part of our graft selection algorithm (Fig. 7), and detailed simulations have become possible. Since the introduction of the criteria, we have not had any postoperative complications associated with graft congestion.

There are some reports that HVC influences graft function and regeneration in LDLT recipients.[2-4] However in healthy donors, there are few reports of how HVC influences the remnant liver.[8,21] In the donor's operation, we have not reconstructed these tributaries, except in 1 case. In this study, mean CV/RLV in the remnant right lobe was surprisingly high at 27.7 ± 10.6% and the maximum CV/RLV was as high as 50.8% (Fig. 6A). Moreover, total bilirubin was significantly high in cases with CV over 20% (Fig. 6B). These results indicate that CV is a latent risk and that estimation of CV using this software is very useful.

In conclusion, CV could be reliably predicted using this 3D-CT software. We believe that this new parameter [(GV − CV)/SLV] deserves to be an essential part of preoperative planning for hepatic vein reconstruction and graft selection.

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ELSEVIER

Living Donor Liver Transplantation for Hepatocellular Carcinoma: A Special Reference to a Preoperative Des-Gamma-Carboxy Prothrombin Value

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ABSTRACT

Background. Des-gamma-carboxy prothrombin (DCP) is a sensitive marker related to vascular invasion of hepatocellular carcinoma (HCC). The aim of this study was to clarify the risk factors of HCC recurrence in living donor liver transplantation (LDLT) with special reference to preoperative DCP values.

Methods. Forty consecutive adult HCC patients who underwent LDLT were examined for a correlation between the DCP value and vascular invasion. Risk factors for recurrence were also investigated using clinicopathological variables including preoperative DCP levels.

Results. The incidence of positive histological vascular invasion in patients with DCP values above 300 mAU/mL was higher than that with those with DCP value below 300 mAU/mL. Other significant risk factors for recurrence were over 5 cm tumor diameter, not meeting the Milan criteria, AFP value >400 ng/mL, histological vascular invasion, poorly differentiated histology, and male gender. Among the patients who did not meet the Milan criteria, those with both no more than 5 cm of tumor diameter and no more than 300 mAU/mL DCP exhibited a good prognosis.

Conclusions. A high DCP value, namely >300 mAU/mL correlated with histological vascular invasion and was one of the strongest prognostic variables. Therefore, special attention should be paid to HCC patients with high DCP values. No correlation between the number of tumor nodules and recurrence was found; therefore, the Milan criteria may require revision regarding the number of tumor nodules.

THE MILAN CRITERIA namely, a single nodule of less than 5 cm in diameter, or three nodules less than 3 cm in diameter,[1] have been widely accepted as indication criteria for cadaveric liver transplantation in hepatocellular carcinoma (HCC) recipients. Recently, a new criterion was proposed from University California San Francisco,[2] extending the Milan criteria. However, indication criteria for HCC in living donor liver transplantation (LDLT) have not been established. The Kyoto group[3] has reported that recipients with HCC advanced beyond the Milan criteria showed favorable outcomes and with mostly related organ donors. Therefore, they concluded that other criteria for HCC are necessary in living compared with cadaver liver transplantation.

The following risk factors for HCC recurrence after liver transplantation are well known: poorly differentiated histology, vascular invasion, tumor diameter over 5 cm, and high alpha-fetoprotein (AFP) level (over 300 ng/mL).[4–7]

Des-gamma-carboxy prothrombin (DCP) is known to be a sensitive and specific marker of HCC. The DCP level has been reported to be related to proliferation, more aggressive behavior, and vascular (especially portal) invasion of

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tumor cells.[8-10] We previously reported that both DCP and AFP positive status reflect the poorest prognosis after hepatic resection for HCC.[11] Moreover, the clinical significance of DCP, which was originally described from Japan, has been gradually recognized in Western countries. On the other hand, liver transplantation for HCC has not been widely performed in Japan. Therefore, the role of DCP in liver transplantation has not been clarified. The aim of this study was therefore, to clarify the risk factors for recurrent HCC in LDLT, especially focusing on preoperative levels of DCP.

PATIENTS AND METHODS

Forty consecutive HCC patients among 120 adult recipients who underwent LDLT up to March 2004 were included in this study. Those patients were characterized as follows: male:female = 27:13; age over versus within 60 years = 16:24; left versus right lobe graft = 31:9; primary versus recurrent HCC after preceding treatments = 8:32; Milan criteria yes:no = 11:29; TNM stage 1:2:3 = 4:4:32; and Child-Pugh's class A:B:C = 7:16:17.

The selection of the graft, the harvest technique, the recipient operation, and the perioperative patient management of recipients, including immunosuppressive regimen, have been described elsewhere.[12]

All patients underwent monthly follow-up (median = 308 days with 136 days and 628 days as 25th percentile and 75th percentile, respectively). In all patients, serum AFP and DCP concentrations were measured monthly. Bedside abdominal ultrasonography was also performed monthly. Abdominal CT scan was performed at least every 3 months. If either the AFP on the DCP concentration was elevated, bone scintigram and chest and head CT scans were performed.

Measurement of plasma DCP concentrations was performed with a high-sensitivity EIA kit using MU-3 monoclonal antibody (ED036 kit: Eisai Company Ltd, Tokyo, Japan). The DCP concentration was expressed as milliarbitrary unit (mAU)/mL. The normal value of DCP is less than 40 mAU/mL.

Disease-free survivals were compared using clinicopathological variables. In this study, DCP over 300 mAU/mL and AFP over 400 ng/mL were defined as positive values. (The value of AFP over 400 ng/mL was adopted in CLIP score.)

The Mann-Whitney U test was used to compare the two groups for continuous variables and the chi-square test of independence for categorical variables. Differences in disease-free survival rates between the two groups were examined by the log-rank test. A value of $P < .05$ was considered to be significant.

RESULTS

There were only two (5.0%) deaths within 3 months after LDLT. The causes were graft-versus-host disease and multiple organ failure. Recurrence was observed in seven recipients (17.5%) at 3, 3, 4, 5, 7, 9, and 22 months. The sites of recurrence were bones ($n = 4$), lung ($n = 3$), liver ($n = 2$), peritoneum ($n = 2$), and lymph node ($n = 1$).

The median DCP value (25th percentile and 75th percentile) in patients with histological vascular invasion was 314 mAU/mL (72 and 2911 mAU/mL); for those without histological vascular invasion, 41 mAU/mL (20 and 158 mAU/mL; $P < .05$). The incidence of positive histological vascular invasion in patients with a DCP over 300 mAU/mL was 78%; on the other hand, that with a DCP value within 300 mAU/mL was 28% ($P < .05$).

Significant risk factors for recurrence were DCP over 300 mAU/mL ($P < .0001$), tumor diameter over 5 cm ($P < .001$), not meeting the Milan criteria ($P < .05$), AFP value over 400 ng/mL ($P < .05$), histological vascular invasion ($P < .05$), poorly differentiated histology ($P < .05$), and male gender ($P < .05$). Figure 1 depicts disease-free survival curves according to the DCP value and tumor diameter. Both DCP value over 300 mAU/mL and tumor diameter over 5 cm were the strongest determinants of patient prognosis. Early recurrence was observed in patients having either DCP value over 300 mAU/mL or tumor diameter over 5 cm.

All patients who met the Milan criteria are alive without recurrence; however, 22 (76%) of 29 patients who did not meet the Milan criteria are also alive without recurrence. The number of tumor nodules was not related to recurrence.

Figure 2 depicts the disease-free survival in patients who did not meet the Milan criteria. Disease-free survival in patients with both DCP value no more than 300 mAU/mL and tumor diameter no more than 5 cm was clearly better than that in those with either DCP value > 300 mAU/mL or tumor diameter of 5 cm.

DISCUSSION

High DCP values were closely related to histological evidence of vascular invasion. A high DCP value (over 300 mAU/mL) was also one of the strongest prognostic variables. Furthermore, disease-free survival in patients with both DCP value no more than 300 mAU/mL and tumor diameter no more than 5 cm was clearly better than that in patients with either DCP value over 300 mAU/mL or tumor diameter over 5 cm. DCP is known to reflect highly malignant characteristics of HCC, especially portal venous invasion. Koike et al[10] reported that serum DCP level is the

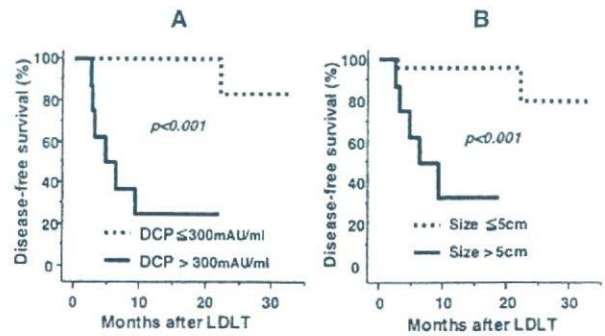

Fig 1. Comparison of disease-free survival. **(A)** Disease-free survival in patients with DCP value over 300 mAU/mL was extremely worse than in those with DCP value no more than 300 mAU/mL. **(B)** Disease-free survival in patients with tumor diameter over 5 cm was significantly worse than in those with tumor diameter no more than 5 cm.

