

Balanced approach can help initial outcomes: analysis of initial 50 cases of a new liver transplantation program in East Asia

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Purpose: To evaluate patient triage pattern and outcomes according to types of liver transplantation as part of a new liver transplant program developed in an East Asian country with a limited number of deceased donors.

Methods: Medical records of initial 50 liver transplantations were reviewed retrospectively.

Results: Twenty-nine patients underwent deceased donor liver transplantation (DDLT) and 21 patients underwent living donor liver transplantation (LDLT). Mean model for end-stage liver disease scores of recipients of DDLT and LDLT were 24.9 ± 11.6 and 13.1 ± 5.4 , respectively ($P < 0.0001$). Twenty-eight patients had HCCs and 17 of them (60.7%) underwent LDLT, which was 80.9% of LDLTs. There were 2 cases of perioperative mortality; each was from DDLT and LDLT, respectively. Median follow-up was 18 months. Overall patient and graft survival rates at 6 months, 1 and 2 years were 95.7%, 93.4%, and 89.8 %, respectively. There was no significant difference in survival between DDLT and LDLT. Overall recurrence-free survival rates of hepatocellular carcinoma (HCC) patients at 6 month, 1, and 2 years were 96.3%, 96.3%, and 90.3%, respectively. There was no significant difference in recurrence-free survival between DDLT and LDLT.

Conclusion: As a new liver transplant program with limited resource and waiting list, patients with critical condition could undergo DDLT whereas relatively stable patients with HCCs were mostly directed to LDLT. We recommend a balanced approach between DDLT and LDLT for initiating liver transplant programs.

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Key Words: Liver transplantation, Donor selection, Liver transplantation program, Outcome, Survival

INTRODUCTION

For several decades since Starzl et al. [1] performed the first successful human liver transplantation in 1967, only selected institutions with enough resources and support could run a liver transplant program. As liver transplantation becomes a standard treatment for end-stage liver disease (ESLD) and early-stage hepatocellular carcinoma (HCC) along with development

of living donor liver transplantation (LDLT) techniques, the number of liver transplant programs is rapidly increasing all over the world, especially in the 21st century. In addition to the unique nature of liver transplantation as a kind of major surgery utilizing large amount hospital resources requiring a team approach, it is influenced by many other nonmedical factors such as legislations for organ donation, socioeconomic status, insurance policies, etc. Therefore, each developing pro-

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gram at different locations in the world may be facing diverse and different issues.

Most Asian countries have an extremely low number of organ donations from deceased donors, whereas most organs are donated from living donors, especially family members. This situation poses another hurdle for new programs to overcome. Olthoff et al. [2] also suggested that, in center experience, less than 20 LDLT could be associated with a significantly greater risk of graft failure, which implies a learning curve, as the center exists. It is important for new programs to develop strategies to overcome those learning-curve periods as quickly as possible.

The purpose of this study is to evaluate patient triage pattern and outcomes according to types of liver transplantation of the initial 50 cases as a new liver transplant program, which was built in a metro city of East Asia with limited number of deceased donors. We also analyzed data from Korean Network for Organ Sharing (KONOS) to identify recent volume and distribution patterns of liver transplantation among different centers.

METHODS

Fifty consecutive patients who underwent liver transplantation at Korea University Medical Center Anam Hospital were included in this study. The first case was performed on 29th of December 2009 and the 50th case was performed on 23rd of March 2013 over a 29-month period. Prospectively collected database was reviewed.

For reference, center-specific data was collected through annual reports of transplant 2012 [3] and KONOS website [4] through internet access.

The Mann-Whitney U test and Kruskal Wallis test were used for continuous variables and the chi-square or Fisher exact test for categorical variables. Bonferroni correction was used as deemed appropriate. PASW Statistics 18.0 (SPSS Inc., Chicago, IL, USA) was employed for all tests. A P-value less than 0.05 was considered to be statistically significant.

