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COMPREHENSIVE REVIEW

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Liver transplantation for hepatocellular carcinoma: Management after the transplant

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Hepatocellular carcinoma (HCC) is an increasingly common indication for liver transplantation (LT) in the United States and in many parts of the world. In the last decade, significant work has been done to better understand how to risk stratify LT candidates for recurrence of HCC following transplant using a combination of biomarker and imaging findings. However, despite the high frequency of HCC in the LT population, guidance regarding posttransplant management is lacking. In particular, there is no current evidence to support specific post-LT surveillance strategies, leading to significant heterogeneity in practices. In addition, there are no current recommendations regarding recurrence prevention, including immunosuppression regimen or secondary prevention with adjuvant chemotherapy. Finally, guidance on treatment of disease recurrence is also lacking and there is significant controversy about the use of immunotherapy in transplant recipients due to the risk of rejection. Thus, outcomes for patients with recurrence are poor. This paper therefore provides a comprehensive review of the current literature on post-LT management of patients with HCC and identifies gaps in our current knowledge that are in urgent need of further investigation.

KEYWORDS

clinical research, hepatology, cancer, malignancy, neoplasia, liver disease: malignant, practice, liver transplantation

Abbreviations: ^{18}F-FDG PET/CT, ^{18}F-fluorodeoxygluclose positron emission tomography/CT; AFP, alpha-fetoprotein; CNI, calcineurin inhibitor; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; DCP, des-gamma-carboxyprothrombin; HCC, hepatocellular carcinoma; LRT, local regional therapy; LT, liver transplantation; mTOR, mammalian target of rapamycin; MVI, microvascular invasion; NLR, neutrophil/lymphocyte ratio; PD-1/PDL-1, death protein 1/programmed death ligand 1; TACE, transcatheter arterial chemoembolization; UCSF, University of California San Francisco; VEGF, vascular endothelial growth factor; Y-90, Yttrium-90 microspheres.

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1 | INTRODUCTION

In this era of rising hepatocellular carcinoma (HCC) incidence, HCC is an increasingly common indication for liver transplantation (LT). In 2015, HCC was the indication for 24% of liver transplant registrants and 27% of liver transplants, rendering it the most common reason for LT and waitlist additions, regardless of underlying etiology.[1]

LT began to evolve as a therapy for HCC when the incidental finding of small HCC in explanted livers was not found to alter outcomes as compared to explants without HCC.[2] The landmark study by Mazzaferro in 1996 then established LT as an effective treatment for early HCC defined by the Milan Criteria (one lesion ≤5 cm or 3 lesions all ≤3 cm without evidence of vascular invasion or extrahepatic spread).[3] Survival following LT for HCC has improved over time with advances in care and is similar to that of nonmalignant indications.[4-8]

Though LT for HCC is a highly effective cure for early stage disease, guidance regarding tailored posttransplant management of this unique population to optimize outcomes is lacking. Given the heterogeneity of HCC burden and tumor biology seen in patients that present for transplantation, it is essential for transplant providers to consider the unique features of a given patient's HCC when devising their posttransplant management plan. This paper aims to comprehensively review the current literature on posttransplant management of patients with HCC, as well as identify gaps in our current knowledge that are in urgent need of further investigation.

2 | HCC RECURRENCE: MAGNITUDE OF THE PROBLEM

Although LT provides an excellent treatment option for long-term survival in selected patients with HCC, posttransplant HCC recurrence is an important negative predictor of posttransplant survival. In the initial study by Mazzaferro and colleagues evaluating the role of LT in cirrhotic patients with small unresectable HCC, 8% of patients experienced HCC recurrence by 4 years after LT.[3] Subsequently, studies focused on patients within Milan criteria using pretransplant data have described posttransplant recurrence in approximately 10%-16% of patients.[9-11] A 2015 systematic review including a heterogeneous group of 61 studies demonstrated a mean rate of HCC recurrence of 16% and mean time from transplant to HCC recurrence of 13 months (range 2-132 months).[12] Of note, nearly 51% of LT recipients in this review were ultimately classified as beyond Milan based upon examination of explant pathology. Notably, as many centers worldwide transplant patients with HCC that are beyond Milan criteria, the magnitude of HCC recurrence may be larger than proposed by these estimates.

3 | PREDICTION OF HCC RECURRENCE

Multiple tumor related factors have been identified to predict the risk of HCC recurrence after LT, and these factors have been incorporated in a number of proposed pre-LT and post-LT prognostic models (Tables 1 and 2).

3.1 | Well-established pretransplant factors predicting HCC recurrence

3.1.1 | Radiographic tumor burden

Traditionally, radiographic tumor diameter and number of tumor nodules have been used as criteria determining eligibility for LT, based on the observation that these morphologic parameters are associated with microvascular invasion (MVI) and HCC recurrence after LT. The Milan criteria[3] have been incorporated into the United Network for Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) policy for priority listing with model end-stage liver disease (MELD)-exception for LT since 2002 (modified as UNOS T2 criteria). Modest expansion of the upper limits of tumor burden, including the University of California San Francisco (UCSF) criteria[24,25] and the "up-to-7" criteria,[26] have resulted in survival only slightly below that using Milan criteria. Further expansion of tumor criteria would result in significantly reduced posttransplant survival, as illustrated in the "Metro-ticket" paradigm of "the further the distance, the higher the price."[26] The decision regarding expansion of transplant tumor criteria must be governed by the ability to achieve a minimal survival threshold to justify expansion and not cause harm to non-HCC patients on the waiting list.[3,27]

