Table 1: Characteristics of APOLT for fulminant hepatic failure

Case	Age (year)	Sex	Blood type	Graft type	GRWR	PVD	Outcome
1	1.8	M	Identical	Left lateral	2.08	–	Died* (POD55, sepsis)
2	1.5	M	Identical	Left lateral	2.00	–	Died† (POD141, sepsis)
3	19.5	M	Identical	Left lobe	0.62	+	Died (POD32, necrotizing enteritis)
4‡	43.3	F	Identical	Left lobe	0.51	+	Died (POD9, graft failure)
5	53.6	M	Compatible	Left lobe	0.61	+	Died (POD25, sepsis)
6	38.6	F	Identical	Right lobe	0.90	+	Died (POD43, sepsis)

GRWR = graft-to-recipient weight ratio (%); PVD = portal vein diversion; POD = post-operative day.
*Portal flow steal phenomenon.
†Retransplantation on day 34 from living donor for recurrent hepatitis.
‡HBV-related fulminant hepatic failure.
Retransplantation on day 29 from living donor for hepatic artery and portal vein thrombosis.

Patient 1, in whom portal blood flow to the native liver was preserved, showed a portal flow steal phenomenon resulting in continuously poor portal blood flow to the graft. Native portal vein diversion at the time of transplantation was indicated in the latter four cases to prevent functional portal flow competition between the graft and remnant native liver (17). Acute cellular rejection that was confirmed by liver biopsy, was observed in 3 patients (patients 2, 4 and 5). Three technical complications occurred in 6 patients, biliary stricture in patient 1 and intra-abdominal bleeding in patients 5 and 6. Retransplantation was indicated in 2 patients: for recurrent hepatitis in patient 2 and for arterial/portal thrombosis in patient 6. All patients died within 5 months of APOLT, due to sepsis in four cases, necrotizing enteritis in one case and graft failure in one case. None of the patients showed sufficient native liver recovery, and none of them were able to withdraw from immunosuppressive therapy.

In the same period, 53 patients had a transplant with standard LDLT for fulminant hepatic failure. Etiology of fulminant hepatic failure was drug-induced in 1, HBV in 15 and of unknown origin in 37. The median age of recipients was 23.3 years (range: 0.1–68.9 years). Recipient and donor characteristics of APOLT or standard LDLT were comparable at the time of transplant. The cumulative 5-year graft and patient survival rates were 58.4% and 60.2% in the standard LDLT group, respectively. The graft survival was significantly lower after APOLT ($p < 0.01$).

APOLT for non-cirrhotic metabolic liver disease (Table 2)

Six patients had a transplant with APOLT for non-cirrhotic metabolic liver disease. Primary native portal vein diversion was indicated in the last four cases. We reported the case of patient 1 with OTCD who did not receive primary ligation of the native portal branch at the time of APOLT (18). After a severe rejection episode, the graft became smaller and the native liver showed compensatory hypertrophy. As a result of the delayed native portal vein diversion, at 26 months after APOLT the graft volume increased properly and was revealed to have acceptable metabolic function. In our previous study, the resistance of portal venous inflow in the graft liver was higher than in the native liver after APOLT (17), and the dominant portal venous flow to the native liver could be readily observed in the event of severe rejection. After the experience of the first two cases, we changed the standard procedure for APOLT of non-cirrhotic metabolic liver disease to indicate native portal vein diversion in all subsequent cases so that the graft liver received the entire portal venous flow. The native liver was supplied by arterial blood flow. In case 2, native partial hepatectomy was done to compensate the hypertrophy of the native liver after native portal vein diversion (12). No significant difference was found in pericellular or perivenular fibrosis in the native liver between the specimen at APOLT and at native hepatectomy. Despite the native portal vein diversion, steatosis of the native liver improved from 80% to 30% (19).

Table 2: Characteristics of APOLT for non-cirrhotic metabolic liver disease

Case	Age (year)	Sex	Original disease	Blood type	Graft type	GRWR	PVD	Outcome
1	3.0	F	OTCD*	Compatible	Left lateral	2.08	+†	Alive
2	5.8	F	OTCD*	Identical	Left lateral	1.34	+‡	Alive
3	52.7	F	Citrullinemia	Identical	Left lobe	0.84	+	Alive
4	5.5	M	Crigler-Najjar (type I)	Compatible	Left lateral	1.23	+	Alive
5	23.5	M	Citrullinemia	Identical	Left lobe	0.78	+	Alive
6	20.2	M	Citrullinemia	Compatible	Left lobe	1.21	+	Died (POD29, sepsis)

GRWR = graft-to-recipient weight ratio (%); PVD = portal vein diversion; POD = post-operative day; POM = post-operative month.
*Ornithine transcarbamylase deficiency.
†PVD for portal flow steal phenomenon (POM 26).
‡PVD for portal flow steal phenomenon (POM 14), and native hepatectomy for compensate hypertrophy (POM66).

Five patients had an episode of acute cellular rejection (patients 1, 2, 3, 4, 6). Patient 3 had biliary stricture and underwent rehepaticojejunostomy 3 years after transplant. Patient 5 had minor biliary leakage that was successfully managed with percutaneous aspiration drainage under ultrasound guidance. Patient 6 died from sepsis on post-operative day 29. The overall cumulative 5-year graft and patient survival rates were 83.3% and 83.3%, respectively.

Seventeen patients received standard LDLT for non-cirrhotic metabolic liver disease in the same study period. Etiology of liver disease was tyrosinemia in four cases; OTCD in three; citrullinemia in three; glycogen storage disease in three; Crigler-Najjar type I in one; familial amyloidotic polyneuropathy in one; methylmalonic acidemia in one and propionic acidemia in one (20,21). The overall cumulative 1- and 5-year graft and patient survival rates were 70.6% and 62.7% and 70.6% and 62.7%, respectively. There was no significant difference in graft and patient survival between APOLT and standard LDLT for non-cirrhotic metabolic liver disease.

APOLT for small-for-size graft (Table 3)

Thirteen patients underwent transplant with APOLT for a small-for-size graft. Small-for-size grafts can be defined by a recognizable clinical syndrome that results from the transplantation of too small a functional mass of liver for a designated recipient (22,23). The definition of a small-for-size graft in this study is an actual GRWR of less than 0.8% (2,3). The original liver disease was biliary atresia in 2 patients; liver cirrhosis in 2 (of which 1 was HBV-related); primary biliary cirrhosis in 3; primary sclerosing cholangitis in 2; Wilson's disease in 2; autoimmune hepatitis in 1 and Budd-Chiari syndrome in 1. The median GRWR was 0.62% (range: 0.45–0.75%). The decision was made pre-operatively in this group of patients to use APOLT.

All patients had histologically proven fibrosis in the native liver, and a pre-operative Doppler study revealed that the blood supply depended on the hepatic artery being dominant rather than the portal vein. Native portal vein diversion was indicated in 10 patients. Six patients had an episode of acute cellular rejection (patients 3, 4, 5, 7, 8, 13) and one patient had chronic rejection (patient 13).

Four patients required relaparotomy for complications: intestinal perforation in patient 3; intra-abdominal bleeding in patients 4 and 9. Patient 7 with primary sclerosing cholangitis underwent native hepatectomy on post-operative day 35 after competent graft regeneration confirmed by CT volumetry and ^{99m}Tc-galactosyl serum albumin scintigraphy, which reflected the general function of the hepatocyte in the graft and native liver (24). The delayed native hepatectomy was intended to eliminate the potential risk of carcinogenecity of the remnant native liver. Interestingly, the explanted native liver showed no histological difference between the specimen at APOLT and at delayed native hepatectomy.

Two patients (patients 4 and 6) had hepatic vein stenosis that was treated by intervention. A metallic stent was inserted in patient 4 after several courses of balloon dilatation, but was thrombosed despite adequate anticoagulation therapy. Biliary complications were observed in 6 patients; biliary leakage in 3 (patients 1, 5 and 10) and stricture in 3 (patients 3, 7 and 8). Hypersplenism was observed in 2 patients (patients 3 and 6) who underwent splenectomy 7 years and 1 year after APOLT, respectively. Patient 6 developed *de novo* autoimmune hepatitis 2.5 years after APOLT (25).

Retransplantation was indicated in 2 patients due to hepatic vein thrombosis in patient 4 and chronic rejection in

Table 3: Characteristics of APOLT for small-for-size graft

Case	Age (year)	Sex	Original disease	Blood type	Graft type	GRWR	PVD	Outcome
1	23.2	F	Wilson's	Identical	Left lobe	0.72	–	Alive
2	47.1	M	LC (HBV)	Compatible	Left lobe	0.51	–	Died (POD35, sepsis)
3	22.9	F	Biliary atresia	Identical	Left lobe	0.48	+	Alive
4	24.1	M	Wilson's	Identical	Left lobe	0.62	–	Alive*
5	48.7	F	PBC	Compatible	Left lobe	0.62	+	Alive
6	15.9	F	Biliary atresia	Identical	Left lobe	0.54	+	Alive
7	20.6	F	PSC	Identical	Left lobe	0.49	+	Alive†
8	44.1	F	PBC	Identical	Left lobe	0.45	+	Alive
9	50.6	F	LC	Identical	Left lobe	0.67	+	Alive
10	30.0	F	PBC	Identical	Left lobe	0.59	+	Died (POD59, sepsis)
11	39.0	F	Budd-Chiari	Identical	Left lobe	0.69	+	Died (POD22, sepsis)
12	19.2	F	AIH	Identical	Right lobe	0.75	+	Alive
13	30.9	M	PSC	Identical	Right lobe	0.68	+	Died‡ (POD372, sepsis)

GRWR = graft-to-recipient weight ratio (%); PVD = portal vein diversion; POD = post-operative day; POM = post-operative month; LC = liver cirrhosis; PBC = primary biliary cirrhosis; PSC = primary sclerosing cholangitis; AIH = autoimmune hepatitis.
*Retransplantation from living donor for hepatic vein thrombosis (POM 33).
†Native hepatectomy after regeneration of graft (POD 35).
‡Retransplantation from living donor for chronic rejection (POM 6).

Table 4: Characteristics of APOLT for ABO-incompatible case

Case	Age (year)	Sex	Original disease	Graft type	GRWR	PVD	Outcome
1	19.6	M	Biliary atresia	Left lobe	0.55	+	Died (POD59, hepatic necrosis)
2	51.4	M	LC (HBV)	Left lobe	0.55	+	Died (POD32, sepsis)
3	13.8	F	Biliary atresia	Left lobe	0.62	+	Alive
4	4.5	F	Biliary atresia	Left lateral	1.37	+	Alive*
5	14.9	M	Biliary atresia	Left lateral	0.63	+	Alive
6	9.8	F	LC	Left lateral	1.16	+	Alive

GRWR = graft-to-recipient weight ratio (%); PVD = portal vein diversion; POD = post-operative day; POM = post-operative month.
*Retransplantation from cadaveric donor (split liver transplantation) for chronic rejection (POM 22).

patient 13. Patient death occurred in 4 of 13 patients, the main cause of death being sepsis. The overall cumulative 1- and 5-year graft survivals were 69.2% and 69.2%, respectively.

