

Management of Recurrent Hepatocellular Carcinoma in Liver Transplant Recipients: A Systematic Review

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Abstract

Hepatocellular carcinoma is the most common form of liver cancer, representing 70% to 85% of primary hepatic malignancies in adults. Liver transplant is an optimal treatment for patients with hepatocellular carcinoma because it eliminates the malignancy as well as the often-underlying liver cirrhosis and restores normal liver function. Since the development of strict selection criteria in hepatocellular carcinoma patients undergoing liver transplant with the implementation of the Milan criteria, patient survival and recurrence rates after liver transplant have dramatically improved. However, several research groups are now seeking to expand this criteria to include more patients with larger tumors who may achieve similar postliver transplant survival rates as those patients meeting current eligibility requirements. Currently, in approximately 20% of patients, hepatocellular carcinoma recurrence is still the rate-limiting event that clearly affects patient survival.

Given the limited number of grafts available for transplant, the poor prognosis of untreated hepatocellular carcinoma, and the recent notion of expanding selection criteria, strategies for reducing the rate of, monitoring and treating hepatocellular carcinoma recurrence, in both pretransplants and posttransplants, are explored in this review. We

review the available literature to better understand current strategies available to optimize long-term clinical outcomes.

Key words: Liver cancer, Recurrence, Liver transplantation

Introduction

Hepatocellular carcinoma (HCC) is the most common form of liver cancer, representing 70% to 85% of primary hepatic malignancies in adults.¹ The incidence of HCC is increasing, likely attributable to the increased prevalence of hepatitis C and possibly nonalcoholic fatty liver disease.² Indeed, a large cohort of patients infected with hepatitis C several decades ago are now expected to seek medical care and present with complications of cirrhosis.³ Because HCC tends to arise in the setting of cirrhosis, liver transplant (LT) is the ultimate life-saving modality because it removes the diseased liver along with macroscopic and microscopic cancer cells.⁴

In the United States, the use of LT for the treatment of HCC has increased exponentially: 985 patients were transplanted for HCC between 1988 and 2001, while 5045 were transplanted for HCC between 2002 and 2007.^{5,6} The 5-year survival in patients transplanted for HCC ranges from 48.2% to 80%.^{4,7-10} However, HCC recurrence is a rate-limiting event, which clearly affects patient survival. Factors associated with tumor recurrence include tumor burden and vascular invasion.^{4,5,7,9,11-17} Recurrence tends to occur in 6.4% to 21.2% of patients^{8,9,11,12} (Table 1). The 5-year patient survival rate after HCC recurrence is only 22%.¹²

Despite the effect of HCC recurrence in LT recipients, there is no established guideline

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Table 1. Tumor Recurrence Characteristics

Name	Number of Patients	Total HCC Recurrences	Intrahepatic Recurrence	Extrahepatic Recurrence	Both Intrahepatic and Extrahepatic Recurrences
Mazzaferro V, et al ⁴	48	4	0	3	1
Ragalia E, et al ¹¹	132	21	4	17	0
Roayaie S, et al ¹²	311	57	9	30	18
Shimoda M, et al ¹³	67	11	5	6	0
Margarit C, et al ¹⁶	103	15	3	12	0
Zimmerman MA, et al ¹⁷	130	17	8	9	0
Sharma P, et al ¹⁹	94	17	6	11	0
Yao FY, et al ²¹	70	8	4	4	0
Kornberg A, et al ²⁴	60	16	4	12	0
Vivarelli M, et al ⁶⁶	216	21 [†]	2	8	2
Zimmerman MA, et al ⁷⁵	97	12	6	6	0
Yoon DH, et al ⁸⁹	429	64 [‡]	4	19	0

Abbreviations: HCC, hepatocellular carcinoma

[†]only 12 reported sites; [‡]only 23 reported sites

addressing its management.¹⁸ An understanding of the clinical experience with HCC recurrence in the available published literature is critical to developing a rational strategy for care of these patients. Our review evaluates pretransplant and posttransplant strategies to prevent, monitor, and treat recurrent HCC in LT recipients.

Materials and Methods

Search strategy and identification of studies

We searched all available studies since 2002, the year the Model of End-Stage Liver Disease score was adopted for organ allocation for patients awaiting liver transplant. As MEDLINE search alone was not sufficiently sensitive, we also searched the bibliographies of identified articles. Two authors (JR and NY) independently reviewed the MEDLINE search results to select articles applicable for inclusion in this review; discrepancies between the 2 authors were adjudicated by a third author (SS) who served as a tiebreaker.

Inclusion and exclusion criteria

We included studies published in scientific journals that provided information about safety, tolerability and/or efficacy of therapies in the setting of liver transplant (orthotopic and living donor) for the treatment of HCC, whether as adjuvant (treatment after transplant but before recurrence) or therapeutic (treatment after recurrence) intervention. This included case reports, case series, retrospective, and prospective studies. Studies were excluded if they did not specify outcome data for patients receiving therapy, were not available in English, or were animal studies.