A strategy combining tumor burden with assessment of response to local regional therapy (LRT) over time as a marker of favorable tumor biology has gained broader acceptance. Patients who exhibit tumor progression despite LRT have significantly worse post-LT outcomes when compared to those who demonstrate treatment response or stable disease following LRT.[28-30] Down-staging represents a structured approach that aims at merging tumor morphologic parameters with objective and sustained response to LRT[31] as an additional risk stratification tool. This approach is supported by the observation that post-LT survival outcomes in those who have been successfully down-staged to conventional Milan criteria and are not significant different than those who meet Milan criteria at presentation.[31] In an effort to standardize criteria for down-staging of HCC prior to LT, OPTN/UNOS recently adopted the UCSF/Region 5 down-staging protocol with specific inclusion criteria[31,32] as a new national policy for granting automatic MELD exception for LT. Initial tumor burden beyond these criteria have been suggested to have an adverse impact on both the probability of successful down-staging[33] and worse post-LT survival.[34] It has been suggested that there is a strong correlation between the initial tumor burden assessed by the sum of the largest tumor diameter and the probability of successful down-staging to within Milan criteria.[33] Furthermore, extending the initial tumor burden beyond the current UNOS down-staging inclusion criteria is associated with a significantly worse 3-year post-LT survival in an analysis of UNOS data.[34]

TABLE 1 Summary of proposed pretransplant selection models (selected)[a]

Pre-LT selection model	Tumor burden	Biomarker(s)	Additional criteria	5-y post-LT overall survival	AUROC
US National Policy[13]	Milan or down-staged to Milan	AFP >1000 ng/mL reduced to <500		80%	
French AFP Model[14]	Size and number (lowest risk: largest tumor ≤3 cm and ≤3 tumors)	AFP (lowest risk: ≤100 ng/mL)		68% if risk score ≤2% vs 47% if risk score >2	0.7
Metro-Ticket 2.0[15]	Tumor number + size of largest tumor	AFP			0.72
TTV-AFP Model[16]	Total tumor volume ≤115 cm^3	AFP ≤400 ng/mL		75% (at 4 y) for those >Milan but within TTV-AFP	0.8
Extended Toronto Criteria (ETC)[17]	No upper limits		(1) Biopsy of largest tumor: poorly differentiated tumors excluded (2) No cancer-related symptoms	68% for those >Milan but within ETC	
Pre-MORAL[18]	Largest tumor size (lowest risk: ≤3 cm)	AFP (lowest risk: <200 ng/mL)	NLR (lower risk <5)	5-yr RFS: 99% low-risk 70% medium-risk 56% high-risk	0.82
HALT-HCC[19]	Hypotenuse between tumor number & largest tumor size[b]	lnAFP	MELD-Na		0.61
NYCA Score[20]	Tumor number + size of largest tumor	AFP response to treatment		Low-risk 75%, acceptable-risk 62%, high-risk 40%	0.73

AFP, alpha-fetoprotein; LT, liver transplantation; MELD, model end-stage liver disease; NLR, neutrophil/lymphocyte ratio; RFS, relapse-free survival.

[a]Proposed criteria based on living donor liver transplant are not included.

[b]By Pythagorean Theorem ($A^2 + B^2 = C^2$); eg, a patient with 3 lesions with largest 4 cm would receive tumor burden score of 5.

TABLE 2 Summary of proposed posttransplant prognostic models (selected)[a]

Post-LT prognostic model	Tumor burden	Biomarker(s)	Other histologic features	5-y recurrence risk/survival	AUROC
RETREAT[21]	Sum of largest viable tumor diameter and number of viable tumor	AFP	Vascular invasion	5-yr recurrence risk 2.9% for RETREAT score 0; 75% for RETREAT score ≥5	0.75
US HCC Consortium[22]	Tumor diameter Tumor number	AFP NLR	Vascular invasion Tumor differentiation	Based on Normogram	0.76
Post-MORAL[18]	Tumor diameter Tumor number		Vascular invasion Tumor differentiation	5-yr recurrence-free survival ranging from 97% in low-risk group to 22% in very high-risk group	0.87
Decaens et al[23]	Tumor diameter Tumor number		Vascular invasion Tumor differentiation	5-yr recurrence risk 14.5% for risk score <4 and 51.5% for risk score ≥5	

AFP, alpha-fetoprotein; LT, liver transplantation; NLR, neutrophil/lymphocyte ratio.

[a]Proposed criteria based on living donor liver transplant are not included.

Despite advances in cross-sectional imaging over the last few decades, radiographic understaging of HCC still occurs in up to 25%-30% of patients.[35-38] Furthermore, misdiagnosis has been reported in 11%-25% (no HCC found in explant).[39,40] To reduce the misdiagnosis rate, a revised UNOS/OPTN imaging policy for HCC was implemented, requiring structured reporting, standardized imaging

protocols for LT centers and equipment specifications for dynamic contrast-enhanced multiphase computed tomography (CT) or magnetic resonance imaging (MRI).[41,42]

