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H. 知的財産権の出願・登録状況

なし

別紙４

研究成果の刊行に関する一覧表レイアウト

雑誌

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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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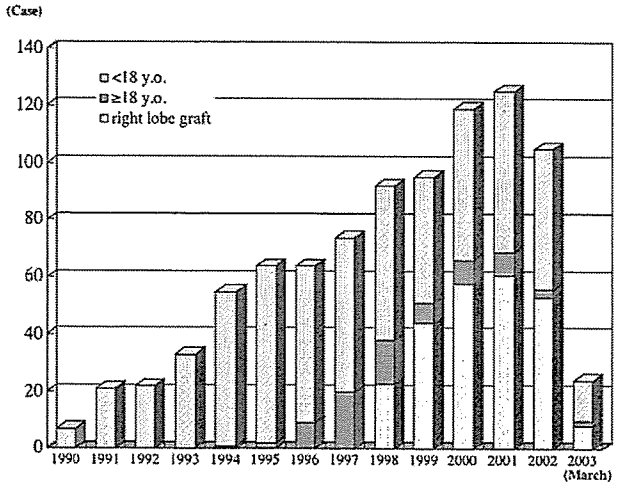

Fig 1. The yearly number of cases in LDLT program at Kyoto University.

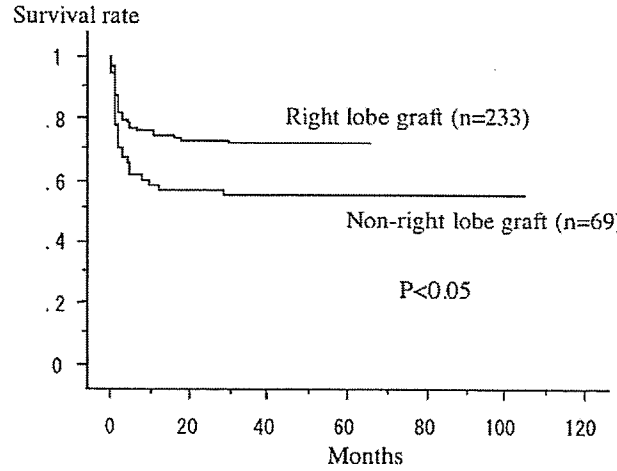

Fig 2. The survival curves of the patients treated with right lobe or non-right lobe grafts in adult-to-adult LDLT at Kyoto University.

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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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,

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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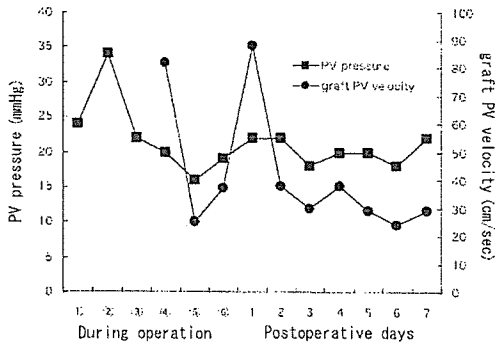

Figure 1. Changes in portal venous pressure and portal venous flow velocity of the graft liver in case 1. Abbreviations: PV pressure, portal venous pressure; graft PV velocity, portal venous flow velocity of the graft liver; During operation ①, at the time of the insertion of a catheter; ②, after the 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

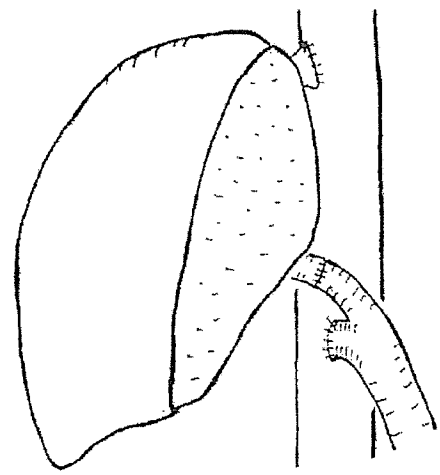

Figure 2. Scheme of the portal venous reconstruction with end-to-side portocaval shunt in case 1. A portocaval shunt by end-to-side anastomosis of the right portal branch and the inferior vena cava was left intact and the right portal vein of the graft was anastomosed to the recipient's left portal branch.

