association between the disease severity and progression of aggressive fibrosis. Retortillo et al. [18] reported that partial live donor grafts showed earlier fibrotic progression compared with deceased whole-liver transplants. Furthermore, Honda et al. [19] reported that hepatitis C virus actively infects and replicates in rapidly dividing hepatocytes via the activation of hepatocyte growth factors. A possible explanation for this could be that the metabolic demands on partial grafts are increased to a greater extent in sicker patients after LDLT, resulting in an increased activation of growth factors and active replication of hepatitis C virus.

Regarding the impact of center experience in performing LDLT, a combination of multiple surgical and non-surgical factors could explain the improved outcomes, as previously reported in the A2ALL study [20, 21]. That study showed a significant improvement in graft outcome after the first 15–20 cases, which was attributed to improvements in patient selection, perioperative management and surgical techniques. However, it should be noted that both A2ALL and non-A2ALL centers in the USA had extensive experience in performing deceased donor liver transplantation before starting LDLT. This differs from the clinical experience in Eastern countries. At our institutes, many surgical and non-surgical refinements have been introduced over the last 15 years [22]. The main surgical refinements include recipient high hilar dissection [23], controlling portal hypertension by splenectomy [24] and aggressive reconstruction of the middle hepatic vein tributaries [25]. Non-surgical refinements include three-dimensional anatomical and volumetric analysis [26], recipient risk evaluation [27] and the application of early enteral nutrition [28].

The managing strategies for recurrent hepatitis C have also been changed with increasing clinical experience. It has long been difficult to differentiate between acute rejection and early recurrent hepatitis C, and bolus doses of steroids were used to prevent possible rejection, resulting in the development of aggressive hepatitis C, as in other centers [29]. Currently, we treat patients with hepatitis C with a higher but more stable immunosuppression regimen to avoid acute rejection, which require bolus steroids for treatment. The incidence of acute rejection following bolus steroid administration has decreased significantly since Era-II (9/119 vs. 5/238 in Era-I, $p = 0.012$). This was largely due to the administration of interferon, which allowed for higher rates of biochemical and viral responses [14].

The relationship between PVP and the presence of major shunt vessels seems to be mutually related. Advanced liver disease causes an increased PVP, resulting in the creation of major shunts, which then reciprocally decrease the PVP. Moreover, the PVP after reperfusion is determined by the graft compliance, PV inflow and the regenerative activity of the graft [9]. Therefore, we believe that the development of major shunt vessels is one of the significant factors reflecting the hepatic disease severity, and thus the MELD scores [22]. The current results showing the significance of major shunt vessels implied that a deteriorated recipient condition had a significant impact on the short-term graft outcomes. However, the PVP had no significant impact in the current series, possibly because a higher PVP was intentionally controlled by splenectomy [13]. A lack of PVP modulation might have resulted in a finding that the PVP was a significant indicator for inferior graft survival.

The significant weakness of this study might be the learning curve bias. Since 2004, we have introduced many surgical and non-surgical refinements in LDLT, including splenectomy for high PVP [13], the introduction of a vessel sealing system [13], aggressive reconstruction of the middle hepatic tributaries in right lobe LDLT [25], the introduction of early enteral nutrition for preventing septic complication [28] and tailored antiviral treatment for recurrent hepatitis C [14]. However, our data showed that the accumulation of experiences significantly improved the outcomes in difficult cases.

In conclusion, the graft outcomes in patients with high MELD scores and the presence of hepatitis C were particularly poor. In patients with these risk factors, LDLT should be performed at experienced centers and/or by experienced surgeons.

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Liver Regeneration and Venous Collateral Formation in the Right Lobe Living-Donor Remnant: Segmental Volumetric Analysis and Three-Dimensional Visualization

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Background. In left lobe (LL) living-donor liver transplantation (LDLT), hepatic venous congestion (HVC) caused by ligation of the middle hepatic vein tributaries is unavoidable in the right lobe (RL) donor remnant.
Methods. To clarify the impact of HVC on liver regeneration and venous collateral formation (VCF), we used three-dimensional computed tomography to examine the volumes of total/segmental liver and HVC and the degree of VCF; preoperative data were compared with data obtained on postoperative day (POD) 35 in 13 LL LDLT donors.
Results. On POD 35, the congestion rate decreased from 32.5% to 1.6% and the total liver regeneration rate was 81.7%. Preoperatively, the anterior sector-to-RL volume ratio was significantly lower, and the posterior sector-to-RL volume ratio was significantly higher than postoperatively (56.7% vs. 52.9%, $P<0.01$, and 36.9% vs. 41.5%, $P<0.01$, respectively). There was no correlation between degree of HVC and liver regeneration. Obvious VCF was found in five (38.5%) cases. The RL and posterior sector volume per square meter of body surface area in the VCF group were significantly lower than that in the non-VCF group (412 cm^3/m^2 vs. 492 cm^3/m^2, $P<0.01$, and 140 cm^3/m^2 vs. 190 cm^3/m^2, $P<0.01$, respectively). The preoperative congestion rate and liver regeneration rate were not significantly different between the groups.
Conclusions. Reconstruction of the middle hepatic vein tributaries in the RL donor remnant might not be necessary in LL LDLT, because the HVC improved dramatically by POD 35 regardless of the development of VCF.

Keywords: Congestion, Hepatic vein, Left lobe graft, Living-donor liver transplantation, Reconstruction.

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Since the first study in 1989, living-donor liver transplantation (LDLT) has been widely accepted worldwide as the treatment of choice for end-stage liver failure (*1*). Although the use of the right lobe (RL) as a graft has been increasingly successful, the problem of donor safety exists. In LDLT, it was reported that the incidence of donor complications based on 1841 donors in Japan was significantly higher in donors of the RL than in donors of the left lobe (LL) and the left lateral segment (*2*). In addition, operative mortality for RL donors was estimated to be as high as 0.5%–1.0% (*3*). We have previously reported that LL LDLT was a feasible treatment modality for ensuring minimal mortality and morbidity in donors (*4*) and that the number of biliary complications was significantly lower in LL LDLT than in RL LDLT (*5*). Donor safety is the highest priority in LDLT. Therefore, to minimize the risk to donors, LL LDLT may be an ideal option in LDLT. However, because the grafts usually include the middle hepatic vein (MHV) to improve the venous drainage in LL LDLT, hepatic venous congestion (HVC) in the right anterior sector caused by deprivation of drainage from the MHV tributaries is unavoidable in the RL donor remnant; this can lead to territories with outflow obstruction bearing the risk of insufficient liver regeneration (*6, 7*).

In the preoperative evaluation of donor livers, HVC estimates are based on three-dimensional computed tomography (3D-CT). In RL LDLT, the operative decision for the reconstruction of the MHV tributaries on the recipient side depends on the degree of HVC. However, there is no consensus with regard to the optimal reconstruction strategy on the donor side in LL LDLT. Although it has been reported that drainage of the anterior sector might be

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dependent on intrahepatic venous collaterals between the MHV tributaries and the right hepatic vein (RHV) in the later postoperative phase (*8*), it is unclear how much anastomosis would develop postoperatively. Furthermore, it is still not clear as to how the HVC would influence liver regeneration and venous collateral formation (VCF) in the later postoperative phase.

The purpose of the present study was to better understand liver regeneration and VCF in the RL donor remnant in LL LDLT. We assessed total and segmental donor liver regeneration by comparing 3D-CT data obtained preoperatively with that obtained on postoperative day (POD) 35. We also determined the degree of VCF on POD 35 and examined how the HVC had influenced liver regeneration and VCF.

RESULTS

Preoperative and Postoperative Right Lobe Volume, Hepatic Venous Congestion Volume, Congestion Rate, and Liver Regeneration Rate

The mean (SD) preoperative 3D-CT estimated volumes of the whole liver, the RL, and the HVC were 1207 (40) cm^3 (range, 1029–1491), 801 (126) cm^3 (range, 593–1070), and 260 (81) cm^3 (range, 84–414), respectively. The mean (SD) postoperative volumes of the RL remnant and the actual congestion on POD 35 were 986 (135) cm^3 (range, 765–1232) and 15 (12) cm^3 (range, 0–34), respectively. The mean (SD) congestion rate decreased from 32.5% (10.7%) (range, 14.2%–59.4%) to 1.6% (1.3%) (range, 0.0%–3.4%) on POD 35. The mean (SD) liver regeneration rate on POD 35 was 81.7% (5.8%) (range, 70.1%–92.8%) (Table 1). There was no correlation between the preoperative congestion rate and the liver regeneration rate.

Comparison Between the Moderate and Severe Hepatic Venous Congestion Groups

Among the 13 LL LDLT donors, there were five (38.5%) cases in the moderate HVC group and eight (61.5%) cases in the severe HVC group. There was no significant difference in the rate of complications greater than Clavien grade 1 between these two groups (20.0% vs. 25.0%, *P* value is not significant [NS]); in addition, the liver regeneration rate on POD 35 did not differ significantly between the groups (83.8% vs. 80.4%, *P* value is NS). Postoperative liver function tests such as serum aspartate aminotransferase, alanine aminotransferase, total bilirubin, and prothrombin time were not significantly different between the two groups (Fig. 1A–D).

Preoperative and Postoperative Right Lobe Donor Volume: Segmental Volumetric Analysis

The mean (SD) preoperative estimated volumes of the anterior sector and the posterior sectors of the RL were 450 (71) cm^3 (range, 362–569) and 297 (81) cm^3 (range, 168–429), respectively. The mean (SD) volume ratio of the anterior sector to the RL was 56.7% (8.2%) (range, 44.0%–72.1%), and the mean (SD) volume ratio of the posterior sector to the RL was 36.9% (7.4%) (range, 23.1%–50.6%). The mean (SD) preoperative estimated volumes and mean (SD) segment-to-RL volume ratios were as follows: 163 (66) cm^3 (range, 108–357) and 20.5% (6.9%) (range, 11.9%–37.9%) in segment V, 286 (58) cm^3 (range, 212–400) and 36.2% (7.3%) (range, 22.5%–48.5%) in segment VIII, 129 (60) cm^3 (range, 46–229) and 16.3% (7.1%) (range, 5.9%–28.4%) in segment VI, and 168 (66) cm^3 (range, 92–277) and 20.6% (6.2%) (range, 11.5%–32.7%) in segment VII, respectively. The mean (SD) estimated volumes of the

TABLE 1. Summary of each liver parameter before and after surgery

	Preoperative	Postoperative (POD 35)
Whole liver volume, mean (SD), cm^3	1207 (40)	—
RL volume, mean (SD), cm^3	801 (126)	986 (135)
HVC volume, mean (SD), cm^3	260 (81)	15 (12)
Congestion rate,[a] mean (SD), %	32.5 (10.7)	1.6 (1.3)
Regeneration rate,[b] mean (SD), %	—	81.7 (5.8)
Segmental liver volume, mean (SD), cm^3		
Anterior sector	450 (71)	517 (73)
Segment V	163 (66)	172 (76)
Segment VIII	286 (58)	346 (60)
Posterior sector	297 (81)	413 (102)
Segment VI	129 (60)	175 (72)
Segment VII	168 (66)	238 (103)
Sector-to-RL volume ratio, mean (SD), %		
Anterior sector	56.7 (8.2)	52.9 (7.3)
Segment V	20.5 (6.9)	17.3 (6.5)
Segment VIII	36.2 (7.3)	35.6 (7.2)
Posterior sector	36.9 (7.4)	41.5 (6.9)
Segment VI	16.3 (7.1)	17.8 (7.2)
Segment VII	20.6 (6.2)	23.7 (8.2)

HVC, hepatic venous congestion; POD, postoperative day; RL, right lobe.
[a] Congestion rate (%) was calculated as HVC volume divided by RL volume.
[b] Regeneration rate (%) was calculated as postoperative RL volume on POD 35 divided by preoperative whole liver volume.