Forty patients received standard LDLT for a small-for-size graft during the same period in conjunction with APOLT. The median GRWR in the standard LDLT group was 0.73% (range: 0.60–0.79%). The GRWR was significantly lower for patients receiving APOLT versus those receiving standard LDLT ($p < 0.01$). The overall cumulative 1- and 5-year graft and patient survivals in the standard LDLT group were 65.0% and 65.0%, respectively. No significant difference was observed between the groups.

APOLT for cases of ABO-incompatibility (Table 4)

Six patients had a transplant with APOLT for ABO-incompatibility. Median recipient age was 14.4 years (range: 4.5–51.4 years). Acute cellular rejection was observed in 4 patients (patients 1, 4, 5 and 6). Patient 4 had chronic rejection.

Relaparotomy was indicated for 2 patients: ligation of the collateral vessel in patient 1 and intra-abdominal bleeding in patient 2. Patient 1 underwent ligation of the collateral vessel on post-operative day 9. After an episode of acute cellular rejection, graft portal venous flow decreased and the steal phenomenon of portal flow to the collateral vessel was confirmed by Doppler ultrasonography even though native portal vein diversion was indicated. The graft function did not recover and the native liver function was not sufficient to support the severe dysfunction of the graft. The patient died from hepatic necrosis on post-operative day 59. Three patients had biliary complications: bile leakage in patients 4 and 5, and biliary stricture in patient 6. Patient 4 underwent retransplantation with a cadaveric split graft in post-operative month 22 for chronic rejection. The overall cumulative 1- and 5-year graft survival rates were 66.7% and 44.4%, and the 1- and 5-year patient survival rates were 66.7% and 66.7%, respectively.

Thirty patients, all over 2 years old, underwent standard LDLT with an ABO-incompatible graft. Median recipient age was 30.1 years (range: 2.0–59.3 years). Acute cellular rejection was observed in 9 of 30 patients (30%). The overall cumulative 1- and 5-year graft and patient survival rates were 53.3% and 42.7%, respectively. There was no significant difference in graft and patient survival between APOLT and standard LDLT for ABO-incompatibility.

Profiles of APOLT and standard LDLT (Table 5)

Profiles of APOLT and standard LDLT performed in the same study period are shown in Table 5. The GRWR was significantly lower for patients receiving APOLT versus those who received standard LDLT.

The duration of the operation was significantly longer in the APOLT group (831.2 ± 222.0 min) than the standard LDLT group (690.8 ± 198.5 min).

Acute cellular rejection was detected in 18 of 31 (58.1%) cases of APOLT versus 177 of 505 (35.0%) cases of standard LDLT ($p = 0.02$). Chronic rejection was diagnosed in 2 of 31 (6.5%) cases of APOLT, versus 2 of 505 (0.4%) cases of standard LDLT ($p < 0.01$). The incidence of rejection was higher in the APOLT group.

There were no significant differences in vascular complications between APOLT and standard LDLT. Biliary leakage was observed in 6 of 31 (19.4%) cases of APOLT, versus 30 of 505 (6.0%) in standard LDLT ($p < 0.01$). Biliary stricture was observed in 7 of 31 (22.6%) cases of APOLT, versus 28 of 505 (5.5%) in standard LDLT ($p < 0.01$). Biliary complication was significantly higher in the APOLT group.

The need for retransplantation was significantly greater in the APOLT group (16.1% vs. 4.2% for standard LDLT group, $p < 0.01$). In-hospital deaths occurred in 13 of 31 patients (41.9%), 10 patient deaths (76.9%) were related to infectious complication. The median delay was 32 days (range: 9–184 days) after APOLT.

The 1- and 5-year cumulative grafts were lower after APOLT versus standard LDLT (57.9 and 50.6% vs. 78.8 and 73.8%, respectively), but the difference did not reach statistical significance ($p = 0.45$ and 0.18, respectively).

Table 5: Profiles of Auxiliary partial orthotopic liver transplantation and standard living donor liver transplantation

Characteristics	APOLT (n = 31)	Standard LDLT (n = 505)	p-values
Male/female	13/18	213/292	0.87
Age (year)	25.8 ± 16.8 (1.5–53.6)	18.9 ± 20.4 (0.1–69.1)	0.06
Donor age (year)	43.5 ± 10.3 (20–62)	37.9 ± 10.8 (19–66)	<0.01
GRWR* (%)	0.87 ± 0.47 (0.45–2.08)	1.96 ± 1.27 (0.60–9.68)	<0.01
Cold ischemic time (min)	177.4 ± 111.2 (36–460)	116.7 ± 89.5 (14–943)	<0.01
Warm ischemic time (min)	49.4 ± 13.6 (32–77)	46.9 ± 13.8 (16–145)	0.32
Duration of operation (min)	831.2 ± 222.0 (513–1379)	690.8 ± 198.5 (329–1800)	<0.01
Blood loss/recipient boy weight (g/kg)	116.4 ± 140.4 (6.3–607.3)	119.7 ± 146.0 (8.3–1414.1)	0.89
Acute cellular rejection (%)	58.1	35	0.02
Chronic rejection (%)	6.5	0.4	<0.01
Surgical complications (%)			
Intestinal perforation	3.2	4.1	0.83
Intra-abdominal bleeding	16.1	9.4	0.62
Hepatic artery thrombosis	3.2	2.0	0.86
Portal vein thrombosis	3.2	1.4	0.95
Hepatic vein stenosis	6.5	1.4	0.16
Biliary leakage	19.4	6.0	<0.01
Biliary stricture	22.6	5.5	<0.01
Retransplantation (%)	16.1	4.2	<0.01
Graft survival (1-, 5-year survival, (%))			
For fulminant hepatic failure	0, 0	58.4, 58.4 (n = 53)	<0.01
For metabolic liver disease	83.3, 83.3	70.6, 62.7 (n = 17)	1.47
For small-for-size graft	69.2, 69.2	65.0, 65.0 (n = 40)	1.59
For ABO incompatible case	66.7, 44.4	53.3, 42.7 (n = 30)	0.53
Overall	57.9, 50.6	78.8, 73.8	0.45

GRWR = graft-to-recipient weight ratio (%).

Discussion

The most common indication for APOLT in western countries is fulminant hepatic failure (8). The first successful case of APOLT for fulminant hepatic failure, that is, full native liver regeneration and withdrawal of immunosuppressive therapy was reported in 1991 (26). The indication of APOLT for fulminant hepatic failure remains controversial because APOLT does not rule out potential regeneration of the native liver, resulting in unsatisfactory outcomes (6). In our series of APOLT for fulminant hepatic failure, none of the patients achieved long-term survival. The reasons for our poor results might be application of preemptive portal vein diversion and patient selection. The rationale of portal vein diversion is to prevent the portal flow steal phenomenon. We reported that the native liver has less resistant than the graft in fulminant hepatic failure (17), however, sufficient portal blood flow might be essential for native liver recovery and subsequent regeneration. An experimental study reported that the necessity of portal vein diversion in APOLT was dependent on the pathophysiology of the remnant native liver (27). The efficiency of portal vein diversion for fulminant hepatic failure, a paradox between the functional competition and the native liver recovery, remains unclear. Moreover, the optimal APOLT candidate for fulminant hepatic failure has not yet been clearly defined. A previous study suggests that native liver recovery is more likely to occur in those with a short interval between jaundice and encephalopathy (28). The median interval between onset of jaundice and encephalopathy was 42 days in our series. This delay might be one of the reasons for the poor outcome.

Bismuth et al. reported that the main advantage of APOLT for fulminant hepatic failure, that is, the potential for withdrawal of immunosuppressive therapy, was rarely achieved and that the indication of APOLT for fulminant hepatic failure should therefore be reconsidered because of the high degree of technical complications (6,10). We fully agree with this suggestion. While our experience of APOLT for fulminant hepatic failure is limited, based on the poor outcome, we also consider that APOLT should have a limited place in the treatment of fulminant hepatic failure. There might be a possibility, however, that APOLT could be used in toxic injury such as acetaminophen toxicity where recovery of the native liver is more likely than in idiopathic or viral fulminant hepatic failure (29–31).

In the case of non-cirrhotic metabolic liver disease, APOLT had a satisfactory outcome in our series with a 5-year graft survival of 83.3%. After the initial two cases of the portal flow steal phenomenon, we changed the standard procedure for APOLT of non-cirrhotic metabolic liver disease to indicate native portal vein diversion in all subsequent cases whereby the graft liver receives the entire portal venous flow. Concern remains about the dysfunction of the remnant native liver after portal vein diversion, which may

negate the support of a patient's life and the possibility of future gene therapy. However, it has been reported that occluded portal flow induces hepatocyte apoptosis rather than necrosis in the embolized lobe without changing the functional efficiency of the hepatocyte (32,33). Our previous report showed that ligation of the native portal vein had no detrimental effects on the native liver supplied by arterial flow only (17,34). The remnant native liver may sustain the recipient's life if the native portal vein is transected. APOLT with portal vein diversion is an effective technique to induce graft regeneration and to avoid functional portal flow competition in non-cirrhotic metabolic liver disease.

With regard to our experience of APOLT for small-for-size grafts, the patients had high surgical complications and unsatisfactory patient survival. Recent technical improvements in left lobe donation have led to the use of right lobe grafts in adult-to-adult LDLT to overcome problems encountered with small-for-size grafts (35). After a period of APOLT using left lobe grafts, which partially relieved the problems of small-for-size grafts, right lobe LDLT was systematically introduced from February 1998. The cumulative 1-year graft survival rate of right lobe LDLT was 76.8%, which was significantly higher than that of APOLT for small-for-size grafts ($p < 0.01$, $n = 168$). Moreover, in some cases, if the functional volume of the right lobe was not sufficient for recipients, right lobe with middle hepatic vein graft was indicated with special attention to donor safety. The overall cumulative 1-year graft survival rate of right lobe with middle hepatic vein graft was 82.2% ($n = 28$). Our current strategy is to consider the right lobe as the first choice followed by APOLT with a right lobe graft for small-for-size grafts.

The graft survival in children younger than 2 years old receiving an ABO-incompatible graft is similar to those receiving compatible grafts. The survival is gradually affected with age by specific complications associated with blood type mismatching such as focal hepatic necrosis due to microcirculatory disturbance and multiple non-anastomotic biliary strictures attributable to arteriole insufficiency (36). In our LDLT program, an ABO-incompatible graft was unavoidable in 12% of the recipients. Despite the application of pre-operative plasma exchange, splenectomy and enhanced immunosuppression, the 5-year graft survival was less than 50% in an adult population. The application of APOLT to ABO-incompatible cases improved graft survival; however, graft survival was not satisfactory. Recently, an intra-portal infusion protocol was introduced (37), and improved patient survival was observed in ABO-incompatible cases. We modified the protocol from intra-portal to intra-hepatic arterial infusion from December 2001. Although it is still a tentative trial, intra-hepatic arterial infusion protocol dramatically improved survival with 1-year graft survival of 85% (data not shown). After the introduction of a novel immunosuppression protocol, APOLT is not adopted for ABO-incompatible cases. Further study of hepatic artery infusion therapy is now underway in order to transcend the ABO-barrier.

