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Indication of Liver Transplant for HCC: Current Status and Future Directions

Julian K. Horwitz[1] · **Vatche G. Agopian**[1,2]

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Abstract

Purpose of Review Liver transplantation remains the gold-standard treatment for cirrhotic patients with early stage, surgically unresectable hepatocellular carcinoma (HCC). In this review, we describe the current state of liver transplantation (LT) for HCC.

Recent Findings We review recent advances in expanded indications for LT, diagnostics with liquid biopsy and biomarkers, and the emerging role of immunotherapy in this patient population.

Summary Although the shortage of liver allografts necessitates a restrictive HCC selection policy, future advances in patient selection, liquid biopsy technologies and systemic therapies have the potential to improve access to liver transplantation even in patients with expanded indications, without compromising on post-transplant outcomes.

Keywords HCC · Liver transplantation · Downstaging · Immunotherapy

Introduction

Liver transplantation remains the gold-standard treatment for cirrhotic patients with early-stage, surgically unresectable hepatocellular carcinoma (HCC). While historical outcomes were defined by prohibitively high recurrence and mortality rates, improved patient selection and waitlist management have dramatically improved outcomes [1–4]. Currently, approximately 16% of recipients in the United States (US) have HCC Model for End-Stage Liver Disease Model (MELD) exception points at the time of transplant [5•]. In this review, we describe the current state of liver transplantation (LT) for HCC. We specifically focus on expanded HCC indications for LT, recent advances in diagnostics with liquid biopsy and biomarkers, and the emerging role of immunotherapy in this patient population.

Epidemiology

HCC represents the most common primary liver malignancy. Globally, HCC is the fifth most common cancer and the third leading cause of cancer death [6, 7]. With an overall 5-year survival rate of approximately 18% and a case fatality ratio of > 0.9, HCC prognosis remains dismal [8]. Between 2008 and 2017, the incidence of HCC in the US has increased by 1.7% annually [9].

Due to the association between HCC and chronic liver disease/cirrhosis, the incidence of HCC varies by geographical region. Risk factors similarly vary, with hepatitis B (HBV) being the most frequent etiology in Asia, hepatitis C (HCV) in Japan, and metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) and alcohol in Europe and North America [6]. Worldwide, 70–80% of HCC cases occur in the background of hepatitis B and C [10]. With respect to HCV, the introduction of direct acting antivirals (DAAs) has significantly increased the rate of post-treatment sustained virologic response (SVR), which has been shown

✉ Vatche G. Agopian
vagopian@mednet.ucla.edu

Julian K. Horwitz
julian.horwitz@swedish.org

[1] Dumont-UCLA Transplantation Center, Department of Surgery, Division of Liver and Pancreas Transplantation, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

[2] Liver Transplantation and Hepatobiliary Surgery, Department of Surgery, David Geffen School of Medicine at UCLA, Ronald Reagan Medical Center, Los Angeles Suite 8501-B, USA

to reduce the risk of HCC [11]. However, even after achieving SVR, patients with cirrhosis continue to have a ~ 1% per year incidence of HCC [12]. Similar to HBV, MASLD and MASH-related HCC can occur in the absence of cirrhosis in 20–30% of cases [6].

Diagnosis and Staging

Among patients with cirrhosis, the annual incidence of HCC ranges from 2 to 4% [13]. HCC surveillance in this population has proven to be both cost-effective and capable of improving early tumor detection and patient survival [14, 15]. The American Association for the Study of Liver Diseases (AASLD) recommends routine screening using ultrasound and alpha-fetoprotein (AFP) every 6 months in patients with cirrhosis [16••]. For lesions ≥ 1 cm on ultrasound, further characterization with multiphasic computed tomography (CT) or magnetic resonance imaging (MRI) is recommended. In cirrhotic patients, the diagnosis of HCC can be made on the basis of cross-sectional imaging alone, using the Liver Imaging Reporting and Data System (LI-RADS) criteria [17]. A LI-RADS 5 lesion, "definitely HCC" (92–99% risk), exhibits arterial hyperenhancement and at least one of the following: venous phase "washout," ≥ 50% growth within 6 months, or capsule enhancement if ≥ 2 cm. At present, the AASLD recommends against routine biopsy for indeterminant lesions.