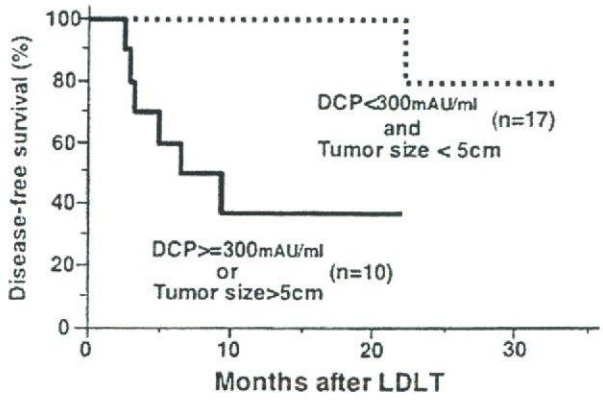

Fig 2. Disease-free survival in patients who did not meet the Milan criteria. Disease-free survival in patients with both DCP value no more than 300 mAU/mL and tumor diameter no more than 5 cm was clearly better than that in those with either DCP value over 300 mAU/mL or tumor diameter over 5 cm.

most useful predisposing clinical parameter for the development of portal venous invasion. Vascular invasion is one of the most important risk factors; however, microscopic vascular invasion is hardly assessed before surgery. Tang et al[11] reported that serum DCP levels significantly correlated with clinicopathological factors, such as vascular invasion, tumor differentiation, and tumor recurrence. We also confirmed a significant correlation between serum DCP value and the histological vascular invasion in the resected HCC specimens (data not shown). Since a preoperative high DCP value can predict positive histological vascular invasion, special attention should be paid to HCC patients with values over 300 mAU/mL.

Regarding the criteria for transplantation in HCC, all patients who met the Milan criteria are alive without recurrence. However, 22 (76%) of 29 patients who did not meet the Milan criteria are also alive without recurrence. Yao et al[2] reported patients with HCC meeting the following criteria: solitary tumor ≤ 6.5 cm, or no more than three nodules with the largest lesion 4.5 cm and total tumor diameter ≤ 8 cm, had survival rates of 90% and 75.2% at 1 and 5 years, respectively, after liver transplantation versus a 50% 1-year survival for patients with tumors exceeding these limits (P = .0005). They concluded that the current criteria for liver transplantation based on tumor size may be modestly expanded while still preserving excellent survival after liver transplantation. Kaihara et al[3] reported many patients who did not meet the Milan criteria survived without tumor recurrence after LDLT; therefore, different patient selection criteria are necessary in LDLT to save those with advanced HCC. In this study, the number of tumor nodules was not correlated with recurrence. Marsh et al[13] reported that depth of vascular invasion, lobar distribution, lymph node status, and largest tumor size were independent predictors of tumor-free survival; tumor number was not found to be significant in multivariate analysis. Furthermore, among the patients who did not meet the Milan criteria, the disease-free survival in patients with both DCP value no more than 300 mAU/mL and tumor diameter no more than 5 cm was clearly better than that in those with either DCP greater than 300 mAU/mL or tumor diameter over 5 cm. Until now, only one patient has experienced recurrence at 2 years after LDLT among the patients with both DCP no more than 300 mAU/mL and tumor diameter no more than 5 cm. Therefore, the Milan criteria should be corrected regarding the number of tumor nodules.

In conclusion, a high DCP value was closely related to histological vascular invasion; DCP value over 300 mAU/mL was one of the strongest prognostic variables. Therefore, special attention should be paid to HCC patients with high DCP values (over 300 mAU/mL). No correlation was found between the number of tumor nodules and recurrencs; therefore, the Milan criteria may need to be amended regarding the number of tumor nodules.

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ORIGINAL ARTICLE

Effect of intraportal infusion to improve small for size graft injury in living donor adult liver transplantation

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intra-portal infusion, living donor adult liver transplantation, small for size graft injury.

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Summary

The most important problem in the living donor adult liver transplantation (LDALT) is a small for size graft. Although a right lobe graft is used in many cases in order to avoid small for size graft, for a donor, the risk has few in left lobe graft. We evaluate the effect of an intraportal infusion treatment to the small for size graft. One hundred and twelve patients who underwent LDALT were studied. The graft weight recipient standard liver volume ratio (GV/SLV) of these patients were 50% or less. We divided the patients into following two groups; infusion group ($n = 53$) and control group ($n = 59$). For the infusion group, 16 G double lumen catheter was inserted into portal vein and nafamostat mesilate (protease inhibitor which stabilize coagulofibrinolytic state; 200 mg/day), prostaglandin E_1 (vasodilator and hepatoprotective effect; 500 μg/day) and thromboxane A_2 synthetase inhibitor (vasodilator and anticoagulant effect; 160 mg/day) were administrated continuously for 7 days. Small-for-size graft syndrome was defined as bilirubin >10 mg/dl and ascites >1000 cc on postoperative day (POD) 14. Comparison examination of a background factors and postoperative bilirubin and amount of ascites was carried out. The mean GV/SLV did not have the difference at 39.1% of infusion group, and 38.3% of control group ($P = 0.58$). By the control group, 15 patients (25.4%) were small-for-size graft syndrome, however, there was only two (3.8%) small-for-size graft syndrome in infusion group ($P = 0.04$). The bilirubin levels of infusion and control group on 7 and 14 POD were 9.9 and 7.8 vs. 9.5 and 10.5 mg/dl, respectively. The amount of ascites of infusion group on 7 and 14 POD were 870 and 430 cc, respectively. On the contrary, in control group, the amount of ascites on 7 and 14 POD were 1290 and 1070 cc, respectively. Bilirubin levels and the amount of ascites on 7 and 14 POD were lower in the patients with infusion group then those with control group. There were no differences between infusion group and control group in age, sex and Child's classification. The intraportal infusion had an effect in prevention of hyperbilirubinemia and loss in quality of excessive ascites in the patients with small for size graft. This was suggested to be what is depended on the improvement of the microcirculation insufficiency considered one of the causes of small-for-size graft syndrome.

Introduction

The first successful living donor adult liver transplantation (LDALT) patient was reported by Hashikura *et al.* in 1993 [1]. The major concern of LDALT is the adequacy of the size of the graft [2–4]. Harvesting a larger graft poses a higher risk for the living donor [5,6]. On the contrary, a small for size graft may not only be functionally inadequate for the recipient, but will also sustain injury characterized by cholestasis and histological features of ischemia after implantation [4]. The exact mechanism leading to injury of a small for size graft after liver transplantation remains unknown. It has been suggested that excessive portal flow secondary to relative portal hypertension may be the cause and that portal decompression may improve graft survival [7]. In experimental and clinical study, some drugs such as prostaglandin E_1 [8–11], thromboxane A_2 synthetase inhibitor [12–16] or nafamostat mesilate [17–19] have been reported to be effective on liver resection and posttransplant graft function. In this report, we evaluate the effect of an intraportal infusion treatment using such drugs to improve the small for size graft injury.

Patients and methods

One hundred twelve consecutive patients who underwent LDALT were studied. The graft weight recipient standard liver volume ratio (GV/SLV) of these patients were 50% or less. We excluded ABO incompatible case and auxiliary partial orthotopic liver transplantations (APOLT) case.

The main indications for LDALT were cholestatic diseases ($n = 20$), fulminant hepatic failure ($n = 28$), hepatocellular carcinoma ($n = 37$), liver cirrhosis ($n = 20$), and others ($n = 7$). Eighty-one patients received ABO identical grafts and 31 patients received ABO compatible grafts. The left plus caudate lobe as used for 102 cases, and the right lone was used for 10 cases.

A preoperative evaluation for potential living donors included a completed history and physical examination, an abdominal computed tomography scan, and angiogram. The computed tomography scan was used to calculate the size of the whole liver and the extended left lobe. The angiogram assessed the hepatic arterial supply, especially to the left lobe, and the diameters of the hepatic arteries. The SLV was calculated according to the formula, while the weight of the procured left lobe, labeled as GV, was measured on the back table. Subsequently the ratio GV/SLV could be calculated.