RESULTS

Among the 50 patients, 29 underwent DDLT and 21 underwent LDLT. Grafts from extended criteria donors were used in 18 cases (62%) among 29 DDLTs according to the definitions by Durand et al. [5]. There was one donation after cardiac death (Maastricht category IV) and one ABO-incompatible LDLT. Patient characteristics and comparison between DDLT and LDLT are summarized in Table 1. Mean model for end-stage liver disease (MELD) score of DDLT and LDLT was 24.9 ± 11.6 and 13.1 ± 5.4 , respectively, which was statistically significant

($P < 0.001$). Statistical significance was still present even after MELD score was recalculated counting HCC as 21 of MELD score ($P = 0.010$). When patients were stratified by KONOS status, which was used in Korea for allocation of deceased donor liver, most patients in DDLT group belonged to status 1 and 2A. On the other hand, most patients in LDLT group belonged to status 2B and 3 ($P < 0.001$). There were 4 status 1 patients and all of them were diagnosed with fulminant hepatic failure. There were 2 more patients with fulminant hepatic failure but listed as status 2A due to hepatitis B surface antigen positivity, which could not be listed as status 1 in Korea. Among 17 patients of status 2A in DDLT group, 10 patients were listed for encephalopathy alone, 4 patients were for ascites alone, 2 patients were for variceal bleeding alone, and 1 patient was for both encephalopathy and ascites. The most common cause of liver transplantation was hepatitis B virus related liver cirrhosis ($n = 31$) followed by alcoholic cirrhosis ($n = 9$). All 6 patients with fulminant hepatic failure underwent DDLT.

HCC was combined in 28 patients. Seventeen of those patients (60.7%) underwent LDLT, which comprised 80.9% of all LDLT cases. Among patients with HCC who underwent DDLT, 81.8% were within Milan criteria [6]. On the other hand, only 35.3% of patients with HCC who underwent LDLT were within Milan criteria. There were significant differences between DDLT and LDLT in operation time and cold ischemic time, but no significant difference was noted in other variables. No hepatic artery thrombosis was noted and one hepatic artery stenosis was treated with balloon angioplasty.

In LDLT group, 18 patients received right lobe graft. Modified right lobe graft [7] was used in 10 patients. Extended right lobe graft [8] and right lobe graft without middle hepatic vein reconstruction were used in 4 and 2 cases respectively. In the remaining 2 patients, only parts of tributaries were selectively reconstructed. Among 3 patients who received left lobe graft, 2 patients received conventional left lobe graft and 1 patient received left lobe including caudate lobe. There was no mortality or significant morbidity among living donors. Median graft-recipient weight ratio was 1.07 (range, 0.69–1.66). Correlation coefficient (R^2) between preoperative volumetry and actual graft volume was 0.794 ($P < 0.001$) with a mean difference of 67 gm, which was 9% of the mean graft volume.

There were 2 perioperative mortalities (1 DDLT, 1 LDLT) from cardiac events, which were excluded from follow-up analysis. Median follow-up was 18 months. Overall patient and graft survival rates at 6 months, 1 and 2 years were 95.7%, 93.4%, and 89.8%, respectively (Fig. 1). There was no significant difference in survival between DDLT and LDLT ($P = 0.470$). Two cases of HCC recurrence were observed in LDLT group and no case in DDLT group during follow-up. Overall recurrence-free survival rates of HCC patients at 6 months, 1, and 2 years were

Table 1. Patient characteristics and comparison between deceased donor liver transplantation and living donor liver transplantation

Characteristic	Total (n = 50)	DDLT (n = 29)	LDLT (n = 21)	P-value ^{a)}
Sex				
Male : Female	29 : 21	15 : 14	14 : 07	0.291
Age (yr)				
Recipient	52.1 ± 9.6	51.3 ± 9.2	53.1 ± 10.3	0.491
Donor	39.8 ± 13.9	45.0 ± 14.5	32.5 ± 9.0	0.001
MELD score	20.0 ± 11.1	24.9 ± 11.6	13.1 ± 5.4	<0.001
MELD score (HCC as 21)	24.3 ± 8.1	27.1 ± 9.5	20.5 ± 2.8	0.010
CTP score	9.5 ± 2.9	10.7 ± 2.7	7.9 ± 2.4	<0.001
KONOS status				<0.001
1	4	4	0	
2A	18	17	1	
2B	25	7	18	
3	3	1	2	
Underlying liver disease				0.027
HBV-LC	31	14	17	
HCV-LC	1	0	1	
Alcoholic LC	9	6	3	
Cryptogenic LC	1	1	0	
FHF	6	6	0	
PSC	1	1	0	
PBC	1	1	0	
Presence of HCC	28	11 (37.9)	17 (80.9)	0.005
Tumor burden				0.036
<Milan	15 (53.6)	9 (81.8)	6 (35.3)	
Milan–UCSF	7 (25.0)	2 (18.2)	5 (29.4)	
>UCSF	6 (21.4)	0 (0)	6 (35.3)	
Operation time (min)	877.4 ± 273.2	764.7 ± 273.5	1033.1 ± 185.1	<0.001
Cold ischemic time (min)	292.6 ± 197.4	367.0 ± 118.9	190.0 ± 237.9	<0.001
Anastomosis time (min)	55.1 ± 53.5	60.2 ± 69.9	48.3 ± 13.6	0.723
RBC transfusion (unit)	25.3 ± 23.1	24.8 ± 16.4	26.1 ± 30.4	0.293
LOS (day), median (range)	21 (12–269)	26 (14–269)	21 (12–154)	0.237
Bile leakage/stenosis	4	2	2	0.512
CMV infection	22	14	8	0.474
Acute cellular rejection	6	4	2	1

