REVIEW ARTICLE

Hepatocellular Carcinoma in Patients Listed for Liver Transplantation: Current and Future Allocation Policy and Management Strategies for the Individual Patient

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Liver transplantation can provide definitive cure for patients with cirrhosis and hepatocellular carcinoma (HCC) when used appropriately. Advances in the management of HCC have allowed improved control of HCC while waiting for liver transplantation and new approaches to candidate selection particularly with regard to tumor burden and downstaging protocols. Additionally, there have been recent changes in allocation policy related to HCC in the U.S. that cap the HCC MELD exception at 34 points and implement a 6-month delay in a HCC MELD exception. This review examines the U.S. liver transplant allocation policy related to HCC, comprehensively details locoregional therapy options in HCC patients awaiting liver transplantation, and considers the impact of an increasing burden of HCC on future liver graft allocation policy. ***Liver Transpl 21:1543-1552, 2015***. © **2015 AASLD.**

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Hepatocellular carcinoma (HCC) is the third most common cause of cancer death with a worldwide incidence of 700,000 annually.[1] After decades of significant increase of HCC incidence in Western countries, it has recently shown evidence of peaking in the United States.[2,3] Up to 90% of patients with HCC have preexisting cirrhosis, and the 5-year risk of HCC among patients with cirrhosis ranges from 5% to 30%.[4] Hepatitis B and C virus, alcoholic liver disease, and hereditary hemochromatosis result in the highest rates of HCC development.[4] Without treatment, 5-year survival of HCC is roughly 20%.

Liver transplantation can provide a definitive cure for patients with cirrhosis and HCC. According to Organ Procurement and Transplantation Network (OPTN) data as of June 26, 2015, approximately 5% of patients listed for liver transplantation in the United States have HCC. One-year liver transplant wait-list dropout rates for patients with HCC are estimated between 10% and 40%,[5-7] and the US liver transplant allocation policy provides increased priority for patients with HCC within certain size criteria (Milan criteria) to allow for a transplant opportunity before tumor progression. With worsening organ shortage, viable options to delay transplant for patients with HCC are increasingly attractive. Locoregional therapies have evolved to limit tumor progression and can serve as a bridge to liver transplantation before the tumor burden is prohibitive.

The future impact of HCC on liver transplantation is unclear. Although significant concern exists about the

Abbreviations: AFP, alpha-fetoprotein; cTACE, conventional transarterial chemoembolization; DAA, direct acting antiviral; DEB, drug-eluting bead; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LRT, locoregional therapy; MELD, Model for End-Stage Liver Disease; MWA, microwave ablation; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OPTN, Organ Procurement and Transplantation Network; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; SVR, sustained virological response; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; UCSF, University of California, San Francisco; UNOS, United Network for Organ Sharing; Y90, Yttrium-90.

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burden of HCC on allocation, improved therapies for hepatitis C virus (HCV) promise to reduce the contribution from viral liver disease. Variable access to these medications presents a short-term limitation. This review examines the US liver transplant allocation policy with regard to HCC, comprehensively details the locoregional approach in HCC patients awaiting liver transplantation, and considers the future of HCC and its role in liver transplant allocation.

HEPATOCELLULAR CARCINOMA IN TRANSPLANTATION AND CURRENT ALLOCATION POLICY

The Model for End-Stage Liver Disease (MELD) score predicts 90-day mortality from liver disease and has been the backbone for US liver transplant allocation since February 2002. This system prioritizes patients with the highest liver disease mortality risk instead of time on the waiting list in accordance with the Department of Health and Human Services' 1998 Final Rule. The MELD system uses a single priority score but is applied to a heterogeneous group of liver diseases, capturing risk more accurately for some disease states than others. It is an urgency-based priority system and does not reflect posttransplant outcomes. Adaptations have been made to the standard MELD system to account for disease states whose risk is underprioritized by MELD, for which HCC is the prime example. The HCC prioritization model attempts to capture both urgency and outcome components.

Urgency Component

Using calculated MELD scores for liver graft allocation, underprioritization of HCC occurs because the 3-month mortality risk predicted by the MELD score is often less immediately threatening than the risk of tumor progression. The transplant community addressed this problem by assigning MELD exception points for patients in need of higher priority. MELD exception points are intended to equate predicted risk of dropout from tumor expansion in patients with HCC to the 3-month mortality predicted by the MELD score in non-HCC patients.