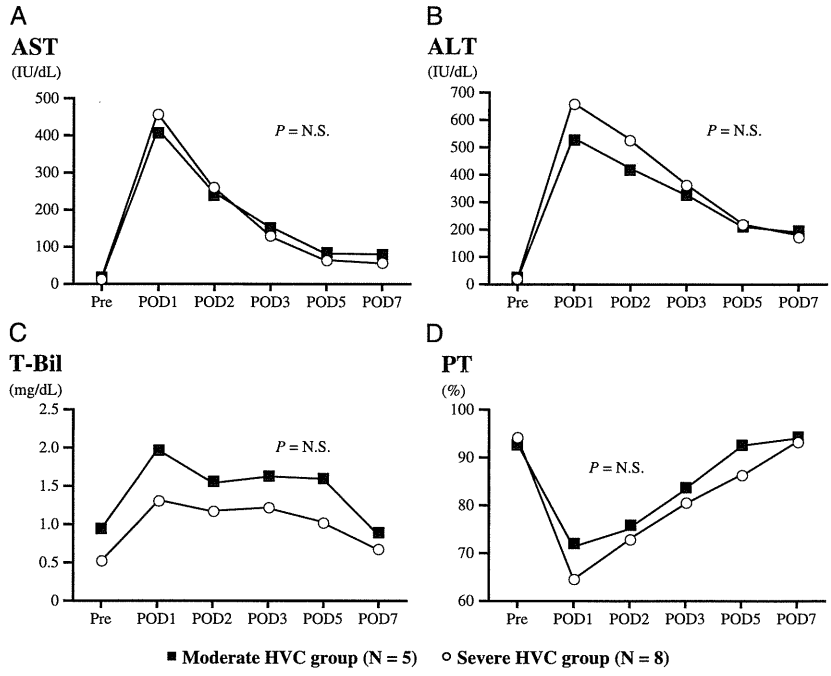

FIGURE 1. Postoperative serial change in liver function tests in the moderate and severe HVC groups. Postoperative liver function tests such as serum AST, ALT, T-Bil, and PT were not significantly different between the two groups. A, AST. B, ALT. C, T-Bil. D, PT. ALT, alanine aminotransferase; AST, aspartate aminotransferase; HVC, hepatic venous congestion; NS, not significant; POD, postoperative day; PT, prothrombin time; T-Bil, total bilirubin.

anterior sector and the posterior sector on POD 35 were 517 (73) cm^3 (range, 396–650) and 413 (102) cm^3 (range, 238–573), respectively. On POD 35, the mean (SD) volume ratio for the anterior sector to the RL remnant and the posterior sector to the RL remnant was 52.9% (7.3%) (range, 38.6%–62.0%) and 41.5% (6.9%) (range, 31.1%–55.9%), respectively. The mean (SD) estimated volumes on POD 35 and mean (SD) segment-to-RL volume ratios were as follows: 172 (76) cm^3 (range, 112–390) and 17.3% (6.5%) (range, 10.9%–34.4%) in segment V, 346 (60) cm^3 (range, 260–445) and 35.6% (7.2%) (range, 22.9%–47.6%) in segment VIII, 175 (72) cm^3 (range, 54–300) and 17.8% (7.2%) (range, 4.8%–29.4%) in segment VI, and 238 (103) cm^3 (range, 124–407) and 23.7% (8.2%) (range, 14.0%–39.7%) in segment VII, respectively (Table 1).

On POD 35, the anterior sector did not atrophy but became enlarged, regardless of the degree of HVC, and of course, the posterior sector became enlarged. However, the ratio of the anterior sector volume to the RL volume on POD 35 was significantly lower, and the ratio of the posterior sector volume to the RL volume on POD 35 was significantly higher than preoperatively (56.7% vs. 52.9%, $P<0.01$, and 36.9% vs. 41.5%, $P<0.01$, respectively) (Fig. 2A, B). According to detailed segmental volumetric analysis, on POD 35, the ratio of segment V volume to the RL volume was significantly lower and the ratio of segment VII volume to the RL volume was significantly higher than preoperatively (20.5% vs. 17.3%, $P<0.05$, and 20.6% vs. 23.7%, $P<0.01$, respectively); however, there were no significant differences in this volume ratio for segments VIII and VI (36.2% vs. 35.6%, P value is NS, and 16.3% vs. 17.8%, P value is NS, respectively) (Fig. 2C–F).

Comparison Between the Venous Collateral Formation Group and the Non–Venous Collateral Formation Group

Among all 13 cases, obvious VCF between the MHV tributaries and the RHV was found in 5 (38.5%) cases (Fig. 3A–E), in which 1 (7.7%) case simultaneously developed intrahepatic venous anastomoses between the MHV tributaries and the inferior right hepatic vein (IRHV) (Fig. 3E). The comparison between the VCF group and the non-VCF group is summarized in Table 2. There was no significant difference in the rate of complications greater than Clavien grade 1 between the two groups (20.0% vs. 25.0%, P value is NS). Postoperative liver function tests were not significantly different between the two groups. Additionally, there was no significant difference in the preoperative congestion rate and the liver regeneration rate on POD 35 between the VCF and the non-VCF groups (35.9% vs. 30.4%, P value is NS, and 80.1% vs. 82.6%, P value is NS, respectively). The preoperative RL volume per square meter of body surface area (BSA) in the VCF group was significantly lower than that in the non-VCF group (412 cm^3/m^2 vs. 492 cm^3/m^2, $P<0.01$). Although the volume per square meter of BSA of the anterior sector was not significantly different between the VCF and non-VCF groups (250 cm^3/m^2 vs. 266 cm^3/m^2, P value is NS), the volume per square meter of BSA of the posterior sector was significantly lower

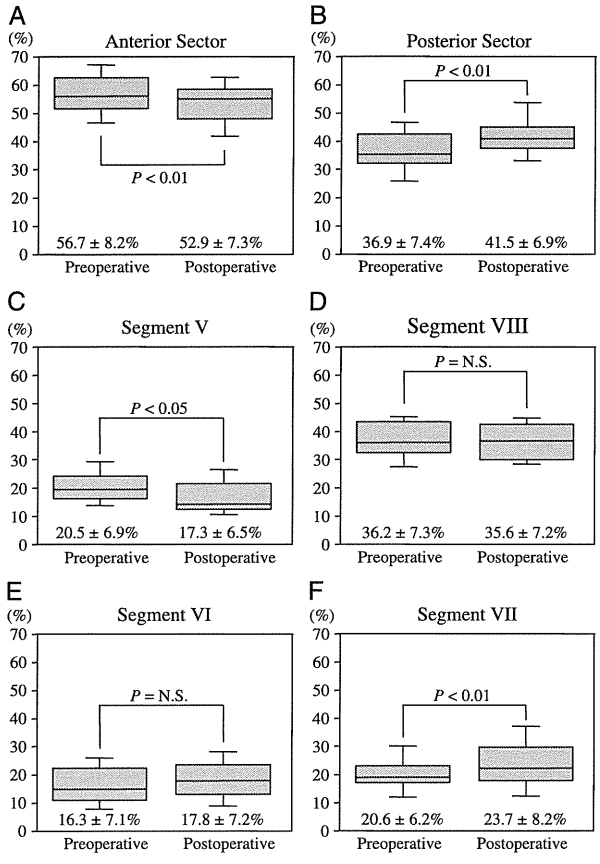

FIGURE 2. Comparison of preoperative and postoperative segmental liver-to-RL volume ratios. A, Anterior sector. B, Posterior sector. C, Segment V. D, Segment VIII. E, Segment VI. F, Segment VII. The postoperative anterior sector-to-RL volume ratio was significantly lower than preoperatively, and the postoperative posterior sector-to-RL volume ratio was significantly higher than preoperatively ($P<0.01$ and $P<0.01$, respectively). Postoperatively, the segment V-to-RL ratio was significantly lower, and the segment VII-to-RL ratio was significantly higher than preoperatively ($P<0.05$ and $P<0.01$, respectively). There were no significant differences in this ratio for segments VIII and VI, preoperatively and postoperatively. The liver segment-to-RL volume ratio is represented by box-and-whisker plots. The data (%) are shown as the mean value±standard deviation. The line in the box represents the median; the upper and lower lines of the box represent the 75th and 25th quartiles. The upper and lower lines outside of the box represent the 90th and 10th quartiles. NS, not significant; RL, right lobe.

in the VCF group than in the non-VCF group (140 cm^3/m^2 vs. 190 cm^3/m^2, $P<0.01$).

DISCUSSION

LDLT is an established procedure for the treatment of patients with end-stage liver disease, especially in Japan and other Asian countries, where deceased donors are not often available. In Western countries, LL LDLT has not generally been recognized as a feasible procedure because of the problem of graft size. The initial experience related to LL grafts demonstrated a higher incidence of small-for-size syndrome graft failure and recipient complications. Consequently, RL grafts have been used routinely at many centers (*9–11*). However, although the use of the RL as a graft has been increasingly successful, the problem of donor safety still exists. We have previously reported that the outcomes of LL LDLT were comparable with those of RL LDLT, although small-for-size syndrome occurred more often in LL LDLT. In addition, the overall donor morbidity rates were comparable between LL and RL, whereas postoperative liver function tests and hospital stay were significantly improved in LL donors (*12*). Donor safety should be the highest priority. Therefore, LL LDLT is considered the first choice in our institution.

