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Hepatocellular Carcinoma and Recurrence Rate: Comparison of Living and Deceased Liver Donor Transplantation

Michele Finotti¹¹Surgery Unit, Treviso Regional Hospital, Italy

*Corresponding author: Michele Finotti, Surgery Unit, Treviso Regional Hospital, Italy

Introduction

Hepatocellular carcinoma (HCC) represents the 75-85% of primary liver tumors. Chronic liver disease, in particular cirrhosis, is the leading risk factor for HCC [1]. Liver Transplantation (LT) is an effective therapy for HCC, allowing an oncological resection of the tumor and a resolution of the underlying liver dysfunction. However, due to the shortage of liver grafts and a concomitant increase of candidates for LT, a longer waiting time for LT is occurring [2]. In patients affected by HCC, a longer waitlist is associated with a higher risk of drop out, especially due to tumor progression. In the last years, Living Donor Liver Transplantation (LDLT) has been evaluated as a viable option to Deceased Donor Liver Transplantation (DDLT) to reduce waitlist mortality and/or the risk of patient drop out.

With the increased experience in LDLT for patients with HCC, concerns have been raised about the outcome in terms of HCC recurrence and Overall Survival (OS) compared to DDLT. The aim of this paper is to summarize the available studies comparing DDLT versus LDLT in patients affected by HCC, especially in terms of HCC recurrence rate.

HCC Recurrence after LDLT

The correct patient selection and prioritization for LT are ongoing matters of debate in DDLT. Variables such as number, dimension and bio markers of HCC, especially AFP, have been proposed to select the patients with lower risk of HCC recurrence and the best OS after LT. The Milan criteria (a single tumor size of ≤ 5 cm or up to 3 tumors with sizes ≤ 3 cm in diameter with no macrovascular invasion) are widely apply to select HCC patients for LT [3-6]. However, different selection criteria have been proposed, such as utility models (based on radiologic morphology) biology models, or a combination of the two [7]. HCC recurrence is an essential variable also in the LDLT, and a debate has

been raised about the HCC recurrence after LDLT compared to DDLT.

Some studies showed that LDLT was associated with a higher HCC recurrence rate, compared to DDLT [8-11]. Some features related to the LDLT procedure have been proposed as possible explanations.

In the LDLT the graft used is different compared to DDLT. The whole organ is usually used in the DDLT, while the right liver graft is mainly used in adult LDLT. Some studies suggested that the consequent liver regeneration after LDLT, with a rapid increase in growth factors and cytokines, might stimulate HCC recurrence. Furthermore, the small-for-size grafts have been associated with higher endothelial growth-factor expression and angiogenesis [12-16].

However, the implication of these factors in HCC recurrence is questioned [17]. A technical aspect has been suggested as possible further explanation of higher HCC recurrence in LDLT showed in some studies. In particular, in the recipient, the preservation of the native inferior vena cava, the longer hepatic artery and bile duct might be associated with insufficient tumor removal and HCC residue and dissemination.

Another variable introduced with the LDLT compared to DDLT is the waiting time list. In the LDLT the waiting time list is drastically reduced, with the potential to overcome the organ shortage, reducing the waitlist mortality and the risk of drop out due to HCC progression. For example, Bhangu et al. reported the waiting time for LDLT patients (2.8 ± 2.4 months) was significantly shorter than DDLT (7.9 ± 9 months; $P < 0.001$), and some center reported a median of 44 days [18,19].

However, time in the waiting list is another important

indirect selection criterion that can influence the HCC recurrence. During the waiting time, the patient is usually observed and, in some cases, treated with loco regional treatments, such as TACE or ablative techniques (MWA or RFA). The waitlist and the response to the loco regional treatments could show the patient with a more aggressive HCC pattern. In the LDLT this “test of time” is significantly reduced compared to DDLT, and the results of the higher HCC recurrence can be the consequence of the inclusion of patient with aggressive tumor [8, 10, 11, 20-24].

Last but not least, patients who underwent LDLT often exceeded the most common HCC inclusion criteria (Milan criteria, UCSF) and the criteria used for DDLT are not the same for LDLT. Most studies report an LDLT offered to a patient affected with a more advanced HCC, raising concern about the ethical aspect [25]. All these factors would predispose the LDLT to have a worse outcome in terms of OS, RFS and HCC recurrence. However, as previously reported, the data are inconsistent.

