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ORIGINAL ARTICLE

Living donor liver transplantation for primary biliary cirrhosis: retrospective analysis of 50 patients in a single center

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Summary

Although living donor liver transplantation (LDLT) is accepted as an alternative therapy for primary biliary cirrhosis (PBC), the postoperative results are not well known. Fifty patients with PBC underwent LDLT at Tokyo University Hospital. Their clinical records were retrospectively analyzed. Postoperative death occurred in four patients within 2 months (mortality, 8%), while later death occurred in three patients. In the median follow-up period of 35 months (range 4–84 months), the 1, 3, and 5-year overall survival rates were 90%, 88%, and 80%, respectively. The laboratory data indicated that graft function was sufficient. No recurrence of PBC was confirmed. Multivariate analysis indicated that an updated Mayo score of <10 was a significantly favorable factor for short hospitalization (hazard ratio, 9.52; 95% confidence interval, 1.14–79.5; $P = 0.03$). In conclusion, LDLT provides a satisfactory long-term survival with the PBC patients.

Introduction

Primary biliary cirrhosis (PBC) is a cholestatic liver disease that causes bile duct destruction and progresses in most cases to cirrhosis and death through liver failure. PBC is histologically characterized by a chronic inflammatory process that affects the small interlobular bile ducts. Without therapy, the average life expectancy of symptomatic and asymptomatic PBC patients once diagnosed is 7.5 and 16 years, respectively. Medical therapy only slows the disease progression and liver transplantation remains the only hope of cure [1–3].

Living donor liver transplantation (LDLT) is established as one of the effective treatment options for end-stage liver failure. Because of severe graft shortage, its clinical significance is increasing [4]. Especially in Japan, where deceased donor liver transplantation continues to be unpopular, LDLT has a central role in liver transplantation therapy.

Historically, successful adult-to-adult LDLT was first performed for PBC in 1993 [5]. We previously reported the short-term results of 18 PBC cases [6], indicating that LDLT can be an alternative treatment for PBC. Since this report, there have been a number of advances in the surgical techniques for LDLT. Left liver grafts were previously the only type of graft available for LDLT, but they did not always meet the metabolic demands of adult recipients. The Hong-Kong group was the first to transplant a right liver graft, which has had a large impact on the initiation of adult-to-adult LDLT [7]. In the present sequential report, we reviewed the clinical experience of 50 PBC patients who underwent LDLT, to examine the feasibility of LDLT for PBC.

Patients and methods

Patients

From January 1996 to June 2004 at Tokyo University Hospital, 286 patients underwent LDLT. Among them, 50 patients (17%) were indicated for PBC and were the subjects of the present study. The baseline characteristics of the 50 patients are summarized in Table 1. The median

Table 1. Baseline characteristics.

Age (year)*	52 (35–66)
Gender	
Male	8 (16%)
Female	42 (84%)
Updated Mayo risk score*	9.5 (6.3–13.7)
MELD score*	12.7 (2.3–39.2)
Accompanied disease	
Osteoporosis with pathologic fracture	4 (8%)
Sjögren's syndrome	3 (6%)
Hepatitis C	2 (4%)
Hepatocellular carcinoma	1 (2%)
Preoperative liver function*	
Aspartate aminotransferase (IU/l)†	88 (10–429)
Alkaline phosphatase (IU/l)‡	375 (106–1492)
Total bilirubin (mg/dl)§	9.6 (1.4–38.6)
Prothrombin time (INR)	1.4 (1.1–2.3)
Albumin (g/dl)	2.8 (1.7–3.7)

MELD; model for end-stage liver disease.
*Values are expressed as median (range).
Normal range: †9–38, ‡60–201, §0.3–1.3.

age was 52 years (range 35–66). There were 42 female patients (84%). The median updated Mayo risk score and preoperative serum total bilirubin level were 10 (range 6–14) and 9.6 mg/dl (range 1.4–38.6), respectively. One patient had hepatocellular carcinoma. During the study period, there were 12 candidates of LDLT for PBC, in whom LDLT was abandoned. The reason for the abandonment was uncontrollable infection of the recipient in five cases, absence of an appropriate living donor in four, and loss of the recipient's will to undergo LDLT in three cases.

Operation

The selection criteria of recipients and donors were reported previously [6]. We determined the donor and type of liver graft required to fulfill the following criteria: the volume ratio of the estimated volume of the liver graft to the standard liver volume (SLV, [8]) of the recipient was >40% [9]. In a low-risk case (updated Mayo risk score <15), we permitted a liver graft with a ratio >30%. The remaining liver of a donor must be >30% of the whole liver [10]. The volume of the whole liver and its sectors of the donor were also estimated from enhanced computed tomography [11]. The updated Mayo risk score was calculated according to the formula advocated by Murtaugh *et al.* [12]. If platelet count was <50 000/μl, we added splenectomy to treat thrombocytopenia.