In LL LDLT, the incidence of HVC in the right anterior sector caused by deprivation of drainage from the MHV tributaries is unavoidable. Left hepatectomy of the liver is a standard procedure in oncological liver surgery. Consequently, not much attention has been paid so far to the HVC of the remnant and reconstruction of the MHV tributaries is not usually performed. Indeed, even if transient liver dysfunction has occurred, HVC has been known to improve, with the liver returning to an almost normal level of function at POD 30 (*7*). In cases of HVC in the early postoperative phase, Doppler ultrasonography can show an absence of venous blood flow and reversed flow, indicating that the portal vein (PV) may be acting as a drainage vein owing to the presence of an acute hepatic outflow obstruction. However, by POD 7, Doppler ultrasonography can show a normal hepatopetal flow in the anterior PV (*13*). Therefore, in the later postoperative phase, drainage of the right anterior sector is believed to be dependent on the intrahepatic venous anastomoses between the MHV tributaries and the RHV (*8, 14*). Indeed, several reports have demonstrated that the collaterals can develop within several days after LDLT (*15, 16*). However, it is unclear as to how much anastomosis can develop postoperatively. Furthermore, it is still not clear as to how the HVC would influence liver regeneration and VCF in the later postoperative phase. Donor safety should be the highest priority as emphasized before. Death of donors can have a negative impact in various areas. After the death of a donor in New York in 2002, the frequency of LDLT was reduced by 51% in that city and by 21% in the United States as a whole (*17, 18*). Therefore, we find it difficult to understand such a phenomenon with regard to the RL donor remnant.

In liver transplant recipients receiving an RL graft, the reconstruction of the MHV tributaries has been performed using interposition grafts to prevent HVC. Cheng et al. (*19*) reported that there was no clinically significant difference in recipient outcome between the recipients who showed occlusion of the interposed graft and those recipients whose interposition grafts remained patent; however, graft regeneration was lower in the occluded group than that in the patent group. Whether the interposition grafts have remained patent is not considered to be clinically significant in the later postoperative phase, because the intrahepatic venous network between the MHV tributaries and the RHV is generally present (*8, 14*). However, this venous network has not been established yet in the early postoperative phase.

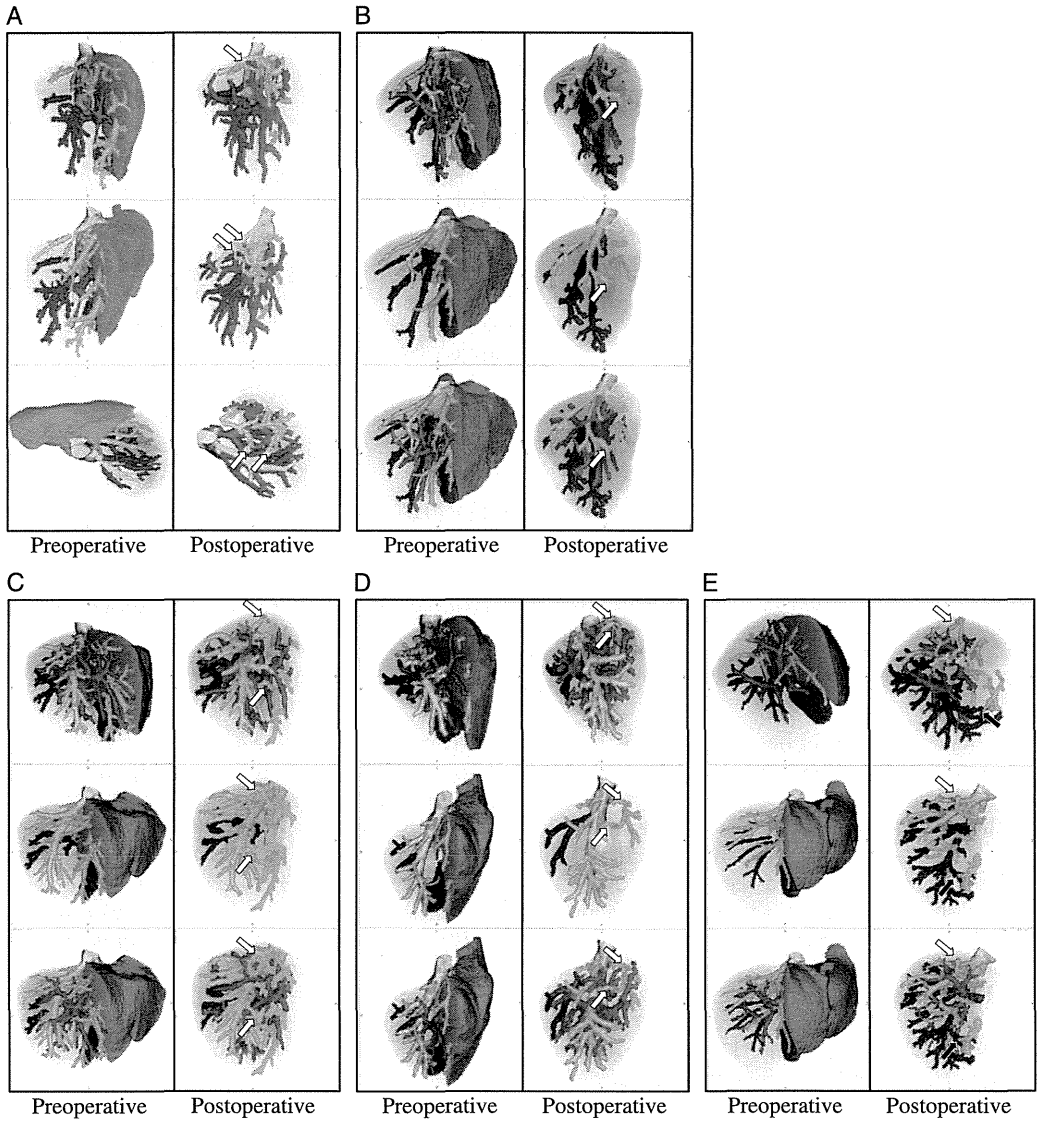

FIGURE 3. 3D-CT images of VCF visualization. Among all 13 cases, VCF between the MHV tributaries and the RHV (*white arrows*) was found in 5 cases (A–E). Of these cases, one simultaneously developed intrahepatic venous anastomoses between the MHV tributaries and the IRHV (*black arrows*) (E). The left and right sides of the figure represent preoperative and postoperative 3D-CT images, respectively. The RHV and IVC are colored aqua blue. The MHV tributaries, IRHV, and PV are colored yellow, red, and dark blue, respectively. 3D-CT, three-dimensional computed tomography; IRHV, inferior right hepatic vein; IVC, inferior vena cava; MHV, middle hepatic vein; PV, portal vein; RHV, right hepatic vein; VCF, venous collateral formation.

Therefore, to prevent liver dysfunction during this early period and eventual graft failure, the concept of the reconstruction of the MHV tributaries is an accepted modality (*8, 20*). We have previously reported that the MHV tributaries should be reconstructed in transplant recipients if the calculated HVC is more than 20% (*20*). However, there are no criteria for the reconstruction of the MHV tributaries in the RL remnant of donors in LL LDLT, and the reconstruction of the MHV tributaries has not usually been performed. The reasons for this are as follows: (1) the reconstruction procedure is difficult as it should be performed in situ and not on a back table; (2) it is necessary to create an additional wound to obtain the interposition graft; (3) because the imbalance between inflow and outflow can be mild in donors as compared with recipients (*21*), the impact of the congestion on the liver is believed to be mild in comparison to the impact on the recipients; (4) liver function will return to almost normal levels at POD 30 regardless of the degree of HVC (*7*); and (5) the collaterals between the ligated MHV tributaries and the RHV can develop within several days after LDLT (*15, 16*). However, it is still unclear as to the amount of intrahepatic venous

TABLE 2. Comparison between VCF group and non-VCF group

	VCF group (n=5)	Non-VCF group (n=8)	*P*
Preoperative factor			
Congestion rate,[a] mean (SD), %	35.9 (7.5)	30.4 (1.8)	NS
Serum AST level, mean (SD), IU/dL	21 (4)	19 (13)	NS
Serum ALT level, mean (SD), IU/dL	25 (6)	19 (20)	NS
Serum T-Bil level, mean (SD), mg/dL	0.8 (0.4)	0.8 (0.3)	NS
Serum PT level, mean (SD), %	94 (6)	93 (9)	NS
RL volume/BSA, mean (SD), cm^3/m^2	412 (28)	492 (22)	<0.01
Anterior sector volume/BSA, mean (SD), cm^3/m^2	250 (25)	266 (45)	NS
Posterior sector volume/BSA, mean (SD), cm^3/m^2	140 (31)	190 (37)	<0.01
Postoperative factor			
Regeneration rate,[b] mean (SD), %	80.1 (3.3)	82.6 (6.4)	NS
Complications greater than Clavien grade 1, n (%)	1 (20.0)	2 (25.0)	NS
Peak serum AST level, mean (SD), IU/dL	480 (156)	400 (110)	NS
Peak serum ALT level, mean (SD), IU/dL	680 (348)	523 (196)	NS
Peak serum T-Bil level, mean (SD), mg/dL	1.6 (0.4)	2.0 (1.0)	NS
Bottom serum PT level, mean (SD), %	67 (2)	70 (10)	NS

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; HVC, hepatic venous congestion; NS, not significant; POD, postoperative day; PT, prothrombin time; RL, right lobe; T-Bil, total bilirubin; VCF, venous collateral formation.

[a] Congestion rate (%) was calculated as HVC volume divided by RL volume.

[b] Regeneration rate (%)was calculated as postoperative RL volume on POD 35 divided by preoperative whole liver volume.

collateral development there would be, and how much influence the HVC would have on liver regeneration and VCF in the later postoperative phase.

