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Hepatocellular Carcinoma Recurrence and Death Following Living and Deceased Donor Liver Transplantation

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We examined mortality and recurrence of hepatocellular carcinoma (HCC) among 106 transplant candidates with cirrhosis and HCC who had a potential living donor evaluated between January 1998 and February 2003 at the nine centers participating in the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL). Cox regression models were fitted to compare time from donor evaluation and time from transplant to death or HCC recurrence between 58 living donor liver transplant (LDLT) and 34 deceased donor liver transplant (DDLT) recipients. Mean age and calculated Model for End-Stage Liver Disease (MELD) scores at transplant were similar between LDLT and DDLT recipients (age: 55 vs. 52 years, $p = 0.21$; MELD: 13 vs. 15, $p = 0.08$). Relative to DDLT recipients, LDLT recipients had a shorter time from listing to transplant (mean 160 vs. 469 days, $p < 0.0001$) and a higher rate of HCC recurrence within 3 years than DDLT recipients (29% vs. 0%, $p = 0.002$), but there was no difference in mortality or the combined outcome of mortality or recurrence. LDLT recipients had lower relative mortality risk than patients who did not undergo LDLT after the center had more experience ($p = 0.03$). Enthusiasm for LDLT as HCC treatment is dampened by higher HCC recurrence compared to DDLT.

Key words: A2ALL, DDLT, HCC, LDLT, MELD, recurrence

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Introduction

With careful selection criteria such as the Milan criteria, patients transplanted for hepatocellular carcinoma (HCC), most of whom have underlying cirrhosis, have survival rates comparable to individuals transplanted for nonmalignant liver diseases (1–3). Liver transplant as a potential cure for HCC is limited by the shortage of organs, with up to 30% of patients developing contraindications to transplantation while waiting for a donor (3–5). The use of adult-to-adult living donor liver transplantation (LDLT) may shorten waiting time and possibly decrease waitlist mortality in patients (6,7). The extension of living liver donation to adult recipients with HCC has understandably generated controversy with respect to candidate selection, donor risk and recipient allograft outcomes (8–10). In addition, patients with more aggressive tumor biology, who would otherwise drop off the waiting list due to tumor progression, might be 'fast-tracked' to transplant, and this may lead to an increased recurrence rate of HCC post-transplant (11).

We have analyzed clinical and tumor characteristics of 106 patients with cirrhosis and known HCC pre-transplant who were evaluated for LDLT at the nine centers participating in the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) (12) between 1998 and 2003. About 55% of these patients went on to LDLT, while about 32% received a deceased donor liver transplant (DDLT). These two groups allowed us to determine if outcomes differed between patients with HCC receiving LDLT versus those receiving DDLT.

Methods

Data collection and definitions

Data for this study were derived from the A2ALL Retrospective Cohort Study and were supplemented by data from the Scientific Registry of Transplant Recipients (SRTR) made available through a data use agreement. The A2ALL Retrospective Cohort Study data include 819 patients who had a potential living donor evaluated between 1/1/1998 and 2/28/2003. The cohort included 106 patients with cirrhosis and known HCC. Study enrollment was defined as the date when the first potential live donor underwent history and physical examination for each recipient. For posttransplant survival, recipients of LDLT were compared to recipients of whole or split liver DDLT, and for overall survival, recipients of LDLT were compared to waitlisted patients including those who subsequently underwent DDLT. Recipients whose procedure was aborted due to recipient reasons were included in either the LDLT (n = 2) or DDLT (n = 1) group as appropriate. Recipients of domino transplants (n = 2) were included in DDLT group. The model for end-stage liver disease score (MELD) was calculated as previously described (13,14) and was capped at 40. For each LDLT recipient, the experience of the center at the time of the transplant was defined as the case number of that LDLT at the center (i.e. the number of LDLTs previously performed at the center plus one). The major endpoints studied were HCC recurrence and death. The duration of follow-up since the time of transplant, censored at recurrence or death, ranged from 2 to 6.5 years, median 3.7 years. Among the patients who had recurrence or died, the time from transplant to HCC recurrence or death ranged from 0 to 3.9 years, median 10.5 months.

Preoperative radiological and laboratory studies

Tumor staging was based on the prevailing modification of the tumor node metastasis (TNM) staging classification utilized by the Organ Procurement and Transplantation Network (OPTN) (15). All patients had computed tomography (CT) and/or magnetic resonance imaging (MRI) for liver tumor staging at the time of listing, and at 3–6 month intervals until transplant.