Follow-up

Anti-mitochondrial antibody (AMA) and/or anti-M2 antibody were checked before and every 6 months after LDLT. In this study, positive anti-M2 antibody was regarded as positive for AMA.

We considered that postoperative liver function was abnormal when one or more of the serum levels of the following liver function tests, performed at the last follow-up time, exceeded the upper normal limit by two or more times, i.e. aspartate aminotransferase >76 IU/l, alkaline phosphatase >402 IU/l, or total bilirubin >2.6 mg/dl. Immunosuppression in the recipients was induced and maintained by tacrolimus and prednisolone as described previously [13]. We did not perform protocol biopsy.

Multivariate analysis

In the 44 patients who are currently surviving, a multivariate analysis using a logistic regression model was performed to estimate the influence of the following independent factors on postoperative hospital stay (divided by clinically relevant cutoff points: more or less than 40 days). The factors included intraoperative blood loss, gender, Model for End-Stage Liver Disease score [14], preoperative serum total bilirubin level, graft weight/SLV ratio, age, blood typing of the donor and recipient, and updated Mayo risk score. The results were expressed as adjusted hazard ratios with 95% confidence intervals and *P*-values from the likelihood-ratio test. Significance was defined as a *P*-value of <0.05. All continuous data were expressed as median with range. Calculations were performed using Statview 5.0 computer software (SAS, Cary, NC, USA).

Results

Operation data

The operation-related data are described in Table 2. The transplanted liver graft was right hemiliver in 12 cases (24%), extended right hemiliver in three cases (6%), right lateral sector in six cases (12%), left hemiliver in three cases (6%), and left-hemiliver with caudate lobe in 26 cases (52%). The median ratios of graft weight to recipient SLV and graft to body weight was 44% (range 33–88) and 0.92% (0.66–1.78), respectively. There was no mortality among donors.

Short-term results

The median hospital stay was 44 days (range 25–193). The serum total bilirubin level gradually decreased and, in 30 patients (60%), was within the normal range 4 weeks after transplantation (median 1.1 mg/dl, range 0.2–15.3, Fig. 1). The median follow-up period was 35 months (range 4–84). Reoperation was performed 30 times in 21 patients (42%). Among them, 15 patients (71%) underwent reoperation during the first hospitalization. The causes of

Table 2. Operation-related data.

Blood type matching	
Identical	38 (76%)
Compatible	12 (24%)
Transplanted liver graft	
Left hemiliver	3 (6%)
Left hemiliver + caudate lobe	26 (52%)
Right hemiliver	12 (24%)
Extended right hemiliver	3 (6%)
Right lateral sector	6 (12%)
Graft weight (g)*	465 (330–838)
Graft/SLV ratio (%)*	44 (33–88)
Graft/body weight ratio (%)*	0.92 (0.66–1.78)
Recipient's liver weight (g)*	1206 (392–2610)
Blood loss (ml)*	3905 (963–9830)
Blood transfusion*	
Total (ml)	5820 (1560–11 900)
Red blood cell (ml)	800 (0–2400)
Fresh frozen plasma (ml)	4800 (560–6800)
Platelet concentration (ml)	300 (0–1600)
Operation time (min)*	865 (676–1670)
Splenectomy added	
Yes	15 (30%)
No	35 (70%)
Biliary reconstruction	
Bilio-entero anastomosis	16 (32%)
Duct-to-duct anastomosis	34 (68%)

SLV; standard liver volume.
*Values are expressed as median (range).

reoperation and other post-transplant complications are listed in Table 3. Acute rejection occurred in 18 patients (36%).

Survival

Seven patients died during the follow-up period, among which four patients died within 2 months after LDLT (mortality 8%). The causes of these early deaths were pneumonia followed by sepsis in two patients, brain hemorrhage in one, and simultaneous thrombosis of the portal vein and the hepatic artery in one patient. The updated Mayo risk scores of the four patients were 10, 11, 11, and 14, respectively. The late deaths occurred at 4, 12, and 47 months after transplantation because of uncontrollable chronic rejection, virus-associated hemophagocytic syndrome, and pneumonia, respectively. The 1, 3, and 5-year patient survival rates were 90%, 88%, and 80%, respectively (Fig. 2). No retransplantation was performed.