The donor hepatectomy was performed according to our standard technique [11–13]. Intraoperative cholangiography and ultrasonography ware performed, followed by cholecystectomy. The arteries supplying the left love were dissected and divided at their branching site from the either right or the proper hepatic artery. The transection of the liver parenchyma, after a dissection of the left hepatic artery and portal and hepatic veins, was performed with the liver fully perfused. The recipient operation was performed using our standard technique described before [13–17]. Using electromagnetic flow probes, the arterial blood flow was measured in recipients after performing anastomosis of all the vessels after 30 min of equilibration, but before biliary reconstruction. Biliary anastomosis was performed as an end-to-side hepaticojejunostomy on a Roux-en-Y loop, or end-to-end hepaticocholedochostomy. The initial immunosuppressive regimen consisted of tacrolimus or cyclosporin and steroids. Duplex Pulse Doppler ultrasonography was performed every postoperative day (POD) in all recipients to confirm the patency of the blood viscosity.

We divided the patients into following two groups; first 59 patients as control group and the other 53 patients as infusion group. For the infusion group, 16 G double lumen catheter was inserted into portal vein through umbilical vein or mesenteric vein and nafamostat mesilate (protease inhibitor which stabilize coagulofibrinolytic state) (200 mg/day), prostaglandin E_1 (vasodilator and hepatoprotective effect) (500 μg/day) and thromboxane A_2 synthetase inhibitor (vasodilator and anticoagulant effect; 160 mg/day) were administrated just after reperfusion continuously for 7 days. Median follow-uptime is 54 month in control group and 35 month in infusion group.

Small-for-size graft syndrome was defined as bilirubin >10 mg/dl and ascites >1000 cc on POD 14. Comparison examination of a background factors and postoperative bilirubin and amount of ascites was carried out.

Parametric variables were compared using the unpaired Student's *t*-test, while nonparametric variables were compared using a chi-square analysis. The survival probability of recipients was determined by the Kaplan–Meier methods. A *P*-value of <0.05 was considered significant.

Results

There was no complications related to infusion tube. Recipient characteristics were summarized in Table 1. No difference was seen in age, gender and Child's classification between the groups. In control group, 18 patients (30.5%) were fulminant hepatic failure and 14 patients (23.7%) were cholestatic diseases patients. On the contrary, in infusion group, 25 patients (47.1%) were hepatocellular carcinoma. The mean GV/SLV and GRWR did not have the difference at 39.3% and 0.78% of infusion group, and 38.3% and 0.77% of control group ($P = 0.58$; Table 1).

The bilirubin levels of infusion and control group on 7 POD and 14 POD were 9.9 and 7.8 vs. 9.5 and 10.5 mg/dl, respectively. There are no significant differences in bilirubin levels between control and infusion group on POD7 and 14. However, bilirubin levels and the amount of ascites on 7 and 14 POD were lower in the patients with infusion group then those with control group, and in the control group, bilirubin levels getting higher after 7 POD, although in the infusion group, bilirubin levels decreased after 7 POD (Fig. 1).

The amount of ascites of infusion group on 7 and 14 POD were 870 and 430 cc, respectively. On the contrary, in control group, the amount of ascites on 7 and 14 POD were 1290 and 1070 cc, respectively. The amount of ascites was significantly fewer in the infusion group than control group on POD 7 ($P = 0.07$) and 14 ($P = 0.02$; Fig. 2).

We defined small for size graft syndrome as the as bilirubin >10 mg/dl and ascites >1000 cc on POD 14. By the control group, 15 patients (25.4%) were small-for-size graft syndrome, on the contrary, there was only two (3.8%) small-for-size graft syndrome in infusion group ($P = 0.04$; Fig. 3, Table 2).

Table 1. Recipient and operative characteristics.

Factors	Control ($n = 59$)	Infusion ($n = 53$)	*P*-value
Recipient			
Age	44.7 ± 14.8	42.2 ± 13.7	0.34
Male/female	27/32	21/32	0.64
Child A/B/C	3/14/24	0/16/27	0.19
Indication			
Cholestatic diseases	14	6	0.02
Fulminant hepatic failure	18	10	
Hepatocellular carcinoma	12	25	
Liver cirrhosis	10	10	
Others	5	2	
Graft and operation			
LL/RL	51/8	51/2	0.14
GV/SLV (%)	38.3 ± 7.8	39.3 ± 7.6	0.58
GRWR (%)	0.77 ± 0.15	0.78 ± 0.16	0.59
Operation time (min)	751 ± 231	742 ± 223	0.84
Blood loss (g)	7184 ± 8831	7798 ± 9697	0.72

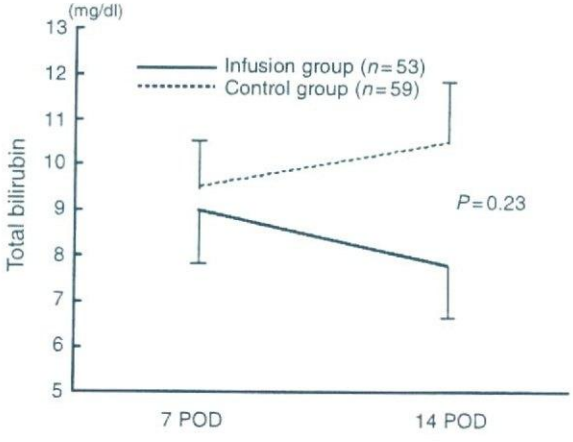

Figure 1 Change in total bilirubin levels after LDALT. The bilirubin levels of infusion and control group on 7 and 14 POD were 9.0 and 7.8 vs. 9.5 and 10.5 mg/dl, respectively. There is no difference between infusion and control group.

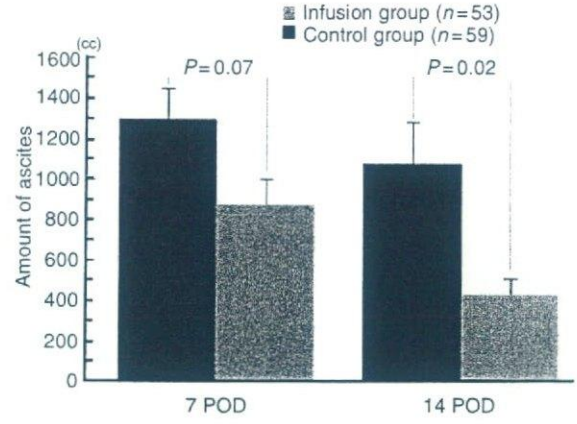

Figure 2 Change in amount of ascites after LDALT. The amount of ascites of infusion group on 7 and 14 POD were 870 and 430 cc, respectively. On the contrary, in control group, the amount of ascites on 7 and 14 POD were 1290 and 1070 cc, respectively. The difference is statistically significant in amount of ascites on POD 7 and 14 ($P < 0.05$).

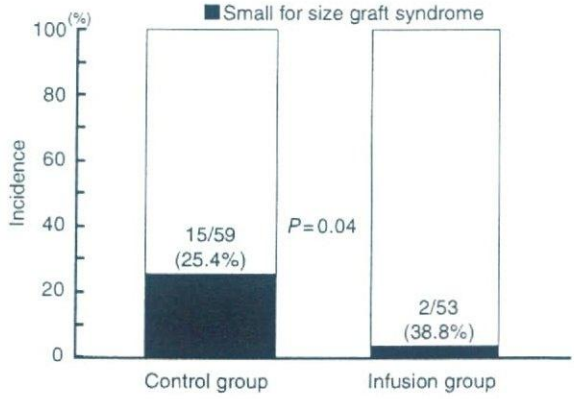

Figure 3 Small for size graft syndrome. We defined small for size graft syndrome as the as bilirubin >10 mg/dl and ascites >1000 cc on postoperative day (POD) 14. By the control group, 15 patients (25.4%) were small-for-size graft syndrome, on the contrary, there was only two (3.8%) small-for-size graft syndrome in infusion group ($P = 0.04$).

Table 2. Postoperative complications.

Complications	Control ($n = 59$)	Infusion ($n = 53$)	*P*-value
Bilirubin on POD 14 >10 mg/dl	19 (32.2)	15 (28.3)	0.81
Ascites on POD 14 >1000 cc	14 (23.7)	2 (3.8)	0.01
Acute cellular rejections	22 (37.3)	16 (30.2)	0.55
Biliary complications	20 (33.9)	7 (13.2)	0.02
Vascular complications	5 (8.5)	2 (3.8)	0.52
Infections	35 (59.3)	30 (56.6)	0.92
Small for size graft syndrome	15 (25.4)	2 (3.8)	0.04

Values in parenthesis are percentage.