Histopathologic studies

In the analysis of HCC characteristics in the native liver explant, tumor size and number of tumors were recorded to determine tumor stage (T1 – T4) according to the OPTN-modified TNM, Milan (1) and University of California San Francisco (UCSF) criteria (3). Histologic grade based on the modified Edmonson and Steiner criteria (16) and the presence or absence of vascular invasion were also recorded. In patients with multiple lesions in the liver explant, the highest tumor histologic grade was recorded.

Human subjects protection

The study was approved by the Institutional Review Boards and Privacy Boards of the University of Michigan Data Coordinating Center and each of the nine participating transplant centers.

Statistical analysis

Descriptive statistics (means, standard deviations and proportions) for various patient characteristics were calculated separately for patients who eventually received an LDLT, a DDLT or no transplant. For LDLT and DDLT recipients, explant tumor characteristics were also summarized. Statistical differences between the LDLT and DDLT recipients' characteristics and explant tumor characteristics were evaluated using chi-square and *t*-tests. A cumulative incidence function to display the probability of receiving LDLT or DDLT, dying on the waitlist, and remaining alive without transplant over time since donor evaluation (17) was calculated using the SAS macro 'comprisk' developed at Mayo Clinic (18). Freedom from HCC recurrence, recurrence-free survival and patient survival were estimated by Kaplan-Meier methods and unadjusted comparisons made using the log-rank test. In the case of complete separation (no HCC recurrence in DDLT), the effect of LDLT was tested by Cox regression likelihood ratio test. Potential predictors of time from transplant to death, HCC recurrence or the combined endpoint were tested by fitting multivariable Cox regression models. Covariate effects were reported as hazard ratios (HR) with 95% confidence intervals (CI). A wide range of covariates were evaluated. Recipient variables included age, gender, race, etiology of underlying liver disease, calculated MELD score at transplant, HCC staging at enrollment, pretransplant HCC tumor ablation and/or chemotherapy, and AFP at listing, enrollment and transplant; donor and transplant-related variables included donor age, LDLT case number (10), transplant era, time from listing to transplant, time from donor evaluation to transplant, explant characteristics (stage, grade and vascular invasion), transplant center, year of transplant and cold ischemia time. We also investigated whether there was a survival advantage for HCC candidates who pursued LDLT, comparing the relative mortality risk for LDLT recipients to that of waitlisted candidates including those who subsequently underwent DDLT. A modified Cox regression model of time from first donor evaluation to death was fitted, using the method of sequential stratification (17). Briefly, for all LDLTs performed at a given number of days since first donor evaluation, a separate comparison group (stratum) was created that included all patients alive and without transplant prior to the time of the index LDLT(s). The survival of the index LDLT patient(s) was compared to that of the other patients in that stratum, and the results across all LDLT strata were pooled in a stratified Cox regression. The variance was adjusted to account for patients who were in the comparison groups of multiple strata. Patients without LDLT at entry into a stratum were censored if they later received an LDLT. All analyses were performed using SAS version 9.1 (SAS/STAT 9.1 User's Guide, SAS Publishing, Cary, NC: SAS Institute Inc., 2004). P values <0.05 were considered to be statistically significant.

Results

Overall outcome

The overall course of the 106 patients with HCC from the beginning of the first potential living donor evaluation is shown in Figure 1. By the end of follow-up, 10

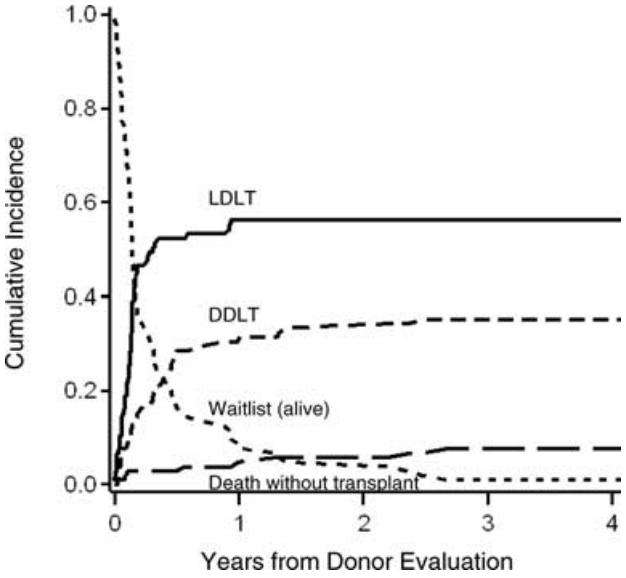

Figure 1: Cumulative probability over time of LDLT, DDLT, death without transplant, and remaining alive on the waitlist, from the point of first potential living donor evaluation (based on the cumulative incidence function).

