Viewpoint

Down staging of hepatocellular carcinoma—can we push the boundaries?

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Liver transplantation (LT) has been the cornerstone of treatment of early hepatocellular carcinoma (HCC) within Milan criteria due to favorable long-term survival rates (1). Since the introduction of the Model for End Stage Liver Disease (MELD) exception point allocation system in 2002, patients with HCC have received priority listing. Multiple revisions have occurred to balance the increasing priority patients with HCC receive over sicker patients with non-HCC indications given the severe shortage of donor livers. For patients with HCC under consideration for liver transplant, various forms of locoregional therapy (LRT) are used to prevent progression beyond Milan criteria (Bridge) or to decrease tumor burden to within Milan criteria (Downstaging) with the goal to decrease post-transplant recurrence of their HCC. Due to non-standardized downstaging criteria used by various regions, the United Network for Organ Sharing (UNOS) implemented MELD score exception as policy in 2017 to patients who were downsized to Milan criteria using the University of California, San Francisco criteria (2).

The article by Mehta *et al.* (3) is the first study on the national experience of tumor downstaging utilizing the UNOS database. The authors performed a retrospective analysis of 3819 patients who had undergone LT between 2012 and 2015. They compared the post-LT outcomes between patients who presented with HCC within Milan criteria (n=3,276) versus two downstaging groups—those with initial tumor burden meeting the UNOS downstaging (UNOS-DS) criteria (n=422) and all-comers down staging (AC-DS) group (n=121) who had initial tumor burden beyond UNOS-DS criteria. This study confirmed the validity of the UNOS-DS criteria by demonstrating similar 3-year post-LT survival between patients always within Milan criteria (83%) and those in the UNOS-DS group (79%) but significantly lower survival in the AC-DS group (71%, P=0.04 *vs.* Milan). They noted a higher 3-year post-LT HCC recurrence in the UNOS-DS (12.8%) and AC-DS (16.7%) groups compared to the Milan group (6.9%). Interestingly, both downstaging groups had considerably higher proportion of patients with explant tumor stage beyond Milan criteria (32.5% and 40.5% respectively) as well as high rate of vascular invasion on the explant (23.7% and 16.9% respectively).

The large cohort of downstaging groups (n=543) allowed this study to look at pre-LT predictors of post-LT outcomes. In multivariable analysis, the predictors for worse post-LT survival were AFP ≥100 ng/mL at the time of LT (HR 2.36, P=0.009) and receiving a LT in short wait region or mid wait region (HR 3.07, P=0.005). On the other hand, the only significant predictor for post LT HCC recurrence was AFP ≥100 ng/mL at the time of LT (HR 2.59, P=0.02 versus AFP <100).

As pointed out by the authors, one of the limitations of the study was reliance on the pre-LT data provided by the LT centers to UNOS. The underestimation of the tumor burden prior to LT may have led to the high proportion

of patients in the down staging groups with explant tumor stage beyond Milan criteria. A similar inaccurate reporting of tumor sizes at the margins of Milan criteria was demonstrated by Samoylova *et al.* (4). Another drawback of this study is the short median post-LT follow up of 1.9 years which could underestimate the post-LT HCC recurrence rate. While the study showed that the only independent predictor for post-LT HCC recurrence in the down staging groups was AFP ≥100 ng/mL, only 5.7% and 5% patients in UNOS-DS and AC-DS groups respectively had AFP ≥100 ng/mL. Although this demonstrates the value of AFP elevation, it also emphasizes the shortcomings of relying on AFP to predict tumor biology. In order to reduce the risk of post-transplant mortality and HCC recurrence, AFP and wait times must be integrated into dynamic models which recognize the role of tumor biology.

As per the new UNOS policy that became effective in May 2019, MELD exception scores for patients with HCC cap at a Median MELD at Transplant (within the Donor Service Area) minus 3. This change will result in longer wait times to transplant for patients with HCC as they receive less listing priority. This prolonged wait time gives us the opportunity to better assess tumor biology after downstaging to select patients with less aggressive tumors for LT and not solely rely on radiologic tumor size and number at presentation. Selecting better candidates could theoretically decrease risk of post-LT HCC recurrence. Further refinement of patient selection can occur by incorporating AFP based models as another aspect of tumor biology for predicting recurrence free survival like the prognostic model by Duvoux and colleagues (5) or Metroticket 2.0 model by Mazzaferro *et al.* (6). The extended Toronto criteria (7) for LT used a biological assessment tool comprising tumor grade, cancer related symptoms and AFP to select patients beyond Milan criteria for transplantation. Increased wait time would also underline the importance of LRT as a bridge or for downstaging. In the study by Mehta *et al.* (3), type of LRT used was not mentioned in any of the groups. Multicenter studies comparing various modalities of LRT, including newer strategies of stereotactic body radiation therapy and transarterial radioembolization as well as combination of LRTs for downstaging are required to provide further direction to optimally manage patients with unresectable HCC.

There have been progressive increasing wait times for LT in patients with HCC due to changes in organ allocation policies to address overprioritization of HCC over non-HCC indications and the continued shortage of donor organs. The work by Mehta *et al.* supports the restriction of down staging to those patients with HCC within the UNOS criteria as expansion beyond these limits result in inferior outcomes. The study further highlights the importance of radiographic responses and AFP reductions considering longer wait times as valuable surrogates for tumor biology and improved patient selection. Future study to improve patient selection in those beyond the UNOS down staging criteria needs to consider tumor biology as reflected by radiographic response not just initial tumor burden and degree of AFP reductions.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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