Results

Pretransplant—prevention of hepatocellular carcinoma recurrence

Preoperative variables

Several clinical variables that independently influence HCC tumor recurrence after LT, and patients' survival has been identified that include tumor size, serum α -fetoprotein (AFP) level, vascular invasion, and tumor cell differentiation. Other donor factors, such as older donor age, have been implicated, but further studies are required to characterize the effect of these influences.¹⁹

Tumor size

Many studies have found that increasing tumor burden is directly related to HCC recurrence after transplant. Mazzaferro and associates showed that survival is associated with size and number of tumors.⁴ Patient survival was significantly increased when the transplant criteria included a single tumor (5 cm in diameter or smaller), or no more than 3 tumor nodules (each less than 3 cm in diameter). Overall, recurrence-free 4-year survival for patients meeting these criteria was 83% compared with only 59% in those whose tumor size surpassed the selection parameters.⁴ However, despite appropriate preoperative imaging, 27% of patients were assigned incorrect staging, mostly under-staged before LT, likely having a negative effect on survival.

Since 2002, a Model of End-Stage Liver Disease priority has been given to HCC patients within the Milan criteria which has led to a 6-fold increase in the proportion of patients with HCC who are transplanted.²⁰ However, the even broader University of California, San Francisco (UCSF)

criteria were developed to increase further patient eligibility for transplant while achieving satisfactory survival rates. The UCSF criteria include solitary tumor ≤ 6.5 cm, or 3 or fewer nodules with the largest lesion ≤ 4.5 cm and total tumor diameter ≤ 8 cm without gross vascular invasion.^{21,22} Several studies have revealed that survival rates achieved with LT in HCC patients are comparable when UCSF criteria compared with Milan criteria are used for patient selection.^{8,21,22} The risk of developing tumor recurrence is the main argument against expanding eligibility criteria.^{13,23,24} In a recent metaanalysis of 74 studies by Germani and associates, the authors found that patients receiving LT beyond the Milan criteria have increased risk of recurrence and worse overall survival, which includes an increased risk of death if transplanted outside the Milan criteria, but within the more inclusive UCSF criteria.²⁵ Therefore, relaxing the tight parameters defined in the Milan criteria on pre-LT tumor size adversely affects post-LT outcomes.

Alpha-fetoprotein level

There is increasing interest in using AFP levels to predict patient survival and HCC recurrence in liver transplant recipients. For instance, the results of 2 recent studies identified that AFP levels greater than 400 $\mu\text{g/L}$ were associated with decreased overall survival after LT.^{26,27} Using the Scientific Registry of Transplant Recipients database, one study identified total tumor volume and AFP level $> 400 \mu\text{g/L}$ as the only predictive factors of patient survival after transplant.²⁶ However, HCC recurrence could not be evaluated. Likewise Merani and associates showed that patient survival was increased if the AFP level was reduced $< 400 \mu\text{g/L}$ with locoregional control when compared with those patients whose AFP level did not decrease with treatment.²⁷

The rate of AFP increase also has been associated with recurrent HCC in liver transplant recipients.^{28,29} Vibert and associates found that HCC recurrence occurred significantly more often in patients who had a rise in AFP $> 15 \mu\text{g/L/mo}$ before transplant.²⁸ Using multivariate analysis, Han and associates found that a preoperative AFP increase of 50 $\mu\text{g/L/mo}$ was an independent predictor of HCC recurrence.²⁹ Different preoperative AFP cutoff values have been proposed in the literature, and determining the correct value in terms of selection criteria to apply to these patients is still debatable.

Vascular invasion/differentiation of hepatocellular carcinoma

Moderately to poorly differentiated HCC, presence of vascular invasion, and lymph node metastasis of the tumor also have been recognized as significant predictors for recurrence.⁷ Studies have confirmed that both microvascular invasion and macrovascular invasion seen on liver explant's correlate with an increased incidence of HCC recurrence after LT.³⁰ While macrovascular invasion can be observed on preoperative imaging studies, microvascular invasion is much more difficult to predict. Several groups have reported that increasing tumor size, number of nodules, and degree of differentiation predicts the presence of microvascular invasion.³¹⁻³⁸ Tumor size greater than 2-5 cm has been correlated with increased risk of microvascular invasion, as has the existence of multiple tumor nodules and lower histologic grade. Conversely, the degree of tumor cell differentiation is inversely associated with recurrent disease in that well-differentiated HCC is associated with decreased risk for recurrence.³⁹ Cillo and associates studied 48 patients with HCC in a prospective manner and found that patients with moderately to well-differentiated tumors had a 75% actuarial survival rate and 92% recurrence-free survival rate.⁴⁰ Thus, the degree of tumor differentiation and presence of vascular invasion before LT are predictors of post-LT HCC recurrence, but both are determined on explant pathology and are not as useful clinically during the selection process.

Metastatic disease

Metastatic disease found in HCC patients before LT is an absolute contraindication to transplant, and these patients should not receive LT, as their long-term survival is presumably poor.