Pathologic staging for HCC is denoted by the American Joint Committee on Cancer (AJCC) Tumor, Node, and Metastasis (TNM) staging system [18]. However, treatment recommendations for HCC are heavily influenced by the patient's underlying liver function. Hence, clinical staging systems that incorporate both tumor burden and liver function are critical algorithm-based treatment tools. The Barcelona Clinic for Liver Cancer (BCLC) staging system is currently the most commonly used such system, and it subdivides HCC patients as: very early stage (BCLC 0), early stage (BCLC A), intermediate stage (BCLC B), advanced stage (BCLC C), and terminal stage (BCLC D) [19••].

Resection vs. Transplantation

Surgery, whether liver resection or liver transplantation, is the predominant curative-intent therapy for HCC beyond 2 cm [16••]. Thanks to advances in patient selection, both modalities achieve 5-year patient survival rates of approximately 70–80% [5•, 20]. For patients with limited tumor burden determined by morphometric tumor characteristics, well-maintained liver function, and lack of clinically significant portal hypertension, the AASLD favors resection over other treatment options [16••]. Such patients should have compensated cirrhosis without evidence of portal hypertension, such as ascites, varices, splenomegaly, low platelet count (< 100 k per μL), or a hepatic venous pressure gradient over 10 mmHg, as well as a sufficient future liver remnant to minimize the risk of post-hepatectomy liver failure [21, 22]. The main drawback of liver resection is the high 5-year recurrence rate of 50–70%, as compared to 11–18% after liver transplantation [23–25]. However, the benefit of reduced recurrence rates must be viewed in the context of liver transplant wait times due to a shortage of grafts, as well as the risk of waitlist dropout due to tumor progression while awaiting LT. Indeed, depending on donor availability, on an intention-to-treat basis, overall survival may favor surgical resection due to waitlist drop-out [26].

In the event of a recurrence following surgical resection, patients can be considered for a salvage liver transplant. Factors associated with unsalvageable recurrences include pre-operative disease beyond Milan criteria, the presence of microsatellite lesions, and microvascular invasion [27]. While some studies have shown no differences in 5-year overall survival between salvage and primary LT for HCC, a recent meta-analysis by Guerrini et al., indicated that salvage LT has slightly poorer 5-year disease-free and overall survival rates compared to primary LT [28].

Organ Allocation

In 1996, Mazzaferro et al. published their landmark paper, which demonstrated excellent outcomes after LT for HCC when using the Milan criteria: (1) single tumor ≤ 5 cm in diameter; (2) up to three tumors, each one not exceeding 3 cm; (3) no macrovascular invasion; (4) no extrahepatic involvement [29]. The Milan criteria have since been well-validated and accepted as the gold-standard selection criteria for HCC patients undergoing LT evaluation [30, 31].

The success of the Milan criteria led to a significant increase in the proportion of LT performed for HCC, aided by the MELD exception point policy beginning in 2002 [5•]. This policy was established to account for the increased rate of waitlist drop relative to physiologic MELD scores of these patients [31]. Initially, T1 tumors (one lesion < 2 cm) were awarded 24 MELD exception points, and T2 tumors (one tumor ≤ 5 cm or up to three tumors each ≤ 3 cm) were awarded 29 MELD exception points, with additional points awarded every 3 months. These scores were subsequently reduced in 2003 and then again in 2005 as new evidence suggested that HCC patients were being over-prioritized relative to their risk of waitlist dropout [32]. In 2015, the "cap and delay" policy revision was implemented, which mandated a 6-month waiting period for patients with T2 tumors prior to receiving 28 MELD exception points (capped at 34 points), thus allowing for the identification of patients with

aggressive tumor biology in order to minimize futile post-LT outcomes [33]. The MELD exception point policy was once again revised in 2019, the current policy, in order to account for geographic disparities in access to LT as well as to help curb "MELD inflation." Currently, patients within Milan criteria with an AFP below 1000 ng/mL receive three points below the median MELD at transplant (MMaT-3), based on a 150-nautical miles radius of each donor hospital [31, 34]. Initial analysis of the MMaT-3 policy suggests that it is effective at reducing over-prioritization (especially in low-MELD regions) without affecting the rate of waitlist dropout [34].

While the Milan criteria remains the accepted selection criteria for LT candidates with HCC, there are concerns that it is too restrictive, as only ~ 30% of HCC patients qualify [35]. In 2001, Yao et al. developed the UCSF criteria: one tumor ≤ 6.5 cm or up to three tumors with each tumor ≤ 4.5 cm and sum of diameter of all tumors ≤ 8 cm [36]. The UCSF criteria have been externally validated to have comparable post-transplant outcomes to the Milan criteria, and, importantly, it forms the basis of the UCSF downstaging criteria [37–39]. In addition to the UCSF criteria, multiple other expanded criteria have been proposed, although less commonly used in the US, such as the Up-to-7-criteria, total tumor volume, extended Toronto criteria, and Kyoto criteria [40–43] (Table 1).