Initially, the number of MELD exception points assigned for HCC was arbitrarily chosen. Subsequent United Network for Organ Sharing (UNOS) population level analyses suggested that the initial exception MELD score given to patients with HCC was too high. Automatic MELD exception points were decreased in 2003, 2004, and 2005, and a waiting period for the upgrade was implemented in 2014. In October 2015, UNOS implemented new allocation policy in which patients with tumors meeting the Milan criteria are listed for 6 months at their calculated MELD. If the tumor remains within the appropriate limits for 6 months, they are given 28 points with MELD increases every 3 months thereafter equivalent to 10% mortality risk capping at 34 points.

Despite the adjustments to the MELD exception system for HCC patients, transplant candidates with HCC are likely still overprioritized relative to noncancer candidates. The overprioritization occurs because the MELD exception system is a noncontinuous risk model informed primarily by the state of the lesion at diagnosis, and HCC patients' priority increases regardless of tumor response to management provided it remains within the Milan criteria. Using a continuous model equating priority to a dynamic score estimating wait-list dropout may increase risk assessment accuracy. Risk factors identified for wait-list dropout of HCC patients include tumor size,[8-11] tumor number,[8,9,12] MELD score,[10-12] and alpha-fetoprotein (AFP).[10,11,13,14] Scoring systems with these risk factors can be used to stratify patients by wait-list dropout risk and could be updated dynamically as the variables change for individual patients.[10,13] Despite recommendations from a national conference,[15] there are no current efforts to include this into allocation policy.

Outcome Component

Liver transplant remains the best chance for the cure of HCC in the setting of cirrhosis because it addresses both the tumor and the underlying cirrhosis. However, posttransplant HCC recurrence limits the utility of liver transplant for large tumor burden and must be considered when offering liver transplantation. Several early studies showed high rates of posttransplant recurrence for patients with large tumor burdens but recognized a role for liver transplant in patients with small tumors. In 1996, Mazzaferro et al.[16] described a pretransplant tumor profile referred to as the Milan criteria that resulted in acceptable posttransplant HCC recurrence rates (single tumor up to 5 cm or no more than 3 tumors up to 3 cm each). The Milan criteria predicted 85% overall and 92% disease-free survival at 4 years and remains the most broadly accepted limits for liver transplantation in patients with HCC.

Patients within the Milan criteria are eligible to receive the automatic MELD exception points described previously. In order to receive standard MELD exception points in the United States, there must be at least 1 tumor 2 cm or greater, the total tumor burden must be within the Milan criteria, and there must be no evidence of macrovascular invasion or extrahepatic spread. In order to qualify as HCC lesions, they must meet cross-sectional imaging specifications defined by the OPTN, including contrast enhancement of the lesion in late hepatic arterial images, size >2 cm, plus 1 of the following:

1. Washout on portal venous/delayed phase.
2. Late capsule or pseudocapsule enhancement.
3. Growth by 50% or more obtained on imaging <6 months apart.
4. Biopsy proven HCC.

In addition, images must be reviewed by an OPTN-approved transplant hospital, and all applications not meeting strict and detailed imaging definitions will

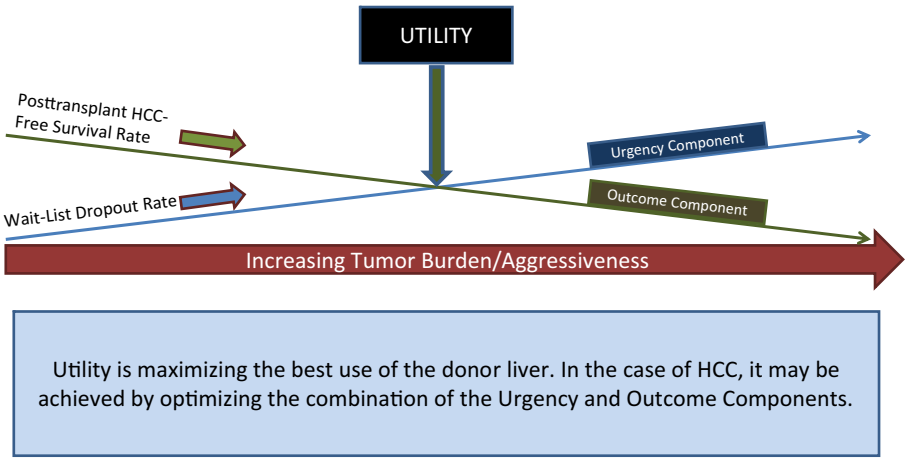

Figure 1. Diagram of the relationship between the urgency and outcome components and utility pertaining to liver transplantation for candidates with HCC.

require prospective review by the regional review board.