Preoperative staging

Implementation of rigorous selection criteria for LT in patients with HCC has led to improved recurrence-free survival over the past several decades. Preoperative staging is critical to appropriate patient selection and ultimately to organ allocation. However, up to 66% of patients are often staged incorrectly before transplant.^{41,42} Despite identifying the aforementioned clinical parameters that group patients as "high risk," cancer recurrence is often the result of microfoci of extrahepatic

disease.^{12,43} Limitations of preoperative imaging and tumor growth while on the waiting list likely prevents achievement of the full survival benefit of LT.⁷ Accurate quantification of tumor size and number with the addition of tumor biomarkers and the degree of differentiation would reduce use of LT in more-advanced disease, thus maximizing allocation of LT to those persons most likely to benefit.

Locoregional therapy before liver transplant

While waiting for LT, HCC is often treated to down-stage the tumor and/or prevent disease progression, with the aim of prolonging wait list time, preventing posttransplant recurrence, and improving overall posttransplant survival.⁴⁴⁻⁴⁶ These treatments usually involve locoregional control with radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), or acetic acid injection and transarterial chemoembolization (TACE) (Table 2). Yet, it is currently unclear if locoregional therapy truly has a positive effect on preventing posttransplant

recurrence and improving posttransplant outcomes. Several retrospective and prospective studies have shown conflicting results regarding whether or not locoregional therapy decreases posttransplant HCC recurrence.

Transarterial chemoembolization

Clinical studies examining the role of TACE alone in treating HCC before transplant have failed to demonstrate a survival benefit and found no significant effect on recurrence of HCC after transplant.^{12,47,48} A study evaluating TACE monotherapy before transplant showed an association with recurrence in patients who had partial necrosis after TACE compared with those with better response after TACE.⁴⁹

Radiofrequency ablation

Studies exploring the use of pre-LT RFA have shown mixed results. Lu and associates investigated 52 patients accepted for LT who underwent RFA as pretreatment.⁵⁰ Forty-one of 52 patients underwent

Table 2. Locoregional Therapy in Patients Waiting for Liver Transplant

Name	Year	Type of Study	Number of Patients/ Type of Transplant	Treatment	Result
Porrett, et al ⁵²	2006	Retrospective	31 treated, 33 control/ OLT unspecified	Combination of locoregional pretransplant therapy. (14 RFA, 6 HACE, 3 Yttrium-90 ablation, 5 RFA + HACE, 2 PEI + HACE, 1 PEI + RFA)	Pretransplant locoregional hepatic therapy did not benefit the patients. No improvements in posttransplant outcomes.
Decaens, et al ⁴⁷	2005	Retrospective	100 treated, 100 control/OLT unspecified	TACE	No improvement in after LT overall and disease-free survival.
Mazzaferro, et al ⁵¹	2004	Prospective	50 treated/44 DDLT, 6 split liver graft [†]	RFA	Pretransplant RFA is an effective treatment for HCC patients before LT, but should be used in combination with other treatments. 2 HCC recurrences after transplant.
Yao, et al ⁵⁴	2005	Retrospective	103 treated, 65 control/ 142 DDLT, 26 LDLT	Preoperative LRT	May benefit survival of patients with pathologic T2 and T3 HCCs.
Yao, et al ⁵⁵	2005	Prospective	30 treated/14 DDLT, 2 LDLT [‡]	9 RFA, 7 RFA + TACE, 5 TACE, 3 TACE + PEI, 2 TACE + percutaneous RFA, 4 resection	Pretransplant LRT successfully down-staged tumors and reduced recurrence rates
Bharat, et al ⁵⁶	2006	Retrospective	46 treated, 51 untreated/ OLT unspecified	36 TACE, 5 RFA, 1 PEI, 4 TACE + RFA	Successfully down-staged tumors and improved long-term survival. Long-term recurrence-free survival increased with complete tumor necrosis with LRT.
Millonig, et al ⁵⁷	2007	Prospective	116 treated/OLT unspecified	TACE	Patients with diseases within the Milan criteria who responded to therapy had improved survival rates.
Lu, et al ⁵⁰	2005	Retrospective	52 treated/40 DDLT, 1 LDLT [‡]	RFA	41 patients had a liver transplant. Post-OLT survival rates at 1- and 3-years were 85% and 76%. No patients had a HCC recurrence.

