



Hepatocellular carcinoma and liver transplant: beyond the Milan criteria and the risk of “short-blanket” syndrome

Stefano Gitto^{1#}, Stefano Di Sandro^{2#}, Paolo Magistri², Pietro Andreone³, Fabrizio Di Benedetto²

¹Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy; ²Hepato-Pancreato-Biliary Surgery and Liver Transplantation Unit, ³Internal and Metabolic Medicine, AOU di Modena and University of Modena and Reggio Emilia, Modena, Italy

#These authors contributed equally to this work.

Correspondence to: Pietro Andreone. Internal and Metabolic Medicine, AOU di Modena and University of Modena and Reggio Emilia, Modena 41126, Italy. Email: pietro.andreone@unimore.it.

Provenance and Peer Review: This article was commissioned by the editorial office, *Hepatobiliary Surgery and Nutrition*. The article did not undergo external peer review.

Comment on: Mehta N, Dodge JL, Grab JD, *et al.* National experience on down-staging of hepatocellular carcinoma before liver transplant: influence of tumor burden, alpha-fetoprotein, and wait time. *Hepatology*. 2020;71:943-54.

Submitted Nov 06, 2019. Accepted for publication Nov 21, 2019.

doi: 10.21037/hbsn.2019.11.34

View this article at: <http://dx.doi.org/10.21037/hbsn.2019.11.34>

Liver transplant (LT) is considered the best option for patients with hepatocellular carcinoma (HCC) confined into the liver and generally associated with liver cirrhosis (1). The Milan criteria (MC) represent a milestone in the selection of these patients (2). Therefore, basing on MC, the 5-year survival rate after LT could increase to 70%, with a HCC recurrence rate lower than 10% (2). Despite that, too many patients affected by HCC may not benefit from LT due to a tumor stage beyond the selection criteria. Over the last two decades, authors and physicians tried to overcome the MC exploring the opportunity to safely transplant patients beyond (3). Notably, the donor shortage and the competition between patients listed due to HCC and those listed for other indications, force physicians in selecting candidates with the best transplant benefit (3).

Nowadays, the majority of patients listed for LT receive loco-regional treatments (LRTs) for HCC with the aim to control the tumor progression waiting for the LT and to improve post-LT outcome (4). Furthermore, LRTs allow down staging the tumor burden at diagnosis with the possibility to transplant patients unsuitable for LT at the first tumor evaluation (4).

Although the MC remains a strong predictor of post-LT survival, many patients showed good or poor post-LT outcome in spite attending or not those criteria. The strongest evidence, which has recently affirmed, demonstrates that the biological tumor behaviour may

impair results even in patients with safe morphological criteria (tumor size and number). By this way, the relevance of the alpha-fetoprotein and tumor response to the LRTs has significantly grown up. Indeed, the most recent staging systems include the consideration of tumor biology's clues such as the progression after LRTs or the absolute value and trend of the alpha-fetoprotein before transplant (5-7).

Accordingly, the Metroticket 2.0 is one of the most accurate models able to predict post-LT HCC related survival basing on tumor number and size and alpha-fetoprotein evaluated at the last re-staging time (5).

On 2016, Mazzaferro *et al.* (8) proposed a philosophical framework about the transplantable tumor (TT) including all the pre-operative variables related to the tumor stage, opportunity of downstaging, and response to the LRTs before the transplant. TTs were classified into 8 stages with progression from lower stage with fewer priorities to the transplant until the highest stage with highest priority. A recent study tried to validate the prediction power of this staging system on a real patient cohort, exploring the correlation between the stages and the dropout risk before LT and the correlation between tumor stages and risk of post-LT HCC related death (9). Therefore, the TT staging appeared predictive for both higher and lower risk classes. However, it resulted inaccurate for the intermediate classes. Indeed, patients classified at intermediate risk appeared

having benefit from a delayed transplant (longer than 2 months since the last tumor staging) (9). The message to delay a LT in view to improve the post-LT patient survival should be taken with caution. Although selected patients may benefit of a postponed transplant, in term of overall survival and specific tumor survival compared to an earlier transplant, the risk of patient drop-out waiting for a delayed transplant may be the really worst scenario for the patient himself.

Mehta *et al.* (10) recently approached this complex issue with a well-designed national study. Authors retrospectively analysed data from United Network for Organ Sharing (UNOS) database about LT for HCC between 2012 and 2015. Candidates were classified into the following subgroups: (I) “Milan criteria” group (patients with HCC continuously within homonym criteria); (II) “UNOS-DS” group (UNOS down-staging inclusion criteria: 1 lesion >5 and ≤8 cm, 2–3 lesions at least one >3 and ≤5 cm with total tumor diameter ≤8 cm, or 4–5 lesions each ≤3 cm with total tumor diameter ≤8 cm); (III) “AC-DS” group (initial tumor burden exceeding UNOS-DS inclusion criteria with no upper burden limit).

