Curr Hepatology Rep (2017) 16:33–38
DOI 10.1007/s11901-017-0330-5

HEPATIC CANCER (A SINGAL AND A MUFTI, SECTION EDITORS)

Changes in Liver Transplant Criteria for Hepatocellular Carcinoma

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Published online: 23 January 2017

Abstract
Purpose of Review There have been several recent policy changes in liver transplantation for hepatocellular carcinoma (HCC). We outline the most recent changes in allocation policy for HCC prior to transplant and the rationale behind them.
Recent Findings The United Network for Organ Sharing recently adopted a new allocation policy for HCC to better balance organ availability between HCC and non-HCC waitlist candidates and exclude patients with rapidly progressive HCC. This policy includes a mandatory 6-month waiting period prior to application of model for end-stage liver disease (MELD) exception points and a cap of 34 points.
Summary The new policies have changed the landscape of liver transplantation for HCC in the USA. The allocation policy should better select HCC patients who would have the best post-transplant outcome and balance liver transplant benefits between HCC and non-HCC patients.

Keywords HCC · LT · MELD · Milan · UNOS · Hepatocellular carcinoma · End-stage liver disease · Liver transplant

This article is part of the Topical Collection on *Hepatic Cancer*

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Introduction

The incidence of hepatocellular carcinoma (HCC) in the USA has increased significantly over the last decade due to an increase in advanced hepatitis C cases and emergence of non-alcoholic fatty liver disease [1•]. More than 28,000 individuals are diagnosed with HCC each year in the USA with over 23,000 deaths from HCC annually [1•]. HCC is projected to become the third most common cause of cancer-related deaths in the USA by 2030 [2]. Overall survival and treatment allocation depends on stage at presentation, with only early stage patients typically having curative treatment options. In selected patients with early stage HCC, liver transplantation (LT) can provide the best long-term outcomes. LT not only has the potential to cure HCC and prevent HCC recurrence but also alleviates liver disease-related complications by replacement of the underlying cirrhotic liver. Since 2002, patients listed for LT for HCC have been able to receive enhanced priority within the model for end-stage liver disease (MELD) allocation system through the application of MELD exception points. The rationale for the prioritization is that patients with HCC often have a low calculated MELD score but face significant risk of waitlist dropout due to tumor progression. However, there have been several analyses showing that excessive priority on the LT waitlist has been given to patients with HCC resulting in disproportionately high waitlist dropout among non-HCC patients [3, 4]. This imbalance has prompted several changes to the MELD exception system over the last 15 years. In this article, we will explore changes in LT criteria for HCC, with a focus on the most recent changes in allocation policy implemented in 2015.

Pre-MELD Era History of Liver Transplantation for HCC

Prior to the mid-1990s, due to high recurrence rates and poor outcomes, HCC was considered a contraindication for LT. In the era where patients with advanced stage HCC were undergoing LT, reported 5-year post-LT survival rates were less than 40% [5–7]. Contemporary criteria for LT were established in a study by Mazaferro et al., showing the efficacy of LT in patients with early stage HCC [8]. Post-LT outcomes of patient within Milan criteria (solitary tumor less than 5 cm or no more than three tumors with none greater than 3 cm in diameter) were excellent, with 8% post-LT recurrence rates and 4-year post-LT survival rates of 75% [8]. This restricted criteria soon became widely accepted and validated among numerous cohorts of patients undergoing LT for HCC with a resultant improvement in 5-year post-LT survival and decrease in HCC recurrence rates [9, 10].

