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Liver transplantation and hepatocellular carcinoma 2023: a narrative review of management and outcomes

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Background and Objective: Hepatocellular carcinoma (HCC) is a leading cause of morbidity and mortality in the United States. For certain patients, liver transplantation (LT) may be curative. The determination of which patients would benefit most from transplant and have the lowest risk of post-transplant recurrence has evolved as technology and treatments have expanded. We aim to review epidemiological changes in the HCC landscape, selection criteria for transplant, organ allocation, bridge therapies and post-transplant recurrence, and identify points for palliative care involvement.

Methods: Literature review was performed using PubMed MeSH searches in addition to reference list review. Additional information was retrieved from government regulatory and procurement organizations.

Key Content and Findings: Metabolic and alcohol-associated liver diseases have surpassed hepatitis C as the leading causes of LT over the last decade, and have also risen as the underlying conditions seen in patients with HCC requiring LT. The United Network for Organ Sharing (UNOS) coordinates organ allocation, which includes disease severity, waitlist time, blood type, and distance from donor hospital. It has progressed to incorporate treatment response and alpha-fetoprotein into its listing criteria for patients with HCC, in addition to the well-established Milan Criteria (MC, one tumor <5 cm, ≤3 tumors ≤3 cm). Therapies to bridge patients until LT include locoregional therapies as well as immunotherapy. Dropout on the waitlist is seen up to 20% either due to decompensation or progression of disease. Recurrence of HCC post-transplant remains challenging. Given this, current guidelines recommend early palliative care involvement regardless of transplant listing status for both symptom management and advance care planning.

Conclusions: For patients with HCC with favorable tumor biology, LT can be curative. However, given the symptom burden while awaiting LT and the notable number of patients who are unable to receive a transplant, early palliative care is critical in appropriate management of HCC.

Keywords: Hepatocellular carcinoma (HCC); liver transplantation (LT); palliative; downstaging; outcome

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Introduction

Background

Hepatocellular carcinoma (HCC) is the sixth most frequent tumor in the United States (US) and the fourth leading cause of death (1). HCC occurs mostly in the setting of chronic liver disease and cirrhosis, and its incidence is growing (1). Liver transplantation (LT) can be an effective treatment option for eligible patients with HCC, providing excellent post-transplant outcomes with a low risk of HCC recurrence, especially when strict criteria for patient selection and post-transplant management are followed (2).

Rationale and knowledge gap

Selection models have moved beyond simple radiographic tumor burden and now incorporate indices of tumor biology (3). As models continue to evolve, additional aspects of tumor biology, such as response to locoregional therapy (LRT), may be incorporated as the field strives to expand access to LT to those will benefit most from it (4). The demand has led to the expansion of LT for HCC beyond the Milan Criteria (MC), using down-staging (5). While the UNOS-DS (United Network for Organ Sharing-down-staging) criteria expands the indications for transplant for HCC beyond the traditional MC, there is interest in the outcomes of patients with tumor burden beyond UNOS-DS criteria (5). The upper tumor limits are yet to be determined.

Objective

The present literature review focuses on recent epidemiological trends, selection criteria, organ allocation, bridge therapies and post-transplant recurrence. We present this article in accordance with the Narrative Review reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-23-341/rc).

Methods

Information was gathered predominantly using PubMed search tools to identify studies relating to "carcinoma, hepatocellular", "liver neoplasms", "survival rate/trends", "liver transplantation", "United States", "treatment outcome". Reference lists of articles were reviewed, and relevant findings were included. Government regulated organ procurement and transplant registry websites were separately reviewed, and standardized reported data was collected and aggregated. See Methodology Table below for further information (*Table 1*).

Recent epidemiological trends

The underlying liver disease states that lead to LT have dramatically evolved over the last few decades (1). As the opioid epidemic spread across the country, the total number and proportion of patients requiring LT for hepatitis C virus (HCV) rose accordingly (6). The introduction of direct acting antiviral treatments (DAAs) to cure HCV in 2013 provided hope for many and was a pivotal moment in the fields of infectious diseases and transplant hepatology (7). As a result, the number of patients listed for LT due to HCV has continued to decline, but cases of metabolic-associated steatohepatitis (MASH, formerly non-alcoholic steatohepatitis) and alcohol-associated liver disease (ALD) have risen steadily and in 2015 surpassed HCV as the leading indications for LT (6). Disparities within this rise have emerged, most notably that by 2019, 47.7% of men without HCC listed for LT had ALD, compared to 29.4%

Table 1 Methodology table

Items	Specification
Date of search	1/14/2023
Sources	PubMed, OPTN, SRTR
Search terms used	"carcinoma, hepatocellular" [MeSH], "liver neoplasms" [MeSH], "survival rate/trends" [MeSH], "liver transplantation" [MeSH], "United States" [MeSH], "treatment outcome" [MeSH]
Timeframe	1990–2023
Inclusion and exclusion criteria	Non-English language articles were excluded
Selection process	Individual authors selected articles independently

of women. Women were more commonly listed for MASH, although ALD was still prevalent. The last decade has shown a growing body of research published on early LT for patients with acute alcohol-associated hepatitis (AH) (6,8,9).

