

# Comparative Review of LDLT and DDLT Outcomes in Hepatocellular Carcinoma Patients

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**Abstract:** Hepatocellular carcinoma (HCC) remains one of the most common and deadly cancers globally. Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and a leading cause of cancer-related mortality worldwide, particularly in regions with high prevalence of viral hepatitis. Liver transplantation (LT) offers a curative option for select HCC patients by treating both the tumor and underlying liver disease. Deceased donor liver transplantation (DDLT) has traditionally been the gold standard; however, its effectiveness is limited by organ shortages, long waitlist times, and the risk of tumor progression beyond transplant criteria. Living donor liver transplantation (LDLT) has emerged as a viable alternative that can significantly reduce wait times, particularly in regions with limited access to deceased donor organs. While LDLT offers logistical and timing advantages, concerns remain regarding possible differences in long-term survival, recurrence risk, and the impact of partial grafts on tumor biology. A direct comparison of LDLT and DDLT outcomes in HCC patients remains critical to informing transplant decision-making. To compare overall survival (OS), intention-to-treat overall survival (ITT-OS), disease-free survival (DFS), and recurrence rates in HCC patients undergoing LDLT versus DDLT.

**Keywords:** Hepatocellular Carcinoma, Liver Transplantation, LDLT, DDLT, Meta-Analysis, Tumor Recurrence, Survival Outcomes.

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## I. INTRODUCTION

### A. Hepatocellular Carcinoma

The most prevalent form of primary liver cancer, hepatocellular carcinoma (HCC), makes up 75–85% of all liver cancers globally and is a major cause of cancer-related death, especially in regions like East Asia and sub-Saharan Africa where viral hepatitis is prevalent [1].

Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are risk factors for HCC and are the two leading causes worldwide. Due to its integration into the host genome, HBV can cause HCC even in the absence of cirrhosis, whereas HCV promotes carcinogenesis by causing fibrosis and chronic inflammation. Aflatoxin B1 exposure (especially in Africa and Asia), alcoholic liver disease, non-alcoholic steatohepatitis (NASH), obesity, diabetes mellitus, and hereditary disorders such as hemochromatosis are other noteworthy risk factors [2].

Chronic liver inflammation and damage are the primary causes of genetic and epigenetic changes that contribute to the pathophysiology of HCC. Genes like TERT, TP53, CTNNB1, and AXIN1 are frequently mutated, and this causes abnormal activation of carcinogenic pathways such as MAPK, PI3K/AKT/mTOR, and WNT/β-catenin. These molecular alterations encourage malignant transformation and interfere with normal hepatocyte growth [3].

Clinically, HCC is frequently found by surveillance imaging and may not show any symptoms in its early stages. Right upper quadrant pain, exhaustion, inadvertent weight loss, jaundice, ascites, and, in decompensated cases, hepatic encephalopathy are some of the symptoms that may appear as the disease worsens [4].

Dynamic imaging methods like contrast-enhanced CT or MRI, which demonstrate arterial phase enhancement and venous/delayed phase washout, are typically used to confirm

the diagnosis of HCC. Liver biopsy is not required if imaging is typical. Alpha-fetoprotein (AFP), des-gamma-carboxy prothrombin (DCP), and AFP-L3 are serum indicators that are occasionally employed as adjuncts [5].

The Barcelona Clinic Liver Cancer (BCLC) system, which divides patients into groups according to tumor burden, liver function (Child-Pugh score), and Eastern Cooperative Oncology Group (ECOG) performance status, is the most widely used staging method. Because the BCLC approach connects staging to suggested treatments, it is frequently used [6].

Liver function and stage determine the course of treatment. For early-stage disease, there are curative treatments such as liver transplantation, liver resection, and radiofrequency ablation. While advanced HCC is treated with systemic therapy, patients in the intermediate stage may benefit from locoregional therapies such as trans arterial chemoembolization (TACE). Today, the most common first-line systemic combination is atezolizumab with bevacizumab, which is followed by immunotherapy medicines like nivolumab and pembrolizumab, as well as alternatives like sorafenib, lenvatinib, and regorafenib [7].

The American Association for the Study of Liver Diseases (AASLD) recommends regular surveillance for hepatocellular carcinoma (HCC) in high-risk patients, including those with chronic HBV infection or cirrhosis, with biannual ultrasound exams, potentially accompanied by alpha-fetoprotein (AFP) testing. It has been demonstrated that surveillance increases overall survival and early discovery [8].

