Editorial on Milan Criteria

Twenty years of Milan criteria and live-donor liver transplantation in the US: a contrast in transparency, regulation, and expectation

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In September 2016, the University of Chicago and Peking Union Medical Center co-sponsored a conference in Beijing, People's Republic of China marking the twentieth anniversary of the Milan criteria (1). The occasion presented an opportunity to review and contrast the differences in transparency, professional self-regulation, policy development, and evidence-based practice between two interrelated areas in the practice of adult liver transplantation: liver transplantation for hepatocellular cancer (HCC) and the use of the living liver donor. While both clinical practices began in the 1990's, they have taken decidedly different administrative and professional paths.

Early experience with liver transplantation as a treatment for HCC was associated with poor results characterized by rapid tumor recurrence and limited patient survival. These unacceptable results were influenced by the wide variability in degree of cirrhotic decompensation among transplant recipients and tumor number, size, and stage at the time of transplantation. It was not until Mazzaferro's group demonstrated acceptable outcomes with liver transplantation for patients with cirrhosis and small HCCs did liver transplantation become widely accepted as the best treatment (1). With introduction of the Model for End-Stage Liver Disease (MELD) prioritizing the allocation of deceased donor livers to the "sickest first", an accommodation for patients with compensated cirrhosis and HCC was needed. It was observed that physiologically stable cirrhotic patients (with low MELD scores) and HCC might not receive allocation of a deceased donor liver before their tumor growth expanded beyond the Milan criteria, thus systematically prohibiting transplantation. Consequently, in an effort to allow access to deceased donor liver allocation for HCC candidates, the practice of assigning MELD exception points for HCC was introduced and has subsequently undergone five revisions over thirteen-years (2,3). Modifications to the value of exception points have been based on outcome analysis for each modification period. Throughout the process it has been demonstrated that the awarded exception points have been too generous, resulting in significant disparity in allocation rate of deceased donors between candidates with and without HCC. More recent analysis has supported modification of the exception points awarded by introducing a 6-month waiting period after initial listing prior to the awarding of exception points and capping the maximum allowed exception value at a MELD of 34 (4).

In summary, Milan criteria established liver transplantation as the treatment of choice for patients with cirrhosis and small HCCs. The practice and institution of policy was supported by appropriate studies demonstrating acceptable and predictable outcomes for the use of a limited resource. And while many argue that Milan is too restrictive, it has prevailed as an appropriate indication for deceased donor liver allocation for twenty years in the US, balancing the expected benefits of the transplant encounter for all listed candidates (4). The transparent process of policy creation and modification with respect to the Milan criteria and allocation demonstrates a data-based and just system seeking to balance the interests of all candidates listed and competing for a scarce resource. Each phase and modification has been preceded by public disclosure and robust debate. In addition, the same public and transparent debate continues with respect to adopting less restrictive criteria for allocation among recipients with

HCC. Unfortunately, due to limitations in the availability of deceased donor organs, expansion to less restrictive criteria will further exacerbate the disparity between need and supply and in some cases, result in inferior and unacceptable outcomes for all candidates. This process is in contradistinction to the adoption and practice of live-donor liver transplantation (LDLT) for adult recipients with HCC.

Expansion of the practice of LDLT for adult recipients began to emerge in the medical literature in 1998 (5). Unlike the measured and transparent way in which the process of live-donor liver transplantation began in 1989 for pediatric recipients, its extension to adult recipients and rapid dissemination was cause for concern (6,7). Consequently, the practice of adult-to-adult LDLT has not benefited from the same transparent, organized, and regulated constructs developed for indications and allocation in deceased donor transplantation. As a result, the indications, techniques, and outcomes for donors and recipients have been disclosed piece-meal in case-based publications and individual series. The most robust literature for the US practice comes from the A2ALL cohort study (8). Two publications from the A2ALL cohort describe the practice of LDLT for HCC within the US (9,10). The initial retrospective cohort study reported a significantly higher rate of recurrence of HCC within three years among recipients of LDLT compared to recipients of deceased donor liver transplantation (DDLT), 29% *vs.* 0% respectively. The authors concluded that the enthusiasm for LDLT as a viable treatment for HCC is severely dampened by the higher rate of recurrence compared to DDLT (9). A more recent paper expanding the initial A2ALL cohort further validated the higher five-year recurrence rate of HCC among LDLT recipients when compared to DDLT with a hazard ratio of 2.35. In addition, LDLT recipients had a significantly greater percentage of tumors exceeding Milan and UCSF criteria and a shorter waiting time before transplantation than DDLT recipients. Interestingly, the overall survival between both groups was not significantly different. The authors concluded that the higher recurrence rate was likely due to differences in tumor characteristics, pre-transplant HCC management, and waiting time (10).