In addition to underlying primary liver diseases, many patients listed for LT have concomitant HCC. The landscape of LT for HCC has paralleled the changes in patients transplanted for primary liver diseases. Between 2014 and 2019 there was a 22% decline in the proportion of patients listed for LT for HCV related HCC and a 14.5% increase in the proportion of patients listed for LT for MASH related HCC (6). By 2019 MASH was the most common etiology of HCC in women listed for LT (45.3%), while HCV was declining but was still the most common precipitant in men (37.8% *vs.* 31% for MASH). Racial disparities were apparent, with HCV representing a much higher burden of HCC related LT listings in Black patients compared to White and Hispanic patients, potentially indicating higher barriers to HCV treatment amongst Black patients. Among Asian patients, hepatitis B virus (HBV) was the most common etiology of HCC related LT listings, found in 47.5% of those listed for LT with HCC in 2019.

The field of LT was transformed, once again, by the COVID-19 pandemic in 2020. There was an initial decline in the total number of transplants as resources were focused on control of the pandemic. What emerged after, however, was a striking increase in the number of transplant listings for ALD, and specifically AH (6). Between November 2020 and May 2021 the percent of LTs for ALD nationwide increased steadily, and skewed towards a younger and sicker patient population as compared to the years immediately prior (6). The number of LT performed for HCC declined during that time.

Allocation of organs

The first successful LT was performed in 1967, but the National Organ Transplant Act of 1984 represents the start of the current era of transplantation (10). It established the UNOS and the registry to monitor transplant data and outcomes (11,12). UNOS allocation of LT currently considers multiple factors including disease severity, waitlist time, blood type, and distance from donor hospital. Allocation policies have evolved to decrease bias and improve post-transplant outcomes.

Initially waitlist time and whether the recipient was hospitalized determined priority, but to better emphasize illness severity the Child-Turcot-Pugh class system was implemented (12,13). In 2002 UNOS began utilizing Model for End stage Liver Disease (MELD) and in 2016 transitioned to the MELD-Na score, which incorporates serum sodium. In 2023 the MELD model was adjusted again, now accounting for sex and albumin, to decrease gender-based disparities in LT against women (12,13).

Currently in the US those patients with UNOS T1 (one tumor up to 2 cm) or UNOS T2 (one tumor up to 5 cm or three tumors up to 3 cm) are eligible to receive MELD exception points after a mandatory wait time of six months (Median Meld at Transplant minus 3-MMaT minus 3) (12). The guidelines for what makes a patient with HCC eligible for exception points, and more broadly a viable transplant candidate, have changed over time. The 1996 publication of the MC found that patients with small, unresectable HCC who underwent LT with either one tumor under 5 cm in diameter or no more than three tumors under 3 cm in diameter had a four-year 83% recurrence-free survival rate (2). This became the standard for determining which patients with HCC would have acceptable survival outcomes post-LT until further research on tumor biology and treatment responsiveness emerged.

Researchers found that patients outside of the MC but with a low alpha-fetoprotein (AFP) value had better survival outcomes post-LT than patients within the MC but with elevated AFP levels (14). An AFP level >1,000 ng/mL was found to have such poor outcomes associated with it that it became an exclusion criterion for receiving UNOS exception points, and ranges of AFP levels are now incorporated into post LT prognostication models (14).

Beginning in 2001 with the less restrictive University of California San Francisco (UCSF) criteria, increasing ranges of tumor size combinations were shown to be safe for LT (15). Studies have since demonstrated that larger, treatment responsive tumors that were able to be downstaged from UCSF criteria to Milan, or from beyond UCSF to within, have good survival outcomes post LT (4,5,14,15). By transplanting patients whose tumors are responsive to treatment, UNOS is better able to select a population that will do well post-LT. UNOS now combines downstaging data with AFP changes to provide exception points to the best possible candidates (12).

