

Liver transplantation for hepatocellular carcinoma from living-donor vs. deceased donor

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Abstract: With the increasing prevalence of living-donor liver transplantation (LDLT), the possible increased recurrence rate of hepatocellular carcinoma (HCC) in LDLT recipients in comparison with deceased-donor liver transplantation (DDLT) recipients has become a matter of debate. The aim of this review is to encompass current opinions and clinical reports regarding differences in the outcome, especially the recurrence of HCC, between LDLT and DDLT. In reviewing literatures, some studies reported increased recurrence rates among LDLT recipients, a majority of authors, including large database studies, reported comparable recurrence-free survival and recurrence rates between LDLT and DDLT. The postulated reasons for the increased recurrence in LDLT were the effect of graft regeneration on tumor progression, fast-tracking of patients into liver transplantation, and the more aggressive tumor characteristics in LDLT, however, many Asian LDLT centers have reported the comparable outcomes with those of DDLT in Western countries, even with the expanded criteria for HCC. In the absence of a prospective study regarding the use of LDLT versus DDLT for HCC patients, there is no evidence to support the higher HCC recurrence after LDLT than DDLT, and LDLT remains a reasonable treatment option for HCC patients with cirrhosis, especially in Asian countries where the number of deceased donor is scarce.

Keywords: Liver transplantation; deceased donor; living donor; hepatocellular carcinoma (HCC); recurrence; deceased donor liver transplantation (DDLT); living-donor liver transplantation (LDLT)

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Introduction

Since the landmark report of the Milan criteria by Mazzaferro *et al.* (1), which demonstrated comparable outcomes of patients with hepatocellular carcinoma (HCC) having a single tumor smaller than 5 cm in diameter or up to three tumors smaller than 3 cm in diameter with no vascular invasion or extra-hepatic disease determined by preoperative imaging studies, deceased-donor liver transplantation (DDLT) has become an established treatment for cirrhotic patients with HCC. In Asian countries, where the number of deceased donor is extremely

small, living-donor liver transplantation (LDLT) has been developed as an alternative treatment for end-stage liver diseases, and has become an established treatment for those with HCC (2).

With the accumulation of LDLT cases for patients with HCC, the impact of LDLT (the procedure and the partial graft) on the recurrence of HCC after liver transplantation has become an important topic of debate in comparison with DDLT (3,4). The aim of this review was to encompass the current opinions and clinical reports regarding the differences in outcome, especially the recurrence of HCC, between LDLT and DDLT.

The differences between LDLT and DDLT in terms of tumor recurrence

There are definite differences other than the graft type between LDLT and DDLT, such as a shorter waiting time, good quality graft with normal liver function and shorter ischemic time, and pretransplant treatment optimization for HCC, which might potentially contribute to improve survival in LDLT recipients. While these characteristics seem advantageous for the better control of HCC recurrence, some of these characteristics, on the other hand, may lead to a favorable milieu for tumor progression and recurrence (4).

The hypothesized mechanism in experimental studies for the faster tumor progression and the higher recurrence rates in LDLT is that growth factors and cytokines released during rapid regeneration of the partial grafts from the partial graft might contribute to tumor progression and recurrence (5-8). An ischemic-reperfusion injury facilitated by a small-for-size graft and the rapidly regenerating liver parenchyma in LDLT setting may increase vascular endothelial growth factor expression and angiogenesis, which might accelerate the tumor progression and recurrence.

One of the probable explanations for the higher recurrence rates in LDLT is “fast-tracking” patients into liver transplantation (4,9). In the DDLT setting, patients with biologically aggressive HCC might drop off the waiting list due to tumor progression beyond the criteria during the wait-time, however, owing to the shortened wait time in LDLT program, such patients might not be recognized during such a short wait-time, resulting in a possible higher frequency of HCC recurrence in LDLT. This scenario might account for the higher HCC recurrence in the LDLT setting. Bhangui *et al.* (10) performed a prospective intention-to-treat study demonstrating that shorter waiting time in LDLT prevented the dropouts but worsened the outcomes of LDLT in patients with advanced HCC when compared with DDLT patients with comparable MELD scores. In contrast, Chao *et al.* (11) failed to show an association between waitlist time and outcome after DDLT or LDLT for HCC.

