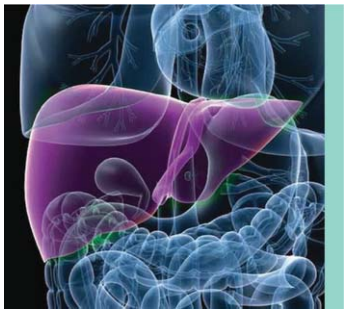

Model for End-Stage Liver Disease Exception Points for Treatment-Responsive Hepatocellular Carcinoma

Neehar D. Parikh, M.D., and Amit G. Singal, M.D., M.S.*[†,‡]

Liver transplantation (LT) is an efficacious curative treatment for select patients with hepatocellular carcinoma (HCC). The transplant allocation system assigns Model for End-Stage Liver Disease (MELD) exception points to patients with HCC to reflect their wait-list mortality and prioritization for LT. The most recent change in allocation policy mandates a 6-month observation period before priority listing and a maximum score of 34 points. This change not only promotes more equitable allocation of donor organs between HCC and non-HCC patients but also provides an opportunity to assess tumor biology. Although patients with good tumor biology will have treatment-responsive HCC and remain within Milan criteria while awaiting transplantation, those with poor tumor biology will have tumor progression and drop off the waiting list. In this article, we review the evidence and implications behind MELD exception points for patients with HCC.

LT is a preferred treatment for patients with HCC because it removes both the tumor and the cirrhotic liver, thereby maximizing recurrence-free survival rates. Although MELD scores accurately predict 3-month mortality for most patients with cirrhosis, it underestimates risks of mortality and waiting list dropout for patients with HCC. Starting in 2002, HCC patients were provided with MELD exception points to balance their risk of tumor progression and dropout to the 3-month liver-related mortality risk of non-HCC patients. Given subsequent data suggesting HCC patients were at advantage compared with non-HCC patients, the MELD exception policy was adjusted several times, including decreases in

Abbreviations: HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; TACE, transarterial chemoembolization; UNOS, United Network for Organ Sharing.

From the *Department of Internal Medicine, University of Michigan, Ann Arbor, MI, [†]Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX, and [‡]Harold C. Simmons Cancer Center, UT Southwestern Medical Center, Dallas, TX.

Potential conflict of interest: Dr. Singal is on the speakers' bureau for Bayer Pharmaceuticals.

Received 2 December 2015; accepted 10 February 2016

View this article online at wileyonlinelibrary.com

TABLE 1. MODEL FOR END-STAGE LIVER DISEASE EXCEPTION POINTS FOR PATIENTS WITH HEPATOCELLULAR CARCINOMA

Year	MELD Exception Points
2002	29 exception points for T2 lesions
	24 exception points for T1 lesions
2003	24 exception points for T2 lesions
	20 exception points for T1 lesions
2004	24 exception points for T2 lesions
	No exception points for T1 lesions
2005	22 exception points for T2 lesions
	No exception points for T1 lesions
2015	Natural MELD score at time of listing for T2 lesions
	28 exception points after 6 months
	Maximum of 34 MELD exception points

exception points in 2003 and 2005 and the most recent change in 2015 (Table 1).

In contrast with prior changes that focused on number of exception points awarded to HCC patients, the most recent change addresses timing of exception points. Previously, patients were awarded priority listing with a MELD exception score of 22, which was increased every 3 months. Under the current policy, patients are initially listed with their natural MELD score and awarded a MELD exception score of 28 points after a 6-month waiting period, which then increases every 3 months to a maximum score of 34 points. In a modeling study using Scientific Registry of Transplant Recipients data, Heimbach and colleagues[1] found 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 yielded transplant rates of 108.7, 65.0, 44.2, and 33.6 for HCC patients, compared with 30.1, 32.5, 33.9, and 34.8 for non-HCC candidates. The authors concluded a 6- to 9-month delay reduces disparity in transplant rates between HCC and non-HCC candidates and creates more equal access to LT.