Scatton et al. (*6*) reported that in the LL donor remnant without an MHV, the regeneration rate of segment VI was lower and the regeneration rate of segments II and III were higher in the global congestion group at 1 month after hepatectomy. Similarly, in this series, the ratio of the anterior sector volume to the RL volume calculated on POD 35 was significantly lower than that calculated preoperatively, whereas this ratio for the posterior sector on POD 35 was significantly higher than preoperatively. However, the anterior sector did not atrophy and became enlarged regardless of the degree of HVC. In the present study, among the 13 cases, obvious VCF between the MHV tributaries, the RHV, and the IRHV was found in 5 (38.5%) cases on POD 35. In contrast to what we had expected, the preoperative congestion rate was not significantly different between the VCF group and the non-VCF group. The fact that the congestion rate decreased from 32.5% to 1.6% on POD 35, and that there was no correlation between the preoperative congestion rate and the liver regeneration rate, might suggest that tiny intrahepatic anastomoses could develop in all cases, even though they could not be visualized using 3D-CT. Preoperative RL volume per square meter of BSA in the VCF group was significantly lower than that in the non-VCF group. Furthermore, the volume per square meter of BSA of the anterior sector was not significantly different between the groups, and that of the posterior sector was significantly lower in the VCF group. From these facts, it is reasonable to assume the following: (1) the smaller the RL donor remnant is, the more overloaded it will become owing to PV inflow; (2) the posterior sector will be more affected by PV inflow, because the anterior branch may be acting as a drainage vein owing to an acute hepatic outflow obstruction; (3) the greater the PV inflow overload is, the more VCF there will be; (4) in the case of obvious VCF, overload may be caused not only by outflow block but also by extra inflow.

In conclusion, in LL LDLT, although the HVC caused by ligation of the MHV tributaries is unavoidable in the RL donor remnant, the HVC had improved dramatically by POD 35 regardless of the development of obvious VCF. There was no correlation between the preoperative congestion rate and the liver regeneration rate. Therefore, the reconstruction of the MHV tributaries in the RL donor remnant may not be necessary in LL LDLT.

MATERIALS AND METHODS

Patients

From May to November 2009 at Kyushu University Hospital, 13 patients underwent LL LDLT. A total of 13 donors were thus the subject of this study. The donors included 11 men and two women. Their median age was 34 years (range, 21–53) and their median body mass index was 22.3 kg/cm^2 (range, 17.8–25.9). Median values estimated using preoperative 3D-CT for total liver volume, extended left and caudate lobe volume, and RL volume were 1189 cm^3 (range, 1029–1491), 409 cm^3 (range, 322–492), and 792 cm^3 (range, 593–1070), respectively. For all donors, 3D-CT was performed preoperatively and on POD 35.

Three-Dimensional Reconstruction and Volumetry

The procedures used have been described elsewhere (*7, 22, 23*). Briefly, multidetector helical CT (MDCT) images were obtained using 2-mm-thick slices represented on CT machines. Enhancement was achieved using an intravenous bolus injection of nonionic contrast medium (Iopamion, Schering, Erlangen, Germany) at a speed of 5 mL/sec. Two types of 3D-CT software were used to achieve 3D reconstruction of the liver, HVC area, and portal and hepatic venous branches from the MDCT data. One type of 3D-CT software was ZIO M900 (Zio Software Inc, Tokyo, Japan), with which it was possible to freely fix the cutoff line. The other was liver segmentation software (Hitachi Medico, Tokyo, Japan), which was used to calculate

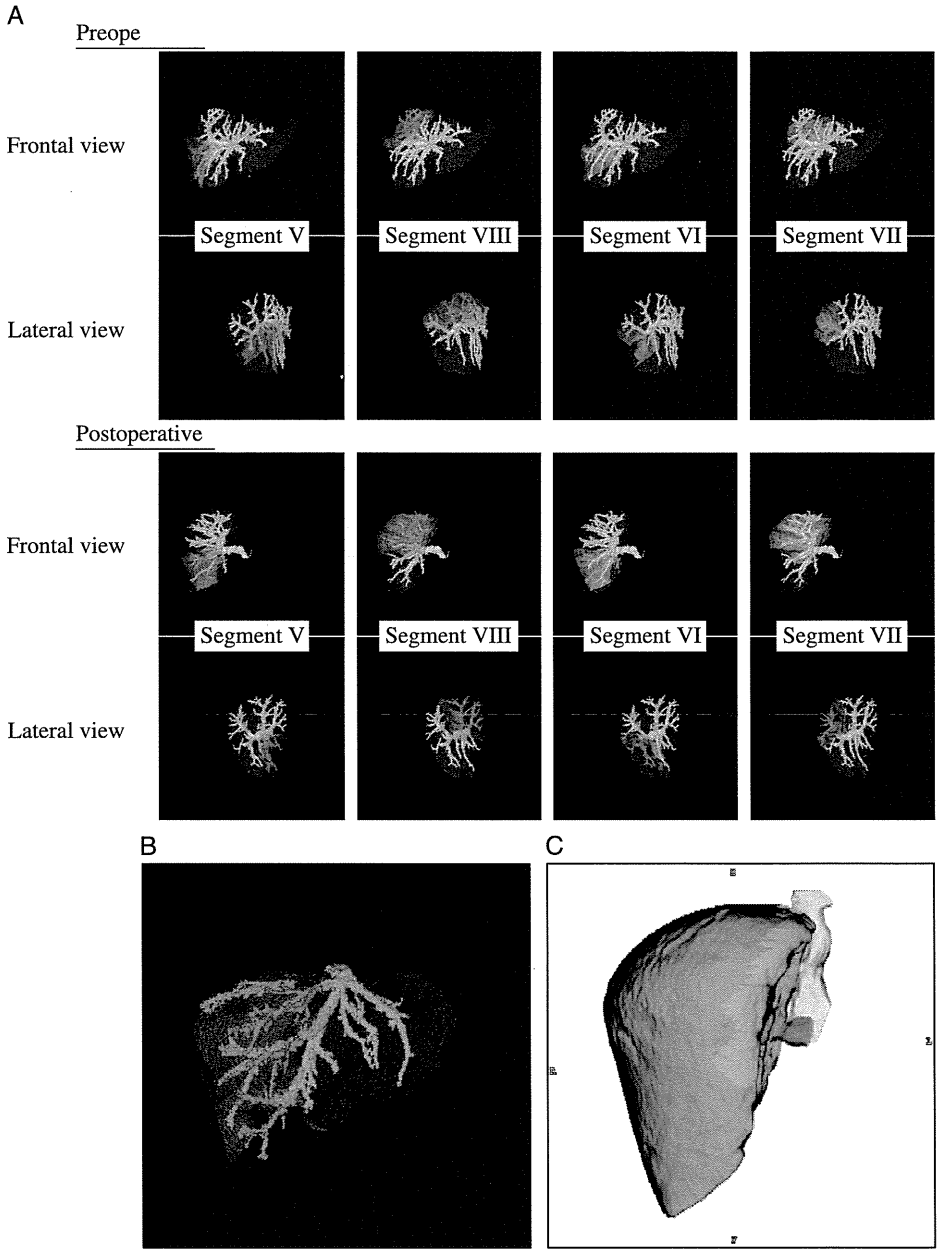

FIGURE 4. 3D-CT images of preoperative and postoperative segmental liver volumes and HVC. A, Preoperative and postoperative segmental liver volumes were calculated using liver segmentation software. Each segmental liver volume was calculated automatically from each PV branch territory and is described in frontal and lateral views. PV and each segmental PV branch are colored green and pink, respectively. The segmental liver volumes are colored light orange. B, Preoperative HVC volume of the MHV tributaries was automatically calculated from each hepatic venous branch using liver segmentation software. HV and the MHV tributaries are colored aqua blue and pink, respectively. Preoperative HVC volume is colored light orange. C, Postoperative HVC volume of the actual congestion area on POD 35 was rendered by two-phase CT using ZIO M900. It was calculated using the difference in attenuation between the congestion area and the noncongestion area. IVC and PV are colored aqua blue and dark blue, respectively. Postoperative HVC volume is colored purple. 3D-CT, three-dimensional computed tomography; HVC, hepatic venous congestion; IVC, inferior vena cava; MHV, middle hepatic vein; POD, postoperative day; PV, portal vein.

the liver volume and the volume of each vessel's (both portal and hepatic venous branches) territories from their diameter and length.

Total and Segmental Liver Volumes, the Ratio to the Right Lobe, and the Liver Regeneration Rate

Total and segmental liver volumes were calculated using liver segmentation software. The volume of the RL was calculated from the right PV territory, and the segmental liver volume of each PV branch was calculated automatically (Fig. 4A). Each volume ratio was calculated as follows: volume of a given segment divided by RL volume (%). The liver regeneration rate was calculated as follows: postoperative RL volume on POD 35 divided by preoperative whole liver volume (%).

Hepatic Venous Congestion Volume and the Congestion Rate

The preoperative HVC volume of the MHV tributaries was automatically calculated from each hepatic venous branch using the liver segmentation software (Fig. 4B). The 3D image reconstructed using this software could reflect the actual congestion volume. The postoperative HVC volume of the actual congestion area on POD 35 was rendered by two-phase CT using ZIO M900 software (Fig. 4C). The CT findings showed that the congestion area had become hyperattenuated because of poor drainage of the contrast medium (*24*). The postoperative HVC volume on POD 35 was calculated using the difference in attenuation between the congestion area and the noncongestion area. The detailed procedures have been described elsewhere (*7*). The congestion rate was calculated as follows: HVC volume divided by RL volume (%). The 13 LL LDLT donors were divided into two groups depending on the degree of congestion rate as previously described (*7*); the congestion rate of the moderate HVC group ranged from 10% to 30%, and that of the severe HVC group was greater than 30%.

Venous Collateral Formation Visualization

Postoperative VCF visualization on POD 35 was obtained from the MDCT data using ZIO M900 software. Detection of the connection between the MHV tributaries, the RHV, and the IRHV using the 3D-CT software was defined as "obvious VCF." Therefore, cases in which the MHV tributaries were patent, and in which the collateral connection could not be found, were not recognized as VCF. The 13 LL LDLT donors were divided into two groups: the VCF group and the non-VCF group.

Evaluation of Postoperative Clinical Parameters

Postoperative liver function tests such as serum aspartate aminotransferase, alanine aminotransferase, total bilirubin, and prothrombin time were measured on PODs 1, 2, 3, 5, and 7. Complications were classified according to Clavien's classification (*25*).

Graft Selection

The criteria for graft selection have been described elsewhere (*7, 8*). Briefly, an LL graft was initially considered as a graft with respect to donor safety. An RL graft was selected when an LL graft was insufficient for the recipient and the remnant liver volume of the donor was greater than 35%.

Surgical Procedure

The surgical procedures for donors have been described elsewhere (*4, 5, 8*). Briefly, donor hepatectomy was performed with intermittent inflow occlusion under the hanging maneuver. In LL grafts, the MHV was procured with the liver graft. Therefore, the MHV tributaries were ligated under hepatectomy. None of the MHV tributaries were reconstructed on the donor side.

