THE MEDICAL BULLETIN OF
SISLI ETFAL HOSPITAL

DOI: 10.14744/SEMB.2024.87864
Med Bull Sisli Etfal Hosp 2024;58(1):1–9

Review

Impact of Living Donor Liver Transplantation on the Improvement of Hepatocellular Carcinoma Treatment

Yucel Yankol, Oswaldo Aguirre, Luis A. Fernandez

Department of Surgery, Chicago Stritch School of Medicine, Loyola University Medical Center, Abdominal Transplant Center, Maywood, IL, United States

Abstract

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related deaths, with increasing incidence. There are different treatment options, but only 30%-40% of HCC cases are diagnosed at an early stage for curative treatment. With the implementation of Milan Criteria for liver transplantation (LT) in HCC cases and its use for organ allocation with successful outcomes, LT has become an optimal treatment. Seeking new criteria for LT and developing updated algorithms for HCC treatment has become a hot topic nowadays. With the experience in living donor liver transplantation (LDLT), especially in Asian countries, LDLT was established and adopted with different criteria for HCC treatment, especially including criteria beyond Milan's size and number of tumors. Living donor grafts are uniquely different than deceased donor grafts as they are not considered a public resource. A living donor graft is rather a private gift intended for a specific recipient. Living donor livers are not limited by organ allocation systems, and this significant advantage of LDLT has opened new frontiers in the treatment of HCC. Improvements in LDLT have had remarkable parallel effects in the successful treatment of HCC as supported by a growing body of literature in the past decade.

Keywords: Criteria, hepatocellular carcinoma, living donor liver transplant

Please cite this article as "Yankol Y, Aguirre O, Fernandez LA. Impact of Living Donor Liver Transplantation on the Improvement of Hepatocellular Carcinoma Treatment. Med Bull Sisli Etfal Hosp 2024;58(1):1–9".

Hepatocellular carcinoma (HCC) is a global health problem with high related death rates and increasing incidence. HCC usually arises in chronically diseased livers and without treatment has a low median survival rate. Many different treatment options exist including resection, percutaneous ablation, locoregional therapies, and/or liver transplant (LT) but only 30%-40% of them have a chance for for curative treatment. Most of the cases are diagnosed at a late stage for curative treatment. During the past several decades, LT has become an optimal treatment for HCC.LT can treat intrahepatic metastasis and multi-centric carcinogenesis in the setting of chronic liver disease similtaneously.[1]

Since 1996, Milan Criteria (MC) has been accepted worldwide for LT in HCC treatment for cirrhotic patients. MC has been used for organ allocation with successful outcomes.[2] Over time, the development of new criteria for LT and updated algorithms for HCC treatment became a hot discussion. With the matured experience in living donor liver transplantation (LDLT), especially in Asian countries, LDLT was established and adopted for HCC treatment, especially including criteria beyond the size and number of tumors established by MC. Living donor grafts are uniqely different than deceased donor. Living donor grafts are not a public resource. A living donor graft is a private gift intended for

Address for correspondence: Yucel Yankol, MD. Department of Surgery, Chicago Stritch School of Medicine, Loyola University Medical Center, Abdominal Transplant Center, Maywood, IL, United States
Phone: +90 532 592 67 91 **E-mail:** yyankol@yahoo.com

Submitted Date: November 10, 2023 **Accepted Date:** January 07, 2024 **Available Online Date:** April 05, 2024

a specific recipient. Living donor livers are not limited by organ allocation systems, and this significant advantage of LDLT has opened new frontiers in the treatment of HCC.

Historical Background

Hepatocelluler Carcinoma

Hepatocellular carcinoma is an important contributor to worldwide cancer and cancer-related death burden. The estimated worldwide incidence rate per 100,000 person-years was 9.3 in 2018 and the mortality rate was 8.5. Worldwide close to 1.1 million new HCC cases and 600,000 deaths per year were recorded. Hepatocellular carcinoma usually arises in chronically diseased livers, most commonly secondary to chronic HBV and HCV infection. In Asia and Africa, the incidence of HCC is significantly higher than in Western countries. This is mainly related to the high prevalence of chronic HBV infection representing more than two-thirds of cases worldwide. Concurrently, HCC incidence has significantly increased in Western countries over the past several decades. Most HCC cases in Western countries develop in patients with chronic liver disease due to viral hepatitis, alcohol metabolic syndrome, and non-alcoholic fatty liver disease (NAFLD). With more robust recent worldwide vaccination policies and effective treatment options for both HBV and HCV infections, NAFLD has become the major cause of HCC, followed by alcoholic liver disease. In addition, epidemiologic studies of HCC have re-focused on metabolic syndrome, diabetes, obesity, tobacco use, dietary factors, genetic studies, and aflatoxin B1 (AFB1) in the past decades. Especially with climate change, AFB1 exposure will be an important risk factor for future decades.[1] Hepatocellular carcinoma treatment requires a complex multimodal therapeutic approach. Despite the remarkable improvements in arterial locoregional therapies, percutaneous ablation techniques, and medical treatment options; resection and LT are still potential curative treatment options for HCC in selected patients. Resection is the appropriate treatment for resectable HCC lesions in patients with good hepatic functional reserve. Resection as a therapeutic option remains limited at approximately 30% related to the patient's liver reserve and the high recurrence risk of more than 70% at 5 years.[3] There is no discussion that LT is the most effective treatment option for suitable HCC patients due to the advantage of treating both HCC and underlying liver disease. In contrast, some centers such as Park et al.[4] from Korea, have published data concluding that primary LDLT is not a good option in early HCC patients with poor biology because tumor recurrence is similarly high and survival is poor.