There are a variety of paths to final transplantation. Deceased donor transplants can come from donors after cardiac or after brain death. Transplanting HCV positive organs into HCV negative recipients has grown in popularity and the human immunodeficiency virus

Table 2 Selection criteria

Model/ criteria name	Year	AFP (ng/mL)/ biologic parameters	Tumor burden parameters	Overall survival	Recurrence free survival
Milan (2)	1996	N/A	Single tumor ≤5 cm or up to 3 tumors each ≤3 cm	4-year 75%	4-year 83%
UCSF (3)	2001	N/A	Single tumor ≤6.5 cm or up to 3 tumors with largest ≤4.5 cm and total tumor diameter ≤8 cm	5-year 75.2%	–
Up-to-7 (18)	2009	N/A	Sum of largest tumor size and number ≤7	5-year 71.2%	–
French AFP (19)	2012	AFP ≤100 AFP 100–1,000 AFP >1,000	Largest diameter: ≤3, 3–6, >6 cm Number of nodules: 1–3, ≥4	Score ≤2: 67.8%±3.4% Score >2: 47.5%±8.1%	Score ≤2: 8.8%±1.7% Score >2: 50.6%±10.2%
TRAIN (20)	2016	AFP slope ≥15 NLR >5	Radiographic response	<1 within Milan: 8.4% <1 outside Milan: 26% >1 within Milan: 35% >1 outside Milan: 100%	–
Metroticket 2.0 (21)	2018	AFP <200 AFP 200–400 AFP 400–1,000	Sum of tumor size and number ≤7	–	–
NYCA (22)	2018	AFP response	Tumor size: 0–3, 3–6, >6 cm Tumor number: 1, 2–3, ≥4	Low-risk: 75% Acceptable risk: 62% High-risk: 40%	Low-risk: 90% Acceptable risk: 70% High-risk: 42%

AFP, alpha-fetoprotein; N/A, not applicable; UCSF, University of California, San Francisco; NLR, neutrophil to lymphocyte ratio; NYCA, New York/California.

(HIV) Organ Policy Equity Act (HOPE Act), which passed in 2013 and was implemented in 2015, allowed for the transplantation of HIV positive organs into HIV positive recipients (16,17). Lastly, living donor transplant is becoming more common, despite a small decrease in 2020 likely due to the COVID-19 pandemic. Unfortunately, 18% of patients on the wait list for transplant in 2020 were removed from the list after becoming too sick for transplant or dying (16,17). This exemplifies the persistent fragility of this population, and the need for advance care planning and palliative care (PC) involvement regardless of transplant candidacy and even while goals are still life prolonging.

Selection criteria, risk scores, and living donor liver transplant (LDLT)

For over two decades the MC have guided patient selection for LT with low rates of recurrence and acceptable post-transplant survival (2). Despite this, many have argued that the MC are overly restrictive and lack markers of tumor biology. In 2001, Yao *et al.* proposed the University of California San Francisco criteria (single tumor ≤6.5 cm or up to 3 tumors ≤4.5 cm with total tumor diameter ≤8 cm) and demonstrated that expanding tumor burden beyond MC did not lead to worse outcomes with a 5-year survival of 75% (3).

Various expanded selection criteria based on differing tumor numbers and sizes have since been reported (see *Table 2*) (2,3,18-22). One such criteria named the "up-to-7", proposed by Mazzaferro, limits total tumor size and number to 7. In a study of >1,000 patients with HCC exceeding MC on explant pathology, those patients meeting the up-to-7 criteria had equivalent 5-year survival compared to those with MC. As the number of reported expanded selection criteria continued to increase, the so-called "Metroticket model" by Mazzaferro and colleagues suggested that

increasing tumor burden beyond MC translated into worse outcomes (21). While expanding criteria beyond MC has allowed more patients with HCC access to LT, there is a limit to what radiographic and pathologic criteria alone can safely achieve. Newer selection models incorporating markers of tumor biology are increasingly used to better select patients for transplant.

The best understood marker of HCC is AFP, which is highly associated with pathologic characteristics and decreased survival in patients with HCC (23). Various upper AFP limits have been suggested above which patients should be excluded from transplant, with AFP >1,000 ng/mL having been shown in multiple studies to be one of the strongest predictors of poor outcomes (24). In addition to the absolute AFP, there is evidence that the dynamic change of AFP, such as a rapidly increasing AFP pre-transplant, is a poor prognostic indicator in HCC patients undergoing transplant (22). Given this, it is no surprise that combining both radiographic tumor burden with AFP has been crucial in developing selection criteria for patients beyond traditional MC.

In 2012, the French AFP model was reported incorporating AFP, as it independently predicted tumor recurrence and correlated with vascular invasion (19). The model combined tumor size (up to 3, 3–6, and >6 cm), number of masses, and AFP. It demonstrated a better ability to predict HCC recurrence than MC alone, and showed acceptable outcomes in certain patients beyond MC but with an AFP ≤100 ng/mL. Mazzaferro *et al.* created the Metroticket 2.0 model in 2018, incorporating AFP into the original up-to-7 criteria (21). This second Metroticket model demonstrated that as AFP increased, lower tumor burden is needed to achieve excellent outcomes (i.e., up-to-7 if AFP <200 ng/mL, up-to-5 if AFP 200–400 ng/mL, and up-to-4 if AFP 400–1,000 ng/mL). More recently, the New York/California (NYCA) score was developed using the dynamic AFP response between the maximum and final pretransplant AFP, as this response was shown to predict outcomes (4). The AFP response was combined with tumor number and size to create the NYCA score which outperformed the MC and French AFP models in predicting HCC recurrence. This model was recently validated and the authors concluded that incorporating AFP response into selection criteria allows for safe expansion beyond MC, offering LT to patients who might be otherwise be denied LT (22). Selection models have moved beyond simple radiographic tumor burden and now incorporate indices of tumor biology. As models continue to evolve, additional aspects of tumor biology, such as response to LRT, may be incorporated as the field strives to expand access to LT to those will benefit most from it.

