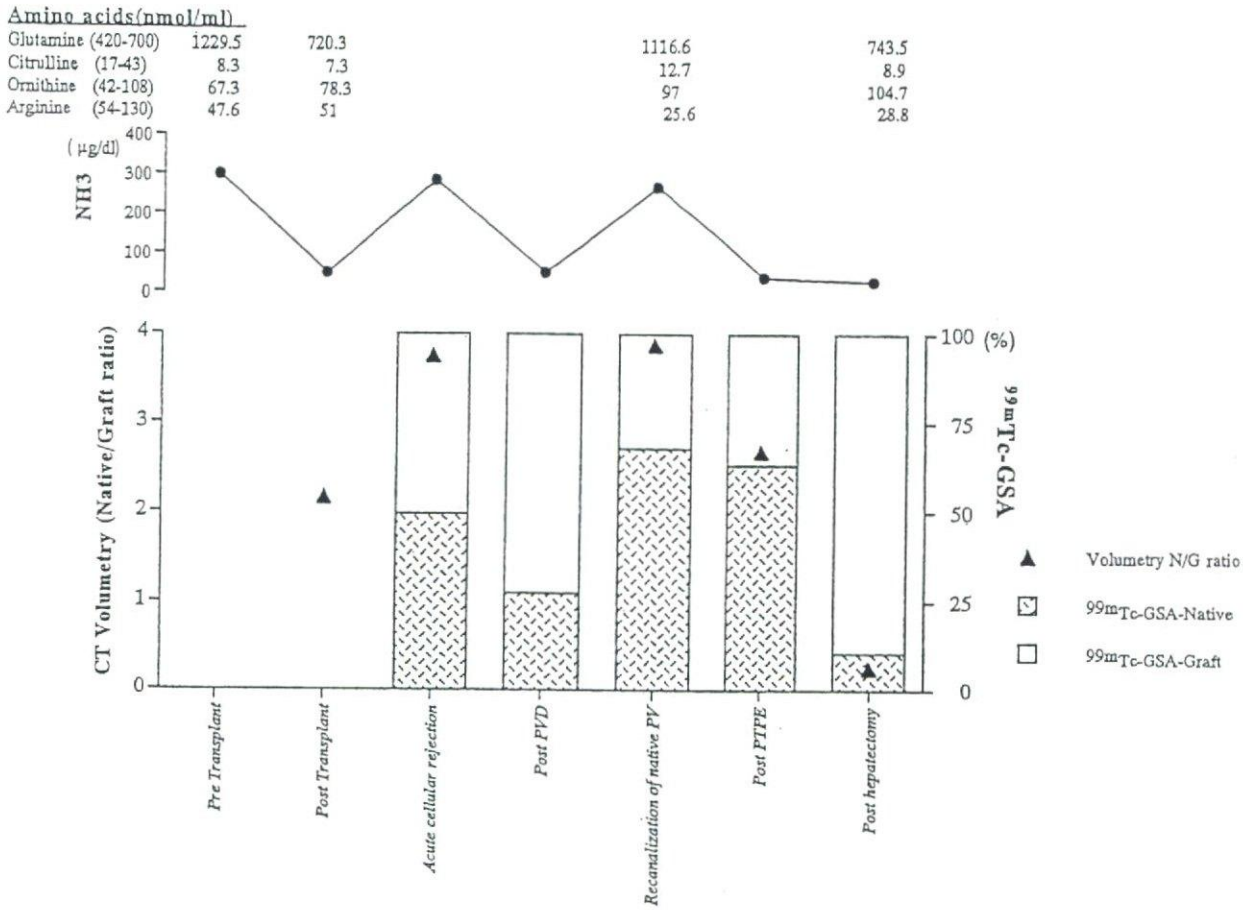

Fig 2. Changes of the native and graft liver in CT volumetry and ^{99m}Tc-GSA scintigraphy evaluation.

(native to graft liver ratio, 0.25; Fig 1B). A ^{99m}Tc-GSA scintigraphy study showed the uptake in the graft versus native caudate lobe to be 89.5:10.5%. During an 18-month follow-up, the patient has been doing well without an episode of relapsed hyperammonemia and protein restriction or additional medication for the metabolic disorder.

DISCUSSION

We have performed 6 cases of APOLT for noncirrhotic metabolic liver disease (citrullinemia in 3, OTCD in 2, Crigler-Najjar syndrome type I in 1) in our 940 LDLT series. One of the problems of APOLT is functional portal flow competition between the graft and native liver. To obtain a sufficient demand for metabolic correction of the original disease, an adequate functional graft volume is necessary. Adequate volume of the functional hepatocyte is different for each liver disease and type of native hepatectomy to correct the original liver disease, because there are several variations of enzyme activity in the native liver segments.[4] We used CT volumetry and ^{99m}Tc-GSA scintigraphy in APOLT cases to evaluate the anatomic and functional volume in the graft and native liver. Figure 2 shows the changes in CT volumetry and ^{99m}Tc-GSA scintigraphy after APOLT. The anatomic volume of the graft might not always be relevant to functional volume. Subsequent CT volumety and ^{99m}Tc-GSA scintigraphy are useful to evaluate anatomic and functional liver volume after APOLT.

After APOLT, the graft showed severe rejection and shrank quickly. The remnant native liver had grown enough to take over the function of the graft in this case. Even after successful treatment of the rejection, the graft liver lost the portal blood flow to the native liver. The graft liver had difficulty increasing its volume again because it already lost much of the portal blood flow to the native side.[8]

After native PVD, the graft volume increased properly and was shown to have acceptable metabolic function. In our previous study, the resistance of portal venous inflow in the graft liver was higher than the native liver after APOLT,[10] and the dominant portal venous flow to the native liver could be observed readily in the event of severe rejection. After the experience of the current case, we changed the standard procedure for APOLT of noncirrhotic metabolic liver disease, meaning we indicated that the native PVD in all subsequent cases and the graft

liver received the entire portal venous flow. The native liver was supplied by arterial blood flow.