Despite the Milan criteria's broad use, the absolute limit of HCC burden for liver transplant is controversial. Several studies found acceptable posttransplant HCC recurrence rates with tumor burden greater than the Milan criteria.[17,18] These staging systems include the University of California, San Francisco (UCSF) criteria (single tumor up to 6.5 cm or 3 or fewer tumors up to 4.5 cm with the total tumor burden no larger than 8 cm)[19] and the up-to-7 rule (number of tumors added to the size in cm of the largest tumor no larger than 7).[17] Despite a larger tumor burden, some patients still have a low risk of recurrence after transplant, though there is some uncertainty in identifying these patients before transplant given the heterogeneity of tumor biology. The risk of recurrence appears to be a continuum as tumor size and number increase, but there is no clear cutoff for radiographically apparent HCC at which the recurrence risk is 0.[20] There is a continuous risk assessment score available called "The Metroticket" whereby the number of tumors and the size of the largest tumor can be used to predict posttransplant recurrence risk.[17] This score describes a continuum of posttransplant recurrence risk predictions instead of a dichotomous threshold like the Milan criteria. Use of a continuous scoring system like the Metroticket could help the selection of patients with larger tumor burden of HCC for transplant priority. A posttransplant survival cutoff of 60% has been suggested as a lower limit for transplanting HCC beyond the Milan criteria.[21]

As a diagnostic test, serum AFP is criticized for suboptimal test characteristics and is not included in surveillance guidelines by prominent hepatology societies.[22] However, AFP could play a role in risk stratifying HCC lesions already diagnosed. Dichotomous cutoffs of 100 ng/mL, 250 ng/mL, and 400 ng/mL have shown value for predicting risk of recurrence or identifying acceptable risk tumors for transplant priority.[23-26] Combining AFP with size criteria or other biomarkers may increase the ability to discriminate high-risk from low-risk HCC.[24-26] Currently, AFP is not used in UNOS protocols for automatic exception points but can be considered in a case-by-case basis by regional review boards for nonstandard priority petitions.

"Downstaging" is shrinking tumors outside of the Milan criteria with locoregional therapy (LRT) to scale into the Milan criteria. A systematic review[27] of 8 studies[28-35] assessing the posttransplant outcomes of patients with tumors downstaged to within the Milan criteria found survival and disease-free survival rates at 1, 3, and 5 years comparable to those for patients who were never outside of the Milan criteria. Specific downstaging protocols have been developed and validated, including Yao et al.[35] who studied a protocol taking a maximum tumor burden (1 lesion between 5 and 8 cm, 2 to 3 lesions between 3 and 5 cm with total tumor diameter no larger than 8 cm, or 4 to 5 lesions no bigger than 3 cm with total tumor diameter no larger than 8 cm), reducing it to within the Milan criteria, and waiting 3 months between treatment success and transplant. This protocol yielded posttransplant 4-year survival rates of 92.1%, with no HCC recurrence after a median posttransplant follow-up of 25 months. Comparison between patients undergoing downstaging with this protocol and patients within the Milan criteria at inclusion showed no difference in 5-year posttransplant survival and recurrence-free survival.[36] Other protocols with various inclusion and success criteria exist with reasonable posttransplant disease-free survival.[30,37] Although no individual protocol is universally followed, most centers require downstaging to within the Milan criteria with a period of waiting between achieving downstaging and transplantation (see Downstaging Locoregional Therapy below). For patients with AFP $>$ 1000 ng/mL before treatment, an AFP goal of $<$ 500 ng/mL is recommended.[15]

Uncertain size criteria for acceptable disease burden and downstaging goals obscure best prioritization practices for patients with tumors beyond the Milan

