Long-term survival outcome between living donor and deceased donor liver transplant for hepatocellular carcinoma: Intention-to-treat and propensity score matching analyses

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Running head:

Outcomes of HCC after LDLT and DDLT

Synopsis:

With intention-to-treat analysis, survival outcomes were analyzed from time of listing rather than from time of transplant, LDLT offered survival benefits to HCC patients. Outcomes of LDLT and DDLT were comparable after propensity-score matching to control for pretransplant differences.

Abstract

Background

Previous studies comparing outcomes of hepatocellular carcinoma (HCC) patients after living donor liver transplantation (LDLT) and deceased donor liver transplantation (DDLT) showed conflicting results and most studies measured survival outcomes from the time of liver transplantation (LT).

Method

This retrospective study aimed to evaluate the long-term outcomes of HCC patients listed for LT using intention-to-treat (ITT) and propensity score matching (PSM) analyses. Clinico-pathological data were retrieved from a prospectively collected database.

Results

From 1995-2014, 375 HCC patients were listed for LT. ITT-LDLT group had 188 patients, whereas ITT-DDLT group had 187 patients. Twenty-seven patients (14.4%) and 122 patients (65.2%) were delisted from LDLT and DDLT waitlist, respectively. The 1-, 3- and 5-year overall survival rates were significantly better in ITT-LDLT group than ITT-DDLT group (94.1 vs. 77.5%, 81.4 vs. 48.7% and 75.9 vs. 40.8%). High alpha-fetoprotein (AFP) and ITT-DDLT treatment arm were independent poor prognostic factors affecting overall survival. LDLT group (n=161) had more young patients, poorer liver function, higher AFP, more tumors outside Milan/UCSF criteria, when compared with DDLT group (n=85). After PSM, the 1-, 3- and 5-year recurrence-free survival rates were similar between matched LDLT and matched DDLT groups (87.7% vs. 90.8%%, 76.9% vs. 83.1% and 72.2% vs. 81.5%).

Conclusion

Survival benefit of LDLT was observed for HCC patients with ITT analysis. Despite a more advanced tumor stage, overall and recurrence-free survival rates were comparable between LDLT and DDLT using PSM analysis.

Background

Liver transplantation (LT) is an ideal treatment for early stage nonresectable hepatocellular carcinoma (HCC). Outcomes from early reports of LT for HCC were disappointing and there was concern whether it was justified to transplant HCC patients.(1-3) It was not until the landmark paper from Mazzaferro et al. that demonstrated a 4-year survival rate of 75% after deceased donor liver transplantation (DDLT) for HCC patients under Milan criteria (solitary HCC ≤5cm or up to 3 tumors, each ≤3cm and in the absence of vascular invasion and extrahepatic disease).(4) On the other hand, living donor liver transplantation (LDLT) flourishes in Asia due to great shortage of deceased organs. LDLT has become an attractive option for HCC patients because it represents a potentially unlimited supply of good quality grafts that come with no competition and waiting time. It is controversial whether DDLT and LDLT provide similar outcomes for HCC and the results in literature were conflicting. (5-11). In order to reflect the true picture of LDLT and DDLT approaches for HCC, patients who dropout from waitlist should be included in outcome analysis. Two studies from France showed that there was no difference in overall survival between DDLT and LDLT by intention-to-treat (ITT) analysis, i.e. to consider survival of patients from the time of listing. (12, 13) However, the problem of organ shortage is more prominent in Asia where living donor graft is an important organ source. Early results from the authors' center showed that there might be survival benefits in HCC patients with potential living donors, although the recurrence rate was higher after LDLT. (14, 15) The previous analysis was limited by small patient number and short follow-up time. In the present study, the long-term survival outcome of all adult HCC patients enlisting for LT was analyzed using ITT and propensity score matching (PSM) analyses.

Method

Study design

This was a retrospective study from Queen Mary Hospital, the University of Hong Kong, Hong Kong. All data was retrieved from a prospectively collected database. The study was approved by the institutional review board. All adult HCC patients enlisted for LT from 1995 to 2014 were analyzed. All patients who had unresectable HCC would be evaluated for LT. Tumor evaluation was based on contrast imaging, either computed tomography (CT) or magnetic resonance imaging (MRI). Diagnosis of HCC was made according to American Association for the Study of Liver Diseases (AASLD) guideline.(16)

Enlisting for DDLT

Before 2002, radiological Milan criteria were used for DDLT selection. After 2002, the selection criteria were expanded to the University of California, San Francisco (UCSF) criteria (solitary tumor ≤6.5cm, or up to 3 tumors, each with a maximum size ≤4.5cm and total diameter ≤8cm).(17) All potential candidates were evaluated in multidisciplinary transplant committee and were listed in DDLT waiting list if eligible. All patients were prioritized according to the Model for End Stage Liver Diseases score (MELD). (18) From October 2009, a MELD bonus score of 18 was granted to T2 HCC patients (solitary tumor 2-5cm, or multiple tumors ≤3 and each ≤3cm) who remained at T2 for ≥6 months after diagnosis. An additional 2 MELD score was granted every 3 months if tumors remained within T2. (19) The choice of bridging therapy to control tumor growth was discussed in a multidisciplinary transplant committee.

Enlisting for LDLT

Option of LDLT was discussed with all HCC patients. Patients with tumors outside UCSF criteria were also considered for LDLT, provided that there was no major vascular invasion and no distant metastasis. In general, a liver graft ≥40% of recipient estimated standard liver volume (ESLV) based on Urata formula would be considered adequate.(15, 20) All living donation was evaluated and approved by an independent Human Organ Transplantation Board. In the present study, patients would be considered as ITT-LDLT group if they had at least one potential live donor who had started donor workup. Reasons for ineligibility for live donation of live donor were recorded.