There will be a concern about dysfunction of the remnant native liver after PVD, which may negate the support of a patient's life and the possibility of future gene therapy. However, it was reported that occluded portal flow induces hepatocyte apoptosis rather than necrosis in the embolized lobe without changing the functional efficiency of hepatocyte.[11,12] The remnant native liver may sustain the recipient's life if the native portal vein is transected.

PVD is an effective technique to induce graft regeneration and to avoid functional portal flow competition. An unexpected event in this case was the recanalization of the native portal flow through cavernous transformation after PVD. Subsequent Doppler echography is important to evaluate the native portal flow after PVD. We performed PTPE for the native liver to obtain sufficient regeneration of the graft liver, because the GRWR was not sufficient to sustain the patient's metabolic demand after native right hepatectomy. PTPE also effectively increased both the volume and functional capacity of the transplanted graft liver in this case.

PVD for APOLT for noncirrhotic metabolic liver disease patients effectively prevents functional portal flow competition. A postoperative CT scan and ^{99m}Tc-GSA scintigraphy were useful to evaluate functional and anatomic liver volume after APOLT. Evaluation of the functional volume of the graft is important because it is often dissociated from anatomic volume.

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End-to-Side Portocaval Shunting for a Small-for-Size Graft in Living Donor Liver Transplantation

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In the development of adult-to-adult living donor liver transplantation (LDLT), the small-for-size graft has been associated with poor clinical outcome. Persistent portal hypertension or portal venous overperfusion are considered to be causative factors, and partial diversion of portal flow to systemic circulation may be effective for avoiding injuries that occur in the small-for-size (SFS) graft. Recently, we constructed an end-to-side portocaval shunting using 1 of the portal branches and anastomosed the other branch with the portal vein of the graft in 2 cases of LDLT recipients transplanted with a SFS graft. With the suppression of portal hypertension, as well as sufficient portal flow to the graft, the recipients recovered successfully with favorable graft function. This new and simple technique may be able to be used as a feasible and effective method to attenuate the SFS syndrome. (*Liver Transpl 2004;10:807–810.*)

Living donor liver transplantation (LDLT) was initiated in pediatric patients to decrease mortality among patients on the cadaveric donor liver waiting list.[1] With excellent patient and graft survival, encouraging results in pediatric LDLT have led to the development of an adult-to-adult LDLT program. As the number of adult LDLTs performed has been increasing, it has been clarified that the size of the graft liver is associated with the clinical outcome. In our previous report,[2] when the graft-to-recipient weight ratio (GRWR) was less than 0.8%, the graft survival rate was significantly worse than with larger grafts. The clinical manifestations, referred to as the small-for-size (SFS) syndrome, consist of poor bile production, delayed synthetic function, prolonged cholestasis, and intractable ascites, leading to septic complications and higher mortality. Although a variety of recipient and donor factors are involved in the occurrence of SFS syndrome, persistent portal hypertension or portal venous overperfusion are suggested to be important mechanisms of SFS graft injury. Animal experimental studies[3,4] have shown that partial diversion of portal flow to systemic circulation through a mesocaval shunt can improve the function of an SFS graft liver. A recent clinical report[5] also has demonstrated that a mesocaval shunt with downstream ligation of the superior mesenteric vein was effective in preventing SFS syndrome in a recipient transplanted with a SFS liver graft (GRWR of 0.61%). On the basis of these findings, it is plausible that surgical procedures to attenuate portal venous overperfusion might protect a SFS graft from the injuries associated with SFS syndrome. In this article, we describe our new method of using a simple portocaval shunting in LDLT with a SFS graft.

Cases

Case 1

A 16-year-old man collapsed during rugby practice. He was diagnosed with heat stroke, with a core body temperature of 42°C. Because he became comatose and liver function deteriorated markedly, he underwent LDLT for fulminant hepatic failure. He also developed renal failure caused by rhabdomyolysis, which was reflected by a drastic increase in serum creatine phosphokinase concentration to 128,800 IU/L and necessitated hemodialysis before operation. The donor was his mother, who weighed 51 kg; the patient's body weight was 90 kg. A right lobe graft without the middle hepatic vein was transplanted. The graft weight and GRWR were 496 g and 0.55%, respectively. In the recipient, the mean portal venous pressure (PVP) was 24 mm Hg at the time of the insertion of a catheter.[6] It increased to 34 mm Hg after clamping of the portal vein (Fig. 1). As a standard procedure to avoid splanchnic congestion during the anhepatic period, a portocaval shunt by end-to-side anastomosis of the right portal branch and the inferior vena cava (IVC) was constructed. After the hepatic venous reconstruction, the small graft was supposed to undergo portal venous overperfusion; therefore,

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Abbreviations: LDLT, living donor liver transplantation; GRWR, graft-to-recipient weight ratio; SFS, small-for-size; PVP, portal venous pressure; IVC, the inferior vena cava; PFV, portal vein flow velocity; ALT, alanine aminotransferase; TB, total bilirubin; PT, prothrombin time; NH_3, ammonia.

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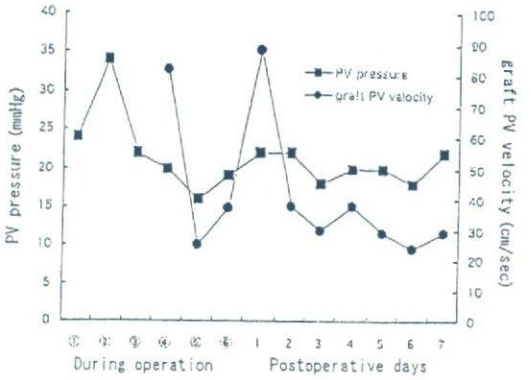

Figure 1. Changes in portal venous pressure and portal venous flow velocity of the graft liver in case 1. Abbreviations: PV pressure, portal venous pressure; graft PV velocity, portal venous flow velocity of the graft liver; During operation ①, at the time of the insertion of a catheter; ②, after the clamping of the portal vein; ③, during the anhepatic period with portocaval shunting; ④, after reperfusion of the graft with the shunt clamped; ⑤, after opening the shunt; ⑥, at the end of the operation.

the portocaval shunt was left intact and the right portal vein of the graft was anastomosed to the recipient's left portal branch (Fig. 2). After the reperfusion of the graft with the portal blood, the portal venous pressure was still high (20 mm Hg), when the shunt was occluded and subsequently decreased to 16 mm Hg by opening the shunt. The mean portal vein flow velocity (PFV) of the graft calculated by Doppler ultrasonography decreased from 82 cm/second to 25 cm/second after opening the shunt. Monitoring the PVP in the portal trunk and PFV of the graft, we decided to leave the shunt open (Fig. 1).