Statistical Analysis

Statistical analysis was performed using Student *t* test and chi-square test. The data were considered significant when the *P* value was less than 0.05. All analyses were performed with the use of StatView software (Version 5.0, Abacus Concepts, Berkeley, CA).

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Strategies for Successful Left-Lobe Living Donor Liver Transplantation in 250 Consecutive Adult Cases in a Single Center

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BACKGROUND: Living donor liver transplantation (LDLT) using left-lobe grafts was not generally recognized as feasible due to the problem of graft size.

STUDY DESIGN: We retrospectively evaluated strategies for successful left-lobe LDLT in 250 consecutive cases stratified into 2 eras: Era 1 (n = 121), in which surgical procedures were continually refined, and Era 2 (n = 129), in which established procedures were used.

RESULTS: Graft volume (GV) did not affect the incidence of graft function or survival. Era 2 patients had decreased portal vein (PV) pressure at closure (16.0 ± 3.5 mmHg vs 19.1 ± 4.6 mmHg, $p < 0.01$), increased PV flow/GV (301 ± 125 mL/min/100g vs 391 ± 142 mL/min/100g, $p < 0.01$), and improved graft survival rate (1-year: 90.6% vs 81.8%. $p < 0.01$) despite the smaller GV/standard volume (SLV) ratio (36.2% ± 5.2% vs 41.2% ± 8.8%, $p < 0.01$) compared with Era 1. Patients in Era 2 had lower PV pressure and greater PV flow ($y = 598\text{-}5.7x$, $p = 0.02$) at any GV/SLV compared with cases in Era 1 ($y = 480\text{-}4.3x$, $p < 0.01$), representing greater graft compliance. Univariate analysis for graft survival showed that Era 1, Model for End-Stage Liver Disease (MELD) score ≥20, inpatient status, closing portal venous pressure ≥20 mmHg, no splenectomy, and operative blood loss ≥10L were the risk factors for graft loss, and multivariate analysis showed that Era 1 was the only significant factor ($p < 0.01$). During Era 2, development of primary graft dysfunction was associated with inpatient recipient status ($p = 0.02$) and donor age ≥45 years ($p < 0.01$).

CONCLUSIONS: The outcomes of left-lobe LDLT were improved by accumulated experience and technical developments. (J Am Coll Surg 2013;216:353–362. © 2013 by the American College of Surgeons)

Although living donor liver transplantation (LDLT) is becoming an established procedure for treating patients with end-stage liver disease, particularly in countries where deceased donors are rarely available, a critical issue in considering LDLT is that donor safety is not guaranteed.[1-3] When LDLT was first introduced for adults, left-lobe LDLT was the only option because of the risk of remnant liver failure in the donor after right-lobe donation.[4] However, because of the smaller graft volume (GV) and its possible association with inferior outcomes after left-lobe LDLT, right-lobe LDLT is performed worldwide, but the concept of left-lobe LDLT has been largely ignored except in Japan.[5,6] Nevertheless, the increased risk of morbidity and mortality of healthy donors after right-lobe donation should be taken seriously.[3]

Surgical and nonsurgical refinements in LDLT over the last decade have substantially improved the outcomes of LDLT. Consequently, the issue of GV might become less important based on accumulated experience and technical refinements. In 2009, the Hong Kong group[6] stated that small GV, defined as GV/standard liver volume (SLV) <40%, has been overcome in the context of right-lobe LDLT and has become less important in terms of graft outcomes. The Kyoto group[7] reduced their lower limit of the graft-to-recipient weight ratio (GRWR) in LDLT to 0.6% in combination with portal pressure control. In such situations, combined with the use of smaller grafts with institutional lower limits, left-lobe grafts could be considered instead of right-lobe grafts and could become the primary mode of LDLT again.

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Abbreviations and Acronyms

GRWR = graft-to-recipient weight ratio
GV = graft volume
GW = graft weight
HA = hepatic artery
LDLT = living donor liver transplantation
MELD = Model for End-Stage Liver Disease
PV = portal vein
SLV = standard liver volume

We have long advocated the feasibility of left-lobe LDLT and have performed 250 consecutive left-lobe LDLTs since 1997. During this time, we made various surgical and nonsurgical modifications and refinements. Therefore, the aim of this study was to evaluate the impact of progressive refinements on graft outcomes of left-lobe LDLT performed at a single center. We also sought to identify the factors associated with dysfunctional left-lobe grafts performed using current methods.

METHODS

Patients

Between May 1997 and May 2012, 250 consecutive left-lobe LDLTs in adults were performed at Kyushu University Hospital, under approval of the Ethics and Indications Committee of Kyushu University. The first adult left-lobe LDLT was in a patient with acute liver failure.[8] The major refinements to the surgical techniques and therapies applied are listed in Table 1, with the time of implementation according to the case numbers of left-lobe LDLT.

Graft selection process

Our institute exclusively used left-lobe grafts before December 2000, and the left-lobe LDLT was indicated if the predicted GV/SLV was ≥30%.[9] Since December 2000, we have used right-lobe grafts for selected patients once its effectiveness and safety had became affirmed worldwide.[10] However, a right-lobe graft, without the middle hepatic vein, could be considered if the predicted GV/SLV was ≥35% and the donor's remnant liver volume was ≥35% of the total liver volume.[2] At Kyushu University Hospital, a left-lobe graft with predicted GV/SLV ≥35% is the primary graft type and if it is not available, a right lobe graft is the secondary graft type. However, graft selection is still carried out on a case-by-case basis, considering anatomic and recipient factors. For example, a right-lobe graft is favored for a recipient with a Model for End-Stage Liver Disease (MELD) score ≥25.

For the first 38 cases, graft volumetry was assessed 2-dimensionally using 3-mm thick CT slices and image-analysis software (NIH image 1.61). In subsequent cases, 3-dimensional reconstruction of the liver was performed with helical CT data using zio-M900 software (Zio Software Inc), followed by virtual hepatic lobectomy and calculation of the predicted GV.[11]

Table 1. Refinements of Surgical Techniques and Therapies for Left-Lobe Living Donor Liver Transplantation

First author	Year	Surgical techniques or therapies	Case no.
Nishizaki[8]	2001	Adult-to-adult cases, predicted GV/SLV ≥30%	1
Ikegami[12]	2001	Left-lobe graft with the caudate lobe	17
Shimada[15]	2004	Splenic artery ligation	37
Hiroshige[11]	2003	Three-dimensional CT-based graft volumetry	39
Suehiro[13]	2005	Graft venoplasty and recipient cavoplasty	50
Soejima[2]	2012	Predicted GV/SLV ≥35%	102
Ikegami[16]	2009	Splenectomy for portal venous pressure control	122

GV, graft volume; SLV, standard liver volume.

Surgical procedures

The surgical procedures in the donors and recipients for left-lobe LDLT are summarized as follows. The first 16 left-lobe grafts included the middle hepatic vein without the caudate lobe. From case 17 on, we used left-lobe grafts with the caudate lobe.[12] Parenchymal transection was performed using the Cavitron Ultrasonic Surgical Aspirator (CUSA Valleylab Inc) and a saline-linked radiofrequency dissecting sealer (Tissuelink Tissuelink Medical Inc) using the hanging maneuver.[3] After donor hepatectomy, the graft was perfused, weighed, and stored in University of Wisconsin solution (Viaspan, DuPont Inc).

From case 50 on, venoplasty was performed on the back table to create a wider outflow orifice.[13] The long intervening venous septum was incised perpendicularly, and the underlying liver parenchyma was removed using the Cavitron Ultrasonic Surgical Aspirator. This incision was then stretched along the axis of the septum, and the vessel edges were approximated using interrupted 6-0 polydioxanone sutures. An incision was also made to the superficial veins to create a wide venous orifice, if possible.

The left-lobe grafts were transplanted into the recipient without veno-venous bypass. Portal vein (PV) pressure was continuously monitored during liver transplantation surgery using a cannula (Medicut LCV-UK catheter 14G, Nippon Sherwood Inc) located in the superior mesenteric vein via a terminal jejunal vein. After the hilar dissection, the native liver was completely mobilized from the vena cava. Once the graft was ready for implantation, the PV was tied off and the right hepatic vein was also divided using stapling devices (Endo-GIA 60-2.5, Covidien). Total hepatectomy

was performed after clamping the middle and left hepatic veins. A large side clamp (Potts Liver Transplant Clamp, GEISTER) was applied to control the vena cava with the middle and left hepatic venous orifices. An incision was made to divide the septum between the middle and the left hepatic veins and create a common orifice. The incision was extended to the anterior wall of the vena cava, and simple cavoplasty was performed to increase the size of the anastomosis.[14] The anastomosis was performed with simple intraluminal mattress sutures using 5-0 continuous polydioxanone sutures with an RB1 needle (Ethicon Inc). Short hepatic veins were not reconstructed in any recipient. Hepatic artery (HA) reconstruction was performed under a microscope. Intraoperative PV and HA flows were measured in the recipients after reperfusion using an ultrasonic transit time flow meter (Transonic System, Transonic Systems Inc). From case 41 on, biliary reconstruction was performed by duct-to-duct biliary anastomosis using interrupted 6-0 polydioxanone sutures.

From case 37 forward, splenic artery ligation was performed in 16 patients with splenomegaly to control PV pressure.[15] From case 122 on, we started to perform aggressive splenectomy to control portal pressure.[16] The introduction of tieless splenectomy using a vessel-sealing system (LigaSure Atlas, Valleylab Inc) and endo-stapling devices (Endo-GIA 60-2.5, Covidien) enabled us to perform bloodless procedures. All of the major shunt vessels ($\geq$10 mm) were ligated to prevent portal flow stealing phenomena. After implantation of the graft and shunt ligation, splenectomy was indicated when the PV pressure was $\geq$20 mmHg. For patients with hepatitis C, splenectomy was universally indicated regardless of the PV pressure, for post-LDLT antiviral treatment.

Groups

As described above, we implemented several technical refinements for left-lobe LDLT at Kyushu University; these refinements were introduced during the first 121 cases. Therefore, the 250 consecutive left-lobe LDLT cases were divided into 2 groups: Era 1 (n = 121, up to case 121) and Era 2 (n = 129, from case 122 on) for the analyses (Table 1).