Surgery

LT was performed under standard technique as described previously.(14) Explant livers were examined for tumor size, number, differentiation and microvascular invasion by specialist pathologists. Patients with incidental HCC on explant liver were excluded from the present study.

Immunosuppression

Immunosuppression regimen was standardized. Induction agents consisted of Basiliximab and hydrocortisone. Maintenance regimen consisted of calcineurin inhibitors (CNI) (tacrolimus or cyclosporine) and mycophenolate mofetil. The latter would be discontinued 3 months after LT. Mammalian target of rapamycin (mTOR) inhibitors (sirolimus or everolimus) were available from 2006 as CNI sparing agents. Steroid was only prescribed to patients who had autoimmune liver disease or with history of rejection or as CNI sparing agent.

Patients' follow-up

Serum alpha-fetoprotein (AFP) and contrasted CT thorax and abdomen were done

every 3 months for the first 3 years after LT and thereafter every 6 months. Recurrence was made on radiological and/or biochemical grounds, and confirmed by histological examination whenever possible. Treatment modalities for recurrent HCC included hepatic resection, ablative therapy, transarterial chemoembolization and systemic therapy.

Statistical analysis

Overall survival was calculated from the time of listing to death of any cause in ITT analysis. Overall and recurrence-free survival after LT was calculated from time of LT to death of any cause and tumor recurrence, respectively. Propensity scores were generated using a multivariable logistic regression model based on the baseline demographics and preoperative tumor characteristics difference between the LDLT and the DDLT groups. Matching process using the nearest neighboring method in 1:1 ratio was performed. (21, 22) Continuous variables were presented as median with range. Comparison between groups was done using Pearson's chi-squared test or the Mann-Whitney U test where appropriate. Overall and recurrence-free survival rates were analyzed using the Kaplan-Meier method and compared using the log-rank test. Cox regression analysis was used to define variables that predicted survival. Significant factors from univariate analysis ($p < 0.1$) were entered for multivariate analysis. Statistical significance was defined as p-value <0.05 and all tests were performed two-tailed. All calculations were done using SPSS version 22.0.

Results

Intention-to-treat analysis

There were 375 adult HCC patients enlisted for LT (188 patients were in ITT-LDLT group and 187 patients were in ITT-DDLT group). The median follow-up period was

62 (1-274) months. Twenty-seven patients (14.4%) dropped out from ITT-LDLT group as 24 potential live donors were deemed unsuitable and deceased donor grafts were available in another 3 patients. A total of 214 patients (187 ITT-DDLT and 27 patients from ITT-LDLT group) were waitlisted for DDLT and 122 (65.2%) patients dropped out. Reasons for dropout were tumor progression (n=60, 49.2%) and liver decompensation/ other comorbidities (n=56, 45.9%). At the time of analysis, 161 and 85 patients underwent LDLT and DDLT respectively, and 7 patients are active on the waiting list. (Figure 1a)

Table 1 showed the patient demographics and tumor characteristics at time of listing for LT. Compared with the ITT-DDLT group, patients in the ITT-LDLT group were younger and had more tumors outside Milan and UCSF criteria. Majority of patients in ITT-LDLT group (92.6%) did not receive bridging therapy, whereas 62.6% patients in ITT-DDLT group underwent bridging treatment for tumors. There was no difference in Child's grade, MELD, tumor size, tumor number and pre-LT AFP level between the two groups. More ITT-LDLT patients had salvage transplant (26 vs. 15.5%) for recurrent HCC.

The 1-, 3- and 5-year overall survival rates were significantly better in the ITT-LDLT group than the ITT-DDLT group (94.1 vs. 77.5%, 81.4 vs. 48.7% and 75.9 vs. 40.8%). (Figure 1b) In multivariate analysis, AFP >600ng/ml [HR=1.76 (1.15-2.69), p=0.009] and ITT-DDLT [HR=3.20 (2.32-4.42), p<0.001] were independent poor prognostic factors affecting overall survival. (Supplementary table 1)

At the time of transplantation

Table 2 showed the patient demographics and tumor characteristics of LDLT (n=161) and DDLT (n=85) groups before matching. Compared with DDLT group, LDLT

patients were younger (55 vs. 57 years), had less HBV infection (77.6 vs. 89.4%), lower MELD (11 vs.12) and a higher pre-transplant AFP level (27 vs.13ng/ml). The radiological tumor size was larger (2.9 vs. 2.4cm) in the LDLT group. Over half of the patients in both groups had solitary tumor on pretransplant imaging. More patients in LDLT group had tumors outside Milan and UCSF criteria. Pathological tumor characteristics including tumor number, tumor size, differentiation, microvascular invasion and satellite nodules were similar between two groups.

Propensity score matching analysis

Owing to differences in baseline demographics and tumor characteristics between LDLT and DDLT group, propensity score matching was performed using preoperative factors, including age, HBV infection, MELD, pre-LT AFP level, tumor size and tumor number. After matching, demographics characteristics were comparable between LDLT (n = 65) and DDLT (n = 65) groups. Pathological features of tumors were also similar between the two groups. (Table 2) Waiting time to LT was significantly longer in DDLT than LDLT group patients (250 vs. 24 days). Compared with the deceased donors, live donors were younger (35 vs. 50 years). As partial grafts were used in LDLT, median graft weight, graft weight to recipient ESLV and graft-to-recipient weight ratio (GRWR) were significantly smaller in the matched LDLT group. Cold ischemic time was significantly shorter in the matched LDLT group while warm ischemic time was similar. (Table 3)