The higher rejection episodes in APOLT series are a consequence that requires further investigation. Immunological differences in the responses to orthotopic and auxiliary allografts were reported in an experimental study, given the increased expression of class II MHC antigen on hepatocytes in auxiliary liver transplantation, and the increase in the rejection response to the auxiliary grafts (38). Auxiliary liver allografts were also demonstrated to be more susceptible to rejection than non-auxiliary allografts (39). Further histopathological studies into the mechanisms of susceptibility to rejection in APOLT cases are currently underway.

Unlike standard LDLT, the incidence of biliary complications and the need for retransplantation were shown to be higher in APOLT cases. According to our present study, we conclude that APOLT should have a restricted indication in the treatment of fulminant hepatic failure, small-for-size grafts and ABO-incompatibility. Conceptual changes were made in the treatment of small-for-size grafts, through the introduction of LDLT using right lobe with or without middle hepatic vein graft, and in the treatment of ABO-incompatible cases, through the use of a novel intra-hepatic arterial immunosuppression protocol. Non-cirrhotic metabolic liver disease may be a suitable indication for APOLT.

Acknowledgment

This work was supported in part by grants from the Scientific Research Fund of the Ministry of Education and by a Research Grant for Immunology, Allergy and Organ Transplant from the Ministry of Health, Labor and Welfare, Japan.

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American Journal of Transplantation 2005; 5: 1339–1346
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2005.00817.x

Impact of Right Lobe with Middle Hepatic Vein Graft in Living-Donor Liver Transplantation

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Technical improvements in adult-to-adult living-donor liver transplantation (LDLT) have led to the use of right-lobe grafts to overcome the problems encountered with 'small-for-size grafts'. The major controversy remains that the venous drainage from anterior segment substantially depends on tributaries of the middle hepatic vein (MHV), and deprivation of such tributaries may critically influence the postoperative graft function. Right-lobe grafts with MHV could resolve the potential problem of congestion in anterior segment. From December 2000 to January 2004, we performed 217 right-lobe LDLTs for adult patients. Of these, 40 patients received a right lobe with MHV graft (18.4%). The overall cumulative 3-year graft survival rate of a right lobe with (n = 40) and without MHV (n = 177) was 86.2% and 74.8% (p = NS). The proximal side of the MHV and the drainage vein of segment IV to the MHV (the left medial superior vein) were preserved in 24 patients. All of them needed venous interposition graft for anastomosis. All patients had a patent right hepatic vein (RHV) and MHV anastomosis during the follow-up period. We adopted the right lobe with MHV graft in 40 LDLT cases. Vein graft is essential for safe MHV anastomosis in cases which preserve proximal side of the MHV.

Key words: Hepatic vein reconstruction, liver transplantation, living donor, right-lobe graft

Received 24 October 2004, revised 24 November 2004 and accepted for publication 15 December 2004

Introduction

The accumulating results of living-donor liver transplantation (LDLT) are comparable to those of cadaveric transplantation (1). Experience of and technical improvements in left-lobe donation have led to the use of right-lobe grafts in adult-to-adult LDLT to overcome the problems encountered with 'small-for-size grafts'. We have reported that the use of 'small-for-size grafts' (<1.0% of recipient body weight) leads to lower graft survival, probably through enhanced parenchymal cell injury and reduced metabolic and synthetic capacity (2).

The major controversy about right-lobe LDLT remains that the venous drainage from the anterior segment depends substantially on tributaries of the middle hepatic vein (MHV), and deprivation of such tributaries may influence the postoperative graft regeneration (3). We have reported that the regeneration of the posterior segment was significantly greater than that of the anterior segment. Despite deprivation of MHV tributaries, a graft will regenerate to meet the metabolic demand (4). However, some patients substantially suffered from complications related to 'small-for-size graft'. In some right-lobe grafts, regional volume of the MHV might be dominated over the right hepatic vein (RHV), and the functional liver volume could be reduced in such type of the grafts. To maximize the benefit of right-lobe graft, several technical modifications have been reported, such as additional venous reconstruction of segment V and VIII (5–8).

The application of right lobe with MHV graft could resolve the potential problem of congestion in the anterior segment (6). However, sufficient drainage veins of the remnant donor liver might not be certified due to the presence of tributaries from segment IV to the MHV (left medial superior vein) (9). Preservation of the drainage veins of segment IV to the MHV in the donor might be important for surgical innovation in right lobe with MHV LDLT.

Recent developments in imaging studies have made it possible to visualize the distribution of the hepatic vessels without hepatic dissection (10). Preoperative three-dimensional (3D) computed tomography (CT) volumetry and computer-assisted volumetric analysis according to the hepatic venous anatomy (MeVis, Germany) were adopted as a noninvasive and objective evaluation for application of a right lobe with MHV graft (11). The computer-assisted preoperative donor risk analysis is helpful for providing volumetric calculations, relating the volume of the compromised areas to total graft or remnant liver. We describe the surgical techniques and outcome in 40 cases of

hepatic vein reconstruction in LDLT using right lobe with MHV grafts, while preserving the significant drainage veins of segment IV to the MHV remaining in the donor.

Patients and Methods

During the period from June 1990 to January 2004, 966 LDLTs were performed in 922 patients at Kyoto University Hospital. Right-lobe LDLT was first carried out in February 1998, and we have since carried out 345 right-lobe LDLTs. Since the initiation of the right lobe with MHV graft procedure for adult patients (>18 years old) in December 2000, we have performed a total of 217 cases of right-lobe LDLTs for adult patients in the same period. Of these, 40 patients received a right lobe with MHV graft (18.4%). Nineteen cases of right-lobe LDLT with additional vein reconstruction of the anterior segment were excluded from the study.

The patients were 29 males and 11 females, with a median age of 49.7 years (range: 18.8–65.7), and a median weight of 64.3 kg (range: 37.1–99.0). Median model for end-stage liver disease (MELD) score was 19.0 (range: 4.0–37.0). The indication for transplantation was hepatocellular carcinoma with hepatitis C virus (HCV) cirrhosis in 17 patients; hepatocellular carcinoma with hepatitis B virus (HBV) cirrhosis in 4; liver cirrhosis in 9 (HCV in 6, HBV in 1 and alcoholic in 2); biliary atresia in 3; fulminant hepatic failure in 2; primary biliary cirrhosis in 2; glycogen storage disease in 1; retransplantation in 1 and a metastatic neuroendocrine tumor (pancreatic polypeptide-secreting tumor) in 1. Six patients received blood-type incompatible grafts (Table 1).

Immunosuppression consisted of tacrolimus and low-dose steroids (12). Patients who received blood-type incompatible transplants had preoperative plasma exchange or double-filtration plasmapheresis in order to reduce the anti-ABH antibody titer. Prostaglandin E1, cyclophosphamide and additional steroids were administered from the portal vein or hepatic artery postoperatively (13).

Donor evaluation

Potential donors were evaluated through the use of liver function tests, determination of blood type, HLA typing and determination of anatomical variation and graft size using 3D CT volumetry. The potential indication for right lobe with MHV grafting was a graft-to-recipient weight ratio (GRWR) of less than 1.0% with right-lobe graft, as determined by preoperative 3D CT volumetry. If the regional volume of the MHV dominated over the RHV and the remnant liver volume in the donor was shown to be over 35% of the whole liver volume, then the entire MHV could be included with the graft. If not, the proximal side of the MHV, which is the concourse of the segment IV drainage vein (left medial superior vein), should be left in the donor to reduce the risk of venous congestion in segment IV. The MHV dominance in right lobe was defined as follows:

regional volume of vein 5 + vein 8/right-lobe volume × 100 > 40%.

Donor operation

Before parenchymal transection, the right lobe was mobilized and the sizeable right inferior hepatic vein (RIHV; >5 mm) was preserved with a caval cuff for reconstruction. After careful definition of biliary anatomy in the hepatic hilum using intraoperative cholangiography, the right hepatic duct was transected. The right portal vein and the right hepatic artery were temporally clamped to clarify the parenchymal transection line.

The surface markings of the donor liver consisted of a line from a point to the middle of the gallbladder fossa anteriorly and inferiorly/dorsally to the left side of the RHV entry to the vena cava. An 8-mm Penrose drain was passed between the RHV superiorly and the portal bifurcation inferiorly to maintain the cutting plane during parenchymal dissection (hanging maneuver technique) (14).

The initial parenchymal transection line should be same as the standard right-lobe donation. When encountering the MHV or V5 peripherally, the cutting line was modified to the left side of the MHV. Parenchymal transection was continued until the junction of the MHV and left hepatic vein without inflow occlusion. The MHV was transected distal to the common trunk with the left hepatic vein. When the hepatic vein from segment IV (left medial superior vein) had a significant drainage region in the remnant liver as determined by 3D CT volumetry, the proximal side of the MHV and the drainage vein of segment IV to the MHV were preserved in the donor (right lobe with partial MHV graft). Perfusion of the graft was done through

Table 1: Characteristics of 217 Right-Lobe Living-Donor Liver Transplantation With or Without Middle Hepatic Vein

	With MHV (n = 40)	Without MHV (n = 177)	p-value
Donor demographics			
Age (years)	41.3 ± 11.8 (range: 21–61)	40.1 ± 11.4 (range: 19–64)	NS
Weight (kg)	58.5 ± 10.5 (range: 40–80)	63.6 ± 10.9 (range: 42–107)	NS
Operation time (min)	432 ± 74.8 (range: 308–528)	402 ± 82.1 (range: 198–660)	NS
Blood loss (g)	243 ± 217 (range: 25–1030)	239 ± 241 (range: 5–2300)	NS
Blood-type combination (identical: compatible: incompatible)	29:5:6	109:34:34	NS
Recipient demographics			
Sex	Male, 29; female, 11	Male, 83; female, 94	
Age (years)	50.1 ± 12.8 (range: 18–66)	42.9 ± 15.2 (range: 16–69)	NS
Weight (kg)	64.3 ± 13.8 (range: 37.1–99.0)	60.0 ± 11.4 (range: 28.3–96.0)	NS
MELD score*	18.8 ± 7.1 (range: 6–37)	20.5 ± 9.2 (range: 6–54)	NS
Operation profiles			
Cold ischemic time (min)	128 ± 83 (range: 30–372)	99 ± 85 (range: 30–372)	NS
Warm ischemic time (min)	59 ± 16 (range: 27–100)	45 ± 16 (range: 22–114)	<0.001
Operation time (min)	781 ± 200 (range: 400–1415)	730 ± 178 (range: 337–1291)	NS
Blood loss (g)	5977 ± 6776 (range: 320–33 000)	7088 ± 9768 (range: 350–60 000)	NS
Graft weight (g)	678.9 ± 165.2 (range: 445–1270)	699.3 ± 120.9 (range: 425–1080)	NS
GRWR** (%)	1.10 ± 0.26 (range: 0.70–1.70)	1.20 ± 0.28 (range: 0.60–2.40)	NS

*Model for end-stage liver disease.
**Graft-to-recipient weight ratio.

