

“Left at right” liver transplantation with heterotopic implantation of left liver graft in the right subphrenic space

Reappraisal and technical concerns for decision making

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Abstract

Conventional orthotopic implantation of left liver grafts is technically demanding and requires consideration of limited space and vascular complications. The study proposed a modified approach termed “left at right” liver transplantation (LAR-LT), wherein left liver grafts were rotated and implanted in right subphrenic spaces. The selection of recipients for this approach is based on the measurement of the right subphrenic space width and left liver graft length, in which a rotated left liver graft could be comfortably placed in the right subphrenic space. A total of 36 recipients who had undergone LAR-LT between July 2006 and December 2017 were retrospectively reviewed. None of recipients died of complications related to this approach immediately after operation. All grafts showed remarkable increment in liver volume and bi-directional regeneration to fit well within the right abdominal cavity. Meanwhile, the alignment of the biliary tree in LAR-LT is quite straight, making no difficulty in both anastomosis during operation and dealing with biliary stenosis afterward. As such, long-term outcome of LAR-LT is satisfactory. Keeping in mind certain technical concerns, a heterotopic LAR-LT might be safely applied as an alternative with an easier reconstruction procedure for select patients.

Abbreviations: IVC = inferior vena cava, LAL-LT = left at left liver transplantation, LAR-LT = left at right liver transplantation, LDLT = living donor liver transplantation, LT = liver transplantation, MHV = middle hepatic vein, SLV = standard liver volume.

Keywords: heterotopic implantation, left at right, left liver graft, liver transplantation, outcome

1. Introduction

Along with the improvement in surgical technique and perioperative patient care, liver transplantation (LT) has become a common and routine operation at numerous transplantation centers worldwide.^[1,2] Nowadays, LT is an optimal treatment for patients with end-stage liver disease or hepatocellular carcinoma. Moreover, deceased donor split LT and living donor LT (LDLT) have been popularized to alleviate the shortage of liver grafts. The success in split LT and LDLT has rendered wide usage of left liver grafts for adult LT.^[3–5] However, the traditional orthotopic

implantation of left liver grafts in the epigastric region is technically demanding and requires consideration of limited space, inferior vena cava (IVC) compression, or vascular inflow and outflow kinking related to the huge liver graft.^[6,7] Occasionally, heterotopic placement of a left lateral liver graft in the right upper quadrant fossa was initially described by Dunn et al.^[8] Accordingly, the institute modified this thought and first reported a series of left liver LTs, wherein the grafts were rotated 180° and heterotopically implanted in the right subphrenic space, and termed the procedure as “left at right” liver transplantation (LAR-LT).^[9,10] As previously reported, the initial results showed that LAR-LT was feasible and non-inferior to traditional orthotopic implantation of the left liver graft in the epigastric space. This study, therefore, aims to reassess the long-term outcome and applicability of this technique as an alternative procedure for left liver graft LT. Apart from this, the decision-making process with respect to selecting suitable recipients for LAR-LT in a clinical scenario has also been well described.

2. Materials and methods

2.1. Patients

A total of 902 LTs were performed at the Organ Transplantation Institute of Chang Gung Memorial Hospital at Linkou, Taiwan, between January 2002 and December 2017. Among those, 91 patients had undergone LT using left liver grafts. Since the first LAR-LT was performed in July 2006, 36 recipients who had undergone LAR-LT were retrospectively reviewed under the approval of the institutional review board from Chang Gung Memorial Hospital at Linkou. Of these recipients, 15 were males and 21 were females with a median age of 55 years (range, 4–66 years).