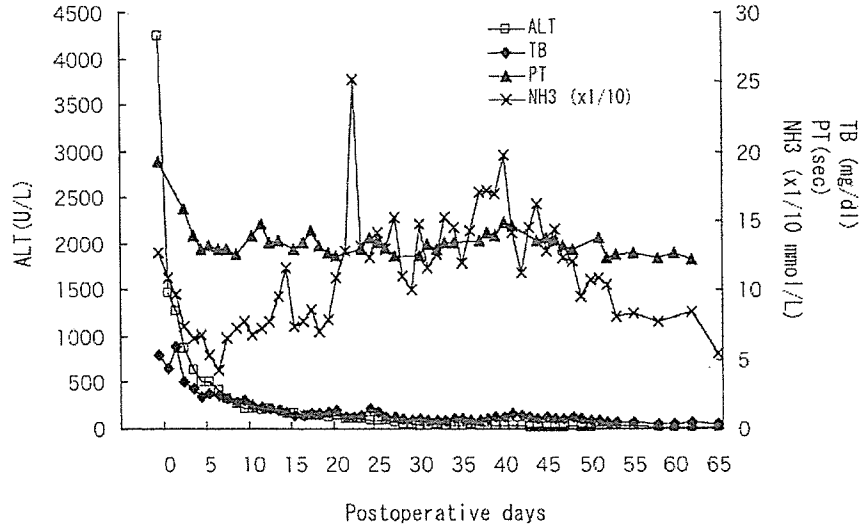

Figure 3. Changes in the liver function test results in case 1. Serum transaminase level and total bilirubin concentration decreased promptly and prothrombin time was normalized within 1 week.

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]

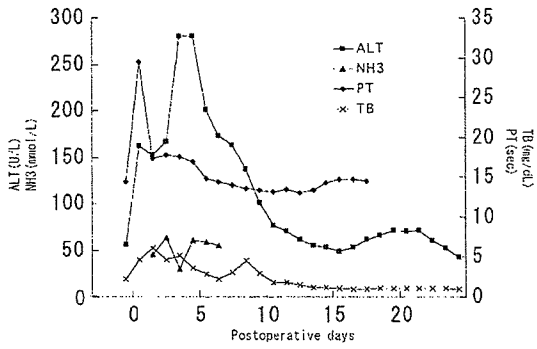

Figure 4. Changes in the liver function test results in case 2. The postoperative course was uneventful with a successful graft function. With no SFS syndrome or hyperammonemia, the patient was discharged on day 25.

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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Noninvasive Evaluation of Graft Steatosis in Living Donor Liver Transplantation

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Background. Hepatic steatosis affects graft function as well as postoperative recovery of donors in living donor liver transplantation. Liver macrovesicular steatosis in living donors was assessed using quantitative X-ray computed tomography (CT) analysis and histological examination of intraoperative liver biopsy.

Methods. A total of 266 living donors with complete pretransplant CT data and intraoperative "time 0" biopsy were included in the study. Liver biopsy specimen obtained during donor operation was examined for macrovesicular steatosis and was classified as none; mild (<30%); moderate (30%–60%); or severe (>60%). Liver-to-spleen CT attenuation values ratio (L/S ratio) on noncontrast-CT was evaluated for its usefulness as an index of hepatic steatosis in comparison with other parameters including body mass index (BMI) and serum liver function tests (gamma-glutamyl transpeptidase, alanine aminotransferase, aspartate aminotransferase, cholinesterase, and total cholesterol) using receiver operating characteristic (ROC) analysis.

Results. Histological grade of macrovesicular steatosis was none in 198 patients (74.4%), mild in 50 (18.8%), moderate in 15 (5.7%), and severe in 3 (1.1%). The median L/S ratios for the respective histological grades were 1.20 (range: 1.00–1.46), 1.12 (0.83–1.37), 1.01 (0.74–1.21), and 0.90 (0.70–0.99) ($P<0.0001$). The ROC curve for L/S ratio was located closest to the upper left corner, and the area under the curve of L/S ratio was significantly larger than that of any other preoperative variables.