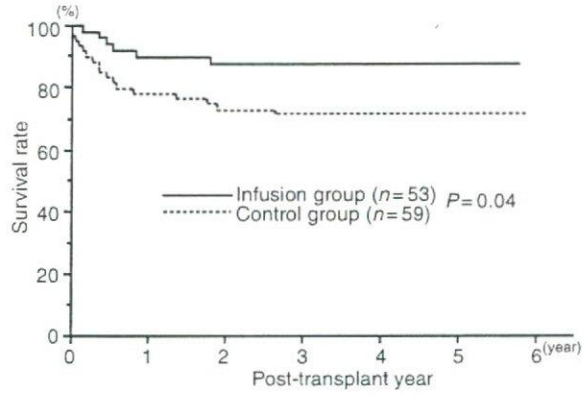

Figure 4 Kaplan–Meier patient survival curves of 112 patients with LDALT according to intraportal infusion treatment. In control group, the 1, 3 and 5 year patients' survival rates were 74.1%, 72.3% and 72.3%, respectively. And in infusion group, the 1, 3 and 5 year patients' survival rates were 86.6%, 86.6% and 86.6%, respectively. The patient survival rate was higher in the patients with infusion group than those with control group and the difference is statistically significant ($P = 0.04$).

Figure 4 demonstrates the Kaplan–Meier patient survival curves of 112 patients with LDALT according to intraportal infusion treatment. In control group, the 1, 3 and 5 year patients' survival rates were 74.1%, 72.3% and 72.3%, respectively. And in infusion group, the 1, 3 and 5 year patients' survival rates were 86.6%, 86.6% and 86.6%, respectively. The patient survival rate was higher in the patients with infusion group than those with control group and the difference is statistically significant ($P = 0.04$).

Discussion

Living donor adult liver transplantation can be performed successfully using a smaller graft [20–24]. Our previous report [2] described that a graft estimated as 26% of the recipient SLV was transplanted successfully to a patients with fulminant hepatic failure. Lo *et al.* [3] also reported that a graft estimated as 25% of the recipient SLV was successfully transplanted to patients with fulminant hepatic failure. But the minimal graft volume for successful LDALT depends on the pretransplant condition and disease of the recipient in each case.

To avoid small for size graft syndrome, right lobe graft has been used for LDALT [25–29]. Marcos *et al.* [25] and many other surgeons concluded that right lobectomies for living donation can be performed safety with minimal risk to both donor and recipient although providing adequate liver mass for an average size adult patient. Lo *et al.* [30] reported that LDALT using the extended right lobe living graft can extend the donor is relatively small compared with the recipient. However, concerning the safety of the donor, Sakamoto *et al.* and Sugawara *et al.* [26,28,31] reported that right lobectomy from living donors is a safe procedure with acceptable morbidity, but some care should be taken early after the operation for donors with small residual liver and aged donors. We also reported that postoperative liver functions including total bilirubin and ALT levels of the right lobe donors were significantly higher than those of left lobe donors [5]. From these findings, we use left lobe with caudate lobe graft to minimize the risk of the donor [21,32]. Recipient survival may depend on not only size and quality of the graft but recipient status. Our previous report suggested that intractable ascites was characteristics of small-for-size graft and small for size grafts <30% of SLV can be used careful intraoperative and postoperative management until the grafts regenerate [21].

Man *et al.* [33] reported that in a rat model, the portal hemodynamic changes in small for size grafts are transient, and the progressive damage of the graft may result from microcirculatory failure because of irreversible endothelial injury after reperfusion. To minimize the small for size graft injury, several methods were used. Ku *et al.* [7] reported an improved of canine liver transplantation using a quarter-graft with the aid of a porthepatic vein shunt. The effect of a porthepatic vein shunt on portal vein decompression should be an important factor for preventing graft injury after circulation in an extremely small graft. Clinically, Boillot *et al.* [34] completely divided the superior mesenteric venous flow by a mesocaval shunt with downstream legation of the superior mesenteric vein in order to avoid graft congestion and failure by overperfusion. To avoid outflow disturbance, De Villa *et al.* [27] recommended a recipient venoplasty with a, aching venoplasty of multiple graft hepatic veins to create a singlewide outflow orifice.

Different from these surgical methods, we performed intraportal infusion to improve small for graft injury. Recently, Tanabe *et al.* [35] and Shimazu *et al.* [36] showed the feasibility of controlling rejection and other

complications in adult-ABO incompatible liver transplantation under intraportal infusion therapy. They performed intraportal infusion therapy after transplantation with methylpredonisolone, prostaglandin E_1, and gabexate mesilate.

Our previous report also demonstrated that the regeneration rate of small graft was over 2.0 in 1 week after transplantation [21]. From this finding, we supported small grafts by intraportal infusion treatment first 1 week after transplantation. In our study, the drugs we used were prostaglandin E_1, thromboxane A_2 synthetase inhibitor and nafamostat mesilate. The effects of prostaglandin E_1 are hepatoprotective effect and improve microcirculation. We have reported that prostaglandin E_1 improves hepatocyte and sinusoidal cell function on isolated perfused rat liver [8,9]. The effects of thromboxane A_2 synthetase inhibitor are to improve microcirculation, hepatoprotective effect and inhibit platelet aggregation. We also reported that thromboxane A_2 synthetase inhibitor improves hepatocyte and sinusoidal cell function on isolated perfused rat liver [12–16]. The effects of nafamostat mesilate is to stabilize coagulant and fibrinolytic system and anti-inflammatory effect, and we reported that nafamostat mesilate stabilized coagulation and fibrinolysis in hepatic resection [17,18].

In summary, from our results of 112 LDALTs using intraportal infusion treatment, intraportal infusion treatment had an effect in prevention of hyperbilirubinemia and loss in quality of excessive ascites in the patients with small for size graft. Intraportal infusion also reduced in incidence of small for size graft syndrome in LDALT.

In conclusion, intraportal infusion treatment is suggested to be useful to improve small for size graft function. This was suggested to be what is dependent on the improvement of the microcirculation insufficiency considered one of the causes of small foe size graft syndrome.

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Impact of Graft Hepatic Vein Inferior Vena Cava Reconstruction with Graft Venoplasty and Inferior Vena Cava Cavoplasty in Living Donor Adult Liver Transplantation Using a Left Lobe Graft

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Background. Hepatic venous reconstruction is critical in living donor adult liver transplantation (LDALT) because outflow obstruction in small for size graft may lead to graft dysfunction or loss. We describe the usefulness of venoplasties of the graft hepatic vein (HV) and graft HV-recipient inferior vena cava (IVC) reconstruction in LDALT using a left lobe graft.

Methods. Sixty patients who underwent LDALT were studied. We divided the patients into following two groups: venoplasty group (n=30) and control group (n=30). For the patients with venoplasty group, venoplasty of the graft and recipient IVC cavoplasty was made to widen the orifice. Comparison examination of a background factors and postoperative bilirubin and the ascites was carried out.

Results. The mean graft volume standard liver volume ratio (GV/SLV) did not have the difference at 41.7% of venoplasty group, and 42.1% of control group (p=NS). The diameter of the hepatic vein in control and venoplasty group before and after venoplasty is 26.9±5.5, 28.2±2.9, and 34.1±3.9 mm, respectively. The diameter of the hepatic vein after venoplasty is larger than that of before venoplasty and of control ($P<0.05$). Mean total bilirubin level on postoperative day (POD) 7 is 13.8±9.3 mg/dl in control group and 7.0±3.3 mg/dl in venoplasty group ($P<0.05$). Mean amount of ascites on POD 7 and 14 are 1576±1113 and 1397±1661 cc in control group, and 736±416 and 550±385 cc in venoplasty group, respectively ($P<0.05$). Two-year survival rate is 75.2 % in control group and 86.6 % in venoplasty group ($P<0.05$).

Conclusions. We conclude that in LDALT using left lobe graft, HV-IVC reconstruction with graft venoplasty and IVC cavoplasty is useful not only to prevent outflow block but also to improve graft function.

Keywords: Venoplasty, Living donor liver transplantation, Small for size graft.