Liver Transplantation in HCC Treatment

The first LT series was reported by Thomas Starzl in 1963 with three cases of which one was a pediatric 3-year-old biliary atresia case, and two cases were adults with primary liver cancer. Both cases unfortunately ended with early hospital mortality. Four years after the first attempts, longer survivals were achieved in four patients by Starzl.[5] LT truly reached global success and acknowledgment as an established therapeutic option in the 1980s due to the effects of numerous developments in liver preservation (hypothermic perfusion utilizing the University of Wisconsin -Belzer solution), surgical techniques, immunosuppression treatment (cyclosporine by Sir Roy Calne), and appropriate clinical and medical follow-up. Liver transplantation is currently the only lifesaving and definitive treatment for end-stage liver disease, acute liver failure, some metabolic diseases, and some liver tumors. However many people still die on the waiting list due to a global shortage of deceased donor liver grafts.

To overcome the size disparity of the graft for a pediatric recipient, reduced-size liver transplantation was performed by Bismuth et al.[6] in 1981 and reported in 1984. Following years split-graft liver transplantation was then performed by Pichlmayr et al.[7] in 1988. With the experience of in-situ donor hepatectomy in reduced-size and split-graft DDLT the addition of the hepatobiliary surgery experience paved the way for LDLT. Although LDLT was initially considered as early as 1969, the first documented attempt was in a pediatric patient by Raia et al.[8] in 1987 and the first successful LDLT was achieved in a pediatric patient by Strong et al.[9] in 1989. Though the first pediatric LDLT attempts were performed in Western countries, adult LDLT improved and flourished in Asian countries, where deceased donation was low and hepatobiliary surgery was already well developed. Data from many studies shows that LDLT outcomes are similar to DDLT outcomes.

With the improvements in DDLT, early experience of HCC treatment with LT was discouraging due to higher recurrence rates and decreased patient survival. Many centers reported 5-year survival rates of 18% to 35.6% with recurrence rates of 39% to 42.9% till 1991.[10] In the early 1990s, two important discussion topics surrounded identifying risk factors for recurrence and selection criteria for LT. The Pittsburgh group showed that lymph node metastasis, vascular invasion, tumor number, and size were the main risk factors for recurrence.[11]

Mazzaferro et al.[2] from Italy's National Cancer Institute reported the MC for LT in HCC cases in 1996, demonstrating similar outcomes in HCC cases compared to LT for other diseases. The use of MC (single tumor ≤ 5cm or 3 tumors

≤ 3cm) worldwide has resulted in better outcomes in LT for HCC. It was a single-center retrospective study with 35 cases meeting MC criteria between 1991 and 1994. As a result, MC has been included in important practice guidelines. A worldwide shortage of liver donors limits LT. With the development of the MC, restricting high-risk HCC patients from LT was successfully used to ensure an acceptable recurrence rate and post-LT survival.[10] However over time, transplant experiences demonstrated that patients identified to be beyond MC on explant histopathology still had acceptable survival rates and thus a discussion for extending patient selection criteria for LT was fueled. The MC has been considered too restrictive by many investigators, particularly during the last two decades. MC may exclude a significant number of patients who could benefit from LT. Importantly, tumor numbers and sizes are often underestimated by preoperative imaging.[4] Additionally, many HCC patients die due to cancer progression while waiting on the transplant list. This waitlist mortality is different depending on region, but can be as high as 40%. Discussions regarding new criteria and LT algorithms for HCC ensued. The first extended criteria beyond MC (single tumor ≤6.5cm or 2-3 tumor ≤4.5cm and total tumor size ≤8cm) was published by Yao et al.[12] (UCSF Criteria). This was a study with 60 cases between 1988 and 2000, with a 75.2% survival rate at 5 years. UCSF criteria expanded the recipient population by only 10% with respect to MC and with acceptable survivals.

Living Donor Liver Transplantation in HCC Treatment

Adopting the UCSF criteria for LT for HCC patients, many centers started to report excellent outcomes with their new criteria.[13-27] There are numerous reports of both LDLT and DDLT with the new size and number limitation beyond MC. Though LDLT attempts continued in Western countries, significant progress was achieved in Asian countries, where religious and cultural beliefs do not allow deceased donations. LDLT allows many Asian centers not only to develop their center-specific expanded criteria, but also allows case-by-case evaluation with acceptable results without the limitations of allocation systems. Thus, LDLT for treatment of HCC has been adopted worldwide over the past decade (Table 1). LDLT is an important alternative to decrease waitlist times and theoretically limit HCC progression. LDLT offers a therapeutic surgical opportunity to patients with HCC out of the listing criteria for DDLT, as well as for patients who meet the criteria but are not able to wait because of end-stage liver disease. Additional advantages of LDLT include the excellent quality of the liver graft, the ability to carefully plan the surgery, minimization of ischemia times, and independence from adeceased donor waiting list.[28]