Conclusion. L/S ratio calculated from preoperative CT can be a useful tool to discriminate hepatic macrovesicular steatosis. Based on the present results, the optimal cut-off value for L/S ratio to exclude more than moderate steatosis would be 1.1.

Keywords: Liver-to-spleen CT attenuation values ratio, Receiver operating characteristic analysis, Macrovesicular steatosis, Living donor liver transplantation.

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In cadaveric liver transplantation (CLT), fatty infiltration of the liver is common among the brain-dead donor population. Most centers will use cadaveric grafts with up to 30% macrosteatosis (*1*), and there are reports of successful CLT with extensive hepatic microsteatosis (*2*). However, the presence of significant macrosteatosis (>60%) has been associated with primary nonfunction (PNF) of the graft liver, a condition that is catastrophic to liver transplant recipients (*3–5*). In living donor liver transplantation (LDLT), graft steatosis is one of the risk factors for graft dysfunction, and it is thought that the presence of severe macrovesicular steatosis is an absolute contraindication for the use of that organ for transplantation (*6*). In addition, hepatic steatosis affects postoperative recovery of the living donor (*7*). It is therefore very important to accurately diagnose the grade of donor hepatic steatosis in preoperative donor evaluation.

Several methods, including abdominal ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), body mass index (BMI) [kilograms/(height in meters)], waist/hip ratio, and liver function tests, have been used for evaluating hepatic steatosis (*8–10*). While these modalities are useful for investigating liver diseases, liver biopsy is still essential for diagnosis of hepatic steatosis and is the gold standard for the majority of patients (*11, 12*). Although liver needle biopsy is considered a relatively safe procedure, it has been reported that up to 5% of patients require hospitalization after the procedure and the incidence of significant bleeding is 1% with a fatal outcome in 1 of 10,000 patients (*13, 14*). To minimize such complications of needle biopsy, a noninvasive method would be required to evaluate hepatic steatosis in living donors before donor surgery.

Noncontrast-CT is currently one of the best radiological techniques for diagnosing of hepatic steatosis. The purpose of this study was to evaluate the accuracy of liver-to-spleen CT attenuation values ratio (L/S ratio) on noncontrast-CT in comparison with BMI or serum liver function tests for predicting hepatic steatosis.

PATIENTS AND METHODS

Donor Selection

Selection criteria for living donors in our institute were in principal based on age (20 to 60 years), ABO-blood type

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compatibility, estimated graft size (greater than 1.0% of recipient body weight), and estimated residual liver volume (greater than 30% of the whole liver). Donor candidates with suspicion of hepatic steatosis were put on a diet and exercise program and later reevaluated.

Donor and Recipient Profiles

A total of 266 living donors with complete pretransplant CT data and histological assessment of intraoperative "time 0" liver biopsy was included in this study. There were 137 male and 129 female donors. Donor age, body weight, and BMI were 19–66 (median 38) years, 39–108 (median 61.3) kg, and 17.4–34.3 (median 22.6) kg/m^2, respectively. Selected graft types were left lateral segment in 122 donors, left lobe in 62, and right lobe in 82. Graft-to-recipient weight ratios (GRWR) for each graft types were 2.60 (range: 0.89–6.87), 0.96 (range: 0.61–1.56), and 1.14 (range: 0.66–3.18), respectively. Age and body weight of the recipients were 0.3–68.9 (median 11.1) years and 4.3–108 (median 28) kg. Primary disease of the recipients consisted of cholestatic disease in 138 patients, liver cirrhosis in 42, fulminant hepatic failure in 23, liver tumor in 23, metabolic liver disease in 20, retransplant in 12, and others in 8.

Donor Biopsy and Histological Assessment

During donor surgery, after confirming that there was no abnormal finding in the peritoneal cavity on gross examination, the "time 0" wedge biopsy was taken from the liver. When graft livers were left lateral segment, left lobe, or right lobe, biopsy specimen was taken from segment III, segment IV, or segment V, respectively.