Short-term & long-term outcomes

There was no difference in short-term perioperative outcomes between the 2 groups after matching. There was no hospital mortality in LDLT group, whereas 2 patients (3.1%) in DDLT group died in early postoperative period. Postoperative

complications were also similar between groups. (Table 3) The 1-, 3- and 5-year overall survival was comparable between the matched LDLT and the matched DDLT group (95.4 vs. 98.5%, 80.0 vs. 92.3% and 73.4 vs. 84.4%), whereas the 1-, 3- and 5-year recurrence-free survival was also similar (87.7% vs. 90.8%, 76.9% vs. 83.1% and 72.2% vs. 81.5%). (Figure 1c) The median time to recurrence was 88.4 months in the matched LDLT group and 70.5 months in the matched DDLT group. The pattern of recurrence was mostly extrahepatic and most patients with tumor recurrence received various treatment modalities, including resection, ablation, TACE and systemic therapies. (Table 3)

Prognostic factors affecting overall and recurrence-free survival were determined by univariate and multivariate analyses. (Supplementary Table 2 and 3) Multivariate analysis showed that AFP >600ng/ml [HR=2.83 (1.07-7.48), p=0.036], tumor beyond UCSF criteria [HR=2.36 (1.11- 5.04), p=0.026] and microvascular invasion [HR=3.79 (1.81-7.94), p<0.001] were independent poor prognostic factors for overall survival. Same factors predicted worse recurrence-free survival; AFP >600ng/ml [HR=3.44, (1.39-8.50), p=0.007], tumor beyond UCSF criteria [HR=2.56 (1.22-5.35), p=0.013] and microvascular invasion [HR=3.64 (1.75-7.56), p=0.001]. (Table 4)

Discussion

The present study demonstrated that LDLT resulted in significant survival benefits for HCC patients when compared to DDLT, even though tumor status were more advanced by ITT analysis. This can be explained by lower dropout rate and shorter waiting time in ITT-LDLT group. After adjusting for potential confounding factors by PSM, LDLT and DDLT groups had similar long-term survival rates.

Whether LDLT or DDLT is more beneficial for HCC patients is controversial. It

would take a well-designed randomized controlled trial to address this question, but this is simply ethically unacceptable for obvious reason. A number of non-randomized comparative studies had addressed this question and the results were conflicting. (5-11, 23) Data from the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) showed that the unadjusted 5-year HCC recurrence was significantly higher after LDLT although there was no difference in overall survival. (6) In the authors' previous study, LDLT was associated with higher recurrence rate but comparable overall survival. We postulated that the inferior oncological outcomes of LDLT might be related to a high proportion of patients with salvage transplantation and the "fast tracking" effect. (14) Other studies showed the opposite results. In a Korean study, recurrence-free survival was comparable but LDLT patients had a better 5-year overall survival. (8) Several studies from Western centers also showed similar overall and recurrence-free survival after LDLT and DDLT. (10, 11, 23) In these studies, LDLT itself was not a significant predictor for recurrence/survival but tumor differentiation (9) and microvascular invasion (11, 23) predicted worse oncological outcomes.

The caveat is that survival data was evaluated from the time of LT in all these studies, and therefore the effect of dropout and waiting time was not considered. There were only two reports from French centers that evaluated HCC patients who underwent transplant using ITT analysis. (13, 23) In both studies, there was no difference in ITT-overall survival, overall survival and recurrence-free survival after LT. Our study is the first study in the literature that demonstrated a significant survival benefit with LDLT using ITT analysis. The 5-year ITT overall survival was 75.9% in ITT-LDLT and 40.8% in ITT-DDLT group. It was clearly a result of a substantially higher risk of waitlist dropout and death. This phenomenon is almost universal in Asia-Pacific

regions where deceased organ donation rate is low and LDLT is the major source of liver grafts. The present study has also shown that the overall and recurrence-free survival after LDLT and DDLT were comparable after PSM. Ultimately, what predicted survival and tumor recurrence were tumor biology (i.e. tumor stage and microvascular invasion) but not the transplant approach.

LDLT offers a unique opportunity of timely transplantation without competition and minimal waiting time. Living donor graft is a dedicated gift, and there is no consensus on a standard limit of tumor number and size for LDLT. Policy or listing criteria for LDLT varies widely among centers. The guiding principle of LDLT is that there should be “acceptable” recipient outcomes to justify the risk of a living donation. Unlike in DDLT, justice to all patients (both HCC and non-HCC) on waitlist comes first and therefore, standard criteria are adopted.(24, 25) Most LDLT centers allow a modest expansion of Milan/UCSF criteria. This is why PSM was used in our study to minimize pre-transplant differences between LDLT and DDLT patients. LDLT and DDLT should be viewed as complementary; the choice between them depends on availability of deceased donor, waiting time, waitlist dropout and expertise of transplant center. Our dropout rate was very high at 65.2% despite the use of aggressive bridging treatments but it represented the desperate deceased organ shortage in Asia-Pacific region. (26) Without LDLT, most HCC patients would have dropped out and died. It is not a matter of allocation policy or priorization but a matter of organ shortage. Therefore once patients who had waitlist dropout were included, the survival benefits that LDLT offered were indisputable.

Our study does have some limitations. It was a retrospective study with a relatively small patient number. As mentioned previously, randomized controlled trial would be ideal to avoid selection bias. Nonetheless, the present study was the first study to use

PSM to minimize the effects of possible confounding factors that might affect the overall outcome. In conclusion, a substantial survival benefit of LDLT was observed for HCC patients with ITT analysis in the present study. Despite a more advanced tumor stage, overall and recurrence-free survival rates were comparable between LDLT and DDLT using PSM analysis. LDLT allowed timely transplantation with a negligible waiting time and significantly less dropout rate.