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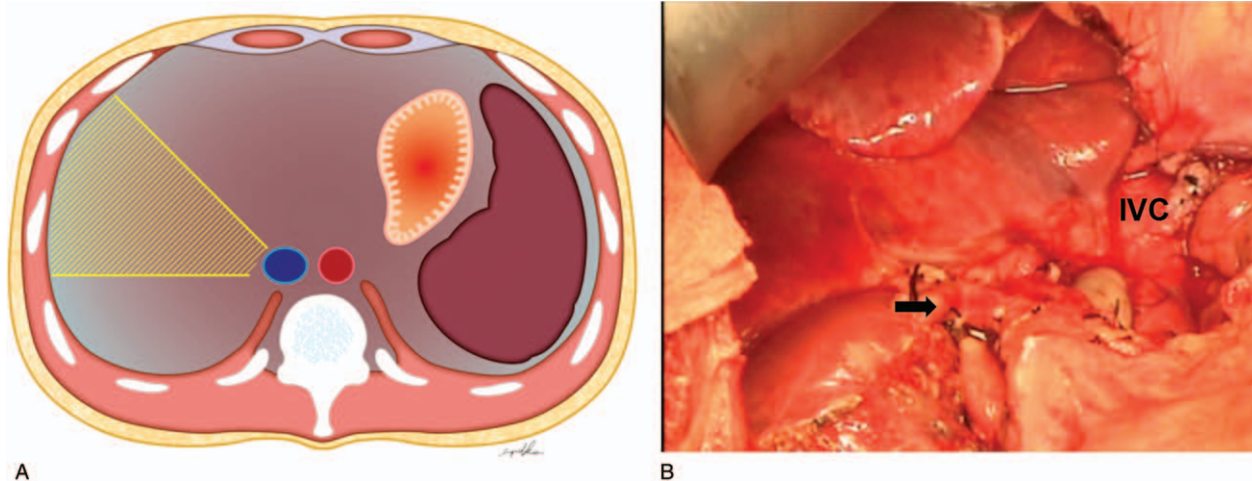


Figure 1. Illustration of optimal placement of rotated left liver graft in the right subphrenic space for LAR-LT. (A) The recommended position for left liver graft. The graft's axis is better placed in the shaded zone (45° area) of the right abdominal cavity. Blue, inferior vena cava. Red: abdominal aorta. (B) The tip of the lateral segment could be slightly folded upward under the diaphragm. Arrow indicates the graft's hilum. IVC=inferior vena cava, LAR-LT = left at right liver transplantation.

2.2. Preparation of liver grafts

Left liver grafts were obtained from deceased donors and living donors. In deceased donors, the general principles to determine donors for liver splitting have been well stated by the institute before.^[4,5] By the aid of ultrasonography, the graft weight of the right and left hemi-livers could also be estimated by an equation described by us previously. In situ separation of hepatic lobes was performed before liver graft procurement for all donors. The cut point of left and right hepatic ducts was determined by intraoperative cholangiography, and the main trunk of the middle hepatic vein (MHV) and the caudate lobe were included in the left liver graft.

In living donors, magnetic resonance cholangiopancreatography and dynamic liver computed tomography (CT) were routinely employed for the assessment of biliary and vascular anatomy and graft volume before operation. Procurement of left liver graft was performed using a procedure similar to the standard procedure described in detail previously. Generally, the caudate lobe was not included in the left liver grafts from living donors. The main trunk of the MHV was also not included in the left liver graft to secure donor safety, and venous drainage of Segment 4 was reconstructed via a cryopreserved venous graft if indicated.

With regard to pediatric recipients, only the left lateral segment was obtained as a graft. All transections of liver parenchyma were performed using Cavitron Ultrasonic Surgical Aspirator (CUSA; Valleylab, Inc., Boulder, CO), and inflow vascular control was not applied during hepatectomy for both deceased and living donors.