3.1.2 | Alpha-fetoprotein

Growing evidence suggests alpha-fetoprotein (AFP) to be a powerful prognostic biomarker in LT.[43] AFP has been included in virtually every prognostic model in LT for HCC (Tables 1 and 2), but there is no consensus on an AFP cut-off value to be applied as an exclusion criterion for LT. AFP levels as low as 16 to 20 ng/mL have been associated with poor post-LT outcomes[3,43] A much higher AFP level of >1000 ng/mL before LT is associated with particularly poor post-LT survival, regardless of the tumor burden.[14,44] A new UNOS policy has recently been implemented, requiring those with an AFP >1000 ng/mL to show a decrease in AFP to <500 ng/mL with LRT before LT can be undertaken. This policy is supported by a recent analysis of UNOS data showing that a decrease in AFP from >1000 to 101-499 ng/mL before LT, mostly as a result of LRT, would result in a greater than twofold reduction in post-LT mortality and an almost threefold reduction in HCC recurrence.[45]

Many other approaches in using AFP to refine LT selection criteria have been explored. A multicenter French study incorporated a number of AFP thresholds within a prognostic score that included AFP, largest tumor diameter, and number of tumor nodules.[14] The Metroticket version 2.0 presented a continuum of AFP in combination with the sum of the largest tumor diameter and number of tumor nodules to predict post-LT survival.[15] A positive AFP slope resulting from rising AFP values over time also appears to correlate with a higher risk of post-LT HCC recurrence,[30,46-49] but the AFP slope threshold that predicts worse post-LT outcomes has varied from one study to another. It has also been shown in several large series that pre-LT AFP response to LRT significantly affects recurrence.[20,50] It is important to note that AFP is not entirely specific to HCC-related production and can be elevated in the setting of hepatic inflammation, including in the setting of viral hepatitis.

3.2 | Well-established explant features predicting HCC recurrence

3.2.1 | Microvascular invasion

The presence of MVI on explant is strongly associated with HCC recurrence and reduced survival after LT[51,52] (Table 2). The incidence of MVI is almost twice as high in tumors larger than 5 cm compared to smaller tumors.[38,53-56] Patients with multiple tumors are 2 times more likely to have MVI as a solitary tumor.[57] AFP >1000 ng/mL[56] and positive uptake on PET[58] have also been associated with a greater likelihood of MVI. Nevertheless, the lack of a standardized histological definition of MVI creates heterogeneity across studies, and the presence or absence of MVI cannot be reliably determined prior to LT (45). Biopsy of the tumor has a very low sensitivity for MVI detection.[59] A noninvasive approach involving a contrast-enhanced computed tomography based biomarker derived from a HCC "venous invasion gene" gene expression signature, referred to as "radiogenomics,"[59] has shown promise, but the usefulness of radiogenomics in LT candidates with early stage HCC requires further study. Similarly, the creation of a radiographic-radiomic model using clinical and contrast-enhanced computed tomography factors to predict MVI for HCC may have an application for early stage HCC patients considering LT, though further research is needed.[60]

3.2.2 | Histological grade of tumor differentiation

Poorly differentiated tumor grade has been identified in many studies as an important risk factor for HCC recurrence after LT[54,61,62] (Table 2). Several groups have proposed using pre-LT biopsies of the largest tumor to exclude patients with poorly differentiated HCC from LT, while placing no restrictions in the upper limits in tumor burden as long as there was no radiographic evidence of macro-vascular invasion. Based on this approach, the University of Padova group reported a 5-year actuarial survival rate of 75% and a recurrence-free probability of 92%.[63] Using the same approach but also excluding those with cancer-related symptoms and poor performance status, the University of Toronto reported a 5-year post-LT patient survival of 69% (vs 78% with Milan) and HCC recurrence probability of 30% (vs 13% with Milan).[17] Poorly differentiated tumor grade and vascular invasion were found in the explant in 8% and 40% respectively. A major concern about liberalizing tumor burden and relying on biopsy assessment of tumor histologic grade is that the overall agreement of preoperative needle core biopsy with explant histopathology was poor according to one study, in which a significantly lower percentage of cases were identified as poorly differentiated tumor grade by biopsy compared to explant (15% vs 28%).[56] In addition, in a more recent series, the correlation with explant pathology was poor and had no utility over Milan criteria alone in predicting post-LT recurrence.[64] At present, given the limitations of histologic assessment noted in current available evidence, no guidelines support routine use of biopsy to help guide eligibility of transplant for those with HCC.

3.3 | Other potential predictors of HCC recurrence

3.3.1 | Other biomarkers

Aside from AFP, a number of serum biomarkers have been reported to be associated with the risk of HCC recurrence, including des-gamma-carboxyprothrombin (DCP),[65-67] AFP-L3%, and absolute AFP-L3.[65] Some studies have also suggested that inflammatory biomarkers, including neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio, can predict tumor recurrence after LT.[18,68] Nevertheless, other studies did not confirm the association

between these inflammatory biomarkers and outcome after LT for HCC mostly within Milan criteria.[19,69] The role of these biomarkers in clinical practice, especially with respect to candidate selection for LT, has not yet been clearly defined.