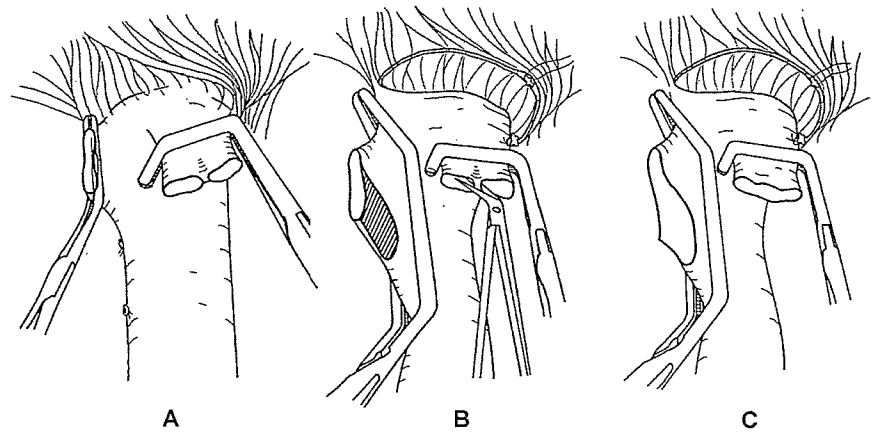


Figure 1: Skeltonization of the inferior vena cava and the hepatic veins to allow adequate spacing for the hepatic vein anastomosis (A,B). The orifice of the RHV was enlarged with a downward incision and an anterior wall excision making an oval orifice to obtain sufficient outflow (B,C).

the right portal vein with a histidine-triptophan-ketoglutarate solution (Dr. Franz Köhler Chemie, Alsbach-Hähnlein, Germany).

Back-table operation

In the case of a right lobe with partial MHV graft, the stump of the MHV was too short to be anastomosed directly to the recipient MHV, and the MHV orifice was not always close enough to the RHV to make a common cuff plasty. The vein graft, i.e. the recipient's portal branch, left portal vein or inferior mesenteric vein or donor's ovarian vein, was prepared according to the size of MHV and was anastomosed as an interposition graft to the MHV stump on the back table (6-0 polypropylene, Prolene, Ethicon, Japan).

Recipient operation

After a total hepatectomy, the top vena cava was freed from its diaphragmatic attachments, by dividing the phrenic veins, and was skeltonized to allow adequate spacing for the hepatic vein anastomosis (Figure 1). During the anhepatic period, a portosystemic shunt was made between the right portal branch and the inferior vena cava (IVC) to prevent portal hypertension in the patients without collaterality. The orifice of the RHV was enlarged with a downward incision and an anterior wall excision making an oval orifice to obtain sufficient outflow. Anastomosis of the RHV was accomplished in an end-to-end fashion with a continuous suture (5-0 Prolene). Significant RIHV was anastomosed to the sidewall of the IVC, the recipient RIHV or the stump of the portosystemic shunt. The interposition vein graft was anastomosed to the recipient's MHV with an interrupted suture in the anterior wall. The patch graft technique was used with an interrupted suture if tension was seen in the anterior wall of the MHV anastomosis. Portal and arterial reconstructions were carried out according to our previous report (15). Biliary reconstruction was carried out with duct-to-duct anastomosis in 36 cases, and with Roux-en-Y hepaticojejunostomy in four cases with 6-0 polydioxanone suture.

Statistical analysis was performed using the generalized Wilcoxon test. Actuarial survival rate was calculated with the nonparametric Kaplan-Meier method and was compared with the Wilcoxon test throughout the study. p-values < 0.02 were considered significant.

The study was approved by the international review board and informed consent was obtained in all the cases.

Results

Donor outcome

A comparison was made between right lobe with MHV grafts from living donors (n = 40) and graft cases without MHV (n = 177).

The median right lobe with MHV graft donor operation time was 420 min (range: 308–528), and median blood loss was 195 g (range: 25–1030). No blood transfusion was given during the donor operation. Four (10%) out of 40 donors experienced complications that required treatment, including two cases of biliary leakage, one of biliary stricture and one of liver failure. Biliary leakage was successfully resolved with percutaneous aspiration. Biliary stricture was treated by reexploration surgery. The liver failure was caused by unsuspected nonalcoholic steatohepatitis and small remnant liver volume. The donor underwent domino liver transplantation, but died from sepsis 9 months after the initial operation (16).

Of 177 donors of a right lobe without MHV graft in our center, duration of the donor operation was 402 ± 82.1 min and blood loss was 239 ± 241 g. There was no significant difference in duration of surgery or blood loss in the donors between right lobe with or without MHV graft operation. Nineteen (10.7%) out of 177 donors experienced complications that required treatment: 14 cases of biliary leakage; 1 of pulmonary embolization; 3 of wound infection and 1 of wound hernia. Nine donors with biliary leakage required endoscopic nasobiliary tube drainage (17).

To evaluate the impact of right-lobe donation, postoperative liver function tests in the donors were analyzed in relation to the type of graft carried out. However, asparate aminotransferase (AST) and serum bilirubin levels showed no significant difference between right-lobe donation either with or without MHV graft (Figure 2).

Recipient outcome

The median recipient operation time for right lobe with MHV graft was 753 min (range: 400–1415), and the median blood loss was 4100 g (range: 320–33 000). The median cold and warm ischemic time was 103 (range: 30–372) and 57 min (range: 27–100). The median graft weight was 675 g (range: 445–1270), and the median GRWR was 1.10% (range: 0.70–1.70%).

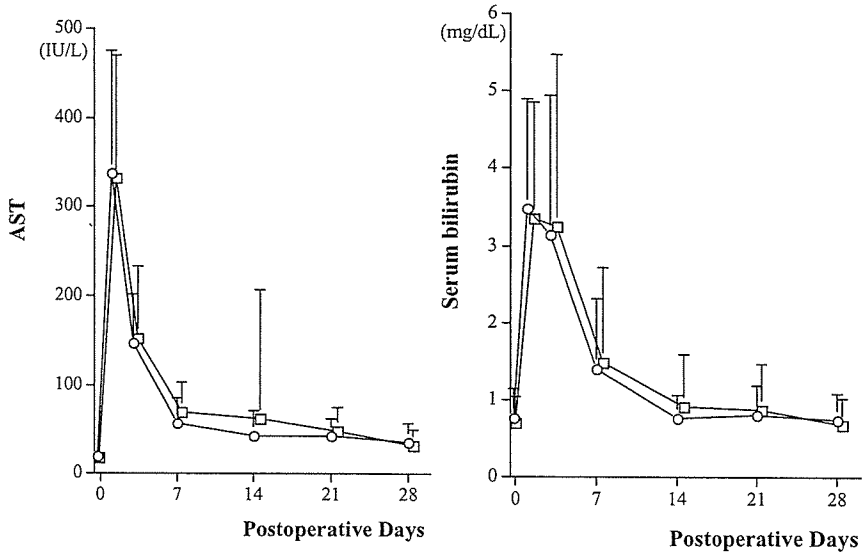


Figure 2: Postoperative liver function tests in the donors. ○: Right lobe with middle hepatic vein graft; □: Right lobe without middle hepatic vein graft.

Among 177 recipients of a right lobe without MHV graft, duration of the recipient operation was 730 ± 178 min and blood loss was 7088 ± 9768 g. The graft weight and GRWR range was 699.3 ± 120.9 g and 1.20 ± 0.28%. The cold and warm ischemic time was 99 ± 85 and 45 ± 16 min, respectively. There was no significant difference in duration of surgery, blood loss and GRWR in the recipients between right lobe either with or without MHV graft. However, the warm ischemic time was significantly longer in the right lobe with MHV graft group ($p < 0.001$).

With regard to liver function tests, there was no significant difference in AST or prothrombin levels between the two groups. Although preoperative serum bilirubin level was significantly lower in the right lobe with MHV graft group ($p < 0.02$), serum bilirubin clearance was much delayed and persistent hyperbilirubinemia was observed in the right lobe without MHV graft group (Figure 3).

Venous reconstruction

With regard to the patients who had right lobe with MHV graft, a direct MHV anastomosis was possible in 12 patients in an end-to-end fashion (30.0%). Of these cases, the common cuff technique of the MHV and RHV in the graft after venoplasty, as reported by Lo et al. (18), was indicated in four. The proximal side of the MHV and the drainage vein of segment IV to the MHV (left medial superior vein) were preserved in 24 donors and a venous interposition graft was necessary in these cases: native portal vein in 19 cases; native inferior mesenteric vein in 2; donor's ovarian vein in 2 and native portal vein patch graft in 1. A Y-shaped portal vein graft was adopted in 13 cases, an I-shaped vein graft in 10 and a patch graft in 1, according to the distance between graft and recipient MHV (Figure 4).

Fourteen RIHV were reconstructed in 13 patients (46.4%). All patients had a patent RHV and MHV anastomosis confirmed by routine Doppler ultrasonography and/or CT/magnetic resonance imaging (MRI) at least 1 month after transplantation. There were no complications related to the hepatic vein anastomosis during the follow-up.

One patient had portal vein thrombosis 19 days after LDLT, and this was successfully treated by reexploration surgery. Two patients developed biliary leakage, which was resolved by percutaneous aspiration. Four cases developed biliary stricture, and this was treated with endosopic retrograde biliary drainage (19). Causes of death were sepsis in one patient, intraabdominal bleeding in one, multiple organ failure secondary to small intestinal perforation in one and severe pneumonia in one. The overall cumulative 3-year graft survival rate of right lobe with MHV graft was 86.2%, with a median follow-up of 18 months (range: 6–36). The cumulative 3-year graft survival rate of 143 right lobe without MHV graft for the same period was 74.8% (Figure 5; $p = 0.38$, NS).

Discussion

Right-lobe LDLT can provide an adequate graft size to compensate for the metabolic demands in most adult recipients, and the clinical outcome has improved in our series (5). One of the controversies in right-lobe LDLT is the potential congestion in the graft anterior segment due to the deprivation of the MHV tributaries. Techniques of venous reconstruction and the graft selection remain an open question.