2.3. Liver graft implantation

Generally, all LTs were started by total hepatectomy with IVC preservation. The decision to perform LAR-LT was made after considering a few factors as follows. Importantly, the right subphrenic space should be wide enough for the placement of a rotated left liver graft. The width of the right subphrenic space in terms of distance between IVC and the right side abdominal wall should be more than 75% of graft width (from liver cut surface to

the tip of lateral segment). The optimal position of the liver graft was with its axis placed at a 45° zone starting from 9 o'clock direction as shown in Figure 1A. The tip of the lateral segment could be slightly folded upward under the diaphragm without jeopardizing the vascular flow of the graft (Fig. 1B). Generally, LAR-LT was performed for left liver LT as long as recipient met the aforementioned concerns in the institute; otherwise, traditional implantation of the left liver graft in the epigastric space that termed left at left liver transplantation (LAL-LT) was performed.

The procedure of graft implantation in LAR-LT was performed as previously described and shown in the supplemental film (Supplemental Digital Content 1, <http://links.lww.com/MD/D108>). Briefly, the venous outflow of the liver graft was reconstructed depending on the type of left liver graft. The left hepatic vein was anastomosed to the recipient's IVC or orifice of the right hepatic vein as appropriate, whereas side-to-side anastomosis between the graft's IVC and the recipient's IVC were performed for liver grafts containing IVC procured from the deceased donor. Subsequently, the liver graft was reperused after the reconstruction of the portal vein in an end-to-end fashion between the graft's left portal vein and the recipient's portal trunk. Microscopic vascular anastomosis of the hepatic artery was performed soon after hemostasis. Finally, the bile duct was reconstructed by duct-to-duct anastomosis or Roux-en-Y hepaticojejunostomy without T-tube stenting as appropriate.

2.4. Follow-up after LT

After transplantation, all recipients stayed in the transplantation intensive care unit for postoperative managements. Biochemical analyses of the blood samples and hepatic Doppler ultrasonography were routinely performed at regular intervals as previously described. The postoperative immunosuppressive regimen consisted of a combination of methylprednisolone, tacrolimus, and mycophenolate mofetil, and the dosages of the immunosuppressants were adjusted based on the recipient's clinical status. Dynamic liver CT was performed at 1 month, 3 months, 6 months, 12 months, and yearly afterward if indicated after transplantation to evaluate graft condition and regeneration.

Table 1	
Clinical characteristics of patient who received LAR-LT.	
Characteristics	LAR-LT n=36
Donors	
Age (yrs), median (range)	32 (18–53)
Sex (Male:Female)	32:4
Deceased donor split LT	8 (22.2%)
Medical reasons of brain deaths	
Cerebrovascular accident	6
Motorcycle traffic accident	2
Living donor LT	28 (77.8%)
Recipients	
Age (yrs), median (range)	55 (4–66)
Sex (Male:Female)	15:21
Hepatitis status	
Hepatitis B positive	14 (38.9%)
Hepatitis C positive	9 (25%)
Hepatitis B and C positive	1 (2.8%)
None	12 (33.3%)
Indication of LT	
Viral cirrhosis	10 (27.8%)
Hepatocellular carcinoma	13 (36.1%)
Alcoholic liver cirrhosis	8 (22.2%)
Primary biliary cirrhosis	1 (2.8%)
Biliary atresia	1 (2.8%)
Other liver cirrhosis	3 (8.3%)
MELD score, median (range)	16 (6–32)
Grafts	
Weight (gm), median (range)	400 (230–700)
GRWR (%), median (range)	0.80 (0.56–1.92)
Outcome	
Death	14 (38.9%)
Alive	22 (61.1%)

LAR-LT = left at right liver transplantation, LT = liver transplantation, MELD = model for end-stage liver disease, GRWR = graft recipient weight ratio.

2.5. Statistical analysis

All statistical analyses were performed using the statistical Software Prism 5.0 (GraphPad Software, San Diego, CA) for Windows. The end-point outcome was overall survival, which was measured from the date of LT to the date of death or the end

of this study. The Kaplan–Meier method was carried out to construct survival curves, and it was further compared by the log-rank test. A P value of less than .05 was considered as statistically significant.