Genomic biomarkers have the potential to discriminate HCC recurrence risk. In one study, allelic imbalance in chromosome 9/18 microsatellites was found to strongly correlate with recurrence in HCC beyond Milan criteria.[70] In another study on patients with tumor beyond Milan criteria, the presence of progenitor cell markers (either CK19 or S2 signatures) had significantly greater HCC recurrence rate and lower survival than those without these gene signatures.[71]

3.3.2 | Positron emission tomography scan

Several studies have suggested that ^{18}F-fluorodeoxygluclose positron emission tomography/CT (^{18}F-FDG PET/CT) was a prognostic marker in LT for HCC, showing good correlation between ^{18}F-FDG avid tumors and unfavorable histopathological tumor characteristics including microvascular invasion and poorly differentiated tumor grade.[58,72,73] Nonuptake of tumor on ^{18}F-FDG PET/CT may allow the use of liberal tumor size criteria in living donor LT according to studies from Korea and Japan.[74,75]

3.3.3 | Hepatitis C virus infection

Hepatitis C virus (HCV)-associated cirrhosis is a well-established risk factor for HCC, and antiviral treatment with viral eradication is associated with a significant decline in HCC risk overall. Recent reports, however, have raised concern that antiviral therapy with directly acting antivirals may lead to an unexpected increased risk of HCC recurrence after potentially curative therapy, including resection and ablation.[76-78] This concern has not been supported by subsequent studies and pooled or meta-analyses.[79-82] In addition, although data on posttransplant recurrence specifically are limited, direct-acting antiviral therapy has not been associated with increased post-LT recurrence risk.[83] Thus antiviral treatment decisions should be made in the context of organ access and clinical characteristics of the patient,[84] but should not be avoided specifically to prevent HCC recurrence.

3.3.4 | Donor characteristics

Several donor characteristics, including older donor age[85,86] and nonlocal livers,[86] have been implicated as risk factors for HCC recurrence following LT. These findings require confirmation. The effects of graft type (living donor vs deceased donor) on HCC recurrence after LT have yielded conflicting results. When comparing living donor LT and deceased donor LT in the post-MELD prioritization era, a meta-analysis showed no significant difference in HCC recurrence rates between these grafts.[87] However, it should be emphasized that having a potential live donor at listing compared to not has been associated with increased survival for patients with HCC, likely related to a lower dropout rate and a shorter waiting period for LT.[88] In one study, those receiving allografts donated after cardiac death did not experience a higher rate of recurrence compared to donation after brain death organs.[89]

3.4 | Prognostic models

Proposed models based on variables that are available before LT generally follow the principle of combining tumor morphologic parameters (diameter, number, or volume) with measures or surrogates of tumor "biology" metrics (Table 1). They include AFP and other biomarkers (DCP, NLR). Pre-LT biopsy of the tumors has also been used to determine histologic grade of differentiation and to exclude poorly differentiated tumors for LT. Although these prognostic models were intended to improve selection of candidates with good post-LT outcomes, the patient populations were highly heterogeneous and most of these prognostic models were based on retrospective data collection. Consequently, these models still require vigorous testing and prospective validation using well-defined criteria for the upper limits in tumor burden and specific thresholds for these biomarkers.

The post-LT prognostic models are based on explant tumor histopathologic characteristics, and they most commonly include measures of tumor burden, tumor grade of differentiation, and the presence or absence of vascular invasion (Table 2). The majority of these prognostic models also include AFP and/or other biomarkers. The post-LT prognostic models help identify candidates at high risk for HCC recurrence and provide a reference for the expected incidence of HCC recurrence. These models are also helpful in the development of standardized post-LT surveillance strategies and the identification of the appropriate subgroups at sufficiently high risk for HCC recurrence to be considered for clinical trials using neoadjuvant therapy to reduce the risk of HCC recurrence.

3.5 | Knowledge gaps

- AFP is currently the most widely utilized serum biomarker but there is no consensus on standardized cut-off values and/or dynamic changes in AFP levels to guide clinical decision making.
- Standardization of the definition of MVI is needed for both reporting and research purposes.
- Most other biomarkers remain investigational and have not yet been adopted in routine practice, and better biomarkers are still needed.
- Further exploration of the impact of specific liver-directed therapies and the correlation with post-LT risk of HCC recurrence are needed.

- Many pre- and post-LT prognostic models have been proposed but still require prospective independent validation. An ideal pre-transplant model would lead to improved post-LT outcomes by incorporating surrogates of tumor "biology" metrics with conventional morphologic parameters. Post-LT models would be useful in developing standardized post-LT surveillance strategies and identification of subgroups to be considered for future neoadjuvant therapy to reduce HCC recurrence.

4 | POSTTRANSPLANT HCC SURVEILLANCE

Surveillance may improve survival through access to earlier and perhaps curative treatment of recurrence.[90-93] To be most effective, post-LT HCC surveillance should be done in the window of time that covers most recurrences, includes imaging of locations where recurrences are known to occur and with modalities that have good sensitivity and specificity. Unfortunately, although studies have looked at timing, risk factors, and characteristics of HCC recurrence, there remains a lack of data to guide serum and imaging tests and their frequency. Specifically, there are no trials to date studying surveillance protocols and their impact on post-LT outcomes.

4.1 | HCC recurrence patterns

Although the timing of posttransplant tumor recurrence is variable, peak HCC recurrence occurs within 2-3 years after transplant[89,94] (Table 3). Early HCC recurrence defined as within the first year of LT portends the worst prognosis.[87,88,92] This could occur due to nondetected extrahepatic metastases that may be present before LT and as a consequence of circulating HCC clones engrafting and growing in a target organ after LT. The plausible explanation for late HCC recurrence (within 2-5 years of LT) could be a second unknown hit that may lead to late engrafting of HCC cells that are less in number and remained latent for a long time during the post-LT period. HCC recurrence after >5 years of LT, though infrequent, has been described.[85] These data suggest that although surveillance should be most intense during the first 2 years, it should be maintained until at least 5 years post-LT for high-risk patients as longer time to recurrence is a predictor for improved outcomes after treatment of recurrent HCC[23,90,95,96]

The pattern of HCC recurrence extends from hepatic to extrahepatic and from single site recurrence to multiple site recurrence[85,90,92,93,97-99] (Table 3). The most common extrahepatic sites are lungs and bones. However, HCC recurrence can also occur in adrenal glands, soft tissue (eg, local recurrence of biopsy tracks), peritoneum, and brain.

