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Is graft size a major risk factor in living-donor adult liver transplantation?

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Abstract Graft size is known to be a major risk factor in living donor adult liver transplantation (LDALT). The aim of this study is to reassess whether graft size is a critical factor in LDALT or not. A series of 75 LDALTs excluding auxiliary transplantation and ABO blood-type incompatible transplantation were analyzed. The patients were divided into two groups, according to graft volume (GV) and standard liver volume (SLV): group 1 (small-size group) (GV/SLV: <40%), and group 2 (non-small-size group) (≥40%). Perioperative clinical data were compared between the two groups, including graft survival and postoperative complications. These parameters were also compared under the conditions of cirrhotic recipients. No difference in graft survival was found between the two groups. No difference was found in incidence of postoperative complications, such as intractable ascites and persistent hyperbilirubinemia. Even in cirrhotic patients with Child–Pugh's class C, there was no difference in graft survival between the two groups. Risk factors related to graft loss were a preoperative urgent status due to chronic liver disease, pre-operative hyperbilirubinemia of over 10 mg/dl, and ABO blood type of not identical but compatible combination between donor and recipient. Graft size is not always considered to be a major risk factor in LDALT, although the number of patients was small in this study. Therefore, a left-lobe graft, even a "small-for-size" graft for adult recipients, remains a feasible option in LDALT.

Keywords Small-for-size graft · Left-lobe graft · Graft survival · Cholestasis · Intractable ascites

Introduction

Graft size is known to be a major risk factor in living donor adult liver transplantation (LDALT) [1, 2, 3, 4]. Kawasaki et al. [5] reported that a GV and SLV ratio of more than 30% is a safe limit. Lo et al. [6] reported that a graft with GV/SLV of less than 40% should be regarded as a marginal graft that would have a lower success rate. Together with other reports [1,,2, 3, 4], the graft volume is considered to be ideally over 40% of the standard liver volume. To avoid a "small-for-size" graft, right-lobe grafts have been increasingly used in LDALT [7, 8, 9, 10], however, a critical comment has been raised that mortality of the right-lobe donor was significantly high [11]. From an ethical point of view, the risks for the living donor have to be minimized. The removal of a left lobe of the liver for donation is a more conservative surgical procedure than right lobe removal. The potential risks in right-lobe donors have been reported to be higher than those in left-lobe or lateral-segment donors [12, 13, 14]. We previously reported that a "small-for-size" graft in which GV/SLV is less than 30% can be

used with careful perioperative management [15]. Furthermore, we reported that a left-lobe graft, usually a "small-for-size" graft, is an important option in LDALT, judging from the standpoint based on both donor safety and benefit of the recipient [16]. Therefore, it is recommended that left-lobe grafts be used.

LDALT is considered to be one of the procedures still on a learning curve. Both the minimum graft volume and the risk factors closely related to graft survival in LDALT remain unclear, therefore, it is extremely important to assess these problems. The aim of this study is to clarify whether graft size is a critical risk factor for graft survival in LDALT.

Patients and methods

Patient cohort

We included 73 LDALTs, except for auxiliary transplantation and blood-type incompatible cases, from May 1997 to July 2002 in this study. The patient group consisted of 31 men and 42 women, ranging in age from 18 to 70 years. The indication for LDALT consisted of fulminant hepatic failure in 24 cases, primary biliary cirrhosis in 16, viral liver cirrhosis including hepatocellular carcinoma in 24, primary sclerosing cholangitis in 2, familial amyloid polyneuropathy in 2, and other reasons in 5. There were 58 left-lobe grafts and 15 right-lobe grafts. All left-lobe grafts were extended left-lobe grafts including the middle hepatic vein; 44 of the 58 left-lobe grafts included the left caudate lobe.

All patients had a monthly follow up, and the median follow-up period was 358 days with 94 days and 1019 days as a 25th percentile and 75th percentile respectively. Graft survival was defined as the time period between LDALT and graft loss, either by patient death or by graft failure necessitating a retransplant.