3. Results

3.1. Patient characteristics

The clinical characteristics of donors and recipients who received LAR-LT are summarized in Table 1. Left liver grafts were obtained from 8 split livers of deceased donors and 28 living donors. Most of the recipients were females (n=21), accounting for 58.3%, and the median age of recipients was 55 years (range, 4–66 years). Three major etiologies including viral cirrhosis (n=10, 27.8%), hepatocellular carcinoma (n=13, 36.1%), and alcoholic liver cirrhosis (n=8, 22.2%) had the highest indication for LT. The median model for end-stage liver disease (MELD) score of recipients during LT was 16 (range, 6–32). The median graft-recipient-weight-ratio (GRWR) was 0.80% (range, 0.56%–1.92%), in which the median graft weight was 400 g (range, 230–700 g). Overall, there were 22 recipients (61.1%) who were still alive till the end of the study.

3.2. Graft outcomes

Protocol dynamic liver CT was performed for every recipient at 1, 3, 6, and 12 months after LT to assess graft condition unless special concerns. All grafts had remarkable increment of liver volume, and most liver grafts could regenerate to reach standard liver volume^[11] (SLV) at 1 month after LT. The median ratio of liver volume to SLV was 0.97 (range, 0.73–1.64) at 1 month after LT (Fig. 2A). Generally, the right subphrenic area had a relatively larger space enough for the graft to comfortably grow anteriorly, posteriorly, and eventually fit well in the right abdominal cavity. Specifically, the left abdominal space was usually very limited in pediatric recipients, and thus the rotated graft implanted in the right subphrenic space might be prone to regeneration of liver volume (Fig. 2B). The ratio of liver volume to SLV in pediatric recipients was 1.33 at 1 month and 1.66 at 3 months after LT.

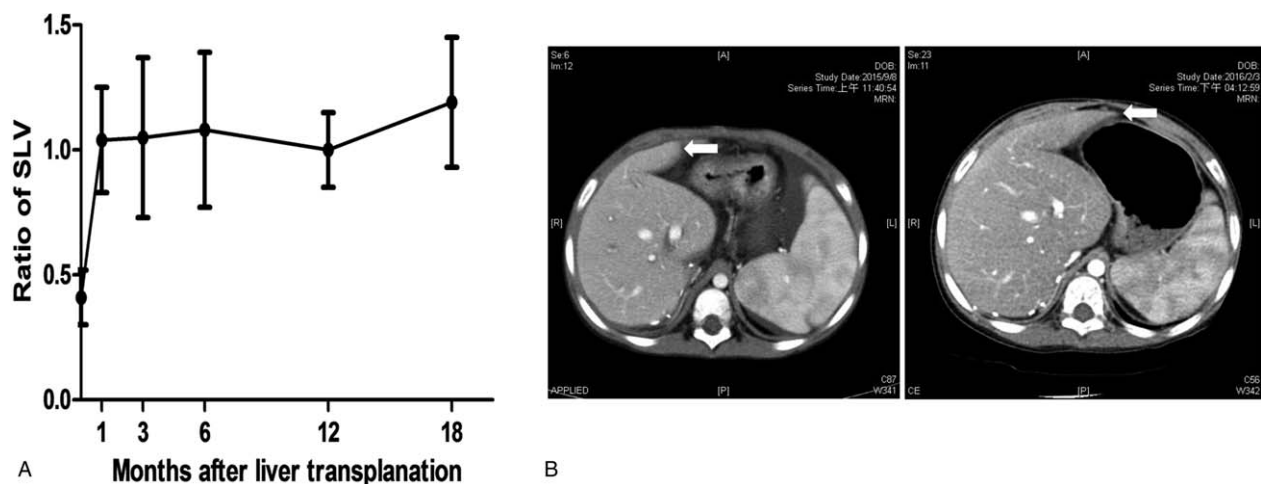


Figure 2. Regeneration of liver grafts. (A) All grafts had remarkable increment in liver volume, and most liver grafts could reach the SLV at 1 month after LT. (B) In a pediatric recipient, the right subphrenic area had relatively larger space, enough for the graft to comfortably grow and fit well in the right abdominal cavity. The ratio of liver volume to SLV was 1.33 at 1 month (left) and 1.66 at 3 months (right) after LT. LT = liver transplantation, SLV = standard liver volume.