Table 1: HCC patient characteristics

Characteristics[a]	LDLT (n = 58) Mean (SD) or n (%)	DDLT (n = 34) Mean (SD) or n (%)	p-Value[b]	Nontransplant (n = 14) Mean (SD) or n (%)
Sex			0.66	
Male	45 (78%)	25 (74%)		10 (71%)
Female	13 (22%)	9 (26%)		4 (29%)
Race			0.42	
White	47 (81%)	27 (79%)		11 (79%)
African American	0 (0%)	1 (3%)		2 (14%)
Other	11 (19%)	6 (18%)		1 (7%)
At listing				
Tumor stage ≥ T3	27 (47%)	8 (24%)	0.067	1 (7%)
AFP (ng/mL)[c]	36 (27)	27 (22)	0.184	18 (12)
Tumor ablation sessions immediately prior to or at listing	0.78 (1.1)	0.62 (1.1)	0.53	0.33 (0.7)
≥ 1 tumor ablation sessions immediately prior to or at listing	24 (41%)	12 (35%)	0.94	2 (14%)
At enrollment				
Age	54.5 (8.9)	51.7 (9.6)	0.16	54.7 (7.9)
Lab MELD	11.8 (4.8)	13.5 (5.3)	0.11	12.5 (4.7)
AFP (ng/mL)[c]	42 (34)	16 (13)	0.023	83 (70)
Tumor ablation sessions prior to enrollment	0.86 (1.3)	0.74 (1.2)	0.64	0.42 (0.7)
≥ 1 tumor ablation sessions prior to enrollment	26 (45%)	14 (41%)	0.73	4 (29%)
Median interval between listing and enrollment (days)	37	180	0.001	57
At transplant				
Age	54.6 (9)	52.1 (10)	0.21	
Lab MELD	13 (5)	15 (7)	0.08	
Time from listing to transplant	160 (184.9)	469 (369.8)	<0.0001	
Median interval between listing and transplant (days)	95	373	<0.0001	
HCV etiology of cirrhosis	35 (60%)	25 (74%)	0.20	
Tumor stage ≥ T3	32 (55%)	13 (38%)	0.05	
AFP (ng/mL)[c]	44 (36)	13 (10)	0.019	
Tumor ablation sessions between enrollment and transplant	0.45 (0.6)	0.56 (1.0)	0.52	
≥1 tumor ablation sessions between enrollment and transplant	22 (38%)	11 (32%)	0.59	
Median follow-up post-LT censored at death (years)	4.0	3.4	0.039	

[a]Numbers of missing values for [LDLT, DDLT, nontransplant] were [0, 0, 0] for sex and race, [7–10, 6–10, 5–6] for listing variables, [0–3, 0, 0–3] for enrollment variables and [0–5, 0] for transplant variables.
[b]p-Values for comparison of LDLT and DDLT. Chi-square tests were used for proportions; two-sample *t*-tests were used for continuous variables.
[c]Median on raw scale (median absolute difference about the median), p-value from *t*-test on log scale.

patients had died awaiting transplant (median time from donor evaluation to death: 9 months, range 0.3–32 months) and four patients were still waiting for transplant (median time from donor evaluation to last follow-up: 31 months, range 1–69 months). Of the 92 transplanted patients, 58 received an LDLT and 34 received a DDLT. One year after donor evaluation, the cumulative probabilities of receiving an LDLT, receiving a DDLT, dying on the waiting list and remaining alive without transplant were 0.56, 0.31, 0.05 and 0.09, respectively. Two years after donor evaluation, the respective probabilities were 0.56, 0.33, 0.06 and 0.05.

