

Locoregional therapy as a bridge to liver transplantation for hepatocellular carcinoma within Milan criteria: from a transplant oncology viewpoint

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Provenance: This is an invited Editorial commissioned by Editor-in-Chief Yilei Mao (Department of Liver Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China).

Comment on: Agopian VG, Harlander-Locke MP, Ruiz RM, *et al.* Impact of Pretransplant Bridging Locoregional Therapy for Patients With Hepatocellular Carcinoma Within Milan Criteria Undergoing Liver Transplantation: Analysis of 3601 Patients From the US Multicenter HCC Transplant Consortium. *Ann Surg* 2017;266:525-35.

Submitted Jan 05, 2018. Accepted for publication Jan 24, 2018.

doi: 10.21037/hbsn.2018.01.07

View this article at: <http://dx.doi.org/10.21037/hbsn.2018.01.07>

The role of bridging locoregional therapy (LRT) for patients with hepatocellular carcinoma (HCC) within Milan criteria before liver transplantation (LT) has been controversial. Recently, Agopian *et al.* (1) retrospectively investigated the impact of bridging LRT on post-LT HCC recurrence and survival based on 3,601 patients undergoing LT from 2002 to 2013, collected in the US Multicenter HCC Transplant Consortium. They observed no significant differences in the recurrence-free survival (RFS) among patients not receiving RT and the type and combination of treatment modality [transarterial chemoembolization (TACE), thermal ablation (radiofrequency or microwave ablation), and others] used. The increasing number of LRT and the dynamic serum alpha-fetoprotein (AFP) changes were correlated with a higher risk of HCC recurrence. The authors concluded that LRT improved survival only in the subset of patients who achieved complete pathologic response (cPR) with a superior 5-year RFS of 72% compared to both untreated patients (69%; $P=0.01$) and LRT-treated patients not achieving cPR (67%; $P=0.01$). Admittedly, this is a benchmark study, and the authors should be congratulated on undertaking a sophisticated analysis in a large, heterogeneous cohort of patients.

However, several unanswered, critical questions are as follows: (I) since cPR is an unknown variable at the time of LT, who should receive bridging LRT? In this study, the

selection criteria were highly variable and were affected by both patient (e.g., model for end-stage liver disease, AFP, and radiographical size and number of tumors) and center-specific factors (e.g., practice pattern and the anticipated wait-time according to the United Network for Organ Sharing region); (II) the data are lacking on whether patients had undergone any HCC treatments before listing, and the decision-making is again surgeon- or center-dependent, which might also have affected oncological outcomes (2,3); (III) the study comprises patients treated until 2013. Therefore, other modalities that recently emerged as an effective alternative LRT for HCC (e.g., drug-eluting beads TACE, Y90 radioembolization, and stereotactic radiation therapy) (4-6) should be considered when revising the liver allocation policy. In addition, dynamic AFP and other biological markers of aggressive tumor biology, such as neutrophil-lymphocyte ratio, C-reactive protein, and positivity for fluorine-18-fluorodeoxyglucose-positron emission tomography, should preferably be incorporated in patient selection (7); (IV) over 60% of patients in the study population had hepatitis C. Their viral status and whether they had received antiviral therapy post-LT, especially with the interferon-free regimens using direct-acting antivirals (8), have not been analyzed; (V) antineoplastic immunosuppression (9) and a novel immunotherapy using natural killer cells (10) might open up a new horizon to

reduce post-LT HCC recurrence.

When we zoom out from the US, the problem gets even more complicated. A huge discrepancy exists in the treatment guidelines for HCC between East (11) and West (12). Of note, growing evidence suggests that laparoscopic liver resection might expand resectability in cirrhotic patients with HCC (13,14), making it difficult to standardize the indication of LT for HCC across the globe. Whether the acceptable range of HCC recurrence should be equivalent between living and deceased donor LT remains debatable.

The time has come for experts in the field of transplantation medicine and oncology to discuss in an international framework under the concept of "Transplant Oncology" (7) and provide a bona fide multidisciplinary cancer care for our patients in desperate need.

Acknowledgements

None.

Footnote

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

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Cite this article as: Hibi T, Sugawara Y. Locoregional therapy as a bridge to liver transplantation for hepatocellular carcinoma within Milan criteria: from a transplant oncology viewpoint. *HepatoBiliary Surg Nutr* 2018;7(2):134-135. doi: 10.21037/hbsn.2018.01.07