Immunosuppression

The basic immunosuppression protocol consisted of tacrolimus or cyclosporine with mycophenolate mofetil and steroids. Mycophenolate mofetil was used from case 42 on. The target tacrolimus level was 10 to 14 ng/mL for 1 month after LDLT, and was decreased to 7 to 10 ng/mL over the next few months. The target cyclosporine level was 150 to 250 ng/mL for 1 month after LDLT and was decreased to 100 to 150 ng/mL over the next few months. Mycophenolate mofetil was started at a dose of 2 g daily, and tapered down to 1 g daily over 1 to 3 months and tapered off at 6 months. One gram of methylprednisolone was given after reperfusion, decreased from 200 mg to 20 mg daily over 1 week, then switched to oral prednisolone, which was tapered off at 3 months.

Post-transplant medical care

Perioperative prophylaxis consisted of intravenous cefotaxime (4 g/day) and ampicillin sulbactam (6 g/day) 4 times daily for 3 days after LDLT, and was started 30 minutes before surgery. The central venous catheters that had been placed in the internal jugular vein were usually removed within 5 days after LDLT and replaced with a peripheral catheter. Prolonged ascites drainage over 14 days is commonly seen after left-lobe LDLT. The amount of ascites drained via the indwelling abdominal drains was recorded. The fluid loss due to drainage of the ascites was the corrected using intravenous sodium containing 5% albumin solution to maintain serum albumin level $\geq$3.5 mg/dL.

Primary graft dysfunction

Primary graft dysfunction was defined as graft insufficiency with possible early graft loss, without technical, anatomic, immunologic, or hepatitis-related issues.[17] It was defined as delayed hyperbilirubinemia, with total bilirubin $\geq$20 mg/dL, usually occurring after postoperative day 7 and persisting for 7 or more consecutive days.

Smaller graft size has been the major obstacle in LDLT, and hyperbilirubinemia with or without intractable ascites output after LDLT has been called small-for-size graft syndrome. However, studies have documented that small grafts do not necessarily cause or correspond to such clinical outcomes, which could be attributed to multiple factors including disease severity, portal pressure, graft regeneration, and donor age.[17] Therefore, we applied the term *primary graft dysfunction* to represent a poorly functioning graft after LDLT.

Statistical analysis

All analyses were performed in a retrospective manner. Values are expressed as the mean $\pm$ standard deviation. Variables were analyzed using the chi-square test for categorical values or the Mann-Whitney test for continuous variables. Multivariate analyses for categorical variables were performed using the logistic regression model. Cumulative survival analyses were determined using the Kaplan-Meier method with the log-rank test and Cox proportional hazards multivariate model. Only significant variables were enrolled in multivariate analyses. Linear regression was used to compare the relationship between continuous variables. Values of $p < 0.05$ were considered statistically significant.

Table 2. Patient Demographics

Variables	Era 1 (n = 121)	Era 2 (n = 129)	p Value
Recipient age, y	47.5 ± 15.6	51.4 ± 15.1	0.04
Recipient sex, male, n (%)	52 (42.9)	42 (32.6)	0.09
Body mass index, kg/m^2	21.7 ± 4.7	22.5 ± 3.6	0.13
MELD score	15.7 ± 7.4	16.4 ± 7.3	0.29
Child C, n (%)	42 (38.5)	67 (61.5)	0.02
Diseases, n (%)			
Acute liver failure	29 (24.0)	13 (10.1)	0.01
Cholestatic cirrhosis	34 (28.1)	37 (28.7)	
Postnecrotic cirrhosis	51 (42.1)	75 (58.1)	
Others	7 (5.8)	4 (3.1)	
Major shunt vessels, ≥10 mm, n (%)	25 (20.7)	45 (34.9)	0.01
Donor age, y	35.4 ± 11.2	34.9 ± 10.2	0.77
Donor sex, male	91 (74.6)	41 (46.6)	<0.01
Incompatible blood type donor, n (%)	1 (0.8)	9 (7.0)	0.01
GV, g	452 ± 89	399 ± 62	<0.01
GV/SLV, %	41.2 ± 8.8	36.2 ± 5.2	<0.01
GRWR, %	0.84 ± 0.25	0.71 ± 0.13	<0.01
Cold ischemic time, min	67 ± 68	67 ± 33	0.89
Warm ischemic time, min	37 ± 7	39 ± 13	0.08
HA flow, mL/min	112 ± 71	102 ± 55	0.23
PV flow, L/min	1.33 ± 0.54	1.54 ± 0.56	<0.01
PV flow/GV, mL/min/100g	301± 125	391 ± 142	<0.01
Operation time, min	745 ± 161	741 ± 143	0.84
Operative blood loss, L	6.7 ± 11.5	6.7 ± 21.2	0.96
Splenectomy, n (%)	9 (7.4)	89 (69.0)	<0.01
Duct-to-duct biliary reconstruction, n (%)	50 (41.3)	83 (64.3)	<0.01
Acute cellular rejection, n (%)	28 (23.1)	13 (10.1)	<0.01
Cytomegalovirus infection, n (%)	28 (23.1)	28 (21.7)	0.78
Bile duct stenosis, n (%)	37 (30.0)	13 (10.1)	<0.01
HA thrombosis, n (%), n (%)	3 (2.5)	0 (0.0)	0.07
PV thrombosis	3 (2.5)	3 (2.3)	0.94
Primary graft dysfunction, n (%)	18 (14.9)	9 (7.0)	0.04
1-year graft survival rate, %	81.8	90.6	<0.01

Unless stated otherwise, data are reported as means ± SD.
GRWR, graft-to-recipient weight ratio; GV, graft volume; HA, hepatic artery; MELD, Model for End-Stage Liver Disease; PV, portal vein; SLV, standard liver volume.

RESULTS

Characteristics of the recipients, donors, and grafts

The recipients in Era 1 were younger than those in Era 2 (Era 1 vs Era 2: 47.5 ± 15.6 years vs 51.4 ± 15.1 years, p = 0.04, Table 2). There were no differences in terms of the recipients' sex, body mass index, or Model for End-Stage Liver Disease (MELD) score between the 2 eras. The distribution of recipient disease was significantly different between the 2 eras (p < 0.01): acute liver failure was more common in Era 1 (24.1% vs 10.1%), and postnecrotic cirrhosis was more common in Era 2 (42.1% vs 58.1%, p < 0.01). There were more patients with major shunt vessels ≥10 mm in Era 2 than in Era 1 (20.7% vs 34.9%, p < 0.01).

Graft volume was significantly larger in Era 1 than Era 2 (452 ± 89 g vs 399 ± 62 g, p < 0.01), as was GV/SLV (41.2 ± 8.8 % vs 36.2 ± 5.2 %, p < 0.01) and graft-to-recipient weight ratio (GRWR) (0.84 ± 0.25 % vs 0.71 ± 0.13 %, p < 0.01, Table 2). The GV/SLV was more frequently in the range of 40.0% to 49.9% in Era 1, and 35.0% to 39.9% in Era 2 (Fig. 1A).

In terms of donor characteristics, there was no significant difference in donor age. However, there were more male donors in Era 1 (74.6% vs 46.6%, p < 0.01),

and there were more blood-type incompatible donors in Era 2 (0.8% vs 7.0%, $p < 0.01$).

Regarding surgical factors, there were no significant differences in operation time, blood loss, cold or warm ischemic time, or HA flow between the 2 eras. Portal vein flow (1.33 ± 0.54 L/min vs 1.54 ± 0.56 L/min, $p < 0.01$) and PV flow/GV (301 ± 125 mL/min/100 g vs 391 ± 142 mL/min/100 g, $p < 0.01$) were significantly greater in Era 2 than in Era 1. Splenectomy was predominantly performed in Era 2 (7.4% vs 69.0 %, $p < 0.01$); splenectomy was performed in 9 patients in Era 1 to treat pancytopenia for inducing preemptive interferon treatment for hepatitis C ($n = 8$) and to reduce the lymphocyte count in blood type incompatible LDLT ($n = 1$).

Acute cellular rejection (23.1% vs 10.1%, $p < 0.01$), bile duct stenosis (30.0% vs 10.1%, $p < 0.01$) and primary graft dysfunction (14.9% vs 7.0%, $p = 0.04$) occurred in significantly fewer cases in Era 2 than Era 1. No significant differences were observed in terms of cytomegalovirus infection, HA, and PV thrombosis between the eras.

Graft volume/standard liver volume and graft outcomes

The maximum total bilirubin concentrations within 1 month after left-lobe LDLT were also plotted against GV/SLV (Fig. 1B). Grafts with maximum total bilirubin ≥20 mg/dL were evenly distributed with GV/SLV and GRWR. The GV/SLV in the serial left-lobe LDLT cases are plotted in Figure 1C. The in-hospital mortality ($n = 29$) rates in patients with grafts with GV/SLV ≥35% and <35% were 12.6% and 9.2%, respectively ($p = 0.44$). Therefore, GV did not affect in-hospital mortality. The proportions of grafts with GV/SLV <35% were 23.1% in Era 1 and 37.2% in Era 2 ($p = 0.01$), and the 1-year graft survival rates were 81.8% in Era 1 and 90.6% in Era 2, respectively ($p < 0.01$, Fig. 2).

Portal vein pressure and graft outcomes

In Era 2, the graft in- and outflows had been fully optimized, maximizing the graft venous drainage and decompression of the graft inflow by splenectomy. Portal vein pressures at laparotomy were 23.4 ± 6.1 mmHg and 23.9 ± 5.8 mmHg in Era 1 and Era 2, respectively, and were not significantly different ($p = 0.50$). However, PV pressure at the end of the operation was significantly higher in Era 1 than in Era 2 (19.1 ± 4.6 mmHg vs 16.0 ± 3.5 mmHg, $p < 0.01$, Fig. 3A). The mean volume of the explanted spleen was 423 ± 267 g.

Total bilirubin on day 14 after left-lobe LDLT (8.8 ± 8.7 mg/dL vs 6.2 ± 7.5 mg/dL, $p = 0.02$) and the drained ascites volume (0.87 ± 1.21 L/day vs 0.34 ± 0.66 L/day, $p < 0.01$) were significantly lower in Era 2 than in Era 1.