Evaluation and selection of graft

Evaluation and selection criteria for a liver graft were described previously [15, 16]. Briefly, the standard liver volume was calculated according to the formula developed by Urata et al. [17]. Liver volume was estimated by preoperative computed abdominal tomography (CT) scanning, and in principle, GV divided by SLV over 30% is the ideal requirement. Our policy requires that a left-lobe graft is selected first and that the volume of the left-lobe graft is clearly less than 30% of SLV and approximately 25% of SLV, if this is not the case a right-lobe graft or auxiliary partial graft is chosen. Preoperative assessment of a three-dimensional CT was routinely performed, to ensure the parenchymal division line and the number and size of draining veins [18].

Surgical technique and postoperative care

The graft harvesting technique, recipient operation and perioperative patient management of recipients, including immunosuppression regimen, are described elsewhere [15, 16]. Briefly, the right-lobe grafts were excised using an ultrasonic dissector and electrocautery at the right side of Cantlie's line, which meant no middle hepatic vein was included in any of the right-lobe grafts. All branches from the middle hepatic vein were divided between the silk ties, except in one case. In all left-lobe grafts, the right first Glisson's branch including portal vein and hepatic artery were clamped; a demarcated line was observed on the right side of Cantlie's line. Parenchymal division was performed along a line 5 mm right of the demarcated line, therefore, all left-lobe grafts included a middle hepatic vein and a part of the anterior segment, which was perfused from left side vascular vessels. During the parenchymal division inside the liver, the cutting plane was made near the anterior Glisson's branch and right hepatic vein.

Grouping

The patients were divided into two groups, according to graft volume and standard liver volume: group 1 (small-size group; GV/SLV $<40\%$), and group 2 (non-small-size group; GV/SLV $\geq 40\%$). Perioperative clinical data were compared between the two groups, including graft survival and postoperative complications. These parameters were also compared for the conditions of cirrhotic recipients. Urgent status due to chronic liver disease was defined as patient's status requiring critical care in hospital due to chronic liver, including plasma exchange and continuous hemodiafiltration.

Statistics

The data were expressed as medians (25th percentile and 75th percentile). Comparisons of continuous variables were made using the Mann-Whitney U test. The chi-square test was used to compare the qualitative data. Graft survival was calculated by the product limit method of Kaplan and Meier, and the differences in the survival between the groups were then compared using the log-rank test. The software of StatView (Version 4.11; Abacus Concepts, Berkeley, CA94704–1014, USA) was used for all analyses on a Macintosh computer. A P value of less than 0.05 was considered statistically significant.

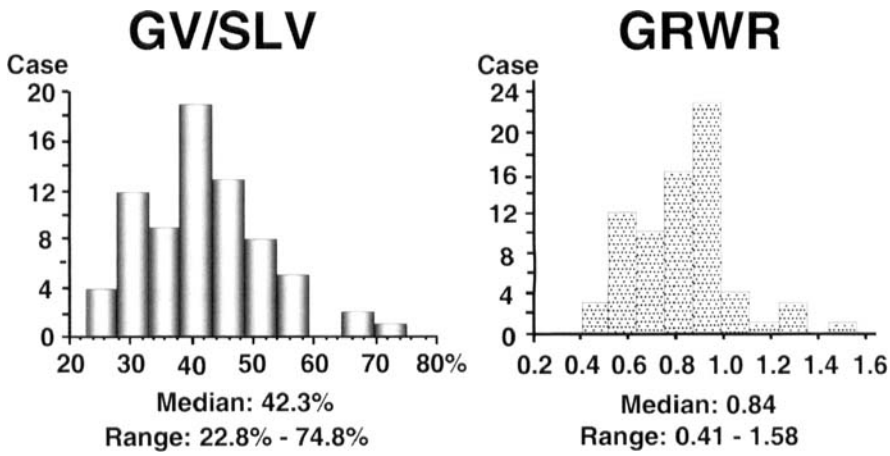

Fig. 1 Distribution of cases according to graft size; most grafts were "small-for-size" grafts