TABLE 3 HCC recurrence time and location

Study and time period	Patients with recurrence	Time to recurrence (months)	Hepatic recurrence	Extrahepatic recurrence	Multisite recurrence
Roayaie et al 1998-2002	57/311 (18%)	12.3 (1.5-60.3)	9 (16%)	30 (53%)	18 (32%)
Cescon et al 1997-2009	34/283 (12%)	12 (1-118)	3 (9%)	7 (21%) lung = 3 bone = 2 peritoneum = 2	24 (71%)
Escartin et al 1988-2005	28/184 (15%)	Early <12 months = 5.7, late ≥12 months = 33.5	7 (25%)	21 (75%) lung = 7 bone = 5, adrenal = 2 peritoneum = 2 skin = 2 lymph node = 2 central nervous system (CNS) = 1	11 (39%)
Valdivieso et al 1996-2008	23/182 (9%)	23.4	2 (9%)	16 (70%) lung = 9 bone = 3 adrenal = 2 lymph node = 2	5 (22%)
Kornberg et al 1994-2007	16/60 (27%)	23 (4-58)	4 (25%)	12 (75%) lung = 5 bone = 4 adrenal = 1 peritoneum = 1 CNS = 1	
Sharma et al 2002-2008	17/94 (18%)	25.2	6 (4%)	6 (4%) lung = 1 adrenal = 3 abdominal soft tissue = 2	11 (65%)
Mehta et al 2002-2012	84/721 (12%)	13	22 (26%)	84 (100%) lung = 37, bone = 25, peritoneum = 22	21 (25%)
Fernandez-Sevilla et al 1991-2013	70/493 (14.2%)	17	2 (2.8%)	51 (72.9%)	17 (24.3%)
Sapisochin et al 2000-2012	121/780 (15.5%)	14	16 (13.2%)	63 (52.1%)	42 (34.7%)

4.2 | Recommendations for post-LT surveillance

There are currently no clinical trial data to guide a recommendation for a specific surveillance protocol though expert groups have published consensus statements based upon the data available.[12] With recent advances in systemic treatment, the implementation of surveillance programs may result in earlier detection that may improve survival in patients with recurrence who are able to be treated with surgical, local, or systemic treatment. Therefore, all liver transplant recipients with HCC should be enrolled in a surveillance program.

As there are no specific evidence-based risk stratification criteria that can be formally recommended, there is significant variation in surveillance practices between programs. In general, we recommend cross sectional imaging with either multiphase CT or multiphase MRI should be performed at least every 6 months for at least 2-3 years posttransplant as the majority of patients recur in this time. Many programs continue surveillance until 5 years posttransplant based upon the low likelihood or recurrence beyond this point; however, data on the best or most cost-effective length of surveillance are also not available to guide recommendations. Given the small amount of data for AFP in patients posttransplant, and the relatively low cost of this test, AFP level should be checked every 6 months for 5 years.[100,101] There are not enough data to validate use of other biomarkers such as AFP-L3% or DCP in a routine surveillance program after LT for HCC.

Imaging for lung metastases with noncontrast CT chest should also be performed every 6 months in this period as well. Bone metastases may also be a site of recurrence, but given the low sensitivity of bone scan we do not recommend routine imaging with bone scan. Patients may present either with an elevation of alkaline phosphatase or with pain at the site of bone metastasis, and in case of these signs or symptoms further imaging may be performed at that time.

Risk-based screening has been proposed by several groups, including by Mehta and colleagues recommending screening based on RETREAT score (no screening if RETREAT score = 0 due to estimated recurrence risk <3%, every 6 months for 2 years if score = 1-3, up to 5 years for those if score = 4, and every 3 to 4 months for 2 years followed by every 6 months until year 5 if score ≥5).[21,102] Although the RETREAT criteria could be considered for clinical use, these data must be prospectively validated and there are no published prospective studies of specific risk stratification-based surveillance strategies. Ultimately risk-based screening would be desirable if it were shown to be safe and perhaps most cost effective.

4.3 | Knowledge gaps

- Prospective validation of imaging every 6 months as a surveillance strategy is needed in the liver transplant recipient population. In addition, data regarding the relative benefits of different lengths of surveillance are needed.
- Risk-stratified surveillance protocols must also be rigorously studied, perhaps including whether there are patients at sufficiently low risk that there is no benefit to surveillance.
- Whether post-LT surveillance improves HCC-related outcomes remains to be proven.

5 | STRATEGIES FOR PREVENTION OF HCC RECURRENCE

5.1 | Immunosuppression

The immunosuppression regimen of the patient is a possible factor in preventing HCC recurrence, as the immune system is a major defense against cancer, either by attacking dysplastic cells themselves or by controlling viruses linked to cancer.[103] Additionally, as the immunosuppression regimen can change over time, so can the significance of HCC recurrence post-LT, as early recurrence may have a different biological behavior and identity compared to late HCC recurrence.[104]

Table 4 lists the different types of immunosuppression medications and the possible manner in which they can affect HCC recurrence post-LT, including the potential mechanisms involved. Though medication profiles may be strategically used to address HCC recurrence, in practice multiple factors are weighted in formulating the optimal immunosuppression regimen for a specific patient such as consideration of side effects and comorbidities including kidney dysfunction.