For patients with HCC, LDLT is an attractive alternative to waiting for a suitable deceased donor liver transplant (DDLT). While the initial study comparing outcomes of LDLT to DDLT for HCC showed higher HCC recurrence in the LDLT group, more recent studies have demonstrated similar post-transplant outcomes (25,26). Several recent analyses have shown the clear benefit of LDLT for HCC including a superior 5-year intention-to-treat survival of 68% for LDLT *vs.* 57% for DDLT, as well as significant reduction in the dropout risk, indicating it should be utilized more often (27,28). Transplantation for advanced HCC beyond MC is more suitable for LDLT, as opposed to DDLT, where the scarcity of organs requires allocation to those with optimal expected survival. A recent study from India described an experience with LDLT for HCC in patients who had undergone downstaging of portal vein tumor thrombosis, which otherwise carries a dismal prognosis (29). In total, 25 patients with portal vein tumor thrombosis were successfully downstaged after treatment with stereotactic body radiation and transarterial chemo- or radio-embolization (TACE or TARE). The 5-year overall and recurrence-free survival was 57% and 51%, respectively, comparable to survival in patients undergoing LDLT without portal vein thrombosis. This report highlights the evolving role that LDLT plays in the treatment of HCC.

Bridge therapy, response and waiting time

Management of patient with HCC on the waiting list aims to avoid disease progression. There is a lack of randomized controlled trials (RCTs) recommending neo-adjuvant therapies to reduce drop out risk due to tumor progression. An international consensus conference in 2012 reported no benefit for bridge therapy in patients with UNOS T1 tumors, but it might be appropriate for UNOS T2 lesions if their transplant wait time was expected to be six months or longer (30). However, the optimal bridge therapy has yet to be reported and is guided by multi-disciplinary tumor boards with most patients receiving one LRT prior to transplant. Many options exist including trans-arterial chemoembolization, trans-arterial radioembolization also known as y90, thermal ablation, resection, systemic therapy, radiation, and immunotherapy (31-41). Bridge therapy is being utilized significantly more in the modern era. Kwong *et al.* recently reported an analysis of over 20,000

liver transplant candidates with HCC exception points and found the proportion of patients receiving at least one LRT increased to 92% in the year 2018 compared to 42% in 2003 (42). In that study, TACE was still the most utilized therapy (50% in 2018) while thermal ablation accounted for 22%. Furthermore, y90 increased significantly over the time period, comprising 19% of LRT in 2018 compared to less than five percent in 2013 (42).

A phase 2 trial from Salem *et al.* found that in patients with HCC Barcelona Clinic Liver Cancer (BCLC) Stage A or B, treatment with radioembolization y90 significantly prolongs time to progression compared to TACE (26 *vs.* 6.8 months; P=0.002) (33). Of the patients listed for LT, those receiving y90 had a transplant rate of 87% *vs.* 70% for TACE. This trial proposed that y90 may reduce waitlist drop out, and thus has changed practice for this institution (Northwestern) (34). Furthermore, Kim *et al.* recently reported on the RASER trial which was a single center study evaluating the efficacy of y90 in 29 patients with early-stage HCC <3 cm not amenable to ablation (43). The trial found a complete tumor response in 83% of patients and a partial response of 17% by mRECIST criteria. The authors concluded that y90 was successful and well tolerated with a low complication rate in patients with early-stage HCC when ablation was not favorable based on tumor location. The LEGACY study by Salem *et al.* studied 162 patients with solitary HCC <8 cm to assess selective radioembolization with y90 to the tumor bearing hepatic segment termed "radiation segmentectomy" rather than traditional lobar y90 infusion (44). Radioembolization was performed in 21% of patients prior to LT with a median follow up 30 months. For the entire cohort, the objective response rate was 88% with 66% of patients exhibiting duration of response >6 months and a three-year overall survival of 93% in patients undergoing LT. Complete pathological necrosis was achieved when the dose exceeded 400 Gy arguing that this should be the "threshold" dose.