This policy change also facilitates selection of patients with good tumor biology and lower risk of posttransplant recurrence. Tumor burden is an imperfect surrogate for tumor biology because there is variation in natural history and treatment responsiveness between patients. Although patients meeting Milan criteria, that is, a single tumor less than 5 cm or two to three tumors each less than 3 cm without vascular invasion or metastatic disease, typically have high recurrence-free survival rates, posttransplant recurrence is observed in approximately 10% of patients.[2] Similarly, some patients with tumors exceeding Milan criteria have good tumor biology and are at low risk for posttransplant recurrence. Unfortunately, many markers of tumor biology are not available pretransplant (e.g., presence of microvascular invasion), not validated (e.g., circulating tumor cells), or insufficiently accurate (e.g., alpha-fetoprotein levels). Although short wait times may reduce the risk for dropout and pretransplant mortality, it does not allow adequate time to assess tumor biology. An analysis of the United Network for Organ Sharing (UNOS) database found HCC patients transplanted in short waiting-time regions have significantly higher risk for posttransplant mortality than those transplanted in long waiting-time regions (hazard ratio 1.55, 95% confidence interval 1.38-1.74).[3] Similarly, a multicenter study with 881 HCC patients found waiting times less than 6 months are predictive of posttransplant recurrence (hazard ratio 3.0, 95% confidence interval 1.2-7.0).[4]

In regions with long wait times for LT, HCC patients are often treated with locoregional therapy, such as transarterial chemoembolization (TACE), 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 (Fig. 1). 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.[5] Combining treatment response with tumor burden and alpha-fetoprotein level after first locoregional therapy defined a subgroup of patients with very low risk for tumor progression and dropout (1-year probability rate, 1.3%). Although the authors proposed these patients might not require the same listing priority as other HCC patients, restricting MELD exception points from these patients might be selecting against those with the best posttransplant outcomes, because characteristics associated with a lower risk for dropout are the same as those associated with better posttransplant outcomes. Persistent disease after locoregional therapy is associated with higher posttransplant tumor recurrence rates, independent of tumor

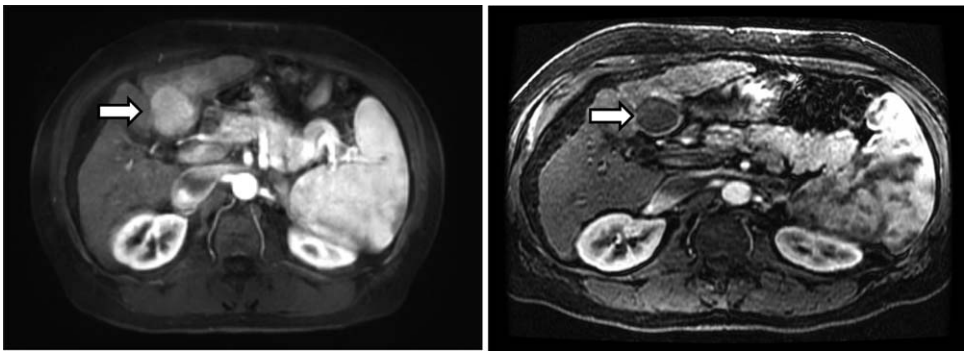

FIG 1 Treatment-responsive HCC: patient with complete response to therapy 3 months after TACE. Arrow denotes pretreatment tumor (left) and response to therapy with lack of arterial enhancement (right).

