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ORIGINAL ARTICLE

Is left lobe adult-to-adult living donor liver transplantation ready for widespread use? The US experience (1998–2010)

Reza F. Saidi, Nicolas Jabbour, YouFu Li, Shimul A. Shah & Adel Bozorgzadeh

Division of Organ Transplantation, Department of Surgery, University of Massachusetts Medical School, Worcester, MA, USA

Abstract

Objectives: Living donor liver transplantation (LDLT) is an accepted treatment for patients with end-stage liver disease. To minimize risk to the donor, left lobe (LL) LDLT may be an ideal option in adult LDLT.

Methods: This study assessed the outcomes of LL-LDLT compared with right lobe (RL) LDLT in adults (1998–2010) as reported to the United Network for Organ Sharing (UNOS) Organ Procurement and Transplantation Network (OPTN).

Results: A total of 2844 recipients of LDLT were identified. Of these, 2690 (94.6%) underwent RL-LDLT and 154 (5.4%) underwent LL-LDLT. A recent increase in the number of LL-LDLTs was noted: average numbers of LL-LDLTs per year were 5.2 during 1998–2003 and 19.4 during 2004–2010. Compared with RL-LDLT recipients, LL-LDLT recipients were younger (mean age: 50.5 years vs. 47.0 years), had a lower body mass index (BMI) (mean BMI: 24.5 kg/m^2 vs. 26.8 kg/m^2), and were more likely to be female (64.6% vs. 41.9%). Donors in LL-LDLT had a higher BMI (mean BMI: 29.4 kg/m^2 vs. 26.5 kg/m^2) and were less likely to be female (30.9% vs. 48.1%). Recipients of LL-LDLT had a longer mean length of stay (24.9 days vs. 18.2 days) and higher retransplantation rates (20.3% vs. 10.9%). Allograft survival in LL-LDLT was significantly lower than in RL-LDLT and there was a trend towards inferior patient survival. In Cox regression analysis, LL-LDLT was found to be associated with an increased risk for allograft failure [hazard ratio (HR): 2.39)] and inferior patient survival (HR: 1.86).

Conclusions: The number of LL-LDLTs has increased in recent years.

Correspondence

Reza F. Saidi, Division of Organ Transplantation, Department of Surgery, University of Massachusetts Medical School, 55 Lake Avenue North, S6-426, Worcester, MA 01655, USA. Tel: + 1 508 334 2023. Fax: + 1 508 856 1102. E-mail: reza.saidi@umassmemorial.org

Introduction

Living donor liver transplantation (LDLT) is currently an accepted and standard procedure for the treatment of patients with end-stage liver disease.[1–3] The percentage of all liver transplantations performed in the USA that use tissue from living donors is < 10%, whereas > 40% of kidney transplantations use a kidney sourced from a living donor. The slow rate of growth in LDLT is mainly related to the associated risks for donors.[2] Living donor liver transplantation carries a higher risk for the donor than live kidney donation.[3] The risks specific to liver donation are at least partially related to residual liver volume. Over the last several years, the transplant community has focused mainly on minimizing risk for the donor and several studies have specifically focused on methods of reducing the amount of liver removed from the donor as a simple and easy way to decrease morbidity and mortality risks for the donor.[4–7] Because the left lobe represents a markedly small percentage of the liver, it is assumed that removing the left lobe from the donor implies a considerably lower risk for liver failure or any other major complication in the donor. However, few reports have analysed data on the impact of left lobe transplantation for the recipient, patient survival and need for

Table 1 Donor and recipient characteristics in right lobe (RL) and left lobe (LL) living donor liver transplantations (LDLTs) carried out in the USA during 1998–2010

