Living-related transplantation for hepatocellular carcinoma: How far do we travel beyond Milan?

Hepatocellular cancer (HCC) in the presence of cirrhosis of the liver has provoked debate ever since the availability of orthotopic liver transplantation (OLT). Initially, when OLT was still considered an ‘experimental’ procedure, patients with liver tumors were considered to be ideal candidates for this procedure since their survival without transplantation was short and in many cases the accompanying liver disease was less severe. As OLT became an established procedure, demand for organs outstripped the supply and the use of this precious resource for a poorer survival group like patients with HCC came under scrutiny. With growing experience, it became apparent that patients with large or bilobar tumors and those with vascular invasion often developed tumor recurrence quickly and the survival benefit of OLT in such patients was questionable.

The landmark article from Mazzaferro et al brought to light simple ‘Milan’ criteria that helped identify a patient subgroup with four-year-survival rate following OLT that was equivalent to that in non-tumor groups with an acceptably low tumor recurrence rate of 10%. The Milan criteria were enthusiastically adopted by the transplant community and validated. However, these criteria denied many patients access to this potentially life-saving treatment, leading to several attempts to expand the criteria for selection of patients with HCC for OLT. This was based on the recognition that size and number were only surrogate markers for systemic spread, and that larger tumors without vascular invasion may do equally well. Modern imaging is likely to more easily detect HCCs of 2 cm which were missed by techniques used in 1996 at the time of development of the Milan criteria, thus leading to patients being excluded today, but who may have been eligible 10 years ago. The presence of a larger number of these small tumors may have no impact on prognosis.

The advent of living donor liver transplantation (LDLT) has added another important ethical angle to the debate. Donor scarcity, which led to the development and use of selection criteria in the first place is clearly not an issue in the LDLT setting as each patient provides an exclusive donor unavailable to other recipients. However, the LDLT donor is a healthy person undergoing major surgery with its attendant morbidity and risk of mortality in the hope of providing long life to a loved one. The risks of adult-to-adult living liver donation cannot be underestimated. The recent audit of the multi-center A2ALL study group revealed that 26% of patients had a complication that was potentially life-threatening, 2% had a life-threatening complication and 3 of the 393 donors (0.8%) died. Multiple readmissions for complications were required in 4% of donors. Clearly, this sacrifice on the part of the donor should be justified by good returns. In an emotional moment, family members may opt for LDLT even with a relatively low chance of ‘cure’. In an unregulated environment, thus, patients with even large tumor bulk may be subjected to LDLT. However, it is the ethical duty of the medical profession to scientifically examine the available data so that patient families may be provided reliable information on the true likelihood of benefit following LDLT in terms of achieving the desired aim of long-term patient survival.

An increasing number of articles including the one by Pandey et al in the current issue of the Journal look at survival in patients undergoing transplantation beyond the Milan criteria. Metastatic disease is an absolute contraindication in all series. Modern imaging in the form of high resolution CT, bone scan and PET scan in those tumors that are PET-avid provide reasonable information on this with simple tests. Factors such as high tumor marker levels and tumor de-differentiation have been found to adversely affect survival. Waiting period for cadaveric OLT also helps since tumors that have a poor biological behaviour tend to progress faster leading to such patients dropping out of the transplant wait list on re-scanning. However, this ‘screening’ modality is not available to patients undergoing LDLT, since the donor is available almost immediately. This phenomenon may explain the reports of poorer survival with LRLT (or LDLT) compared to cadaveric transplantation for patients with similar disease.

Vascular invasion, even at an early stage, has been identified as a poor prognostic marker and most centers would exclude patients with obvious tumor thrombus in the main portal vein or its 1st order branch. Significance of invasion or occlusion of more peripheral branches has not been studied in depth, and may well be an issue with the improved resolution of current scanning techniques.

Tumor number does not seem to be an important issue in patients with hepatitis B. In the large series from the Asan Medical Center, Seoul, patients with up to 10 lesions underwent liver transplantation safely; in contrast, size of lesions seems to be an important determinant of the
outcome with most studies supporting a size limit of 5 to 6.5 cm.\textsuperscript{6-13}

It must also be remembered that, in patients with HCC, the liver tumor is not the sole determinant of overall survival. The underlying condition of the patient i.e. age and MELD score\textsuperscript{18} and the disease leading to cirrhosis are equally important; the presence of hepatitis C has been shown is an independent risk factor for tumor recurrence.\textsuperscript{19}

The article in the current issue of the Journal\textsuperscript{15} is an audit of the policy of offering LDLT to all comers willing to undergo LDLT for HCC. The only tumors excluded were those associated with major vascular invasion and metastatic spread. On analysis, patients within the Milan criteria did extremely well, which comes as no surprise. However, it is the group with tumor beyond the Milan criteria that needs further examination. Though the authors quote the tumor-free survival as 70% at 3 years, it must be noted that this figure excludes early mortality for other reasons. The number of such non-tumor deaths was fairly high, as has been the experience in other series of liver transplant for HCC using expanded criteria.\textsuperscript{6} If one includes these non-tumor deaths, the overall survival rate in this cohort drops to a poor 23% at 3 years. Survival rates among patient groups defined by the other published extended criteria such as the UCSF criteria (one tumor <6.5 cm or two tumors, none > 4.5 cm, total tumor load not > 8cm)\textsuperscript{8} or the recently published Asan criteria (any number, none >5.5 cm)\textsuperscript{13} are not mentioned. Though the authors conclude that LDLT gives a hope of survival to patients even beyond the Milan criteria, this conclusion is possibly too optimistic given that the overall mortality in this group is very high. LDLT donors must be given a true picture of what overall survival benefit will accrue in the recipients of their organ who are beyond current published criteria for LDLT.

In this context, Majno and Mazzafero\textsuperscript{20} have proposed the simple and elegant ‘Metro ticket price’ concept – the further one goes, the more one pays i.e. the more you deviate from the Milan criteria, the greater the price you pay, in terms of risk of recurrence.

Based on current literature, it is clear that the Milan criteria are too strict and reasonable survival can be achieved by their sensible expansion. How much expansion is appropriate is however an issue that still needs to be resolved.

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References


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