Abbreviations: DDLT, deceased-donor liver transplant; HACE, hepatic arterial chemoembolization; HCC, hepatocellular carcinoma; LDLT, living-donor liver transplant; LRT, locoregional therapy; OLT, orthotopic liver transplant; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transarterial chemoembolization

[†]Either from in vivo splitting of deceased- or living-related donor; [‡]Not all patients in study received OLT

transplant and 3 dropped out owing to tumor progression. The 1- and 3-year survival rates after LT were 85% and 76%, which is comparable to overall survival after LT in patient's without HCC.⁵⁰ Additionally, no patients developed recurrent HCC by the end of the study at 3 years. When use of RFA as pre-LT treatment was studied prospectively, the 2 recurrences observed in 50 patients were in patients with partial response to RFA, both with tumors > 5 cm.⁵¹ In a retrospective study of 64 patients undergoing pretransplant ablative therapy, Porrett had conflicting results.⁵² The authors found no significant difference between the treated and untreated groups in overall survival, disease-free survival, cancer recurrence, or mortality from cancer recurrence after 36 months of follow-up.⁵² While it is difficult to discern a positive effect of pre-LT RFA based on these conflicting studies, RFA may inhibit tumor progression in patients on the wait list and decrease HCC recurrence after LT. More studies are required to make strong evidence-based conclusions on this treatment for evaluating HCC recurrence.

Transarterial chemoembolization, percutaneous ethanol injection, or acetic acid injection and radiofrequency ablation

A recent study from Lao and associates described a significant benefit in reducing the likelihood of recurrence in patients awaiting transplant for HCC who undergo any type of monotherapy (RFA, TACE, PEI) as pretreatment.⁵³ The authors reported a lower incidence of recurrence in patients with T1 and T2 tumors associated with any type of pretransplant therapy, which is in direct contrast with the previous aforementioned studies, but consistent with the observations of Yao and associates, who demonstrated that locoregional therapy before transplant conferred a survival benefit for larger tumors.^{53,54} In a subgroup analysis of patients with T3 tumors, the 1- and 5-year recurrence-free survival of the 29 patients with preoperative treatment was 93.1% and 85.9%, significantly better than the 1- and 5-year respective survival rates of 68.6% and 51.4% for the 7 patients in the group without preoperative treatment.⁵⁴ In a prospective study of 30 patients by Yao and associates evaluating the outcome of patients treated with locoregional therapy intended for tumor down-staging, the authors found no evidence of HCC recurrence in patients who had been treated.⁵⁵ Thirty patients were enrolled, and 21

met criteria for down-staging with locoregional therapy. Sixteen of 21 patients received LT, with no episodes of recurrence at a median follow-up of 16 months; however, the authors note the relatively short follow-up.⁵⁵ Several other investigators have found that patients with a complete or partial response to locoregional therapy trend toward improved survival, although this finding is not statistically significant.^{56,57} Owing to the lack of large multicenter randomized prospective trials, no firm conclusions can be made yet on the role of locoregional therapy as a pretreatment modality to prevent HCC recurrence and improve survival after LT.

Adjuvant chemotherapy

Systemic chemotherapy has been studied as an adjuvant agent during the initial LT with the goal of decreasing HCC recurrence in high-risk patients. Sorafenib has gained attention owing to its positive effects on survival in HCC patients who have not undergone LT. Although promising, using sorafenib before LT to decrease the incidence of recurrence of HCC after LT has not been sufficiently evaluated. Borentain and associates published a case report of a patient treated with sorafenib before transplant, in which the transplant was safely performed and in which histologic examination showed complete necrosis of the largest tumor nodule.⁵⁸ In a case series of 7 patients, Saidi and associates also showed that sorafenib did not negatively affect the postoperative course and seemed relatively safe in LT recipients.⁵⁹

In a pilot study of 33 HCC patients listed for transplant by Truesdale and associates, 10 patients were treated with sorafenib before LT. The authors found that the sorafenib group had a higher rate of early biliary complications (67% compared to 17% in the control group). Additionally, there was more acute cellular rejection in the sorafenib group compared with the control group (67% vs 22%).⁶⁰ However, overall death rates were not significantly different in either group. There was no comment on sorafenib's effect on HCC recurrence by the investigators in this study. In a retrospective study by Saab and associates, sorafenib was given to 8 patients with a higher risk of HCC recurrence based on presence of poor tumor differentiation, tumor staging beyond the Milan criteria, and presence of lymphovascular invasion. The authors found in this small study that in treated patients compared with

controls, recurrence was increased for patients with microvascular invasion (0% vs 57%), tumors exceeding UCSF criteria (17% vs 43%), and tumors showed both features on explant pathology (0% vs 50%).⁶¹ Additional large-scale studies are required to evaluate sorafenib use before LT regarding efficacy and safety.

Another systemic agent with potential activity against recurrent HCC includes¹³¹ I-labelled metuximab (also known as licartin). It is a murine monoclonal antibody directed against HCC cells with a certain antigen, HAb18G/CD147. A group from China tested licartin in a placebo-controlled randomized double-blind study of 60 patients after LT with HCC as adjuvant therapy.⁶² Thirty patients received licartin 3 weeks after LT. While the follow-up was short, the results are optimistic. At 1-year follow-up, the recurrence rate in the treatment group was 26.7% compared with a recurrence rate of 57.1% in the control group with a difference of 30.4%, which was statistically significant. Additionally, the survival rate increased by 20.6% in the treatment group compared with the control group, and medication was well tolerated without any treatment-related toxic effects.⁶²

