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Moving Towards Personalizing MELD Exceptions in Liver Transplantation for Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) has become a leading indication for liver transplantation (LT) in the United States over the past 2 decades, accounting for nearly 25% of all LTs conducted yearly.(1) Access to HCC-related LT has been primarily accomplished through granting Model of End-Stage Liver Disease (MELD) exception points, which aim to balance the risk of death and waitlist dropout with post-LT HCC recurrence. Given the finite number of organs, this increase in HCC-related LT has come at the expense of end-stage liver disease patients. Thus, in order to better balance waitlist dropout between HCC and non-HCC listed patients, MELD exception policies have undergone several changes since instituted in 2002.(2) Nevertheless, inequities exist in waitlist mortality and survival benefit from LT between HCC and non-HCC candidates.(3) Furthermore, all eligible HCC patients meeting Milan criteria (one HCC less than 5 cm or up to three HCCs, each less than 3 cm) receive the same MELD exception prioritization, despite having variable rates of tumor progression, waitlist dropout, and post-LT recurrence based on their individual tumor biology. In the face of this inadequate one-size-fits-all paradigm, continual efforts are necessary to optimize prioritization for HCC patients.

In the article by Mehta *et al.*,(4) the authors retrospectively analyzed the United Network of Organ Sharing (UNOS) database from 2011-2014, in order to define characteristics of HCC-exception eligible patients that portend a low risk of wait-list dropout. The authors restricted their analysis to regions with protracted average wait times for LT and identified 4 independent predictors of waitlist dropout including Child Pugh A cirrhosis, MELD<15, AFP<20, and a unifocal HCC 2-3 cm in maximum diameter.

Patients meeting all four criteria comprised 11.9% of all HCC patients with MELD-exceptions, and demonstrated the lowest risk of waitlist dropout (5.5% vs 20.0%; p<0.001) and highest intention to treat survival (94.0% vs 78.5%; p<0.001) when compared to all other HCC patients at 1-year from listing. These criteria maintained good performance characteristics (c-statistic=0.69) in a national validation cohort from 2015-16, which included the period after the institution of the most recent MELD-exception policies requiring a 6-month waiting period prior to the granting of exception points. The authors conclude that patients with this lowest risk of dropout should receive less priority for LT than average risk patients. This is compatible with a recent policy proposal from UNOS to exclude patients with unifocal 2-3 cm HCC who demonstrate a complete radiological response to locoregional therapy from attaining a MELD exception.(5) Although the policy was not ultimately adopted, the results of the analysis from Mehta *et al.* suggest that it should be revisited.

There are, however, notable limitations to this analysis that should temper the conclusions from the authors. First, the UNOS database lacks important granularity, particularly dynamic changes on the waitlist and missing data on locoregional therapies. These deficiencies resulted in the proposal of a static model based solely on listing characteristics, which can be problematic. A "low-risk" patient with a single tumor, compensated liver disease and low AFP at listing may develop declining liver function, new lesions, and rising AFP which would limit application of locoregional therapy and/or alter their risk-profile. Similarly, post-locoregional therapy decompensation may change the waitlist dropout in otherwise low-risk candidates. In these and other circumstances, a safety net framework would be necessary to salvage these patients. Secondly, the analyses included a large proportion of patients who did not receive locoregional therapy prior to LT. With utilization of pre-LT locoregional therapy now a universal practice in the era of a 6-month mandatory wait time HCC exception policy, and with forthcoming changes in the regional median MELD at transplant, the result of this study may not entirely apply to contemporary HCC patient populations. Finally, de-prioritizing these lowest risk HCC patients may lead to an "enrichment" of higher risk candidates, with the unintended effect of increasing the rate of post-LT HCC recurrence and consequently the risk of short-term mortality. A dynamic model simultaneously evaluating evolution of both liver function and tumor burden over the waitlist period, while more complex, may ultimately be necessary to truly maximize the transplant benefit of scarce donor organs.

In summary, Mehta *et al.* make a compelling argument that low risk patients with HCC should be considered for lower priority for HCC exception, which is a welcomed step to differentially prioritize HCC

candidates based on individualized factors. Implementation of such a policy requires further data and modeling of its impact on waitlist mortality and access to LT. Ultimately, validation of better biomarkers of tumor biology through either direct sampling, or non-invasive means (i.e. circulating tumor cells, DNA methylation patterns, radiomics, etc.) may better guide transplant priority decision making. While these technologies are being developed and refined, defining and deprioritizing low risk HCC patients is a practical approach towards harmonizing benefits and risks for all patients on the LT waitlist.

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