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INVITED COMMENTARY

'5-5-500' – yet another extended criteria for HCC or a truly innovative development?

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A landmark study by Mazzaferro *et al.* [1] has cemented the role of liver transplantation as a key treatment option for patients with hepatocellular carcinoma (HCC) and established the Milan criteria as the benchmark for access to transplantation for these patients.

However, over the last 2 decades, the Milan criteria have come under intense scrutiny and are now largely regarded as too restrictive, limiting the access to transplantation for many patients who would otherwise achieve good clinical outcomes. Alternative criteria have been defined [2] achieving comparable outcomes with Milan. However, these criteria continued to rely primarily on clinical and radiological parameters whilst gradually, our understanding of tumour biology has shifted the emphasis on the role of noninvasive biological testing as a surrogate marker of HCC behaviour. New criteria combining radiology with biological markers have been defined, improving the accuracy of the Milan criteria [3].

Living donor liver transplantation added a new dimension to the management of HCC, questioning the use of restrictive criteria in the context of an available transplant option albeit governed by a different equipoise. Various extended criteria in this setting demonstrated successful outcomes [4] and led to a call for different indications for deceased donor and living donor liver transplantation for HCC. Whilst a universally accepted consensus seems impossible, locally defined extended criteria should stand ethical and societal scrutiny and provide additional benefits over and above the time-tested Milan criteria [5].

In this issue of Transplant International, Shimamura *et al.* [6] propose a new set of extended criteria for transplantation of patients with hepato-cellular carcinoma. Beyond the development of a new set of rules, this study is uniquely set in the context of living donor liver transplantation (LDLT).

Data from 965 patients with a diagnosis of HCC and undergoing LDLT in all liver transplant centres in Japan were used to generate the new set of criteria. Living liver donation is the only realistic chance of transplantation (and hence survival) in Japan, illustrated by the fact that fewer than 30 patients diagnosed with HCC underwent a deceased donor transplant to date. Although living donation is a private gift from the donor to the recipient, acceptable outcomes in terms of

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cancer recurrence are expected both from a recipient as well as a donor point of view, to offset the surgical risks associated with the donation process. Accordingly, Shimamura *et al.* considered a socially and ethically acceptable outcome in terms of cancer recurrence (that could well be applied to deceased donor transplantation), aiming to achieve the highest number of transplanted patients with a <10% 5-year recurrence rate and an overall 5-year survival in excess of 70%.

Using a multitude of donor and recipient data including explant pathology and tumour biology markers, the authors defined a new '5-5-500' rule based on tumour size (largest ≤5 cm diameter), number of HCC nodules ≤5 and alpha-fetoprotein (AFP) ≤500 ng/ml. Whilst this combination is not entirely innovative [3], the authors defined new thresholds relevant to their population, which increased eligibility for transplantation by 19% with only a 7.3% 5-year recurrence rate.

The Milan criteria are approved by the Japanese government as the basis for insurance cover for transplantation. Whilst this may be fair in a system that relies primarily on deceased donation, this may not be the case in a setting where transplantation is provided through living donation and is thus up to the donor and recipient to decide what may be acceptable in terms of outcomes and risks. However, this places a significant financial burden on the families embarking in LDLT and adds numerous logistical and local institutional ethical challenges prior to the transplant being undertaken. Furthermore, the lack of cohesive acceptance criteria between institutions leads to a 'postcode lottery' for access to the service. In this context, the '5-5-500' rule sets the new scene, ensuring equity of access between the national insurance system and the private sector, whilst increasing access to a life-saving treatment option and maintaining excellent clinical outcomes. However, it also sets the new boundaries in selecting candidates, as those within Milan but outwith the '5-5-500' rule would have unacceptably high recurrence rates, defeating the purpose of transplantation.

In this cross-sectional study, 31% of patients were outside the conventional Milan criteria, confirming the limited accuracy of pretransplant imaging and acknowledging that tumour biology is the most important factor predicting outcomes and recurrence. Whilst the Milan criteria were a surrogate marker for tumour behaviour, recent criteria have attempted to include various tumour markers as more accurate predictors of HCC behaviour. Whilst these remain crude approximations, for now they appear to be better than a set of criteria based on radiological imaging. This point is well illustrated by this study, with the '5-5-500' rule' able to identify patients at a higher risk of recurrence, irrespective of whether they were within or outwith Milan criteria. This questions the universal relevance of the Milan criteria and appears to suggest that any biological criteria thresholds (e.g. AFP) may be set differently in different countries to ensure outcomes that are acceptable from a societal and ethical point of view whilst accounting for the overall supply of transplantation.

Conceptually, this study also raises the inevitable question as to whether selection criteria for HCC (or indeed any other indication) should be the same for deceased donor and living donor transplantation. This is more challenging to answer as the results presented may be difficult to interpret and generalise to a system that relies primarily on deceased donation, where the notion of equitable access has a different connotation from that of an insurance based restrictive access to treatment.

The concept of '5-5-500' is an evolutionary "upgrade" of the Milan criteria, but the applicability within a deceased donor setting remains to be determined. Whilst the rule may apply to a similar extent, it would be important to define the added benefit, be it an increased access to transplantation or a better selection of patients who would benefit and balance these with the competing indications for transplantation. In this context, the role of bridging therapies (radiofrequency ablation, trans-arterial chemotherapy or even resection) and the impact on a potential application of the '5-5-500' rule remains to be established.

The '5-5-500' rule proposed by Shimamura *et al.* is after all, another set of criteria to increase access to transplantation for patients with HCC. However, it is an innovative development that has challenged the established rules, in order to provide equitable and insurance covered access to more patients whilst maintaining excellent outcomes. In doing so, the authors have reminded us the very purpose of any criteria defining access to a limited resource.

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