MELD Era History of Liver Transplantation for HCC

In 2002, the MELD prioritization system replaced the Child-Pugh system for liver transplantation. The United Network for Organ Sharing (UNOS) adopted the modified TNM stages T1 (single <2 cm tumor) and T2 (tumor <5 cm but >2 cm) which incorporated the Milan criteria into their MELD-based prioritization system for LT. Changes in allocation are summarized in Fig. 1. Patients with T1 HCC were initially awarded a MELD score of 24, and those with T2 HCC patients were awarded a MELD score of 29. In 2003, this was reduced to MELD exception scores of 20 for T1 HCC patients and 24 for T2 HCC patients. Even with the reduction, the additional exception points led to a significant proportion of LTs being conducted for HCC, with 86% of T1 HCC patients and 91% of T2 HCC patients being transplanted within 3 months of initial listing [11]. These early data raised concerns that excessive priority was being given to HCC patients compared to non-HCC patients. One prospective study of patients meeting Milan criteria and listed for LT from 1998 to 2002 found that the predictors for dropout were a single tumor >3 cm and multifocality. When compared to T1 stage, patients with T2 HCC had a notably higher risk of waitlist dropout (HR 9.0; 95% CI 2.0–40.1) [12]. There was also concern of high false positives among T1 tumors with review of explants showing 30–40% of T1s having no HCC [13]. Thus, T1 priority was dropped from the prioritization list for HCC in 2004. In 2005, this was further modified with decrease in MELD exception score from 24 to 22 for T2 HCC followed by every 3 month upgrades if the tumors remained within T2 criteria. Despite these numerous adjustments to the MELD exception policy, more recent data have continued to show that patients with HCC continued to be over prioritized for LT compared to non-cancer patients [14••].

2015 UNOS Changes to Liver Transplantation Policy for HCC

In October 2015, as a result of concern regarding discrepancy between transplant rates among HCC and non-HCC patients, UNOS eliminated the 22 and 25 MELD exception scores and implemented in its place a 6-month MELD exception waiting time for patients, after which candidates still within Milan criteria would receive 28 points. This then increases every 3 months to a maximum score of 34. This cap was implemented in part due to the "Share 35" policy, where regional sharing occurs when a patient is listed with a MELD ≥35 [15].

The rationale for the change in MELD exception for HCC was based on the persistent inequity in transplant access between HCC and non-HCC patients despite prior changes in MELD exception policy. The justification for the wait time prior to granting MELD exception was based upon a modeling study using UNOS data: the authors showed an immediate MELD exception score of 22, a 3-month delay before granting 25 exception points, a 6-month delay before granting 28 exception points, and a 9-month delay before granting 29 exception points would result in transplant rates of 108.7, 65.0, 44.2, and 33.6 for HCC candidates, compared with 30.1, 32.5, 33.9, and 34.8 for non-HCC candidates [14••]. Thus a 6- to 9-month delay in granting MELD exception had the potential to reduce disparity in transplant rates between HCC and non-HCC candidates, improving LT access equity.

This policy change also facilitates selection of patients with good tumor biology and lower risk of post-transplant recurrence,

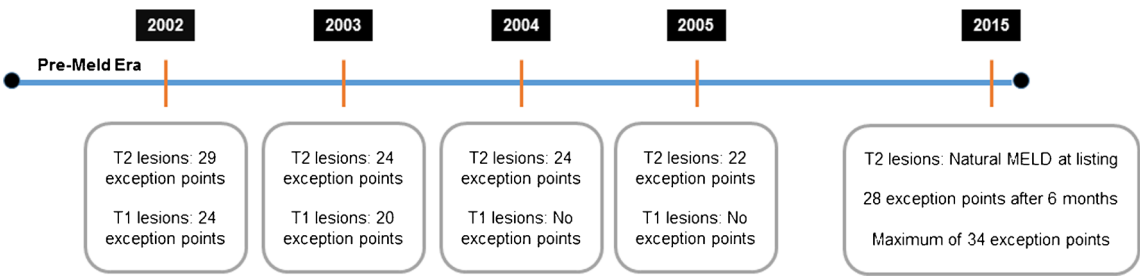

Fig. 1 UNOS MELD allocation policy changes from 2002 to 2015

which occurs in about 10% of patient who undergo LT for HCC [16]. Established risk factors for HCC recurrence include tumor burden (size and number), alpha-fetoprotein (AFP) level, wait time prior to liver transplant, and liver function [12, 17–20]. Tumor burden can be an inadequate surrogate for tumor biology because there is variation in the stage at diagnosis and treatment responsiveness. Short wait times may reduce the risk for dropout and pretransplant mortality; however, it does not allow adequate time to assess tumor biology. One analysis of the UNOS database found patients with HCC who underwent transplant in short waiting-time regions had significantly higher post-transplant mortality than those transplanted in long waiting-time regions (HR 1.55, 95% CI 1.38–1.74) [21]. A multicenter study with 881 HCC patients similarly found waiting times less than 6 months are predictive of post-transplant recurrence (HR 3.0, 95% CI 1.2–7.0) [22•].