With the advantages of LDLT at many centers, especially in Asia, started to evaluate their HCC patients on a case-by-case basis. They started to evaluate the risk factors for recurrence, chance of survival, and strong wishes of the patient, donor, and her/his family for every cases separately.[13-27] The review and meta-analysis by Zhu et al.[29] conducted in 5 European, 11 North American, 2 South American, 10 Asian, and 1 African countries with 5,379 patients, concluded that surgeons expanded the criteria for LDLT in HCC patients in the region with insufficient deceased donation. Unfortunately, Daoud et al.[30] from Houston Methodist Hospital, Texas, US, reported the data from 11,928 LT for HCC patients from the United Network for Organ Sharing (UNOS) between 2002 and 2013. In this analysis, less than 1% (82) of cases were beyond the Milan and USCF criteria, and around 2% (291) were beyond the MC and within the USCF. Of 11,928 cases, 97% (11,555) were within the MC. No statistically differences in 1-, 3-, and 5-year survival rates were reported between the three groups. In addition, Zhu et al.[29] concluded that LDLT outcomes are similar to DDLT outcomes, which was also supported by the same outcomes both from Western[21, 30] and Asian[13] centers' reported data.

The group from the University of Toronto, Canada, reported that the liver patients on their list with living liver donors have a lower risk of death than patients without living liver donor candidates. This is a 33% low risk of death in a country with a high deceased donation rate. Post-transplant outcomes are similar for both LDLT and DDLT. Interestingly, even with a potential living donor, there was an important dropout rate (14.6%) from the list, two-thirds of them due to HCC progression, which is different from Asian countries' experience.[21] In Asia and other countries with a low deceased donation rate, the majority of the HCC patients would have dropped out and died without a LDLT.[6]

In 2002, Bruix et al.[3] proposed that HCC expanded treatment criteria for LDLT different than that for DDLT. This was added to the BCLC staging classification and treatment schedule, which is an accepted guideline worldwide. The proposed criteria were single tumor <7 cm or 3 tumors all <5 cm or 5 tumors all <3 cm, which extended the limits beyond both the USCF criteria and MC. Following the literature review, it was concluded that the availability of LDLT had opened the potential for an expansion of the criteria beyond those conventionally applied. Based on the achievement of 50% survival at 5 years in patients with early HCC in whom the waiting time allowed for tumor progression without reaching criteria for exclusion (extrahepatic

Table 1. Proposed Extended criteria beyond the UCSF and MC for LT for HCC under the impact of LDLT

Authors	Year	Criteria & Center	Country	Characteristics of Criteria	Survival Rate
Bruix et al.[3]	2002	Barcelona -Barcelona Clinic	Spain	Single tumor ≤7cm or	>50% (5 years)
Llovet et al.[23]	2018	Liver Cancer		3 tumors ≤5 cm or 5 tumors ≤3 cm	80.2% (5 years)
Ito et al.[32]	2007	Kyoto-Kyoto University	Japan	Number ≤10, size ≤5cm	67% (5 years)
Kaido et al.[14]	2013			and DCP ≤400mAU/ml	82% (5 years)
Sugawara et al.[31]	2007	5-5 rule-Tokyo University	Japan	Number ≤5, size ≤5cm	70% (5 years)
Akamatsu et al.[17]	2014	5-5-500 rule-Hokkaido University		and AFP ≤500 ng/ml	80% (5 years)
Shimamura et al.[36]	2019				75.8% (5 years)
Jonas et al.[33]	2007	Berlin -Multicenter	Germany	No limit tumor number, size ≤6 cm, and total size ≤15 cm	62% (3 years)
Lee et al.[13]	2008	#Asan – Asan Medical Center	S.Korea	Number ≤6 and Size ≤5 cm No gross vascular invasion	73.2% (3 years)
Zheng et al.[24]	2008	#Hangzhou – Zhejiang University	China	Total size ≤8 cm or	87.7% (5 years)
Chen et al.[15]	2014	#CLTR- China Liver Transplant		Total size ≥8 with grade 1 and 2	66.3% (5 years)
Hu et al.[18]	2016	Registry		histopathology and AFP≤ 400ng/mL No limit size and number with Hangzhou criteria	
Dubay et al.[39]	2011	#Extended Toronto -	Canada	No limit size and number	70% (5 years)
Sapisochin et al.[25]	2016	Toronto University		No vascular invasion	68% (5 years)
Goldaracena et al.[21]	2019			No extrahepatic disease No cancer-related symptom Biopsy of largest tumor not poorly differentiated	79% (5 years)
Shirabe et al.[26]	2011	Kyushu – Kyushu University	Japan	No number limit and Size	71.2% (5 years)
Uchiyama et al.[20]	2017			≤ 5 cm and DCP ≤300 Mau/ml	82.1% (5 years)
Kim et al.[16]	2014	Samsung – Samsung Medical Center	S.Korea	Number ≤7, size ≤6cm and AFP ≤1000 ng/mL	89.6% (5 years)
Lee et al.[19]	2016	National Cancer Center	S.Korea	Number ≤10 and negative PET	82.1% (5 years)
Azoulay et al.[27]	2017	#Ministry of Health	France	No limit size and number No extrahepatic disease No vascular invasion	73.2% (5 years)
Wong et al.[28]	2019	#University of Hong-Kong	China	No limit number and size No extrahepatic disease No vascular invasion	80% (5 years)
Ince et al.[22]	2020	Malatya – Inonu University	Türkiye	No limit number, size ≤6 cm Well or moderate tumor differentiation AFP ≤200 ng/ml and GGT≤104 U/L	79.7% (5 years)

LDLT and DDLT were performed together in these studies and outcome comparison done between LDLT and DDLT.

spread/macroscopic vascular invasion), a set of expanded criteria had been developed. This is currently under evaluation for BCLC guidelines.[3] At that time, many centers had ongoing studies on LDLT in HCC patients beyond MC with their criteria and/or case-by-case evaluation which would be published in full in the following years.[13, 15, 31-33] LDLT offered an opportunity to assess the applicability of LT for the treatment of patients with increased HCC tumor burden.