Postoperatively, the PVP and PFV transiently increased on day 1, however, they decreased and became stable at between 18 and 22 mm Hg and between 24 and 38 cm/seconds, respectively. The flow through the shunt was also detected by Doppler ultrasonography. Although he required mechanical ventilatory support and continuous hemodiafiltration for a long time after operation, the immediate postoperative graft function was successful. Serum transaminase levels and total bilirubin concentration decreased promptly, and prothrombin time was normalized within 1 week (Fig. 3). On day 9, according to the CT volumetry, the graft volume was estimated at 930 mL, indicating favorable regeneration. Nonetheless, plasma ammonia concentration began to increase at 3 weeks after operation and remained at more than 100 mmol/L for 4 weeks. On day 51, Tc-99m GSA (asialoglycoprotein receptor) scintigraphy revealed a normal value of liver uptake index, which suggested that the shunt flow was minimal. Thereafter, the ammonia level decreased spontaneously. He was weaned from hemodialysis and discharged with satisfactory liver function on day 66.

Case 2

A 55-year-old man weighing 67 kg underwent LDLT for chronic hepatitis B–related liver cirrhosis and multiple hepatocellular carcinoma. A right lobe graft without the middle hepatic vein was transplanted from his wife, who weighed 49 kg. The graft weight and GRWR were 470 g and 0.70%, respectively. In the recipient operation, a portocaval shunt by end-to-side anastomosis of the right portal branch and the IVC was constructed during the anhepatic period. Judging from the distance between the portal veins of the graft and the recipient, the right portal branch of the recipient was cut off from the IVC and anastomosed to the portal vein of the graft. Then, a new shunt between the left portal branch and the IVC was made. The PFV of the graft was 43 cm/second at the end of the operation; however, it exceeded 100 cm/second despite the shunt being patent during the first 4 days after operation. Afterward, it began to decrease gradually and fell below 50 cm/second within 8 days. The postoperative course was uneventful with a successful graft function (Fig. 4). With no SFS syndrome or hyperammonemia, the patient was discharged on day 25.

Discussion

Although the pathogenesis of SFS syndrome is multifactorial and has not been clearly identified, a small size of graft is a major contributing factor. Because cadaveric grafts are rare in Japan, LDLT with an SFS graft is sometimes inevitably selected as the only chance for treatment with fully informed consent. Attempts to

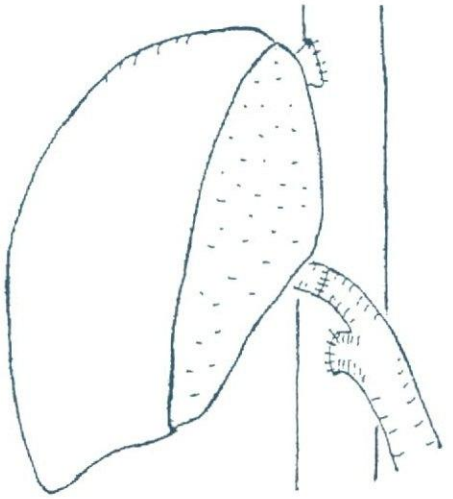

Figure 2. Scheme of the portal venous reconstruction with end-to-side portocaval shunt in case 1. A portocaval shunt by end-to-side anastomosis of the right portal branch and the inferior vena cava was left intact and the right portal vein of the graft was anastomosed to the recipient's left portal branch.

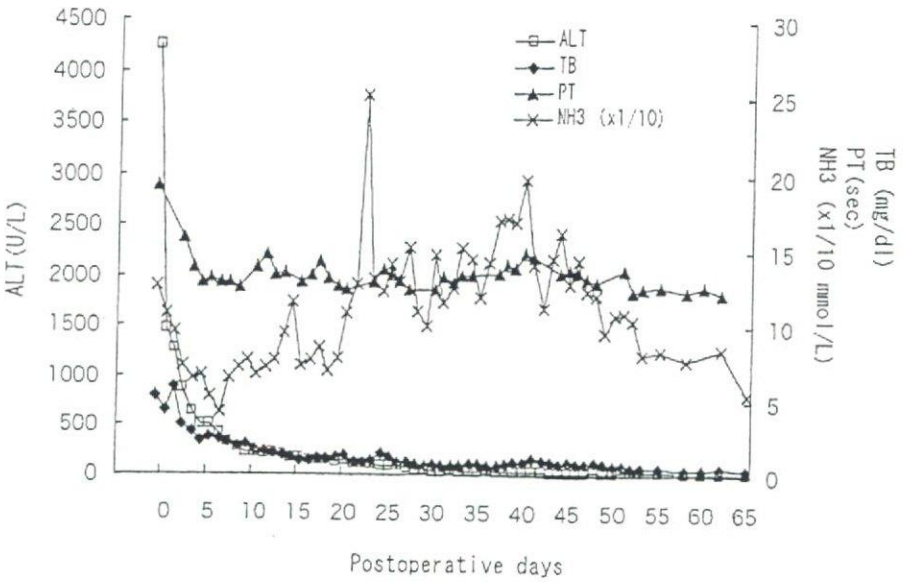

Figure 3. Changes in the liver function test results in case 1. Serum transaminase level and total bilirubin concentration decreased promptly and prothrombin time was normalized within 1 week.

reduce the risk of SFS syndrome have been made, such as auxiliary transplantation,[7] dual liver grafts,[8] splenic artery ligation,[6] and the prevention of outflow obstruction of the anterior segment in the right lobe graft by reconstruction of additional drainage veins or inclusion of the middle hepatic vein.[9] However, from the viewpoint of donor safety, these techniques cannot always be used. Even with these methods, the results have not been satisfactory in some cases. A simple and safe modality to efficiently avoid SFS syndrome is required.