Variable	RL-LDLT (n = 2690)	LL-LDLT (n = 154)	P-value
Donor age, years, mean ± SD	38.8 ± 10.2	37.1 ± 10.1	NS
Donor weight, kg, mean ± SD	77.4 ± 16.9	80.1 ± 16.3	0.02
Donor BMI, mean ± SD	26.5 ± 8.6	29.4 ± 18.7	< 0.001
Donor gender, female, %	48.1%	30.9%	0.0008
Recipient age, years, mean ± SD	50.5 ± 7.1	47.0 ± 6.9	< 0.001
MELD score, mean ± SD	14.6 ± 5.9	14.7 ± 5.9	NS
LoS, days, mean ± SD	18.2 ± 21.9	24.9 ± 26.1	< 0.001
Wait time, days, median	315.6 ± 27.2	363.5 ± 27.5	NS
Recipient weight, kg, mean ± SD	78.5 ± 17.1	68.3 ± 17.6	< 0.001
Recipient BMI, mean ± SD	26.8 ± 5.0	24.5 ± 4.4	< 0.001
Rejection at 1 year, %	17.1%	15.9%	NS
Recipient gender, female, %	41.9%	64.6%	< 0.001
Retransplantation, n (%)	255 (10.9%)	23 (20.3%)	0.0006

SD, standard deviation; BMI, body mass index in kg/m^2; MELD, Model for End-stage Liver Disease; LoS, length of hospital stay; NS, not significant.

liver retransplantation.[8–10] The aim of this paper was to analyse the impact of allograft selection [left lobe (LL) vs. right lobe (RL)] on outcomes in recipients after LDLT.

Materials and methods

Data were collected from the United Network for Organ Sharing (UNOS) and refer to transplantations reported between 1998 and 2010. The following information on recipients in both the LL- and RL-LDLT groups was collected: patient age; sex; Model for End-stage Liver Disease (MELD) score; hospital length of stay; waiting time prior to transplantation; body mass index (BMI); rejection at 1 year, and retransplantation rate. The following information on donors was collected: age; weight; BMI, and sex. Missing values were imputed with the mean values. The definition of small-for-size syndrome was at the discretion of the centre.

Chi-squared and Student's t-tests were used to compare proportions and means, respectively. Graft and patient survival were the primary outcomes measured. Kaplan–Meier analysis was used for allograft and patient survival estimates. Continuous variables were categorized using exploratory data analysis, and assumptions of proportional hazards were met by extended Cox regression models with time-dependent covariates. Variables for which > 20% of values were missing were excluded from analysis. Initially, the following factors were included for unadjusted analysis: recipient age; recipient sex; donor age; donor sex; diagnosis; MELD score; length of stay; race, and acute rejection. An unadjusted comparison of survival was performed using the log-rank test. Hazard ratios (HRs) were estimated using Cox proportional hazards methodology and estimates are reported as HR [95% confidence interval (CI)]. Multivariate Cox modelling was performed using potential risk factors and covariates found to be

statistically significant in unadjusted Cox models. Statistical significance was indicated by a P-value of < 0.05.

This study was reviewed by the University of Massachusetts Medical School Institutional Review Board (IRB) and deemed appropriate for exemption from IRB oversight as no personal identifiers were used among datasets.

Results

A total of 2844 patients underwent LDLT during the study period (1998–2010); 2690 (94.6%) patients underwent RL-LDLT, and 154 (5.4%) underwent LL-LDLT. The demographic and clinical characteristics of donors and recipients are shown in Table 1. Preoperative MELD scores, wait times and rates of acute rejection at 1 year were similar in both groups. Donor age was similar in both groups, but donor weight and BMI were slightly higher in the LL-LDLT group, which also included a higher percentage of male donors. Compared with RL-LDLT patients, recipients of LL-LDLT were younger (mean age: 50.5 years vs. 47.0 years), had a lower BMI (mean BMI: 24.5 kg/m^2 vs. 26.8 kg/m^2), and were more likely to be female (64.6% vs. 41.9%). Recipients of LL-LDLT had a significantly longer mean length of stay (24.9 days vs. 18.2 days) and a higher retransplantation rate (20.3% vs. 10.9%).

Allograft survival in both groups is shown in Fig. 1. Allograft survival after RL-LDLT was better than that after LL-LDLT. In Cox regression LL-LDLT was associated with an increased risk for allograft failure (HR: 2.39) and patient death (HR: 1.86) (Table 2).

