Title: Living - donor versus deceased - donor liver transplantation for patients with hepatocellular carcinoma

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Key words: Liver transplantation, living donor, hepatocellular carcinoma

Abbreviations: 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.

**Disclosure statement**

All authors declared no conflict of interest.

**Abstract**

With the increasing prevalence of living - donor liver transplantation (LDLT) for patients with hepatocellular carcinoma (HCC), some authors have reported a potential increase in the HCC recurrence rates among LDLT recipients compared to deceased-donor liver transplantation (DDLT) recipients. 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.

While some studies report impaired recurrence - free survival and increased recurrence rates among LDLT recipients, others, including large database studies, report comparable recurrence - free survival and recurrence rates between LDLT and DDLT. Studies supporting the increased recurrence in LDLT have linked graft regeneration to tumor progression, but we found no association between graft regeneration/ initial graft volume and tumor recurrence among our 125 consecutive LDLTs for HCC cases.

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.

**Key words**: deceased donor liver transplantation, hepatocellular carcinoma, living donors, living - donor liver transplantation, recurrence

**Introduction**

Hepatocellular carcinoma (HCC) is the 7th most common cancer overall and the 3rd most common cause of cancer-related death worldwide[1](#_ENREF_1),[2](#_ENREF_2). Since the landmark report of the Milan criteria by Mazzaferro et al.[3](#_ENREF_3), which demonstrated comparable outcomes of patients with HCC having a single tumor smaller than 5 cm in diameter or up to 3 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[4](#_ENREF_4),[5](#_ENREF_5). Similarly, in Asian countries where living - donor liver transplantation (LDLT) comprises the majority of liver transplantation procedures, LDLT has become an established treatment for HCC patients with end-stage liver disease[6](#_ENREF_6),[7](#_ENREF_7). LDLT is now considered a promising treatment for HCC patients in Western countries, not only to compensate for the shortage of donor organs but also to reduce the dropout rate on the waiting list[8](#_ENREF_8).

 With the accumulation of LDLTs for HCC patients, the impact of LDLT on recipient outcome compared with DDLT, especially the recurrence of HCC after liver transplantation, has become an important topic of debate[9](#_ENREF_9). 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.

**Studies comparing LDLT and DDLT for HCC patients**

Studies comparing LDLT and DDLT for HCC patients are summarized in Table 1.

*Studies reporting a poorer outcome in the LDLT setting*

Park and colleagues[10](#_ENREF_10) 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 noteworthy finding of this study was that the smaller the LDLT graft, the poorer the recurrence - free survival. Based on this finding, Park et al.10 suggested that the physiology of the small graft may stimulate tumor recurrence.

The results of the A2ALL cohort in USA also demonstrated an impaired outcome in LDLT recipients. In their initial report[11](#_ENREF_11), they found a higher rate of recurrence within 3 years in LDLT than in DDLT (29% versus 0%, p=0.002), but there was a clear tendency toward more aggressive tumor characteristics in the LDLT group. The same group recently published an updated report[12](#_ENREF_12), 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 was likely due to differences in the tumor characteristics, pretransplant HCC management, and waiting time.

Vakili and colleagues, reporting the Lahey Clinic experience[13](#_ENREF_13), found a significant difference in the HCC recurrence rates (29% for LDLT and 12% for DDLT, p<0.05), but survival after LDLT was significantly better than that following DDLT for HCC during the same period (p=0.02).

Lo et al. from Hong Kong[14](#_ENREF_14) also reported a significantly higher incidence of HCC recurrence, 29% in LDLT and 0% in DDLT (p=0.029). While the tumor characteristics were comparable between groups, the authors speculated that LDLT as a salvage transplantation, microscopic vascular invasion, and liver regeneration led to the difference in the recurrence rate.

*Studies reporting a comparable outcome*

Sandhu and colleagues of the Toronto group[15](#_ENREF_15) reported that LDLT and DDLT both provide similarly low recurrence rates and high survival rates. They 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.

In a well-designed study by Bhangui et al.[16](#_ENREF_16), an intention-to-treat analysis was conducted with recurrence rate representing the primary endpoint, comparing 36 LDLT cases and 147 DDLT cases. The authors demonstrated that both LDLT and DDLT provided similar recurrence - free survival rates (88% versus 86% at 5 years) for patients with HCC. The dropout rate and waiting time were significantly lower in the LDLT group than in the DDLT group, and there was also a trend toward a longer time to recurrence in the LDLT group, which may guarantee additional advantages with LDLT.