The stage of the tumor, liver reserve, and availability of curative treatments all affect the prognosis in HCC, which varies greatly. While patients with advanced disease and impaired liver function frequently have a median lifespan of fewer than 12 months without appropriate therapy, patients who undergo curative resection or transplantation have 5-year survival rates of above 50% [9].

Artificial intelligence in image analysis, liquid biopsies (such as circulating tumor DNA), and immunogenomic profiling to customize treatments are some of the newer research fields in HCC. To combat drug resistance and increase survival in advanced disease, new therapies like CAR-T cell therapy and epigenetic modification are also being researched [10].

### *B. Living Donor Liver Transplantation [LDLT]*

A portion of a healthy person's liver is surgically removed and transferred into a patient who has end-stage liver disease or hepatocellular carcinoma (HCC) as part of a surgery known as living donor liver transplantation (LDLT). By taking use of the liver's special capacity for regeneration, this method enables the livers of both the donor and the recipient to return to their normal size in a matter of weeks [11].

The shortage of dead donor organs, which can result in protracted waiting periods and the advancement of HCC past the point at which a person is eligible for a transplant, is the primary justification for LDLT. Timely transplantation is made possible by LDLT, which is especially important for patients whose liver tumours are growing quickly [12]. Donors go through a thorough evaluation that includes psychosocial screening, liver function tests, and liver volumetry using CT or MRI. Because it offers sufficient volume and reduces the possibility of small-for-size syndrome, the right lobe is usually utilized in adult patients [13].

With reconstruction of the hepatic artery, portal vein, hepatic veins, and bile duct, LDLT is a technically challenging procedure that requires significant liver resection from the donor and implantation into the recipient. To prevent biliary leakage or vascular problems, surgical precision is essential [14].

LDLT carries several hazards for the donor, despite its general safety. Bile leaks, infections, hemorrhage, and in rare instances, liver failure or death, are among them. High-volume transplant hospitals have a substantially lower donor morbidity rate, although the estimated mortality risk is between 0.2% and 0.5% [11].

Following a partial hepatectomy, the liver regenerates rapidly. In 6–8 weeks, both donors and receivers usually reach 80–90% of their liver volume. The main way to prevent liver dysfunction and small-for-size syndrome is to make sure that the graft-to-recipient weight ratio (GRWR) is more than 0.8% [15].

In areas where access to deceased donor organs is restricted, LDLT is especially crucial in the treatment of HCC. It offers comparable long-term results to deceased donor liver transplantation (DDLT) and is appropriate for patients who meet or are downstaged to Milan or other extended criteria [16].

Over 70% of patients with HCC who meet the Milan criteria and undergo LDLT have reported 5-year survival rates. Rapid LDLT performance can help lower waiting dropout rates, increasing overall longevity for patients who qualify for transplants [17].

Laparoscopic and robotic donor hepatectomy techniques are recent advancements in LDLT that are intended to lessen donor discomfort, blood loss, hospitalization, and surgical complications [18].

Liver cancer and end-stage liver disease can both be safely and effectively treated with LDLT. With careful patient selection, donor safety procedures, and surgical skill, LDLT provides outstanding results and keeps developing thanks to clinical research and technology breakthroughs.

### C. Deceased Donor Liver Transplantation [DDLT]

A liver from a deceased person who is either brain-dead or circulatory-dead is transplanted into a patient who has end-stage liver disease or hepatocellular carcinoma (HCC) as part of a life-saving medical procedure known as Deceased Donor Liver Transplantation (DDLT). It is the most widely done type of liver transplantation in the world and is still the gold standard in many places, especially those with established programs for dead donors [19,20].

Acute liver failure, hereditary metabolic disorders, sequelae from cirrhosis, and HCC that meets transplant requirements are the main indications for DDLT. Patients with HCC in particular who meet the Milan criteria—one tumor  $\leq 5$  cm or up to three tumors  $\leq 3$  cm without vascular invasion or metastasis—have minimal recurrence rates and high post-transplant survival [21].

The Model for End-Stage Liver condition (MELD) score, which assigns patients a score depending on the severity of their condition and their probability of dying, is typically used to allocate donor livers. Since its implementation, the MELD approach has greatly increased liver allocation's efficacy and fairness while lowering waitlist mortality [22,21].

The donor liver is used in place of the diseased liver during the DDLT operation. Expert surgical skills and perioperative management are required for the difficult surgery, which involves vascular (hepatic artery, portal vein, and hepatic veins) and biliary repair [23].

With one-year survival rates above 85% and five-year rates ranging from 65 to 75%, contingent on the indication and center experience, outcomes following DDLT have improved dramatically [24].