TABLE 1. Comparisons of LRT Modalities

Modality	Types	Advantages	Contraindications
TACE	cTACE DEB-TACE	Increase intratumoral chemotherapy concentration Multiple choices for chemotherapy	Child-Pugh score C, poor performance status, left to right shunt, active inspection, bleeding, advanced stage cancer, bilirubin > 3-7 mg/dL
TARE	TheraSphere SirSpheres	Reduced risk of posttherapy embolization syndromes	Bilirubin > 2 mg/dL, severe liver function perturbations
Ablation	PEI RFA MWA	90% to 97% complete ablation rate for HCC within the Milan criteria	Large tumors, Child-Pugh C cirrhosis, anatomic location (high dome location near the diaphragm or adjacent to critical extrahepatic structures)

criteria with or without downstaging. Most regions in the United States review priority petitions for such tumors on a case-by-case basis with a regional review board rather than automatically grant increased priority.

Utility

An allocation model based on utility (best use of the liver graft) would need to incorporate both urgency and outcome components. Figure 1 depicts the relationship between the urgency and outcome components and utility. The current system attempts to achieve utility by prioritizing HCC patients but limiting prioritization to those within the Milan criteria. As discussed above, this method is limited by insensitivity to changing tumor characteristics after attempts at therapy and by lack of clarity on the existence of an ideal size threshold. Again, models that can be applied at any time to determine transplant priority and that can change based on changes in tumor characteristics in real time could be useful. One potential method is to model adjusted MELD scores to equate transplant benefit between HCC and non-HCC patients.[38] Work into defining utility models for HCC patients exists, but it is limited at this point.

EFFECT OF HEPATOCELLULAR CARCINOMA ON LIVER TRANSPLANT ALLOCATION

The number and proportion of liver transplant candidates receiving MELD exception points for HCC has been increasing, and the effects of an increased demand for liver transplant grafts for HCC on the allocation system should be thoroughly analyzed. The current allocation of HCC creates a "MELD escalator" effect where exception MELD points increase regardless of management. This unidirectional progression of MELD exception points likely contributes to inflation of MELD scores at transplant across the United States. In fact, this effect was found to be the primary driver of MELD inflation in all regions independent of geography.[39] Balancing the urgency and outcome components for patients with HCC is essential to ensure the equity of deceased donor allocation. As discussed above, this may be best achieved by using a continuous scoring system reflecting response to treatment and tumor biology, using surrogates like biomarkers, growth rate, and size.

MULTIDISCIPLINARY HEPATOCELLULAR CARCINOMA MANAGEMENT

Integral to understanding the effect of HCC on liver transplant allocation is appreciation of management options for bridging therapy and downstaging. HCC management in liver transplant candidates is unique in that effective therapy for cancers <2 cm is withheld in favor of allowing further growth. Allocation policy creates an incentive to wait for tumors to grow to within the Milan criteria in order to obtain transplant priority. Once the tumor has reached the Milan criteria lower limit, the goal becomes tumor burden control until liver transplant. Bridging therapy is appropriate for patients already within the Milan criteria and buys time while the MELD exception points increase. LRT is the dominant bridging modality. For patients whose tumors are beyond the Milan criteria, LRT is used for downstaging to become eligible for MELD exception points. Resection is rarely possible in patients awaiting liver transplant because of advanced liver disease; however, patients who undergo resection with pathology suggesting more advanced/aggressive intrahepatic HCC can be considered for salvage with liver transplantation.[40,41] Systemic therapy with sorafenib is also an option for treating HCC.

Bridging Locoregional Therapy

There is no clear consensus about when and how to employ LRT for bridging. Drawing from transplant waitlist dropout risk, average waiting periods of 3 and 6 months or greater are suggested thresholds to employ bridging therapy. LRT modalities can be divided into transarterial and ablative strategies (Table 1).

Transarterial therapy, consisting of transarterial chemoembolization (TACE) and radioembolization, includes the delivery of chemotherapy or brachytherapy directly

to the tumor through its feeding hepatic arterial branches. Hepatic arterial circulation supplies the majority of blood supply to tumors. Conversely, the portal circulation provides the majority of flow to normal liver parenchyma. This allows transarterially delivered treatments to provide selective toxicity to a tumor, particularly in the setting of occlusive embolization. Ablation therapy involves the percutaneous application of chemicals, extreme temperature, or electrical current to injure tumor cells.