Since the grafts from living donors are not limited by restrictions imposed by the organ allocation system, and the indication for LDLT in patients with HCC often depends on institutional or case-by-case considerations, balancing the burden on the donor, the operative risk, and the overall survival benefit for the recipient, the expansion of criteria

can be easily done without impairing equitability (2). Thus, many LDLT centers adopt the expansion criteria for LDLT recipients, and the advanced tumor characteristics of LDLT recipients can reasonably explain the higher recurrence rate in the LDLT setting (9). Actually, the majority of Asian transplant centers have established and adopted own extended criteria beyond those of Milan or the University of California, San Francisco (UCSF) (2). According to some early studies, differences in patient tumor characteristics between LDLT and DDLT remain a main reason for the higher recurrence rate in LDLT. Additionally, in the majority of studies comparing LDLT and DDLT for HCC patients, tumor burdens such as the size, number, vascular invasion, and poor differentiation have proved to be independent risk factors for HCC recurrence after liver transplantation, all of which may lead to a rational explanation for the impaired recurrence-free survival of LDLT compared to DDLT (12).

Finally, some authors argue that the technique of LDLT per se goes against the principles of oncologic surgery (13,14). During LDLT, the meticulous dissection and mobilization of the liver might increase the possibility of tumor capsule violation or tumor dissemination through the hepatic veins, thus promoting tumor dissemination. Meticulous preservation of the native vena cava and the bile duct/hepatic artery/portal vein in the hepatic hilum might also increase the risk of leaving the residual tumors.

Studies comparing LDLT and DDLT for HCC patients

Studies comparing the recurrence-free survival after LDLT and DDLT for HCC patients are summarized in *Table 1*. There were ten single-institutional reports (3,10,13-15, 17-19,21,22) and three multi-center reports (16,20,23).

Park and colleagues (18) from Korea recently reported poorer recurrence-free survival among 166 LDLT recipients (81% at 5 years) compared to 50 DDLT recipients (94% at 5 years; $P=0.045$). The study was notable in that the smaller the LDLT graft was, the poorer the recurrence-free survival was. They suggested that the physiology of the small graft may stimulate tumor recurrence. The results of the A2ALL cohort in USA (20) demonstrated an impaired outcome in LDLT recipients, in which HCC recurrence remained significantly different between LDLT and DDLT after adjustment for tumor characteristics. They concluded that the higher recurrence observed after LDLT

Table 1 Studies comparing living donor liver transplantation (LDLT) and deceased donor liver transplantation (DDLT) for hepatocellular carcinoma (HCC)