To date, few meta analysis comparing the HCC outcome after LDLT or DDLT are available. In 2012, Lian et al. evaluated 1310 patient affected by HCC underwent to LDLT or DDLT in seven studies. Six were retrospective cohort studies, one was a prospective study, none was randomized trial [20]. To note, the tumor-related baseline variables, such as the TNM stage, size, and number of tumors, tumor differentiation, microvascular invasion, MELD score, Child-Pugh class, percentage of patients beyond the Milan or UCSF criteria, and treatment before LT were comparable between groups in all studies. In the LDLT groups, a significantly shorter waiting period and cold ischemia time have been showed. At 1, 3 and 5 years the LDLT and DDLT recipients had similar OS rate with no significant heterogeneity among the studies, except for the 5-year survival rates (4 studies showed a statistically significant heterogeneity; $P = 0.13$, $I^2 = 47\%$). Similarly, the RFS at 1,3 and 5 years was similar between LDLT and DDLT with no significant heterogeneity among the studies. The HCC recurrence rate at 1,3 and 5 years showed a similar pattern, but varying degrees of heterogeneity were found in the studies comparisons at 1,3 and 5 years [20].

An additional analysis was performed comparing LDLT and DDLT in patients with HCC Milan criteria in or out. At 1,3 and 5 year the OS and RFS were similar between the two groups within the Milan criteria, while the LDLT recipients had a greater 1-year recurrence rate than DDLT recipients (insufficient data were available to perform a 3- and 5-years comparison). In the patients beyond Milan criteria, the OR, RFS and recurrence rate were similar between DDLT and LDLT [20].

In 2019, Zhang et al. published a meta-analysis selecting, with strict inclusion criteria, seven studies, reporting a significantly increased risk of HCC recurrence in the LDLT group compared to DDLT group ($P = 0.01$) [26]. Zhu et al. performed a meta-analysis comparing LDLT and DDLT in twenty-nine studies with 5376 HCC patients with an Intention to Treat analysis (ITT). At 1,3 and 5 year the OS, DFS and HCC recurrence were similar between the LDLT and DDLT groups. Furthermore, LDLT was associated with better 5-year intention-to-treat patient survival than DDLT ($RR = 1.11$, $95\% CI = 1.01-1.22$, $P = 0.04$) [27].

The inconsistent data reported by the previous meta-analyses can be explained by some bias associated with the studies. These meta analyses compared multiple studies that often have an extremely heterogeneous transplanted population. HCC staging system, selection criteria, pre-LT treatment, waitlist time, donor preservation, surgical technique, and post LT management are some of the most variables that contribute to increase the complexity of LDLT evaluation. Furthermore, the evaluation of the outcome starting not at the time of the LT but at the waitlist (ITT analyses) is another factor leading to different results among the studies.

Conclusion

Deeping in the studies that reported a higher HCC recurrence rate in LDLT compared to DDLT, most of them reported patients with higher levels of AFP, more tumors beyond Milan and/or UCSF criteria and micro vascular invasion. Furthermore, less pre-LT ablation therapy is used in patients treated with LDLT due to the shorter waiting time compared to DDLT. Thereby, the main reasons for a different outcome reported by some studies and higher HCC recurrence in LDLT compared to DDLT could not be related to the type of technique per se (LDLT or DDLT), but probably to the different patient’s selection.

Transplant benefit might be the correct way to evaluate the real outcome of LDLT compared to DDLT. Most of the studies evaluated only the post LT outcomes, without including the results for patients on the waitlist. In particular, a percentage of patients listed for DDLT will drop out from the waitlist due to tumor progression, while in the LDLT group with a shorter waiting time allows these patients with more aggressive HCC pattern to be transplanted, affecting the final outcome. With this consideration, probably the transplant survival benefit in the LDLT is not correctly evaluated compared to DDLT [20]. In the last years, studies with an ITT analysis (evaluating the outcome from the time of listing, and not from the time of LT), showed comparable results in terms of OS and HCC recurrence among LDLT and

DDLT groups [28]. In particular, Goldaracena et al. showed a transplant benefit of LDLT compared to DDLT in an ITT analysis associated with a reduction in the drop out rate in the LDLT groups. Similar results were obtained by Wong et al. that performed a ITT and propensity score matching analysis of 375 patients with 5-year OS of 81.4% for LDLT versus 40.8% for DDLT.

In conclusion, LDLT was firstly associated with a higher HCC recurrence. In the last years, most studies showed similar results comparing LDLT to DDLT in terms of HCC recurrence and OS, especially at ITT analysis. To date, no randomized studies are available comparing LDLT to DDLT. The different outcome between LDLT and DDLT might be related more to the variables associate with the procedure (patient selection, HCC staging, waitlist, pre- and post-LT treatment) than the procedure itself.

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*Corresponding author: Michele Finotti, Email: mi6le@libero.it

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