Conflicting comparisons of different modalities has led to the heterogeneity of treatments, generally based on local expertise. There is presently insufficient evidence to recommend any particular treatment strategy over another[42]; furthermore, there is limited evidence of the efficacy of LRT in overall survival or prevention of transplant dropout. There is a large heterogeneous amount of literature studying the effect of LRT on wait-list dropout[43] with rate estimates ranging between 4% and 57% depending on population, tumor limit for wait-list removal, type of LRT modalities, and follow-up period. This has led to consensus practice of LRT used in patients requiring either downstaging or with expected transplant wait time >6 months.[42]

Transarterial Chemoembolization

Conventional transarterial chemoembolization (cTACE) in patients with HCC is performed by selective catheterization of the tumor's feeding artery. Protocols for cTACE are highly variable and dependent on local practice. A variety of chemotherapeutic agents have been used including single-drug therapy with doxorubicin or cisplatin, or triple-drug therapy with a mixture of cisplatin, doxorubicin, and mitomycin C. Recent drug shortages have changed drug selection, but doxorubicin is still commonly employed as a single agent in the United States.[44]

Technical variables have been partially standardized by the introduction of drug-eluting beads (DEBs) which bind doxorubicin, irinotecan, or epirubicin. In addition, DEB-TACE eliminates the need for lipiodol. DEB-TACE has the theoretic advantage of positioning the drug for release in the precapillary arterioles where the particles lodge, increasing the intratumoral concentration of the drug while reducing systemic drug and related systemic side effects. Contraindications to TACE include decompensated cirrhosis (Child-Pugh class C), encephalopathy, a diminished performance status (Eastern Cooperative Oncology Group [ECOG] >1), uncorrected left to right shunt, active infection, and uncorrectable bleeding diathesis. Relative contraindications include bilirubin from 3 to 7 mg/dL, advanced cancer stage, portal vein thrombosis, iodinated contrast allergy, biliary obstruction, and renal insufficiency.[43]

Survival benefit following TACE has been demonstrated prospectively in patients with unresectable (intermediate disease) HCC and Child-Pugh A and B cirrhosis.[45] Benefits for bridging or posttransplant survival are less clear with current consensus that LRT should be used in patients with >6 months to expected transplant, given the high dropout rate of patients with >1 year on the wait list.[42]

Transarterial Radioembolization

The utility of external beam radiation is limited by surrounding tissue damage (radiation-induced liver disease) that occurs when radiation doses sufficient to treat adenocarcinomas are applied to the liver. This limitation was the impetus for the development of Yttrium-90 (Y90) transarterial therapy. TARE uses glass microspheres or resin beads impregnated with Y90. TheraSphere (Nordion Inc., Kanata, Ontario, Canada) is approved for treatment of unresectable HCC. SirSpheres (Sirtex Medical Inc., Woburn, MA) are approved for the treatment of metastatic colorectal cancer but are also frequently used for HCC based on local expertise and practice patterns. Beads concentrate in precapillary arterioles within tumor with maximum penetration (<1 cm), limiting the radiation dose to surrounding tissue. As with TACE, injection is performed as selectively as possible in patients with HCC to avoid exposure of the surrounding hepatic parenchyma.[46]

Patient selection is similar to TACE, though TARE requires better preserved liver function. A bilirubin limit of <2.0 mg/dL is used to minimize radiation-induced liver disease. Selective administration permits extension of application in some patients. One advantage of TARE over TACE is less severe postherapy embolization symptoms, permitting outpatient therapy in most cases. Use of Y90 can result in radiation pneumonitis if excessive arteriovenous shunting exists through the liver.

No prospective randomized comparison studies of TACE and TARE have been published in patients with HCC, though response rates and survival of intermediate disease appear comparable. Retrospective series of HCC patients treated with TARE suggest large tumors, and portal vein involvement may be indications for TARE over TACE.[46] In addition, retrospective series have demonstrated that TARE may be more effective for downstaging than TACE in selected populations.[47]

Ablation Therapy

Percutaneous ethanol injection (PEI) was the original technique used for local ablation of HCC and the first available alternative to surgical resection. Injection of ethanol into the tumor causes cellular dehydration, chemical vascular occlusion, and necrosis of the lesion. PEI performs well in inducing complete tumor necrosis in HCC lesions of <3 cm with a good safety profile, though multiple treatment sessions may be required.