The Mount Sinai group[17](#_ENREF_17),[18](#_ENREF_18) reported comparable recurrence - free survival between LDLT (n=36) and DDLT (n=165 ; 74% versus 83% at 2 years, p=0.3). When stratified by tumor size (5 cm diameter) and the existence of microvascular invasion, there was still no difference between groups.

Sotiropoulos and colleagues of Essen, Germany[19](#_ENREF_19),[20](#_ENREF_20), also supported the comparable recurrence - free survival rates between LDLT and DDLT for HCC (75% versus 81% at 3 years).

Hwang et al. of Korea[21](#_ENREF_21) performed a nationwide survey regarding this issue. Among 237 LDLTs and 75 DDLTs for HCC, the 1 - and 3 - year recurrence - free survival rates were 83% and 80%, and 88% and 82%, respectively, with no significant difference between them.

A comparison of outcomes after liver transplantation obtained from database studies revealed comparable patient survival rates between LDLT and DDLT. According to a report from the Japanese Liver Transplantation Society Registry[22](#_ENREF_22), a total of 6097 LDLTs were performed in Japan by the end of 2010, and 1225 (32%) were indicated for HCC, which was the most common indication in adult patients. The 1-, 3-, 5-, and 10-year cumulative survival rates of LDLT for HCC were 85%, 74%, 69%, and 60%, respectively. Todo and colleagues[23](#_ENREF_23) performed a detailed survey using the same database (up to the end of 2005), comprising 653 patients who had undergone LDLT for HCC in Japan. At 1, 3, and 5 years, overall patient survival was 83%, 73%, and 69%, and disease-free survival was 77%, 65%, and 61%, respectively. Based on preoperative imaging studies, 62% were within the Milan criteria and 38% were beyond the Milan criteria, with 5-year recurrence - free survival rates of 90% and 61%, respectively (p<0.001). These findings do not differ much from those obtained in the DDLT database of the United States and Europe[24-27](#_ENREF_24), and may validate the use of LDLT for HCC patients.

**Current opinions regarding the difference between LDLT and DDLT**

A randomized clinical study would be best to resolve the debate regarding the use of LDLT versus DDLT for HCC patients, but this is indeed difficult, if not impossible, to realize given the complicated decision-making process involved in LDLT. No prospective study has been conducted to date.

The Toronto group[28](#_ENREF_28) recently 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 1232 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: 1.02-2.49; p=0.041). In contrast, there was no difference in overall survival between LDLT and DDLT (hazard ratio 0.97, confidence interval: 0.73-1.27; p=0.808). As mentioned by the authors of the paper, however, all involved studies were retrospective, had a low data quality score with poor reporting of baseline patient characteristics and an inadequate statistical approach, and were heterogeneous in critical aspects such as indication criteria and basal tumor characteristics, which warrant further well-designed studies to determine whether differences in HCC recurrence are due to study biases or biologic differences.

A recent review article by experts[29](#_ENREF_29) concluded the following: Although there is no evidence for recurrence rates to guide the choice between DDLT and LDLT for HCC, the higher recurrence rates reported by several authors cannot be ignored. Because of 1) differences in the allocation policies for deceased - donor livers and in the availability of deceased - donor livers, 2) local, regional, and national differences in the potential waiting times for DDLT, and 3) national legal requirements, patients with HCC and their donors should be offered LDLT with the understanding that estimates of the waiting time for DDLT and the potential for dropout due to HCC progression need to be weighed against the potential for a lower dropout rate and a higher recurrence rate after LDLT. Because the existing literature is far from definitive and the outcomes are far from uniform, however, patients should be informed that a true risk-versus-benefit balance for DDLT and LDLT for HCC cannot be fully and accurately assessed at this time. Nonetheless, the weight of the evolving evidence suggests that tumor biology is likely the key factor driving HCC recurrence after DDLT or LDLT; the graft type and waiting time are less likely to be important independent risk factors.

**Postulated theories for differences between LDLT and DDLT**

LDLT provides several advantages compared with DDLT, such as a shorter waiting time, good quality graft with normal liver function and shorter ischemic time, and pretransplant treatment optimization, which might contribute to improved survival in LDLT recipients. Some of these characteristics, on the other hand, may lead to a favorable milieu for tumor progression[9](#_ENREF_9).