Values are presented as mean ± standard deviation or number (%) unless otherwise indicated.

DDLT, deceased donor liver transplantation; LDLT, living donor liver transplantation; MELD, model for end-stage liver disease; HCC, hepatocellular carcinoma; CTP, Child-Turcotte-Pugh; KONOS, Korean Network for Organ Sharing; LC, liver cirrhosis; FHF, fulminant hepatic failure; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; UCSF, University of San Francisco; LOS, length of stay; CMV, cytomegalovirus.

^{a)}DDLT vs. LDLT.

96.3%, 96.3%, and 90.3%, respectively. There was no significant difference in recurrence-free survival between DDLT and LDLT ($P = 0.339$).

KONOS Data

During the last 5 years from 2009 to 2013, 5,712 liver transplantations were performed in 42 different centers in Korea. Centers were grouped into 3 different categories according to cumulative number of liver transplantations performed during the study period. Groups 1, 2, and 3 were defined as centers performing more than 100 cases, more

than 20 but less than 100 cases, and less than 20 cases for that period, respectively (Table 2). The proportion of DDLT was calculated from each center and results are shown in Fig. 2. There were nine centers in group 1 and 88.4% of all liver transplantations were performed in those centers. In group 3, centers showed significant heterogeneity in proportion of DDLT. There was a significant difference in proportion of DDLT between groups 1 and 2 (26.9 vs. 55.1, $P = 0.001$), but no significant differences were observed between groups 1 and 3, and groups 2 and 3 ($P = 0.066$ and $P = 0.862$).