Radiofrequency ablation (RFA) has overtaken PEI as the preferred ablative modality for early HCC in the United States. A percutaneous electrode is inserted into the tumor under ultrasound or computed tomography guidance, and electromagnetic waves cause coagulation necrosis of tumor cells. Multiple studies show better local disease control and 3-year survival benefit for RFA compared to PEI for tumors of >2 cm.[48-50] However,

RFA has a marginally increased major complication rate of approximately 3% (intraperitoneal bleeding, pneumothorax, hemothorax, bowel injury, liver abscess, liver failure, and tumor tract seeding) that in some cases precludes transplantation.[51]

Microwave ablation (MWA), like RFA, uses extreme heat to cause tumor necrosis. Heat can adversely impact biliary structures limiting application to some tumors. Treating tumors near large vasculature structures can be limited by heat loss into the vessel. One advantage of MWA is that it is less affected than RFA by heat loss that results from large, adjacent vascular structures. Higher intratumoral temperatures, larger ablation zones, reduced treatment times, and imperviousness to increasing electrical impedance of tumor tissue during treatment are all potential advantages of MWA.

Selection of appropriate patients includes both clinical and anatomic features. The effectiveness of ablation therapy is limited by the number and size of lesions. Best results occur in patients with 1 to 2 tumors that are <3 cm. Treatment zones can be extended to 5 cm or greater using multiple probes, newer bipolar probes, or strategies that combine intra-arterial therapies with ablation to induce peritumoral hyperemia, enhancing TACE. Good performance status and Child-Pugh A and B cirrhosis are important to avoid liver decompensation. RFA effectively ablates tumors in 90% to 97% of patients within the Milan criteria, with no vascular invasion or extrahepatic disease, with preserved performance status, and with Child-Pugh A or B cirrhosis. Local recurrence rates in this population are 5% to 10%; however, new lesions or recurrent lesions at 5 years are common (80%).[51]

Downstaging Locoregional Therapy

LRT is also used to downstage patients with HCC. Intra-arterial and ablation therapies can be used separately or combined for large or multiple tumors. In one of the first studies looking at a downstaging protocol for patients with extensive intrahepatic disease, Yao et al.[52] enrolled 30 patients with HCC meeting a size criteria (1 lesion between 5 cm and 8 cm, 2 or 3 lesions with at least 1 lesion >3 cm but all 5 cm or less with total tumor volume no more than 8 cm, or 4 to 5 lesions all 3 cm or smaller with a total tumor burden 8 cm or less) and treated them with a protocol involving TACE, laparoscopic RFA, or resection alone or in combination. Seventy percent met successful downstaging criteria to within the UCSF criteria (single tumor no larger than 6.5 cm, up to 3 tumors no larger than 4.5 cm, and total tumor volume not exceeding 8 cm). Those patients were eligible for transplant after a 3-month mandatory delay from successful downstaging. There were no HCC recurrences, and overall 2-year intention-to-treat survival was 81.8%.

Chapman et al.[28] enrolled 76 potential transplant candidates with the goal of shrinking the tumor to within the Milan criteria. Twenty-four percent achieved downstaging success and 22% of the total cohort underwent liver transplantation. Seventy-five percent of explants showed >90% tumor necrosis. After median 19.6 months of follow-up, HCC recurrence occurred in 1 patient (6%). Several other studies suggest LRT is successful for downstaging; however, attempts to show survival benefit resulted in mixed outcomes.[27,53]

Tumor response to LRT predicts risk for posttransplant HCC recurrence, so including time from treatment as a criterion for transplant has been suggested for patients undergoing downstaging.[28,54] The "ablate and wait" concept is intended to identify candidates who have lower risk of posttransplant HCC recurrence and expose tumors with "bad biology."[20] Using downstaging protocols including ablate and wait, 30% of patients may be appropriately excluded from transplant because of disease progression, with the remainder showing excellent posttransplant outcomes.[20] This is probably secondary to unrecognized lymphovascular or extrahepatic metastases. Tumor progression may be a risk factor that is independent of the pretreatment tumor burden, suggesting its usefulness in a wide range of tumor sizes both within and outside the Milan criteria. Tumors infrequently worsen over the timeframe between LRT and transplant, suggesting that increasing waiting time will not disadvantage patients who might otherwise have benefitted from more immediate transplant.[20] The exact time to wait is not completely clear but likely between 3 and 6 months. The next step in this important consideration is to identify tumor-specific or serological factors that will predict bad biology. Some options are under development, but likely a long way from evidence of efficacy let alone clinical usefulness.