Figure 3. Endoscopic management of biliary stenosis in LAR-LT. The alignment of the biliary tree in LAR-LT is quite straight, which makes dealing with biliary stenosis afterward easier. The biliary stenosis (left) were well treated by endoscopic dilatation (right). LAR-LT=left at right liver transplantation.

Additionally, there were no extrahepatic vascular complications in terms of portal inflow and venous outflow twist or kinking observed in the recipients in the study during the follow-up period.

3.3. Biliary complications

Among recipients with biliary complication, most recipients were successfully managed by endoscopic biliary stent treatment for biliary stenosis in a duration from 4.5 months to 24 months (Fig. 3). Two recipients failed to be managed by endoscopic treatments were subjected to percutaneous biliary dilatation: 1 regained patency of the bile duct 3 months after but died of de novo gastric cancer at 6.9 years after LT and the other suffered from small-for-size liver dysfunction and refractory biliary tract infection leading to graft failure and death at 10.6 months after LT^[9] (Table 2). One recipient whose biliary stenosis could not be

treated by either endoscopic or percutaneous biliary dilatation was well rescued by Roux-en-Y hepaticojejunostomy and was still alive with normal liver function during the end of the study.

3.4. Recipient outcomes

During the follow-up period, 14 recipients died between 10 days and 6.9 years after LT. The clinical features and major events leading to death for these patients are summarized in Table 2. Of these, graft dysfunction associated with complicated bacterial infections was noted in 5 recipients. One recipient (No. 599) had HCV recurrence followed by graft failure as well as pneumonia, leading to death at 3.6 months after LT, and 1 recipient (No. 654) who had a clinical course similar to that of acute humoral rejection, as previously described, died at 10 days after LT.^[12] One recipient (No. 363) encountered postoperative internal bleeding resulted in mortality at 16 days after LT despite re-

Table 2
Clinical characteristics of LAR-LT recipients who encountered major events and death.

Recipient No.	Age/sex	Indication of Transplantation	MELD	Graft type	Graft weight (gm)/ GRWR (%)	Major events	Follow-up periods
347	60/F	HCC, HCV liver cirrhosis	14	LDLT	320/0.60	De novo gastric cancer	6.9 years
363	51/M	HBV ESLD	11	LDLT	300/0.75	Internal bleeding	16 days
371	46/F	HCC, HBV liver cirrhosis	11	LDLT	285/0.57	Small-for-size, graft failure	10.6 months
436	63/F	Primary biliary cirrhosis	18	LDLT	325/0.80	Cholestasis liver, graft failure	12.5 months
489	50/M	Alcoholic liver cirrhosis	19	LDLT	380/0.95	Pneumonia	19 days
491	42/F	Autoimmune liver cirrhosis	20	LDLT	320/0.61	Small-for-size, graft dysfunction, nosocomial infections	42 days
498	60/M	HCC, HCV liver cirrhosis	11	LDLT	420/0.86	Bile leakage, heart disease	4 months
599	65/F	HCV ESLD	12	LDLT	400/1.01	HCV recurrence, pneumonia	3.6 months
654	60/F	Autoimmune liver cirrhosis	21	LDLT	380/0.99	acute humoral rejection	10 days
780	63/M	HBV ESLD	19	LDLT	400/0.92	Intracranial hemorrhage	3.6 months
786	66/F	HCV ESLD	15	LDLT	325/0.91	complicated bacterial infections	3 months
808	57/M	Alcoholic liver cirrhosis	19	Split DDLT	700/1.52	Renal failure	14.3 months
856	53/M	Alcoholic liver cirrhosis	21	Split DDLT	690/1.53	cerebellum multiple infarction followed by brain edema	49 days
940	59/F	Alcoholic liver cirrhosis	19	Split DDLT	380/0.72	Graft dysfunction ,complicated bacterial infections	4.1 months

LAR-LT = "left at right" liver transplantation, MELD = model for end-stage liver disease, GRWR = graft recipient weight ratio, F = female, M = male, HBV = hepatitis B virus, HCV = hepatitis C virus, ESLD = end-stage liver disease, DDLT = deceased donor liver transplantation, LDLT = live donor liver transplantation.

