Commentary

Influence on the other patients in the waiting list when expanding the Milan criteria

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Abstract: The extended criteria beyond the Milan have been a matter of debate regarding liver transplantation for patients with hepatocellular carcinoma (HCC). Hangzhou criteria are unique in providing an opportunity of liver transplantation for patient with a large HCC over 8 cm provided that the histology grade is favorable and AFP level is less than 400 ng/mL. The present paper successfully demonstrated the non-inferiority of the Hangzhou criteria in terms of both the patient survival and the recurrence free survival when compared to the other criteria among the 6,554 patients with HCC undergoing liver transplantation from the China Liver Transplant Registry. Another important point includes the influence of the expanded criteria of HCC on non-HCC patients. It may vary widely, depending on the composition of the waiting list population and the scarcity of available liver grafts in the corresponding transplant region and in the individual institution. A morality on waiting list should be kept in spite of the expanded criteria for HCC patients.

Keywords: Hangzhou criteria; Milan criteria; liver transplantation; hepatocellular carcinoma (HCC)

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The extended criteria beyond the Milan (1,2) have been a matter of debate regarding liver transplantation for patients with hepatocellular carcinoma (HCC). Among numerous expansions, Hangzhou criteria, proposed by Zheng *et al*. (3) in 2008, was based on the 195 patients with HCC, reporting a survival rate similar to that achieved by the Milan (5-year survival rates: 72% *vs*. 78%) for patients carrying HCC defined as, (I) total tumor diameter less than or equal to 8 cm, or (II) total tumor diameter more than 8 cm, with histopathologic grade 1 or 2 and peroperative AFP level less than or equal to 400 ng/mL, simultaneously.

In the present paper (4), the same group successfully demonstrated the non-inferiority of the Hangzhou criteria in terms of both the patient survival and the recurrence free survival when compared to the Milan (1,5), Valencia (6), University of California San Francisco (7), and University Clinic of Navara criteria (8), among the 6,554 patients with HCC undergoing liver transplantation from the China Liver Transplant Registry. In addition, Hangzhou criteria showed the greatest expansion and the most excellent prognostic-predicting capacity among the four sets of criteria. This is a well-conducted retrospective study with an appropriate statistical analyses based on a large cohort, and clearly demonstrated that the Milan criteria can be expanded safely and effectively.

Hangzhou criteria are unique in providing an opportunity of liver transplantation for patient with a large HCC over 8 cm provided that the histology grade is favorable and AFP level is less than 400 ng/mL. However, it is well recognized that the both microscopic/macroscopic vascular invasion and/or poor differentiation is often encountered in resected HCC specimen above 5 cm in diameter (9), which was not detected in preoperative examination. If the presence of vascular invasion in histology was never considered with the exclusion of cases with vascular invasion in preoperative evaluation, it may hamper the present results. In this regard,

detailed information of macroscopic vascular invasion had better be presented.

Hangzhou criteria seem noteworthy in including both histology and biomarker (AFP) which was indicated for tumors with a large burden. In contrast to uniform inclusion of these factors as proposed in the other criteria (10,11), it seems rational to adopt these factors for cases with a large tumor burden since the variables of tumor morphology, biology, and pathology may become significant problem in such cases. Although they mentioned that the requirement for histology of Hangzhou criteria as a disadvantage to be accepted as an expanded criteria, this is only for cases with large tumor burden and seems rational in a certain sense. Nowadays, it is widely accepted that expanded criteria should consider not only the size-and-number characteristics of tumor presentation but also composite the morphology, biology, and pathology of tumors in the analyses of the recurrence among HCC patients (12).

While it is widely accepted that the Milan criteria is too strict in terms of post-transplant recurrence rate and that it can definitely be expanded to some extent without impairing patient outcome (13), however, we have to always be aware of that any kind of expansion in size or number of the tumor includes the potential to worsen the post-transplant survival in patients with HCC. The "metroticket paradigm" well describes this principle; the longer the distance beyond the conventional indication criteria with more aggressive tumor burden, the higher is the price in terms of postoperative impairment in survival. This is why there have been only retrospective studies advocating the expanded criteria beyond the Milan (14), and no prospective study has ever challenged the matter of expanded criteria, all which have resulted in one of the major reasons for a low level of recommendation of the expansion in major guidelines (13).

There seems to be several flaws in the methodology of the present study. Without the explanation for the exclusion of the large number of cases (over 2,000) due to the lack of necessary parameters, readers could not completely validate the present data. In addition, the cases having discrepancies between preoperative findings and pathological results were reported to have been excluded from the study. There was no description for donor characteristics. All these ambiguous patient selection and donor allocation may weaken the present results, while the absolute large size of the cohort may complement these deficits.

The allocation policy of the China Liver Transplant Registry is unclear (15). An excessive expansion of inclusion criteria will result in a significant increase in the organ demand, with a consequent increase in waiting time and a deterioration of overall patient survival among patients with HCC as a whole living in the corresponding region. What is more, the allocation system should take into account that how much the extension of criteria for HCC patients will negatively influence on the waiting-list of patients without HCC. According to the studies based on US transplant registry by Markov models (16), patients beyond the Milan would need to achieve 5-year survival of above 60% to prevent a substantial decrease to the life-year available to the entire population of candidates for liver transplantation. In this regard, the present result seems to satisfy the minimal requirement for the expansion. The influence of the expanded criteria on non-HCC patients may vary widely, depending on the composition of the waiting list population and the scarcity of available liver grafts in the corresponding transplant region and in the individual institution. Any expansion by each institution should take into account the current mortality on the waiting list, and should only be allowed when a low morality on waiting list will not be substantially increased by the expanded criteria for HCC patients (13). In this sense, the present study without the clarified allocation policy seems to fall short despite the significant increase in the number of HCC patients who could reap a benefit of liver transplantation. The authors appropriately mentioned in discussion as follows; "Although the post-transplant survival is acceptable for the expanded criteria, we still observed decrease in the survival rates for the patients exceeding Milan but fulfilling the expanded criteria compared with those fulfilling Milan. It is a different matter whether those newly recruited patients by the expanded criteria are still good enough to be considered for liver transplant. For our part, a tumor-free survival of >80% and >55% at 1 and 5 years, respectively, is acceptable. Therefore, the patients exceeding Milan but fulfilling the expanded criteria may still be appropriate for liver transplant, particularly in China, which bears the greatest HCC burden worldwide." This paragraph concisely and directly summarizes the noteworthy findings and the deficits of the study.

In conclusion, this is a well-conducted retrospective study based on the large cohort of patients with HCC, and may contribute to the ongoing debate of beyond the Milan. Meanwhile, the influence of the expansion on the non-HCC patients in waiting list should be given more weight than the extent of expansion among HCC patients.

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Footnote

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

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