Histological grading of macrovesicular steatosis of "time 0" biopsies was performed by two independent pathologists (S.M., H.H). Macrovesicular steatosis was defined as hepatocytes containing one large vacuole of fat displacing the nucleus peripherally, and graded as none, mild (<30%), moderate (30%–60%), and severe (>60%) based on the percentage of hepatocytes containing cytoplasmic fat droplets, as previously reported (*15*).

Calculation of L/S Ratio

All CT examinations were performed with a CT-W3000 (Hitachi Medical Systems, Tokyo, Japan). Scanning parameters were 120 kV, 200 mA, collimation of 7 mm, and table speed of 10 mL/s with reconstruction increments of 7 mm.

In noncontrast-CT, attenuation of normal liver is greater than the spleen. It has been reported that when this is reversed with a difference in liver-spleen attenuation of greater than −10 Hounsfield units, the liver is suspected to be steatotic (*16*). Hepatic and splenic attenuation values were measured on noncontrast-CT scans by using 16 circular region-of-interest (ROI) cursors in the liver and four in the spleen. In the liver, four ROIs were located in each of the right anterior, right posterior, left medial, and left lateral segments. This method was originally developed by us to raise the validity of the result by means of reducing errors in measurement and disappearance of overlap in each segment. All measurements were manually obtained in regions of uniform parenchymal attenuation, with care being taken to avoid vessels, artifacts, and other areas that might have spuriously increased or decreased measurements. The four measurements in each segment of the liver and spleen were averaged.

In this study, the ratio of attenuation values in the liver to those in the spleen (L/S ratio) was evaluated for its efficacy as a marker for steatosis in the liver (Fig. 1). Calculation of L/S ratio was as follows:

$$\text{L/S ratio} = \frac{\text{Average attenuation value of liver (16 points)}}{\text{Average attenuation value of spleen (4 points)}}$$

Inter-segmental variation of L/S ratio was also analyzed.

Statistical Analysis

Values are shown as median and range. For statistical comparison, chi-squared test or Fisher's exact probability test for categorical data, Kruskal-Wallis test or Mann-Whitney test for continuous data, Friedman test or Wilcoxon signed-ranks test for L/S ratio data of hepatic segments, and Cox-Mantel test for Kaplan-Meier survival curve were used. *P* values of less than 0.05 were regarded as statistically significant. To compare the preoperative diagnostic accuracy of L/S ratio, BMI, gamma-glutamyl transpeptidase (GGTP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), cholinesterase (ChE), and total cholesterol (T-CHO) receiver operating characteristic (ROC) analysis was used with the "time 0" biopsy taken as the gold standard. The ROC curve can be drawn by plotting sensitivity (or "true-positive rate") on the

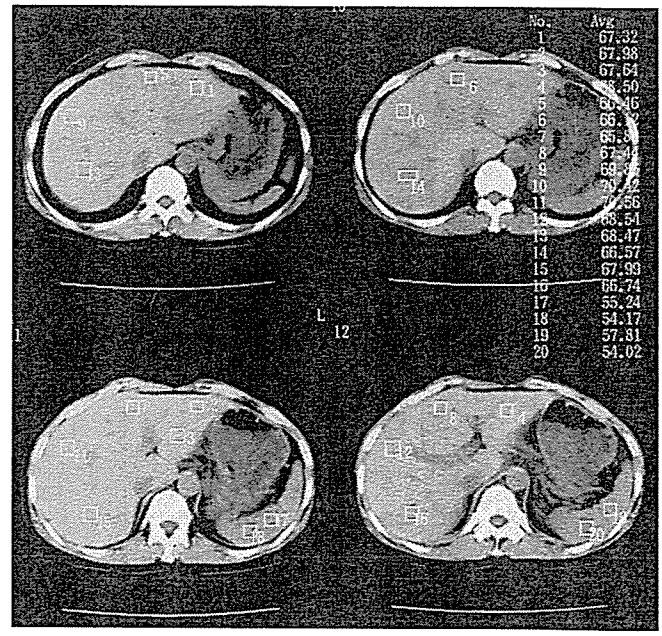

FIGURE 1. Calculation of liver-to-spleen CT attenuation values ratio. Hepatic and splenic attenuation values were measured on noncontrast-CT scans by using 16 circular region-of-interest (ROI) cursors in the liver and four in the spleen. In the liver, each four ROIs were measured at right anterior, right posterior, left medial, and left lateral segments. The size of one picture is 8×9 cm. Four sequential slices used for calculation of L/S ratio are demonstrated.