Systemic Therapy

Sorafenib, a tyrosine kinase inhibitor that inhibits vascular endothelial growth factor, is the only approved systemic chemotherapy for advanced HCC. A 2008 multicenter, randomized, double-blind, placebo-controlled trial of sorafenib in therapy-naïve Child-Pugh class A patients with advanced HCC showed a 3-month increase in survival time and time to radiographic progression over placebo.[55] Sorafenib-induced disease stability by Response Evaluation Criteria in Solid Tumors[56] criteria (RECIST) for at least 28 days in 43% of treated patients compared to 32% in the placebo arm.

As a bridging therapy, there are limited data on the use of sorafenib. In a case series of 7 patients on the liver transplant list receiving sorafenib for HCC,[57] 5 patients were treated with sorafenib (in addition to LRT or resection) before transplant, whereas 2 received sorafenib for posttransplant recurrence. Three patients developed side effects requiring dose adjustment, and sorafenib was permanently discontinued in 1 patient. In short follow-up, none of the patients who received pretransplant sorafenib developed posttransplant HCC recurrence. One patient

developed early hepatic artery thrombosis and required transplantation. Given its action inhibiting vascular development, its safety after transplant has been questioned.[58,59] Among patients who received sorafenib until the time of transplant,[60] 15 patients with HCC receiving sorafenib were compared to 64 patients with HCC who did not receive sorafenib before transplantation. Patients who received sorafenib had tumors outside the Milan criteria, poorly differentiated tumors, elevated AFP, or poor response to LRT. All patients in both groups received at least 1 type of conventional therapy (TACE, RFA, or resection). There was no difference in wait-list dropout rate between the 2 groups. Despite a larger tumor burden, there was no increase in 30-day incidence of biliary leak, bleeding, wound infection, need for surgery, or bacteremia in the sorafenib group. There was a similar incidence of biliary stricture, incisional hernia, or mild-to-moderate cellular rejection on 1-year follow-up. In median follow-up 19.7 months, survival rate was similar for the 2 groups. Trials combining sorafenib with LRT modalities for advanced stage HCC are also underway with the goal of reducing undetected vascular or extrahepatic spread and reducing wait-list dropout and posttransplant recurrence. Thus far, there are encouraging results and an acceptable safety profile in phase 2 studies.[61]

Sorafenib as adjuvant therapy after liver transplant has been studied in patients with HCC beyond the Milan criteria in small case series with limited follow-up.[62,63] Both studies were promising for prolonging overall survival, but they were criticized for their small size and limited follow-up.[59] More rigorous study is called for, and a trial for the use of sorafenib as adjuvant therapy after liver transplant is ongoing.[64]

FUTURE OF HEPATOCELLULAR CARCINOMA AND ITS IMPACT ON LIVER TRANSPLANT ALLOCATION

The future incidence of HCC will be determined by competing forces: increasing nonalcoholic steatohepatitis (NASH) versus the impact of direct acting antivirals (DAAs) on HCV. Although there is significant optimism about the decreased contribution from HCV liver disease, should HCC incidence remain stable or increase in the future, the US allocation system will continue to be stressed by large numbers of cancer patients.

Age-adjusted incidence rates are increasing in the United States but so is survival suggesting effective surveillance or management strategies.[65] HCV is present in up to 47% of patients[66] and is associated with a 15 to 20 times increased risk of HCC compared to non-HCV subjects.[67] New DAA regimens are a significant advancement in effectiveness and tolerability. Advanced fibrosis is likely necessary for the development of HCC in patients with HCV, and the cure of HCV can halt progression and induce regression of hepatic fibrosis.[68,69] Despite the predicted decrease in the HCV disease burden with more effective and tolerable HCV treatment options, the short-term future may include a continued contribution from older HCV patients who have been cirrhotic for a longer duration. In fact, the prevalence of HCC in the aging HCV population appears to still be increasing. Patients born between 1941 and 1960 with HCV and HCC will have the largest demand for liver grafts in the near future,[70] potentially delaying for a time the complete realization of reduced HCC from effective treatment even in the instance of universal availability of HCV medications.