Starting with the first published data by Todo et al.[34] from Japan in 2004 and followed by Lee et al.[13] from Korea in 2004 survival rates between 60% and 67% were reported for LDLT in patients beyond MC. Todo et al.[34] analyzed 316 cases who received LDLTx for HCC between 1989 and 2003 at 49 centers in Japan. They reported that AFP level, tumor size, vascular invasion, and bipolar distribution were independent risk factors for HCC recurrence. The grade of histologic differentiation of HCC showed a close correlation with tumor characteristics and recurrence. In addition, with the

advantage of LDLT, some centers began to push the limits of size and number with no invasion of major vascular structures and no evidence of extrahepatic disease, as reported in 2007 by Haberal et al.[35] from Türkiye.[30] With an overall 50.3% survival rate at 5 years, this report was promising for future studies.

Lee et al.[13] from Asan Medical Center in South Korea presented one of the pioneer studies in extended criteria for LDLT in HCC in an experienced LDLT center. Asan's criteria included cases with tumor size ≤5cm, tumor number ≤6, and no gross vascular invasion. They reported a 73.2% overall survival rate at 3 years in 186 cases between 1997 and 2004. In 2007, Sugawara et al.[31] from the Japanese Liver Transplantation Society utilized a 5-5 rule (up to five nodules with a maximum diameter of 5 cm) and reported a 94% recurrence-free survival rate at 3 years after LDLT. In 2019, with the addition of AFP ≤500mg/mL as a biological parameter, criteria were modified as a "5-5-500 rule." The overall 5-year survival was reported at 75.8%, and 5-5-500 criteria expanded the recipient population by 19% in comparison to MC with acceptable survivals.[36] With the new limits, Mazzaferro et al.[37] from Italy's National Cancer Institute expanded the criteria more than for the previous MC: up-to-7 – (Metro ticket) criteria (up to 7 tumors, with the size of the largest tumor up to 7cm). Their data showed that, using this criteria in the cases without microvascular invasion had a similar survival rate within MC cases. Microvascular invasion affects all outcomes including for both LDLT and DDLT.

Given the expanded limits for HCC in LDLT and growing body of literature, this now allowed the discussion of the biological selection criteria and unique treatment options. We discussed our selection criteria and outcomes with a manuscript with my previous transplant team from Memorial Sisli Hospital, Istanbul, Türkiye.[38] In addition to our experience, many LDLT centers from Türkiye, Asian countries, and a few centers from Western countries published their results without any size and number limitations, but including biological behavior parameters and/or a case-by-case basis.[13-27]

The University of Toronto group, a Western LT center, is one of the few centers that published their extended criteria with no tumor size and number limitation, showing the advantage of LDLT. In 2011, Dubay et al.[39] proposed the Extended Toronto Criteria (ETC), with no limit in tumor size and number, no vascular invasion, no extrahepatic disease, no cancer-related symptoms, and no poorly differentiated pathology from the biopsy of the largest tumor. This was a prospective study with a 79% overall survival rate and a 78% disease-free survival rate at 5 years.[21]

New prognostic biomarkers for HCC are hot topics and have been studied, mostly from experienced LDLT centers, and additionally from DDLT centers seeking to study the outcomes of HCC patients undergoing LT. The most well-known and studied biomarker is the serum alpha-fetoprotein (AFP) level.[40] Other promising biomarkers for HCC recurrence are: des-gamma-carboxy prothrombin or protein induced by vitamin K absence or antagonist II (DCP or PIVKA-II), E-cadherin, beta-catenin, and high HCC expression of GPC-3 but additional research is necessary to establish the prognostic role of these biomarkers in the future.[41]

In 2007, Todo et al.[10] from Japan introduced AFP≤200ng/mL and PIVKA II (DCP)≤100mAU/mL as a marker correlated with good biological behaviors of the HCC that could help to extend the indication for HCC treatment with LDLT. Lee et al.[42] from the National Cancer Center in Korea reported that beyond the MC with PET-negative status and a total tumor size <10cm showed similar overall survival and disease-free survival compared to MC recipients undergoing LDLT. In addition, Hong et al.[43] reported that serum AFP levels and 18 F-fluorodeoxyglucose positron emission tomography scan (18F-FDG PET) positivity represent new biological criteria in place of morphological factors that can improve the risk stratification of tumor recurrence better than the MC for LDLT recipients with HCC.[22,37] Although AFP is the most widely used tumor marker for HCC it may not be the optimal indicator because only half of all tumors secrete this protein.