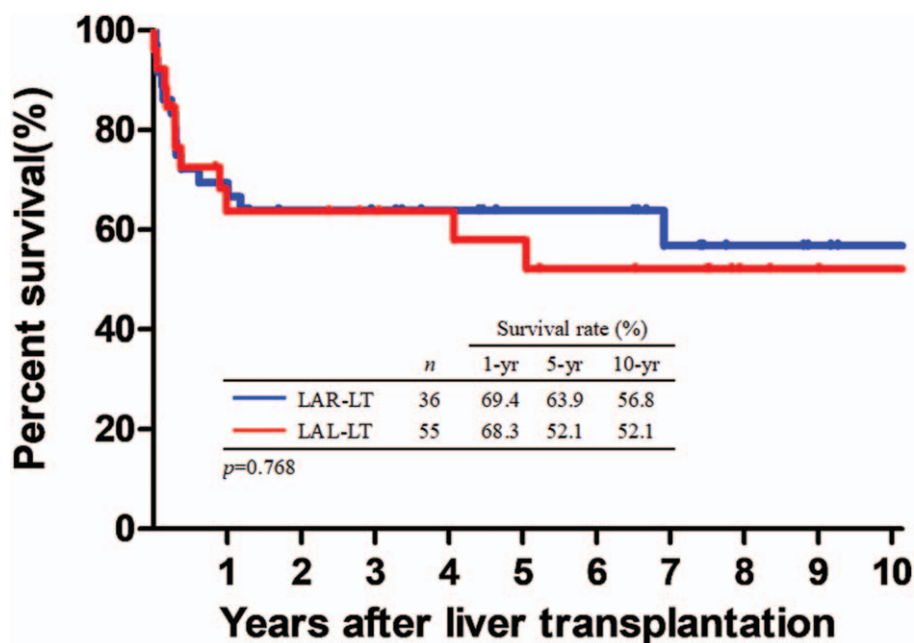


Figure 4. Comparison of Kaplan–Meier cumulative overall survival of the patients underwent liver transplantation using left liver grafts. ($P = .768$) LAR-LT, left at right liver transplantation. LAL-LT, left at left liver transplantation.

laparotomy for cease bleeding, and another recipient (No. 489) had nosocomial pneumonia and died at 19 days after LT. Early bile leakage was noted at 1 recipient (No. 498) who developed a series of severe infection and death of cardiopulmonary failure 4 months after LT. However, there were 4 recipients who died of events unrelated to graft dysfunction.

The longest follow-up time for the recipient who was still alive during the end of this study was 11.9 years. The median follow-up period for these recipients was 5.7 years (range, 5.1 months to 11.9 years). Moreover, all these recipients have good graft function and are regularly followed up at the institute's clinic now. The 1-year survival rates of LAR-LT and LAL-LT were 69.4% and 68.3%, respectively. The survival curve of LAR-LT was non-inferior to that of traditional LAL-LT and showed no significant difference between the 2 groups. (Fig. 4, $P = .768$)

4. Discussion

With a modified implantation of left liver grafts, the initial report has shown that LAR-LT is feasible and has outcomes comparable with the conventional LAL-LT.^[9] Although this approach has drawn the attention of some transplantation centers, many concerns still exist leading to rare utilization of this modification for left liver LT.^[13] Hence, the present report gathered more experience of LAR-LT and reassessed long-term outcomes of this procedure for left liver LT. To the best of our knowledge, this is the largest series of left liver LT using LAR-LT reported in the literature. Meanwhile, the study also describes many technical concerns for aiding the decision-making process while selecting a suitable clinical scenario for performing LAR-LT.