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Figure Legends

Figure 1a Flow chart illustrating hepatocellular carcinoma patients according to intention-to-treat analysis

Figure 1b Overall survival of ITT-LDLT and ITT-DDLT groups

Figure 1c Overall and recurrence-free survival of matched LDLT vs. matched DDLT patients

Figure 1a. Flow chart illustrating hepatocellular carcinoma patients according to intention-to-treat analysis

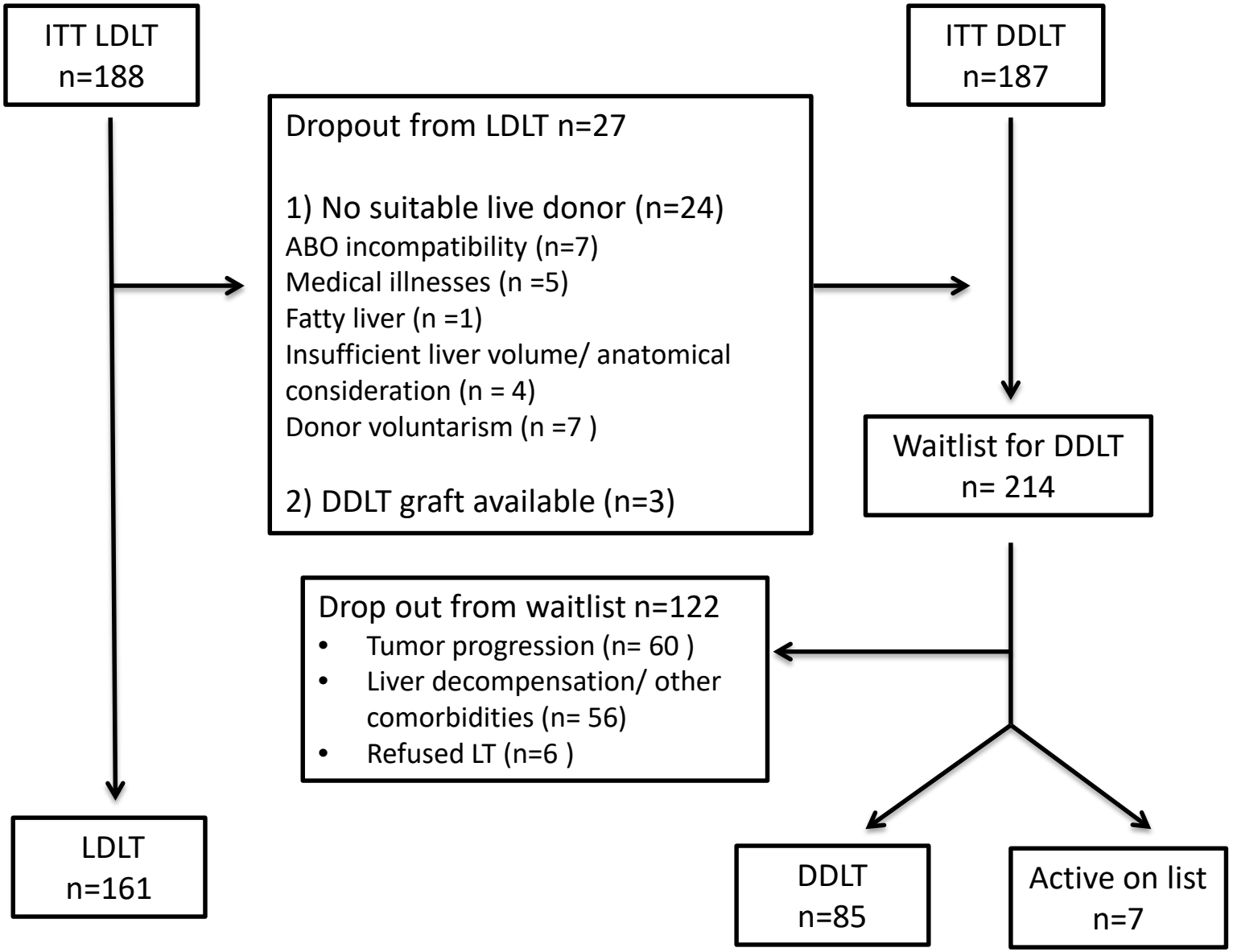
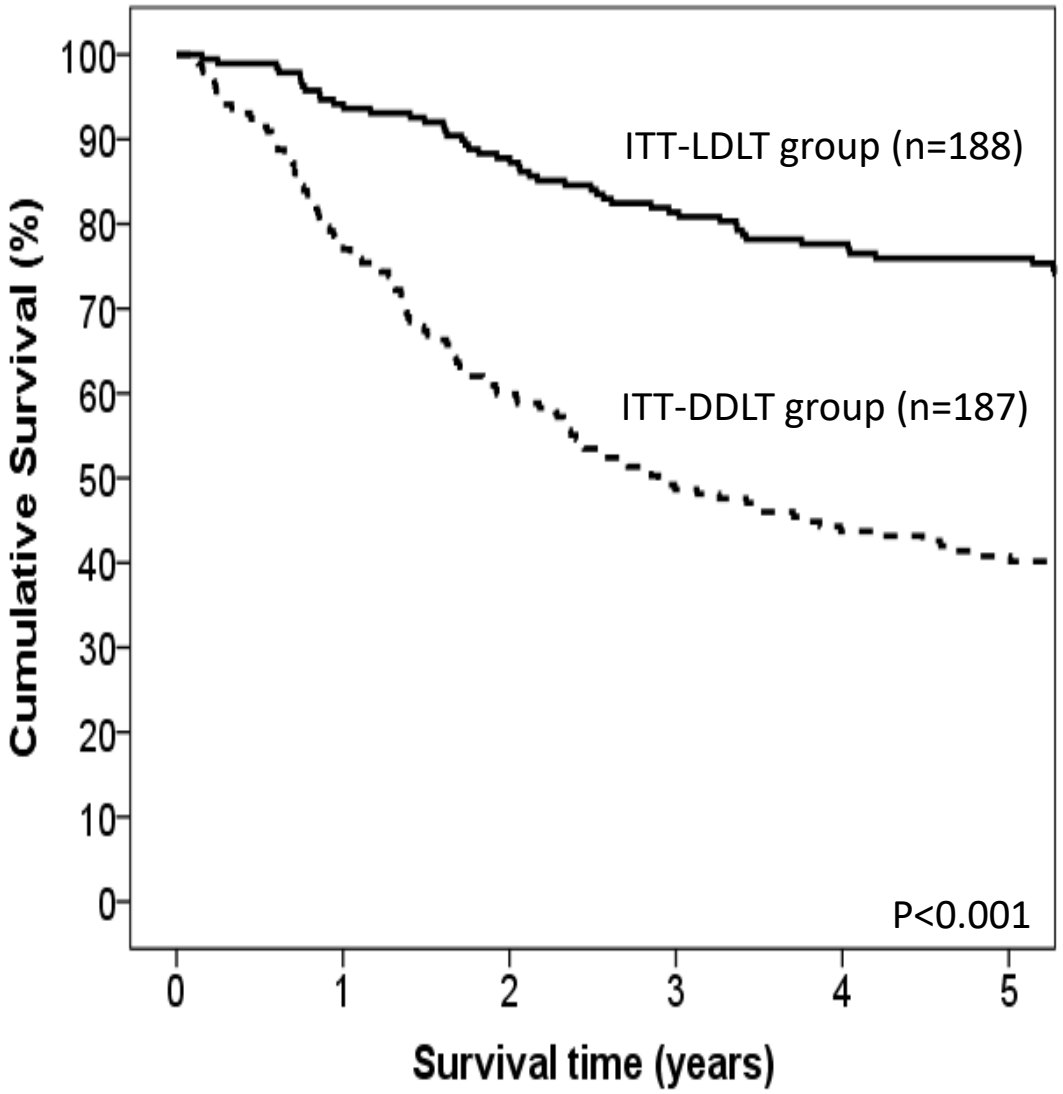
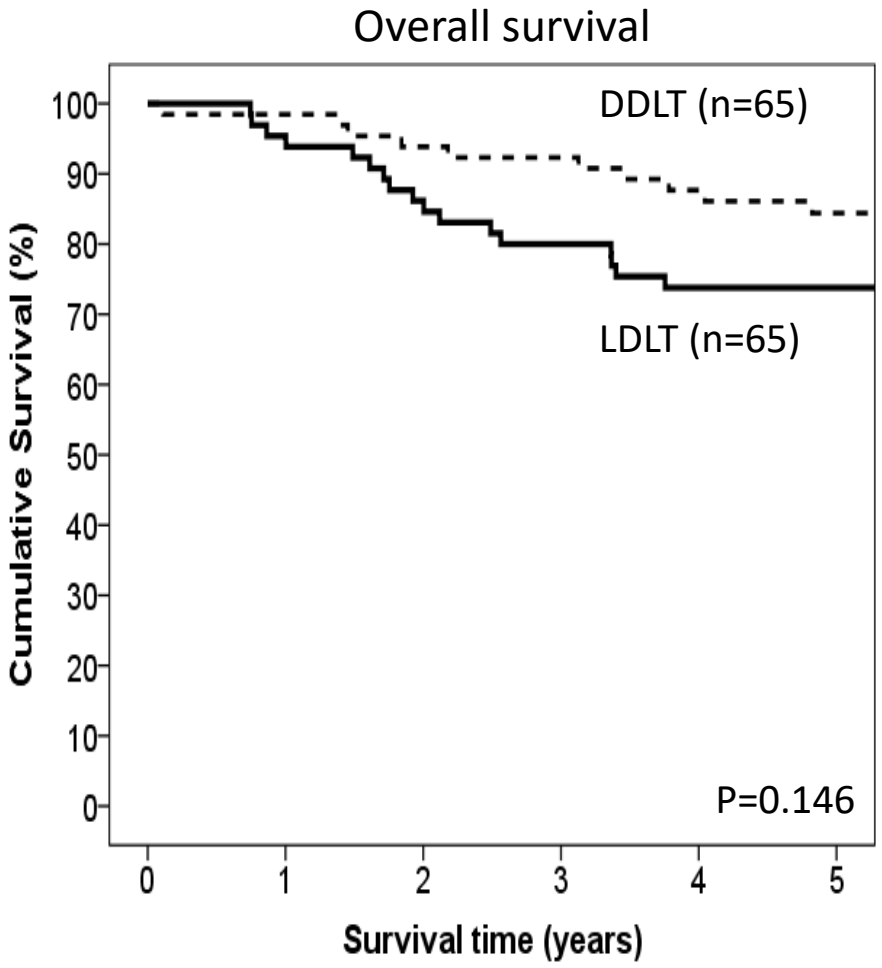