Other than sorafenib and licartin, no systemic treatment has been shown to prolong survival in patients with locally advanced or metastatic HCC in a randomized prospective trial. Standard systemic chemotherapy, usually based on a doxorubicin regimen, does not provide a clear benefit in terms of survival or in preventing recurrence. Several studies of adjuvant chemotherapy in patients with HCC undergoing LT have shown mixed results. The varied treatment regimens, small sample size, and poor quality of studies without adequate controls make it difficult to establish a conclusion on this practice. In a prospective randomized study from Soderdahl and associates from Sweden evaluating whether adjuvant chemotherapy could prevent recurrence in 42 patients undergoing LT for HCC, adjuvant therapy with low-dose doxorubicin did not improve survival or prevent recurrence.⁶³ Three-year overall survival and disease-free survival in the control group were 70% and 50%. In the chemotherapy group, both overall survival and disease-free survival were 63%. Freedom from recurrence at 3 years was 55% in controls and 74% in the chemotherapy group. None of these differences was statistically significant, and only 59% of patients

tolerated the prescheduled number of doses owing to adverse events of the medication.⁶³

Several recent studies highlight a potential benefit with use of adjuvant chemotherapy; however, sample size for each study is small. Hsieh and colleagues studied 45 patients after LT for HCC, assessing the use of adjuvant gemcitabine and cisplatin chemotherapy on disease-free survival.⁶⁴ The authors found that patients who fit the Milan criteria and patients who did not fit Milan criteria (but received adjuvant chemotherapy) did better with respect to disease-free survival than did a group of patients who did not fit Milan criteria and did not receive chemotherapy. The chemotherapy regimen was fairly well tolerated, with 100% completion rate of chemotherapy, although the study was small and not randomized.⁶⁴ This study revealed that there may be promise in treating LT patients who fall outside of Milan criteria with adjuvant chemotherapy.

In the most recent randomized prospective trial, Zhang and associates evaluated the efficacy of postoperative adjuvant chemotherapy with the FOLFOX chemotherapy regimen in LT patients who did not meet the Milan criteria.⁶⁵ Fifty-eight patients were randomized to either a FOLFOX treatment group after LT or LT alone. The authors concluded that the treatment group had improved median survival by 4.57 months with combination chemotherapy. The 1- and 3-year survival rates were 89.7% and 79.3% with chemotherapy versus 69.0% and 62.1% without chemotherapy. The 6-month tumor-free survival rate was 24.1% higher with chemotherapy than without. The recurrence rate after LT was significantly different between the 2 groups at 6 months, but not at 3 years.⁶⁵ The chemotherapy regimen was generally well tolerated. Post-LT adjuvant chemotherapy with the FOLFOX regimen did not prevent tumor recurrence after LT, but may have improved the survival of HCC patients after LT who did not meet the Milan criteria.⁶⁵

Posttransplant—Immunosuppression effects on hepatocellular carcinoma recurrence

Current evidence suggests that standard immunosuppression regimens with calcineurin inhibitors (CNI) and corticosteroids increase the risk of HCC recurrence (Table 3). Cyclosporine and tacrolimus, the most-common immunosuppressants used, have been reported to increase posttransplant risk of recurrence of HCC in a dose-dependent

Table 3. Effect of Immunosuppression on Hepatocellular Carcinoma Recurrence

Name	Year	Type of Study	Number of Patients/ Type of Transplant	Treatment	Authors' Comments
Vivarelli, et al ⁶⁶	2008	Retrospective	139 (60 TAC, 79 CSA)/OLT unspecified	Calcineurin inhibitors	High exposure to TAC or CSA increased HCC recurrence rates. Choice of calcineurin inhibitor did not affect risk of recurrence.
Kneteman, et al ⁷⁰	2004	Retrospective	40 /all DDLT	Sirolimus-based immunosuppression	Immunosuppression improved HCC recurrence and survival rates in Milan and Extended Criteria Groups.
McAlister, et al ⁶⁹	2001	Prospective	56 /OLT unspecified	Combination of sirolimus and tacrolimus	Combination had positive results. Multicenter, randomized, controlled trial needed to compare benefits to other immunosuppressants.
Trotter, et al ⁶⁸	2001	Retrospective	39 (17 TAC, 22 CSA and sirolimus)/32 DDLT, 7 LDLT	Sirolimus	Sirolimus may be an effective immunosuppressant.
Toso, et al ⁷¹	2007	Prospective	70 /all DDLT	De novo sirolimus-based immunosuppression	Associated with beneficial outcomes after liver transplant.
Wang, et al ⁷²	2010	Case Study	1 /OLT unspecified	Sirolimus + sorafenib	Further studies needed to determine efficacy of sirolimus in combination with sorafenib.
Zhou J, et al ⁷⁴	2006	Retrospective	36 /OLT unspecified	Conversion to sirolimus-based immunosuppression.	Patients converted to sirolimus-based regimen may have a decreased rate of recurrence and metastasis. Conversion also may improve renal function.
Toso C, et al ⁷⁸	2010	Retrospective	2491 (109 sirolimus-based, 2382 other immunosuppressants) /OLT unspecified	Sirolimus-based immunosuppression	Sirolimus-based and anti-CD25 antibody induction regimens significantly improved survival rates, while the other regimens did not.
Zimmerman MA, et al ⁷⁵	2008	Retrospective	97 (52 CNIs + mycophenolate mofetil + corticosteroids; received sirolimus + CNIs) /80 DDLT, 17 LDLT	Sirolimus-based immunosuppression	Patients in sirolimus regimen had greater 1- and 5-year survival rates (95.5% and 78.8% vs 83% and 62% for CNI-based regimen). Sirolimus patients had slight improvement in renal function.
Vivarelli M, et al ⁷³	2010	Prospective	62 (31 tacrolimus-based, 31 sirolimus-based) /OLT unspecified	Sirolimus-based immunosuppression	Patients in sirolimus regimen had a greater 3-year survival rates (95.5% and 78.8% vs 83% and 62% for CNI-based regimen). Sirolimus patients had slight improvement in renal function.
Chinnakotla, et al ⁷⁷	2009	Retrospective	227 (106 TAC + mycophenolate mofetil, 121 sirolimus) /226 DDLT, 1 LDLT	Sirolimus-based immunosuppression	Patients in sirolimus regimen had a greater frequency of recurrence-free survival at 1, 3 and 5 years. Sirolimus patients did not have an increased rate of surgical complications.