In the recent 2022 update of the BCLC Treatment algorithm for LT candidates with wait time of greater than six months; ablation, TACE or y90 can all be used for bridging (45). In addition, the new version stratifies with the goal of getting more patients to transplant including small multifocal HCC and subgroup of BCLC B patients who were successfully downstaged to within MC. For BCLC-0 and A patients who are not LT candidates, ablation is the preferred approach (45). Bridge therapies also are tailored to the specific number of tumors, location of the tumor and their relationship to major vascular and biliary structures. Practice patterns are driven by tumor characteristics as previously mentioned but also are influenced by institutional practice.

With respect to wait time, the optimal time from HCC diagnosis to transplant has yet to be elucidated. Time to transplant is a double-edged sword as rapid movement to transplant may result in transplanting aggressive tumors that have not yet had their biology tested and thus are susceptible to increased recurrence. Whereas prolonged wait time is associated with dropout from the LT wait list, reported up to 20% in the literature at one year. Halazun *et al.* analyzed 6,160 HCC patients from the UNOS database undergoing LT and found that patients transplanted in regions with short wait times (median 1.6 months) was an independent predictor of poor overall survival (HR 1.55, P<0.0001) (46). Mehta *et al.* analyzed 911 patients undergoing LT from three centers in the US with short, medium, long wait times with the goal of finding a "sweet-spot" (47). In their study, wait list dropout was 18% at 11.3 months, and they found that patients with very short wait times (<6 months) or very long (>18 months) were associated with an increased risk of HCC recurrence (HR 1.60, P=0.043) (47). As we move forward to find the optimal wait time, the literature must harmonize and come to a consensus as to whether HCC diagnosis is the first time point or is it the time of listing at a transplant center. Inevitably there is a time lapse as to when patients are diagnosed and then referred and then listed at a transplant center.

Response to bridge therapy can be variable and criteria used to evaluate response to treatment are of upmost importance. Regardless of the LRT chosen, data show that complete pathologic response (cPR) and degree of tumor necrosis on explant review is associated with reduced recurrence and improved survival (48). In an analysis from the US Multicenter HCC Transplant Consortium, DiNorcia *et al.* found that of 3,439 patients undergoing LT, 23% had cPR and these patients had significantly lower 1 and 5-year incidence of HCC recurrence (1.3% and 5.2%) and improved 1 and 5-year survival rates (92% and 75%) compared to those patients who did not achieve cPR (48). Interestingly, short wait time patients and those receiving more than three LRT were less likely to achieve cPR.

The first criteria to evaluate response to treatment was the response evaluation criteria in solid tumors (RECIST) where a complete response was the disappearance of all target lesions (49). The RECIST criteria was then "modified" to mRECIST where a complete response is the disappearance

of any intra-tumoral arterial enhancement (50). Uniform agreement on which criteria to evaluate tumor response is important to provide homogeneity in the literature. The European Association for the Study of the Liver (EASL) criteria has also been used which takes into account tumor necrosis and has a similar concept as mRECIST with respect to tumor viability and uptake of contrast by the tumor on arterial phase CT or MRI (51).

Downstaging *vs.* all-comers

The percentage of LT performed for HCC continues to rise resulting in an increased number of HCC patients on the waiting list (52). This demand has led to the expansion of LT for HCC beyond the MC, using down-staging. Tumor down-staging utilizes LRT to treat HCC with initial tumor burden exceeding MC to within acceptable LT criteria. Radiographic response to LRT is a marker of favorable tumor biology while tumor progression implies aggressive tumor biology and higher post-LT HCC recurrence (53). Down-staging aims to select a subset of patients with response to LRT who will do well following LT. Down-staging has been proven to be an effective bridge to LT. In 2015, the UCSF group published their single-center experience using a down-staging protocol and found that those successfully down-staged to within MC had outcomes similar to those always within MC with a 5-year post-LT survival of 78% (54). In 2017, UNOS and the Organ Procurement and Transplantation Network (OPTN) formally adopted the UCSF/Region 5 down-staging protocol (UNOS-DS). Patients meeting these criteria who are successfully down-staged to within MC receive automatic exception points after a 6-month waiting period (55). These criteria were validated in a large multicenter study as well as UNOS database study again showing similar outcomes for patients down-staged to within MC as compared to those always within MC (56). More recently, the first and only multicenter prospective study on tumor-downstaging based on the UNOS-DS protocol from the MERITS-LT consortium, comprising of seven centers from four UNOS regions, demonstrated a >80% probability of successful down-staging with a 2-year HCC recurrence of 7.9% (57). The Italian XXL trial was the first RCT of down-staging in which patients with HCC beyond MC were randomized to either LT or further LRT with systemic therapy. The trial's LT group had superior tumor-free and overall survival compared to the control group (5-year survival 77% *vs.* 31%), concluding that downstaging-tumor response could contribute to expanding HCC transplant criteria (58).