In our previous study, a PVP of more than 20 mm Hg in the early period after LDLT showed a close association with morbidity and poor graft function.[6]

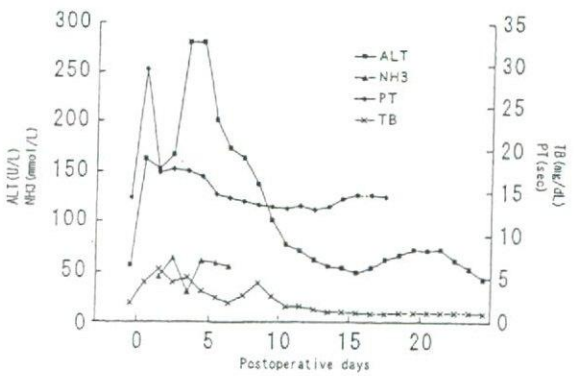

Figure 4. Changes in the liver function test results in case 2. The postoperative course was uneventful with a successful graft function. With no SFS syndrome or hyperammonemia, the patient was discharged on day 25.

The current technique can be an option for attenuating the portal hypertension when such an elevated PVP is observed in a patient transplanted with an SFS graft. Compared with the previously reported procedure,[5] this is technically simple and should be feasible in most cases. However, there are 2 possible drawbacks with this technique: (1) The portal blood flow competition between the graft and the shunt may cause graft dysfunction because of portal hypoperfusion. (2) The portocaval shunt causes deleterious effects, such as hyperammonemia. However, tactics against both risks can be prepared. If the portal blood is directed predominantly through the shunt, the portal inflow to the graft will be restored by banding the portal branch to the shunt and will be adjusted to the optimal level with the guide of Doppler ultrasonography during the operation. Also, if hyperammonemia is persistent after operation and the symptom is uncontrolled by medical treatment, closure of the shunt can be performed safely as long as graft liver regeneration is confirmed. Because the current technique has been applied and shown to be effective in only 2 cases, the safety and feasibility should be confirmed through accumulation of experience.

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ELSEVIER

Living Related Liver Transplantation

Y. Takada and K. Tanaka

ABSTRACT

The introduction of cyclosporine was a major advance in liver transplantation, leading to increased numbers of liver transplant cases and, at the same time, a relative shortage of available donor organs. As one of the modalities to decrease the mortality rate on the waiting list, living related liver transplantation (LRLT) was initiated. In the LRLT program of Kyoto University, which started in June 1990, the number of cases has increased yearly as its application expanded from pediatric to adult patients. A landmark in LRLT was the introduction of right lobe grafts, which have become a standard procedure in adult-to-adult living donor liver transplantation. The basic immunosuppressive regimen consisted of tacrolimus and low-dose steroids from the beginning of our LRLT program. However, since documentation of significant improvements in clinical efficacy with Neoral compared to Sandimmun-based immunosuppression, the role of cyclosporine in LRLT is now being reevaluated.

SINCE THE INTRODUCTION of cyclosporine (CyA) in the early 1980s, the clinical results of liver transplantation drastically improved. However, the broadened indications and growing number of referrals have led to an increasing disparity between the number of patients waiting for transplantation and the number of cadaveric liver donors, resulting in a high mortality among candidates on the waiting list. In an attempt to narrow this gap, transplant centers began to employ innovative surgical techniques, such as reduced-size liver transplantation and split-liver transplantation.[1,2] Following the evolution of these techniques, living related liver transplantation (LRLT) was initially reported by Raia et al[3] in 1989. In 1990, Strong et al[4] reported the first successful LRLT, which was followed by Broelsch et al[5] and us.[6] LRLT was first performed in children, in which the gap between demand and supply of liver grafts was most serious. With excellent graft/patient survivals and proven donor safety, LRLT has become a routine procedure; waiting list mortality has decreased in children. Encouraging results in pediatric LRLT led to the development of adult-to-adult living donor liver transplantation (LDLT).[7,8]

LDLT provides several advantages to the recipient. In elective cases, the transplant operation can be scheduled before the candidate develops life-threatening complications of end-stage liver disease. Excellent graft viability can be expected because the donor is always healthy and hemodynamically stable, and preservation time is minimized. LDLT is also advantageous in patients who are discriminated against with current organ allocation systems such as those with hepatocellular carcinoma. On the other hand, donor safety is of prime importance in LDLT, because the procedure subjects a healthy person to major surgery, potential morbidity, and mortality. The risk for the donor is balanced by the great benefit to the transplant recipient, as well as to donor self-esteem.[9] This article presents an overview of the development of LDLT at Kyoto University as well as the role of CyA as an immunosuppressive agent in LDLT.

EXPANDED APPLICATION OF LDLT FROM PEDIATRIC TO ADULT PATIENTS

The use of the left lateral segment (Couinaud segment II to III) grafts is more frequent in pediatric LDLT, because it carries less risk for the donor and provides adequate hepatocyte mass for most pediatric recipients. When LDLT is applied in larger or older children, graft size matching may be achieved by using a left lobe graft (segment II to IV). This extension seems acceptable, because the risk of donor hepatectomy is usually similar to that of left lateral

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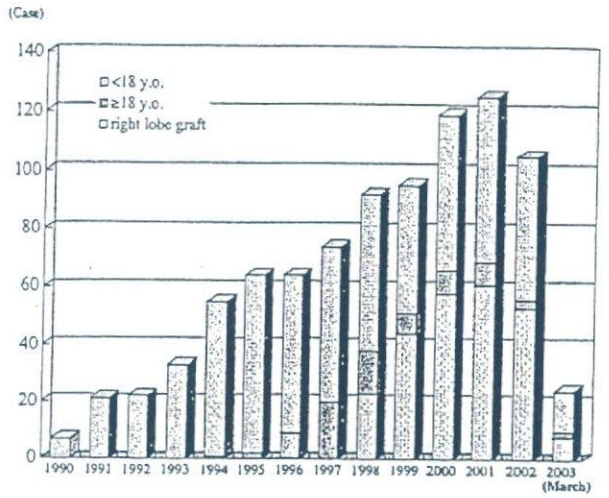

Fig 1. The yearly number of cases in LDLT program at Kyoto University.