(*Transplantation* 2005;80: 964–968)

For living donor adult liver transplantation (LDALT), graft function is dependent on adequate inflow and outflow. Hepatic venous reconstruction is especially critical because outflow obstruction and/or stenosis may lead to graft dysfunction (*1–4*). Optimum graft function is largely dependent on adequate inflow and outflow, which are matters of technical perfection in organ transplantation (*4*). All vascular anastomoses are important although hepatic venous reconstruction is extremely critical in living donor liver transplantation (LDLT) because of the short hepatic veins and limited working anastomotic space (*5, 6*). These conditions require a perfect primary anastomosis because a redo would be difficult, if not impossible (*7*). Early experience in segmental liver transplantation was mostly with left side grafts, for with several techniques of outflow reconstruction has been developed. Emond et al. advocated triangulation methods to create a wide outflow orifice (*8*). Egawa et al. developed the use of the middle hepatic vein and the left hepatic vein with a right caudad extension on the inferior vena cava (IVC) (*5*), whereas Kubota et al. recommended a triple-recipient hepatic vein reconstruction with creation of a long venous trunk (*6*). We report our experience and analyze the clinical outcomes with a modified technique of recipient cavoplasty and graft venoplasty to allow only a single outflow anastomosis.

PATIENTS AND METHODS

Patients

Sixty consecutive living donor adult liver transplantations (LDALT) using left lobe graft performed at Kyushu University Hospital and Gunma University Hospital were studied. The main indications for LDALT were cholestatic liver diseases (n=21), liver cirrhosis (n=7), hepatocellular carcinoma (n=22), and fulminant hepatic failure (n=10). Forty-two patients received ABO identical grafts and eighteen patients received ABO compatible grafts.

A preoperative evaluation for potential living donors

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included a completed history and physical examination, an abdominal computed tomography scan, and angiogram. The computed tomography scan was used to calculate the size of the whole liver and the extended left lobe. The angiogram assessed the hepatic arterial supply, especially to the left lobe, and the diameters of the hepatic arteries. The standard liver volume (SLV) was calculated according to the formula of Urata et al. (*9*), whereas the weight of the procured left lobe, labeled as GV, was measured on the back table. Subsequently the ratio GV/SLV could be calculated.

Donor Procedure (Graft Hepatic Vein Venoplasty)

The donor left hepatectomy was performed according to our standard technique (*11–13*). Intraoperative cholangiography and ultrasonography ware performed, followed by cholecystectomy. The arteries supplying the left love were dissected and divided at their branching site from the either right or the proper hepatic artery. The transection of the liver parenchyma, after a dissection of the left hepatic artery and portal and hepatic veins, was performed with the liver fully perfused. After full mobilization of the liver and division of the hilar structures, the right hepatic vein (RHV) and the middle (MHV) and left hepatic veins (LHV) are cross-clamped and another clamp is placed on the vena cava wall proximal to clamped hepatic veins, just as a transverse side clamp of the vena cava. For last 30 cases we performed venoplasty, and former 30 cases were control.

A venoplasty was performed to fashion a singlewide outflow orifice according to the methods with was reported by De Villa et al. (*3*) (Fig. 1A). Although multiple veins may be detected as separate on preoperative imaging studies, they were often obtained attached by an intervening septum. Three techniques for graft venoplasty have been employed. If two veins were connected by a relatively long intervening septum, a plasty of this septum was performed in order to make outflow circumference more uniform and to depress the septum. This made done by making an incision perpendicular to the septum and removing the directly underlying liver parenchyma using CUSA. This incision was then stretched along the axis of the septum, and the vessel edges were approximated using interrupted 6-0 PDS sutures leaving the knots on the extraluminal side (Fig. 1B, C). The orifice diameter was measured using a caliper before and after venoplasty. This venoplasty took about 10 to 20 min.

Recipient Procedure (IVC Cavoplasty)

The recipient operation was performed using our standard technique described before (*13–17*). In the recipient, the diseased liver was removed leaving the IVC intact with the RHV and the trunk of MHV and LHV clamped separately, then the RHV was sutured close. After side-clamping the IVC, the septum between the MHV and the LHV was incised to create a common orifice, and the IVC wall was incised to widen the orifice.

The size of this opening was adjusted by extending it on the IVC or by suturing adjunct vessel edges as in the venoplasty described above, leaving the diameter about 1-2 mm wider than that of the graft hepatic vein. A single hepatic vein anastomosis was performed, whenever possible, assuring the correct orientation of the graft and recipient vessels. The anastomosis was carried out using interluminal everting technique using 5-0 PDS sutures without leaving a growth factor for left side grafts.

Postoperative Management and Evaluation

The amount of ascites was measured with total of fluid from drainage tube placed in left and right subphrenic space and Winslow foramen. The drainage tubes were removed when fluid collection less than 200 ml/day, and all recipients had at least one drainage tube on POD 14.

Duplex Pulse Doppler ultrasonography was performed every postoperative day in all recipients to confirm the patency of the blood viscosity.

Parametric variables were compared using the unpaired Student's t test, while nonparametric variables were compared using a chi-square analysis. The survival probability of recipients was determined by the Kaplan-Meier methods. A P value of <0.05 was considered significant.

RESULTS

The donor, recipient and graft characteristics were summarized in Table 1. There is no difference between venoplasty and control group in the donor and recipient factors. In control group, cholestatic diseases is most frequent (14/30;

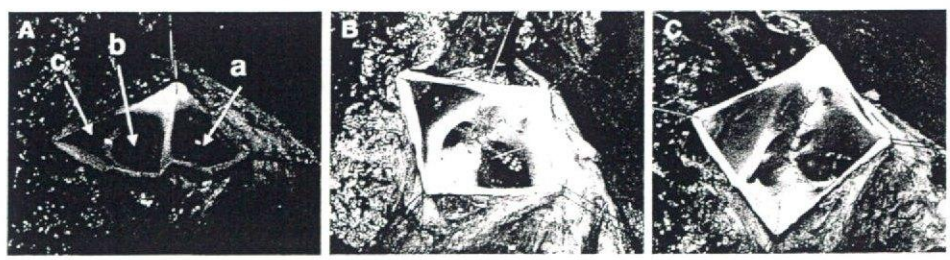

FIGURE 1. Venoplasty and cavoplasty techniques. (1) Before venoplasty. There are three lumen including left hepatic vein, middle hepatic vein, and caudate lobe branch. The diameter of the hepatic vein is 30 mm. (a) Left hepatic vein. (b) Middle hepatic vein. (c) Caudate branch. (2) During venoplasty. An incision across the septum is made and the directly underlying liver parenchyma is removed using the CUSA, and interrupted sutures are placed to close the incision, resulting in a wider and more uniform outflow orifice. (3) After venoplasty. Graft hepatic vein became one big orifice. The diameter of the hepatic vein is 35 mm.

TABLE 1. Donor, recipient, and graft characteristics

Factors	Venoplasty group	Control group	P value
n	30	30	
Donor			
Age (years)	31.9±12.1	39.4±14.2	0.14
>50 years	6 (20.0%)	7 (23.3%)	0.99
Male/female	23/7	24/6	0.91
Recipient			
Age (years)	50.9±11.4	53.4±7.6	0.47
Male/female	16/14	14/16	0.87
Bilirubin level (mg/dl)	11.1±8.8	10.6±8.3	0.82
Child B/C	5/25	5/25	1.00
MELD score	20.6±5.3	21.1±5.4	0.72
Indication			
Cholestatic disease	7	14	0.18
Fulminant hepatic failure	7	3	
Hepatocellular carcinoma	13	9	
Liver cirrhosis	3	4	
Graft			
Graft volume/standard liver volume	41.7±7.8	42.1±8.9	0.89
Graft recipient weight ratio	0.77±0.17	0.81±0.20	0.98

47%), on the other hand, hepatocellular carcinoma is most frequent (13/30; 43%) in venoplasty group. For high-risk cases, we use right lobe graft, and the risk of cholestatic cases in this study were same as hepatocellular cases. The preoperative bilirubin levels, Child score, and MELD score in each group were similar. The mean GV/SLV did not have the difference at 41.7% of venoplasty group, and 42.1% of control group (p=NS). In addition, the mean GRWR did not have the difference at 0.77% of venoplasty group, and 0.81% of control group (p=NS).

It has been reported that older donors (>50 yrs) were risk factor for graft survival in LDLT (*18*). In this study, donor age of the control group was higher than that of venoplasty group, but it was not significant. The number of older aged donor (>50 yrs) in control and venoplasty group were 7 (23.3%) and 6 (20.0%), respectively (P=0.99). And there was no difference between older donors (>50 yrs) and younger donors (<50 yrs) in bilirubin levels, amount of ascites, and graft survival in this study.