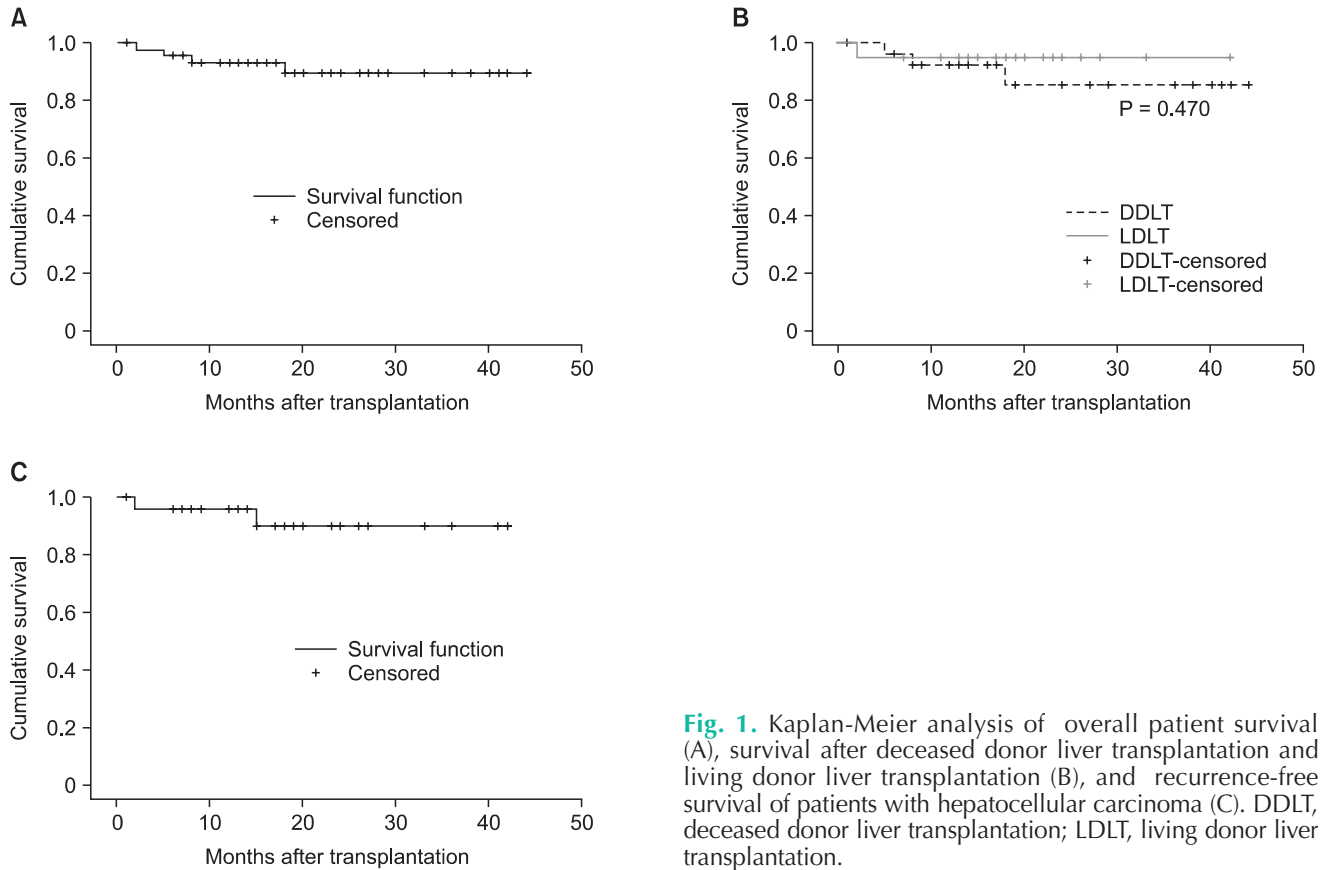


Fig. 1. Kaplan-Meier analysis of overall patient survival (A), survival after deceased donor liver transplantation and living donor liver transplantation (B), and recurrence-free survival of patients with hepatocellular carcinoma (C). DDLT, deceased donor liver transplantation; LDLT, living donor liver transplantation.

Table 2. Group-specific liver transplantation data

Variable	Group 1	Group 2	Group 3	Total
No. of centers	9	11	22	42
Case no. of LT	5,052 (88.4)	487 (8.5)	173 (3.0)	5,712
Case no. of DDLT	1,164 (76.4)	270 (17.7)	89 (5.8)	1,523
Proportion of DDLT (%)				
Median	22.5	52.8	55.0	NA
Mean ± SD	26.9 ± 12.8	55.1 ± 16.0	54.3 ± 38.7	NA

Values are presented as number (%) unless otherwise indicated.

Groups 1, 2, and 3 are defined as centers performing more than 100 cases, more than 20 but less than 100 cases, and less than 20 cases for that period, respectively.

LT, liver transplantation; DDLT, deceased donor liver transplantation; SD, standard deviation; NA, not applicable.

DISCUSSION

Even though liver transplantation became the standard treatment for ESLD and early-stage HCC and the number of liver transplant programs is rapidly increasing all over the world, there are a limited number of recent publications about outcomes from new liver transplant programs [9-11].

According to KONOS data [4], 37 centers performed liver transplantations in the year of 2013, which was only 20 centers in 2006. As shown in Table 2, 5,052 cases of all liver transplantations (88.4%) were performed in 9 centers (group

1) during last 5-year period. On the other hand, 22 centers (group 3) performed less than 20 cases for 5 years and 10 of them performed equal or less than 5 cases for that period. This implies that many centers are trying to establish a liver transplant program and many of them have difficulties thriving. Even though center-specific outcome data are not available from KONOS, center-specific transplant volume data does suggest that many new programs are not experiencing enough cases to overcome their learning curve in a reasonable time frame. Although total volume was relatively small, centers in group 2 maintained their volume in a consistent manner,

which seemed to be an important issue for new programs.

The proportion of DDLT and LDLT is another aspect that needs to be considered. In most Asian countries, due to the scarcity of deceased organ donation, the proportion of LDLT overwhelms DDLT, which makes new programs face more difficulties.

During the last 5 years, 26.3% (1,523/5,712) of all liver transplantation was DDLT and 73.3% (4,189/5,712) was LDLT in Korea [4]. As shown in Fig. 2, where 42 centers are sorted by the number of liver transplantation performed in each center for the last 5 years, well-established and experienced centers (group 1) are performing more LDLTs than DDLTs. Medium-sized centers are performing a significantly larger proportion of DDLT than Group 1 ($P = 0.066$) and those centers showed a relatively stable pattern in proportion of DDLT within group 2. In contrast, group 3 showed heterogeneous pattern in proportion of DDLT, most likely from a small number of total transplantation volume and inconsistent occurrence of liver transplantation. This finding suggests that preparation of either DDLT or LDLT alone has a significantly negative impact on volume increase in new liver transplant programs.