Author	LDLT vs. DDLT	Country	Year	Study period	Type of LT	Case number	Recurrence free survival			P	Criteria used	Outside Milan (%)	Difference in tumor characteristics	Median follow-up period (months)
							1-year	3-year	5-year					
Hu <i>et al.</i> (15)	LDLT > DDLT	China	2015	1999–2009	LDLT	389	78	64	62	<0.001	Hangzhou criteria	6	More aggressive in DDLT	16
Ninomiya <i>et al.</i> (16)	LDLT = DDLT	Japan (LDLT); USA (DDLT)	2015	2002–2010	DDLT	6,471	66	49	42	NS	Kyushu criteria	4	More aggressive in LDLT	15
Xiao <i>et al.</i> (17)	LDLT = DDLT	China	2014	1999–2012	LDLT	84	85	56	53	NS	Hangzhou criteria	69	None	27
Park <i>et al.</i> (18)	LDLT < DDLT	Korea	2014	1999–2010	DDLT	276	73	49	45	0.045	UCSF	72	None	35
Sandhu <i>et al.</i> (19)	LDLT = DDLT	Canada	2013	1996–2009	LDLT	58	88	75	70	NS	Toronto criteria	28	None	38
Kuilik <i>et al.</i> (20)	LDLT < DDLT	USA	2012	1998–2010	DDLT	287	86	75	70	0.05	UNOS	32	More aggressive in LDLT	31
Bhangui <i>et al.</i> (10)	LDLT = DDLT	France	2011	2000–2009	LDLT	97	90	81	73	NS	UCSF	59	None	60
Li <i>et al.</i> (14)	LDLT = DDLT	China	2010	2005–2009	DDLT	100	80	66	56	NS	UCSF	30	None	58
Di Sandro <i>et al.</i> (13)	LDLT = DDLT	Italy	2009	2000–2007	LDLT	36	100	89	88	NS	Milan	27	None	50
Sotiropoulos <i>et al.</i> (21)	LDLT = DDLT	Germany	2007	1998–2006	DDLT	120	93	89	86	NS	UCSF	21	None	25
Lo <i>et al.</i> (22)	LDLT < DDLT	Hong Kong	2007	1995–2004	LDLT	38	71	42	–	NS	UCSF	79	None	–
Hwang <i>et al.</i> (23)	LDLT = DDLT	Korea	2005	1992–2002	DDLT	101	76	41	–	NS	Milan	68	None	–
Gondolesi <i>et al.</i> (3)	LDLT = DDLT	USA	2004	1988–2002	LDLT	25	–	96	96	NS	UNOS	20	None	–
					DDLT	154	–	91	89	NS	UCSF	31	None	–
					DDLT	45	88	75	–	NS	UCSF	44	None	–
					DDLT	55	–	81	–	NS	UCSF	–	More aggressive in LDLT	33
					DDLT	43	93	71	71	0.029	UCSF	26	None	26
					DDLT	17	100	100	100	NS	–	29	None	45
					DDLT	237	83	80	–	NS	–	27	None	15
					DDLT	75	88	82	–	NS	–	29	None	–
					DDLT	36	82	74	–	NS	UNOS	53	None	–
					DDLT	165	90	83	–	NS	–	–	None	–

DDLT, deceased donor liver transplantation; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; LT, liver transplantation; UCSF, the University of California, San Francisco; UNOS, United Network for Organ Sharing

was likely due to differences in the tumor characteristics, pretransplant HCC management, and waiting time between the programs. Lo *et al.* (22) from Hong Kong also reported a significantly higher incidence of HCC recurrence in LDLT (29%) than in DDLT (0%) ($P=0.029$). While the tumor characteristics were comparable between the groups, the authors speculated that LDLT in a salvage fashion, higher incidence of microscopic vascular invasion in LDLT, and liver regeneration led to the higher recurrence rate in LDLT.

In contrast, majority of reports have demonstrated the comparable outcomes. Sandhu and colleagues (19) of the Toronto group compared the results of 58 LDLT cases with those of 287 DDLT cases having comparable tumor characteristics, in which the 1-, 3-, and 5-year recurrence-free survival rates were 88%, 75%, and 70%, and 86%, 75%, and 70%, respectively. Bhangu *et al.* (10) conducted a well-designed intention-to-treat analysis with recurrence rate representing the primary endpoint, comparing 36 LDLT cases and 147 DDLT cases, in which both LDLT and DDLT provided similar recurrence-free survival rates (88% *vs.* 86% at 5 years). The dropout rate and waiting time were significantly lower in the LDLT group than in the DDLT group, and the time to recurrence in LDLT tended to be longer than in DDLT, which may guarantee additional advantages with LDLT. Similar results were reported by other authors as listed in *Table 1*.

Systematic review and meta-analysis

A randomized clinical study would be best to settle the controversy regarding the differences in outcomes among LDLT versus DDLT for HCC patients, but this is indeed difficult, given the complicated decision-making process and multidisciplinary approach involved in liver transplantation for HCC patients. No prospective study has ever challenged the matter, however, there were two systematic reviews with meta-analyses so far. Grant *et al.* (24) performed a meta-analysis on 12 retrospective studies comparing the recurrence rates and recurrence-free survival between LDLT and DDLT recipients. A total of 633 LDLTs and 1,232 DDLTs were enrolled, and the study provided evidence of lower disease-free survival after LDLT compared with DDLT for HCC [hazard ratio =1.59; confidence interval (CI): 1.02–2.49; $P=0.041$]. In contrast, there was no difference in overall survival between LDLT and DDLT (hazard ratio =0.97; CI: 0.73–1.27; $P=0.808$).