Our standard technique of harvesting the right-lobe graft requires the transection of the MHV tributaries from the anterior segment to leave the entire MHV in the donor (20,21). To prevent congestion in the anterior segment, several technical modifications were reported. Fang et al. have adopted an extended right-lobe graft with the MHV

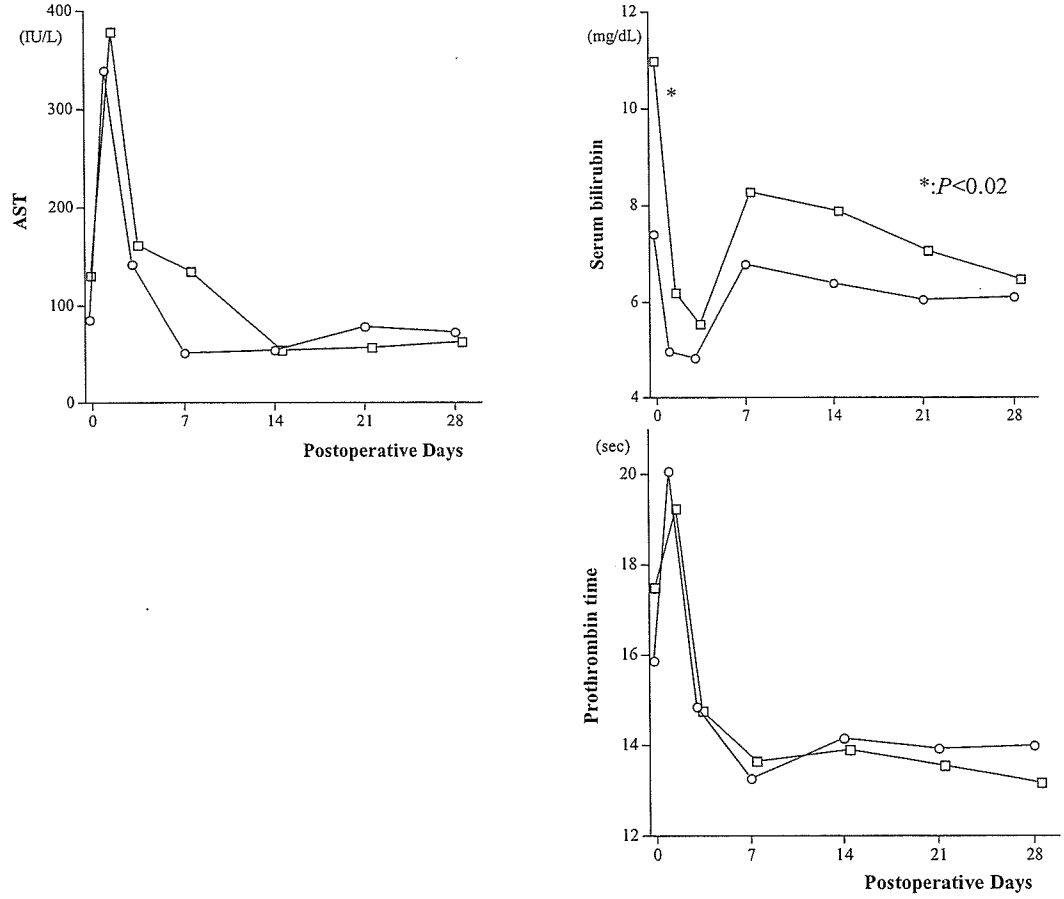
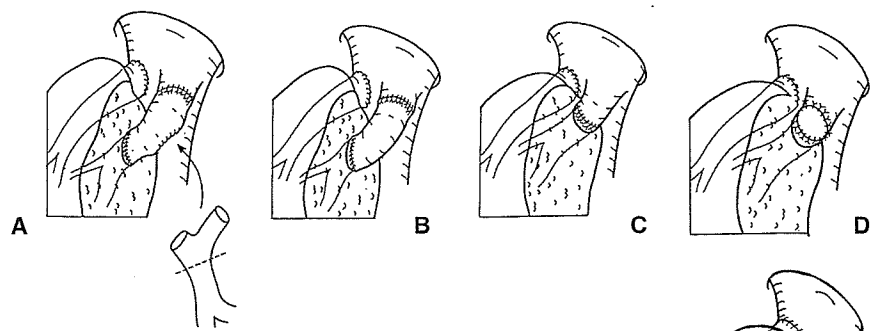


Figure 3: Postoperative liver function tests in the recipients. ○: Right lobe with middle hepatic vein graft; □: Right lobe without middle hepatic vein graft.



- A. Y-shaped portal vein graft (n=13)
- B. I-shaped vein graft (n=10)
- C. Direct anastomosis (n=12)
- D. Patch graft (n=1)
- E. Venoplasty (n=4)

Figure 4: The type of middle hepatic vein anastomosis with/without the use of interposition vein graft. (A) Y-shaped portal vein graft (n = 13), (B) I-shaped vein graft (n = 10), (C) direct anastomosis (n = 12), (D) patch graft (n = 1); and (E) venoplasty (n = 4).

(6,22), and reconstruction of the MHV with an interposition vein graft has also been adopted by the Toronto group (23). Reconstruction of the segment V/VIII branches using jump grafts has been reported both with and without the intraoperative MHV clamp test to confirm graft congestion in some centers (8,24). However, additional venous reconstruction of the anterior segment did not significantly reduce graft congestion defined on MRI despite the patency of reconstructed drainage veins in our previous series (25).

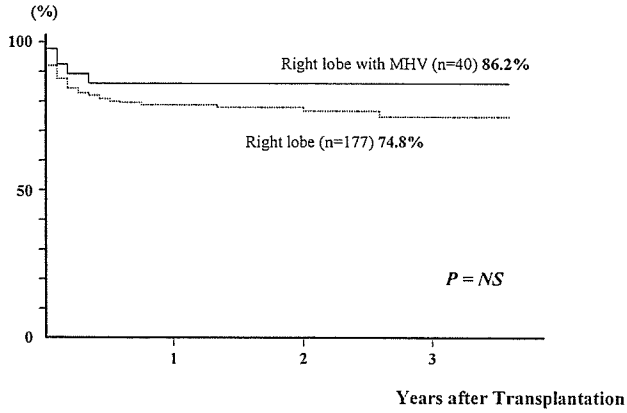


Figure 5: The overall cumulative graft survival rate in right lobe with/without middle hepatic vein.

Based on our previous study, graft congestion in the anterior segment could be well tolerated and improved through intrahepatic anastomosis when the portal and arterial inflow and the RHV outflow were preserved (5,25). Although the regeneration of the posterior segment was shown to be superior to that of the anterior segment, the lack of anterior segment regeneration was resolved by a compensatory regeneration of posterior segment and the graft congestion in the anterior segment did not affect the overall graft regeneration (4). After the initiation of right lobe with MHV graft, however, we experienced some patients who suffered from complications related to 'small-for-size graft'.

Our recent study revealed that right lobe with MHV graft showed no congestion on MRI imaging (26). However, it remains open to question whether or not right lobe with MHV graft should be indicated in all adult recipients. Nakamura et al. suggested that 26.5% of the MHV had proper branches that internally drained from the anterior segment (27). Kinkhabwala et al. reported that 26% of the accessory venous reconstruction from the anterior segment was necessary in right-lobe LDLT (28). We agree with these results that the reconstruction of MHV tributaries was not always necessary and should be indicated according to the preoperative imaging study.

A graft without MHV reconstruction would be given a 'functional liver volume' that corresponded to area drained by the RHV (and RIHV if reconstructed), while a graft with MHV reconstruction would have the anterior segments included in the right-lobe calculation with 3D volumetry. In our preliminary study of 3D CT volumetry in right-lobe LDLT series, the regional volume of V5 and V8 in right lobe was 29.4 ± 11.1% (range: 12.4–56.7%) and 18.0% of the grafts showed MHV dominant (n = 52; data not shown). The importance of drainage vein in the anterior segment could be emphasized in the MHV dominant graft. Moreover, the tolerability of congestion in anterior segment and the compensate regeneration of posterior segment might not be guaranteed in the MHV dominant right-lobe graft. We recommend right lobe with MHV graft or additional vein reconstruction of the anterior segment in the MHV dominant right-lobe graft.

Recently, the Kaohsiung group provided an adequate algorithm for determining the extent of donor hepatectomy in right-lobe LDLT either with or without MHV. The decision to take MHV with the graft was made based on the donor-to-recipient body weight ratio and the size of the MHV tributaries from the anterior segment (29). The initial indication for right lobe with MHV graft in our institution was the GRWR < 1.0% using right-lobe graft. Figure 6 shows our current algorithm for the graft selection after the initial experience of 40 right lobes with MHV LDLTs. The graft selection should be made according to the RHV/MHV dominance, GRWR and remnant liver volume. It is important for avoiding the possibility of anterior segment congestion having information of the MHV dominant before an operation with 3D volumetry. If the graft selection is inconclusive, further discussion should be necessary to secure the recipient benefit as well as donor safety considering the graft quality and metabolic load of the recipient.

The inflow modulation of in 'small-for-size graft' might be an another important issue. Our study showed that elevated portal vein pressure (>20 mmHg) is strongly associated with poor patient survival attributable to 'small-for-size syndrome'. Further elucidation of the pathogenesis behind this phenomenon and efforts to modify portal vein pressure will be a key to improving results (30). Moreover, our recent study suggested that partial diversion of portal flow to systemic circulation and splenic artery ligation might be effective for avoiding injuries that occur in 'small-for-size graft' (31). The same technical modification was adopted in some centers in order to avoid graft congestion and failure by portal overperfusion (32,33). The decrease of portal vein pressure may be able to be used as an effective method to attenuate the 'small-for-size syndrome'. Further discussion about portocaval shunt and splenic artery ligation should be necessary to make a conclusion for the graft selection in right-lobe LDLT.

In determining whether a donor can provide adequate liver volume at acceptable risks, it is important to know not just the remnant liver volume but also the anatomical factors that may affect the functional capacity of the donor remnant liver. It was reported that 9.5% of patients had a left medial superior vein originating from the MHV and draining predominantly the left medial superior segment (27). The impairment of regeneration and functional recovery of segment IV after right lobectomy with MHV has been reported, while the overall regeneration of the remnant liver was not affected by the MVH harvesting in right-lobe LDLT (34).

The mean regional volume of the left medial superior vein in 3D CT evaluation was 159.3 ± 28.8 mL and the

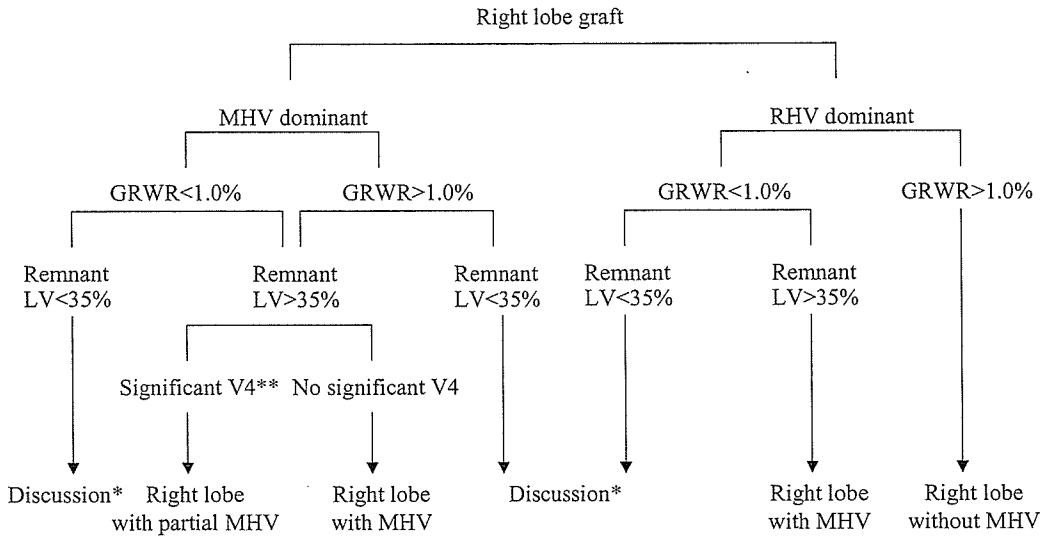


Figure 6: Algorithm for the graft selection. RHV: right hepatic vein; MHV: middle hepatic vein; GRWR: graft-to-recipient weight ratio; LV: liver volume. RHV dominant: regional volume of vein 5 + vein 8/right-lobe volume × 100 < 40% MHV dominant: regional volume of vein 5 + vein 8/right-lobe volume × 100 > 40% *Discussion for; additional vein reconstruction of V5/8, dual graft, auxiliary liver transplantation, ligation of splenic artery and/or partial portocaval shunt, exclude from potential donor candidate **V4: drainage vein of segment IV to the MHV (left medial superior vein).

percentage of the regional volume of left medial superior vein in remnant liver was 40.5 ± 8.0% (range: 27.9–49.9%) in our series (n = 52, data not shown). To obtain more evidence of the segment IV drainage vein and RIHV, a further study of '3D volumetric analysis' is now underway in order to clarify the exact role of these drainage veins. Evaluation of the regional volume of the left medial superior vein is important for the donor safety.