The benefit of LDLT over waiting for DDLT has been shown clear by Berg et al. [12]. The benefit was magnified as centers gained more experience. However, triage between DDLT and LDLT is affected by many factors such as regional average time on waiting lists, legislation about organ distribution and priority, medical condition of candidates, availability of living donor, and institutional preference and resource, etc. As new

liver transplant programs develop, both increasing volume and keeping optimal outcomes are important. However, these can sometimes be conflicting. Maintaining capability of both DDLT and LDLT with an adequate waiting-list formation in cooperation with hepatologists seems to be essential for new programs. For our instances, the waiting list was developed in cooperation with hepatologists even before the set-up and training of the surgical team was completed, although the waiting list was mostly composed of status 2B candidates at that phase. Although recent studies showed comparable outcomes between DDLT and LDLT in selected cases [13-15], those results are from well-established and experienced centers that already have overcome the learning-curve period over some time. On the other hand, Olthoff et al. [2] clearly showed that inferior outcome was noticed during early phase of LDLT programs from the United States. In their report, 1-year graft survival rate was 81%. The better outcome from our center seems to be related to ample training and experience of transplant members at a high volume center, which could help minimize the learning-curve period as well as careful patient selection for LDLT. It would be advisable to consult large volume centers for high-risk candidates before triage between DDLT and LDLT to maintain optimal outcome, especially during the learning-curve period. Sometimes, one might have to refer patients with high enough risks that cannot be handled to large volume centers, at least during the initial phase of the program.

Our data showed that most of the high-risk patients including all 6 patients with fulminant hepatic failure could undergo DDLT. On the other hand, 60.7% of HCC patients who had low MELD score underwent LDLT. Interestingly, tumor burden was also significantly different between DDLT and LDLT. Most HCC patients (9/11) in DDLT group were within Milan criteria, whereas only 35.3% of HCC patients (6/17) in LDLT group were within Milan criteria and another 35.3% (6/17) were above University of San Francisco criteria [16]. This finding explains that LDLT was more preferentially used for stable HCC patients, and we believe this helped our initial outcomes. Compared to the national average survival rate of 86.18% at 1 year and 80.30% at 3 years [4], results of our center stayed above those rates. Because availability of deceased donor is significantly different depending on geographical location, it might be difficult to generalize our experience. However, strategies such as training of surgical teams at large volume centers, intimate cooperation with hepatologists establishing and managing waiting lists for DDLT before starting a LDLT program, maintaining capability of both DDLT and LDLT, and consultation with large volume centers as needed can help the initial phase of a new program from not only transplant volume but also outcome perspective.

In conclusion, a balanced approach between DDLT and LDLT using such strategies can help the initial outcome of new liver transplant programs.

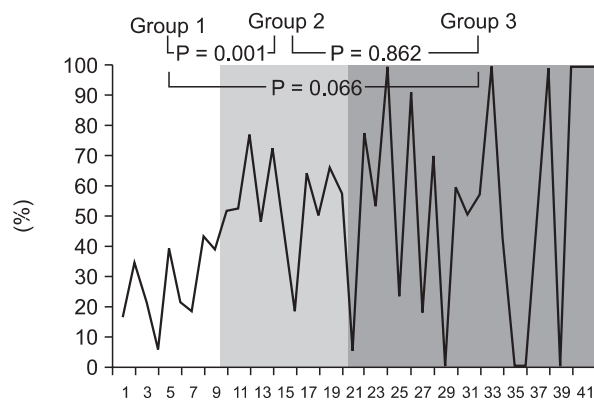


Fig. 2. Proportion of deceased donor liver transplantation (DDLT) compared to total number of liver transplantation in each center in Korea. Y axis represents percentage of DDLT. X axis represents individual centers sorted by the number of liver transplantation performed during last 5 years (2009–2013). Center 1 depicts the center where the largest number of liver transplantation was performed. Centers are divided into 3 groups: centers in group 1 (white zone, center 1–9) performed more than 100 cases, centers in group 2 (light gray zone, center 10–20) performed between 20–100 cases, and center in group 3 (dark gray zone, center 21–42) performed less than 20 cases over last 5 years.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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