Characteristics of LDLT and DDLT recipients

Characteristics of the 58 LDLT and the 34 DDLT recipients with HCC at the time of candidate listing, at the evaluation of the potential donor and at transplant are listed in Table 1. At the time of transplant, the mean age of the recipients, mean laboratory MELD score and proportion with

Table 2: Explant tumor characteristics by transplant type

Characteristics	LDLT (n = 58) Mean (SD) or n (%)	DDLT (n = 34) Mean (SD) or n (%)	p value
Tumor stage ≥ T3	33/55 (60%)	14/31 (45%)	0.18
Tumor nodules ≤ 3	40/55 (73%)	22/30 (73%)	0.95
Diameter of largest nodule (cm)	4.7 (2.8)	3.1 (2.0)	0.013
Largest nodule > 5 cm	17/56 (30%)	3/34 (9%)	0.058
Largest nodule > 6.5 cm	8/56 (14%)	1/34 (3%)	0.21
Bilobar HCC	23/51 (45%)	11/29 (38%)	0.53
Vascular invasion	12/55 (22%)	3/30 (10%)	0.17
Micro invasion	9/55 (16%)	3/30 (10%)	
Macro invasion	3/55 (5%)	0/30 (0%)	
Histologic grade > 3	7/46 (15%)	1/29 (3%)	0.26
Milan/UCSF criteria			0.12
Inside Milan	21/56 (38%)	20/34 (59%)	0.05
Outside Milan but inside UCSF	7/56 (13%)	4/34 (12%)	0.92
Outside UCSF	28/56 (50%)	10/34 (29%)	0.055

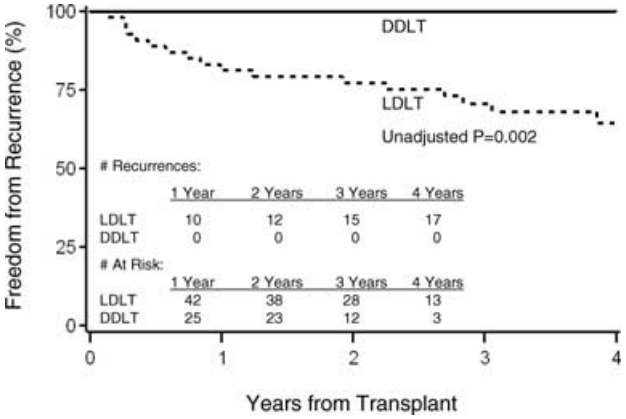

Figure 2: Probability of freedom from HCC recurrence by time since LDLT or DDLT. Freedom from HCC recurrence was significantly lower in LDLT recipients compared to DDLT recipients (p = 0.002, log-rank test).

hepatitis C virus as the underlying etiology of cirrhosis were not significantly different between LDLT and DDLT recipients, respectively. The percentage of patients with HCC stage ≥ T3 at listing, the mean number of tumor ablation sessions at listing, at enrollment, and between enrollment and transplant, and the percentage of patients with at least one tumor ablation session at listing, at enrollment, and between enrollment and transplant were also not significantly different between the two groups. However, mean alpha-fetoprotein (AFP) levels at the time of enrollment (p = 0.023) and transplant (p = 0.019), and the percentage of patients with HCC stage ≥ T3 at transplant were significantly higher in the LDLT group than in the DDLT group. LDLT recipients had a significantly shorter median waiting time compared to DDLT recipients (95 vs. 373 days from listing to transplant; p < 0.0001). Consequently, LDLT recipients had a significantly longer duration of posttransplant follow-up (median 4.0 vs. 3.4 years; p = 0.039).

Liver explant HCC histopathologic characteristics

HCC characteristics in the liver explants suggested more advanced tumors among the LDLT recipients who had significantly larger tumors (p = 0.013), a significantly lower proportion meeting the Milan criteria (p = 0.05) and a higher proportion outside UCSF criteria (p = 0.055). However, there was no significant difference in bilobar HCC, vascular invasion or histologic HCC grade between explants from LDLT and DDLT recipients (Table 2).

Unadjusted posttransplant HCC recurrence and death

After a median potential post-transplant follow-up of 4.0 years, 17 (29%) of 58 patients who received LDLT had HCC recurrence, whereas none of the 34 patients who had DDLT had HCC recurrence after a median follow-up of 3.4 years (Figure 2). The difference in time to recurrence between LDLT and DDLT recipients was statistically significant (p = 0.002). The probability of HCC recurrence was 0.18 at 1 year, 0.22 at 2 years, 0.29 at 3 years and 0.35 at 4 years after LDLT. Of the 17 LDLT recipients with HCC recurrence, 11 died (five from recurrent HCC) and six were still alive at the time of data analysis after a median of 4.2 years (range 3–7 years) after the recurrence was diagnosed. Among the 11 patients who died, the median time from HCC recurrence to death was 6 months (range 1–19 months). Among the entire group of 58 LDLT recipients, 22 died (including 11 who had HCC recurrence). The causes of death were recurrent HCC (n = 5), sepsis (n = 5), recurrent HCV (n = 3), respiratory failure (n = 3), suicide (n = 1), recurrent primary liver disease not due to HCV (n = 1) and other causes (n = 4). Twelve of 34 DDLT recipients died. The causes of death were cardiac arrest (n = 3), stroke (n = 1), respiratory failure (n = 1), sepsis (n = 1), recurrent HCV (n = 2) and other causes (n = 4).