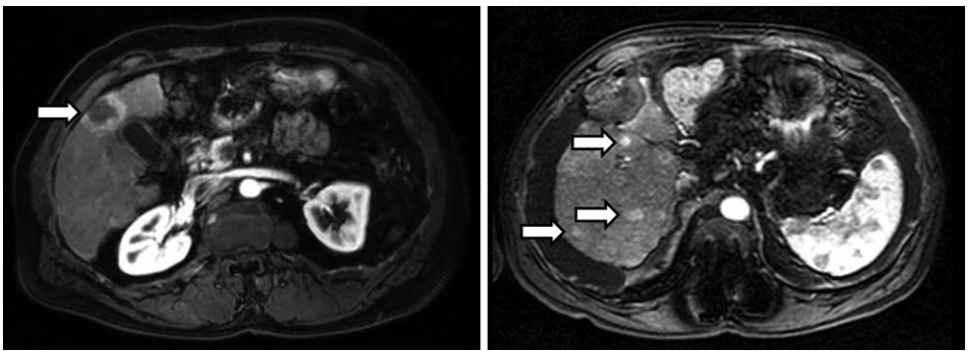

FIG 2 Treatment-nonresponsive HCC: Patient with progressive disease over 6 months despite TACE. Arrow shows initial lesion pretreatment (left) and interval progression, with several new HCC nodules after treatment (right).

burden, and significantly worse posttransplant survival (Fig. 2).[6]

The relationship between treatment response and tumor biology has also been highlighted in the HCC downstaging literature. Downstaging, that is, use of locoregional therapies to bring tumors outside of Milan criteria to within Milan criteria, allows for reduction in tumor burden and provides an observation period to determine tumor biology. In the largest single-center study among 114 patients, Yao and colleagues[7] used a prospective downstaging protocol, with *a priori* inclusion criteria, to evaluate the effectiveness of downstaging and post-LT outcomes. Most importantly, the study protocol required a mandatory 3-month waiting period before LT after downstaging to confirm patients remained within Milan criteria. After a median 9.8-month time from downstaging to LT, downstaging was successful in 65.3% and posttransplant recurrence rates were 7.5%, which was comparable with those who presented within Milan criteria at the center. When a similar downstaging protocol was expanded to several region 5 centers, similar results were observed, with 5-year recurrence rates of 13%.[8] Although these results are favorable, they are not universal, as shown in a systematic review of the literature on downstaging (Fig. 3).[9] Although more data are needed, it appears *a priori* inclusion criteria and a mandatory waiting time before LT to observe tumor biology is an approach that may yield the best outcomes.

SUMMARY

LT plays an important role in the management of patients with HCC, providing the best opportunity for long-term recurrence-free survival. The most recent change in UNOS policy includes a 6-month observation period before priority listing and a cap of 34 points. This policy change will promote more equitable allocation of donor organs between HCC and non-HCC patients on the waiting list. Further, it provides a valuable