Kaido et al.[14] from Japan presented their outcomes with Kyoto criteria, including the level of des-gamma-carboxy prothrombin(DCP) as a biomarker with tumor number ≤10 and tumor size ≤5cm. They reported a 82% overall 5-year patient survival. In addition, Uchiyama et al.[20] from Japan reported Kyushu criteria utilizing DCP level in 2017. They reported 8an 2.1% — a 82.1% overall survival rate and a 80.4% disease-free survival rate at 5 years with criteria including DCP ≤300 to any number of tumors with tumor size ≤5cm. Hwang et al.[44] from South Korea Asan Medical Center proposed using ADV score (AFP, DCP, and tumor volume) as a quantitative prognostic prediction for HCC following LDLT in 2020 which included 843 HCC cases. They concluded that this model can provide reliable information to help decide case selection for LDLT. In 2020, Ince et al.[22] from Malatya Transplant Institute in Türkiye reported their criteria, including blood GGT level below 104 IU/mL, AFP ≤200ng/mL, tumor size ≤ 6 cm with no number limit, and well/moderate differentiation grade. They concluded that hepatoma-specific GGT (HS-GGT, GGT sub-fraction 2) has been used for the diagnosis of HCC and can be a parameter to predict poor survival. With Malatya criteria, they reported a 79.2% overall 5-year survival and extended LT to an additional 27% of patients beyond the use of MC.

A couple of studies had reported that LDLT had a worse recurrence rate compared to DDLT for HCC cases due to the lack of understanding of tumor biology during the waitlist time. Waiting time is mostly shorter for LDLT recipients.[15,18,28] Fast-tracking to LT, growth factor and cytokines released during the rapid regeneration of a partial graft, and surgery technique may be the reason for this worse HCC recurrence rate. The LT community has in part accepted this recurrence risk and recipient survival benefit as well as consideration of the donor's wishes should be taken into account for LDLT candidate selection because LD grafts are not public resources. However, the most recent consensus meeting reports have proposed a minimum of 50% overall survival goal for 5 years after LDLT for HCC.[4] The Transplant Oncology Consensus Conference of the International Liver Transplantation Society working group proposed a minimum of 60% as a benchmark for 5-year postoperative LDLT survival with HCC treatment.[45] The degree of tumor differentiation and microvascular invasion are indicators of biological aggressiveness for HCC. This was shown throughout most of the studies. Preoperative establishment of these indicators seems to be the key to achieving better outcomes. A current review of the literature supports that criteria including biological tumor markers increased overall survival rates significantly, and therefore, biomarkers predictive of tumor biology seem to be elemental to extend the role of LT in future HCC treatment.

Salvage Transplantation was introduced as a new surgical technique by Majno et al.[46] in 2000. With this technique, resection was a primary therapy which was followed by LT after HCC recurrence or decompensation. Another technique to improve the results of LT for advanced HCC with expanded criteria is down-staging the tumor within MC with pretransplant locoregional therapy. With this option, many HCC patients who are not transplantable due to being beyond MC could obtain survival benefits according to the non-transplant treatments. Living donor grafts are considered a private gift to a specific recipient and are not a public resource, and as such, the combination of resection and salvage LDLT technique should be considered and extended. The selection criteria for salvage LDLT seems to be no different than primary LDLT. Hwang et al.[47] from Asan Medical Center reported the results after implementation of their new scoring system (ADV score) which includes AFP, DCP, and tumor volume for salvage LDLT approach. They concluded that using ADV scoring salvage LDLT patients' postoperative outcomes are similar to primary LDLT patients. ADV score can help in the decision-making process regarding salvage LDLT. However, with the poor prognostic sign of previously resected HCC, salvage LDLT should be carefully considered even in patients within MC due to the high early recurrence risk. In addition, advanced HCC recipients with good responses to down-staging therapy tend to obtain satisfactory long-term survival after LDLT and similar outcomes with DDLT.[47]

The most recent reports in the literature are promising regarding the treatment of HCC with portal vein tumor thrombus (PVT) with successful LDLT after an intensive multidisciplinary treatment approach. Historically, PVT in setting of HCC has been identified as a contraindication even in the LDLT setting. Suh et al.[48] from South Korea Seoul National University reported their results in LDLT for HCC patients with PVT. With preoperative AFP level ≤200ng/mL, they reported 87.5% overall and 65.5% disease-free survival at 3 years. In addition, many centers have begun to push the limits for LDLT with ABO-incompatible LDLT, dual graft LDLT, paired exchange, and non-directed liver donation.

The growing experience utilizing LDLT for extended criteria HCC tumors has allowed the transplant community to consider LT as an option for other types of advanced tumors. Further expansion of LT boundaries is currently limited by organ shortages and other less common pathology; for example, unresectable colorectal liver metastasis, intrahepatic cholangiocarcinoma, rare liver metastatic tumors, etc.[49]

Two leader associations (EASL and AASLD) revised their guidelines. They continue to recommend MC as the benchmark for selection and argue that there is a lack of uniform consensus and limitations inherent to retrospective analysis. Literature findings and revised guidelines supported with these literature findings strongly encourage centers moving away from MC to carefully collect prospective data on outcomes using new criteria for selecting patients, especially for LDLT. In 2019, The Transplant Oncology Consensus Conference of ILTS working group discussed selection criteria and acceptable post-transplant outcomes for HCC patients undergoing LDLT versus DDLT. The first reported recommendation from this meeting was that the selection criterion for patients with HCC may be different in LDLT versus DDLT in selected cases, and the second recommendation was that selection of patients outside standard criteria for LDLT may use validated criteria based on AFP (<400 mg/mL) and DCP (<7.5 ng/mL) cutoffs, 18F-FDG PET nonavid tumor, and if applicable, response to locoregional therapy to ensure acceptable tumor biology. There should be no extrahepatic disease or macrovascular invasion.[45]