The probability of patient survival at 1, 2 and 3 years after transplantation was not significantly different for LDLT and DDLT recipients (LDLT: 0.86, 0.76, 0.67, DDLT: 0.76, 0.74, 0.63, p = 0.91). Similarly, the probability of graft survival at 1, 2 and 3 years was not significantly different after LDLT and DDLT (LDLT: 0.79, 0.69, 0.60, DDLT: 0.76, 0.74, 0.62, p = 0.61). The probability of recurrence-free survival at 3 years was lower for LDLT recipients (0.58) than DDLT recipients (0.62), but the difference was not statistically significant (p = 0.38) (Figure 3).

HCC recurrence according to tumor stage

A slightly higher proportion of LDLT recipients (60%) had tumors that were stage T3 or T4 at explant compared with DDLT recipients (45%) (p = 0.18) (Table 2). However, more advanced tumor stage did not account for the higher overall

Figure 3: Probability of recurrence-free patient survival by time since LDLT or DDLT. Recurrence-free survival was lower in LDLT recipients compared to DDLT recipients, but the difference was not significant (p = 0.38, log-rank test).

rate of HCC recurrence among LDLT recipients. No DDLT patient, including 14 patients with stage T3 or T4, had HCC recurrence (Table 3). The difference in time to recurrence between LDLT and DDLT recipients was statistically significant after adjustment for tumor stage (p = 0.0001). Among LDLT recipients, there was no significant association between tumor stage and recurrence (p = 0.62). Of note, one of four LDLT recipients who had no identifiable viable tumor at explant had HCC recurrence. Among the patients who met Milan criteria there were five recurrences among 21 LDLT and 0 recurrence among 20 DDLT recipients (Cox regression likelihood ratio test p = 0.0195).

Predictors of HCC recurrence or death after transplant

There was no statistically significant difference between LDLT and DDLT recipients in the risk of the combined endpoint of HCC recurrence or patient death across all tumor stages (HR = 0.82; 95% CI 0.38–1.79; p = 0.62) after adjusting for period of transplant (1998–2000 vs. 2001–2003), AFP level at transplant, transplant center and recipient age (Table 4). Earlier period of transplant (1998–2000 vs. 2001–2003), higher AFP level at transplant and older recipient age at transplant were each independently associated with a significantly higher risk of the combined outcome of HCC recurrence or patient death. Patients receiving transplants in 1998–2000 had a 4.7-fold higher risk of HCC recurrence or patient death than patients receiving transplants in 2001–2003 (p = 0.0006). Each unit of natural log increase in AFP level at the time of transplant was associated with a 57% higher risk of HCC recurrence or patient death (p < 0.0001). The risk of HCC recurrence or patient death varied significantly at the nine transplant centers (p = 0.0205). Older recipient age at transplant was associated with a 4% higher risk of HCC recurrence or patient death per year of age (p = 0.057). Although transplant waiting time was significantly shorter in the group that received LDLT (p < 0.0001), waiting time to transplant itself was not predictive of HCC recurrence or post-transplant patient death (HR=1.00; p = 0.62).

Table 3: HCC recurrence posttransplant by tumor stage at explant

Stage at explant	LDLT	DDLT	Total
No HCC	1/4	0/5	1/9
T1 or T2	5/19	0/15	5/34
T3	6/17	0/6	6/23
T4	5/16	0/8	5/24
Total	17/58*	0/34	17/92*

*Two LDLT recipients were missing explant tumor stage and had no recurrence.