If the regional volume of the left medial superior vein was significant, then the proximal side of the MHV and the left medial superior vein were preserved in the donor, given that the MHV was divided at the side proximal to the left medial superior vein. If the remnant liver volume was revealed to be less than 35% of the whole liver volume, the potential donor was excluded and another donor candidate or option was considered, such as auxiliary liver transplantation, dual liver transplantation and additional vein of the anterior segment reconstruction (35–37).

Manner of the MHV reconstruction is controversial. It was reported that 7.6% of MHV anastomoses were found to be occluded intraoperatively even in an experienced center (22). Direct end-to-end MHV reconstruction was possible in 40.0% of the patients with entire MHV graft. Skeltonization of the IVC and the hepatic veins are important to allow adequate spacing for the hepatic vein anastomosis. In the case of a MHV divided proximal to the left medial superior vein, vein graft should be used to prevent torsion and tension in the anastomosis, as the MHV is considered too short for safe anastomosis. Recently, the common cuff of the MHV and RHV in the graft after venoplasty has been reported (18). While it is an excellent technique, reconstruction of the outflow of the RHV and distal part of the MHV into a single opening may not be possible if their orifices are far apart, and both may need to be implanted separately into the recipient IVC.

In conclusion, we adopted right lobe with MHV graft in 40 LDLT cases. Although no significant differences were revealed in the donor and recipient liver function tests nor in patient survival between right-lobe LDLT with or without MHV, right lobe with MHV graft should be indicated in very selected patients according to algorithm for the graft selection paying special attention to donor safety. It is hoped that as experience increases and refinements are made to the technique, improved outcomes in right-lobe LDLT will be seen.

Acknowledgment

This work was supported in part by grants from the Scientific Research Fund of the Ministry of Education and by a Research Grant for Immunology, Allergy and Organ Transplant from the Ministry of Health, Labor and Welfare, Japan.

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American Journal of Transplantation 2005; 5: 2754–2763
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2005.01084.x

Living Donor Liver Transplantation for Pediatric Patients with Inheritable Metabolic Disorders

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Forty-six pediatric patients who underwent living donor liver transplantation (LDLT) using parental liver grafts for inheritable metabolic disorders (IMD) were evaluated to determine the outcomes of the surgery, decisive factors for post-transplant patient survival and the impact of using donors who were heterozygous for the particular disorder. Disorders included Wilson disease (WD, n = 21), ornithine transcarbamylase deficiency (OTCD, n = 6), tyrosinemia type I (TTI, n = 6), glycogen storage disease (GSD, n = 4), propionic acidemia (PPA, n = 3), methylmalonic acidemia (MMA, n = 2), Crigler-Najjar syndrome type I (CNSI, n = 2), bile acid synthetic defect (BASD, n = 1) and erythropoietic protoporphyria (EPP, n = 1). The post-transplant cumulative patient survival rates were 86.8 and 81.2% at 1 and 5 years, respectively. Post-transplant patient survival and recovery of the growth retardation were significantly better in the liver-oriented diseases (WD, OTCD, TTI, CNSI and BASD) than in the non-liver-oriented diseases (GSD, PPA, MMA and EPP) and pre-transplant growth retardation disadvantageously affected post-transplant outcomes. Although 40 of 46 donors were considered heterozygous for each disorder, neither mortality nor morbidity related to the heterozygosis has been observed. LDLT using parental donors can be recommended as an effective treatment for pediatric patients with IMD. In the non-liver-oriented diseases, however, satisfactory outcomes were not obtained by hepatic replacement alone.

Key words: Donor selection, heterozygous carrier, mode of inheritance

Received 13 May 2005, revised 12 July 2005 and accepted for publication 27 July 2005

Introduction

The use of liver transplantation (LT) has steadily increased, including for the treatment of some inborn metabolic deficiencies, irrespective of whether the liver is predominantly or only partly involved in disorder (1, 2). In some cases, however, there is a shortage of deceased donor organs and a living donor who is heterozygous for the disorder in question must be employed (3, 4). In pediatric cases of autosomal recessive disorder in particular, the donor is almost always a heterozygote because a parent is usually employed in such cases.

Between June 1990 and December 2003, 578 pediatric patients (aged less than 18 years) underwent initial living donor liver transplantation (LDLT) at Kyoto University Hospital. Of these 578, 46 underwent an LDLT using parental liver grafts for inheritable metabolic disorders (IMD). Although 24 of these cases have previously been reported (3–7), all were evaluated in the present study in order to determine their LDLT outcomes and decisive factors for post-transplant patient survival, and to clarify the impact of the use of heterozygous donors on both donors and recipients.

Patients and Methods

Forty-six pediatric patients with IMD indicated for LDLT at Kyoto University were examined in the present study. These included patients with Wilson disease (WD, n = 21; cirrhosis, 14; fulminant-type, 7), ornithine transcarbamylase deficiency (OTCD, n = 6), tyrosinemia type I (TTI, n = 6), glycogen storage disease (GSD, n = 4; type Ib, 1; type IV, 3), propionic acidemia (PPA, n = 3), Crigler-Najjar syndrome type I (CNSI, n = 2), methylmalonic acidemia (MMA, n = 2), bile acid synthetic defect of the liver (BASD, n = 1) and erythropoietic protoporphyria (EPP, n = 1) (Figure 1). Clinical records of these patients were reviewed to collect the following data: age at onset, gender, time from onset to LDLT, pre-transplant status (at home, in wards and in the intensive care unit (ICU)), the presence and degree of neurological impairments and growth retardation evaluated at the time of LDLT, ABO-blood-type matching, graft types, mode of operative procedure (auxiliary partial orthotopic liver transplantation (APOLT) or not), graft-to-recipient weight ratio (GRWR) calculated by the following formula: ((graft weight weighed after flushing the preservation solution (g)/ patient's body weight (g)) × 100 (%)), survival outcomes and neurological status, physical

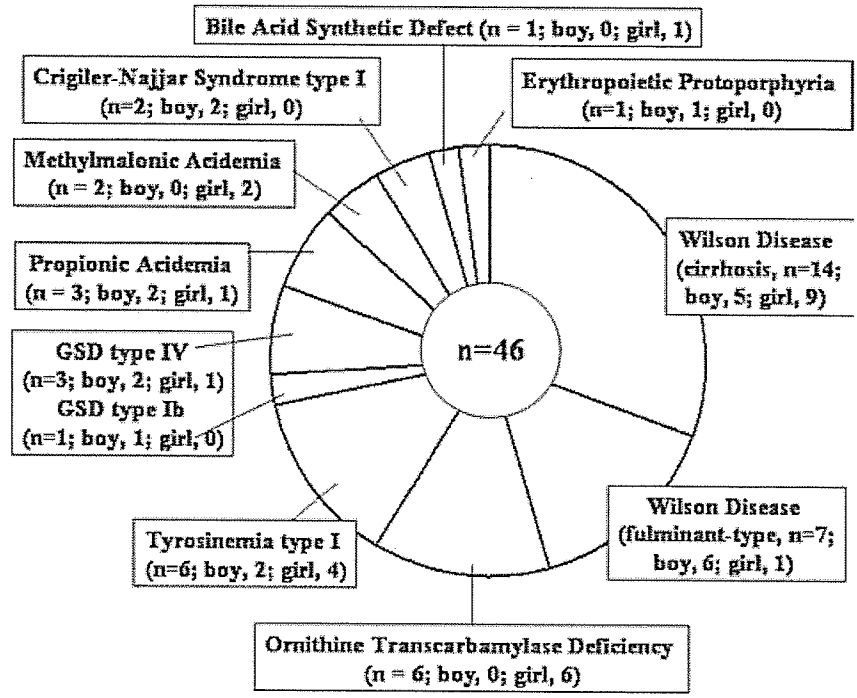

Figure 1: Indications for living donor liver transplantation of 46 pediatric patients with inheritable metabolic disorders at Kyoto University.

growth and quality of life at the latest evaluations. Neurological status was evaluated by a grading scale based on that of Whitington et al. (8) with minor modifications, as shown in Table 1. Physical growth was evaluated by comparing the weight and height of each patient with those in the standard growth curve and is expressed as a multiple of the standard deviation (SD) of the deviation from the standard curve. Growth data were classified into three subgroups, as shown in Table 1. Quality of life was classified into four subgroups also as shown in Table 1.

To clarify decisive factors for post-transplant patient survival, correlations among survival outcomes, whether each disorder predominantly involved the liver (liver-oriented disease group, LOD: WD, OTCD, TTI, CNSI and BASD; n = 36) or partly involved the liver (non-liver-oriented disease group, NLOD: GSD, PPA, MMA and EPP; n = 10), physical growth at the time of LDLT and graft-size matching evaluated by GRWR were investigated.