Surprisingly, there was an increase in the number of LL-LDLT surgeries performed: the average number of LL-LDLTs performed per year was 5.2 in 1998–2003 and 19.4 in 2004–2010 (P < 0.01) (Fig. 2). Left lobe LDLT represented 2.3% of all LDLTs during 1998–2003 and 7.2% of all LDLTs in 2004–2010 (P = 0.01). The US
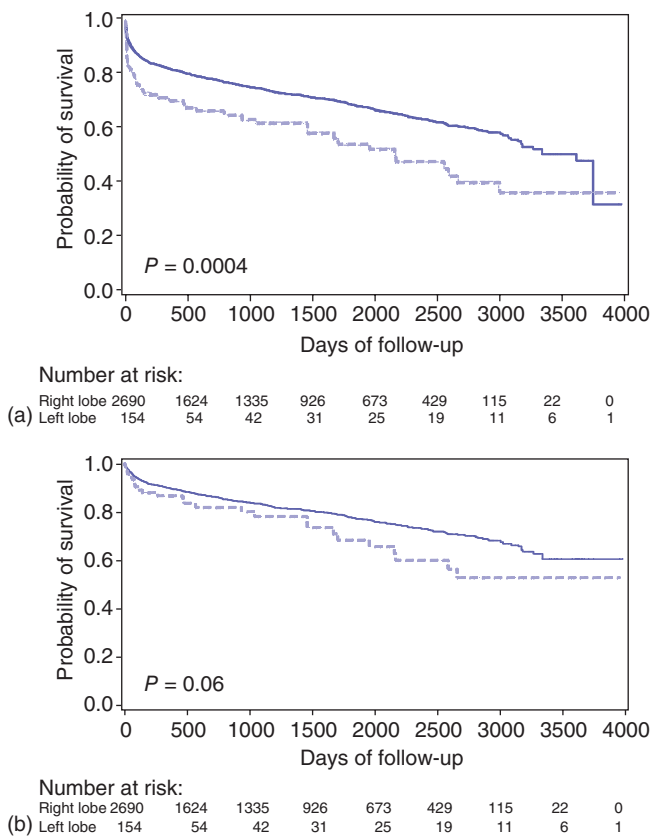
Figure 1 Kaplan–Meier analysis comparing (a) allograft and (b) patient survival in left lobe (dashed line) and right lobe (continuous line) living donor liver transplantation

Table 2 Cox proportional hazard model predicting allograft and patient survival

Variables	HR (95% CI)	*P*-value
Allograft survival		
Recipient age	1.01 (1.01–1.03)	0.0028
Recipient sex (female)	1.24 (1.01–1.54)	0.0380
LL-LDLT	2.39 (1.57–3.65)	< 0.001
MELD score	1.10 (0.89–1.23)	0.1
Recipient BMI	1.01 (0.99–1.04)	0.07
Donor age	1.02 (1.01–1.03)	< 0.001
Donor sex (female)	0.88 (0.71–1.07)	0.2
Patient survival		
Recipient age	1.01 (1.01–1.04)	< 0.001
Recipient sex (female)	1.23 (1.03–1.46)	0.01
LL-LDLT	1.86 (1.33–2.61)	< 0.001
MELD score	1.12 (0.98–1.45)	0.25
Recipient BMI	1.08 (0.95–1.10)	0.09
Donor age	1.00 (0.99–1.05)	0.06
Donor sex (female)	0.78 (0.68–1.11)	0.3

HR, hazard ratio; 95% CI, 95% confidence interval; LL-LDLT, left lobe living donor liver transplantation; MELD, Model for End-stage Liver Disease; BMI, body mass index.

experience in LL-LDLT was arbitrarily divided into two periods to allow outcomes in the more recent period to be assessed. Interestingly, there did not appear to be any improvement in the results of LL-LDLT performed in 2007–2010 (*n* = 80) compared with LL-LDLT performed in 1998–2006 (*n* = 74).

Discussion

Living donor liver transplantation was developed in response to a severe shortage of deceased donors in the face of a growing list of patients awaiting liver transplantation. The success of these procedures has led to the adoption of this technique around the world, mainly in Asian countries, in response to the lack of availability of organs from deceased donors. However, LDLT remains one of the most complicated surgical procedures and is associated with relatively high rates of morbidity for both donor and recipient.[1–3] As a result, growth in the field remains slow compared with that in living donor kidney transplantation. Currently, < 5% of all liver transplantations involve living donors. This rate has decreased over the last 10 years. In 2009, only 215 (3.7%) of 5795 liver transplants in adults were sourced from live donors.[3]