TABLE 1. Preoperative variables according to histological grades of macrovesicular steatosis

	Grade of macrovesicular steatosis (266)				
	None (198)	Mild (50)	Moderate (15)	Severe (3)	*P* values
Preoperative variables					
Donor age (yr)	37 (19–65)[b]	38 (21–61)[d]	48.5 (36–66)[b,d]	38 (30–47)	0.0127
BMI (kg/m^2)	21.9 (17.4–34.3)[a,b,c]	24.3 (18.0–31.6)[a,d]	26.5 (19.4–33.8)[b,d]	25.6 (24.1–26.8)[c]	<0.0001
AST (IU/L)	17 (9–41)[a,b]	20 (11–87)[a]	23 (12–32)[b]	22 (11–25)	<0.0001
ALT (IU/L)	14 (4–123)[a,b,c]	25 (9–142)[a]	26 (15–55)[b]	33 (20–47)[c]	<0.0001
GGTP (IU/L)	16 (7–113)[a,b,c]	29 (10–90)[a]	27 (11–146)[b,e]	47 (30–87)[c,e]	<0.0001
ChE (IU/L)	296 (168–508)[a,b]	345 (237–482)[a]	362 (277–486)[b]	309 (265–517)	0.0006
T-CHO (mg/dL)	188 (120–314)[a,b,c]	202 (139–441)[a]	214 (166–251)[b]	237 (222–249)[c]	0.0013
L/S ratio	1.20 (1.00–1.46)[a,b,c]	1.12 (0.83–1.37)[a,d,f]	1.01 (0.74–1.21)[b,d]	0.90 (0.70–0.99)[c,f]	<0.0001

BMI, body mass index; AST, aspartate aminotransferas; ALT, alanine aminotransferase; ChE, cholinesterase GGTP, gamma-glutamyl transpeptidase; T-CHO, total cholesterol; L/S ratio, liver-to-spleen CT attenuation values ratio.

[a]$P < 0.05$ none vs. mild; [b]$P < 0.05$ none vs. moderate; [c]$P < 0.05$ none vs. severe; [d]$P < 0.05$ mild vs. moderate; [e]$P < 0.05$ moderate vs. severe; [f]$P < 0.01$ mild vs. severe.

vertical (Y) axis and specificity (or "false-positive rate") on the horizontal (X) axis with a given cut-off point and changing the cut-off points from more stringent to less stringent. Because the accuracy of a test depends on its sensitivity and specificity, ROC curves of tests with higher discriminating ability are closer to the upper left corner than curves of those with lower ability (*17, 18*). Area under the ROC curve (AUC) can be calculated using the trapezoidal method (*17*). AUC represents the probability of correctly ranking a randomly chosen pair of persons with and without the disorder. For comparison of two AUC's, the nonparametric method developed by Hanley and McNeil (*17, 19*) was employed.

RESULTS

Graft Steatosis and L/S Ratio

The grade of macrovesicular steatosis as evaluated in the "time 0" biopsy specimens was none in 198 livers (74.4%), mild in 50 (18.8%), moderate in 15 (5.7%), and severe in 3 (1.1%) (Table 1). The median L/S ratio for livers of each histological grade was 1.20 (range: 1.00–1.46), 1.12 (0.83–1.37), 1.01 (0.74–1.21), and 0.90 (0.70–1.21), respectively. The differences among the four groups were statistically significant (Table 1). There were also significant correlations between steatosis grade in "time 0" biopsy specimens and increases in BMI or other blood chemistry results.