The indications for LDLT in HCC or for other disease states are based on the balance between risks to the living donor and benefits to the recipient which is different than DDLT. Safe donation with a low complication rate is mandatory and key for LDLT yet still we must acknowledge that LDLT is an intricate procedure. It is a complex surgery with difficult

techniques including unique physiological demands due to the regeneration of a partial liver graft. Two major problems seem to be donor safety and increased biliary complications. A worldwide survey which included 11,553 living liver donors, reported an estimated risk of donor mortality of 0.2%, transplant rate of the donor 0.04%, and overall morbidity of 24%. There are many reports from other centers that reported their complication rates including our previous center experience.[50] With growing experience and knowledge, the donor and recipient morbidity will be reduced. The goal is zero donor mortality with a low donor complication rate. Currently acceptable complication rate is < 20% for Clavien-Dindo grade 1-2, and <5% for Clavien-Dindo grade 3-4 complications.[45] Successful recipient surgery requires an adequate graft volume, sufficient portal flow, good venous outflow, and a soundbiliary reconstruction.[10]

With technical advances over the course of the past decade, LDLT may offer some advantages over DDLT. LDLT gives an important opportunity and unique chance for timely transplantation without competition from the deceased donor organ pool and with minimal waiting time.[48] A living donor graft is a dedicated gift to an intended person and so this offers an unique advantage to the specific recipient. Despite this advantage, there is no consensus on a standard limit of tumor number and size for LDLT. During the last two decades, HCC treatment with LT has improved remarkably, but there is currently no standard agreement on criteria and it varies widely among centers. There is promising hope for the future of HCC treatment with more robust clinical studies focused on prognostic biomarkers. The literature supports that LDLT has been proven to be a well-tolerated procedure and specifically expanded HCC criteria for LDLT has been proven acceptable in terms of disease-free and overall survival. New technologies to better predict outcomes and response to bridging treatments and determine tumor behavior are being incorporated into evolving criteria. LDLT is likely the best option for patients with HCC beyond MC after an adequate observation period.

Conclusion

Selection criteria remain a matter of debate for HCC treatment with LT. Building upon the contributions of published studies from centers experienced in LDLT, pioneers in LDLT continue to search for the most refined criteria for LT in HCC, including biological, pathological, radiological, genetic, and inflammatory markers of tumor behavior that affect survival and recurrence rates in addition to tumor size and number. LDLT is an attractive option to decrease waitlist times, fast-track patients for LT, and theoretically limit HCC progression without the restrictions of the deceased donor allocation system. Minimizing mortality and morbidity risk for the donor should remain paramount and the known survival benefit to the recipient and wishes of the donor should be considered for LDLT candidate selection. Since living donor grafts are not public resources, the LT community already accepts a slightly higher recurrence risk of HCC after LDLT allowing us to push the limits of the field forward with the increasing experience in living liver donor recipient surgery. Lessons learned in LDLT will likely translate into the expansion of the current criteria established as acceptable for DDLT. The continued improvements in LDLT have demonstrated remarkable parallel effects and have solidified the role of LDLT in HCC treatment.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – Y.Y.; Design – Y.Y.; Supervision – Y.Y.; Materials – Y.Y.; Data collection &/or processing – Y.Y.; Analysis and/or interpretation – Y.Y.; Literature search – Y.Y.; Writing – Y.Y.; Critical review – O.A., L.A.F.

References

1. McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of hepatocellular carcinoma. Hepatology 2021;73 Suppl 1:4–13. [CrossRef]
2. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–9. [CrossRef]
3. Bruix J, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. Hepatology 2002;35:519–24.
4. Park MS, Lee KW, Kim H, Choi YR, Hong G, Yi NJ, et al. Primary living-donor liver transplantation is not the optimal treatment choice in patients with early hepatocellular carcinoma with poor tumor biology. Transplant Proc 2017;49:1103–8. [CrossRef]
5. Starzl TE, Groth CG, Brettschneider L, Penn I, Fulginiti VA, Moon JB, et al. Orthotopic homotransplantation of the human liver. Ann Surg 1968;168:392–415. [CrossRef]
6. Bismuth H, Houssin D. Reduced-sized orthotopic liver graft in hepatic transplantation in children. Surgery 1984;95:367–70.
7. Pichlmayr R, Ringe B, Gubernatis G, Hauss J, Bunzendahl H. Transplantation of a donor's liver to 2 recipients (splitting transplantation)-a new method in the further development of segmental liver transplantation]. Langenbecks Arch Chir [Article in German] 1988;373:127–30. [CrossRef]
8. Raia S, Nery JR, Mies S. Liver transplantation from live donors. Lancet 1989;2:497. [CrossRef]
9. Strong RW, Lynch SV, Ong TH, Matsunami H, Koido Y, Balderson GA. Successful liver transplantation from a living donor to her son. N Engl J Med 1990;322:1505–7. [CrossRef]
10. Todo S, Furukawa H, Tada M; Japanese Liver Transplantation Study Group. Extending indication: role of living donor liver transplan-