While the UNOS-DS criteria expands the indications for transplant for HCC beyond the traditional MC, there is interest in the outcomes of patients with tumor burden beyond UNOS-DS criteria. Patients with tumor burden beyond MC who respond to LRT may have superior survival after LT in comparison to other available treatments. The all-comers down-staging (AC-DS) protocol goes beyond the UNOS-DS criteria with no upfront limit on initial tumor burden. The UCSF group's all-comers experience reported 80% probability of dropout at 3- and 5-year intention-to-treat survival of only 21% (59). Two recent UNOS database studies similarly demonstrated poor outcomes associated with all-comers—including inferior 3-year post-LT survival and high dropout rates after successful DS (57,60). Taken together, these data suggest there is likely a tumor burden limit beyond which down-staging is unlikely to be successful and that all-comers should be carefully selected for transplant.

Similar to patients with significant tumor burden, those with macrovascular invasion of the hepatic or portal veins have limited treatment options and are excluded from both the UNOS-DS and AC-DS protocols. However, LRT can be used to achieve a radiological regression of vascular invasion potentially allowing for a safe window for transplant, similar to the principles of down-staging. Assalino *et al.* conducted a multicenter study of HCC patients transplanted after a complete radiologic regression and reported acceptable 5-year survival of 60%. Recurrence rates were 27% however, a subset of patients with pretransplant AFP <10 ng/mL had favorable post-transplant recurrence of 11% (61). Soin *et al.* reported acceptable survival rates in patients with PVTT with LDLT after successful down-staging with a 5-year survival of 57% (29).

Recurrence: predictors, prevention, and therapy

Despite the implementation of strict criteria, HCC recurrence post LT remains up to 20%, occurring mostly within 2–3 years post LT (5). In a large multicenter study, the median time to recurrence was 17 months and the rates of recurrence were 5.1% at 1 year, 14.3% at 5 years, and 16.4% at 10 years (5). The probability of HCC recurrence was 11.3% at 5 years after LT and 13.3% at 10 years after LT for the MC group (at diagnosis), 19.1% at 5 years and 20.6% at 10 years for the downstaged group (at LT), and 38.9% at 5 years and 41.4% at 10 years for the patients who

Table 3 Main selection criteria used for selecting patients with HCC and cirrhosis for LT

Based on	Donation type	Name	Criteria
Radiology	DD	Milan (2)	Solitary tumor ≤5 cm or up to 3 tumors, each one ≤3 cm
		UCSF (3)	Solitary tumor ≤6.5 cm or up to 3 tumors, each one ≤4.5 cm and total sum ≤8 cm
		Up to seven (18)	Total sum ≤7 cm
	LD	5-5 rule (62)	Up to 5 tumors and total sum ≤5 cm
		AMC (63)	Up to 5 tumors and largest tumor ≤5 cm
Biomarker	LD	MORAL (64)	Calculation based upon AFP and PIVKA II
Radiology, biomarker	DD	AFP (19)	Combined AFP levels, size and number of tumors to create a score
		Metroticket 2.0 (21)	If AFP <200 ng/mL than total sum ≤7 cm
			If 200≤ AFP <400 ng/mL than total sum ≤5 cm
			If AFP ≥400 ng/mL than total sum ≤4 cm
		Pre-MORAL (65)	Combined AFP levels, NLR and largest tumor size to create a score
		NYCA (4)	Tumor # and size of largest tumor
			AFP (max and final)
	LD	Kyushu (66)	Largest tumor ≤5 cm or PIVKA II ≤300 mAU/mL
		Kyoto (67)	Up to 10 tumors and largest tumor ≤5 cm and PIVKA II ≤400 mAU/mL
		SMC (68)	Up to 7 tumors and largest tumor ≤6 cm and AFP ≤1,000 ng/mL
		5-5-500 Rule (69)	Up to 5 tumors and largest tumor ≤5 cm and AFP ≤500 ng/mL
Radiology, biomarker, pathology	DD	RETREAT (70)	Combined AFP levels, total sum of tumor and micro VI to create a score
Clinical, radiology, pathology	DD	Extended Toronto (71)	Without systemic symptoms, without macro VI, without extrahepatic disease, and if beyond Milan not poorly differentiated

HCC, hepatocellular carcinoma; LT, liver transplant; DD, deceased donor; LD, living donor; UCSF, University of California, San Francisco; AMC, Asan Medical Center; MORAL, model of recurrence after liver transplant; AFP alpha fetoprotein; PIVKA II, Prothrombin induced by vitamin K absence II; NLR, neutrophil to lymphocyte ratio; NYCA, New York/California; SMC, Samsung Medical Center; RETREAT, risk estimation of tumor recurrence after transplant; VI, vascular invasion.

failed downstaging 14. PreLT predictors of recurrence were tumor burden (beyond MC at diagnosis), number of LRT >2, and AFP >20 ng/mL at transplantation (5).