Abbreviations: CNI, calcineurin inhibitor; CSA, cyclosporine; DDLT, deceased-donor liver transplant; HCC, hepatocellular carcinoma; LDLT, living-donor liver transplant; OLT, orthotopic liver transplant; TAC, tacrolimus

manner.⁶⁶ However, it is not clear if there is a differential risk with either CNI.

Sirolimus

A novel group of immunosuppressants, mammalian target of rapamycin (mTOR) inhibitors including sirolimus and everolimus, have antineoplastic effects, and can maintain antiproliferative effects at drug levels achieved with current immunosuppression dosages.⁶⁷ When sirolimus is used for immunosuppression after transplant in HCC patients, multiple retrospective studies and case reports have revealed trends of lower recurrence rate and metastasis of HCC after LT.⁶⁸⁻⁷⁸

However, the timing of when to start mTOR inhibitors after LT is debatable, particularly with early reports of hepatic artery thrombosis when sirolimus is used immediately after transplant.^{79,80} It

is also unclear if mTOR should be used at the time of HCC recurrence. Use of sirolimus is not standardized and has been studied in different combinations with other immunosuppressive agents and at different time points, thus the studies are difficult to interpret. In a recent metaanalysis of 5 studies with a total of 2950 participants, Liang and associates found a clear benefit on 1-, 3-, and 5-year patient survival for sirolimus-based immunosuppression versus sirolimus-free regimens.⁸¹ Additionally, sirolimus-based regimens were associated with a significant decrease in HCC recurrence rates with no significant decrease in the frequency of posttransplant complications.⁸¹ Results of an ongoing prospective randomized trial evaluating mTOR-inhibitor-based immunosuppression versus mTOR-free immunosuppression in LT patients are awaited.⁸²

Corticosteroid effect on hepatocellular carcinoma recurrence

Currently, the use of corticosteroids (CS) for immunosuppression in LT is commonly used to prevent and treat LT rejection.⁸³ However, there is also concern that CS may play a role in HCC recurrence after LT. A dated study from Italy found that the withdrawal of steroids by 6 months decreased the risk of HCC recurrence compared with continuous, prolonged steroid use.⁸⁴ Several more-recent studies have evaluated early withdrawal of CS with conflicting results. Chen and associates assessed 54 patients undergoing LT for HCC. They divided patients into 2 groups: a 3-month steroid withdrawal group and a steroid maintenance group. In a 1-year follow-up, the authors found that the incidence of rejection was not different in either group, but tumor recurrence rates were significantly decreased in the steroid withdrawal group compared to the maintenance group, 39% versus 62%. One-year survival rates were not significantly different, which, according to the authors, was likely due to small sample size and short-term follow-up.⁸⁵ While Chen could show a difference in HCC recurrence rates, Kim and associates found no difference in HCC recurrence between patients treated with a short course of CS compared with those treated with prolonged CS treatment after LT. Actually, higher tumor recurrence rates were found in the early withdrawal group compared with late withdrawal, although not statistically significant.⁸⁶ Further prospective randomized studies are required to reach accurate conclusions on the effect of CS on recurrence of HCC and the safety of a quick steroid taper with respect to rejection.

Mycophenolate mofetil

The use of mycophenolate mofetil as an immunosuppressant has increased dramatically in the past decade⁸⁷; however, there currently are not enough data to comment on its effect on HCC recurrence after LT.