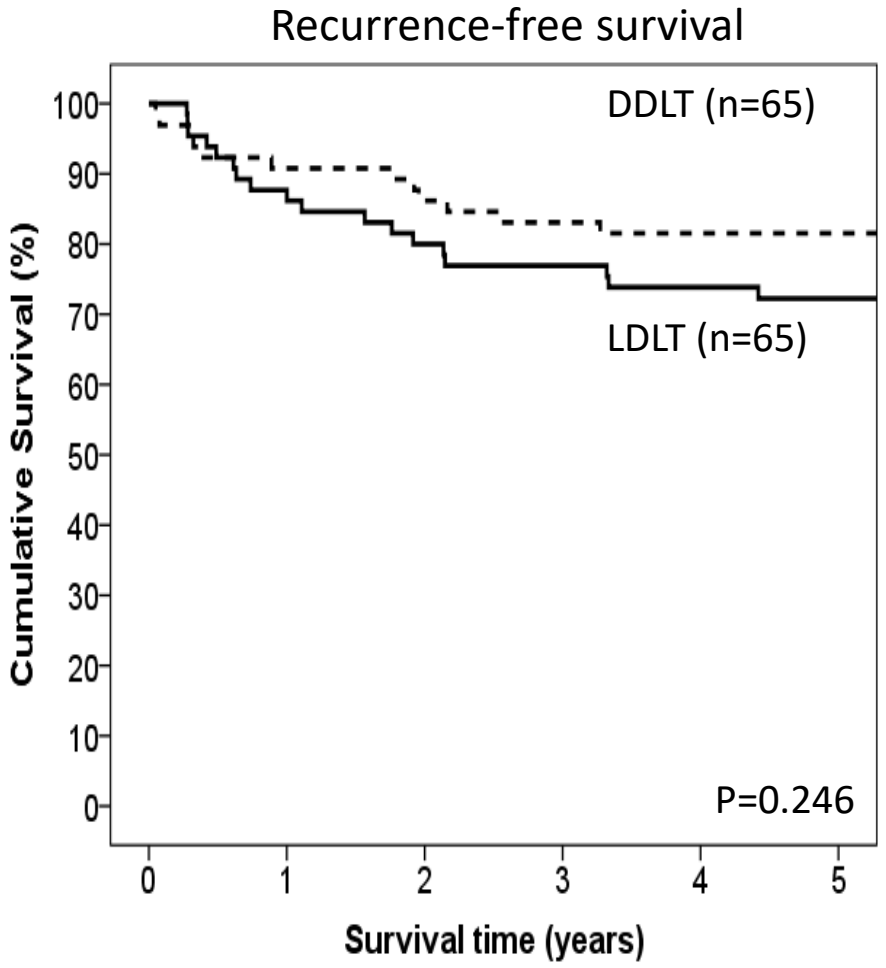
Figure 1b. Overall survival of ITT-LDLT and ITT-DDLT groups