Early recurrence, defined as <2 years is associated with a significantly worse prognosis (5). Liver-only recurrence occurs in 15–40%; extrahepatic disease is likely due to growth of occult metastases. Various risk factors have been described leading to pre- and post-LT scoring systems. *Table 3* summarizes scoring systems including tumor burden and serum biomarkers (2-4,18,19,21,62-71). Serum biomarkers, both static or dynamic such as AFP, neutrophil/Lymphocyte ratio NLR, AFP L3% and s-gamma-carboxyprothrombin have been identified. Disease burden may not necessarily be associated with tumor biology. Numerous studies have shown that AFP responders to LRT consistently had superior post LT outcomes (48). The most important characteristics on explant pathology were micro- and macrovascular invasion, satellite lesions and tumor differentiation.

Given the LT recurrence risk, post LT surveillance offers early identification and treatment and the ability to offer potential curative therapies (70). A surveillance strategy should include cross section imaging of the abdomen such as contrast enhanced computer tomography (CT) or magnetic resonance imaging (MRI) and non-contrast CT for the lungs. Other sites of metastases, such as bones or

brain, should be investigated if clinical suspicion is high. AFP seems to be the only biomarker proved to be efficient to monitor during surveillance and usually is measured every 6 months. To date, there are no standardized surveillance protocols. A minimal surveillance of at least 3 years has been proposed with no difference in RFS between patients undergoing 3 *vs.* 6 months interval follow up scans (70). The UCSF team proposed a surveillance strategy based on RETREAT score (including microvascular invasion, serum AFP at LT, and diameter of the largest nodule plus the total number of nodules on the explant liver) (70). The scoring ranges from no surveillance for patients with a RETREAT score of 0 (based on 3% 5-year rate of recurrence), surveillance every 6 months for 2 years for patients with a RETREAT score of 1–3, surveillance every 6 months for 5 years for patients with a RETREAT score of 4, and surveillance every 3–4 months for 2 years followed by every 6 months for years 2–5 for patients with a RETREAT score of 5 or more. Additional biomarkers such as AFP-L3% and DCP must be validated for monitoring for post LT recurrence.

The influence of immunosuppression on HCC recurrence after LT has been a topic of debate. Some studies suggest that immunosuppression may increase the risk of HCC recurrence by promoting tumor growth and inhibiting the immune system's ability to detect and eliminate cancer cells. Calcineurin inhibitor (CNI) exposure is associated with an increased risk of recurrence and is dose dependent (72). Mammalian target of rapamycin (mTOR) is upregulated in several mutations found in HCC, and when found is considered as a marker of aggressive cancer. MTOR inhibitors (mTORi) have anti-angiogenic and anti-proliferative effects in such cases (73). In several retrospective studies and meta-analyses, mTORi showed a reduction in recurrence and increased survivability, 13.8% *vs.* 8.0%, P<0.001 (74). In an RCT, mTORi were compared to non mTORi immunosuppression; the authors demonstrated a slight advantage in recurrence free survival in the first 3–5 years that disappeared with time. The International Liver Transplantation Society, in its Transplant Oncology Consensus Conference recommended levels of lower than 10 ng/mL for tacrolimus and lower than 300 ng/mL for cyclosporine.

The advent of DAA therapy has raised concerns about the possible adverse effects of DAA on the recurrence and aggressiveness of HCC, but these concerns have proven unfounded. A large retrospective multi-institutional study including nearly 800 patients showed similar overall (HR 0.9) and early HCC recurrence (HR 0.96) in patients receiving DAA and in those who did not (7). A follow-up study in the same cohort reported a significant reduction in risk of death (HR 0.54) in patients treated with DAA (75).

Management of patients with recurrent HCC after LT draws some parallels to management of primary LT, with a clear benefit of treatment modalities with curative intent (5). Therapeutic options post LT differ with the location and extent of recurrence and so does survivability. In a series of 106 patients treated for recurrence of HCC after LT the highest survival rate at 3 years was achieved in the surgery alone group (60%), followed by the group with combined surgical and non-surgical treatment (37%), and non-surgical treatment (11%) (76). In a large retrospective study, recipients who underwent surgical treatment for their recurrence achieved a median survival of 31.6 months (5). A subgroup of patients with isolated and favorable tumor biology would benefit from resection. Patients receiving surgical treatment for recurrence had generally favorable recurrent tumor characteristics. Resections performed were mostly for solitary [70 (69.3%)] and extrahepatic [90 (89.1%)] tumors, with an AFP <200 ng/mL [71 (73.2%)] at the time of recurrence (5).