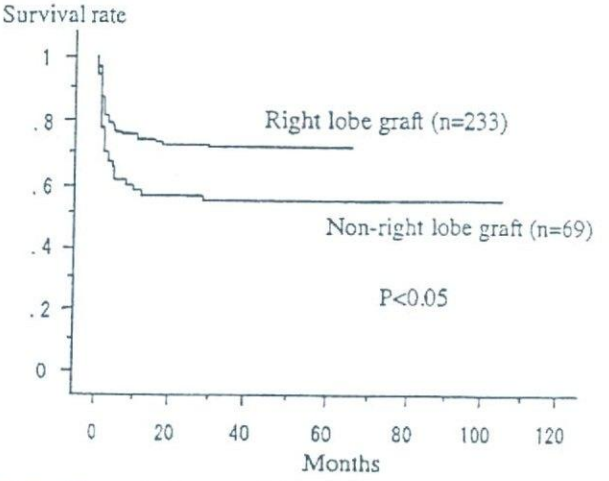

Fig 2. The survival curves of the patients treated with right lobe or non-right lobe grafts in adult-to-adult LDLT at Kyoto University.

segment grafts. However, the turning point was its application in larger teenagers and adults. The clinical significance of graft size mismatching was revealed by the small-for-size graft syndrome, even when full left lobe grafts includes the middle hepatic vein (MHV), namely, poor graft outcomes.[10] This syndrome consists of poor bile production, prolonged prothrombin time, intractable ascites, and prolonged cholestasis, closely associated with surgical and septic complications. The negative impact of small-for-size grafts are particularly pronounced when the recipient is chronically ill with severely deteriorated liver function.

To expand the applications of LDLT to adult patients with the restriction of using a left lobe graft, we introduced auxiliary partial orthotopic living donor liver transplantation (APOLT). In this procedure, a part of the native liver is left intact to compensate for the initial dysfunction in small-for-size grafts.[11] Although the actual survival rate in adult patients with chronic liver diseases treated with this APOLT technique was 60% in our initial results, the procedure failed to solve all cases of the small-for-size problem. Therefore, we started a new program using a right lobe graft from a living donor.

The initial trials of adult LDLT using right lobe grafts were reported from the Hong Kong[12] and the Colorado[13] groups. The right lobe graft was expected to meet the metabolic needs of larger patients and be advantageous to overcome size mismatching in adult recipients. Based on our experience with LDLTs of left lobe grafts, it was believed that the operative burden of the right lobectomy for the donor would be similar to that of a whole left lobectomy including the MHV, in terms of the extent of hilar dissection and the width of parenchymal transection. A subject of major concern was the increased risk to the donor due to the reduced residual liver volume.

Although the safety limit of residual liver volume for the donor has not been precisely estimated, it was believed that a normal liver could tolerate right lobectomy, leaving 30% to 40% of the liver volume.[14] Carefully balancing donor risk versus recipient benefit, we finally decided to introduce right lobe grafting in February 1998.[8] The safety and efficacy of right lobe grafting have been confirmed. Furthermore, we recently have adopted right lobe grafts with MHV (extended right lobe grafts) when the venous drainage pattern of the donor's right hepatic lobe is MHV-dominant.[15] In such cases, the venous drainage from segments V and VIII is substantially dependent on the tributaries of MHV, and the transection of such tributaries entails a greater risk of reduction in graft functional volume due to the venous congestion, which might lead to a critical small-for-size syndrome in the recipient.

Supported by the successful results of right lobe grafting, the number of adult LDLT cases has been remarkably increasing. Figure 1 shows the yearly number of cases in the LDLT program at Kyoto University. Between June 1990 and March 2003, 887 LDLTs were performed for 857 patients including 302 adult patients (more than 18 years old). Along with the increased of number of LDLT cases performed per year (more than 100 cases after 2000), the proportion of the adult cases has increased to more than 50%. Overall 3-year patient survival rates in pediatric and adult patients were 84% and 68%, respectively. In adult primary LDLT, the 3-year patient survival rate was significantly improved among patients treated with right lobe grafts (72%) compared to those with non–right lobe grafts (55%) ($P < .05$, Fig 2).

IMMUNOSUPPRESSION IN LDLT

Because the efficacy of CyA in liver transplantation had been established, CyA was used as a main immunosuppressive agent in some centers for the initial LDLT series.[5] On the other hand, at Kyoto University, the basic immunosuppression regimen consisted of tacrolimus (TAC) and low-dose steroids from the beginning of our LRLT program.[6,16]

Our initial protocol for TAC administration was based on the Pittsburgh experience.[17] High-dose intravenous (IV) induction was performed, in which TAC was given at a dose of 0.075 mg/kg infused over 4 hours every 12 hours, and then switched to oral administration (0.3 mg/kg/d). Since extremely high trough levels were frequently observed in this first protocol, the IV dosage was reduced to 0.03 mg/kg. Finally, to avoid the drastic increase in blood levels of TAC detected even in the low-dose IV induction group, the induction protocol was changed to enteric administration of TAC (orally or via the gastric tube). At present, the dosage of enteric TAC administration is determined to maintain the 12-hour trough level between 10 and 15 ng/mL in the first 2 postoperative weeks.