Recurrence Prediction Models

The risk of recurrence following LT for HCC has been shown to be impacted by tumor morphology, pathologic features, and biologic and inflammatory markers [37, 44]. Although morphometric scoring systems, i.e., Milan criteria, dictate access to LT, prediction models that also incorporate biologic parameters provide additional insight into post-LT recurrence and survival and may aid in candidate selection and organ allocation [45]. Furthermore, new biomarkers, such as DCP (des-gamma-carboxyprothrombin) and AFP-L3 (AFP bound to Lens culinaris agglutinin), have recently demonstrated excellent discriminative power to predict early HCC recurrence after LT [46].

The Metroticket Model, introduced by Mazzaferro et al., uses tumor morphology and AFP levels to predict post-transplant recurrence and survival [45]. A further modification within the Metroticket 2.0 Model was the creation of an AFP-adjusted-to-HCC size criteria, defined as: HCC within the up-to-7 criteria (sum of size of largest tumor (cm) + number of tumors < 7) and AFP < 200 ng/mL; HCC within up-to-5 criteria and AFP 200–400 ng/mL; or HCC within up-to-4 criteria and AFP 400–1000 ng/mL. Patients within criteria had a 5-year overall and recurrence-free survival of 79% and 89%, respectively [45].

The Model of Recurrence after Liver Transplant (MORAL) score incorporates pre-operative neutrophil-to-lymphocyte ratio (NLR), AFP, and tumor size to generate a pre-MORAL score between 0 and 13. The highest risk patients had a 5-year recurrence free survival of 17.9% compared to 98.6% for the lowest risk group [25]. A post-MORAL score is similarly constructed using post-operative variables: tumor grade, vascular invasion status, size, and number of tumors. The combined pre- and post-MORAL score has a c-statistic of 0.91 for predicting HCC recurrence.

Next, the Risk Estimation of Tumor Recurrence After Transplant (RETREAT) score is a validated, risk stratification score based predominately on explant pathology. Patients are assigned a score between 0 and 5 based on size of the largest viable tumor, vascular invasion, and AFP. A score of 0 translates to a 5-year recurrence risk of < 3%, compared to 75% with a score of 5 [47].

Table 1 Liver transplantation criteria for HCC

Transplantation criteria		Post-LT DFS	Post-LT OS
Milian criteria [29]	• One tumor ≤ 5 cm • 2–3 tumors, each ≤ 3 cm	92% 4-year	85% 4-year
UCSF criteria [36]	• One tumor ≤ 6.5 cm • 2–3 tumors, each ≤ 4.5 cm, total tumor volume ≤ 8 cm	91% 5-year	81% 5-year
Up-to-7 criteria [40]	• Diameter of largest tumor (cm) + number of tumors ≤ 7	64% 5-year	71% 5-year
Total Tumor Volume (TTV) [41]	• Total tumor volume ≤ 115 cm^3 • AFP ≤ 400 ng/mL	68% 4-year	75% 4-year
Extended Toronto criteria [42]	• No tumor size or number limitation • No macrovascular invasion • No extrahepatic disease • Biopsy-proven well- or moderately differentiated (if beyond Milan)	30% 5-year	68% 5-year
Kyoto criteria [43]	• ≤ 10 tumors, each ≤ 5 cm • DCP ≤ 400 mAU/mL	30% 5-year	65% 5-year

HCC hepatocellular carcinoma, *AFP* α-fetoprotein, *DCP* des-γ-carboxyprothrombin, *UCSF* University of California San Francisco, *DFS* disease-free survival, *OS* overall survival

Finally, Tran et al. recently developed the REcurrent Liver cAncer Prediction ScorE (RELAPSE) model from the US Multicenter HCC Transplant Consortium (UMHTC) database. They identified maximum AFP, neutrophil–lymphocyte ratio, pathologic maximum tumor diameter, micro/macrovascular invasion, and tumor differentiation as independent risk factors for HCC recurrence, with C-statistic of 0.78 [48•]. Notably, this group, and others, is beginning to utilize machine learning algorithms (MLA) to identify new variables and improve the discriminatory ability of these models [48•, 49].