Notably, the subgroups 2 included patients selected according to UNOS-DS criteria adopted by 2017. The same authors already tested these standards in a multi-centre study with brilliant 5-year post-LT survival (80%) (11).

Authors subdivided the UNOS regions according to the median time from listing to LT [>9 months waitlist times was long wait region (LWR), 3–9 months mid wait region (MWR), and <3 months was considered short wait region (SWR), respectively] and registered the alpha-fetoprotein (AFP) at the time of LT.

Authors analysed data from 3,819 patients (85.8% were in the first subgroup, 11.0% in the second, 3.2% in the third one). The 3-year cumulative post-LT survival was 83.2% in the Milan group, 79.1% in the UNOS-DS group ($P=0.17$ *vs.* Milan), and 71.4% in the AC-DS group ($P=0.04$ *vs.* Milan). Indeed, the Milan and UNOS-DS groups showed the same 3-year survival. However, only in the second and third subgroups, substantial differences in post-LT survival were detected according to the waiting time region. In UNOS-DS group, the 3-year post-LT survival was lower in MWR (72.5%) and SWR (78.7%) compared to LWR (92.3%) ($P=0.009$) with the same (but not statistically significant) trends for AC-DS group (LWR: 93.3%, MWR: 65.7%, SWR: 73.0%).

Post-LT HCC recurrence was observed in 4.4% of patients of Milan groups *vs.* 9.2% and 10.7% of the others two ($P<0.001$).

Then, authors conducted univariate and multivariate

analysis for searching predictors of post-LT survival and HCC recurrence. Notably, authors considered only subgroups at major risk of worse outcome (subgroups 2 and 3). Authors demonstrated that short or mid permanence on waitlist (with consequent short or mid cancer observation before LT) together with AFP >100 ng/mL, strongly correlate with worse post-LT survival. Furthermore, they reported that AFP >100 ng/mL was the only independent predictor of post-LT HCC recurrence.

Data from this study clearly indicate the significance of acquiring a minimal observation time to establish the effectiveness of down-staging (DS) approach. At the same time, AFP level seems to have a chief role in stratifying the risk of HCC recurrence. In this regard, authors used this study to validate the risk estimation of tumor recurrence after transplant (RETREAT) score, suitable for predicting post-LT HCC recurrence in the DS populations. Increasing RETREAT scores not only predicted increased post-LT HCC recurrence but worse post-LT survival too. Remarkably, RETREAT score computes AFP at LT, microvascular invasion, and the sum of the largest viable tumor plus number of viable tumors on explant (12).

Although the study demonstrates important results concerning the correlation between HCC DS and results after LT, some limitations oblige to carefully consider the final messages. First, the correlation between the pre-transplant HCC management and post-LT results should be designed by an intention-to-treat point of view, basing on the necessity to balance the risk of patient drop-out before the transplant and the post-LT survival or HCC specific survival. The effect of the time-to-transplant, fast or slow between listing and transplant, and the patient survival should take into account how many patients have lost the chance to be transplanted because of tumor progression. The different survival reported by Mehta and co-workers among SWR, MWR, and LWR may be re-balanced after an intention-to-treat analysis and this is mandatory. Secondly, although the large collected series and the accurate study methods, the median follow-up of 1.9 years appears significantly short to draw grounded conclusions with risk of HCC recurrence's underestimation. Moreover, the RETREAT score has strongly demonstrated its validity as predictive tool of HCC recurrence after transplant. However, the scientific community has recently concentrated its attention on the pre-transplant variables, with the aim to obtain information as much as possible before LT, rather than after. Indeed, despite the accurate radiological restaging since all the group 2 and 3 patients resulted attending the transplant criteria,

32.5% and 40.5% of patients were outside the criteria at the explant tumor staging. By the Mehta's study (10) we could not understand the interval between the last re-staging and the transplant, thus it results difficult distinguishing between a radiological tumor underestimation or tumor progression in the time between last re-staging and transplant.

The reproducibility of the study results appears difficult since the stratification of wait time is not based on individual variables but on the UNOS regions.

Other open question regards the possible use of AFP for the selection of candidates. This study (10), but also others (5,7), underlined the relevance of AFP for improving the selection criteria in terms of HCC recurrence prediction. However, we well know that 30–40% of HCC are diagnosed with normal serum AFP (13) and this might represent a potential limitation for the clinical application.

Furthermore, other tools for a better selection of LT candidates should be evaluated such as alternative serum markers [e.g., lens culinaris-agglutinin-reactive fraction of AFP (AFP-L3) and protein induced by vitamin K absence or antagonist-II (PIVKA-II)] (14) and/or hepatic gene signature useful for detection of more aggressive cancer (15).

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/hbsn.2019.11.34>). 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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Cite this article as: Gitto S, Di Sandro S, Magistri P, Andreone P, Di Benedetto F. Hepatocellular carcinoma and liver transplant: beyond the Milan criteria and the risk of “short-blanket” syndrome. *HepatoBiliary Surg Nutr* 2020;9(4):518-521. doi: 10.21037/hbsn.2019.11.34