Results

There was no mortality of donors; postoperative complications which prolonged donor's hospital stay were: bile duct stenosis in two cases, abdominal abscess by meticilline-resistant *Staphylococcus aureus* in one, and bile leakage in one. Median postoperative hospital stay of the donors was 11.5 days, ranging from 5 days to 43 days. Graft size as GV/SLV ranged from 22.8% to 74.8%, with a median of 42.3%, and graft recipient weight ratio (GRWR) ranged from 0.41 to 1.58, with a median of 0.84 (Fig. 1).

A comparison of perioperative clinical variables among the two groups is shown (Table 1). Patients in group 1 were younger than those in group 2. Postoperative peak levels of aspartate aminotransferase, alanine aminotransferase and bilirubin in group 1 were lower than in group 2. Postoperative hospital stay in group 1 was shorter than in group 2. Examination of the graft's variables showed that the proportion of left-lobe grafts in group 1 was higher than in group 2. Graft weight, GV/SLV, and graft-recipient weight ratio in group 1 were lower than in group 2. Recipient variables showed no differences, except for gender, which was found in preoperative variables, including the Child–Pugh's class C, urgent status due to chronic liver disease, hyperbilirubinemia, and ascites. Operative time and blood loss in group 1 tended to be lower than in group 2. The incidence of postoperative hyperbilirubinemia (over 10 mg/dl at postoperative day 14) in group 1 was lower than in group 2. No difference was found in other variables, including postoperative intractable ascites, postoperative complications and incidence of acute cellular rejection.

The risk factors closely related to graft survival were: a preoperative urgency status, urgent status due to chronic liver disease, and ABO blood-type compatibility (not identical but compatible combination). A preoperative bilirubin value over 10 mg/dl and Child–Pugh's class C tended to be related to poor graft survival. In contrast, graft kind (left-lobe graft or right-lobe graft) and graft size were not always significant risk factors (Table 2).

When comparing graft survival curves, no significant difference was observed between group 1 and group 2 (Fig. 2). When graft survival curves in cirrhotic recipients, who were classified into the Child–Pugh's class C, are compared, no definite difference was found between group 1 and group 2 (Fig. 3).

Discussion

The distribution of graft size in this study ranged from 22.8 to 74.8% as GV/SLV with a median of 42.3%, and GRWR ranged from 0.41 to 1.58% with a median of 0.84% (Fig. 1). Most grafts in this study were surprisingly "small-for-size". In terms of donor selection criteria, the left-lobe graft is, in principle, selected for use when the donor's graft volume, using an extended left lobe plus caudate lobe, is more than 30% of standard liver volume. If the graft volume is clearly less than 30% of standard liver volume (approx. 25%) a right-lobe graft or an auxiliary partial graft is then selected. The minimum liver volume, needed to meet metabolic demand, was reported to be less than 20% of the liver in non-cirrhotic patients [19]. In LDALT, a liver graft with 25% of the standard liver volume was reported to be successful for fulminant hepatic failure [6]. In this study, a patient with fulminant hepatic failure, whose liver graft was 22.8% of his standard liver volume, quickly recovered and obtained good initial function, although he unfortunately died of chronic rejection on postoperative day 205. However, in general, the graft size is known to critically influence the outcome of LDALT. Tanaka et al. [3] reported that the use of "small-for-size grafts" ($< 1\%$ of graft-recipient weight ratio) leads to lower graft survival. Miller et al. [2] reported that graft function and survival were influenced not only by graft