Whether or not each donor was a heterozygote for the recipient's disorder was determined by the mode of inheritance of each disorder (autosomal recessive inheritance for WD (3), TTI (9), GSD (10), PPA (4), MMA (4), CNSI (4) and BASD (11), autosomal dominant for EPP (12) and X-linked for OTCD (4)). In addition to our standard donor selection criteria, which have been described in detail elsewhere (13,14), some donors who were considered or suspected to be heterozygous carriers for their respective recipient's disorder underwent the following additional medical tests according to the disorder in question: for WD cases, assays for serum ceruloplasmin levels, urine copper excretion and the presence of Kayser-Fleischer corneal ring; for OTCD cases, quantitative serum amino acid analysis (QAAA) and allopurinol loading test (15,16); and for cases of PPA or MMA, serum propionic acid or methylmalonate level and the presence of metabolic acidosis confirmed by blood gas analysis. These additional tests were conducted periodically in the post-transplant period for each heterozygous carrier and each recipient of a heterozygous liver in order to study mortality or morbidity in relation to the use of heterozygous donors. Furthermore, in donor candidates for OTCD patients who showed abnormal findings in the QAAA and/or allopurinol loading test, genetic assay using peripheral blood leukocytes (17) was performed in order to confirm whether or not there were mutations in Xp21, where the ornithine transcarbamylase (OTC) gene lies. We performed genetic assay only for OTCD donors because the presentation of male hemizygotes or female heterozygotes for OTCD can range in severity from fatal neonatal hyperammonaemic coma to asymptomatic adults. Thus, we believe that such individuals require close medical vigilance for the onset of OTCD. With regard to the other autosomal recessive disorders, including the TTI, GSD, CNSI and BASD, no additional examination was performed. For all donors, the recipient's disorder, relationship of the donor to the recipient, donor age, mode of donor hepatectomy, resection rate of the donor hepatectomy calculated from the following equation: (actual graft weight weighed as stated above (g))/ (total liver volume calculated from preoperative computed tomography (CT) volumetry (mL) x 100(%) and immediate and long-term postoperative course were reviewed. In order to determine whether postoperative morbidities were related to the use of heterozygote donors, recipients of heterozygous livers were accompanied by their donors or other family members during follow-up and were asked about their pre-transplant symptoms. Heterozygous donors and other family members were also asked if they suffered symptoms similar to those of the recipients.

Follow-up was continued until January 2005 or death for both donors and recipients.

SPSS commercial statistics software was used for all statistical analyses (SPSS 12.0 for Windows; SPSS, Chicago, IL, USA). Survival was evaluated by the Kaplan-Meier life table analysis with the Breslow-Gehan-Wilcoxon test. Other variables were evaluated in a non-parametric manner. Values were shown as the median (range). The p-values of less than 0.05 were considered to be significant.

Results

Outcomes of LDLT

Seventeen of 46 patients were admitted to the ICU in the pre-transplant period: four of these 17 were admitted to

Table 1: Grading scale for evaluating neurological status and classification of physical growth and quality of life

Grading scale for evaluating neurological status
Grade 0: Seems to be normal spectrum for social interaction, motor skills, language development and learning
Grade 1: Good social interaction, full ambulation but perhaps partially impaired gross and fine motor skills, use of language, mildly delayed development, only modest learning deficits
Grade 2: Definite social interaction, fair ambulation, though possibly limited by spasticity
Grade 3: Limited social interaction, no bipedal ambulation, limited communication through gestures
Grade 4: Responds to noxious stimuli, but no social interaction, no ambulation, no communication
Grade 5: Persistent coma or vegetative state
Classification of physical growth
Normal: More than −1SD* in height
Slightly delayed: More than −2SD* and equal to or less than −1SD* in height
Delayed: Equal to or less than −2SD* in height
Classification of quality of life
Excellent: Neurological status corresponding to a score of 0 on the above scale, and receiving none of or one immunosuppressive drug and no metabolism correcting drugs
Good: Neurological status corresponding to a score of 0 on the above scale, and receiving 2 or 3 immunosuppressive drugs and/or metabolism correcting drugs
Fair: Neurological status corresponding to a score of 1 or 2 on the above scale, irrespective of any medication
Poor: Neurological status corresponding to a score of 3 or more, irrespective of any medication

*Physical growth was evaluated by comparing the weight and height of each patient with those in the standard growth curve, and was expressed as a multiple of the standard deviation (SD) of the deviation from the standard curve.

Table 2: Patients' characteristics

Patients' backgrounds	
Age at the onset (months)	48.6 (0–196)
Gender (Boy/ Girl)	21/ 25
Time from onset to LDLT* (months)	3.9 (0.3–181)
Age at LDLT* (months)	86.5 (1.4–199)
Pre-transplant status	
At home/ in wards/ in the ICU†	11/18/17
Pre-transplant status of physical growth‡	
Height	−0.35SD§ (−9.0SD§ to +3.4SD§)
Weight	−0.40SD§ (−9.0SD§ to +3.1SD§)
Delayed/slightly delayed/normal	16/2/28
Pre-transplant neurological status	
Grade 0/1/2/3/4/5	26/6/9/4/3/1
APOLT¶/total hepatic replacement	3/43
Donors for initial LDLT*	
Father/mother/stepfather	22/23/1
ABO blood type combination (Identical/compatible/incompatible)	26/13/7
Heterozygote/non-heterozygote	40/6
Graft liver (LLS**/LL††/RL‡‡)	25/17/4
GRWR§§ (%)	1.35 (0.61–9.68)

*Living donor liver transplantation; †intensive care unit; ‡represented in how far from the standard growth curve expressed as a multiple of the standard deviation; §standard deviation; evaluated by the grading scale as shown in Table 1; ¶auxiliary partial orthotopic liver transplantation; **left lateral section liver graft (segments II–III according to the Couinaud's nomenclature for liver segmentations); ††left liver graft (segments II–IV); ‡‡right liver graft (segments V–VIII); §§graft-to-recipient weight ratio.

the ICU for severe pre-transplant neurological impairments necessitating artificial ventilator support and the other 13 required intensive care due to severe worsening of their general condition arising from symptoms of hepatic failure other than neurological impairments (Table 2). The disorders of patients who required artificial ventilator support because of severe neurological impairments corresponding to a score of 4 or 5 on the grading scale described above were OTCD in two cases, fulminant-type WD in one and cirrhosis of WD in one. Marked pre-transplant growth retardation was observed in 16 patients; in 15 of these 16, disease onset was in early infancy. Seven of these 46 patients received ABO-incompatible liver grafts. There were 10 postoperative deaths during this study period. Six of the 10 deaths were hospital mortalities (defined as mortalities occurring during the recuperative hospital stay following the LDLT). The other four were observed during the long-term follow-up and two of these four deaths were unrelated to either the original diseases or the LDLT procedure (Table 3). Although the cause of mortality was related to biliary complications in three of the 10 patients who died (Table 3), three other patients suffering from biliary complications (anastomotic leakage in one patient and anastomotic stricture in 2) were managed with surgical and/or radiological intervention and achieved recovery. Several other postoperative surgical complications including hemoperitoneum in one patient, hepatic venous stenosis in two and portal venous stenosis in one were observed, but all of these patients also recovered after surgical and/or radiological intervention. A second LDLT was required for two patients. One of these cases was a 3-year and 8-month-old boy with GSD type IV (Table 3), who underwent initial LDLT using a maternal ABO-incompatible liver graft, which resulted in graft failure due to antibody-mediated rejection (18) arising from the ABO-incompatibility and was replaced by a paternal ABO-incompatible liver graft 6.2 months after the initial LDLT; unfortunately, the boy died of sepsis a month after the second LDLT. The other case was a 13-year-7-month-old girl who underwent an initial LDLT with a maternal ABO-compatible liver graft for cirrhosis due to WD; whereas this initial graft failed due to chronic portal vein thrombosis 126 months after the initial LDLT and was replaced by a paternal ABO-incompatible liver graft. The patient is currently doing well at 16.6 months after the second LDLT. Thirty-five of the 36 surviving patients currently show a normal neurological status

Table 3: Details of the 10 dead patients

Phase of mortality	Disease	Gender	Age at LDLT* (yr, mo)	Time from onset to LDLT* (months)	Cause of mortality	Duration of survival after LDLT* (months)
Hospital mortalities	Tyrosinemia type I	Girl	0y 4m	3.1	Severe graft congestion due to remarkable imbalance between body and graft sizes (GRWR† = 9.68%)	0.6
	GSD‡ type Ib	Boy	13y 2m	156	Systemic candidasis	1.4
	GSD‡ type IV	Boy	3y 8m	33.3	Antibody-mediated rejection due to the use of ABO-incompatible liver graft	7.2
	MMA§	Girl	1y 1m	12.3	Intra-abdominal infection due to major biliary anastomotic leakage	0.5
	MMA§	Girl	12y 2m	146	Aspergillosis	2.2
	Protoporphyria	Boy	15y 6m	84.3	Major biliary anastomotic leakage and candidasis	3.3
Late deaths	WD¶ (fulminant-type)	Boy	16y 6m	2.8	Chronic cholangitis due to biliary anastomotic stricture	50.7
	OTCD#	Girl	7y 2m	14.1	Died in a traffic accident	4.2
	Tyrosinemia type I	Girl	0y 3m	3.0	Died in a traffic accident	18.9
	BASD**	Girl	0y 9m	8.0	Hemolytic ureic syndrome caused by Escherichia coli infection	5.4

*Living donor liver transplantation; †graft-to-recipient weight ration; ‡glycogen storage disease; §methylmalonic acidemia; ¶Wilson disease; #ornithine transcarbamylase deficiency; **bile acid synthetic defect of the liver.

corresponding to a score of 0 on our grading scale. Only one patient, a 13-year-8-month-old boy with fulminant-type WD, in whom the neurological status just before LDLT corresponded to a score of 5 on our grading scale and in whom emergency LDLT using a liver graft from his stepfather was carried out, continues to show neurological impairments pertaining to a score of 3 on our grading scale at 63.7 months after LDLT. Taking these results together, the post-transplant cumulative patient survival rates were 86.9% at 1 year and 81.2% both at 5 and 10 years (Figure 2).

Decisive factors for post-transplant patient survival and evaluation of post-transplant physical growth and quality of life

Post-transplant cumulative patient survival rates were significantly better in the LOD group than in the NLOD group (Figure 3). Furthermore, post-transplant cumulative patient survival rates of patients with normal physical growth or slightly delayed physical growth at the time of LDLT were significantly higher than that of patients with delayed physical growth at the time of LDLT (Figure 4). In addition, physical growth, represented by the deviation from the standard growth curve at the time of LDLT, was significantly correlated with both the age of onset of each disorder and the time from onset to LDLT (Figure 5). Specifically, the earlier the age of onset or the longer the time from onset to LDLT in each patient, the worse the retardation of growth. An ICU-stay during the pre-transplant period did not affect post-transplant cumulative patient survival (Figure 6). Although graft-size matching was not significantly correlated with post-transplant cumulative patient survival rates, the post-transplant survival of patients with GRWR $\geq$ 4.0 tended to be worse than those of other patient groups (Figure 7). The age at onset of each disorder, time from onset to LDLT and physical growth evaluated at the time of LDLT were significantly younger, longer and more inhibited in the NLOD group than in the LOD group, respectively (Table 4). With regards to the 36 surviving patients, a comparison of physical growth and quality of life at the latest evaluations between patients with LOD and those with NLOD showed that physical growth was significantly better in the LOD group than in the NLOD group, whereas quality of life was similar between the two groups (Table 5). Concerning the quality of life, an excellent or good quality of life has been maintained in all surviving patients, irrespective of whether belonged to the LOD or NLOD group, with the single exception of a patient with fulminant-type WD who continues to show neurological impairments corresponding to a score of 3 on our grading scale, as stated above. With regard to the six patients in whom quality of life was determined to be not excellent but good (Table 5), all of these patients are still taking two or more immunosuppressive and/or metabolism correcting drugs. Two patients who underwent LDLT for WD developed de novo autoimmune hepatitis (19), at 18.6 months after LDLT and 87.6 months after LDLT and both of these patients are still receiving three immunosuppressive drugs (a calcineurin inhibitor (CI), azathiopurine and prednisolone), at 38.0 months and 89.6 months after LDLT, respectively. One patient who underwent LDLT for WD is still receiving CI and mycophenolate mofetil at 24.4 months after LDLT