There are several hypotheses other than tumor characteristics to explain the inferior outcome of LDLT. One explanation for the higher recurrence rates in LDLT is fast-tracking patients into liver transplantation, the so - called fast-track effect[11](#_ENREF_11),[30](#_ENREF_30). Some patients with more biologically aggressive HCC might drop off the waiting list due to tumor progression beyond the criteria during the wait-time in the DDLT setting. In contrast, due to the shortened wait time for LDLT candidates, progression of HCC with an aggressive tumor biology might not be recognized during such a short wait-time. This scenario might account for the higher HCC recurrence in the LDLT setting.

Another hypothesized mechanism for the higher recurrence rates in LDLT is that growth factors and cytokines released during rapid regeneration of the partial grafts from living donors might contribute to tumor progression and recurrence[31-34](#_ENREF_31). A rapidly regenerating liver parenchyma and ischemic-reperfusion injury facilitated by a small-for-size graft in LDLT setting might be a more favorable environment for tumor progression and HCC recurrence.

Additionally, some authors[11](#_ENREF_11),[35](#_ENREF_35),[36](#_ENREF_36) insist that the technique of LDLT per se foregoes the principles of oncologic surgery. During LDLT, the meticulous dissection and mobilization of the liver might increase the possibility of tumor capsule violation or tumor embolization through the hepatic veins, thus promoting tumor dissemination. Preservation of the native vena cava and the long native vessel lengths in the hepatic hilum might increase the risk of not removing the foci of residual tumors.

As opposed with the above - mentioned anecdotal explanations, the advanced tumor characteristics of LDLT recipients can reasonably explain the higher recurrence rate in the LDLT setting. Grafts from living donors are not limited by restrictions imposed by the organ allocation system, meaning that the relation of the graft and recipient is usually one-on-one. Consequently, selection criteria based on the tumor burden, such as the tumor size and number, can be considered relative on a case-by-case basis, taking into account the presence of risk factors for recurrence and the chance of survival, as well as the wishes of the donor[37](#_ENREF_37). Consequently, the majority of Asian transplant centers have adopted extended criteria beyond those of Milan or the University of California, San Francisco (UCSF)[38](#_ENREF_38). Based on some 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 the aforementioned 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.

**Our experience**

At our institution, the University of Tokyo Hospital, a total of 423 adult recipients underwent LDLT by the end of 2012. Among them, 125 (30%) patients had HCC. The principle criterion for LDLT for HCC at our center is “up to 5 nodules with a maximum tumor diameter within 5 cm”, which we call the ‘5-5 rule’[39](#_ENREF_39). Of the 125 patients, 118 (94%) were within the 5-5 rule criteria and 109 (87%) were within the Milan criteria. Overall survival of the 125 recipients at 1, 3, and 5 years was 88%, 82%, and 76%, respectively, with a median follow-up period of 8 years. A total of 11 (9%) patients developed HCC recurrence with a cumulative recurrence rate at 1, 3, and 5 years of 6%, 9%, and 11%, respectively.

We compared the graft regeneration rate between patients with HCC recurrence (n=11) and those without recurrence (n=114) to confirm the association of liver regeneration with HCC recurrence. The regeneration rate was calculated as follows : ( graft volume at 3 months after LDLT- initial graft volume)/ initial graft volume x100 (%). As shown in Table 2, there was no difference in the regeneration rate between those with HCC recurrence and those without recurrence. At the same time, the graft type (right versus left) and the initial graft volume ratio to the recipient’s standard liver volume were also compared between groups, revealing no difference. A similar result was reported by the Asan group of Korea[40](#_ENREF_40), in which the graft-recipient weight ratio had no impact on HCC recurrence after LDLT among 181 LDLT recipients with HCC. Our result as well as the report of the Asan group clearly demonstrated that graft regeneration of the partial liver graft has no impact on HCC recurrence, at least in a clinical setting. The independent predictors for HCC recurrence in our series were tumors not within the 5-5 rule (Tokyo criteria), AFP level over 400 ng/ml, and des-gamma-carboxy prothrombin levels over 200 mAU/ml.

**Conclusion**

In conclusion, there is no strong evidence to support higher HCC recurrence after LDLT than DDLT. Additionally, it may be reasonable to use different indication criteria for LDLT and 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 DDLT in the context of paternalism and respect for autonomy of the living donor.