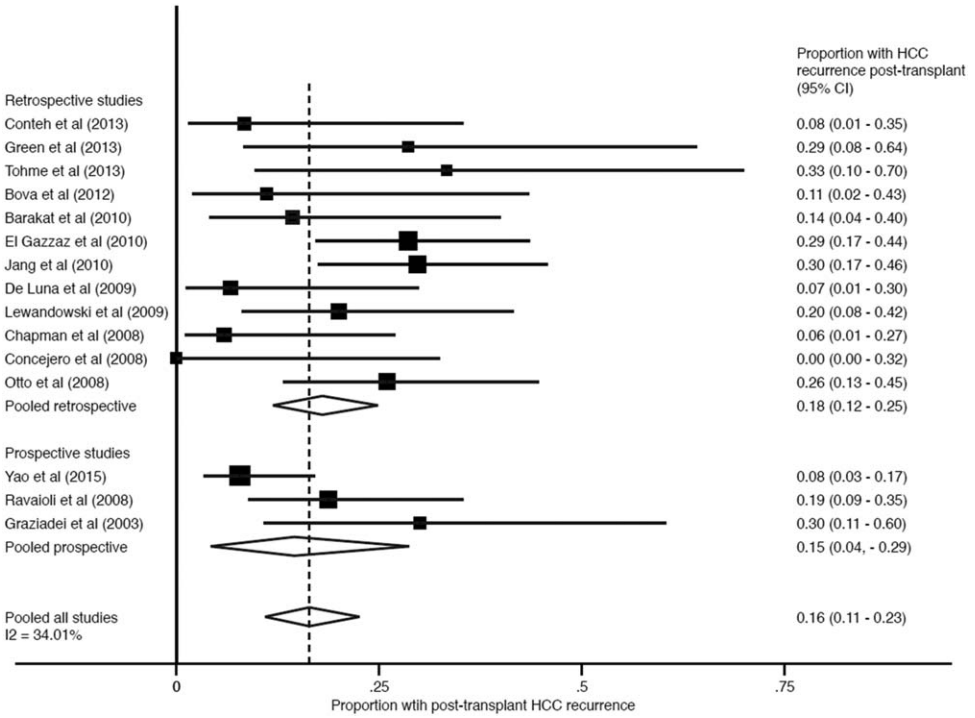

FIG 3 Forest plot of posttransplant HCC recurrence rates among patients who were downstaged to within Milan criteria.

opportunity to go beyond simply using Milan criteria and instead assessing tumor biology to select those at acceptable risk for posttransplant recurrence.

CORRESPONDENCE

Amit G. Singal, M.D., M.S., Medical Director, Liver Tumor Program, Division of Digestive and Liver Diseases, University of Texas Southwestern, 5959 Harry Hines Boulevard, POB 1, Suite 420, Dallas, TX 75390-8887. E-mail: amit.singal@utsouthwestern.edu

REFERENCES

1) Heimbach JK, Hirose R, Stock PG, Schladt DP, Xiong H, Liu J, et al. Delayed hepatocellular carcinoma model for end-stage liver disease exception score improves disparity in access to liver transplant in the United States. Hepatology 2015;61:1643-1650.

2) Sotiropoulos GC, Molmenti EP, Losch C, Beckebaum S, Broelsch CE, Lang H. Meta-analysis of tumor recurrence after liver transplantation for hepatocellular carcinoma based on 1,198 cases. Eur J Med Res 2007;12:527-534.

3) Halazun KJ, Patzer RE, Rana AA, Verna EC, Griesemer AD, Parsons RF, et al. Standing the test of time: outcomes of a decade of prioritizing patients with hepatocellular carcinoma, results of the UNOS natural geographic experiment. Hepatology 2014;60:1957-1962.

4) Mehta N, Heimbach J, Harnois DM, Dodge JL, Burns JM, Lee D, et al., eds. Short Waiting Time Predicts Early Recurrence of Hepatocellular Carcinoma after Liver Transplantation: A Multicenter Study Supporting the ''Ablate and Wait'' Principle. The Liver Meeting; 8 November 2014; Boston, MA.

5) Mehta N, Dodge JL, Goel A, Roberts JP, Hirose R, Yao FY. Identification of liver transplant candidates with hepatocellular carcinoma and a very low dropout risk: implications for the current organ allocation policy. Liver Transpl. 2013;19:1343-1353.

6) Kim YS, Lim HK, Rhim H, Lee WJ, Joh JW, Park CK. Recurrence of hepatocellular carcinoma after liver transplantation: patterns and prognostic factors based on clinical and radiologic features. AJR Am J Roentgenol. 2007;189:352-358.

7) Yao FY, Mehta N, Flemming J, Dodge J, Hameed B, Fix O, et al. Downstaging of hepatocellular cancer before liver transplant: long-term outcome compared to tumors within Milan criteria. Hepatology 2015;61:1968-1977.

8) Mehta N, Guy J, Frenette CT, Sarkar M, Osorio RW, Minteer WB, et al., eds. Multicenter Study of Down-staging of Hepatocellular Carcinoma (HCC) to Within Milan Criteria Before Liver Transplantation (LT). The Liver Meeting; 10 November 2014; Boston, MA.

9) Parikh ND, Waljee AK, Singal AG. Downstaging hepatocellular carcinoma: a systematic review and pooled analysis. Liver Transpl. 2015; 21:1142-1152.