Table 1 Comparison between clinical variables of group 1 and group 2. (*Group 1* small group in which graft volume was < 40% of standard liver volume, *group 2* non-small group, in which graft volume was ≥40% of standard liver volume, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *FHF* fulminant hepatic failure, *PBC* primary biliary cirrhosis, *LC* viral cirrhosis, including hepatocellular carcinoma, *PSC* primary sclerosing cholangitis, *FAP* familial amyloid polyneuropathy, *HAT* hepatic artery thrombosis, *PVT* portal vein thrombosis, CMV cytomegalovirus)

Variables	Group 1 ($n=26$)	Group 2 ($n=47$)	P value
Donor variables			
Age (years)	29 (23, 35)	44 (28, 50)	< 0.01
Gender (male/female)	15/11	33/14	0.31
Blood loss (ml)	788 (470, 1000)	700 (364, 1200)	0.58
Operating time (min)	429 (355, 506)	448 (405, 483)	0.65
Postoperative AST (IU/l)	236 (202, 353)	336 (239, 469)	< 0.05
Postoperative ALT (IU/l)	266 (180, 368)	361 (233, 460)	< 0.05
Postoperative bilirubin (mg/dl)	1.5 (1.3, 1.9)	2.1 (1.6, 3.5)	< 0.01
Postoperative hospital stay (days)	11 (9, 14)	14 (10, 167)	< 0.01
Graft variables			
Graft kind	–	–	< 0.05
Right lobe	0	15	–
Left lobe	7	7	–
Left lobe and caudate lobe	19	25	–
ABO compatibility	–	–	0.55
Identical	22	36	–
Compatible	4	11	–
Graft weight (g)	368 (330, 410)	520 (463, 588)	< 0.01
GV/SLV (%)	32.1 (28.9, 35.7)	45.9 (42.5, 50.5)	< 0.01
GRWR	0.61 (0.56, 0.69)	0.90 (0.83, 0.98)	< 0.01
Recipient variables			
Age(years)	48 (39, 57)	48 (42, 54)	0.95
Gender (male/female)	15/11	16/31	0.08
Diagnosis			
FHF	10	14	–
PBC	5	11	–
LC	8	16	–
PSC	1	1	–
FAP	0	2	–
Others	2	3	–
Preoperative bilirubin (mg/dl)	8.3 (3.2, 17.0)	11.3 (3.6, 17.9)	0.46
Preoperative bilirubin > 10 mg/dl	12 (46.2%)	27 (57.4%)	0.51
Preoperative ascites	10 (38.5%)	21 (44.7%)	0.63
Child–Pugh class			
A	3	5	–
B	2	2	–
C	11	29	–
FHF	10	11	–
Esophageal varices	10 (38.5%)	23 (48.9%)	0.46
Urgent status due to chronic liver disease[a]	2 (7.7%)	8 (17.2%)	0.48
Operating time (min)	717 (621, 838)	797 (716, 926)	0.05
Blood loss (ml)	4510 (2600, 7300)	6040 (4000, 10032)	0.1
Postoperative persistent cholestasis	3 (11.5%)	19 (40.4%)	0.02
Postoperative intractable ascites (> 1 l/day at postoperative day 14)	4 (15.4%)	4 (8.5%)	0.44
Postoperative complications			
Biliary			
Leakage	2	5	–
Stenosis	2	0	–
Bleeding	1	0	–
Vascular			–
HAT	2	1	–
PVT	1	0	–
Infarction	1	2	–
Infection			–
Sepsis	1	1	–
CMV-related	0	2	–
Fungus-related	1	1	–
Others	4	8	–
Acute cellular rejection	6 (23.1%)	16 (34.0%)	–

[a]Defined as patient's status requiring critical care in hospital due to chronic liver, including plasma exchange and continuous hemodiafiltration

size, but also by pre-transplantation disease severity. A graft-recipient weight ratio as low as 0.6% can be used safely in patients without cirrhosis or in patients with Child–Pugh's class A. Transplant recipients with Child–Pugh's class B or C require a graft-recipient weight ratio greater than 0.85% to avoid "small-for-size" syndrome