From a public health perspective, there is a risk of inappropriately discounting HCC risk in patients who achieve sustained virological response (SVR). Achieving SVR is associated with a roughly 75% reduction in risk for development of HCC among patients at any stage of fibrosis.[71] However, among patients with advanced fibrosis, the risk appears to remain elevated—as high as 5% over 10 years.[72] Other estimates suggest a 1% annual rate among patients with cirrhosis with SVR from interferon-based therapy.[73] The rate may actually be higher among populations receiving DAA regimens because DAA's tolerability broadens the applicability of treatment for patients with more advanced fibrosis. From an allocation perspective, this suggests that HCV-related HCC, although likely to decrease, may still contribute significantly to future HCC transplant candidates. Also, optimistic predictions for reduction in HCV-related HCC are tempered by price-related challenges in DAA availability and the possibility of a large undiscovered/unaware HCV population.[74] Cohort screening recommended by the Centers for Disease Control and Prevention is attempting to address the problem of unknown disease burden.

Metabolic risk factors like obesity and diabetes are associated with HCC development,[75] and patients with nonalcoholic fatty liver disease (NAFLD) and NASH account for a growing proportion of patients with HCC. NAFLD prevalence in the United States is enormous: 30% to 46% of the population with 12% of patients meeting criteria for NASH.[76] The incidence of HCC in patients with NASH cirrhosis is roughly 2.6% per year.[77] In a regional UK study, the incidence of HCC rose from 2000 to 2010, and NAFLD accounted for 35% of HCC cases with metabolic risk factors present in 66%.[78] Among patients with NASH, HCC risk appears elevated even in noncirrhotic stages with steatosis significantly associated with HCC development.[79] Age, sex, and metabolic disease are the most important risk factors for HCC in noncirrhotic NASH patients. Among older Japanese men with NASH and metabolic risk factors, 1 study revealed that 75% of patients with HCC had a noncirrhotic fibrosis stage.[80] If this is true for Western populations as well, the future contribution from older male NASH patients to the HCC burden could be immense. Although there is no significant evidence that treatment of NASH reduces risk of HCC, metformin[81] and statins[82] are both associated with reduced HCC risk.

In order to address the disparity in dropout and transplant rates between patients with and without HCC, the OPTN/UNOS Liver and Intestinal Organ Transplantation Committee recently adopted 2 policies related to HCC exception priority. The first caps the MELD exception for HCC patients at 34, which disallows their entrance into a higher priority level created by the Share 35 policy (tiered local and regional priority for patients with MELD scores 35 and over versus those below 35). The second policy establishes a 6-month waiting period after transplant listing before achieving the initial MELD exception. On the basis of liver-simulated allocation modeling data, the 6-month waiting period would reduce the disparity in transplant and dropout rates. It would have the added benefit of allowing short wait-time centers the opportunity to uncover poor biology and fast growing tumors. The 6-month waiting period is supported by recent evidence suggesting poorer survival in HCC patients transplanted sooner after listing compared to later.[83] These two polices regarding HCC allocation were implemented in October 2015.

CONCLUSION

Liver transplant allocation for HCC has numerous dilemmas. The goal of transplanting patients based on "urgency" alone is at odds with optimizing "outcomes" because patients with the most advanced tumors in greatest need of a transplant also have the greatest risk of recurrence. Additionally, equating mortality risk in non-HCC patients to the risk of HCC tumor progression is complicated by the rapid evolution of multidisciplinary treatment options for patients on the wait list. With the recent increasing incidence of HCC and uncertainty about the future, ensuring equity in the transplant allocation system remains a key focus of policy makers. The current system of progressively increasing exception points regardless of treatment effect appears to fall short. Indeed, it may be exacerbating the increasing MELD score at transplant throughout the United States. Recent allocation policy updates were created to help address the outcome disparity between HCC and non-HCC transplant candidates; however, to fully close the gap, a more dynamic system sensitive to both baseline and up-to-date comprehensive tumor data taking into account both dropout risk and posttransplant survival may be necessary.

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