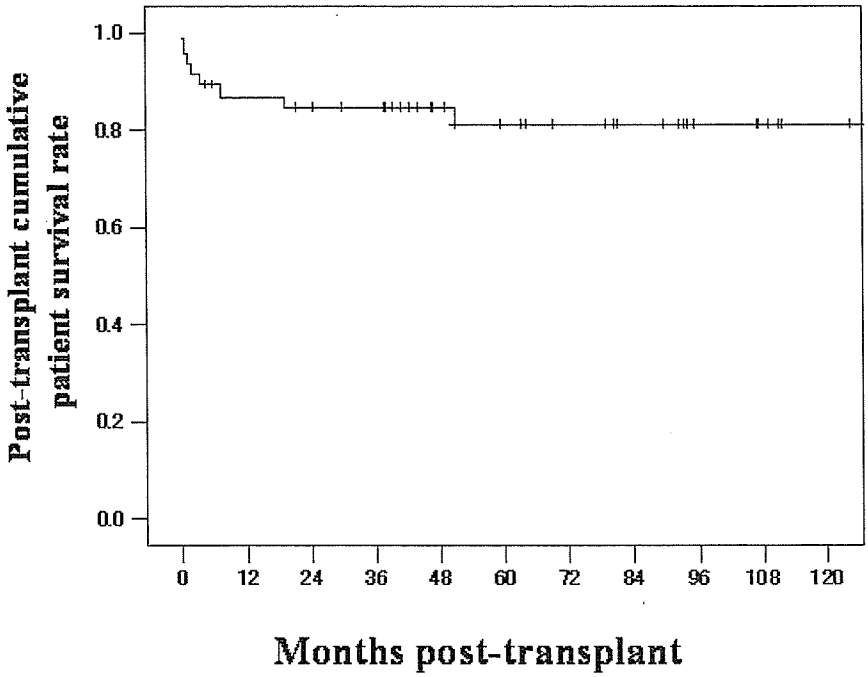

Figure 2: Cumulative post-transplant patient survival rates of living donor liver transplantation for 46 pediatric patients with inheritable metabolic disorders. Post-transplant survival of patients who underwent living donor liver transplantation for inheritable metabolic disorders at Kyoto University resulted in cumulative patient survival rates of 86.9% at 1 year and 81.2% both at 5 and 10 years.

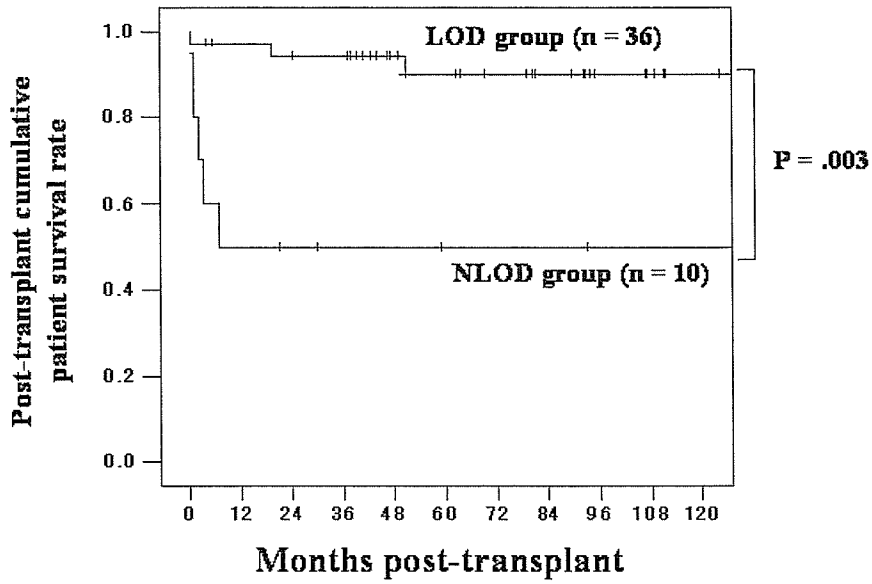

Figure 3: Comparison of post-transplant survival between liver-oriented diseases (LOD) and non-liver-oriented diseases (NLOD) groups. Post-transplant cumulative patient survival rate was significantly higher in patients with LOD than in those with NLOD.

because of mild but refractory acute cellular rejection. The other three patients, all of whom underwent LDLT for PPA, are still receiving CI and carnithine supplementation (6) at 59.3 months, 29.9 months and 21.2 months after LDLT, respectively.

Impact of the use of heterozygous donor

In addition to the 46 donors for initial LDLT, two donors were employed for a second LDLT, as stated above. Both were fathers of patients with autosomal recessive disorders. A preoperative QAAA and allopurinol loading test were performed for the six parental donors of the girls with OTCD. The former analysis revealed normal QAAA profiles in all six parents. The latter test yielded no abnormal findings in the four fathers, but the two mothers had almost twice normal upper values of peak urine orotic acid and orothidine levels after the allopurinol loading. These results suggest that these four fathers were not hemizygotes for OTCD, whereas these two mothers were determined to be heterozygotes for OTCD. As a result, 42 of the 48 donors were heterozygous carriers for the patients' disorders and the other six were non-heterozygotes. No significant differences suggesting the deleterious effects of use of the heterozygous donors on donors' postoperative course were observed between the heterozygote donors and non-heterozygote donors (Table 6). One

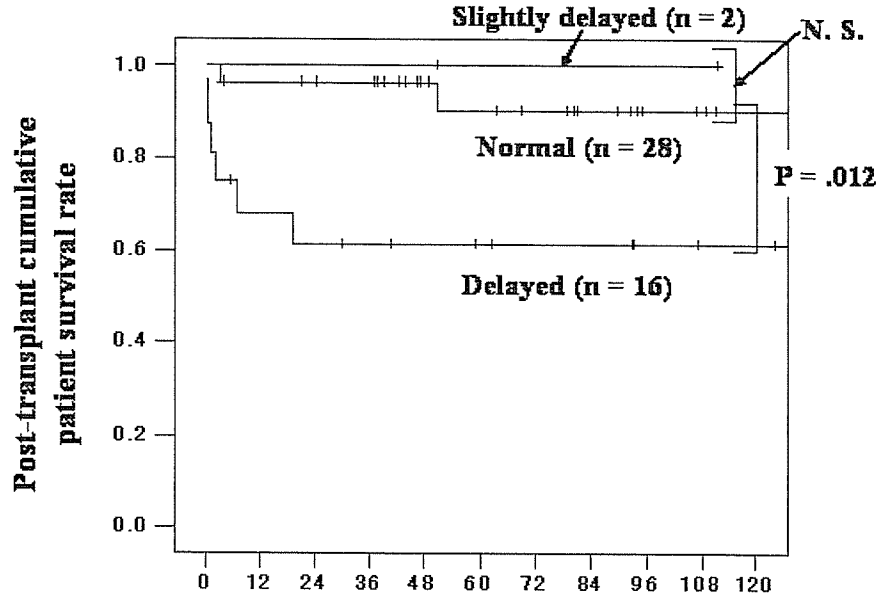

Figure 4: Comparison of post-transplant survival among three classifications of physical growth (normal, slightly delayed and delayed) at the time of living donor liver transplantation (LDLT). Post-transplant cumulative patient survival rates of patients with normal physical growth or slightly delayed physical growth at the time of LDLT were significantly higher than that of patients with delayed physical growth at the time of LDLT.

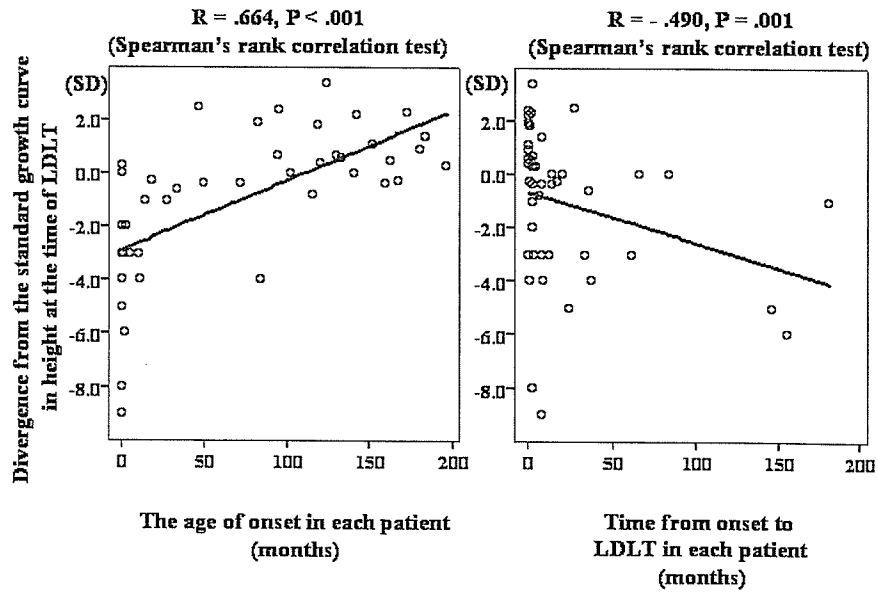

Figure 5: Correlation between physical growth and the age at onset of each disorder or time from onset to living donor liver transplantation (LDLT) in each patient. Physical growth represented in how far form the standard growth curve expressed as a multiple of the standard deviation (SD) at the time of LDLT was significantly correlated with both the age of onset of each disorder and the time from onset to LDLT. Namely, the earlier the age of onset in each patient was or the longer the time from onset to LDLT was, the worse the growth retardation was.

maternal donor, 37 years of age, of a patient who underwent LDLT for WD underwent right hepatectomy, for which resection rate was 61.2% and developed postoperative bile leakage from the cut surface of the liver remnant, which necessitated biliary decompression with the use of endoscopic retrograde nasal biliary drainage. Although the bile leakage was refractory and necessitated a prolonged hospital stay of 59 days before the donor was considered cured, the leakage did not lead to serious difficulties and the donor is currently doing well at 48.2 months after LDLT without any other complications. Two maternal donors of girls with OTCD, both of whom were determined to be heterozygous for OTCD as stated above, were genetically confirmed to have mutations in Xp21, where the OTC gene lies (4), but showed normal OTC activity in liver tissues extracted during donor surgery. No genetic assay was performed in the other 40 heterozygous donors, because the usefulness of genetic evaluations for disorders other than OTCD was considered uncertain at the time of LDLT. Regardless of whether or not they were heterozygotes, no major complications have been observed in any donors. All 48 donors are currently doing well.

Additional specific medical tests for heterozygous donors and recipients of heterozygous livers of the WD, OTCD, PPA and MMA cases have shown no problematic findings. Namely, all donors of WD cases have shown normal serum ceruloplasmin levels and undetectable levels of