Since the US and European multicenter studies comparing TAC versus Sandimmun CyA in adult cadaveric liver transplantation[18,19] as well as a controlled study in pediatric cases[20] showed improved graft survival and lower rates of acute rejection episodes, most centers have used TAC for LDLT. However, with the accumulation of cases managed with TAC, the incidence of adverse reactions, such as neurotoxicity, nephrotoxicity, and diabetes mellitus, has been reported to be relatively high. When TAC-related adverse effects are unresponsive to dose reduction, the patients are often treated by conversion to CyA. Emre et al[21] suggested that conversion to CyA in liver transplant recipients can be accomplished safely, with no increased risk of rejection and excellent long-term outcomes. Also in LDLT patients, favorable outcomes after conversion from TAC to CyA have been reported.[22]

Recently, it has been shown that Neoral, which is the microemulsion formulation of CyA, is more readily absorbed from the gastrointestinal tract than Sandimmun. Furthermore, its absorption is relatively independent of bile flow and food intake.[23] Due to the pharmacokinetic stability provided by this advanced formulation as well as the development of optimal monitoring (C2 monitoring), significant improvements have been documented among liver transplantations with Neoral-based immunosuppression.[24]

Encouraged by these results in cadaveric liver transplantation, studies to evaluate the effects of Neoral-based immunosuppression in LDLT are in progress in centers including our institution.

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Auxiliary Partial Orthotopic Living Donor Liver Transplantation: Kyoto University Experience

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Auxiliary partial orthotopic liver transplantation (APOLT) was initially indicated as a potentially reversible fulminant hepatic failure and non-cirrhotic metabolic liver disease to compensate for enzyme deficiency without complete removal of the native liver. We expand our indication of APOLT for small-for-size grafts to support the function of implanted grafts during the early post-operative period, and for ABO-incompatibility to sustain a patient's life if the patient has a graft failure.

We retrospectively reviewed 31 patients undergoing APOLT from living donor. The indication of APOLT was fulminant hepatic failure in 6, non-cirrhotic metabolic liver disease in 6, small-for-size grafts in 13 and ABO-incompatible cases in 6.

The cumulative survival rate for APOLT at 1 and 5 years was 57.9% and 50.6%, and 78.8% and 73.8% for standard LDLT. None of the patients who underwent transplantation with APOLT for fulminant hepatic failure had long-term patient survival. The incidence of acute cellular rejection was higher in APOLT (58.1%) than standard LDLT (35.0%). Biliary complication was higher and the need for retransplantation was greater in APOLT than standard LDLT ($p < 0.01$).

The results suggest that the indications of APOLT should be reconsidered in view of the risk for complications and retransplantation.

Key words: Auxiliary liver transplantation, living donor liver transplantation

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Introduction

Liver transplantation from a living donor is increasingly accepted with excellent results, usually in coordination with a cadaveric organ transplant program (1). In countries where cadaveric donors are limited, however, living donor liver transplantation (LDLT) is often the only treatment of choice for patients with end-stage liver disease (ESLD). The LDLT program in Kyoto University began in June 1990, and under this program 970 transplants in 920 patients have been carried out in the period up to November 2003. Because of the growing waiting list and the establishment of acceptable results of pediatric LDLT, we have been compelled to expand our indication of LDLT from small children to older children, and even to adults.

Analysis of our studies revealed poor graft survival in older patients receiving small-for-size grafts (2). To treat patients with a graft-to-recipient weight ratio (GRWR) of less than 0.8%, auxiliary partial orthotopic liver transplantation (APOLT) was indicated from 1996 (3). The rationale of APOLT for a small-for-size graft is that the remnant native liver is expected to support the function of the implanted graft during the early post-operative period. The graft liver expands its function in proportion to volume growth. After the graft liver has grown sufficiently, it can be expected to meet the hepatic functional demands of the recipient.

APOLT was initially indicated for potentially reversible fulminant hepatic failure and non-cirrhotic metabolic liver disease (4,5). The double aim of APOLT for fulminant hepatic failure is full native liver regeneration and discontinuation of immunosuppressive therapy (6). The auxiliary graft should support the remnant native liver during regeneration.

The advantage claimed for APOLT in non-cirrhotic metabolic liver disease is that it can compensate for enzyme deficiencies without complete removal of the native liver, which may have to aid the recipient in case of potential graft failure. The remaining native liver could benefit in the future from potential success in gene treatment (7,8).

The other potential indication for APOLT is ABO-incompatible transplantation. Transplants of ABO-incompatible grafts are often unavoidable due to the

limited number of potential donor candidates in the LDLT program. In our LDLT program, 12% of patients had to have an ABO-incompatible graft. A high incidence of early graft failure with a high rate of biliary and vascular complications in ABO-incompatible liver transplantation was reported (9). The remnant native liver could sustain a patient's life if the anticipated graft failure occurred in an ABO-incompatible case.

APOLT from living donors was performed in 31 cases for the following indications: (i) fulminant hepatic failure; (ii) non-cirrhotic metabolic liver disease; (iii) small-for-size graft and (iv) ABO-incompatibility. However, the safety of using this technique in ESLD patients remains open to question. The objective of the present study was to investigate the long-term clinical outcome of the APOLT studies in the Kyoto University LDLT program.

Patients and Methods

Study population

Since APOLT was first indicated in March 1995 for a patient with ornithine transcarbamylase deficiency (OTCD), 31 cases of APOLT have been performed at Kyoto University Hospital. There were 13 male and 18 female patients with a median age of 23 years (range: 1.4–53.7 years) and a median weight of 53.4 kg (range: 11.3–108 kg). The indication for transplantation was fulminant hepatic failure in 6 patients (hepatitis B virus [HBV]-related in 1 and of unknown origin in 5); non-cirrhotic metabolic liver disease in 6 (citrullinemia in 3, OTCD in 2 and Crigler-Najjar syndrome type I in 1); biliary atresia in 7; primary biliary cirrhosis in 3; primary sclerosing cholangitis [PSC] in 2; Wilson's disease in 2; chronic hepatitis B in 2; autoimmune hepatitis in 1; Budd-Chiari syndrome in 1 and cryptogenic cirrhosis in 1. The follow-up period median was 83 months (range: 31–100 months).

Potential donors were evaluated by liver function tests, blood group, anatomical variation and graft size with computed tomography (CT) volumetry. All patients received grafts from family members. There were 14 male and 17 female donors with a median age of 43 years (range: 20–62 years) and a median weight of 57.3 kg (range: 39–81 kg). The indications for APOLT were: (i) fulminant hepatic failure in 6 patients; (ii) non-cirrhotic metabolic liver disease in 6 patients; (iii) small-for-size graft in 13 patients and (iv) ABO-incompatibility in 6 patients.