A class of immunosuppression medications that appears to play a central role in most efforts to control HCC recurrence are the mammalian target of rapamycin (mTOR) inhibitors. Reducing calcineurin inhibitors (CNIs) and adding a mTOR inhibitor may reduce HCC recurrence, given antiproliferative properties against HCC.[125] Specifically, mTOR involves two signaling pathways: mTOR complex1, which is responsible for cell proliferation based on regulatory signals from the immune system, and mTOR complex 2, which affects cellular metabolism.[126] The two main existing mTOR inhibitors are sirolimus (affecting complex 1 and 2) and everolimus (selective for complex 1). Sirolimus has demonstrated antiangiogenic activities linked to a decrease in production of vascular endothelial growth factor (VEGF) and inhibited response of vascular endothelial cells to stimulation by VEGF.[127,128] Data from small single-center retrospective studies, as well as two meta-analyses, suggest that compared to CNI, use of sirolimus reduced the risk of HCC recurrence after LT[118-123,129-131] Efficacy of this strategy may vary depending on the stage of the initial disease or the presence of hepatitis C virus.[132] The SiLVER study is a multicenter randomized controlled trial (RCT) seeking to obtain definitive answers.[124] In this study, though there appeared to be an advantage in the sirolimus group regarding improvement in recurrence-free survival in the first 3-5 years; this benefit is subsequently lost with further follow-up. Everolimus is approved for immunosuppression in LT recipients with low dose CNI and likely has similar effects as

TABLE 4 Immunosuppression and HCC recurrence

Type of immunosuppression medication	Role in HCC recurrence after LT	Proposed mechanism
Steroids[105-108]	Contributing possibly	Reduce strength of immune inflammatory response, inhibit apoptosis and promote migration of malignant cells
Calcineurin inhibitors (CNIs)[109-112]	Contributing possibly	High levels of CNIs oncologically detrimental; decreased HCC recurrence with lower trough levels
Antimetabolites[113-115]	Azathioprine possibly contributing; Mycophenolate mofetil (MMF) role unclear	Role of azathioprine as carcinogen; Although MMF has an antiangiogenesis and antiproliferative action it has not been shown to decrease HCC recurrence; however, it is used in order to decrease CNI levels
Induction agents[116,117]	Antithymocyte globulin (ATG) and Basiliximab role unclear by themselves	Helpful in reducing CNI levels, but because of their disappearing effect on CD25 + cells, including tumor specific cytotoxic T cells, their overall effect is not clear
mTOR inhibitors (sirolimus and everolimus)[118-124]	Possibly decreasing HCC recurrence, although data not clear	Anticancer properties through mTOR inhibition, although when treatment is initiated may be critical regarding effectiveness; everolimus may stabilize HCC progression

HCC, hepatocellular carcinoma; LT, liver transplantation; mTOR, mammalian target of rapamycin.

sirolimus. However, available evidence is from small, single-center studies that lack adequate power to make clear recommendations.[133] Factors that result in reluctance to use mTOR inhibitors immediately post-LT include concern for increased risk of hepatic artery thrombosis and impaired wound healing.[134,135] Therefore, the main impediment to widespread use of mTOR inhibitors for HCC recurrence prevention has been the lack of high-quality studies that demonstrate a benefit. Though mTOR inhibitors have shown some promise to reduce or prevent HCC recurrence in smaller studies, the highest quality data through the SILVER study does not show a benefit. At this time, there is a need for further well-designed multicenter studies to better delineate their use in the post-LT population.

There are certain combination strategies of immunosuppression medications with a greater promise of success at minimizing risk of HCC recurrence. Medications such as steroids and CNIs possibly contribute to HCC recurrence, whereas others such as the mTOR inhibitors, and, to a lesser extent MMF, may have a beneficial effect. Though the optimal combination has yet to be found, an overall goal of reducing CNI with possible eventual complete withdrawal and avoidance of azathioprine and antithymocyte globulin is consistent with a strategy to minimize risk of HCC recurrence. As a counterbalance, the addition of mTOR inhibitors with or without MMF, can help maintain a safe immunosuppression level to avoid rejection, while at the same time not endangering renal function and possibly preventing HCC recurrence. In the context of acute cellular rejection (ACR), the benefit of increased immunosuppression to attenuate alloreactivity must be balanced against the risk of promoting oncogenesis. At present, no RCTs powered to detect differences in de novo tumor formation or HCC recurrence between ACR treatment strategies are available.

Though we seek an optimal medication strategy, the existence of multiple medication-, patient-, and disease-related variables make this challenging. Furthermore, a generalizable medication strategy may not be optimal. Rather, the biological behavior of HCC may prove to be better targeted by a patient-targeted approach, or otherwise, a "personalized" strategy toward immunosuppression. The identification of noninvasive "biomarkers of tolerance" may help identify those patients where "safe" immunosuppression withdrawal may reduce the risk of HCC recurrence.