The fact that DDLT spares living donors from the risk of surgery is one of its main advantages. This strategy is constrained, though, by the lack of deceased donor organs, which results in long waiting periods and occasionally death or tumor growth while patients are still on the list. Patients with HCC may be delisted if their tumor surpasses transplant criteria while they are waiting, which is very difficult for them [25].

In contrast to Living Donor Liver Transplantation (LDLT), DDLT offers whole-liver grafts, which may be advantageous for certain patients. However, it is linked to longer periods of ischemia and higher rates of graft discard, particularly when using donors that satisfy longer criteria (e.g., advanced age or steatosis) [26].

According to research, LDLT and DDLT have comparable survival outcomes when performed at reputable facilities; however, LDLT may offer patients with HCC the advantage of early transplantation and reduced waiting dropout rates [27].

### D. Milan criteria

Mazzaferro et al. created the widely accepted Milan Criteria in 1996 as a means of choosing hepatocellular carcinoma (HCC) patients who would make good liver transplant candidates. Based on a prospective analysis of liver transplant recipients, these criteria showed that post-transplant outcomes were considerably better for patients with a single HCC lesion  $\leq 5$  cm or up to three lesions each  $\leq 3$  cm that showed no signs of extrahepatic dissemination or macrovascular invasion. In particular, the 4-year overall survival rate of 85% and the recurrence-free survival rate of 92% for these patients were similar to those of transplants for liver disorders that are not malignant [28].

The Milan Criteria's implementation has greatly enhanced transplant results for HCC patients. 5-year survival rates for patients who meet these criteria have continuously been between 70 and 80%, which is similar to those of people receiving transplants for non-cancerous illnesses. The Milan Criteria are the gold standard for choosing liver transplant candidates with HCC because of these survival statistics, especially in Western nations and through organ-sharing networks like the United Network for Organ Sharing (UNOS) [29,30].

Furthermore, patients are prioritized for deceased donor liver transplantation (DDLT) and living donor liver transplantation (LDLT) thanks to the Milan Criteria, which have been included into clinical decision-making processes worldwide. Given the limited supply of donor livers, the addition of tumor size and number as selection criteria is a compromise between offering a possibly curative treatment and guaranteeing the best possible organ utilization [31].

Nevertheless, the Milan Criteria are thought to be restrictive even though they are very successful in choosing patients with the best results. Numerous studies have demonstrated that patients with tumor sizes or numbers that marginally surpass the Milan Criteria may still have positive outcomes, particularly if they also have other tumor biology characteristics (such as low levels of alpha-fetoprotein, well-differentiated histology, and a good response to locoregional therapies). The University of California, San Francisco (UCSF) Criteria were developed to expand transplant eligibility and allow for a single tumour measuring up to 6.5 cm, or up to three nodules with the largest not exceeding 4.5 cm and a total tumour diameter of no more than 8 cm, provided there is no evidence of macrovascular invasion or distant metastasis. [32].

Furthermore, according to a further enlarged model known as the "Up-to-Seven" criteria, patients are suitable for transplantation if, in the absence of macrovascular invasion, the total of the number of tumors and the greatest tumor's size in centimeters is less than 7. The biological activity of tumors, such as vascular invasion, AFP level, and differentiation, can be more predictive of outcomes than just size and number, according to this method, which takes into account both tumor burden and shape [33,34].

One significant drawback of the Milan Criteria is that it ignores tumor biology, which includes crucial markers of tumor aggressiveness and recurrence risk, such as serum alpha-fetoprotein (AFP) levels, histological grade, and response to pre-transplant therapy. Research has indicated that while some individuals with tiny tumors but poor differentiation or elevated AFP levels may have worse prognoses, others with tumors outside the Milan Criteria but with good biology have comparable results to those inside the criteria [35].

In conclusion, because of their solid evidence base, predictive precision, and ease of use, the Milan Criteria continue to be the cornerstone for choosing HCC patients for liver transplantation. However, research is continuously being done to incorporate biological markers and treatment response into more thorough selection processes. The goal of these advancements is to increase transplant eligibility while preserving high survival rates and effective organ donation [36].

## II. DISCUSSION

One of the best ways to treat hepatocellular carcinoma (HCC), especially in patients with cirrhosis, is still liver transplantation (LT). Living donor liver transplantation (LDLT) has become more popular as an alternative to deceased donor liver transplantation (DDLT) because of the worldwide shortage of deceased donor organs. Nonetheless, there is ongoing discussion over the relative efficacy of LDLT and DDLT with regard to survival results and recurrence risk.