After adjusting for transplant type, AFP level at transplant, transplant center, and recipient age, patients receiving transplants pre-MELD (before 2/28/2002) had a 3.1-fold higher risk of HCC recurrence or patient death than patients receiving transplants post-MELD (p = 0.0168). In the pre-MELD era 54 liver transplants for HCC were performed with 76% of the patients received an LDLT and 62% of these LDLT recipients had an HCC outside Milan stage. In the post-MELD era, 36 liver transplants for HCC were performed with 58% of the patients received a DDLT and 38% of these DDLT recipients had an HCC outside Milan stage (Table 5).

Comparison of relative mortality risk from time of donor evaluation

A modified Cox regression model from the time of donor evaluation to death, adjusted for candidate age and laboratory MELD demonstrated that relative mortality risk after LDLT, once a center had performed at least 20 LDLT cases overall, was significantly lower than for the comparison group of waitlisted candidates including those who subsequently underwent DDLT (HR = 0.38; 95% confidence interval 0.16–0.91; p = 0.03). Patients with HCC who received an LDLT performed within the first 20 cases at a center had a similar mortality risk to those in the comparison group (HR = 0.95; 95% confidence interval 0.48–1.87; p = 0.88). After adjustment for tumor stage ≥T3, similar results were obtained (cases >20: HR = 0.39, p = 0.049; cases ≤20: HR = 0.95, p = 0.88).

Discussion

In this study, we found that patients with HCC who underwent LDLT had a significantly higher HCC recurrence rate than their DDLT counterparts. The reasons for this difference are not completely explained by the data available for this analysis. The organ allocation system in the United States (both pre- and post-MELD) assigned higher priority to patients with stage T2 (and previously T1) HCC. Patients with HCC that exceeded these criteria were not eligible for high priority for transplantation and were less likely to be offered a liver from a deceased donor. For most HCC patients meeting the criteria after the implementation of MELD, expeditious access (within 30–90 days of listing) to

Table 4: Cox regression model predicting HCC recurrence or death from time of transplant (n = 58 LDLT, n = 34 DDLT)

Variable	p-Value	Hazard ratio	95% confidence limits	
LDLT vs. DDLT	0.62	0.82	0.38	1.79
Transplant year 2001–2003 vs. 1998–2000	0.0006	0.21	0.09	0.52
Log AFP at transplant	<0.0001	1.57	1.28	1.92
Recipient age at transplant	0.0571	1.53 (per 10 years)	0.99	2.38
A2ALL transplant centers*	0.0205	Range (0.34, 4.13)		

*Hazard ratios compare each center with the A2ALL overall center average.

a deceased donor transplant rivaled access to LDLT (14). This may have resulted in patients within criteria receiving DDLT while patients outside of criteria received LDLT. A DDLT offer would not be passed up if it occurred prior to the LDLT, even if a potential live donor had already been evaluated and accepted. Since the study spanned the pre-MELD and post-MELD periods, this factor may have contributed to LDLT recipients having more advanced tumors than DDLT recipients. Although the percentage of patients with tumors outside Milan criteria receiving LDLT in the pre- and post-MELD eras were similar (25/42 vs. 10/15, respectively), a much higher proportion of LDLT recipients had tumors that were outside of the UCSF criteria (50% vs. 29%). However, the higher rate of HCC recurrence in the LDLT group cannot be attributed solely to more advanced disease, given the absence of recurrence in those with advanced HCC in the DDLT group as well as the presence of unexpectedly high recurrence rates in patients with earlier stage HCC who underwent LDLT. In this study, there was no evidence of recurrence amongst the 14 DDLT patients with T3 or T4 stage HCC on explant after a median follow-up of 3.6 years. This remarkable lack of recurrence in these patients who exceeded Milan and UCSF tumor stage criteria is not in line with those groups' published findings (1,3). While it is possible that some DDLT patients may develop HCC recurrence after a longer duration of follow-up, most studies have shown that over 90% of patients with recurrent HCC are diagnosed within the first two post-transplant years (2,5,19,20). In our study, the majority of recurrences in the LDLT group occurred within the first year (median time to recurrence of 10 months). Of concern was the 26% recurrence rate among LDLT patients with stage T1 or T2 HCC disease. These study findings suggest DDLT as a superior 'cancer curative' procedure, and warrants further prospective study.

Table 5: Numbers of patients and posttransplant HCC recurrence by transplant type, milan criterion, and MELD era

Tumor status at explant	Pre-MELD (n = 54)	Post-MELD (n = 36)
DDLT*		
Within Milan	7 (13%)	13 (36%)
Outside Milan	6 (11%)	8 (22%)
LDLT**		
Within Milan	16 (30%)	5 (14%)
No. of recurrences	5	0
Outside Milan	25 (46%)	10 (28%)
No. of recurrences	7	5

*There were no recurrences among DDLT recipients.
**Two LDLT recipients were missing explant tumor status and had no recurrence.

