Editorial

# Loco-regional treatments on the liver transplant waiting list: unmasking hepatocellular carcinoma (HCC) biology

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*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.

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Hepatocellular carcinoma (HCC) is the sixth most prevalent cancer worldwide and is a leading cause of morbidity and mortality in patients with cirrhosis (1). Although it is the second most common indication for liver transplantation in Europe (2), the optimal management of patients awaiting liver transplantation is still not established (3). One of the most concerning events for such patients is for the tumor to progress beyond transplant eligibility and effectively for the patient to drop out of the wait list with previous reported rates of 11% at 6 months and 57% at 12 months (4). To prevent this from happening, the concept of bridging therapy has emerged. Unfortunately, most of the evidence regarding the use of bridging therapy, specifically transarterial chemoembolization (TACE), has failed to show any consistent positive impact on the outcome of patients following liver transplantation (5). The European Association for the Study of Liver has suggested that patients with HCC on the waiting list should undergo bridging therapy if the expected wait time is longer than 6 months (6). Recommendations from international consensus groups and the American Association for the Study of Liver Disease suggested that patients with OPTN T1 HCC, meaning single tumors under 2 cm of size, should be closely monitored with follow-up imaging as there is no evidence that bridging therapy is beneficial. On the other hand, patients with OPTN T2 HCC, meaning those between 2 to 5 cm, should receive bridging therapy, especially if the wait time is expected to be longer than 6 months (7,8). Although important in the management of patients with HCC, the above recommendations are based on very low-quality evidence and have a conditional strength of recommendation. Given the low quality of evidence currently available, it is imperative that we better understand the impact of bridging therapy on patients with HCC.

The article by Agopian *et al.* recently published in *Annals of Surgery* attempted to answer this question (9). Based on the United States Multicentric HCC Transplant Consortium regrouping 10 of the 11 United Network for Organ Sharing (UNOS), Agopian *et al.* have been able to analyze data from 3,601 patients, which is likely the largest ever published cohort of patients with HCC within Milan criteria who underwent liver transplantation. The cohort included patients from 2002 to 2013 and focused on known pre-transplant HCC, excluding those with non-HCC tumors and those with tumors that were identified incidentally on the explant. The main outcomes of interest assessed the rate of cancer recurrence, recurrence-free survival (RFS), and survival over a median follow-up of 4 years. To be able to adjust for known confounders, they included multiple demographic, clinical, laboratory, radiologic, and histologic variables making for a well-constructed study. Regarding the type of locoregional therapy (LRT) received, patients were classified in four major groups including those who underwent TACE alone,

ablation alone, combination of the previous two, or any other treatment modality.

Overall, the cohort included 2,854 (79.3%) patients who received LRT and 747 (20.7%) who did not. The most common type of LRT received was TACE in 53.4% of patients. The authors showed that the use of LRT did not have any impact on HCC recurrence and/or RFS. This contradicts previous reports where the use of LRT, more specifically TA(C)E, was independently associated with lower incidence of post-transplant HCC recurrence (10). The reported rates of RFS in patients who received LRT was comparable to those who did not at 1, 3, and 5 years (89%, 77%, 68% *vs.* 85%, 75%, 68%, P=0.490). The cumulative 5-year cancer recurrence rate was 11.2% for those who received LRT and 10.1% for those who did not (P=0.474).

An interesting result that has emerged from this study is that patients who received 3 or more sessions of LRT were more likely to have higher HCC recurrence rates, and lower RFS when compared to those who received 2 or fewer sessions and even to those who did not receive any LRT. Rates of RFS at 5 years were 71%, 63%, and 51% for those with 0 to 2, 3, and 4 or more LRT sessions respectively (P<0.001). Furthermore, although achieving complete pathologic response (cPR), meaning the absence of HCC on the explant, is known to be a protective factor against HCC recurrence after liver transplantation, this was not the case when looking at those who received 3 or more LRT sessions (11,12). Not only was achieving cPR in those with 3 or more LRT sessions lead to higher cancer recurrence rates than those who received 1 or 2 LRT sessions (15.2% *vs.* 3.9%, P<0.001), but it was also associated with a worse outcome compared to those who did not receive any LRT (15.2% *vs.* 10.1%, P=0.039). This persisted on multivariate analysis despite adjustment with known variables associated with worse outcomes. Given the size of the cohort and the strong and consistent signal identifying 3 or more LRT sessions as a poor prognostic marker, it is unlikely to be a type 1 error. It is also unlikely that it is directly related to the treatment modality itself as this was confirmed for those receiving TACE alone, ablation alone, or a combination of both.

There are several points regarding this study that deserve comment. Firstly, the selection criteria for performing LRT varied and it is plausible that patients who were allocated to bridging treatments were expected to feature longer on the waiting list or had larger tumors at presentation. Although the tumor characteristics on the explanted liver are presented, there is no information on the initial size of tumors. To minimize such a selection bias, a propensity score matching between patients receiving and not receiving LRT should ideally have been performed and the initial tumor size should have been taken into account. Secondly, drop-out rates from the transplant waiting list were not assessed; such an approach ("intention-to-treat transplant benefit") would more accurately assess the risk and benefits of LRTs as bridging therapies. Thirdly, although repeated TACE sessions has previously been associated with an increase in cancer stem cells (13), it is more plausible that multiple LRTs were a surrogate marker of more aggressive tumor biology. Another potential explanation that the authors have unfortunately not assessed is related to the impact of time spent on the waiting list. The data clearly show that UNOS regions with long wait list were more likely to receive 2 or more session of LRT compared to regions with short or medium wait times where most patients receive 0 or 1 session. Given that waiting list time is associated with the exposure, in this case the total number of LRT sessions, and that it likely has an impact on the outcome, it is an important confounder that should have been addressed.

Unfortunately, as this study focused only on patients who were transplanted, it only gives a partial picture and may not help the decision-making of physicians treating patients with HCC who are still waiting for a liver transplant. It does however reinforce the idea of a dynamic assessment of the tumor biology and treatment response while the patient inevitably waits for an organ. Clearly, current criteria that are based solely on tumor size and number of lesions are not ideal as they miss important aspects of the tumor biology. A recently published article by Mazzaferro attempted to provide a framework helping physicians with rules for staging and allocation of organ in this patient population (14). These take into consideration patient characteristics, laboratory values including MELD and AFP, dynamic radiological evolution, and the application of bridging therapy. Although promising, this still requires validation in large multicentric trials. Another study worth mentioning, by Lai *et al.*, applied the novel concept of intention to treat survival benefit in order to be able to identify key variables that would divide patients in high- or low-benefit groups (15). Based on the European Hepatocellular Cancer and Liver Transplantation (EurHeCaLT) Project regrouping more than 2,100 patients, four variables were found to exert a large amount of benefit in terms of gained months of survival. These included an AFP under 1,000 ng/mL, laboratory MELD at liver transplant above 13, and the absence of progressive disease or complete response based on the mRECIST criteria.

 

In conclusion, this well-constructed large cohort study did not show a beneficial impact of LRT on patients with HCC within Milan criteria who received a liver transplant, but it identified the total number of LRT sessions as a potential marker associated with a worse outcome. This is probably a surrogate marker of more aggressive tumor biology and can actually help in preventing futile transplants. Assessing what truly makes this subset of patient at risk of higher cancer recurrence and lower RFS remains uncertain. Future studies should focus on the tight interplay between tumor biology and response to bridging therapy, and its impact on drop-out rates in regions with varying wait time. In the meantime, we advocate the use of loco-regional treatment on the waiting list, particularly for an estimated waiting list time of more than 6 months.

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## Footnote

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

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