Surveillance for hepatocellular carcinoma recurrence

Currently, there is a dearth of literature on the subject of monitoring HCC patients after LT for recurrence. Because HCC recurrence after LT clearly affects outcomes and survival, it is a priority for early discovery. There is no standardized way to monitor these patients across institutions; however, most

programs combine regular imaging studies with AFP levels at regular close intervals for several years. At our institution, University of California, Los Angeles, patients are split into categories depending on their risk of recurrence. Any patient with lymphovascular invasion or explant pathology suggestive of high risk will receive surveillance imaging of the chest, abdomen, and pelvis, and AFP levels every 3 months for 2 years. After 2 years, the patients undergo surveillance every 6 to 12 months for 3 years. If there is no lymphovascular invasion, the patient receives surveillance imaging every 6 months for 3 years, then annually for 2 years. Both patient groups undergo testing for AFP levels every 3 months for life. It is unclear if this is the best strategy, as there is no literature on the subject. It should be a goal to make a standardized method for monitoring these patients across institutions that is based on randomized data. Additionally, it is unknown if other HCC biomarkers, such as AFP-L3, DCP, and ferritin levels would be useful in this population.

Posttransplant—Treatment of hepatocellular carcinoma recurrence after transplant

Resection

Very few treatment options are available for patients with recurrent HCC after LT. Most patients present with disseminated disease and are not candidates for surgical therapy.⁸⁸ Surgical resection often is used in a subgroup of patients with localized recurrence as it may confer a survival advantage. A few groups have reported results in a small number of patients suggesting increased survival for patients undergoing resection. Roayaie and associates observed 57 recurrences in 311 patients who had transplants for HCC.¹² Five patients underwent liver resection and 7 patients underwent lung resection. Survival in patients treated with surgical resection was significantly better than those who were not: patients who underwent resection had a 47% survival rate at 5 years compared with a twenty-two percent 5-year survival rate for patients with recurrence who did not undergo resection.¹² Kornberg and associates also identified survival advantage for patients undergoing surgical resection for recurrent HCC.²⁴ The authors evaluated 16 recurrences after LT in 60 patients transplanted for HCC. Seven patients were candidates for surgical resection, while 9 patients received only adjuvant treatment or general medical support. Median

survival duration after recurrence was 65 months in patients amenable to surgical therapy, and 5 months in patients unsuitable for surgical intervention. Multivariate analyses identified late after LT tumor relapse and surgical therapy as independent predictors of long-term survival after tumor relapse.²⁴ While aggressive resection of recurrent disease is not possible in many patients, survival advantage may be achieved in patients with localized disease. The small size of the studies in the literature limits their validity, and no conclusions can be made.

Locoregional therapies

Select patients with unresectable HCC recurrence may undergo locoregional therapy with potential improvement in survival. In a recent retrospective case control study by Zhou and associates of 28 patients with unresectable recurrent HCC, TACE was found to be associated with longer survival after LT after diagnosing HCC recurrence.⁸⁸ The median overall survival after LT for patients in the TACE group was 865 days compared with 228 days for those in the nonchemoembolization group ($P = .0133$). While Zhou's study has shown that locoregional therapy may be effective in prolonging survival for patients with HCC recurrence after LT, locoregional therapy does not seem to prevent the recurrence of new lesions.⁸⁸ In a study by Ko and associates, 28 patients who underwent TACE after LT were evaluated for tumor response, 68% of patients obtained targeted tumor reduction in size by 25%.⁴³ Nevertheless, intrahepatic recurrence or extrahepatic metastasis occurred in 75% of patients in the 3-month follow-up and 93% in the 6-month follow-up, with

65% of patients having extrahepatic metastases. It is likely that any survival benefit locoregional therapy may confer to patients with HCC recurrence after transplant is due to control of the recognized tumor rather than preventing new recurrences.⁴³

Sorafenib

Sorafenib has gained significant interest in treating patients with HCC recurrence after LT, and has shown promising results with minimal adverse effects (Table 4).^{45,58-61,86-87} Yoon and associates found that after treating HCC recurrence with sorafenib, 6 of 10 patients showed a best response of stable disease compared with palliative chemotherapy that resulted in stable disease of best response in 4 of 24 patients.⁸⁹ Patients on sorafenib also had longer time to progression than did the chemotherapy group, with 5.4 months to progression in sorafenib group versus 1.6 months in the chemotherapy group.⁸⁹

Furthermore, Kim and associates performed a retrospective study analyzing 9 patients who received sorafenib after LT for HCC and found that there were no unexpected complications from interactions with immunosuppression and 4-month survival was $84\% \pm 15\%$. One patient had complete radiological remission, and 1 patient with lung recurrence was treated for nearly 18 months.⁹⁰ Additionally, in a case report from Yeganeh and associates, the authors reported a complete remission after starting sorafenib in a post-LT patient with a solitary metastatic pulmonary lesion. The patient was continued on treatment for 2 years with sorafenib with tolerable adverse events and a complete response.⁹¹ Evidence from the limited studies to date indicates that sorafenib can be used in patients with recurrent HCC