Living donor liver transplantation involves several issues that are currently unsettled and the procedure itself is still evolving; the complete resolution and standardization of these aspects would probably lead to a noticeable increase in the number of LDLTs performed. These issues refer to either donor- or recipient-associated factors. Donor safety is the most compelling factor, but, despite all measures implemented, to date over 20 live liver donors have reportedly died and one is currently in a vegetative state.[2,4] The outcome of the choice between the left and right lobes of the liver may have an impact on liver-specific complication rates in the donor[5–15] because LL transplantation means that less liver mass is removed, but it may not affect the rate of non-liver-related complications. Umeshita *et al.* reported on the incidence of donor complications based on 1853 donors recorded in the Japanese Registry of LDLT.[16] The incidence of complications was significantly higher in RL donors than in donors of LL and lateral segment grafts.[16] Lo[17] also reported the incidence of donor complications based on a survey of 1508 transplantations performed at five Asian centres. Again, complication rates were higher in RL donors (28.0%) than in left lateral segment (9.3%) or LL (7.5%) donors. Moreover, RL donors experienced more serious complications, such as cholestasis, bile leakage or stricture, portal vein thrombosis, intra-abdominal bleeding and pulmonary embolism.

However, the difference between right and left lobe donation in terms of recipient outcome has not been completely resolved. Balancing donor safety with achieving a satisfying outcome for the recipient is a key issue in the process of living donation. At the start of adult LDLT, LL-LDLT was the only option available
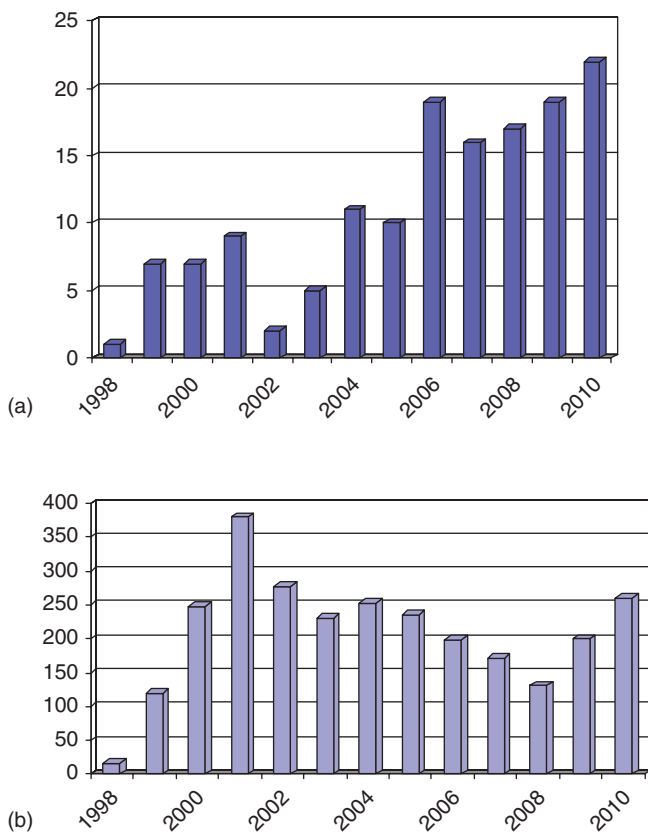
Figure 2 Numbers of (a) left lobe and (b) right lobe living donor liver transplantations carried out in the USA (registered in the United Network for Organ Sharing database) during 1998–2010

venous outflow and high portal inflow in LDLT and have led to great improvements in graft function.[25–34] These techniques include left portal and left hepatic vein shunts, hemiportocaval shunt, splenic artery ligation or embolization, and venous outflow modulation.[25–34] These techniques are used to modulate portal inflow to limit the negative effect of high flow in smaller grafts. The theoretical advantage of these techniques on overall outcomes in recipients of smaller grafts has not been widely studied and may impact the choice between the left and right lobes. Botha *et al.* showed that LL-LDLT using even smaller grafts (GRWR < 0.8) can be performed safely with good outcomes by constructing a hemi-portocaval shunt to prevent the development of small-for-size syndrome while ensuring adequate liver volume.[32]