A higher rate of HCC recurrence among patients who underwent LDLT was previously reported by one of the A2ALL centers (11). It was hypothesized that putting patients with HCC on a fast track to transplant may not provide adequate time to assess the tumor's biological behavior. Inclusion of patients with more aggressive tumors in the LDLT group may account for the higher recurrence rate compared to DDLT recipients who had a significantly longer waiting time (median 95 vs. 373 days from listing to transplant). The significantly higher AFP levels at enrollment ($p = 0.023$) and at transplant ($p = 0.019$) among the patients who underwent LDLT are evidence of more aggressive tumor biology in the LDLT group overall and may have contributed to the significantly higher ($p = 0.002$) HCC recurrence rate.

Other groups have examined the outcome of LDLT in the setting of HCC. Some have utilized LDLT for HCC only after exhausting alternative therapies (resection, trans-arterial chemo-embolization or radiofrequency ablation) or in patients whose synthetic dysfunction is the major indication for transplant (21). A recent publication on LDLT recipients with HCC divided the patients into three groups based on pretransplant therapy: patients without any therapy (higher MELD scores with less advanced tumors), patients with one or two sessions of ablative treatment, and patients with three or more sessions of treatment, reflecting differences in the median time elapsed from the diagnosis of HCC to LDLT (22). The patients who received one or two sessions of ablative therapy had the best 4-year survival and the lowest recurrence rate. The importance of at least two ablative sessions for the most effective tumor 'kill', within a short time interval pending transplant intervention, was associated with the best HCC-free post-transplant patient survival and has been highlighted in two other prospective reports (4,5). In one small study, LDLT provided timely transplantation with much shorter waiting times (24 days) than DDLT (344 days). However, as in the current study, HCC recurrence was observed following LDLT (2/20) but not DDLT (0/6) (7).

Another possible explanation for the higher HCC recurrence rate after LDLT relates to the technique of living

donor transplant. There is typically a more meticulous dissection of the recipient liver prior to transplant, with preservation of the native vena cava, as well as more hepatic artery and bile duct length. It is possible that LDLT is therefore a less optimal cancer operation, leaving residual tumor or violating tumor capsule. Greater manipulation of the native liver may also lead to tumor embolization through the hepatic veins. These technical requirements of the procedure of LDLT may influence the recurrence of tumor to a greater degree than that attributed to shorter waiting time and it is hoped that the prospective study in progress will clarify this point. However, this does not explain the higher recurrence rate in patients with small tumors.

Despite a higher recurrence rate, the overall mortality and 3-year recurrence-free survival rates in the LDLT group were similar to those of the DDLT group. The role of LDLT in HCC is reinforced by our finding of a lower relative mortality risk compared to those who did not undergo LDLT, when the time of potential live donor evaluation was used as the starting time for survival analysis. However, the early survival advantage of LDLT for HCC recipients may not result in an advantage in long term survival due to the alarming rate of HCC recurrence observed in our study. In order to answer the question: 'what is the best cancer treatment for a patient with a small HCC and a potential living donor?', further prospective study, in progress, is required. In the future, application of histological and molecular tools such as proteomics or genomics may help to select patients with less aggressive tumor biology who have a low risk of recurrence and may derive benefit from LDLT without the need for a prolonged observation period with its attendant risks.

There are several limitations to our study. The two groups were not randomized. The comparisons in our paper between those patients who received LDLT and those who did not receive LDLT may not necessarily be applicable to HCC patients who do not have a potential LDLT donor. Our finding of an increase in recurrence after LDLT may be offset by mortality on the waiting list for DDLT. Multivariable analysis to test whether LDLT was associated with HCC recurrence independent of other predictive factors was not possible due to the absence of recurrence in the DDLT recipients. Our study included early as well as later center experiences with LDLT, which may have introduced unmeasured confounding variables resulting from changes in clinical practice over the study period (10). The reasons why the LDLT rate for HCC recipients was not 100% once a living donor came forward have been detailed in another report (23).

Finally, the lack of recurrence of HCC in the DDLT patients was an unexpected finding. The literature would suggest that there should have been a substantial rate of recurrence, particularly in those patients who exceeded T2 criteria.

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