The diameter of the graft hepatic vein in control group and venoplasty group before venoplasty is 26.9±5.5 and 28.2±2.9 mm, respectively. No difference was seen between control and venoplasty group before venoplasty. On the other hand, after venoplasty, the diameter of the hepatic vein was widen to 34.1±3.9 mm. The diameter of the hepatic vein after venoplasty is larger than that of before venoplasty and of control (P<0.05).

In the patients with control group, wave form of hepatic vein by Doppler sonography becomes monophasic after 7 POD; on the other hand, in the patients with venoplasty group, triphasic pulsate wave form was kept after 28 POD.

Postoperative graft function was evaluated by total bilirubin level on POD 7 and amount of ascites on POD 7 and 14. Mean total bilirubin level on POD 7 is 13.8±9.3 mg/dl (range; 0.9-29.5 mg/dl) in control group and 7.0±3.3 mg/dl in venoplasty group (range; 2.3-14.9 mg/dl). The difference is statistically significant in total bilirubin level on POD 7 (P<0.05). Mean amount of ascites on POD 7 and 14 are 1576±1113 cc (range; 476-5303 cc) and 1397±1661 cc (range; 292-6778 cc) in control group, and 736±416 cc (range; 380-1884 cc) and 550±385 cc (range; 100-1982 cc) in venoplasty group, respectively. The differences are statistically significant in amount of ascites on POD 7 and 14 (P<0.05).

Two-year survival rate is 75.2% in control group and 86.6% in venoplasty group. The difference is statistically significant (P<0.05).

We defined small-for-size graft syndrome as hyperbilirubinemia (total bilirubin level > 10 mg/dl on POD 14) and refractory ascites (amount of ascites > 1000 cc on POD 14) (*16,17*), and by the control group, eight patients (27%) were small-for-size graft syndrome; on the other hand, there were two patients (7%) with small-for-size graft syndrome in venoplasty group.

DISCUSSION

LDLT was initially introduced in pediatric liver transplants and then extended to adult-to-adult liver transplants (*19*). To avoid small-for-size graft, a right lobe graft was used in living donor liver transplantation (LDALT) (*20–24*). The graft volume is enough with the right lobe graft; however, congestion-related complications are seen in many cases. Lee et al. (*4*) and other many authors reported that the necessity of MHV drainage reconstruction in right lobe grafts, which do not have MHV trunk in certain instances.

The most important problem in the LDALT is a small-for-size graft (SSG). Although a right lobe graft is used in many cases in order to avoid SSG, for a donor, the risk has few in left lobe graft (*11*). Our previous reports demonstrated that risk factors related to graft loss were a preoperative urgent status due to chronic liver disease, preoperative hyperbiliru-

binemia of over 10 mg/dl, and ABO blood type of not identical but compatible combination between donor and recipient. Minimum GV in adult-to-adult LDLT should be 30% less than the recipient's SLV in patients without cirrhosis, whereas 45% less was required in patients with cirrhosis. Therefore, if estimated graft weight is more than 40%, a left-lobe graft remains a feasible option in LDALT (*16*). We also reported that splenectomy or splenic artery ligation is considered to be beneficial for improving the outcome in LDALT using a left lobe graft (*17*). The graft volume has been advocated to be ideally over 40% of the standard liver volume. In adult recipients, if a left lobe graft is selected, the graft volume is often less than 40% of the standard liver volume. On the other hand, we have recently reported that a left lobe graft still remains an important option for LDALT (*10, 11*). To minimize the risk of the donor, we use left lobe graft for LDALT, however, the risk of small for size graft for the recipient is higher than the right lobe graft. From our left lobe graft experiences, wave form of hepatic vein was pulsate in early time after transplantation, but then getting flat in many cases which mean compromised outflow. Moreover, these cases showed hyperbilirubinemia and refractory ascites, which are characteristics of small for size graft. It means the enough outflow is needed for not only right lobe graft but also left lobe graft.

Although obtaining multiple graft hepatic veins in one cuff is an advantage, the presence of an interventing septum may limit the flexibility and distort the configuration of the vessels. The septoplasties described herein are designed to make the configuration of the outflow orifice uniform and easier to anastomose to the recipient hepatic vein (*3*). The graft venoplasties in this series were easily performed, prevented multiple anastomoses that, in effect, helped reduced graft ischemia time, and were not significantly associated with outflow problems.

On the recipient side, we use the anterior IVC wall to create enough outflow trunk. For left side grafts, which included left lateral segment grafts for pediatric case and left lobe grafts for both pediatric and adults, the LHV or common orifice of the MHV and LHV for an end-to-end anastomosis was initially used. Egawa et al. reported a 10.2% complication rate with this technique (*5*), although Emond et al. reported 33% hepatic outflow obstruction with an end-toend LHV anastomosis in their earlier cases of reduced-size liver transplantation (*7*). The Kyoto group modified the technique by adding a right caudad incision on the IVC to widen the common orifice created by dividing the septum between the MHV and LHV (*5*). However, 3 of 72 patients in whom this modification was applied still developed hepatic outflow obstruction. Kubota et al. also reported hepatic vein reconstruction in LDLT using left-sided graft (*6*). Different from Kyoto group (*5*), Tokyo Group (*6*) described that according to the venoplasty method, the recipients' HV trunk is made longer and the anastomosis becomes much easier and safer. It is still unclear which is better wide or long in hepatic vein anastomosis in LDLT, especially in adult case, because both groups studied pediatric cases.

Pulse Doppler ultrasonography was widely used after liver transplantation to confirm the patency of the blood viscosity. Normal hepatic veins usually show a triphasic waveform reflecting the cardiac cycle. It has been reported that all of the patients with hepatic vein stenosis showed monophagic waves (*25*). The cause of monophasic wave patterns may be due to transit outflow disturbance caused by graft movement, prenchymal changes associated with other LDALT-related complications, postoperative edema, influence of the patient's respiration, or changes in abdominal pressure. The relative position of the hepatic veins is fixed so that even a slight movement of the graft results in buckling of the vessels and poor flow in the hepatic veins (*23*). The clinical signs of hepatic vein stenosis are usually nonspecific and include congestion of the liver parenchyma with abnormal laboratory values, hepatomegaly, ascites, and pleural effusions.

We performed venoplasty with septoplasty of the graft hepatic vein and incised recipient IVC wall to widen the orifice. With this method, diameter of the graft hepatic vein was widen from 28 mm to 34 mm and pulsatile wave form of hepatic vein by Doppler sonography was kept for at least 28 days. Posttransplant graft function such as hyperbilirubinemia and refractory ascites is also improved. These finding suggest that outflow disturbance might be one of the causes of small for size graft injury and venoplasty and hepatic vein IVC reconstruction improve small for size graft function. Different from right lobe graft which congestion occurred mainly S5 and/or S8, congestion is not occurred in left lobe graft with MHV, but outflow disturbance injured whole graft gently. This injury might be caused to hyperbilirubinemia and refractory ascites, and these injuries were not fatal but lead to another complication.

We conclude that in LDALT using left lobe graft, hepatic vein IVC reconstruction with graft venoplasty and IVC cavoplasty is quite useful to improve not only graft function but patient survival.

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In Situ Dye Injection Bile Leakage Test of the Graft in Living Donor Liver Transplantation

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Background. Bile leakage after living donor liver transplantation (LDLT) remains a serious problem, resulting in lower survival rates. The aim of this study is to clarify the benefits of in situ leakage testing of the cut surface of grafts in LDLT.
Methods. A total of 135 LDLTs were analyzed. The patients were divided into the following two groups according to the in situ dye injection leakage test of the cut surface: test group (n=40) and control group (n=40). The incidence of bile leakage and the risk factors were identified by analyzing the recipients, donors, and transplantation variables.
Results. Bile leakage occurred in 12.5% (10/80) of LDLTs. In the control group, there were nine cases of bile leakage (22.5%). On the other hand, there was only one case (2.5%) of bile leakage in the test group ($P<0.05$). The bile leakage case in the test group was resolved preservationally. However, 2 of the 9 (22.2%) bile leakage cases in the control group required surgery.
Conclusion. Although there is biliary complication, especially bile leakage from the cut surface, as an inevitable consequence of LDLT, this study suggests that there is advantage in conducting bile leakage testing to minimize the incidence of bile leakage from the cut surface, which is associated with a high risk of graft failure.

Keywords: Living donor liver transplantation, In situ bile leakage test, Dye injection.