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| Table 1. Studies comparing LDLT and DDLT for HCC |
| Author | Country | Year | Study period | Type of LT | Case number | Recurrence - free survival | 　 | % Recurrence rate | 　 | Criteria used | % Outside Milan |  Difference in tumor characteristics | Median follow-up period (months) |
| Impaired results in LDLT | 　 | 　 | 1-year | 3-year | 5-year | 　 | 　 | 　 | 　 | 　 | 　 | 　 |
| Park et al.[10](#_ENREF_10) | Korea | 2014 | 1999-2010 | LDLT | 166 | 89 |  | 81 | p=0.045 | 19% | p=0.045 | UCSF | na | none | 35 |
| DDLT | 50 | 96 |  | 94 | 6% |
| Vakili et al[13](#_ENREF_13) | USA | 2009 | 1999-2007 | LDLT | 28 |  |  |  |  | 29 | p<0.05 | UNOS | 25 | none | 41 |
| DDLT | 65 |  |  |  |  | 12 |  |
| Kulik et al.[12](#_ENREF_12) | USA | 2012 | 1998-2010 | LDLT | 100 | 80 | 66 | 56 | 0.05 | 38 | 0.0004 | UNOS | 59 | More aggressive in LDLT | 60 |
| Multi-center | DDLT | 97 | 90 | 81 | 73 | 11 | 30 |
| Lo et al.[14](#_ENREF_14) | Hong Kong | 2007 | 1995-2004 | LDLT | 43 | 93 | 71 | 71 | 0.029 | 29 | 0.029 | UCSF | 26 | More aggressive in LDLT | 33 |
| DDLT | 17 | 100 | 100 | 100 | 0 | 29 |
| Comparable results |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Sandhu et al.[15](#_ENREF_15) | Canada | 2013 | 1996-2009 | LDLT | 58 | 88 | 75 | 70 | ns | 17 | ns | Toronto criteria | 28 | none | 38 |
| DDLT | 287 | 86 | 75 | 70 | 15 | 32 | 31 |
| Bhangui et al.[16](#_ENREF_16) | France | 2011 | 2000-2009 | LDLT | 36 | 100 | 89 | 88 | ns | 13 | ns | UCSF | 27 | none | 58 |
| DDLT | 120 | 93 | 89 | 86 | 13 | 21 | 50 |
| Li et al.[36](#_ENREF_36) | China | 2010 | 2005-2009 | LDLT | 38 | 71 | 42 |  | ns | 50 | ns | UCSF | 79 | none | 25 |
| DDLT | 101 | 76 | 41 |  | 55 | 68 |
| Sandro et al.[35](#_ENREF_35) | Italy | 2009 | 2000-2007 | LDLT | 25 |  | 96 | 96 | ns | 4 | ns | Milan | 20 | none | NA |
| DDLT | 154 |  | 91 | 89 | 11 | 31 |
| Sotiropoulos et al.[20](#_ENREF_20) | Germany | 2007 | 1998-2006 | LDLT | 45 | 88 | 75 |  | ns | 12 | ns | UCSF | 44 | none | NA |
| DDLT | 55 |  | 81 |  | 14 |  |
| Hwang et al.[8](#_ENREF_8) | Korea | 2005 | 1992-2002 | LDLT | 237 | 83 | 80 |  | ns | 18 | ns |  | 27 | none | 26 |
| Multi-center | DDLT | 75 | 88 | 82 |  | 16 | 29 | 45 |
| Gondolesi et al.[17](#_ENREF_17) | USA | 2004 | 1988-2002 | LDLT | 36 | 82 | 74 |  | ns | 19 | ns | UNOS | 53% | none | 15 |
| DDLT | 165 | 90 | 83 | 　 | 19 | 　 |

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

Table 2. Graft characteristics and HCC recurrence

|  |  |  |  |
| --- | --- | --- | --- |
| 　 | Patients with recurrence (n=11) | Patients without recurrence (n=114) | p |
| Regeneration rate at 3 months (%) | 90 ±24 | 93 ±34 | 0.732 |
| Graft type: right/left | 4/7 | 36/78 | 0.702 |
| Initial graft volume ratio to standard liver volume (%) | 46 ±9 | 47 ±9 | 0.842 |