Table 2 Risk factors related to graft survival

Variables		1-Year survival	*P* value
ABO compatibility	Identical ($n=58$)	86.20%	0.01
	Compatible ($n=15$)	58.20%	–
Preoperative bilirubin >10 mg/dl	Present ($n=39$)	69.50%	0.08
	Absent ($n=34$)	93.10%	–
Child–Pugh class C[a]	Present ($n=39$)	79.40%	0.22
	Absent ($n=12$)	90.90%	–
Urgent status due to chronic liver disease[b]	Present ($n=10$)	51.40%	0.009
	Absent ($n=63$)	84.10%	–
Graft kind	Left lobe ($n=58$)	79.00%	0.47
	Right lobe ($n=15$)	84.60%	–
Graft size	Extra-small ($n=7$)	85.70%	0.4
	Small ($n=19$)	65.00%	–
	Medium ($n=34$)	83.50%	–
	Medium-large ($n=13$)	90.90%	–

[a]Fulminant hepatic failure was excluded
[b]Defined as patient's status requiring critical care in hospital due to chronic liver, including plasma exchange and continuous hemodiafiltration

and related complications. Makuuchi et al. [4] also recommended that a larger graft is necessary for high-risk patients with primary biliary cirrhosis (updated Mayo risk scores of more than 12). In contrast, in this study it is of great interest that no significant difference in graft survival rates was found between the two groups, not only in all patients but also in a subgroup of cirrhotic patients with Child–Pugh's class C in which the influence of a "small-for-size" graft is enhanced on outcome of LDALT. When assessing the reasons why graft survival rate of the Child–Pugh's class C patients in group 2 (with a larger graft) tended to be poorer than in group 1 (with smaller graft), one possible reason is that the incidence of urgent status due to chronic liver disease in group 2 (27.6%) tended to be higher than that in group 1 (18.2%). Another possible reason was the incidence of liver cancer in group 2 (31.0%) which tended to be higher than in group 1 (18.2%), furthermore, two patients in group 2 died of cancer recurrence (6 months and 24 months after operation, respectively). Graft-survival analysis was carried out using two subgroups: patients with acute liver failure and those with chronic liver insufficiency (data not shown). In the subgroup of patients with acute liver failure, the graft survival in group 1 (with smaller graft) tended to be better than that in group 2 (with larger graft). In contrast, the graft survival in group 1 was similar to that in group 2 in the subgroup of patients with chronic liver insufficiency (especially Child–Pugh's class C patients) (Fig. 3).

From an ethical point of view, donor safety has priority. Unfortunately, in LDALT, the need of larger-size grafts for children has encouraged the use of right hepatic lobes from living donors. As a result, mortality of right-lobe donors was reported to be nearly 1% in western countries [11]. In Japan, however, donor mortality was not reported until July 2002 (in more than 2,000 LDLTs). We previously reported that postoperative peak values of aspartate aminotransferase and total bilirubin in right-lobe donors were higher than in left-lobe donors. Furthermore, postoperative hospital stay in right-lobe donors was longer than in left-lobe donors. These facts clearly indicate that potential risks in right-

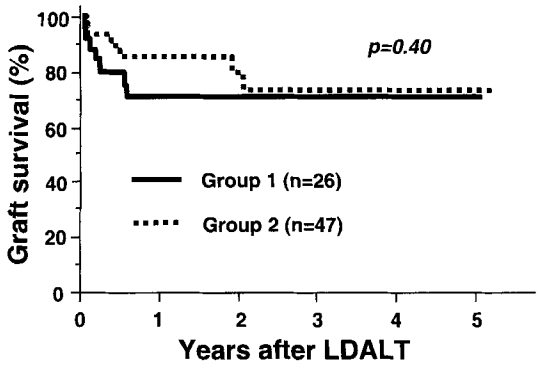

Fig. 2 Graft survival according to graft size. No significant difference in graft survival was found among the four groups. *Group 1* small-size group, in which graft volume was <40% of standard liver volume, *group 2* non-small-size group, in which graft volume was ≥40% of standard liver volume