Liang *et al.* (25) also performed similar meta-analysis based on 7 retrospective studies with a total of 1,310 participants. They found comparable patient survival rates [1 year: odds ratio (OR) =1.03, 95% CI: 0.62–1.73; 3 years: OR =1.07, 95% CI: 0.77–1.48; and 5 years: OR =0.64, 95% CI: 0.33–1.24] and disease-free survival rates (1 year: OR =0.86, 95% CI: 0.54–1.38; 3 years: OR =1.04, 95% CI: 0.69–1.58; and 5 years: OR =1.11, 95% CI: 0.70–1.77). As discussed by both authors of the papers, however, all involved studies were retrospective, had a low data quality score with poor reporting of baseline patient characteristics, and were heterogeneous in critical aspects such as indication criteria and basal tumor characteristics, all which do not give a strong evidence to the results of meta-analyses. In addition, recent US registry study found no significant difference in outcomes between whole and partial grafts among HCC patients (26).

A review article by experts (27) concluded as follows: although there is no strong evidence to support the higher HCC recurrence rates in LDLT than DDLT, the reported higher recurrence rates in LDLT recipients cannot be ignored. In addition to taking into account the differences in organ allocation, graft availability, and organ transplant law and allocation system, liver transplant candidates with HCC and their potential live donors should be informed following risks and benefits; the waiting time for DDLT may lead to the dropout due to HCC progression which could be avoided by the prompt LDLT, however, the prompt LDLT may mask the aggressive tumor characteristics which may lead to a higher HCC recurrence rates. Nevertheless, the tumor characteristics and biology seem to have significant impact on the recurrence, while the graft type and waiting time are less important as a possible risk factor.

Asian perspective regarding liver transplantation for HCC

Milan criteria are also standard indication criteria for liver transplantation for HCC patients in Asian countries. However, in Asia where LDLT is mainstay for liver transplantation, situations are somewhat different from region to region. Unlike DDLT, LDLT is not limited by the restrictions imposed by the nationwide allocation system, and the indication for LDLT in patients with HCC often depends on institutional or case-by-case considerations, balancing the burden on the donor, the operative risk, and the overall survival benefit for the recipient. In Japan, each

center developed institutional expansion criteria, while National Insurance covers only those within the Milan criteria (28,29). In Taiwan (30) and Hong Kong (31), UCSF criteria is adopted. In mainland China, Hangzhou or Chengdu criteria is used with a satisfactory outcome (32). In Korea, UCSF or Milan is basically used, but LDLT can be offered for any HCC without distant metastasis under National Insurance coverage (33). In conclusion, Milan criteria are still the gold standard criteria of liver transplantation for HCC patients worldwide, and seem best to be included in the treatment algorithm for HCC to set the tumor burden limitation. Nevertheless, it is widely accepted that the Milan criteria is too strict in terms of post-transplant recurrence rate (34) and that it is currently expanded to some extent without impairing patient outcome in Asian countries (2), however, we have to always be aware of that any kind of expansion in size or number of the tumor includes the potential to worsen the post-transplant survival in patients with HCC.

The indication of liver transplantation for HCC in terms liver functional reserve is based on the model for end-stage liver disease (MELD) score with additional points in Western countries (35). Consequently, liver transplantation can be offered for those with Child class A as shown in guidelines, if they satisfy Milan criteria (36,37). In contrast, in Asian countries, where liver grafts are extremely scarce, liver transplantation is recommended for those with decompensated liver cirrhosis (Child class B and C) in patients with HCC as well as those with other decompensated liver diseases (38).

Conclusions

In conclusion, there is no evidence to support higher HCC recurrence after LDLT than DDLT. LDLT should always be considered as a treatment option for HCC patients with advanced cirrhosis in areas where deceased donors are scarce or for patients whose tumor status interrupts access to grafts from deceased donor.

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Footnote

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