An intersegmental variation of L/S ratio was analyzed in the four segments (left lateral, left medial, right anterior, and right posterior segments) in patients with more than moderate grade steatosis (n=18). The L/S ratios in the left lateral, left medial, right anterior, and right posterior were 0.985, 0.985, 0.89, and 0.945, respectively. Although no statistically significant differences were observed among the four segments, L/S ratio tended to be higher in the left lateral segment than in the right anterior or posterior segments.

ROC Analysis

To compare the abilities of L/S ratio and other preoperative variables to discriminate between none to mild and moderate to severe steatosis, the ROC curves of these tests were determined (Fig. 2). The ROC curve of the L/S ratio was located closer to the upper left corner than that of any other preoperative variables (BMI, GGTP, ALT, AST, ChE, and T-CHO). For statistical comparison, Z statistics for the difference in areas under the ROC curves between L/S ratio and each of the other conventional variables are shown in Table 2. The AUC of L/S ratio was larger than that of any other variables, and the differences were significant, except for comparisons with BMI and ALT (Table 2).

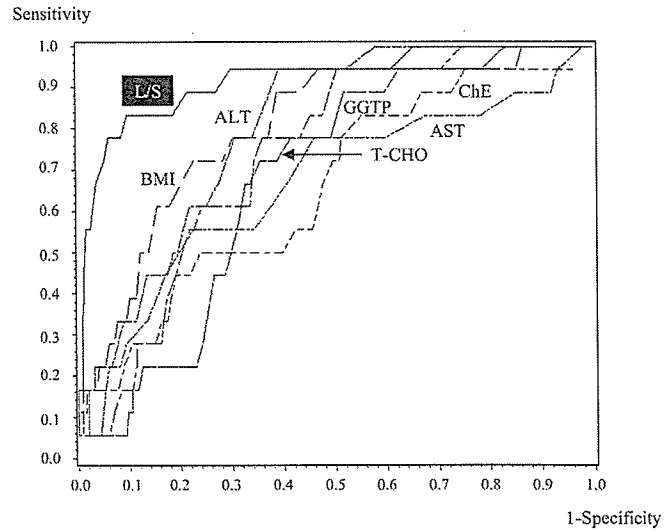

FIGURE 2. ROC curves were determined for L/S ratio, BMI, GGTP, ALT, AST, ChE, and T-CHO, all of which were measured preoperatively in 266 cases of LDLT.

Graft Outcome

Postoperative peak AST and ALT levels in both donors and recipients were higher in patients with moderate to severe macrovesicular steatosis. AST levels in donors with none to mild steatosis and in those with moderate to severe steatosis were 300 IU/L and 362 IU/L ($P<0.05$), respectively. Similarly, ALT levels in the respective donors were 270 IU/L and 388 IU/L ($P<0.05$). Moreover, the respective levels in recipients

TABLE 2. Statistical comparison of areas under the ROC curves between L/S ratio and preoperative variables

	Z statistics vs. L/S ratio	(*P* value)
BMI	1.61206	0.10695
GGTP	3.00589	0.00265
ALT	1.53605	0.12453
AST	2.74714	0.00601
CHE	3.37740	0.00073
T-CHO	2.94694	0.00321

were 295 IU/L and 417 IU/L and 317 IU/L and 418 IU/L, with no statistical differences being observed. However, the 5-year graft survival rates for grafts with none to mild steatosis and those with moderate to severe steatosis were 74.1% vs. 71.8%, but this difference was not significant. PNF was not seen in any of this series.

DISCUSSION

New insights into the mechanisms of failure of fatty livers should result in new prophylactic and therapeutic approaches (*20*). Livers with significant steatosis may increase the severity of ischemia-reperfusion injury and the incidence of graft PNF. Zamboni et al. (*21*) reported that macrovesicular steatosis involving 25% or more of the hepatocytes in the donor liver was significantly associated with shorter post-transplant survival and with a higher number of delayed graft failures. Worldwide, severely steatotic grafts (>60%) are routinely discarded for CLT. On the other hand, use of graft liver with microsteatosis did not influence either short- or medium-term survival (*2*, *22*). In the case of LDLT, due to the limited selection of donors, grafts with moderate to severe grade steatosis have been sometimes used with fully informed consent. Probably due to the minimized cold ischemic time in part, PNF has not been observed in our series (cold ischemic time: 2 hr in this series). However, the risk of using grafts with severe steatosis has also been clearly identified in LDLT (*7*)

