Editorial

Expanding transplantation of patients with a liver cancer without harming allocation: a priority in the era of scarce donation

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The ever-increasing success of liver transplantation (LT) as a life-saving procedure has led to a demand for donor organs far exceeding the supply, a gap that has largely been governed by algorithms founded on strict criteria for organ allocation outweighing the patient's risk of dying in the wait list versus post operatively (1). In the scenario of hepatocellular carcinoma (HCC), this strategy translated into the prioritization of patients with a limited tumour burden restricted to the liver parenchyma without extra hepatic disease, i.e., a single nodule less or equal than 5 cm or up to three nodules each equal or less than 3 cm in size of the Milan criteria (MC), that along 20 years of application has granted patients with a HCC to gain the same survival benefits as patients transplanted for non-neoplastic end-stage liver diseases (2,3). Meanwhile, just because of the aforementioned consolidated role of LT and also of percutaneous ablation alone or prior to LT for patients with limited tumor burden (4), resective surgery has challenged with good success the most advanced HCC (5-7). However, in centres experiencing a change in the demography of the wait list and a decline of listing due to decompensation, there has been a growing interest to moderately expand listing criteria for patients beyond MC, for whom LT may play a role in reverting an otherwise dismal prognosis (8). Then, algorithms combining morphological, biological and clinical variables have been generated with the aim to identify outliers with chances of gaining transplant benefits once the tumour has been down staged within MC through the application of local ablative treatments. Compensating for the increased risk of tumour recurrence driven by expanded cancer burden, criteria of selection were built incorporating additional predictors of recurrence like tumour cell grading or tissue infiltration ratio between neutrophils and lymphocytes, the first correlating with venous invasiveness and peri-tumoral satellites, the second sensing the level of immune surveillance against cancer cells (9). In this perspective, listing criteria built combining TNM with different serum cut offs of alfafetoprotein (AFP), has become an approach that gained popularity in Europe (10). Toso *et al.* showed that patients with a down-staged HCC and low levels of AFP had similar post-transplant survival benefits as any patient within MC (11). However, the patient responsiveness to tumour down-staging with local ablative techniques, impacted by tumour, patient and procedure related differences, not surprisingly, has limited the rate of successful application of similarly expanded listing criteria. Brilliantly elaborating on this, the founder of MC pinpointed the need of switching from static criteria of listing based on tumour staging at presentation toward more articulated criteria based on extended assessment of tumour responsiveness to down staging as a dynamic approach to reliably capture the risk of tumour recurrence post-transplant, in an effort of reconciling principles of selection and allocation (9). While most studies reported 5-year survivals greater than the minimal acceptable standard rate of 50% for patients grafted with

an expanded HCC, in the end expanded strategies resulted in a limited increase of HCC patients accessing transplant whereas the survival benefits in most cohorts resulted by cumulating outcomes of the many patients within MC and of the less numerous patients beyond MC. These are not trivial points as a major constrain to the widespread implementation of expanded policies for listing HCC patients remains the fear of harming other populations in need of LT who compete for organ allocation while lacking alternative options of care.

This was also the concern of the Liver Transplant Centre at University of Toronto that in 1998 elected to refine the selection criteria by shifting from MC based on TNM to a combined algorithm considering patients with any tumour size except those with poor cell grading and symptoms of neoplastic disease assessed by the Karnofsky score, i.e., a validated parameter that reliably stratifies patients with respect to prognosis and treatment indication. Listed by this algorithm ultimately were patients lacking extra hepatic disease or venous invasiveness by tumour cells who were subjected to down staging procedures whenever the waiting time exceeded three months (12). In such an explorative study, 294 patients out of an initial cohort of 362 candidates, were ultimately transplanted and a 70% rate of 5-year survival was recorded. These encouraging outcomes were validated in a second cohort of 210 patients, 41% beyond MC (MC+) and 59% within (MC) (13). On intention to treat analysis, the 5-year survival and risk of tumour recurrence appeared to be marginally, yet not significantly, influenced by MC status (MC+ 69% *vs.* MC 78%, P=0.3 and MC+ 26% *vs.* MC 16%, P=0.09, respectively). However, when pooled with the first cohort published in 2008, extending to 10 years the observation period, patients MC+ (38% of the pool) showed a trend toward a further reduction of actuarial survival (MC+ 50% *vs.* MC 60%, P=0.07) and experienced a significant increase of tumour recurrence (MC+ 33% *vs.* MC 15%, P<0.001). Interestingly, a small subset of patients (12.5%) with pre-transplant AFP levels greater than 500 ng/mL, showed survival significantly shortened (54% *vs.* 75%, P=0.006) and risk of drop out significantly increased (49% *vs.* 11%, P<0.001) compared to patients with lower AFP levels.

Despite we acknowledge the novelty of the Toronto listing algorithm, which includes such important modifiers of prognosis as constitutional symptoms and tumour cell grading, as criteria meant to optimise transplant utility, we could not omit raising some concerns about the validation study. Indeed, mitigating the impact of these criteria there is the small size of the study influencing for sure the significance of survival difference between MC groups, as outlined by P value cut offs approaching significance when the two cohorts were cumulatively analysed. As main methodological caveat there is the assessment of cancer symptoms in patients with advanced liver disease. Indeed, while we recognize the added value of stratifying HCC patients by the performance status score, we also acknowledge how difficult could be in some patients to accurately disentangle constitutional symptoms of cancer progression from those related to underlying advanced liver disease. Of note, liver biopsy properly disclosed well differentiated HCC in 90% of patients, apparently with a limited risk (1.9%) of complications including seeding. However, given the histological heterogeneity of HCC (particularly in MC+ patients), the heterogeneity of bridging local treatment adopted within and between the two groups (MC patients mostly received radio frequency ablation and MC+ patients mostly underwent chemo-embolisation), we wonder how accurate was the confirmation in the explanted livers of pre-transplant histological criteria of selection.

Therefore, in the scenario where listing to LT is driven by increasing need of reconciling patient selection with organ allocation, the Toronto experience holds the merit of widening the selection criteria beyond a pure morphological algorithm. However, for clarifying the relevance of some drawbacks featuring the study, an external validation, as the author themselves claimed concluding their paper, would be of profit, as it should be expected a comparison with algorithms built on a dynamic parameter like responsiveness to bridging therapies.

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Footnote

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

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