Commentary

Can Milan criteria be expanded effectively for liver transplantation in patients with HCC?

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Abstract: The Milan hepatocellular carcinoma (HCC) criteria emerged as the worldwide standard criteria for liver transplant eligibility. However, it has been observed that selected patients with more advanced tumor stage can achieve equivalent outcomes. A large retrospective analysis from Xu *et al*. comparing the Hangzhou HCC criteria with other expanded criteria suggests the Hangzhou criteria can offer the broadest application of liver transplantation for HCC patients without detriment in survival.

Keywords: Liver transplantation; Milan criteria

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In the study by Xu *et al*., a large retrospective analysis from the China Liver Transplant Registry compares post-transplant outcomes based on different levels of hepatocellular carcinoma (HCC) burden (1).

In a cohort of 6,012 patients, the standard HCC liver transplant Milan criteria are compared with a number of validated expanded criteria including the Valencia, University of California San Francisco, University Clinic of Navarra and Hangzhou criteria (*Table 1*).

According to the authors, when compared to the Milan criteria the expanded criteria provided a significant expansion of the applicability of liver transplantation with the largest benefit corresponding to the Hangzhou criteria (51.5%).

When fulfilling but not exceeding the above mentioned different expanded criteria, long term disease free survival rates were comparable to those of the Milan criteria.

Since the Hangzhou criteria correlated with the broadest applicability of liver transplantation without detrimental impact in outcome, the authors focused the analysis further.

The 1-, 3-, 5- and 10-year disease free survival rates for the patients exceeding the Milan criteria, but fulfilling the Hangzhou criteria versus those exceeding the Hangzhou criteria were 81.6%, 64.3%, 56.5% and 37.2% *vs*. 58.2%, 35.1%, 28.2% and 16.3%, respectively (P<0.001).

Exceeding the Hangzhou criteria is pointed out by the authors as an independent risk factor for tumor recurrence in patients exceeding the Milan criteria. Moreover, univariate and multivariate analyses revealed AFP >100 ng/dL and tumor size >8 cm as independent risk factors for tumor recurrence in patients outside Milan criteria but within Hangzhou criteria.

The authors point out that in China about 40% of liver transplants are performed in HCC recipients, and if strictly adhered to the Milan criteria only about 43% of the cohort study would have the opportunity of transplantation. Regarding the subgroup of patients exceeding the Milan criteria, more than 60% did not experience tumor recurrence at 5 years post-transplant.

In sum, the authors conclude that the Milan criteria can be expanded without significant detriment in outcome, and advocate for the Hangzhou criteria to do so.

Once again as with others, this analysis puts transplant clinicians in the conundrum of rethinking the right balance of organ distribution policy for HCC patients in an era of persistent organ shortage (7). It is a point of agreement within a substantial portion of the transplant scientific community that the Milan criteria (single tumor ≤5 cm or 3

Table 1 Details of expanded criteria

Title	Year published	Criteria description
Milan (2)	1996	1 lesion ≤5 cm, or 3 lesions ≤3 cm each
UCSF (3)	2001	1 lesion ≤6.5 cm, or 2-3 lesions ≤4.5 cm each, with a total tumor diameter ≤8 cm
Navarro (4)	2001	1 lesion ≤6 cm, or 2-3 lesions ≤5 cm each
Valencia (5)	2008	1-3 lesions ≤5 cm each, total tumor diameter ≤10 cm
Hangzhou (6)	2008	Total tumor diameter ≤8 cm, AFP ≤400 ng/mL

tumors each <3 cm) provide excellent oncological outcomes comparable to patients without HCC (2), but at the same time can be too strict (8).

The dilemma continues to be twofold; the large discrepancy between organ demand and availability and lack of accurate predictors of tumor recurrence. Relaying solely on measurement of tumor size and number appears to be rudimentary as it leaves out of the predictive equation a big deal regarding tumor biology (9). Similarly, including AFP level as a predictor factor falls short as it is a poor specific biomarker (10).

Pre-transplant tumor biopsy has been proposed to identify predictive biomarkers, however due to tumor multifocality or heterogeneity and risk of tumor cell spread through the biopsy needle track, this approach can be impractical (11,12).

In an effort to overcome difficulty of unveiling tumor behavior, it has been proposed to evaluate tumor response and stability after locoregional therapy in patients outside Milan criteria before being selected for liver transplantation. This strategy appears to aid transplant selection in patients beyond the standard criteria (13).

In conclusion, since we do not have accurate predictors of tumor relapse, rather than to generalize transplant inclusion criteria based on specific expanded morphometric criteria, we should consider pre-transplant response to treatment as a better indicator to define transplant eligibility. Additionally, weighting on live donor liver transplantation for expanded criteria HCC patients could serve as an option to prevent unfair balance in the use of the cadaveric organ pool.

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Footnote

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

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