Although liver needle biopsy may be required for definitive preoperative diagnosis of hepatic steatosis, it is not a universally safe procedure and should not be routinely applied to all living donor candidates. To minimize the risks of liver needle biopsy, noninvasive diagnostic methods using clinical, imaging, and/or biochemical parameters have been investigated (*23*, *24*). In a recent study on living liver donors, Mary et al. (*8*) reported that BMI was a reliable predictor of hepatic steatosis with a positive correlation between increasing BMI and steatosis grade on biopsy. It was also suggested that liver biopsy could be avoided in subjects with normal BMI, but that living donors with high BMI should undergo liver biopsy because biochemical and imaging data are not reliable enough to accurately diagnose the degree of steatosis (*8*).

In the present study, ROC analysis was used to compare the diagnostic ability of L/S ratio to predict the grade of hepatic steatosis with that of other preoperative variables. Because the ROC curve of L/S ratio is closer to the upper left corner of the graph than that of other variables, the sensitivity and specificity of L/S ratio can be considered higher when compared with these variables (BMI, GGTP, ALT, AST, ChE, and T-CHO). The ROC curve is a graph of sensitivity versus specificity, both of which are independent of disorder prevalence, and analysis does not depend on the prevalence of disorder in the actual population to which the preoperative variable may be applied (*17*). Moreover, statistical analysis of the differences in AUCs reveals that L/S ratio could predict >30% hepatic steatosis more accurately than any other variable, although the differences were not significant in comparison with BMI or ALT.

If a liver with less than 30% steatosis is thought to be appropriate for a living donor, the mean ± SD of the L/S ratio in donors with none to mild steatosis was 1.184±0.091. With regard to discriminating between none to mild and moderate to severe steatosis by L/S ratio, when the cut-off level was set at 1.1, the sensitivity and specificity were 0.833 and 0.815, respectively (Table 3), and the ROC curve closely approached the upper left corner. With regard to balance between sensitivity and specificity, the optimal level of L/S ratio to predict >30% hepatic steatosis would be 1.1.

From the results of intersegmental variation of L/S ratio, it is likely that fat deposition is heterogeneous throughout the liver. Because a single biopsy specimen shows the grade of hepatic steatosis only at the area where it was taken, multiple needle biopsies would be necessary to accurately evaluate steatotic changes in the whole liver. On the other hand, evaluation of hepatic steatosis using CT attenuation values enables the assessment of fatty changes in each part of the liver. To simultaneously express a representative value of fatty changes of the whole liver as well as to estimate the risks of both the graft and the remnant liver, the averaged value was employed to determine L/S ratio in the present study.

The present study suggests that L/S ratio on noncontrast-CT can be clinically used as a noninvasive method to correctly evaluate hepatic steatosis. This method is actually feasible because CT examination has been routinely done in donor preoperative evaluation for the assessment of liver anatomy and graft size and the calculation of L/S ratio is not time consuming. By employing this modality, preoperative liver needle biopsy could be omitted for most donors at our institution. However, when hepatic steatosis of more than moderate grade indicated by the L/S ratio does not show any significant improvement regardless of adequate diet and exercise treatment, or is accompanied by other complications including diabetes mellitus and/or hyperlipidemia, liver biopsy is performed to exclude disorders such as nonalcoholic steatohepatitis.

TABLE 3. Assessment for cut-off point of L/S ratio more than 30% steatosis in time zero biopsy according to ROC analysis

Cut-off point of L/S ratio (≥30%)	Sensitivity	Specificity	Diagnostic accuracy
1.2	0.944	0.448	0.481
1.1	0.833	0.815	0.816
1.0	0.556	0.984	0.955
0.9	0.222	0.992	0.940
0.8	0.111	1.000	0.940

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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.