLT. However, there may be disadvantages to LDLT in ALF patients. First and foremost, the limitation of a donor work up under time constraints and psychological pressure may decrease donor safety, violating the most important principle of living donation. Secondly, many transplant centers do not perform LDLT in critically ill-patients because of the high postoperative mortality rate in this setting [61] and some states [62] even consider ALF as a contraindication for LDLT [63].

The A2ALL consortium reported their experience on 13 patients transplanted for ALF [64]. The survival rates were 70% (seven of 10 patients) and 67% (two of three patients) after LDLT and DDLT, respectively. Causes of death included two cases of graft failure and two cases of fungal infection. Of the 10 who donated, five (50%) donors experienced a total of seven complications, a slightly higher rate compared with the rest of the A2ALL donor cohort of 37.7%.

Miwa S *et al.* [65] reported outcomes in 15 adult ALF patients who received either a left lobe (eight patients) or right lobe (seven patients) LDLT, including three auxiliary partial orthotopic liver transplants. Other reports from Asia [66,67] showed similar outcomes highlighting the importance of a critical liver mass necessary to overcome the high metabolic demand of this very sick group of patients. These findings suggest that LDLT is a safe treatment option in selected patients with ALF, particularly in light of the comparable risks to the donor.

Cholestatic liver diseases

Although the literature for deceased donor liver transplantation for primary sclerosing cholangitis (PSC) is abundant, [68–72] only a few reports describe LDLT in the setting of PSC-associated end-stage liver disease [73].

Altered immune regulation is considered to have a role in both PSC and primary biliary cirrhosis (PBC), although the specific immunologic mechanisms remain completely unclear [74,75]. Theoretically, the postoperative course in the LDLT group may be affected by the possible shared genetic background between the recipient and the donor, impacting long-term outcomes.

Primary biliary cirrhosis

PBC is reported to recur after LDLT. Hashimoto and colleagues presented the first series of recurrent PBC after LDLT [76]. In this small study, the high rate of recurrence (33% in 2 years) was in sharp contrast with that of DDLT.

Two single-center studies, both with 50 patients, were recently presented [77,78]. Hasegawa and colleagues [77] presented 3- and 5-year overall survival rates of 88% and 80%, respectively, with a median follow-up period of 35 months. Morioka and colleagues [78] presented 5-year overall survival rates of 67%. The recurrence of PBC was confirmed in 18% of patients within a median of 36 months after LDLT (range 12–123 months). The results of the study suggested that a lower number of HLA mismatches between donor and recipient, and a younger donor age, resulted in better survival, although, data more recently presented indicated that a simple comparison of HLA matching has little or no impact on survival [79]. The most recent registry study from Japan, in which 221 PBC patients were analyzed, reports a 5-year survival rate of 79% [73]. However, because of the limited data on histology, it is difficult to draw a universally acceptable conclusion on the overall long-term outcome of LDLT for PBC.

Primary sclerosing cholangitis

Recurrence of PSC after DDLT has been reported at rates between 1% and 33%, depending on the diagnostic criteria and follow-up [80]. The University of Kyoto reported 28 patients with PSC who underwent LDLT. Among the 22 patients who survived for more than a year, 13 (59%) presented with PSC recurrence with a mean follow-up period of 31 months, five of whom died or required retransplantation for graft failure. The authors concluded that unlike PBC, the recurrence of PSC adversely affects the outcome in LDLT [81]. A U.S. study on 58 patients undergoing liver transplantation for PSC showed equivalent survival outcomes between LDLT and DDLT for PSC with a trend toward higher recurrence rates in patients undergoing LDLT [82].

Rejection

Living donor liver transplantation carries several theoretical immunological advantages. An excellent liver lobe is taken from a stable donor and in most cases is transplanted with a very short cold ischemia into a recipient who may be genetically related. On the other hand, molecular pathways associated with regeneration may regulate proinflammation and consequently play a role in the development of the alloimmune response [83,84].

Studies comparing rejection rates between LDLT and DDLT are scarce and of limited quality. Early reports indicated a lower rate of rejection in a small number of LDLT recipients after a relatively short-term follow-up [85,86].

Data from the adult-to-adult LDLT (A2ALL) retrospective cohort study on 593 liver transplants showed similar proportions of biopsy-proven rejection ($P = 0.97$) and graft loss caused by rejection ($P = 0.16$). Longer cold ischemia time was associated with a higher rate of acute cellular rejection (ACR) in both groups despite much shorter median cold ischemia time in LDLT. The similar rate of biopsy-proven rejection in this cohort of patients suggests that the impact of the type of allograft on the frequency of ACR is relatively minimal and that the living donor liver is far more susceptible to prolonged cold ischemia than the deceased donor allograft. Table 1 summarizes advantages and disadvantages of LDLT over DDLT.

Table 1. Living donor over deceased donor transplantation; advantages and disadvantages.

	LDLT	DDLT
Transplant timing	Based on the A2ALL intention-to-treat analysis, a transplant at MELD <15 may still be beneficial [6]	MELD allocation rules make unlikely a transplant at low MELD scores
Recipient outcome	Higher post-transplant complication rate [9]	Preferred in severely decompensated patients
Donor outcome	~40% overall complication rate 2–3% Clavien Grade 3 and 4 Mortality 1–3/1000 donors [13,14]	N/A
HCV	Antiviral treatment of patients with low MELD score is more likely to achieve SVR. These patients could then have access to LDLT even if MELD is low. [35,36]	Antiviral treatment of patients with high MELD score is characterized by high decompensation and/or high dropout rate. Transplant timing cannot be predicted [35,36]
HCC	Post-transplant survival and recurrence rates are comparable between LDLT and DDLT [48,49]. Potential disadvantages of LDLT are represented by: • Fast-tracking • Rapid cell regeneration • Technical constrains Potential advantages of LDLT are represented by: • Shorter waiting time • Ability to expand indications beyond Milan criteria	Potential advantages of DDLT are represented by: • Selection of patients with more favorable tumor biology (waiting time) • Surgical manipulation and hilar dissection can be minimized Potential advantages of LDLT are represented by: • Limited ability expand indications beyond Milan criteria attributable to allocation algorithms
Acute liver failure	LDLT is a safe alternative to DDLT in patients with ALF Donor risks are not increased compared with elective LDL donation [64–67].	Higher hepatocyte mass may be preferable in large adults with liver failure induced multiorgan failure
Cholestatic liver diseases	No advantage/disadvantage [80–82]	No advantage/disadvantage [80–82]
Rejection	Scarce and low quality data available. Ischemia time may have a worse impact on rejection rate in LDLT than DDLT [86].	Ischemia time has negligible impact in DDLT rejection rates

ALF, acute liver failure; DDLT, deceased donor liver transplantation; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; N/A, not available; SVR, sustained virological response rate.

Conclusions

Our review shows that the decline in LDLT in the United States and Europe in the last decade is not based nor justified by the existing literature. Moreover, in selected cases, LDLT offers significant advantages over deceased donor liver transplantation and should be used more liberally. Although donor morbidity and mortality remains a significant challenge in LDLT, the field has witnessed tremendous surgical, medical, and ethical advancements setting the stage for a much needed reversal of this trend and renewed growth of the field.

Authorship

CQ and CM: designed the study. KH: contributed to the data collection and literature review. CQ and CM: wrote the manuscript. TDU: participated in the revision of the manuscript.

Funding

No funds to disclose for all authors.

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