Bridging and Downstaging

Both the AASLD and International Liver Transplantation Society (ILTS) recommend using neoadjuvant locoregional therapy (LRT), i.e., bridging therapy, for liver transplant candidates with HCC expected to remain on the waitlist for at least 6 months [16••, 50]. Bridging therapy is intended to prevent disease progression and potentially reduce waitlist dropout [51, 52]. In a recent UNOS database analysis, 92.4% of eligible waitlist patients underwent LRT [52]. While the AASLD does not currently favor a particular LRT modality, transarterial chemoembolization (TACE) and ablation are the most commonly utilized; however, there has been a significant increase in the usage of transarterial radioembolization (TARE) over the past decade [52]. Of note, the lack of an AFP response to bridging LRT, even if the tumor remains within Milan criteria, portends an increased risk of post-LT recurrence [53].

For tumors that exceed the UNOS T2 criteria, UNOS recently adopted the UCSF downstaging protocol to establish the UNOS downstaging (UNOS-DS) criteria [16••, 38]. Eligible candidates should initially have either a single lesion 5.1–8 cm, two to three lesions each ≤ 5 cm with the sum of the tumor diameters ≤ 8 cm, or four to five lesions each ≤ 3 cm with the sum of the tumor diameters ≤ 8 cm (with no macrovascular and/or extrahepatic disease). Successful downstaging after LRT is defined by having residual (radiographically viable) tumor within Milan criteria and an AFP ≤ 500 ng/mL, if previously ≥ 1000 ng/mL. Patients must remain with Milan criteria for 6 months after downstaging before receiving MELD exception points [16••]. Studies have shown that > 80% of UNOS-DS criteria patients can be successfully downstaged with either TACE or TARE [54, 55••]. Although long-term overall survival appears to be slightly reduced relative to patients that were always within Milan criteria, excellent 5-year overall survival rates of 68–78% are achievable in downstaged patients [55••, 56].

Patient's beyond UNOS-DS criteria ("all-comers") who achieve downstaging to within Milan criteria have demonstrated impressive post-LT outcomes (5-year overall survival of 71%); however, waitlist outcomes remain dismal, with the 3-year waitlist dropout rate approaching 80% [57, 58]. Additionally, several studies have demonstrated acceptable long-term overall and recurrence-free survival post-LT for highly selected patients with tumor in vein (portal or hepatic vein vascular invasion) [59–61]. AFP level, response to downstaging, and the degree of macrovascular invasion are critical factors in predicting post-LT outcomes and avoiding futility in this patient population [59, 61].

Immunotherapy and Liver Transplantation

With the advent of immune checkpoint inhibitor (ICI)-based regimens for HCC, there has been an increasing interest in the role of immunotherapy in the peri-transplant setting [62]. Currently, systemic therapy is only recommended as first-line treatment in intermediate (BCLC-B, infiltrative) and advanced (BCLC-C) disease, which are beyond both Milan and UNOS-DS criteria [19••]. While the AASLD does not recommend systemic therapy as a bridging therapy, the neoadjuvant use of immunotherapy to bridge or downstage HCC patients does not preclude LT eligibility [16••, 63].

In 2007, the tyrosine kinase inhibitor (TKI) sorafenib (SHARP trial) became the first and only FDA-approved, targeted therapy for HCC, and it remained as such for over 10 years [6]. First-line therapy for advanced HCC transitioned to ICI-based regimens following the 2020 FDA approval of atezolizumab (anti-programmed death (PD) ligand 1 antibody) plus bevacizumab (anti-vascular endothelial growth factor (VEGF) antibody), based on the IMbrave150 trial [64••]. This was followed by the approval of the HIMALAYA trial combination of durvalumab (anti-PD-L1 antibody) plus tremelimumab (anti-CTLA-4 antibody), which is another 1st-line option for patients with prohibitive bleeding risk for bevacizumab [65].

Concern for increased risk of rejection and graft loss has limited the use of pre-LT immunotherapy; however, initial reports suggest that this approach can be safe if there is a sufficient period of "immunotherapy withdrawal" prior to LT [63]. Tabrizian et al. report a series of nine patients that received pre-LT nivolumab. Despite 89% of patients receiving their last dose within 4 weeks of transplant, there were no cases of severe allograft rejection or graft loss. The authors propose that intraoperative blood loss and transfusion requirements may have helped to accelerate drug elimination [66]. In contrast, in a series of five patients at UCSD that received pre-LT nivolumab, the two patients that received their last ICI dose within 3 months of transplant experienced mild-moderate rejection, including one patient that required re-transplant for massive hepatic necrosis. Based on these results, Schnickel

et al., as well as the AASLD, recommend a 3-month waiting period after the last ICI dose before proceeding with LT [16••, 67]. While data is even sparser in the post-LT setting, ICIs should be avoided due to high rates of rejection (32%) [68].