In regions with long wait times for LT, HCC patients are often treated with locoregional therapy to control tumor burden and decrease the chance of dropout. Several studies have suggested treatment responsiveness may be a useful surrogate of tumor biology and can help select optimal transplant candidates. A study among 398 HCC patients listed for LT found lack of complete response to the first locoregional therapy was an independent predictor of dropout [20]. Combining locoregional therapy treatment response with initial tumor burden and AFP level after first locoregional therapy defined a subgroup of patients with very low risk for tumor progression and waitlist dropout (1-year rate, 1.3%). The authors proposed these patients might not require the same listing priority as other HCC patients; however, restricting MELD exception points from these patients would likely select against those with the best post-LT outcomes as characteristics associated with a lower risk for dropout are the same as those associated with better outcomes after transplantation. Persistent disease after locoregional therapy is associated with higher post-transplant tumor recurrence rates, independent of initial tumor burden, with resultant worse survival post-LT [23–25]. Given the favorable outcomes of those patients with small unifocal HCC who undergo locoregional therapy, one policy proposal that is currently being considered by UNOS involves excluding those patients with compensated cirrhosis and a unifocal HCC that is 2–3 cm in size which are eligible for locoregional therapy from obtaining a LT MELD exception. This population would be expected to have an over 50% survival rate at 5 years [26]. If a patient were not eligible for locoregional therapy, then the patient could be granted a MELD exception through petition of the regional review board. Additionally, if a patient were to have a recurrence, they could obtain a MELD exception for LT without waiting the 6-month period.

Although AFP is not currently included in the LT criteria for patients with HCC, it can serve as a surrogate for tumor biology and is an independent predictor for outcomes after LT. In a single-center study of 211 patients transplanted with HCC, AFP >1000 ng/mL was an independent predictor of microvascular invasion (HR 6.8; 95% CI 1.6–19.1); thus, the authors suggested that an AFP >1000 should be an exclusion for LT [27•]. The proposed AFP cutoff is somewhat arbitrary, as others have shown lower AFP cutoffs (200–400 ng/mL), and even the delta AFP prior to LT are significant predictors of vascular invasion, post-LT HCC recurrence risk, and post-LT mortality [28–30]. Consequently, though imperfect, AFP has been endorsed as a factor that should be considered in LT criteria for HCC [31]. Additional prognostic biomarkers for HCC that will aid in prognosticating risk of dropout are being developed and undergoing validation; therefore, we can expect additional tools in prognosticating HCC LT risk in the coming years.

Thus, there has been growing interest in moving beyond tumor burden and assessing tumor biology or surrogates (e.g., biomarkers or response to locoregional therapies) in making decisions about which patients should under LT for HCC [32]. The 6-month waiting period in the most recent allocation policy represents the first attempt to select for tumor biology; however, other factors, such as AFP or treatment responsiveness, have yet to be incorporated into allocation policy.

Expanded Criteria and Downstaging of HCC

Several studies have suggested that the Milan criteria maybe too restrictive and that expansion of Milan criteria for HCC does not worsen outcomes with LT. The UCSF criteria (i.e., a single tumor which was ≤6.5 cm in diameter or two to three tumors, none exceeding 4.5 cm in diameter and whose sum of tumor diameters did not exceed 8 cm) has been shown to be an expansion criterion for HCC that has yielded good post-LT outcomes. In one study of 38 patients meeting USCF criteria, the 1- and 5-year recurrence free probabilities were 95.9 and 90.9%, respectively, which were similar to those of patients transplanted within Milan. There have been several other proposed criteria for HCC expansion, many of which have been reported in the literature and have shown acceptable post-LT outcomes [33]. However, it appears that the response to locoregional treatment and observation period prior to LT (i.e., tumor biology) is an essential factor when considering the success of these cohorts of patients undergoing LT with expanded criteria. Additionally, while expanded criteria for HCC can offer a curative option for patients with locally advanced HCC, it must be weighed against the disparity between those waitlisted for LT and the number of LTs available. The rationale for the recent policy changes for patients with HCC was to better balance access for transplant for patients with and without HCC, and any expansion in the criteria for patients with HCC for LT would possibly tip this balance again in favor of those patients with HCC.