5.2 | Adjuvant systemic therapy

There is no evidence to support the use of adjuvant systemic chemotherapy to prevent post-LT HCC recurrence and this approach is not currently recommended. There is no evidence that adjuvant systemic therapy using doxorubicin provides benefit in preventing HCC recurrence after LT.[136] In an RCT of 58 patients, oxaliplatin-based adjuvant chemotherapy for patients with HCC beyond Milan criteria showed improved 1- and 3-year overall survival in the adjuvant oxaliplatin group. However, there was no difference in the 3-year disease-free survival in both the groups.[137]

Licartin is a promising antineoplastic agent for adjuvant chemotherapy for patients with advanced HCC.[138] It is an immune-radioconjugate containing metuximab, an antibody fragment targeting the HCC-associated antigen HAb18G/CD147, a member of CD147 family that is overexpressed in HCC and fibroblasts. Its expression is associated with cancer cell progression and increased adhesion, invasion, and metastasis. Metuximab is conjugated to the radioisotope Iodine I.[138] In an RCT of 66 HCC patients beyond Milan Criteria, the Licartin group received three doses every 28 days 3 weeks after LT and had a significantly lower HCC recurrence rate compared to the control group (27% vs 57%; $P = .017$).[139] However, larger studies are needed.

The role of pre-emptive adjuvant therapy with sorafenib was initially considered promising but newer data demonstrate there is likely minimal added benefit. Most of these studies are limited to a small number of subjects, single-center studies, and case series.[140-142] One of the largest retrospective studies examined the role of adjuvant sorafenib (25 patients) vs standard of care (20

patients) in patients with advanced HCC on explant pathology. The authors concluded that the use of pre-emptive Sorafenib did not improve recurrence free survival or overall survival.[143] Similarly, data on the use of neoadjuvant sorafenib among patients with potentially curative resection or ablation therapy did not demonstrate a benefit in terms of recurrence.[144]

Immunotherapies have not been studied for prevention of posttransplant recurrence. Currently, a clinical trial examining the effects of nivolumab in patients with high risk of recurrence after curative resection or ablation is underway but does not include LT recipients.[145]

5.3 | Knowledge gaps

- The optimal immunosuppressive regimen to decrease the risk of HCC recurrence is currently unknown.
- Through their antiproliferative properties, mTOR inhibitors are the immunosuppresive agents believed to have the most promising role in preventing recurrence although data are limited and have not yet definitively demonstrated a benefit.
- Data on the use of adjuvant systemic chemotherapy in preventing HCC recurrence are needed.
- With the changing landscape of HCC and approval of new systemic chemotherapeutic agents, future studies are warranted to characterize the efficacy and safety of these agents as adjuvant therapy in LT recipients.

6 | MANAGEMENT OF HCC RECURRENCE

HCC recurrences are usually asymptomatic and diagnosed as a result of surveillance imaging. Management is mainly focused at treatment of biopsy-proven HCC recurrences once they occur given strategies for prevention are limited.

6.1 | Surgical resection

Surgical resection for recurrent HCC has been shown to be an independent predictor of long-term survival if isolated to a single organ.[90,92,146-148] In the largest single center experience, of 106 total recurrences, 25 underwent surgical resection with overall better survival with this approach. In this series, a multivariable risk model was also constructed to predict postrecurrence survival.[148] In a retrospective analysis, Valdivieso and colleagues identified 11/23 patients with HCC recurrence after LT who underwent surgical resection due to intrahepatic and extrahepatic disease; of these, eight patients obtained a R-0 resection.[11] Second recurrence was seen in 50% of the R-0 cases and all 3 of the patients with R-1 resection. Despite this, overall recurrence-free survival was significantly higher in the R-0 cohort (32.3 months vs 6.9 months; $P = .006$) with a 5-year survival rate of 27% (vs 0% at 3 years in the other cohort). Similarly, Regalia and colleagues performed surgical resection of 7/21 patients with post-LT HCC recurrence with both intra- and extrahepatic disease.[147] Patients who underwent surgical resection had a 57% survival rate at 4 years vs 14% survival rate in nonsurgical candidates ($P < .02$). Finally, in a recent French study, 22/70 patients with recurrent HCC after LT who underwent surgical resection (2 intrahepatic and 20 extrahepatic) had a median survival of 35 vs 15 months for nonresected patients ($P < .001$).[92] In carefully selected patients with good functional status and limited disease, resection of isolated extrahepatic recurrent disease in regional lymph nodes, adrenals, and lungs have shown favorable survival.[149-151]

6.2 | Locoregional therapies

Data on liver directed therapy for the treatment of recurrent HCC after LT are lacking and limited to small case series. Zhai and colleagues examined the efficacy of microwave ablation (MWA) in the treatment of intrahepatic recurrence of HCC in 11 LT recipients.[152] Patients tolerated the procedure well with only three cases having tumor progression within 1-7 months after MWA. Survival rates at 1 and 2 years were 51.5% and 15.3% respectively with an average survival time of 17.3 months. Ko and colleagues evaluated the efficacy of transcatheter arterial chemoembolization (TACE) in a cohort of 28 patients with recurrent HCC after living donor LT.[153] Although tumor size was reduced by ≥25% in 19/28 patients, intra- or extrahepatic recurrence occurred in 93% of patients during the 6-month follow-up period after the intervention. The 1-, 3- and 5- year survival rates were 48%, 6%, and 0%, respectively. A single case report described the use of Yttrium-90 microspheres (Y-90) in a LT recipient with intrahepatic HCC recurrence 22 months after transplantation who failed both initial resection and adjuvant chemotherapy.[154] Follow-up imaging 2 months posttreatment showed tumor necrosis and excellent treatment response but no long-term data were reported.