Post-Liver Transplant Management

Despite strict transplant eligibility criteria, HCC recurs in 6–18% of recipients [69]. HCC recurrence in the post-LT setting carries a poor prognosis with a median survival of 10–13 months [69, 70]. While prognostic risk scoring systems can help determine recurrence risk and guide surveillance strategies, there are no standardized risk reduction or treatment algorithms for post-LT recurrences. At present, there is no role for adjuvant therapy post-LT for HCC, and sorafenib has not been shown to improve recurrence-free survival [71].

A national survey performed by Aggarwal et al. found that 96% of transplant centers had an institutional surveillance protocol. The most common strategy involved cross-sectional imaging of the chest and abdomen as well as AFP levels every 3 months for the first year, every 6 months for the second year, and every 6–12 months for the following 3 years [72]. Sixty percent of recurrences occur within the first 2 years post-LT, which is associated with a worse prognosis compared to late recurrences [73]. The most frequent locations for HCC recurrence are extrahepatic only (50–60%), extrahepatic and intrahepatic (30–40%), and then intrahepatic only (15–40%) [69, 74].

Given the role of the adaptive immune system in the immune surveillance of HCC, post-LT immunosuppression is an important consideration [75]. Critically, calcineurin inhibitors (CNI) have been shown to increase the risk of HCC recurrence in a dose-dependent manner [76]. Conversely, mTOR inhibitors have antineoplastic properties, and they have demonstrated improved recurrence-free survival as well as post-recurrence survival in multiple cohort studies [69]. Despite these results, sirolimus failed to improve long-term overall survival (beyond 5 years) post-LT in the randomized control SiLVER trial; however, the sirolimus arm did have improved recurrence-free survival and overall survival up to 3 and 5 years post-LT, respectively [77].

Management of HCC recurrences vary depending on whether the recurrent disease is intrahepatic, extrahepatic, or disseminated [69]. For intrahepatic recurrences, surgical resection provides a clear survival benefit (median survival 21 months vs. 9 months for non-operative management); notably, studies have shown similar overall and recurrence-free survival using ablation, without the morbidity and technical challenges associated with surgical resection in a post-LT patient [78, 79]. Although there are limited data, surgical resection of extrahepatic oligo-recurrences has demonstrated a survival benefit in these patients [69, 80]. Finally, for patients with disseminated post-LT recurrences, treatment options are limited to TKIs, with some recent data suggesting improved survival with lenvatinib over sorafenib [78].

Future Considerations

Considered one of the "holy grails" of HCC research, liquid biopsy is the molecular analysis of solid tumor by-products in the bloodstream. While research regarding the utility of liquid biopsy for HCC patients undergoing LT remains nascent, available data is encouraging and supports its potential utility with regard to patient selection, waitlist management, and early detection of recurrence [81•].

The current state of liquid biopsy in liver transplantation for HCC was recently reviewed by Gonvers et al. [81•]. This group identified eight studies on circulating tumor cells (CTCs), five on circulating mRNA, five on circulating miRNA, two on extracellular vesicles (EVs), and one on circulating tumor DNA (ctDNA). The majority of these studies assessed the prognostic value of these molecular biomarkers on HCC recurrence and post-LT survival. A study by Chen et al. was able to identity pre-LT CTCs in 52% of patients, which positively correlated with tumor size, AFP level, and post-LT recurrence risk [82]. However, this was inconsistent with data from Wang et al., one of the largest studies evaluating CTCs in LT for HCC, which found only post-LT CTCs to be a significant predictor of recurrence [83]. Importantly, in addition to the detection of CTCs, phenotypic assessment as well as transcriptomic profiling of CTCs has the potential to better prognosticate post-LT outcomes in this patient population [84, 85]. Although most of the early HCC detection liquid biopsy literature is in the non-transplant population, there is promising data using both ctDNA methylation signatures and EVs [86, 87]. Sun et al. recently published their HCC EV ECG score, which utilizes three HCC EV subpopulations to detect early-stage HCC with an area under the receiver operating curve of 0.95 [87].

Conclusion

Liver transplantation remains the only curative intent therapy for early stage, unresectable HCC. Although the shortage of liver allografts necessitates a restrictive HCC selection policy, novel advances in expanded indications, liquid biopsy technologies, and systemic therapies have the potential to improve access to liver transplantation without compromising on post-transplant outcomes.

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Compliance with Ethical Standards

Competing interests The authors declare no competing interests.

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•• Of Major Importance

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