In a large study of 661 patients resected for HCC. Fifty-six (16%) of patients with recurrent HCC were listed for LT and 63% ultimately transplanted with 23% drop out due to tumor progression (77). Salvage LT (SLT) is another proposed curative therapy for patients with HCC recurrence post liver resection (rate 70% at 5 years) (78). The long-term oncologic outcomes remain unclear. An intention to treat analysis of 110 patients demonstrated a 5-year ITT OS of 69% and disease-free survival of 60%. The SLT strategy was successful in 56% of patients. It seems that the outcomes of salvage transplantation for recurrent HCC after hepatic resection are, at least, comparable to the results of primary transplantation for HCC even when examined on an intention-to-treat basis.

For patients with unresectable recurrent HCC after LT, LRT has been considered as a potential treatment modality—however, there is scant published data. Systemic therapy has a limited use in recurrence of HCC after LT. Sorafenib, a multi-kinase inhibitor showed a median survival of 10.6 months compared with 2.2 months for supportive care (79). Regorafenib, another multi-kinase inhibitor, is used as a second line treatment and provides median survival of 13.1 *vs.* 5.5 months (80). All of the patients in that trial (n=25) suffered from at least one adverse event. Metronomic capecitabine has the same safety profile as

sorafenib and compared to best supportive care showed increased median OS of 22 *vs.* 7 months, P<0.01 (79).

The use of immunotherapy for the treatment of HCC recurrence is a topic of ongoing research. While immunotherapy has shown promising results in the treatment of advanced HCC, in the setting of LT, it may interfere with immune tolerance against the transplanted liver. In review of the literature, reported graft rejection rates range from 25–54%, with relatively rapid development of graft rejection in patients who did develop it (81). Further research is needed to determine the optimal timing, dosing, and patient selection for immunotherapy in the post-transplant setting.

Future directions

An evolving area of interest is molecular testing in HCC. Genomic assays of HCC have demonstrated several key signaling pathways and signatures associated with HCC progression and survival (82). Such markers will most likely be incorporated into future prognostic scoring system.

A new diagnostic tool known as "liquid biopsy" has emerged over the past few years (83). Circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) are cornerstones of liquid biopsy (83).

In view of certain limitations of traditional imaging and reporting methods, radiomics has emerged as a burgeoning technology that could transform potential pathological and physiological information from routine-acquired images into high-dimensional quantitative and mineable imaging data (84). It has already been demonstrating great potential in the diagnosis, classification and staging, clinical decision assistance, and prognosis and survival predictions of HCC (84).

Immunotherapy has revolutionized the treatment of advanced HCC over the past few years (85). Improved outcomes have been demonstrated in the use of neoadjuvant therapy from early phase trials in various solid tumor types. Several phase 2 trials have shown excellent pathologic response in a resection cohort (86). Early experience with immunotherapy in the pre-LT setting has been discouraged due to scattered reports of severe rejection and graft loss (87). Encouraging data based on case reports and case series have been recently published demonstrating acceptable risk with excellent pathologic response (41). Further investigation is needed to evaluate patient selection, minimal washout and observation period between the last drug dose and transplantation.

HCC diagnosis occurs at advanced stages in nearly two thirds where treatment is ineffective or often delayed. Dropout rates on the wait list due to tumor progression are up to 30%. In addition, quality of life (QoL) is impaired due to symptoms from high tumor burden and psychological distress (88). A recent pilot RCT at an academic center demonstrated that outpatient PC interventions within routine HCC care is feasible and potentially improve QoL and symptoms (89). PC is underutilized for HCC patients and frequently delayed due to inadequate resources, lack of education for non-PC providers and inadequate modeling for integration of PC within liver clinics. A larger study must be explored to understand the benefit of early incorporation of PC in patients undergoing LT with HCC.

Strengths and limitations

This review represents a comprehensive compilation and evaluation of relevant literature and governing body guidelines, as interpreted by experts in the fields of transplant hepatology and surgery. We have included the history of the topic, when relevant, to provide readers with insight into the evolution of transplantation. Despite this, we are unable to fully capture the nuanced decisions that go into individualized patient treatment plans. We also deferred a detailed description of UNOS organ allocation algorithms which are beyond the scope of this review.

Conclusions

LT is the optimal treatment for patients with early-stage HCC. The landscape of LT for HCC has paralleled the changes in patients transplanted for primary liver diseases. The increasing demand for LT for HCC has led to continued efforts to expand LT indications for HCC. Down-staging to within MC provides acceptable long-term survival and UNOS-DS criteria are now accepted national policy. Centers need to be highly selective when pursuing LT for these patients. Implementation of various risk models based on pre- and post-LT risk factors have enabled the classification of patients into low and high-risk groups. The role of immunosuppressive regimens using mTORi in the prevention of recurrence after LT remains controversial. Efforts are needed to identify consistent prognostic biomarkers before and after LT. Improved imaging techniques are needed to define response ahead of pathologic assessments and oncologic outcomes. The use of pre-LT immunotherapy, although encouraging, needs to be

further explored.

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