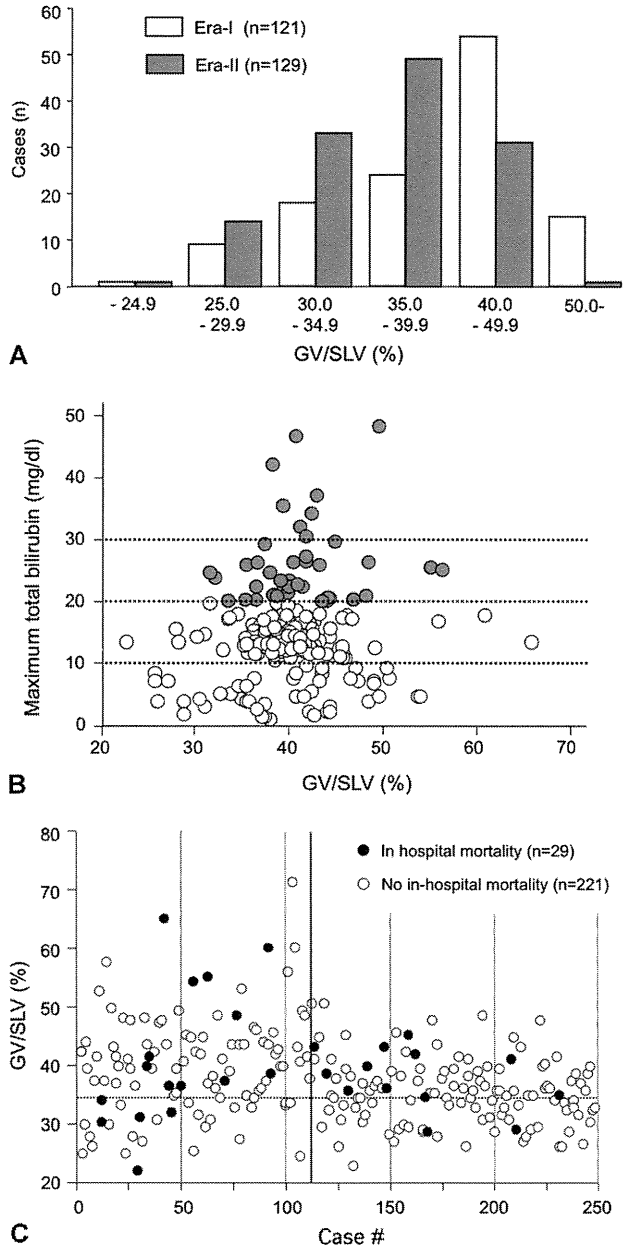

Figure 1. (A) Distribution of actual GV/SLV in Eras 1 ($n = 121$) and 2 ($n = 129$). (B) GV/SLV and maximum total bilirubin level within 1 month after transplantation. (C) GV/SLV with or without in-hospital mortality, in individual cases. GV; graft volume, SLV; standard liver volume.

Graft volume/standard liver volume and portal vein flow

Linear regression analysis was performed to evaluate the relationship between GV/SLV and PV flow/GV (Fig. 4).

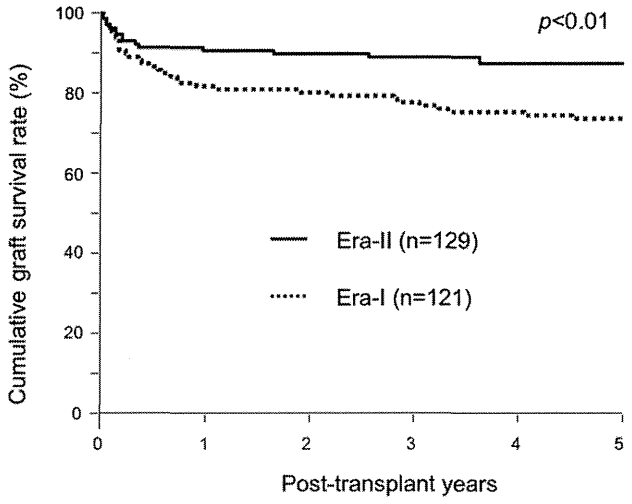

Figure 2. Cumulative graft survival rate in Era 1 (n = 121) and Era 2 (n = 129).

A negative linear correlation was observed between the 2 parameters. Graft PV flow was better in Era 2, characterized by maximum venous outflow and splenectomy (Era 1: $y = 480 - 4.3x$, $r^2 = 0.091$, $p < 0.01$; Era 2, $y = 598 - 5.7x$, $r^2 = 0.043$, $p = 0.02$).

Uni- and multivariate analyses for graft survivals

Univariate analysis for the 5-year graft survivals showed that Era 1 (73.6% vs 87.1%, p = 0.01), MELD score ≥20 (71.9% vs 83.3%, p = 0.02), inpatient status before receiving LDLT (73.6% vs 86.3%, p < 0.01), PV pressure at abdominal closure ≥20 mmHg (85.2% vs 65.3%, p = 0.01), no splenectomy (76.2% vs 86.8%, p = 0.04), and operative blood loss ≥10 L (66.1% vs 82.1%, p = 0.04) were the significant negative factors. Multivariate analysis showed that Era 1 (odds ratio 3.5, 95% CI 1.3 to 10.1, p = 0.01) was the only significant risk factor for graft loss (Table 3).

Causes of hospital mortality included primary graft dysfunction (n = 6), multiorgan failure (n = 6), sepsis (n = 5), intra-abdominal bleeding (n = 4), cerebrovascular accident (n = 2), hepatic artery thrombosis (n = 2), rejection (n = 1), and lymphoma (n = 1).

Risk factors for primary graft dysfunction in the Era 2

Finally, we determined the risk factors for having primary graft dysfunction in left-lobe LDLT, including after the refinement of techniques and treatments (ie, in Era 2). Univariate analysis showed that inpatient status of recipient before LDLT (66.7% vs 29.4%, p = 0.02) and donor age 45 years or more (55.6% vs 15.9%, p < 0.01) were the only risk factors for primary graft dysfunction

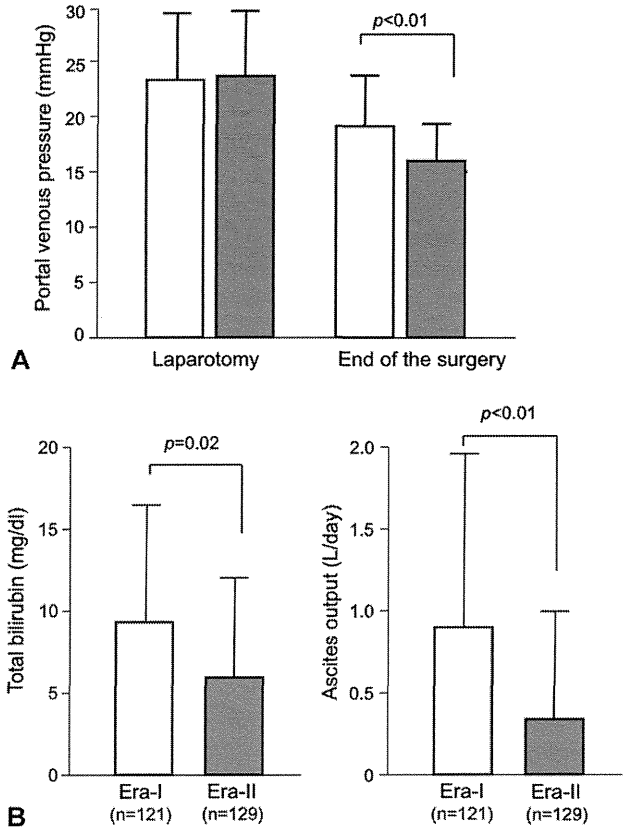

Figure 3. (A) Portal venous pressure at laparotomy and at the end of operation in Era 1 (n = 121) and Era 2 (n = 129). (B) Total bilirubin level and ascites output on postoperative day 14. White bar, Era 1; black bar, Era 2.

(Table 4). Although the number of patients with primary graft dysfunction was small, logistic regression analysis showed that donor age 45 years or greater (yes, odds ratio 5.9, 95% CI 1.4 to 25.2, p = 0.01) and inpatient status of the recipient (yes, odds ratio 4.3, 95% CI 1.1 to 19.2, p = 0.04) were significant risk factors for primary graft dysfunction.

Predicted and actual graft volume in Era 2

The mean predicted and actual GVs were 437 ± 78 g and 400 ± 63 g, respectively, which were significantly different (p < 0.01). The mean predicted and actual GV/SLV ratios were 39.5% ± 6.2% and 36.2% ± 5.2%, respectively, with significant difference (p < 0.01). The mean differences in GV and GV/SLV were 38 ± 55 g and 3.4% ± 5.0%, respectively.

Complications of splenectomy

Complications in splenectomy included pancreas leakage (n = 6, 6.1%), treated percutaneously, and overwhelming

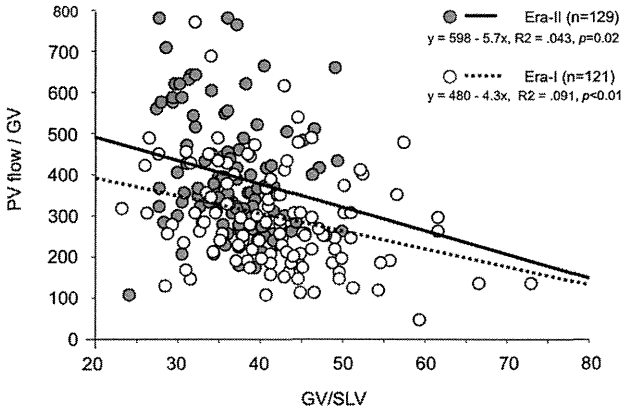

Figure 4. Linear regression analysis for the relationship between GV/SLV and PV flow/GV in Era 1 (n = 121) and Era 2 (n = 129). GV, graft volume; PV, portal vein; SLV, standard liver volume.

postsplenectomy sepsis (n = 3, 3.1%). Two patients had *Streptococcus pneumoniae* sepsis (1 and 2 years after LDLT, respectively) and 1 had *Klebsiella pneumoniae* sepsis 5 years after LDLT. These patients were not vaccinated before LDLT, and they were treated successfully with antibiotics.

DISCUSSION

We have implemented several refinements for left-lobe LDLT, such as wide veno-caval anastomosis and splenectomy to control PV pressure; these have been routinely performed from case 122 on (Era 2). We routinely use left-lobe grafts as the primary graft type in LDLT for patients with predicted GV/SLV ≥35%. By implementing these strategies, graft survival has increased by 10% compared with survival in the preceding era in association with a reduction in the incidence of primary graft dysfunction. Interestingly, implementation of these techniques not only succeeded in reducing PV pressure but also increased the graft PV flow, resulting in increased graft vascular compliance.