Surgical procedures

The operative procedure has been previously described (3,10). Native hepatectomy that varied in graft segment and volume, was performed prior to graft implantation. Graft types were left lateral segment in 8 cases, left lobe in 20 and right lobe in 3. The GRWR range was 0.45–2.08% (median 0.67%). The range of the operation time was 513–1379 min (median: 861 min), the range of the cold and warm ischemic time was 36–460 min (median: 157 min) and 32–77 min (median 48 min), respectively. Blood loss ranged 260–37650 g (median: 2645 g).

In one patient with biliary atresia, the left lateral segment of the native liver was prominently atrophic, and native hepatectomy was not necessary for graft implantation. The patient needed hepatic vein anastomosis with a new orifice of the inferior vena cava (11).

Part of the caudate lobe was resected in an initial 3 patients to shorten distance and to prevent kinking of the portal venous anastomosis. The stump of the native hepatic vein and hepatic artery was used for anastomosis. Twenty-five cases (80.6%) had diversion of the native portal vein to prevent functional portal vein competition between the native and graft liver, meaning that interruption of portal flow to the native liver with all portal flow going through the graft (3,12). Hepatic artery reconstruction was performed using the microvascular technique in all cases without using vascular grafts. Biliary reconstruction was achieved using Roux-en-Y hepaticojejunostomy.

Immunosuppression

The immunosuppression protocol consisted of tacrolimus and low-dose steroids (13). Tacrolimus was begun 1 day prior to transplantation at a dose of 0.15 mg/kg/day divided into two doses, except for cases of hepatic encephalopathy and severe infection. The target for the post-transplantation whole blood trough concentration of tacrolimus was 10-12 ng/mL during the first 2 weeks and around 10 ng/mL thereafter. Steroids were started at graft reperfusion at a dose of 10 mg/kg, and then gradually reduced from 2 mg/kg/day to 0.3 mg/kg/day until the end of the first month. For patients receiving ABO-incompatible grafts, plasma exchange or double filtration plasmapheresis was performed to reduce anti-ABH antibody titers before transplantation. Post-operatively, prostaglandin E1, azathiopurine and additional steroids were administered (14).

Rejection

Acute cellular rejection was diagnosed with liver biopsy. Histological diagnosis and grading of acute rejection were performed according to the criteria proposed by Demetris et al. (15). All the rejection episodes were treated with a steroid bolus injection. Diagnosis of chronic rejection was based on internationally accepted histological criteria (16). Graft failure was defined as patient death or allograft removal regardless of the reason.

Statistical analysis

Values are presented as mean ± standard deviation. Statistical analysis was performed with the generalized Wilcoxon test. Actuarial 1- and 5-year graft survival curves were calculated with the non-parametric Kaplan–Meier method and compared among groups with the Wilcoxon test. p-values of less than 0.01 were regarded as significant throughout the study.

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

Results

APOLT was initiated between March 1995 and September 2001. In the same period we carried out 536 LDLTs. Thirty-one of 536 patients (5.8%) received APOLT (Table 5). None of the patients were lost to follow-up.

APOLT for fulminant hepatic failure (Table 1)

Six patients underwent APOLT for fulminant hepatic failure. Etiology of fulminant hepatic failure was HBV in 1 patient and of unknown origin in 5. The median interval between onset of jaundice and encephalopathy was 42 days (range: 9–140 days). Coma grade at transplantation was grade III in 2 patients and grade IV in 4 patients. All patients necessitated pre-operative plasma exchange and continuous veno-venous hemodiafiltration therapy for progressive encephalopathy, coagulopathy and combined kidney/pulmonary dysfunction.

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.

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肝細胞癌に対する生体肝移植

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はじめに

近年，肝細胞癌に対する治療は肝切除術，エタノール注入やラジオ波焼灼術などの穿刺治療，TAE，肝動注などと多様化がみられ，それぞれの治療成績が着実な進歩を遂げている。しかし，併存する慢性肝障害のために治療法の選択は制限を受け，特に進行肝細胞癌の場合は治療による侵襲を考えて根治的治療が行えないことが少なくない。更に肝炎ウイルスに関連した多中心性発癌による再発が予後に大きな影響を与える。一方，肝移植は癌病変の除去と同時にその背景にある慢性肝疾患を根本的に治療できるという利点があり，肝予備能が低下している症例に対しても適応となり得る。最近本邦でも成人に対する生体肝移植が広く行われるようになり，肝細胞癌に対しても生体肝移植が導入されている。このような現況で実際に肝細胞癌患者を前にした場合，治療の選択肢の一つとして生体肝移植の役割をどのように考えるかについて，これまでの経験をもとに筆者らの考えを述べる。

肝細胞癌に対する肝移植の経緯

欧米での脳死肝移植では，初期の頃は切除不能進行肝細胞癌に対して積極的に肝移植が行われたが，術後再発が多くその成績は不良であった。一方，肝移植実施数の増加に伴い移植臓器不足や医療経済などの問題が深刻化し，適応の見直しがはかられた。その結果，肝細胞癌が単発ならば直径5cm以下，多発ならば3個以下で最大径が3cm以下という，いわゆる「ミラノ基準」が移植適応として一般的に用いられるようになった。

京大移植外科での生体肝移植

生体肝移植では，特定の患者（レシピエント）に対する特定のドナーから肝臓が提供されるため，移植臓器の有効な配分という脳死移植の場合の前提にとらわれることがない。また，「ミラノ基準」は術後再発予防という観点から厳しく設定されたものであり適応拡大できる可能性がある。このような考えから京大移植外科では独自の適応基準を設けて1999年2月より肝細胞癌に対する生体肝移植を開始した（図1）。すなわち移植適応として，肝外病変がなく，肝静脈，門脈主要枝への浸潤・腫瘍栓がないこととし，腫瘍の数や大きさは考慮していない。2002年12月までに，68例の肝細胞癌症例に生体肝移植を行った。背景疾患ではHCVまたはHBV関連肝硬変が60例にみられ，肝機能はChild-Pugh分類Cが30例（44％）であった。癌の進行度は27例（40％）がミラノ基準を超えており，50例（74％）が移植前に他の治療を受けていた。その結果，感染症などが原因の術後死亡が18例，癌の再発後死亡が5例であり，術後3年累積粗生存率は全体で56％であった。癌の再発は生存例も含めて8例に認めた。ミラノ基準内および基準逸脱群の3年無再発生存率は91％ vs. 67％で，逸脱群に低い傾向はあるが有意差は認めなかった（図2）。