Number of patients at risk:						
ITT-LDLT group	188	177	165	153	138.5	127
ITT-DDLT group	187	145	112	91	77	66

Figure 1c. Overall and recurrence-free survival of matched LDLT vs. matched DDLT patients





Number of patients at risk:

LDLT	**65**	**62**	**56**	**52**	**46**	**42.5**
DDLT	**65**	**64**	**61**	**60**	**56**	**49**

Number of patients at risk:

LDLT	**65**	**57**	**52**	**50**	**46**	**41.5**
DDLT	**65**	**59**	**56**	**54**	**48**	**42**

Table 1. Patient demographics and preoperative tumor characteristics in the ITT-LDLT and ITT-DDLT groups

Characteristics	ITT-LDLT group (n =188)	ITT-DDLT group (n =187)	*p value*
Age	55 (30 -73)	56 (31-68)	0.042
Male: Female	152: 36	158: 29	0.413
Hepatitis B viral infection	150 (79.8)	154 (82.4)	0.598
Hepatitis C viral infection	29 (15.4)	24 (12.8)	0.554
Child-Pugh classification			0.159
Grade	81 (43.1)	80 (42.8)	
Grade B	67 (35.6)	80 (42.8)	
Grade C	40 (21.3)	27 (14.4)	
MELD	11.4 (6-45)	12.4 (6-27)	0.132
Radiological size of the largest tumor (cm)	2.8 (0.9-8.8)	2.6 (0.7-6.2)	0.137
Radiological no. of tumor nodules			0.285
One	102 (54.3)	124 (66.3)	
Two	51 (27.1)	36 (19.3)	
Three or above	35 (18.6)	27 (14.4)	
Outside Milan criteria at listing	54 (28.7)	27 (14.4)	0.001
Outside UCSF criteria at listing	20 (11.7)	0 (0)	<0.001
Serum AFP level (ng/ml)	29 (2-144400)	26 (1-26670)	0.158
AFP >600ng/ml	20 (10.6)	21(11.2)	0.870
Resection or RFA before listing	49 (26)	29 (15.5)	0.015
Pre-transplant bridging therapy			<0.001
No bridging	174 (92.6)	70 (37.4)	
TACE	11 (5.9)	82 (43.9)	
Local regional therapy	3 (1.6)	35 (18.7)	

Continuous variable is expressed as median with range.
Categorical variable is expressed as number of patients (percentage).
MELD, model for end-stage liver disease; UCSF, University of California San Francisco; AFP, alpha-fetoprotein; TACE, transarterial chemoembolization

Table 2. Patient demographics and tumor characteristics of the LDLT and DDLT groups before and after propensity score matching

	Before propensity score matching			After propensity score matching		
Characteristics	LDLT group (n = 161)	DDLT group (n = 85)	*p value*	Matched LDLT group (n = 65)	Matched DDLT group (n = 65)	*p value*
Age	55 (30-73)	57 (41-68)	0.015	55 (40-73)	57 (41-67)	0.854
Male : Female	129 (80.1):	72 (84.7):	0.400	54 (83.1):	54 (83.1):	1.000
	32 (19.9)	13 (15.3)		11 (16.9)	11 (16.9)	
Hepatitis B viral infection	125 (77.6)	76 (89.4)	0.012	56 (86.2)	57 (87.7)	1.000
Hepatitis C viral infection	28 (17.4)	7 (8.2)	0.090	5 (7.7)	7 (10.8)	0.763
Child-Pugh classification			0.163			0.211
Grade A	81 (50.3)	32 (37.6)		35 (53.8)	25 (38.5)	
Grade B	48 (29.8)	31 (36.5)		16 (24.6)	22 (33.8)	
Grade C	32 (19.9)	22 (25.9)		14 (21.5)	18 (27.7)	
MELD	11 (6-59)	12 (6-37)	0.007	11 (6-59)	12 (6-37)	0.060
Serum AFP level (ng/ml)	27 (2-117850)	13 (1-7254)	<0.001	20 (2-2592)	14 (1-7254)	0.120
Radiological size of the largest tumor (cm)	2.9 (0.90-8.80)	2.4 (0.70-6.0)	0.010	2.5 (0.9-6.3)	2.5 (1-6)	0.714
Radiological no. of tumor nodules			0.098			0.848
One	85 (52.8)	57 (67.1)		42 (64.6)	43 (66.2)	
Two	47 (29.2)	17 (20.0)		15 (23.1)	16 (24.6)	