Earlier studies, cohort and retrospective, have reported varying results. Because of the shorter waiting periods and lower risk of illness progression and transplant list dropout, some studies have shown a survival benefit linked to LDLT, specifically in intention-to-treat overall survival (ITT-OS). Others, however, pointed to expedited access to transplantation without enough time to evaluate tumor biology and possible pro-regenerative stimuli from partial grafts that could encourage tumor growth as reasons for an increased risk of tumor recurrence.

It is commonly acknowledged that the Milan criteria, which determine transplant eligibility according to tumor size and quantity, are useful indicators of post-transplant outcomes. These standards, however, have come under fire for being unduly restrictive because, when properly chosen, some individuals who did not meet the Milan criteria have shown comparable survival rates. Compared to graft type, biological indicators like vascular invasion, tumor differentiation, and serum alpha-fetoprotein (AFP) levels have become more reliable indicators of survival and recurrence.

Elkomos et al. conducted a systematic review and meta-analysis of 35 studies with 7,822 HCC patients, comparing the results of LDLT and DDLT. There was no statistically significant difference in long-term overall survival (5-, 6-, and 10-year) between the two groups, despite LDLT recipients showing a slight improvement in short-term overall survival (1- and 3-year OS). At several time points, however,

ITT-OS performed noticeably better in LDLT recipients, highlighting the survival benefit brought about by shorter wait times and lower dropout rates.

## III. RESULTS OF PREVIOUS STUDIES

The results of living donor liver transplantation (LDLT) and deceased donor liver transplantation (DDLT) in patients with hepatocellular carcinoma (HCC) were compared in 35 trials totaling 7,822 patients.

### ➤ Overall Survival (OS):

There was no discernible difference in long-term OS (5-, 6-, and 10-year) between LDLT and DDLT recipients, but LDLT demonstrated marginally improved short-term OS at 1 and 3 years (RR = 1.04 and 1.07, respectively).

### ➤ ITT-OS (Intention-to-Treat Overall Survival):

At 1, 3, and 5 years, LDLT showed a considerable improvement in ITT-OS, most likely as a result of shorter wait times and lower dropout rates.

### ➤ Disease-Free Survival (DFS):

At any timepoint (1–10 years), there were no discernible differences in DFS between LDLT and DDLT.

### Recurrence Rates:

The LDLT and DDLT recurrence rates were RR = 1.07;  $p = 0.70$ .

### ➤ Subgroup Analysis:

OS and DFS were equivalent according to the Milan Criteria, LDLT showed a marginally improved OS in individuals who did not meet the Milan criteria,

### ➤ By Region:

across Asia, America and Europe, no significant differences in OS or DFS were observed between LDLT and DDLT.

### ➤ Recurrence Predictors:

Regardless of graft type, poor tumor differentiation, vascular invasion, and high AFP levels (>400 ng/mL) were all substantially linked to lower survival and increased recurrence.

### ➤ Heterogeneity:

Several pooled studies revealed moderate to high heterogeneity ( $I^2 > 60\%$ ).

## IV. CONCLUSION

Living donor liver transplantation (LDLT) delivers similar oncological results to deceased donor liver transplantation (DDLT) in patients with hepatocellular carcinoma (HCC), according to a thorough analysis of 35 trials including 7,822 participants. Long-term overall survival (OS) and disease-free survival (DFS) were statistically equal across the two transplant modalities, while LDLT demonstrated a slight improvement in OS and a notable advantage in intention-to-treat overall survival (ITT-OS).



This implies that LDLT is not only a feasible substitute for DDLT but also might have logistical benefits, particularly in areas with long waitlists and a shortage of available organs.

Crucially, the two groups' risk of HCC recurrence was comparable, allaying earlier worries about increased recurrence rates after LDLT. Subgroup studies also showed that the most important factor influencing post-transplant outcomes is still tumor biology rather than graft type. In particular, vascular invasion, tumor differentiation, and alpha-fetoprotein (AFP) levels were all consistently linked to both recurrence and survival, highlighting the need of including biological markers in transplant eligibility requirements.

These results lend credence to the further use of LDLT, especially in situations where access to deceased donor organs is restricted. In order to maximize results, they also emphasize the necessity of improved patient selection procedures that take into account both biological and anatomical factors. For eligible HCC patients, LDLT should be regarded as an equally effective—and in certain situations, preferred—modality as transplant centers continue to refine their standards and procedures.

In conclusion, if patients are carefully chosen based on tumor behavior and clinical context, LDLT is a viable and oncologically sound approach for treating HCC. To further improve graft allocation and post-transplant performance, future studies should concentrate on standardizing risk classification models and investigating preoperative determinants of tumor biology.

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