適応基準

1　他の治療法では制御不能、または肝機能低下のため治療不可能な腫瘍

2　腫瘍が肝内に限局して脈管侵襲をもたない
（腫瘍径　数は問わない）

移植まで可能な限り ablation 治療を継続
・告知を含めたインフォームドコンセント
・私費治療

図1　肝細胞癌に対する生体肝移植
（京大移植外科）

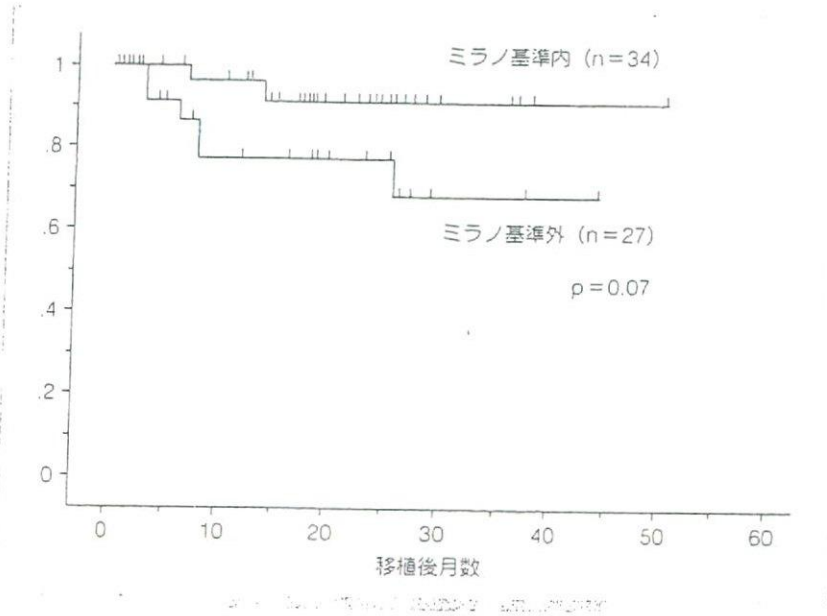

図2　ミラノ基準と累積無再発生存率

今後の展望

術後再発をみると，非腫瘍死を除いた場合ミラノ基準逸脱症例の60％以上が現在も無再発生存中であることは注目に値する。このことから，腫瘍因子からみた適応の拡大は安全かつ可能であると考えられる。合併症による術後死亡率の高さは重要な問題点であり，手術手技や術後管理の更なる改善をはかると同時に，術前におけるリスクファクターの同定が急務である。またドナーのリスク，私費診療という経済面での負担など負の側面とのバランスも考慮しなければならない。しかし，肝機能悪化のため，または繰り返す再発のために他の外科切除や内科治療の適応外と判断された進行肝細胞癌患者にとって，根治性が望める残された治療法として生体肝移植の役割は今後大きくなるものと考えられる。

特集

肝細胞癌

(第104回日本外科学会総会より)

当科における肝癌に対する生体肝移植の成績

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From February 1999 to December 2003, 82 HCC patients (male; 60, female; 22, age; 21～69y. o.) received living donor liver transplantation (LDLT). The indication of LDLT for HCC was unresectable tumor with no extrahepatic lesions nor major hepatic involvement. Half of the patients had advanced carcinoma, which exceeded the so-called Milan criteria. Patient survival at 3-year after LDLT was 66%. Ten patients had recurrence after LDLT. Recurrence rate at 3-year was 18%, with 0% for patients within pathological Milan criteria and with 35% for patients out of pathological Milan criteria. LDLT for unresectable HCC seems to be acceptable even for advanced HCCs.

Key words: Hepatocellular carcinoma, Living donor liver transplantation, Pilot study, Survival, Advanced HCC

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はじめに

肝細胞癌は，多くが慢性肝炎や肝硬変などの背景疾患を持ち，癌の治療を行っても再発を繰り返すのみならず，いつか癌が制御不能な段階に至る．癌を背景疾患とともに治癒させる可能性のある治療として，諸外国では脳死肝移植が行われてきた．しかし，進行肝癌の成績は不良であり[1,2]，現在はミラノ基準（5 cm 以下1個，または3 cm 以下3個以内）[3]をゴールドスタンダードとして早期肝癌に適応が限定され，せいぜいそれをやや拡大した基準（UCSF 基準など）[4]までが用いられている．ドナー不足を背景とする脳死肝移植では，公平にかつ有効に臓器を配分する原則に則る必要がある[5]．しかし，生体肝移植では，公平な臓器配分は不要であり，適する生体ドナーのいる肝癌患者では，有効な移植をめざすことになる．当科では，1999年2月から，肝癌患者に対する生体肝移植を開始した．肝癌に関する生体肝移植の役割や適応は不明であったため，肝内に腫瘍が限局して大血管浸潤がなければ，早期肝癌に限らず移植を行う方針でパイロットスタディーを行った．この考えの背景は，生体ドナーを持つ患者は，進行癌であっても，生体肝移植により生存や治癒の最大限のチャンスを持っており，それを制限しない，ということであった．そうした中で行ってきた当科での肝癌に対する生体肝移植の成績を以下に紹介する．

1. 患　者

1999年2月から2003年12月末までに82人の肝癌患者に生体肝移植を行った．移植直前の画像では腫瘍が認められなかったが，摘出肝に肝癌のみつかった患者9人を含んでいる．男性60人，女性22人で，年齢は21～69歳（中央値；54歳）であった．背景疾患はC型肝炎が最も多かった（表1）．手術の適応を決める最終評価は，術前数週間以内に撮影した頭部・胸部・腹部CTと骨シンチに基づき，肝内腫瘍の画像診断と，遠

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