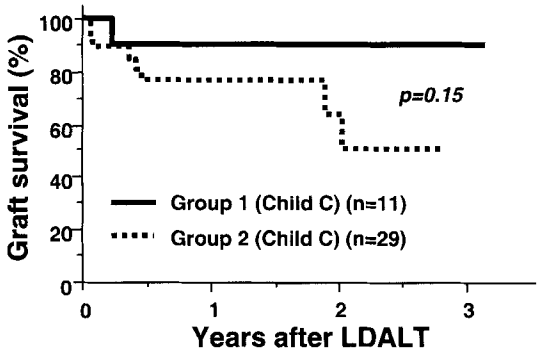

Fig. 3 Graft survival according to graft size in patients with Child–Pugh's class C liver cirrhosis. No difference in graft survival was found among the four groups. *Group 1* small-size group, in which graft volume was <40% of standard liver volume, *group 2* non-small-size group, in which graft volume was ≥40% of standard liver volume

lobe donors were higher than in left-lobe donors; the same results were obtained in this study. To minimize potential risks for living donors, left-lobe grafts for adult recipients (small-for-size grafts), should be carefully reassessed. Factors related to graft failure of "small-for-size" grafts are considered to be: (1) graft injury due to excessive portal flow and/or portal pressure, and (2) excessive metabolic and synthetic demand of recipients. Portal venous decompression was reported to improve survival of canine partial liver transplantation [20]. The effect of a porto-hepatic vein shunt on portal vein decompression might be an important factor for preventing graft injury after recirculation in an extremely small graft. In France, a new technique for adult liver transplantation using a "small-for-size" graft was reported in order to avoid graft congestion and failure by over perfusion, in which the superior mesenteric venous flow was diverted by a mesocaval shunt with downstream ligation of the superior mesenteric vein [21]. Splenectomy of splenic artery ligation might be another alternative to obtain a better outcome in LDALT using "small-for-size" grafts. Splenectomy was reported to generate the following merits: reduction of graft congestion leading to improvement of the hepatic renal functions; improvement of thrombocytopenia persistence after liver transplantation; avoidance of bleeding episodes related to left-sided portal hypertension [22]. Makuuchi et al. [23] also reported that splenectomy in LDLT is an acceptable treatment option in patients with thrombocytopenia or when hepatopetal portal flow must be obtained by closure of splenorenal shunt. However, further investigations are necessary to make definite conclusions.

The following were risk factors closely related to poor graft survival: poor prognostic factors for graft survival; the urgent status due to chronic liver disease; preoperative bilirubin value of more than 10 mg/dl; ABO blood-type compatibility. Urgency status is also known to be one of the risk factors associated with graft loss in cadaveric liver transplantation using whole-liver grafts [24]. Therefore, another therapeutic strategy rather than procurement of a larger-size graft would be necessary for high-risk patients.

Humar [25] recently commented on graft selection, with citation of our previous article (Arch Surg 2002), that transplant teams should not limit themselves to either the left-lobe or right-lobe graft. Rather, the recipient's size should be factored together with the severity of the recipient's liver disease on the best liver graft for that particular recipient with minimal risk to the donor. For smaller recipients or those with model for end-stage liver disease score, a left lobe may be the best choice. For others, especially those with more advanced liver disease, a right lobe could be the best option. This opinion sounds reasonable.

In conclusion, the graft survival rates according to graft size were not different, furthermore, the graft survival rates in patients with Child–Pugh's class C liver cirrhosis were similar. The risk factors affecting the graft survival were preoperative hyperbilirubinemia, compatible but not identical ABO blood type combination between donor and recipient, and the urgent status due to chronic liver disease. The graft size was not always considered to be a critical risk factor for LDALT, therefore, a left-lobe graft, even a "small-for-size" graft, remains a feasible option in LDALT.

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