The advantage of LAR-LT is not only that it has relatively reduced technical difficulty during graft implantation but also that it is theoretically optimal for graft regeneration without subsequent venous complications. As shown in the study, all anastomoses were on the anterior side of the liver graft during

LAR-LT. As such, this approach is relatively easier compared with conventional left liver LT in which all anastomoses are behind the liver graft. Additionally, venous outflow is a critical issue for the success of LT. Without optimal fixation of the liver graft during conventional left liver LT, the hepatic venous outflow is possibly twisted or distorted, leading to outflow obstruction as well as other lethal complications.^[6,14,15] In LAR-LT, the hepatic vein of the liver graft was anastomosed to either IVC or the orifice of the recipient's right hepatic vein, depending on the appropriate option during graft implantation. The study also observed that the graft could show bi-directional regeneration and could easily fit well within the right abdominal cavity; thus, the hepatic vein would stay in its original position without stretching or distortion. However, the incidence of late outflow obstruction because of liver regeneration is up to 6.5% in conventional left liver LT.^[14]

In addition, the porta hepatis comprising the portal trunk and common bile duct is mildly tilted to the right side of the IVC in natural anatomy. Therefore, the direction of portal flow in "left at right" position is more anatomical and straight than that in orthotopic implant position in the left epigastric space that has a sharp angle of portal flow. As a result, this approach could prevent the flexion and angulation of the portal vein and possibly decrease the incidence of portal flow insufficiency.^[16,17] Besides, portal vein stretching might be encountered after the liver graft grows and rotates rightward in orthotopic left liver LT.^[7,18] Similarly, the alignment of the biliary tree in LAR-LT is also quite straight, making both anastomosis during operation and dealing with biliary stenosis afterward easier. As the study showed, in most cases, biliary stenosis could be well treated by endoscopy or percutaneous dilatation.

Moreover, the left liver graft for LAR-LT could be stably placed in the right subphrenic space based on the recommended technical concerns. Subsequently, the liver graft could be smoothly regenerated in the right abdominal cavity. The study

also observed that grafts would regenerate and be shaped according to the space within which they grow. Generally, the left abdominal space was very limited in pediatric recipients, in which a relatively smaller graft consisted of lateral segment or single segment might be considered to place a rotated graft at right subphrenic space if appropriate. After liver regeneration, the left liver graft in right abdominal cavity is much like the right liver graft, as shown in the study.

However, this study might be criticized for its inferior overall outcome as compared with the outcomes of other reports using left liver LT.^[3,19] Nonetheless, technical issues are only the first step for the success of LT, and it is our obligation to truly present and discuss every concern regarding this approach. Currently, there remain several unmet needs for improving long-term outcomes in LT in terms of graft and patient survival, and more efforts should be made to improve the overall outcome of LAR-LT as well. Importantly, none of our recipients died because of complications related to this approach immediately after operation. It is worthy to mention the differences observed in the LAR-LT approach compared with the conventional approach and to draw more attention toward this approach. Although LAR-LT was performed for left liver LT as long as recipient met the technical concerns mentioned here, only 40% of recipients were suitable for this approach in this study. Therefore, the selection of transplantation procedures should still rely on the experience of LT in each transplantation program, and a thoughtful assessment of every concern during LT is recommended to determine an optimal approach of left liver LT.

In conclusion, the study further detailed the decision making for following the LAR-LT approach for left liver LT and demonstrated the whole procedure of this approach during graft implantation. Although the overall outcome was not superior to conventional orthotopic left liver LT, the result of LAR-LT remains satisfactory. Therefore, heterotopic implantation of a rotated left liver graft in the right subphrenic space could be safely applied as an alternative in left liver LT based on an easier reconstruction technique after considering the concerns described in the study for selecting patients.

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