tation for hepatocellular carcinoma. Liver Transpl 2007;13 Suppl 2:S48–54. [CrossRef]
11. Yokoyama I, Todo S, Iwatsuki S, Starzl TE. Liver transplantation is the treatment of primary liver cancer. Hepatogastroenterology 1990;37:188–93.
12. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology 2001;33:1394–403. [CrossRef]
13. Lee SG, Hwang S, Moon DB, Ahn CS, Kim KH, Sung KB, et al. Expanded indication criteria of living donor liver transplantation for hepatocellular carcinoma at one large-volume center. Liver Transpl 2008;14:935–45. [CrossRef]
14. Kaido T, Ogawa K, Mori A, Fujimoto Y, Ito T, Tomiyama K, et al. Usefulness of the Kyoto criteria as expanded selection criteria for liver transplantation for hepatocellular carcinoma. Surgery 2013;154:1053–60. [CrossRef]
15. Chen J, Xu X, Wu J, Ling Q, Wang K, Wang W, et al. The stratifying value of Hangzhou criteria in liver transplantation for hepatocellular carcinoma. PLoS One 2014;9:e93128. [CrossRef]
16. Kim JM, Kwon CH, Joh JW, Park JB, Lee JH, Kim GS, et al. Expanded criteria for liver transplantation in patients with hepatocellular carcinoma. Transplant Proc 2014;46:726–9. [CrossRef]
17. Akamatsu N, Sugawara Y, Kokudo N. Living-donor vs deceased-donor liver transplantation for patients with hepatocellular carcinoma. World J Hepatol 2014;6:626–31. [CrossRef]
18. Hu Z, Qian Z, Wu J, Zhou J, Zhang M, Zhou L, et al. Clinical outcomes and risk factors of hepatocellular carcinoma treated by liver transplantation: a multi-centre comparison of living donor and deceased donor transplantation. Clin Res Hepatol Gastroenterol 2016;40:315–26. [CrossRef]
19. Lee SD, Lee B, Kim SH, Joo J, Kim SK, Kim YK, et al. Proposal of new expanded selection criteria using total tumor size and (18)F-fluorodeoxyglucose - positron emission tomography/computed tomography for living donor liver transplantation in patients with hepatocellular carcinoma: The National Cancer Center Korea criteria. World J Transplant 2016;6:411–22. [CrossRef]
20. Uchiyama H, Itoh S, Yoshizumi T, Ikegami T, Harimoto N, Soejima Y, et al. Living donor liver transplantation for hepatocellular carcinoma: results of prospective patient selection by Kyushu University Criteria in 7 years. HPB (Oxford) 2017;19:1082–90. [CrossRef]
21. Goldaracena N, Gorgen A, Doyle A, Hansen BE, Tomiyama K, Zhang W, et al. Live donor liver transplantation for patients with hepatocellular carcinoma offers increased survival vs. deceased donation. J Hepatol 2019;70:666–73. [CrossRef]
22. Ince V, Akbulut S, Otan E, Ersan V, Karakas S, Sahin TT, et al. Liver transplantation for hepatocellular carcinoma: malatya experience and proposals for expanded criteria. J Gastrointest Cancer 2020;51:998–1005. Erratum in: J Gastrointest Cancer 2020.
23. Llovet JM, Pavel M, Rimola J, Diaz MA, Colmenero J, Saavedra-Perez D, et al. Pilot study of living donor liver transplantation for patients with hepatocellular carcinoma exceeding Milan Criteria (Barcelona Clinic Liver Cancer extended criteria). Liver Transpl 2018;24:369–79. [CrossRef]
24. Zheng SS, Xu X, Wu J, Chen J, Wang WL, Zhang M, et al. Liver transplantation for hepatocellular carcinoma: Hangzhou experiences. Transplantation 2008;85:1726–32. Retraction in: Transplantation 2019;103:1736. [CrossRef]
25. Sapisochin G, Goldaracena N, Laurence JM, Dib M, Barbas A, Ghanekar A, et al. The extended Toronto criteria for liver transplantation in patients with hepatocellular carcinoma: a prospective validation study. Hepatology 2016;64:2077–88. [CrossRef]
26. Shirabe K, Taketomi A, Morita K, Soejima Y, Uchiyama H, Kayashima H, et al. Comparative evaluation of expanded criteria for patients with hepatocellular carcinoma beyond the Milan criteria undergoing living-related donor liver transplantation. Clin Transplant 2011;25:E491–8. [CrossRef]
27. Azoulay D, Audureau E, Bhangui P, Belghiti J, Boillot O, Andreani P, et al. Living or brain-dead donor liver transplantation for hepatocellular carcinoma: a multicenter, western, intent-to-treat cohort study. Ann Surg 2017;266:1035–44. [CrossRef]
28. Wong TCL, Ng KKC, Fung JYY, Chan AAC, Cheung TT, Chok KSH, et al. Long-term survival outcome between living donor and deceased donor liver transplant for hepatocellular carcinoma: intention-to-treat and propensity score matching analyses. Ann Surg Oncol 2019;26:1454–62. [CrossRef]
29. Zhu B, Wang J, Li H, Chen X, Zeng Y. Living or deceased organ donors in liver transplantation for hepatocellular carcinoma: a systematic review and meta-analysis. HPB (Oxford) 2019;21:133–47.
30. Daoud A, Teeter L, Ghobrial RM, Graviss EA, Mogawer S, Sholkamy A, et al. Transplantation for hepatocellular carcinoma: is there a tumor size limit? Transplant Proc 2018;50:3577–81. [CrossRef]
31. Sugawara Y, Tamura S, Makuuchi M. Living donor liver transplantation for hepatocellular carcinoma: Tokyo University series. Dig Dis 2007;25:310–2. [CrossRef]
32. Ito T, Takada Y, Ueda M, Haga H, Maetani Y, Oike F, et al. Expansion of selection criteria for patients with hepatocellular carcinoma in living donor liver transplantation. Liver Transpl 2007;13:1637–44.
33. Jonas S, Mittler J, Pascher A, Schumacher G, Theruvath T, Benckert C, et al. Living donor liver transplantation of the right lobe for hepatocellular carcinoma in cirrhosis in a European center. Liver Transpl 2007;13:896–903. [CrossRef]
34. Todo S, Furukawa H; Japanese Study Group on Organ Transplantation. Living donor liver transplantation for adult patients with hepatocellular carcinoma: experience in Japan. Ann Surg 2004;240:451–9. [CrossRef]
35. Haberal M, Emiroglu R, Karakayali H, Moray G, Yilmaz U, Ozçay F, et al. Expanded criteria for hepatocellular carcinoma and liver transplantation. Int Surg 2007;92:110–5.
36. Shimamura T, Akamatsu N, Fujiyoshi M, Kawaguchi A, Morita S, Kawasaki S, et al; Japanese Liver Transplantation Society. Expanded living-donor liver transplantation criteria for patients