The most serious ethical concerns in LDLT focus on risk to the donor and relate to the principle of 'do no harm'. However, restricting the focus to minimizing donor risk is not sufficient to justify LL-LDLT ethically. Instead, Siegler *et al.* proposed a system called 'double equipoise' in which the ethical acceptability of the LDLT procedure would be determined by balancing donor risks and benefits with recipient risks and benefits.[35–37] Double equipoise should place clear limits on the morbidity and mortality risks donors are allowed to assume and would stipulate that low recipient benefit should discourage surgeons from allowing donors to accept any risk associated with donation. Although left hemiliver donation is clearly a safer operation for the donor,[16,17] the present results suggest that LL-LDLT is not ready for wider use based on recipient outcomes reported to UNOS. The recent increase in the utilization of LL-LDLT did not show any improvements in recipient outcomes over time. Left lobe LDLT is undergoing rapid evolution and is not yet ready for widespread use. Although the transplant community is focused on improving safety levels for live liver donors, overall outcomes in the recipient should not be ignored, especially as the most recent data available do not clearly define the true impact of the choice between the right and left lobes on donor morbidity and mortality.

This study has several limitations. Firstly, it is a retrospective analysis of UNOS data. There are both potential advantages and limitations to any study that uses a large national database. However, the large sample size provides sufficient power to detect meaningful risk factors that may be missed by single-centre studies. As with any analysis of data sourced from the UNOS database, the present conclusions rely on the assumption that no systematic bias has been generated by reporting error or missing data. The groups are extremely unequal in size and the selection criteria for one or the other procedure are not known. However, the primary endpoints in this analysis were allograft and patient survival, which are reliably captured in the UNOS database. Residual or unmeasured confounders that might impact on allograft and patient survival include: surgeon technique; differences in immunosuppression protocols; the fat content and quality of the allograft, and centre-specific practices. Data on other important determinants of success in LDLT, such as recipient and donor selection, choice of RL vs. LL graft, graft weight and

because of the potential risk for the donor in RL-LDLT.[8–10] However, the use of LL grafts in adults was severely limited by the size limits of the LL. An initial report of 13 LL-LDLTs between adults revealed satisfactory results in both donors and recipients, with 11 of 13 patients surviving.[18] Tanaka and Ogura reported an early series of 39 LL-LDLTs in which survival was 82.1% in patients with a graft : recipient weight ratio (GRWR) of ≥ 0.8 (*n* = 28), but only 54.5% in those with a GRWR of < 0.8 (*n* = 11).[19] Based on these unsatisfactory results, this team adopted the RL graft in order to overcome size-related problems.[19] Several reports from single centres in the USA,[7,20,21] Hong Kong,[22] Europe[23] and Japan[24] have shown superior outcomes of RL-LDLT in the recipient.

The present study found that donors in LL-LDLT were heavier and recipients were lighter compared with RL-LDLT donors and recipients, respectively. Although data on allograft weight were not available in the database, it seems that the various transplant programmes were very cautious about the size issue. The inferior outcomes of LL-LDLT compared with RL-LDLT identified in this study cannot be explained by graft size alone. Inflow and outflow are also important to achieving successful outcomes in LDLT. Several technical innovations have been implemented to deal with

quality, GRWR, surgical details, techniques employed to alleviate small-for-size syndrome, and centre and surgeon volume and experience, were not available in the database.

Secondly, few data on the donor and the quality or size of the allograft were available. Thirdly, the study did not look at the potential impact of portal inflow and hepatic vein outflow modulation in smaller grafts. Fourthly, the study was unable to analyse centre-specific outcomes.

In conclusion, the analysis of outcomes of LDLTs carried out in the USA during 1998–2010 shows that outcomes of LL-LDLT were inferior compared with those of RL-LDLT. The lower rate of graft survival in LL-LDLT should be taken into consideration in the overall debate regarding the choice of LL-LDLT vs. RL-LDLT. Because LL donation may be associated with a lower rate of complications in the donor, technical innovations, such as the modulation of inflow and outflow in smaller grafts, should be studied more carefully and may actually lead to the achieving of better results in LL-LDLT. Given refinement of surgical procedures, better graft selection, appropriate graft size matching and careful recipient selection, LL-LDLT may achieve significant progress in outcomes in the future. Left lobe LDLT should be performed under protocol and studied to define the optimal outcomes in experienced centres.

Conflicts of interest
None declared.

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