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Living Donor Liver Transplantation For Hepatocellular Carcinoma Exceeding Conventional Criteria
Questions, Answers and Demands For a Common Language

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In this issue of Liver Transplantation two studies bring new data to the topic of living-donor transplantation (LDLT) for hepatocellular carcinoma (HCC), offering the opportunity for some comments.1,2

Since LDLT became available, two concerns have puzzled hepatologists and surgeons involved with HCC.

a) The impact of the procedure on the results of transplantation. Would Conventional Milan Criteria (CMC), validated for patients on a waiting list for cadaveric LT,3 hold true also for living donation? In addition, the overall impact of the LDLT on intention-to-treat results was difficult to estimate, with the confounding effects of diminishing waiting time and dropouts, a technically more demanding operation, and possibly the loss of a selection effect of waiting time on patients with more aggressive tumors.

b) The impact of the unrestricted graft resource on the access to transplantation. In a condition where the rules have been dictated by scarcity, limiting transplantation to patients with a good prognosis, some patients are not constrained by donor availability: a family member wanting to donate regardless of the degree of benefit for the recipient. What are the limits and the duties associated with this new resource?

The two studies from Kyoto (93 patients) and Essen (34 patients) devoted to LDLT for HCC provide interesting data and thoughts on both points.

In the two studies, macrovascular invasion and distant metastases were firm exclusion criteria, and the two studies present patients as within and without CMC.

For patients meeting CMC. (53% in Kyoto and 56% in Essen), the incidence of recurrences was between 13% and 15%; therefore CMC, when aimed at selecting patients with the lowest chances of recurrence are valid also for LDLT, confirming previous reports.4,5 Overall survival (68% at 4 years in Kyoto and 60% at 3 years in Essen) was similar, but not quite equal, to what has been reported from the best series. Because non-cancer deaths were high (19/93 patients in Kyoto - 20%, and a hospital mortality of 9/34 patients in Essen - 26%), the lower survival observed can probably be attributed to the deliberate choice of not denying LDLT, a technically more complex procedure, to patients with advanced liver disease in both programs, and to patients with ABO incompatible donors in Japan.

For patients exceeding CMC. (47% in Kyoto and 44% in Essen), the situation is more complex. In the Kyoto study, recurrences were more frequent (35% vs. 15% for patients within CMC), but survival was regarded as
similar (59% at 4 years, vs. 68%\(^2\), \(P = 0.65\)). The absence of a significant difference in survival has to be taken with caution, since the small number of patients increased the chance of a type II error, and the follow-up was short. In the study from Essen, the 15 patients who did not meet the Milan criteria at pathology staging had a 3-year recurrence-free survival of less than 50%.

Both studies fail to identify, outside CMC, categories with a predictably better outcome, and show that we lack a common language to investigate and report on these patients. In both studies the area outside CMC was probably vast, including patients just beyond the borders and patients further away, receiving transplantation after a variety of treatments and responses to them, after a wide range of time intervals from the diagnosis of HCC, and for tumors of unequal degrees of differentiation. While this heterogeneity is unavoidable, we need to represent it consistently in order to decrease its confounding effects. A common language is not beyond reach: for the morphologic markers of disease severity (size and number of tumor nodules) for instance, patients could be plotted on a graph as illustrated in Figure 1. Standardization of such minimal requirements for reporting would show how far the patients are outside traditional criteria, and how robust is the claim that new criteria can replace Conventional Milan Criteria in predicting a good outcome.

Outside CMC, however, tumor size and number are insufficient to stratify patients in categories with reasonably predictable outcomes. Understandably so, because CMC, as similar size-number criteria from previous publications,\(^2\) were aimed at predicting a good outcome in patients who fulfilled them, rather than a poor outcome in patients who exceeded them. Additional parameters that enter the HCC equation (i.e. tumor, treatment and time factors, alpha-fetoprotein, molecular signatures of vascular invasion etc.) need to be tested.\(^7,8\) Some of them are easy to define. Criteria of response to treatment are available– possibly a surrogate marker of favorable tumor behavior or a selection tool by increasing observation time– with a category of patients who have been downstaged to within CMC and are stable for 6 months, or an other category of patients who are downstaged to predefined extended criteria, but whose disease does not progress after a variable waiting time.\(^9-11\) Patients outside CMC could be stratified by a biopsy and transplanted if the tumor is well or moderately well differentiated.\(^12\) Patients with tumors that rapidly increase in size, with rising alpha-fetoprotein, and that do not respond to treatment are associated to high chances of dropout from the waiting list for cadaveric organs;\(^13\) they should probably be excluded or studied separately within controlled trials, to know whether LDLT, by decreasing the waiting time, may merely transform dropouts into recurrences.

Beside a structured and reproducible approach, are there any additional duties when using the new supply of organs that LDLT represents? In our opinion, we need to restrict the procedure to an area were it can not be considered futile. This because health resources devoted to transplantation (if not donors –arguably) belong to the community, and because the psycho-social outcome of donors in cases where the recipient transplant has failed is insufficiently known.\(^14\) The limit of 50% survival at 5 years has been taken as a reasonable
point to start discussions in our programs,19 bearing in mind that the benefit of LDLT is better appreciated in terms of gain in life expectancy (linked to recipient age and alternative treatments) than in terms of survival.15 The call for caution concerning LDLT in HCC patients over 60 in the study by Malagò et al. is particularly relevant in this respect.

Within the limits suggested above, LDLT appears as a unique opportunity to probe in a systematic way the largely unexplored territory of the extended indication to transplantation for HCC in which cadaveric graft shortage prevents more liberal selection criteria. Landmarking the area outside CMC into reproducible categories with an intermediate risk of recurrence (whose validity can be tested prospectively) seems to us the most urgent task, is well within reach, and is almost a moral obligation considering the formidable investment of all parties involved in the procedure.

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