Three or above	20 (18.0)	11 (12.9)		8 (12.3)	6 (9.2)	
Beyond Milan criteria at listing	48 (29.8)	13 (15.3)	0.012	12 (18.5)	10 (15.4)	0.816
Beyond UCSF criteria at listing	20 (12.4)	0 (0)	0.001	0	0	1.000
Pathological size of the largest tumor (cm)	3 (0.9-19.5)	2.65 (0.25-9.0)	0.070	3 (0.9-7)	3 (1-9)	0.509
Pathological no. of tumor nodules			0.994			0.759
One	79 (49.1)	38 (44.7)		34 (52.3)	28 (43.1)	
Two	43 (26.7)	21 (24.7)		17 (26.2)	16 (24.6)	
Three or above	38 (23.6)	19 (22.4)		13 (20)	15 (23.1)	
Tumor differentiation			0.572			0.299
Well-differentiated	45 (28)	16 (18.8)		22 (33.8)	12 (18.5)	
Moderately differentiated	91 (56.5)	46 (54.1)		13 (20)	34 (52.3)	
Poorly differentiated	10 (6.2)	6 (7.1)		3 (4.6)	6 (9.2)	
Microvascular invasion	58 (36.0)	20 (23.5)	0.102	17 (26.2)	13 (20)	0.702
Presence of satellite nodules	3 (1.9)	1 (1.2)	1.000	2 (3.1)	1 (1.5)	1.000

Continuous variable is expressed as median with range. Categorical variable is expressed as number of patients (percentage).
MELD, model for end-stage liver disease; AFP, alpha-fetoprotein

Table 3. Donor characteristics, operative outcomes and recurrence pattern of the matched LDLT and DDLT groups

Parameters	Matched LDLT group (n =65)	Matched DDLT group (n = 65)	*p value*
Time on waitlist (days)	24 (1-691)	250 (1-1874)	<0.001
Donor age (years)	35 (20-58)	50 (16-71)	<0.001
Donor BMI	22 (17.1-28.9)	22.9 (17.8-33.3)	0.141
Graft weight (g)	575 (265-903)	1191(544-1800)	<0.001
GRWR (%)	0.84 (0.49-1.39)	1.78 (0.83-3.07)	<0.001
Graft weight/ recipient ESLV(%)	46.9 (25.8-79.2)	100 (44.4-151.4)	<0.001
Blood transfusion (units)	2 (0-43)	5 (0-56)	0.013
Graft cold ischemic time (min)	107 (60-243)	400 (239-633)	<0.001
Warm ischemic time (min)	53.5 (27-89)	51 (26-102)	0.591
Operative time (min)	775 (494-1110)	529 (300-928)	<0.001
ICU stay (days)	3 (1-18)	3 (1-27)	0.389
Hospital stay (days)	15 (8-107)	15 (8-132)	0.371
Hospital mortality	0 (0)	2 (3.1)	0.496
Severe postoperative complications†	17 (26.2)	13 (20)	0.533
Early postoperative complication			
Pulmonary complication	19 (29.2)	21 (32.3)	0.849
Intra-abdominal collection/ abscess	6 (9.2)	4 (6.2)	0.510
Intra-abdominal bleeding	4 (6.2)	1 (1.5)	0.171
Vascular complications	0 (0)	1 (1.5)	0.315
Renal failure	0 (0)	4 (6.2)	0.119
Opportunistic infection	0 (0)	2 (3.1)	0.496
Time to HCC recurrence (months)	88.4 (3.3-217.4)	70.5 (0.6-272.9)	0.279
Tumor recurrence pattern			0.184
No recurrence	55 (84.6)	58 (89.2)	
Intrahepatic recurrence	1 (1.5)	1 (1.5)	
Extrahepatic metastasis	4 (6.2)	5 (7.7)	
Both intrahepatic & extrahepatic recurrence	7 (10.8)	1 (1.5)	

Treatment modality for recurrence		
Hepatic resection	1	1
Ablative therapy	3	0
Transarterial chemoembolization	4	1
Systemic therapy	8	6
Metastasectomy	5	2
Radiotherapy	1	4

Continuous variable is expressed as median with range.
Categorical variable is expressed as number of patients (percentage).
BMI, body mass index; GRWR, graft-to-recipient weight ratio; ESLV, estimated standard liver volume; †Clavien-Dindo Classification Grade IIIa or above

Table 4. Multivariate analyses of independent prognostic factors affecting overall and recurrence-free survival in the matched LDLT and DDLT groups

	HR (95% CI)	*p* value
Overall survival		
Serum AFP >600ng/ml	2.83 (1.07-7.48)	0.036
Tumor beyond UCSF	2.36 (1.11-5.04)	0.026
Microvascular invasion	3.79 (1.81-7.94)	<0.001
Recurrence-free survival		
Serum AFP >600ng/ml	3.44 (1.39-8.50)	0.007
Tumor beyond UCSF	2.56 (1.22-5.35)	0.013
Microvascular invasion	3.64 (1.75-7.56)	0.001