It would appear that the early lack of oversight and regulation within the practice of LDLT has allowed for transplantations for conditions beyond those considered acceptable and noncontroversial. This administrative negligence may have been underlying the early and broad dissemination of the practice. Of concern is the lack of application of meaningful data derived from DDLT to the situation of LDLT, i.e., higher rates of recurrence in the setting of tumors beyond Milan and in situations in which a period of demonstrated stability of tumor biology has not been obtained. Instead, it would appear that in some situations, the LDLT option is used exploitatively, specifically because the tumor number, size and stage is beyond Milan criteria and/or not amenable to down-staging and, therefore, not awarded exception points. The data would clearly indicate that LDLT for the treatment of HCC beyond even the generous UCSF criteria is at best controversial and should not be encouraged or justified when one considers the risk-benefit analysis for the donor and recipient pair. We originally referred to this balance as a double equipoise (7). Unfortunately, the recent discussion of the concept of double equipoise, defining it as a purely utilitarian decision without regard for justice or equity, fails to capture the comprehensive and nuanced understanding of the ethical issues involved (11). At its most basic, the facilitator of the live donor operation (the surgeon) has a moral and ethical responsibility to insure (guide) that the encounter is just and that all parties (donor, recipient, medical team, institution and society) are provided with sufficient material information with which each can make an informed decision about both procedures. Further, when applying the live-donor in situations beyond the standard medical practice, this would at least appear to constitute an experiment and the donor and recipient should be afforded the same protections provided to any human research subject. As stated by Volk *et al.*, "*if LDLT is performed solely out of respect for patient and family 'autonomy', we are abdicating our professional responsibilities*" (12).

With the data currently available defining the expected outcomes of liver transplantation for HCC, the continued advantage provided to candidates listed for DDLT, the lack of overall survival advantage associated with LDLT for HCC, and the recommendation from the international consensus conference (13), it is time that LDLT be performed only for accepted conditions with predictable outcomes. And for those situations in which LDLT is performed for conditions more controversial, the center and surgeon must provide basic research protections for the donor/recipient pair and contribute to the medical community knowledge by IRB disclosure of outcomes.

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Footnote

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References

1. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693-9.
2. Parikh ND, Singal AG. Model for end-stage liver disease exception points for treatment-responsive hepatocellular carcinoma. Clinical Liver Disease 2016;7:97-100.
3. Organ Procurement and Transplantation Network (OPTN) Policies. Policy 9: Allocation of Livers and Liver-Intestines. 9.3 F Candidates with Hepatocellular Carcinoma (HCC). 2016 10/01/2016. Cited 2016 November 1. Available online: https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf#nameddest=Policy_09
4. Heimbach JK, Hirose R, Stock PG, et al. Delayed hepatocellular carcinoma model for end-stage liver disease exception score improves disparity in access to liver transplant in the United States. Hepatology 2015;61:1643-50.
5. Wachs ME, Bak TE, Karrer FM, et al. Adult living donor liver transplantation using a right hepatic lobe. Transplantation 1998;66:1313-6.
6. Singer PA, Siegler M, Whitington PF, et al. Ethics of liver transplantation with living donors. N Engl J Med 1989;321:620-2.
7. Cronin DC 2nd, Millis JM, Siegler M. Transplantation of liver grafts from living donors into adults--too much, too soon. N Engl J Med 2001;344:1633-7.
8. Adult to Adult Living Donor Liver Transplantation Cohort Study. Cited 2016 November 1. Available online: https://www.nih-a2all.org/default.aspx
9. Fisher RA, Kulik LM, Freise CE, et al. Hepatocellular carcinoma recurrence and death following living and deceased donor liver transplantation. Am J Transplant 2007;7:1601-8.
10. Kulik LM, Fisher RA, Rodrigo DR, et al. Outcomes of living and deceased donor liver transplant recipients with hepatocellular carcinoma: results of the A2ALL cohort. Am J Transplant 2012;12:2997-3007.
11. Pomfret EA, Lodge JP, Villamil FG, et al. Should we use living donor grafts for patients with hepatocellular carcinoma? Ethical considerations. Liver Transpl 2011;17 Suppl 2:S128-32.
12. Volk ML, Marrero JA, Lok AS, et al. Who decides? Living donor liver transplantation for advanced hepatocellular carcinoma. Transplantation 2006;82:1136-9.
13. Clavien PA, Lesurtel M, Bossuyt PM, et al. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. Lancet Oncol 2012;13:e11-22.

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