Postoperative liver function and AMA

Before transplantation, AMA was positive in 42 patients (84%). AMA remained positive in 33 patients (66%) at

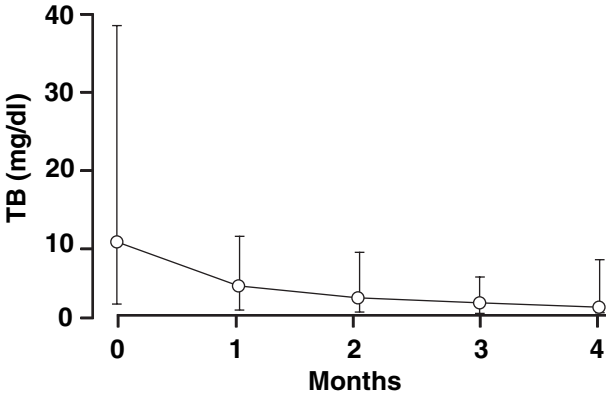

Figure 1 Changes of the serum total bilirubin levels before and after transplantation. The squares, the upper and lower bars indicated the median, maximum, and minimum values of the serum total bilirubin levels of the patients. Four patients, who died in the early period, were excluded.

Table 3. Postoperative results.

Hospital stay (days)	43 (25–193)*
Early death (within 2 months after operation)	4 (8%)
Pneumonia	2
Brain hemorrhage	1
Thrombosis of portal vein and hepatic artery	1
Late death	3 (6%)
Uncontrollable chronic rejection	1
Pneumonia	1
VAHS	1
Reoperation	30 times in 21 pts (42%)
Intra-abdominal abscess	8
Steal of portal flow to collaterals	5
Intra-abdominal hemorrhage	4
Bile leakage	4
Bile duct stenosis	3
Thrombosis of portal vein and/or hepatic artery	2
Detachment of incision	2
VAHS (splenectomy was performed)	1
Perforation of colon	1
Other complications	
Acute rejection	18
Pneumonia	4
Subileus	3
Renal failure	2
Cytomegalovirus infection	2
Brain hemorrhage	1
Pulmonary hemorrhage	1
Angina pectoris	1
Rupture of splenic artery aneurysm	1
Rupture of esophageal varices	1

VAHS, virus-associated hemophagocytic syndrome; pts, patients.
*Value is expressed as median (range).

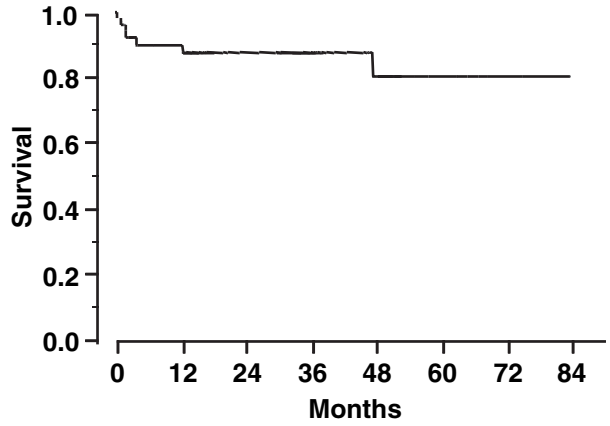

Figure 2 The overall survival curve of the patients undergoing living donor liver transplantation for primary biliary cirrhosis.

Table 4. Anti-mitochondrial antibody before and after LDLT.

Before LDLT	
Positive	42 (84%)
Negative	8 (16%)
After LDLT	
Positive	33
Negative	2
Not examined	1
Death	6
Negative	7
Death	1

LDLT, living donor liver transplantation.

Table 5. Postoperative liver function.

Aspartate aminotransferase (IU/l)†	24 (13–44)*
Exceed the upper limit (%)	2 (4%)
Exceed the upper limit by two times or more (%)	0 (0%)
Alkaline phosphatase (IU/l)‡	225 (123–489)*
Exceed the upper limit (%)	23 (46%)
Exceed the upper limit by two times or more (%)	4 (8%)
Total bilirubin (mg/dl)§	0.7 (0.3–2.2)*
Exceed the upper limit (%)	2 (4%)
Exceed the upper limit by two times or more (%)	0 (0%)

*Values are expressed as median (range).
Normal range: †9–38, ‡60–201, §0.3–1.3.

6 months after transplantation (Table 4). The latest laboratory tests indicated that the serum aspartate aminotransferase, alkaline phosphatase, and total bilirubin levels exceeded the upper limit by two or more times in 0, 4, and 0 patient, respectively (Table 5). Abnormal liver function was found in four patients (8%), in whom acute rejection was denied on biopsy basis. The serum aspartate aminotransferase and total bilirubin levels were within the normal range in 96% of the patients, while the serum alkaline phosphatase level was normal in 54% (Table 5). In the follow-up period, conversion from tacrolimus to cyclosporine was carried out in seven patients (16%) for uncontrollable rejection or the side-effects of tacrolimus.

Table 6. Multivariate analysis to evaluate clinical factors on short hospitalization.