HR, hazard ratio; CI, confidence interval;
AFP, alpha-fetoprotein; UCSF, University of California San Francisco Criteria

Supplementary table 1. Univariate and multivariate analyses of potential prognostic factors affecting overall survival in the ITT groups

	Univariate analysis		Multivariate analysis	
Variables	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Gender (male)	1.43 (0.93-2.22)	0.105		
Hepatitis B viral infection	0.96 (0.65-1.41)	0.823		
Hepatitis C viral infection	1.03 (0.67-1.58)	0.905		
Child-Pugh grade C	0.63 (0.40-0.97)	0.038		
Tumor size (>3cm)	1.07 (0.79-1.45)	0.659		
Multiple tumors	1.02 (0.75-1.38)	0.896		
Outside Milan criteria at listing	0.89 (0.62-1.28)	0.532		
Outside UCSF criteria at listing	0.60 (0.28-1.28)	0.184		
Serum AFP level (>600ng/ml)	1.67 (1.09-2.55)	0.018	1.76 (1.15-2.69)	0.009
Resection or RFA before listing	1.06 (0.74-1.51)	0.752		
ITT-DDLT as treatment arm	3.16 (2.29- 4.36)	<0.001	3.20 (2.32-4.42)	<0.001

HR, hazard ratio; CI, confidence interval; MELD, model for end-stage liver disease; AFP, alpha-fetoprotein; ITT-DDLT, intention-to-treat deceased donor liver transplantation

Supplementary table 2. Univariate and multivariate analyses of potential prognostic factors affecting overall survival in the matched LDLT and DDLT groups

	Univariate		Multivariate	
Variables	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Gender (male)	1.95 (0.59-6.40)	0.273		
Age (<50 years)	1.59 (0.76-3.32)	0.219		
Hepatitis B viral infection	0.66 (0.29-1.43)	0.285		
Hepatitis C viral infection	1.14 (0.35-3.75)	0.830		
Child C	0.56 (0.21-1.45)	0.230		
MELD (>10)	0.87 (0.42-1.79)	0.697		
Tumor size (>3cm)	1.07 (0.52-2.20)	0.859		
Multiple tumor	1.70 (0.82-3.53)	0.156		
Beyond Milan	1.84 (0.91-3.73)	0.089		
Beyond UCSF	2.71 (1.31-5.59)	0.007	2.36 (1.11-5.04)	0.026
Serum AFP level (>600ng/ml)	3.51 (1.44-8.57)	0.006	2.83 (1.07-7.48)	0.036
Microvascular invasion	3.99 (1.91-8.32)	<0.001	3.79 (1.81-7.94)	<0.001
Poorly differentiated tumor	0.90 (0.21-3.80)	0.885		
LDLT as treatment arm	1.59 (0.77-3.28)	0.210		
Postoperative complications	0.92 (0.45-1.85)	0.804		
Waiting time on list (>38 days median)	0.74 (0.37-1.51)	0.410		
Donor age (>50 years)	1.17 (0.54-255)	0.692		
Graft-to-recipient ESLV (<40%)	0.66 (0.20-2.16)	0.489		
Graft cold ischemic time (>110mins)	0.82 (0.39-1.74)	0.608		
Recipient warm ischemic time (>55mins)	1.31 (0.65-2.65)	0.455		
Blood transfusion (>5units)	0.91 (0.44-1.87)	0.797		

HR, hazard ratio; CI, confidence interval; MELD, model for end-stage liver disease; AFP, alpha-fetoprotein; LDLT, living donor liver transplant; ESLV, estimated standard liver volume

Supplementary table 3. Univariate and multivariate analysis of potential prognostic factors affecting recurrence-free survival in the matched LDLT and DDLT groups

	Univariate		Multivariate	
Variables	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender (male)	2.02 (0.61-6.62)	0.248		
Age (<50 years)	1.71 (0.83-3.51)	0.143		
Hepatitis B viral infection	1.41 (0.43-4.64)	0.570		
Hepatitis C viral infection	1.12 (0.34-3.69)	0.850		
Child C	0.66 (0.27-1.60)	0.356		
MELD (>10)	0.90 (0.44-1.84)	0.771		
Tumor size (>3cm)	1.15 (0.57-2.34)	0.695		
Multiple tumors	1.79 (0.87-3.70)	0.113		
Beyond Milan	1.96 (0.98-392)	0.057		
Beyond UCSF	2.94 (1.45-5.97)	0.003	2.56 (1.22-5.35)	0.013
Serum AFP level (>600ng/ml)	4.15 (1.79-9.63)	0.001	3.44 (1.39-8.50)	0.007
Microvascular invasion	3.83 (1.85-7.91)	<0.001	3.64 (1.75-7.56)	0.001
Poor differentiation	0.89 (0.21-3.76)	0.875		
LDLT as treatment arm	1.44 (0.71-2.93)	0.310		
Postoperative complications	0.98 (0.49-1.95)	0.946		
Waiting time on list (>38 days median)	0.80 (0.40-1.61)	0.535		
Donor age (>50 years)	1.13 (0.52-2.45)	0.754		
Graft-to-recipient ESLV (<40%)	0.63 (1.19-2.06)	0.443		
Graft cold ischemic time (>110min)	0.87 (0.41-1.84)	0.712		
Recipient warm ischemic time (>55min)	1.38 (0.69-2.77)	0.361		
Blood transfusion (>5units)	0.87 (0.42-1.77)	0.695		

HR, hazard ratio; CI, confidence interval; MELD, model for end-stage liver disease; AFP, alpha-fetoprotein; LDLT, living donor liver transplant, ESLV, estimated standard liver volume