We also found that GV did not have a significant negative impact on graft outcomes in our series, although this may be one of the most critical factors for determining graft function. The most reasonable explanation for this result seems to be the multifactorial natures of the factors, which determine graft dysfunction and graft loss. Such factors include recipient status, portal hypertension, operative blood loss, donor age, graft steatosis, and post-transplant complications.[18] Therefore, to account for these factors, each transplant center selects its own lower limit for predicted GV for LDLT. As described earlier, we previously used GV/SLV ≥30% as the borderline threshold for graft selection, and have increased this to 35%. The introduction of right-lobe LDLT in 2000 and the large discrepancy between the predicted and actual GV in some cases were largely responsible for this shift, although lower GV/SLV was not an independent factor for short-term graft survival.[9,19] According to the results of this analysis and our own clinical experience, the threshold GV/SLV could be reduced to 30% again, although it is important to consider the difference in predicted and actual GV/SLV (3.4% ± 5.0%) even in Era 2, as shown in Figure 1C. Taking into account the standard deviation, however, the actual GV/SLV could be <25%, for a predicted GV/SLV of 30%. This relatively small error seems to be caused by minor differences in the virtual and actual hepatectomy plane, expansion of the hepatic parenchyma caused by acute injection of contrast medium on CT scans, and graft dehydration caused by hyperosmotic perfusion solution.[19] Therefore, the lower limit of a predicted GV/SLV of 35% was not associated with a significant negative impact in this study, even though the actual GV/SLV was <30% in some grafts.

Significant technical changes from Era 1 to Era 2 were the graft venoplasty with wide veno-caval anastomosis and splenectomy. Venous drainage is a critical determinant of graft function with right- and left-lobe grafts.[20] Unlike right-lobe grafts, the left lobe is located in an unstable position in the body and graft rotation after regeneration may reduce outflow. Our procedure, in which we create a wider horizontal anastomosis, is a modified form of the Kyoto technique applied in pediatric LDLT, in which an additional caudal incision is made on the vena cava.[13] Although the Tokyo group[21] reconstructs the short hepatic vein from the Spiegel lobe, we do not apply the procedure because of collateral drainage veins from the caudate lobe into the middle hepatic vein.

Excessive portal hypertension is well established as a significant risk factor for graft injury. The most widely performed procedure for portal decompression seems to be creation of a porto-systemic shunt, which Boillot and colleagues[22] first reported as mesocaval shunting in 2002, and followed by hemi-portocaval shunting by Troisi and associates.[23] Troisi and coworkers reported that 1-year graft survival was 75% for hemi-portocaval shunting and 20% without, after LDLT, with GRWR <0.8. In Japan, the Kyoto group[24] performed selective hemi-portocaval shunting for left-lobe LDLT with a GRWR <0.8; graft survival in that study was 100%. However, the same group[25] recently reported that splenectomy is increasingly being performed for portal pressure control. We now avoid creating or keeping shunts, favoring instead blocking major shunt vessels, especially for marginal situations, such as extra-small grafts, older grafts, and severe portal hypertension. We created a hemi-portocaval shunt for an

Table 3. Uni- and Multivariate Analyses for Graft Survival

Variables		n	5-y graft survival rate, %	p Value	
				Univariate	Multivariate
Era 1	Yes	121	73.6		
	No	129	87.1	0.01	0.01
Recipient age ≥60 y	Yes	73	82.9		
	No	177	78.2	0.39	–
MELD score ≥20	Yes	77	71.9		
	No	172	83.3	0.02	0.25
Inpatient status	Yes	139	73.6		
	No	111	86.3	<0.01	0.76
Acute liver failure	Yes	43	76.1		
	No	206	80.6	0.33	–
Hepatitis C	Yes	95	77.9		
	No	153	81.1	0.65	–
Hepatocellular carcinoma	Yes	149	80.1		
	No	101	79.6	0.68	–
Major spontaneous shunts	Yes	70	79.8		
	No	180	80.0	0.91	–
Recipient age ≥45 y	Yes	52	76.2		
	No	198	80.9	0.34	–
GV/SLV <35%	Yes	76	78.8		
	No	174	80.2	0.99	–
GRWR <0.7	Yes	92	78.3		
	No	158	80.7	0.76	–
Blood type incompatible	Yes	10	90.0		
	No	240	79.6	0.59	–
Opening PV pressure ≥25 mmHg	Yes	90	82.8		
	No	105	79.4	0.76	–
Closing PV pressure ≥20 mmHg	Yes	50	69.3		
	No	143	85.2	0.01	0.12
Warm ischemic time ≥60 min	Yes	4	66.7		
	No	246	80.4	0.36	–
Cold ischemic time ≥120 min	Yes	17	70.6		
	No	233	80.9	0.31	–
Splenectomy	Yes	98	86.8		
	No	152	76.2	0.04	0.20
Operative time ≥720 min	Yes	123	78.9		
	No	127	79.6	0.81	–
Blood loss ≥10 L	Yes	26	66.1		
	No	224	82.1	0.04	0.21

GRWR, graft-to-recipient weight ratio; GV, graft volume; HA, hepatic artery; MELD, Model for End-Stage Liver Disease; PV, portal vein; SLV, standard liver volume.

extra-small graft with GV/SLV of 23.7%, which resulted in graft dysfunction caused by portal stealing, followed by relaparotomy, closure of the shunt, and graft recovery.[26] We recently had a patient with decreased portal inflow and stealing into an unrecognized gastroesophageal shunt, resulting in primary graft dysfunction and graft loss, even after surgical division of the shunt vessels.[27] As reported by Hessheimer and coauthors,[28] maintaining appropriate portal inflow into a dynamically regenerating liver to prevent excessive portal flow and portal stealing is technically difficult.

To optimize portal hemodynamics, we ligate the major shunt vessels and perform splenectomy. We try to ligate all of the major shunt vessels, even if the PV pressure increases, and then perform splenectomy. In deceased door liver transplantation, Lüsebrink and associates[29] reported that splenectomy caused increased frequency of severe infectious episodes by 2.5 times. However, in our cases of left-lobe LDLT, the prevalence of septic complications was decreased by splenectomy (9.2% vs 15.1%), although this was not statistically significant. The techniques used in splenectomy for portal hypertensive

Table 4. Risk Factors for Primary Graft Dysfunction after Left-Lobe Living Donor Liver Transplantation in Era 2

Variables	No PGD (n = 120) n	%	PGD (n = 9) n	%	p Value
Recipient age ≥60 y	43	35.8	2	22.2	0.39
MELD score ≥20	29	24.2	4	44.4	0.18
Inpatient status before LDLT	35	29.2	6	66.7	0.02
Acute liver failure	13	10.8	1	11.1	0.99
Hepatitis C	46	38.3	4	44.4	0.76
Major shunt vessels ≥10mm	40	33.3	5	55.6	0.18
Donor age ≥45 y	19	15.8	5	55.6	<0.01
GV/SLV <35%	44	36.7	3	33.3	0.83
GV/SLV <30%	14	11.7	0	0.0	0.28
GRWR <0.7	53	44.1	3	33.3	0.51
GRWR <0.6	18	15.0	1	11.1	0.74
Blood type incompatible donor	9	7.5	0	0.0	0.58
PV pressure at laparotomy ≥25 mmHg	53	44.2	4	44.4	0.99
PV pressure at closure ≥20 mmHg	16	13.3	1	11.1	0.84
PV flow/GV ≥250 mL/min/100g	95	79.2	7	77.8	0.23
Splenectomy	81	67.5	7	77.8	0.54
Warm ischemic time ≥60 min	4	3.3	0	0.0	0.57
Cold ischemic time ≥120 min	6	5.0	0	0.0	0.49
Operative time ≥720 min	51	42.5	5	55.6	0.46
Blood loss ≥10 L	9	7.5	1	11.1	0.70

GRWR, graft-to-recipient weight ratio; GV, graft volume; HA, hepatic artery; LDLT, living donor liver transplantation; MELD, model for end-stage liver disease; PGD, primary graft dysfunction; PV, portal vein; PVP, portal venous pressure; SLV, standard liver volume.

splenomegaly are quite different from those applied in patients without portal hypertension.[16] Tieless procedures using a vessel sealing system and end-stapling devices, as laparoscopic splenectomy, can enable safe splenectomy in LDLT with blood loss of <100 mL.[16] However, care must be taken to give a Pneumococcal vaccination before splenectomy to prevent overwhelming postsplenectomy sepsis. We abandoned splenic artery ligation for PV pressure control because of technical difficulties in isolating the splenic artery buried in the nests of collateral vessels and its inadequate clinical effects, as expected.[15]

The increased compliance of the transplanted left-lobe graft could be attributed not only to the increased graft outflow by venoplasty/cavoplasty but also to the hepatic vasodilatation by splenectomy. Regarding the impact of splenectomy in a portal hypertensive situation, recent reports showed that splenectomy effectively decreased hepatic vascular tonus and increased vascular compliance by blocking the endothelin-1 pathway. In a rodent biliary cirrhosis model, Uehara and colleagues[30] showed that endothelin-1 positive cells were abundantly present in an enlarged spleen for controlling portal inflow, and removing such a large spleen improved hepatic microcirculation by decreasing the portal endothelin-1 level. In a small hepatic graft transplantation model in rodents, Kuriyama and associates[31] showed that splenectomy decreased plasma endothelin-1 level and increased hepatic expression of heat-shock protein, resulting in hepatic vasodilatation. Therefore, in the patients in Era 2 with smaller grafts and splenectomy, both vigorous inflow and abundant endothelin-1 from an enlarged spleen were corrected by splenectomy, resulting in increased graft vascular compliance with increased portal flow and decreased portal pressure.

In Era 2, donor age ≥45 years and inpatient recipient status are still the independent risk factors for primary graft dysfunction. In right-lobe LDLT, Moon and colleagues[32] reported that donor age ≥44 years was associated with significantly worse graft survival for patients with GRWR <0.8. Shah and associates[5] reported that grafts ≥44 years had even graft survivals and graft failure rates with the use of larger grafts, with mean GRWR of 1.3. Advanced liver failure with deterioration in the recipient's general condition, including high MELD, advanced Child class, and inpatient status are all difficult challenges in liver transplantation, even in whole liver transplantation.[33] Although Yi and coworkers[34] reported that small grafts with GRWR <0.8 could be used for patients with a high MELD score, and particularly, patients with hepatitis B infection, the 1-year graft survival rate was 13.6% lower than in patients with low MELD scores. In our series of patients, donor age ≥45 years and recipient inpatient status were still risk factors for primary graft dysfunction in Era 2. Additional studies are needed to address these issues.

CONCLUSIONS

In conclusion, the outcomes of left-lobe LDLT were significantly improved by accumulated experience and technical developments including wide veno-caval anastomosis and splenectomy.

Author Contributions

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Drafting of manuscript: Ikegami, Shirabe
Critical revision: Maehara

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