Table 4. Adjuvant Chemotherapy-Sorafenib

Name (Ref)	Year	Type of Study	Number of Patients/ Type of Transplant	Treatment (Pretransplant and Posttransplant)	Authors' Comments
Borentain, et al ⁵⁸	2011	Case study	1/OLT unspecified	Sorafenib (pre) treated with sorafenib.	Liver transplant can be safely performed in a patient. Further trials needed to evaluate safety and efficacy.
Saidi, et al ⁵⁹	2010	Retrospective	7/OLT unspecified	Sorafenib (pre)	Sorafenib seems to be a safe treatment, although more trials are needed.
Yoon, et al ⁸⁹	2010	Retrospective	13/all LDLT	Sorafenib (post)	Sorafenib may be a safe and effective treatment for recurrent HCC.
Saab, et al ⁶¹	2010	Retrospective	16 (8 treated, 8 control)/ OLT unspecified	Sorafenib (post)	Sorafenib may be a safe and beneficial treatment; disease-free and overall survival rates improved. Further trials needed.
Kim, et al ⁹⁰	2010	Retrospective	9/all DDLT	Sorafenib (post)	Sorafenib can be safely administered, but dose adjustments may be necessary. Larger clinical trials needed.
Yeganeh, et al ⁹¹	2009	Case study	1/OLT unspecified	Sorafenib (post)	Complete remission of HCC reported in patient. Further studies needed.

Abbreviations: DDLT, deceased-donor liver transplant; HCC, hepatocellular carcinoma; LDLT, living-donor liver transplant; OLT, orthotopic liver transplant

after LT with tolerable toxicity; however, a dosage adjustment may be required.

Discussion

Liver transplant can be the definitive treatment for a select group of patients with HCC. Not only does LT effectively remove the HCC, but it also replaces the milieu it arose from. A rate-limiting step in transplanting patients with HCC is the risk of recurrent HCC. Indeed, immunosuppressive agents likely increase the risk and rate of recurrent HCC. With the incidence of HCC increasing and the tendency to expand and relax selection criteria for transplant, an understanding of how to treat recurrent HCC is critical.

Preventing recurrent HCC starts with properly selecting patients for liver transplant as therapy for HCC. Specifically, there are several accepted pretransplant predictive factors of posttransplant recurrent HCC: namely, *tumor burden, presence of vascular invasion, and poor tumor differentiation*. Indeed, patients whose HCC total tumor diameter is > 10 cm have 5-fold lower survival probability than do patients with smaller tumor diameters.²⁵ Additionally, patients with a tumor nodule > 5 cm have a 2.5-fold probability of developing recurrence than do patients with smaller tumor nodules.²⁵ Emerging data suggest that absolute or changes of AFP serum concentration also may identify liver transplant recipients at increased risk of recurrent HCC. Although it makes intuitive sense that pretransplant treatment of HCC in patients waiting for liver transplant will decrease the risk of recurrent HCC after surgery, definitive studies are lacking. Use of sorafenib in patients actively waiting for a liver transplant merits further study in regard to perioperative and postoperative safety parameters. The approach to recurrent HCC during the LT period can be classified as either adjuvant or empiric. Unfortunately, studies on treating recurrent HCC under either classification have been limited to small case series and case reports. Nevertheless, an adjuvant approach should be considered in patients at high risk of HCC recurrence such as those with lymphovascular invasion, large tumors found at explant, and those with aggressive tumors.

The approach to treating established recurrent HCC depends if the recurrent lesion is solitary or multifocal. Based on retrospective studies in the

literature, it seems that solitary lesions can often be surgically resected, which is associated with improved survival. In both solitary and multifocal recurrent HCC, systemic therapy also should be considered in the form of sorafenib and/or sirolimus. Sorafenib has shown significant promise in improving overall survival and having a tolerable safety profile in patients with recurrent HCC in the retrospective studies and case reports thus far; however, no prospective studies in LT patients have been performed.^{58,59,61,89-91} Alternatively, there have been several smaller prospective studies on sirolimus, which showed encouraging results in LT patients at high risk for HCC recurrence when used as the *de novo* immunosuppressive agent and in combination with tacrolimus, in addition to the many retrospective studies, which revealed beneficial outcomes in patients on sirolimus for immunosuppression who have recurrent HCC.⁶⁶⁻⁸¹ While promising, there are many unanswered questions regarding the use of sorafenib and sirolimus such as the timing of their introduction after transplant and the length of treatment. Prospective randomized controlled studies evaluating the immunosuppressive regimen in HCC patient's undergoing LT, as well as treatment modalities for recurrent HCC including surgical approaches and systemic chemotherapies are eagerly anticipated in the near future.

Many challenges persist in treating HCC recurrence after liver transplant. Much of the research performed in this field is composed of small retrospective studies, sometimes with no control group as the patient sample size is relatively small. Improving study quality with multicenter prospective trials, while difficult, will lead to a better understanding of appropriate treatment in patients with HCC recurrence postliver transplant.

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