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Due to an extreme shortage of cadaver livers, the incidence of living donor liver transplantation (LDLT) has rapidly increased, especially in Japan (*1–3*). LDLT was initially introduced in pediatric liver transplants and then extended to adult-to-adult liver transplants (*4*). Transplant procedures in LDLT are usually more complex than standard orthotopic liver transplantation, and the introduction of microsurgical techniques in LDLT has reduced hepatic arterial complications. Nevertheless, the occurrence of biliary complication occurs with an incidence of 14 to 38% in LDLT (*5–7*). Our previous report showed that the overall incidence of biliary complication is 43.2% (16/37) (*7*). There were 8 cases (21.6%) of anastomotic stricture, 9 cases (24.3%) of bile leakage and 8 cases (21.6%) of cholangitis, and anastomotic stricture is strongly correlated with partial artery reconstruction and cholangitis ($P<0.01$). Unlike anastomotic stricture and cholangitis, bile leakage occurs early in the postoperative period and causes peritonitis and/or hepatic artery thrombosis, which require surgery or retransplantation. To avoid bile leakage, the donor surgeon needs to operate carefully using special devices. However, it is difficult to find bile leakage of the cut surface during operation. We previously reported that dye injection leakage testing of the cut surface is useful, and we applied this method to donor hepatic resection (*8*). We herein describe the outcome and benefits of in situ leakage testing of the cut surface of the graft in LDLT.

PATIENTS AND METHODS

We studied 80 recent consecutive LDLT cases. These consisted of cholestatic diseases in 20 cases, fulminant hepatic failure in 13 cases, hepatocellular carcinoma in 25 cases, liver cirrhosis in 15 cases, and other diseases in 7 cases. There were 3 left lateral segment grafts, 57 left lobe grafts and 20 right lobe grafts. All of the left lobe grafts were extended left lobe grafts including the middle hepatic vein with the caudate lobe. Regarding the selection of the graft, graft-harvesting technique, recipient operation and perioperative management of recipients, including immunosuppression regimens, have been described previously (*9–12*).

During donor operation, an in situ dye injection leakage test of the cut surface of the graft was conducted as follows; cholecystectomy was performed and a catheter was inserted into the cystic duct for later cholangiography (*8*). Parenchymal transection was commenced from the anterior surface on the demarcation line using CUSA. After completion of parenchymal transection, dye was injected through the catheter. Ten to 15 cc of diluted indocyanine green (ICG) solution was injected into the bile duct, and possible leakage from the cut surface was then evaluated. If dye was seen on the cut surface of the graft or the donor liver, additional stitches were applied (Fig. 1) (*8*). For recipient biliary reconstruction, 15 patients underwent Roux-Y hepaticojejunostomy and another 65 patients underwent end-to-end duct-to-duct anastomosis (*7, 12, 13*). For anastomosis, the leakage test was routinely conducted after the completion of anastomosis (*13*).

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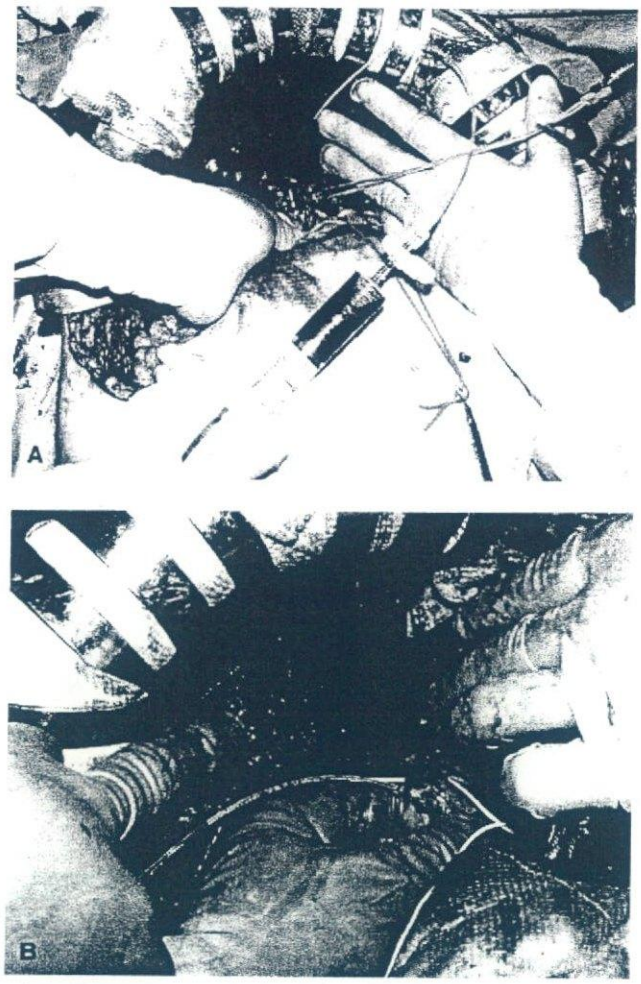

FIGURE 1. Injection of dye from cystic duct into common bile duct. The common bile duct was manually clamped by the surgeon's fingers. The bile leakage test consisted of injection of approximately 10–15 cc diluted indocyanine green solution by means of cholangiography catheter (A). With this procedure, we could recognize small bile leakage sites on the cut surface of the liver and could repair these sites, mainly by Z-suturing using 5-0 PDS sutures (B).

The primary end point was the incidence of postoperative bile leakage. Bile leakage was defined as bilious drainage that continued for more than 1 week. The secondary end points were assessment of bile leakage.

The patients were divided into two groups according to the in situ dye injection leakage test. For the last 40 consecutive cases, we performed an in situ dye injection leakage test, and the former 40 consecutive cases were used as controls. The minimum follow-up period was three months.

The data were expressed as means ± standard deviations. Student's *t* test with continuous variables and the chi-square test of independence with categorical variables were used to compare the two groups. The survival probability of the recipients was determined using the Kaplan-Meier method. A *P* value of < 0.05 was considered statistically significant.

RESULTS

The donor, graft, and recipient demographics are shown in Table 1. Regarding the donor, graft and recipient variables, no difference was found in age, sex, graft type, or the proportion of adults between the two groups. The main indication for LDLT was hepatocellular carcinoma in both groups.

In the test group, 20% of the patients (8/40) showed bile leakage by testing the cut surface, and these leaks from the cut surface were successfully repaired during operation. Bile leakage occurred in 10 (12.5%) of 80 LDLTs. In the control group, there were 9 cases of bile leakage (22.5%). On the other hand, there was only one case (2.5%) of bile leakage in the test group. The difference was statistically significant. On the other hand, postoperative bile leakage from the cut surface of the donor occurred in 3 cases (3.8%), 2 in the control group and 1 in the test group.

Table 2 summarizes the management and clinical course of the patients with bile leakage. All cases of bile leakage occurred early in the postoperative period (6.4±5.4 PODs, range; 2–21). In the control group, 2 (22.2%) of the 9 patients with bile leakage underwent laparotomy, and one patient underwent retransplantation due to hepatic artery thrombosis, which caused bile leakage infection. On the other hand, the case of bile leakage in the test group was resolved preservationally.

Figure 2 demonstrates the Kaplan-Meier graft survival curves of 80 patients with LDLT according to the bile leakage test. In the control group, the 1-, 3- and 5-year patient survival rates were 75.5%, 65.7%, and 65.7%, respectively. In the

TABLE 1. Donor and recipient characteristics

Factors	Test group	Control group	*P* value
n	40	40	
Donor			
Age (years)	35.5 ± 11.8	38.3 ± 12.6	0.87
Male	28	27	0.99
Female	12	13	
Recipient			
Age (years)	44.6 ± 19.0	45.7±16.1	0.91
Male	19	16	0.65
Female	21	24	
Pediatric	4	5	
Adult	36	35	0.99
Left lateral segment	1	2	
Left lobe	30	37	
Right lobe	9	11	0.71
Indications			
Cholestatic disease	11	9	0.90
Fulminant hepatic failure	7	6	
Hepatocellular carcinoma	12	13	
Liver cirrhosis	6	9	
Others	4	3	
Child-Pugh score			0.52
B	4	7	
C	36	33	
Hepatico-jejunostomy	8	7	0.99
Duct-to-duct anastomosis	32	33	

Data are n or means ± SD.