As mentioned above, tumor burden is a suboptimal surrogate for tumor biology and the majority of patients with HCC are

Table 1 Extended Toronto criteria

Criteria	
Disease extent	No limit on intrahepatic disease
	No vascular invasion or biliary tumor thrombus
	No evidence of extrahepatic disease
Symptoms from HCC	No weight loss of >10 kg over 3 months
	ECOG performance status of 0
Differentiation of largest lesion on percutaneous biopsy	No poorly differentiated tumors

diagnosed with imaging alone, so there is typically no direct assessment of histologic features that correlate with tumor biology. In order to more directly assess tumor biology prior to LT, the extended Toronto criteria has been proposed as a way to select which patients may be transplantable beyond Milan criteria [34••]. The authors propose addition of tumor histology (i.e., degree of differentiation on biopsy), HCC related symptoms, and AFP in deciding which patients should be considered for LT. The author's criteria are summarized in Table 1 [34••]. The authors conducted a prospective analysis comparing post-LT outcomes of patients who met traditional Milan criteria to those who met the extended Toronto criteria with long-term outcomes. In total, within their prospective validation cohort, 105 patients were beyond Milan (76 patients beyond UCSF criteria) and 138 patients were within Milan criteria. Though the beyond Milan patients had higher rates of recurrence post-LT (29.8%) in the intention to treat analysis, the patients in the beyond Milan group still had an unexpectedly high 10-year actuarial survival at over 40%, which is far higher than would be expected in patients with intermediate stage HCC who were not eligible for transplant. The authors additionally found that an AFP cutoff of 500 ng/mL was predictive of outcome after LT. The excellent post-LT survival in this beyond Milan group was in part secondary to aggressive post-LT surveillance for and management of recurrent HCC by the center where these criteria was implemented. It is notable that the pre-LT biopsy tract seeding may have led to recurrence in 1.9% of patients, and tumor seeding may also make transplant eligible patients ineligible. While this criteria requires further validation and refinement, it is the most direct measure of tumor biology prior to LT that has been proposed to date [34••].

When tumors are beyond the Milan criteria, without evidence of extrahepatic spread, downstaging is an option to bring the tumors within Milan criteria to allow intermediate stage patients to have access to a curative therapy. Nationally, most regional review boards approve MELD exceptions for patients who can be brought down to within Milan criteria from T3 disease via use of locoregional therapies; however, no national UNOS policy exists. A proposal is currently under review to define acceptable criteria for downstaging nationally, which will ultimately be incorporated in the national UNOS policy. A systematic review and pooled analysis reported post-LT recurrence rates of approximately 17% among downstaged patients with HCC, which is higher than what is seen among those within the Milan criteria, although significant heterogeneity among studies exists depending on patient selection and downstaging protocols [18]. More restrictive patient selection criteria and targeted tumor burden, along with the inclusion of a mandatory observation period, are associated with better outcomes. In one study, which prospectively predefined those who are eligible for downstaging and protocoled the downstaging approach, 65% of patient were successfully downstaged, with 94% 1-year survival and 8% rate of recurrence [35]. With pending UNOS policy changes, we can hope for improved standardization of downstaging nationally.

Conclusions

There have been several changes to the MELD allocation policy over the last 15 years in order to optimize transplantation for HCC. The most recent policy changes implemented in 2015 implement mandates a 6 month waiting period before a MELD exception is granted, with a cap of 34 points. The rationale behind the changes is better balancing equity between transplants for cancer and non-cancer waitlisted patients and also to account for tumor biology. There are several other outstanding issues that will impact allocation policy for HCC in the coming years, including transplant of patient beyond Milan criteria, accounting for tumor biology in transplant, and downstaging patients to within Milan criteria. Together, these changes have transformed the landscape of LT for HCC and we expect continued evolution of the criteria to better reflect risk stratification of patients with HCC being considered for LT.

Compliance with Ethical Standards

Conflict of Interest Dekey Lhewa1 and Neehar D Parikh each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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