Variables	Hazard ratio	95% CI	*P*-value
Updated Mayo risk score <10	9.52	1.14–79.5	0.03
Preoperative T. Bil level <10 mg/dl	4.43	0.52–38.2	0.18
Male	3.68	0.26–52.3	0.34
MELD score <12	0.53	0.07–4.24	0.55
Identical blood type	1.59	0.25–9.99	0.63
Age <50	0.70	0.13–3.92	0.69
Graft/SLV ratio <40%	0.84	0.14–4.84	0.84
Intraoperative blood loss <4000 ml	1.14	0.24–5.36	0.87

T. Bil, serum total bilirubin; MELD, model for end-stage liver disease; SLV, standard liver volume; CI, confidence interval.

Multivariate analysis

Multivariate analysis indicated that only an updated Mayo score of <10 was a significantly favorable factor for a hospitalization stay of <40 days (hazard ratio 9.52, 95% confidence interval 1.14–79.5, $P = 0.03$, Table 6).

Discussion

In this study, the 3- and 5-year overall survival rate was 88% and 80%, respectively, the mortality was 8%, and the liver function of the graft was almost normal (Table 5) in the median follow-up period of 35 months. According to the registry of the Japanese Liver Transplantation Society [15], LDLT was performed in 208 patients with PBC in Japan from 1992 to 2002. The 1, 3, and 5-year overall survival rates of the 208 patients were 77%, 72%, and 72%, respectively. As for deceased donor liver transplantation for PBC, the 5-year overall survival rate is reported to be 68–88% [2,3,16,17]. Considering the previously reported outcomes, the graft- and overall-survivals in this study are satisfactory.

The mortality rate was 17% in our previous study [6], which improved remarkably to 8%. From March 2000, we began to use right liver graft, including extended right liver, right liver, and right lateral sector [18]. In comparison with our preliminary results [6], the proportion of right liver grafts increased in this series (5–42%). The ratio of the obtained graft to the recipient SLV was sufficient (median: 44%), which was because of the use of right liver graft. The use of a right liver-related graft

contributed not only to extending the indication of LDLT, but also to the satisfactory post-transplant results, as shown in this series.

Reoperation was performed 30 times in 21 patients (42%), which seemed to be a high rate. Among the causes of reoperation, however, three patients were related to bile duct anastomosis, two were caused by hepatic artery anastomosis, and five were related to impaired portal flow, respectively (Table 3). One-third of the causes were specific to LDLT; i.e. small size of the bile ducts, the vessels, and the graft. Moreover, most of the reoperations (71%) were performed during the first hospitalization. Meticulous postoperative management, including reoperation, might have contributed to the low mortality. Our results indicate that LDLT for PBC can provide well long-term results if a recipient survive the short-term period after transplantation. To our knowledge, there are no reports of postoperative results of a sufficient number of patients undergoing LDLT for PBC. Our results indicate that LDLT is an alternative therapeutic option to deceased donor liver transplantation for PBC.

The logistic regression test indicated that the updated Mayo risk score (<10) was a significantly favorable factor for shorter a postoperative hospital stay (<40 days). This was compatible with a previous report [6] showing that the conventional and updated Mayo risk models were correlated with the duration of hospitalization. Kim *et al.* [2] suggested that an updated Mayo risk score of >7.8 was associated with a progressively increased mortality in deceased donor liver transplantation. In this study, the updated Mayo risk scores of the four cases with early death were >9.6, which was higher than Kim's criterion. The clinical usefulness of the updated Mayo model was reconfirmed, and almost the same outcomes can be offered even in LDLT.

The recurrence of PBC in a transplanted allograft is well-recognized on histological findings, such as granulomatous cholangitis [19,20]. Recurrence rate after deceased donor liver transplantation is 10.9–17% at 5 years [3,21,22], while a few cases of recurrence have been reported in LDLT [23,24]. However, the details remain unknown. In this series, postoperative AMA was positive in 33 patients (66%) and abnormal liver function was found in four (8%). To diagnose recurrence of PBC, histological findings are indispensable [19,24], although AMA, which frequently remains positive after transplantation, has little clinical significance. Because we did not perform protocol biopsy to avoid the risks of biopsy procedures, we confirmed no recurrence of PBC. Recurrence rate of PBC after LDLT might be higher because of the similarity of the genetic factors between the donor and recipient, who are usually blood-relatives [6]. Although the recurrence might be included among the four patients with abnormal liver function, we could not confirm the hypothesis in the present study.

In conclusion, LDLT is another effective therapeutic choice for PBC with a high survival rate and good liver function. An updated Mayo score is an effective predictive factor for post-transplant prognosis in a PBC patient. Recurrence of PBC after LDLT could not be confirmed in our series.

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