TABLE 2. Bile leakage

Factors	Test group	Control group	*P* value
N	40	40	
Bile leakage	1 (2.5%)	9 (22.5%)	0.02
Postoperative day of onset	6	7.0±5.4	
Range	6	2–21	
Left lateral segment	0	1	
Left lobe	0	5	
Right lobe	1	3	
Hepatico-jejunostomy	1	2	
Duct-to-duct anastomosis	0	7	
Management			
Drainage	1 (100%)	7 (77.8%)	
Reoperation	0 (0%)	2 (22.2%)	
Retransplantation	0	1	
Donor bile leakage	1 (2.5%)	2 (5.0%)	

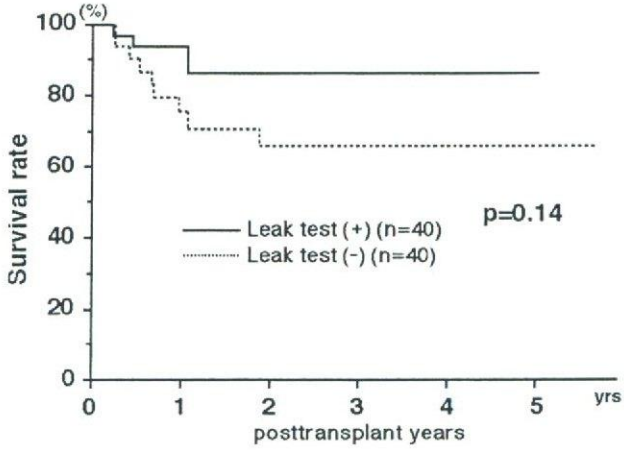

FIGURE 2. The Kaplan-Meier graft survival curves of 40 patients with LDLT according to in situ bile leakage test. In patients with bile leakage test, the 1-, 3-, and 5-year patient survival rates were 93.3%, 86.1%, and 86.1%, respectively. And patients without bile leakage test, the 1-, 3-, and 5-year patient survival rates were 75.5%, 65.7%, and 65.7%, respectively. The graft survival rate was higher in the patients with bile leakage test than those without bile leakage test (P=0.14).

bile leakage test group, the 1-, 3- and 5-year patient survival rates were 93.3%, 86.1%, and 86.1%, respectively. The graft survival rate was higher in the patients who had undergone the bile leakage test than in those who had not (P=0.14).

DISCUSSION

In living donor liver transplantation (LDLT), it has been reported that biliary complications such as biliary stricture, bile leakage, and cholangitis are common. Our previous report demonstrated that the overall incidence of biliary complication was 43.2% (*7*). Of the three biliary complications, bile leakage occurred early in the postoperative period (within 1 month). There are two types of bile leakage: one is anastomotic leakage, and the other is bile leakage from the cut surface of the graft. We routinely performed the bile leakage test after biliary anastomosis (*13*), and the incidence of bile leakage from the anastomotic site was minimized. However, it is difficult to prevent bile leakage from the cut surface of the graft with this leakage test. We also previously reported bile leakage testing using dye injection from a cholangiography catheter after hepatic resection (*8*), and applied this method to LDLT donors.

The aim of the bile leakage test is to detect insufficiently closed stumps of bile ducts on the transected liver surface by elevating biliary pressure. In this study, 26% of the patients in the test group showed bile leakage with this test, and these leaks were successfully repaired; the effective prevention of postoperative bile leakage seemed to be achieved. Including the transient cases, one patient (2.5%) showed bilious drainage despite the test. One possible cause of bile leakage is leakage from a separated bile duct with no communication with the main biliary tree. A bile leakage test cannot always examine all the biliary stumps on the transected liver surface. In this study, however, only one patient (2.5%) developed bile leakage after LDLT compared with nine patients (22.5%) in the control group. Bile leaks from small biliary stumps with some communication with the main biliary tree usually resolve spontaneously with the restoration of peristalsis and papillary function. Bile leaks from the separated parts often involve concomitant interruption of portal or arterial blood supply and also subside with associated partial atrophy of the liver. Therefore, if effective drainage is achieved, it is usually sufficient to observe the patient conservatively as long as careful management of draining to prevent infection is maintained. We believe that surgical intervention is only required when a bile leak originates from injury to a major duct.

In LDLT, bile leakage from the cut surface of the graft is not a major risk factor in graft loss or patient death, unlike hepatic artery thrombosis or biliary anastomotic leakage, and bile leakage from the cut surface has not been discussed in detail cut (*5*, *14–16*). In our series, bile leakage is not a significant risk factor in patient death. However, the posttransplant graft survival rate was lower in the patients that did not undergo the bile leakage test than in those who did (93.3 vs. 75.5 in 1 year, 86.1 vs. 65.7 in 3 and 5 years). The incidence of bile leakage from the cut surface of the graft in LDLT is the same as liver resection (*17*, *18*). Despite technical advances and new liver resection devices, the incidence of bile leakage after liver resection is 4.9% to 8.1% according to recent reports. Tanaka et al. (*19*) reported that postoperative bile leakage occurred in 7.2% (26/363) of the patients and concluded that some instances of leakage are unavoidable. Lo et al. (*20*) reported that biliary complication carried high risk of liver failure and operative mortality after hepatic resection. Our previous report showed that bile leakage occurred in 31 of 679 hepatic resections (4.6%) and, since 1997, none of the 102 cases where an intraoperative bile leakage test was performed was complicated by postoperative bile leakage (*8*). We applied this method to both graft and donor livers in LDLT, and there was one case (2.5%) among the donors and one case (2.5%) among the recipients of bile leakage after operation. These results are better than other reports on bile leakage after hepatic resection.

In conclusion, although biliary complication, especially bile leakage, is an inevitable consequence of LDLT, this study

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suggests the advantage of bile leakage testing of the cut surface to minimize the incidence of bile leakage associated with a high risk of graft failure.

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Clinical Studies

Influence of HLA compatibility and lymphocyte cross-matching on acute cellular rejection following living donor adult liver transplantation

Suehiro T, Shimada M, Kishikawa K, Shimura T, Soejima Y, Yoshizumi T, Hashimoto K, Mochida Y, Maehara Y, Kuwano H. Influences of HLA compatibility and lymphocyte cross-matching on acute cellular rejection following living donor adult liver transplantation.
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Abstract: *Background:* Reports on the relevance of immunogenetic factors in living donor adult liver transplantation (LDALT) are often conflicting or inconclusive. We therefore investigated the human leukocyte antigen (HLA) mismatches, lymphocyte crossmatch positivity, and the reactivity in mixed lymphocyte culture (MLC) in a series of LDALT. *Methods:* A total of 104 LDALT patients were studied. The minimum follow-up was 12 months, and the graft survival rates were assessed. The incidence of the most common complications was analyzed. And the influence of HLA, the flow cytometric analysis findings, enhanced cytotoxic cross-matching and MLC on graft survival, and acute rejection was also investigated. *Results:* As a result, 96 negative cross-matching and eight positive cross-matching cases were identified. Positive cytotoxic cross-matching had a significant effect on graft survival ($P<0.05$), while flow cytometric cross-matching also had an additional effect on acute rejection ($P<0.05$). The MLC of the patients with three HLA mismatches was significantly higher than the MLC of patients with zero HLA mismatches. The incidence of acute cellular rejection (ACR) was higher in the patients with three mismatches than in the other patients, and moderate rejection only occurred in the patients with three mismatches. *Conclusion:* HLA mismatching was not statistically associated with the overall graft survival after LDALT. The graft failure rates were higher in the positive cross-matching cases and therefore a strong immuosuppressant might be needed for positive cross-matching cases.

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Key words: living donor liver transplantation-HLA – cross-matching – rejection – prognosis

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There is still no consensus on the effect of human leukocyte antigen (HLA) matching, cross-matching, or other immunogenetic tests in liver transplantation. For example, Markus et al. (1) and others such as Donaldson et al. (2) found HLA matching, at least for Class I and possibly Class II HLA, to be detrimental to graft survival. However, Nikaein et al. (3) showed HLA-A, B, DR matching to be significantly associated with enhanced graft/patient survival. Markus et al. (1) suggested that these apparently conflicting findings result from what was termed a dualistic effect of HLA matching in liver grafts. They proposed that HLA compatibility reduced graft rejection but could stimultaneously enhance other immunological mechanisms leading to graft dysfunction.

Considerable debate still remains regarding the effect of positive cytotoxic cross-matching in liver transplantation. Hyperacute rejections have rarely been seen in liver transplantation, although Ranter et al. (4) reported one such case, and it is noteworthy that the HLA-specific antibody involved had a titer of 1:30 000, which is far above the 1:2 to 1:8 that is normally encountered. Published reports on the significance of a positive cross-matching are polarized, with some considering it to be an important contraindication for transplantation while others have concluded it to be of no consequence. Therefore, the importance of a positive cross-matching as