with hepatocellular carcinoma based on the Japanese nationwide survey: the 5-5-500 rule - a retrospective study. Transpl Int 2019;32:356–68. [CrossRef]

37. Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, et al; Metroticket Investigator Study Group. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol 2009;10:35–43. [CrossRef]
38. Yankol Y, Hoş G, Kanmaz T, Mecit N, Çakaloğlu Y, Kalayoğlu M, et al. Are the criteria always right? Assessment of hepatocellular carcinoma cases in living donor liver transplantation at a high-volume center. Turk J Med Sci 2021;51:2383–2395. [CrossRef]
39. DuBay D, Sandroussi C, Sandhu L, Cleary S, Guba M, Cattral MS, et al. Liver transplantation for advanced hepatocellular carcinoma using poor tumor differentiation on biopsy as an exclusion criterion. Ann Surg 2011;253:166–72. [CrossRef]
40. Mehta N, Dodge JL, Roberts JP, Hirose R, Yao FY. Alpha-fetoprotein decrease from > 1,000 to < 500 ng/mL in patients with hepatocellular carcinoma leads to improved posttransplant outcomes. Hepatology 2019;69:1193–205. [CrossRef]
41. Lorente L. New prognostic biomarkers of mortality in patients undergoing liver transplantation for hepatocellular carcinoma. World J Gastroenterol 2018;24:4230–42. [CrossRef]
42. Lee SD, Kim SH, Kim SK, Kim YK, Park SJ. Clinical impact of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in living donor liver transplantation for advanced hepatocellular carcinoma. Transplantation 2015;99:2142–9.
43. Hong G, Suh KS, Suh SW, Yoo T, Kim H, Park MS, et al. Alpha-fetoprotein and (18)F-FDG positron emission tomography predict tumor recurrence better than Milan criteria in living donor liver transplantation. J Hepatol 2016;64:852–9. [CrossRef]
44. Hwang S, Song GW, Ahn CS, Kim KH, Moon DB, Ha TY, et al. Quantitative prognostic prediction using ADV score for hepatocellular carcinoma following living donor liver transplantation. J Gastrointest Surg 2021;25:2503–15. [CrossRef]
45. Mehta N, Bhangui P, Yao FY, Mazzaferro V, Toso C, Akamatsu N, et al. Liver transplantation for hepatocellular carcinoma. Working group report from the ILTS Transplant Oncology Consensus Conference. Transplantation 2020;104:1136–42. [CrossRef]
46. Majno PE, Sarasin FP, Mentha G, Hadengue A. Primary liver resection and salvage transplantation or primary liver transplantation in patients with single, small hepatocellular carcinoma and preserved liver function: an outcome-oriented decision analysis. Hepatology 2000;31:899–906. [CrossRef]
47. Hwang S, Song GW, Ahn CS, Kim KH, Moon DB, Ha TY, et al. Salvage living donor liver transplantation for hepatocellular carcinoma recurrence after hepatectomy: quantitative prediction using ADV score. J Hepatobiliary Pancreat Sci 2021;28:1000–13. [CrossRef]
48. Suh KS, Lee HW. Liver transplantation for advanced hepatocellular carcinoma: how far can we go? Hepatic Oncol 2015;2:19–28.
49. Königsrainer A, Templin S, Capobianco I, Königsrainer I, Bitzer M, Zender L, et al. Paradigm shift in the management of irresectable colorectal liver metastases: living donor auxiliary partial orthotopic liver transplantation in combination with two-stage hepatectomy (LD-RAPID). Ann Surg 2019;270:327–32. [CrossRef]
50. Cheah YL, Simpson MA, Pomposelli JJ, Pomfret EA. Incidence of death and potentially life-threatening near-miss events in living donor hepatic lobectomy: a worldwide survey. Liver Transpl 2013;19:499–506. [CrossRef]