6.3 | Sorafenib and other RAF kinase inhibitors

The use of systemic chemotherapy in post-LT HCC recurrence is limited to small studies exploring the use of sorafenib in this setting. Treatment with sorafenib led to a median survival of 12 months (range 1.45-20.1).[116,127,155-158] In approximately 80% of these cases, an mTOR inhibitor was combined for immunosuppression. In a recent meta-analysis by Mancuso and colleagues, patients who received sorafenib for recurrent HCC after LT had an overall 1-year survival ranging from 18%-90% with a pooled estimate of 1 year survival at 63%.[159] In a recent analysis of the US cohort of the GIDEON registry, the safety and tolerability of sorafenib was studied in patients with HCC recurrence who had

undergone LT or resection.[160] Most adverse events occurred in the first 4 weeks of treatment and the incidence of adverse events resulting in discontinuation of drug were similar in both groups. There is no evidence of increased toxicity from sorafenib in the posttransplant setting compared to patients with primary HCC; however, the use of concomitant mTOR inhibitors can increase the rate of dose reduction or discontinuation due to severe side effects. There is also one multicenter retrospective series demonstrating the safety of the use of regorafenib in LT recipients who failed to response to sorafenib.[161]

Data on the use of other systemic chemotherapy agents in this setting are also limited. The use of metronomic capecitabine in 38 patients with post LT HCC recurrence showed a median survival of 22 months compared to 7 months ($P < .01$) in patients who received best supportive care with an acceptable safety profile compared to sorafenib.[162]

6.4 | Immunotherapy

Despite the promise of checkpoint inhibitors in the treatment of several malignancies with excellent outcomes, the use of immunotherapy in transplant recipients is challenging due to the potentially increased risk of allograft rejection and graft loss.[163] Immune checkpoint inhibitors target cell death protein 1/programmed death ligand 1 (PD-1/PDL-1) or cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), all of which are important negative regulators of T cell immune function.[164] Immune checkpoint inhibitors work by restarting an effective antitumor immune response, allowing immune system destruction of tumor cells. However, through this same mechanism, the immune system can also lose the ability to recognize self from non-self and thereby cause immune system mediated adverse events similar to autoimmune diseases. Of importance in solid organ transplant recipients, the PD-1:PDL pathway plays an important role in regulating alloimmunity and transplant tolerance.[165] Therefore, transplant recipients are at particular risk for allograft rejection when immune checkpoint inhibitors are used as cancer therapies. Theoretically, usage of such immunomodulatory agents in transplant recipients may promote the development of allograft injury, severe rejection, and even death.[166]

Nevertheless, HCC represents a promising target for anticancer immunotherapies such as immune checkpoint inhibitors targeting CTLA-4 and PD-1/PDL-1.[166] Recently, two PD-1 checkpoint inhibitors, nivolumab and pembrolizumab, have been approved for advanced HCC as second line therapies. Both medications received conditional Food and Drug Administration approval based on limited phase II data, and unfortunately, recent phase III data showed pembrolizumab failed to improve progression-free or overall survival in patients with advanced HCC.

There have been multiple case reports in the literature of the use of CTLA-4 antibodies and PD-1/PDL-1 antibodies in patients after solid organ transplant. These reports have been in liver, kidney, heart, and corneal transplants, for several tumor types including HCC, melanoma, and non-small cell lung cancer.[166-172] There has only been one small case series from the Mayo Clinic on their single-center experience of PD-1 inhibitor therapy in seven liver transplant recipients, six with HCC and one with metastatic melanoma.[170] Overall, the reported graft rejection rates in the literature have ranged from 25%-54%, with median time to graft rejection 8-19 days after initiation of therapy.[168,172] Several reports have detailed successful treatment of graft rejection with steroids, mycophenolate mofetil, and antithymocyte globulin, but there have also been several reports of rapid graft failure and death from severe allograft rejection. Although there are reports of tumor response in transplant recipients with immune checkpoint inhibitors, it seems that the response rates are lower than that seen in nontransplant patients.[168]

Overall, there appears to be no clear association with time from transplant to treatment or particular immune suppression strategies to predict or mitigate risk of rejection. Interestingly, there are emerging data that staining of liver allograft for PD-1 lymphocyte expression may be predictive, where lack of PD-1 staining lymphocytes in the allograft may be associated with a lower risk of rejection.[170] However, until there are more robust clinical trials that allow prediction and clarification of the risk of graft rejection and loss in transplant recipients, the immune checkpoint inhibitors must be used with extreme caution in these patients.

6.5 | Knowledge gaps

- Despite availability of various treatment strategies, including the use of chemotherapeutic regimens, surgical resection, and liver-directed therapy, long term recurrence free survival is currently rarely achieved and is an important area of further research.
- Data are limited regarding the use of immune checkpoint inhibitors in this population, particularly given the potential increased risk of rejection. Given the lack of robust data or guidelines, further studies should employ a multidisciplinary and multimodal approach tailored to each patient.

7 | CONCLUSIONS

As the incidence of HCC continues to rise, patients with HCC will be an increasingly large proportion of our transplant population. Although we have learned a significant amount about how to cure patients of HCC with transplant and risk stratify for recurrence, there remain many opportunities for improvement in our posttransplant management. We therefore have provided a roadmap of knowledge gaps aimed at guiding the development of studies that will significantly advance posttransplant care of these patients, including in the areas of posttransplant surveillance, prophylactic measures including alteration of the standard immunosuppression regimen, and treatment of established HCC recurrence.

DISCLOSURE

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

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