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EDITORIAL

# A Therapeutic Conundrum: Delaying Ablation of Small Nonresectable Early Hepatocellular Carcinoma to Facilitate Liver Transplantation

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In the United Network for Organ Sharing (UNOS) staging classification of hepatocellular carcinoma (HCC), the Milan criteria, namely, a single tumor $< 5$ cm or up to 3 nodules each $\leq 3$ cm in size[1] are further divided into stage T1 and T2 where T1 identifies a single tumor $< 2$ cm and T2 identifies a single tumor measuring 2-5 cm or 2/3 nodules each $\leq 3$ cm in size.[2] Patients with a T1 tumor do not receive priority in deceased donor allocation because of a low risk of dropout due to tumor progression in modeling studies. The Model for End-Stage Liver Disease (MELD) exception strategy in place since 2004 prioritizes access to liver transplantation of patients with unresectable T2 HCC.[3] As an increasing number of HCC patients has received prioritization with higher transplant rates and lower wait-list mortality compared with patients without HCC at equivalent calculated MELD scores, a debate has been fueled on the appropriateness of this MELD exception in the competition for organ allocation.[4] A modeling study, for which the survival benefits were calculated as the difference between posttransplant and wait-list life expectancy, concluded that the well-intentioned HCC MELD exception policy grants an unfair advantage to wait-listed patients with HCC compared to non-HCC patients, who are transplanted at higher average MELD scores, have a shorter life expectancy on the wait list, and have diminished access to transplantation.[5] A related issue is the management of patients with a T1 HCC, namely, deciding whether it is appropriate to ablate an HCC rather than delay treatment of HCC until the tumor progresses to T2 in order to allow access to transplantation. Importantly, transplant benefit is calculated on the basis of the survival that can be offered with nontransplant therapeutic options.[6]

Mehta et al.[7] explored a "wait and not ablate" strategy weighing the risks of dropout due to tumor progression versus the survival benefits for those reaching transplantation because all patients were kept under aggressive surveillance with contrast imaging and were treated with bridge therapy with radiofrequency ablation whenever a T1 tumor progressed to T2. In their experience, the "wait and not ablate" approach, allowing tumor growth from T1 to T2 before liver transplantation listing, was burdened by a small rate (6/114 [5%] in the initial T1 cohort) of rapid tumor progression beyond T2 during a median of 5 months of observation. In contrast, 12 of 100 patients who progressed from T1 to T2 during a median observation period of 2.4 years dropped out from the wait list because of tumor progression beyond T2 despite locoregional treatment. Ultimately, 53% of the patients in the "wait and not ablate" cohort underwent transplantation, 22% remained on the waiting list, whereas 13% were not listed for a variety of reasons. In an intention to treat analysis, the 5-year survival rate was 55%. The authors propose that the "wait and not ablate" approach stands as a viable treatment strategy under the current system of organ allocation for liver transplantation, which

**Abbreviations:** AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; UNOS, United Network for Organ Sharing.

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results in optimization of treatment of patients with an early detected liver cancer.

This report together with identification of predictors of early tumor recurrence and development of effective bridge therapies to prevent tumor progression while awaiting liver transplantation, should help refine management of patients with a small HCC.[6] At the same time, a strategy whereby patients with a small nonresectable HCC are asked to wait months before intervention after striving to achieve early detection of HCC by regular surveillance appears counterintuitive.[8,9] Avoiding the upfront application of a nontransplant, radical treatment of an early detected cancer may indeed inappropriately inflate the perception of transplant benefits. The rationale for the strategy of Mehta et al.[7] for early nonresectable HCC was an acceptable risk of T1 HCC to progress beyond T2 during 2.4 years of observation. Because the study was retrospective, referral bias is possible. Starting with an initial cohort of 311 patients with nodules of 1.0-1.9 cm in diameter, 53 patients were candidates for hepatic resection and another 120 were removed from the study because of the absence of pathognomonic features of HCC at contrast radiology or tumor growth. Of the remaining 138, 24 (17.4%) ultimately underwent tumor ablation because of the presence of contraindications to transplantation or patient preference. It is therefore temping to say that disposal of study patients may have challenged a correct appreciation of how many false-negative and false-positive diagnoses of HCC have occurred during the study period, whereas diagnosis of HCC was delayed in those patients requiring repeat imaging investigations because of the absence of a histological approach for nodules with uncertain radiological patterns. This is not a trivial point considering that false-positive rates of up to 12% for HCC diagnoses have been reported by UNOS among patients transplanted with T2 MELD exceptions,[10] whereas patients requiring an ultrasound-guided liver biopsy to obtain a final diagnosis of HCC may represent up to 43% of all patients with cirrhosis with a 1-2 cm liver nodule undergoing regular ultrasound surveillance.[11] One is tempted to dispute also the robustness of the authors' conclusions that serum alpha-fetoprotein (AFP) failed to predict tumor progression in the wait list, whereas elevated serum levels of the same marker were a criterion to exclude HCC patients from liver transplantation. The transplant community, in fact, endorses exclusion from liver transplantation of patients with high serum levels of AFP on the basis of the fact that AFP is a recognized predictor of tumor recurrence and increased mortality rates after liver transplantation.[12]

The Achilles' heel of such a "wait and not ablate" strategy for T1 tumors is that it values allocation over utility criteria for transplanting HCC patients and that implementation of the strategy primarily depends on the availability of adequate resources. In addition, even if such a strategy had complied with criteria of transplant benefits guiding the listing of HCC patients during the study period, one wonders whether the same is still true in the upcoming era where nearly all viral hepatitis patients (who represent a majority of listed patients) may have their underlying liver disease either attenuated or cured by safe and tolerable antiviral regimens that are expected to increase access to and outcome of both transplant and nontransplant therapeutic options.[13]

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