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JOURNAL DISCUSSION
Living-Donor Grafts for Patients with Hepatocellular Carcinoma
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Pomfret EA, Lodge PA, Villamil FG, Siegler M. Should we use living donor grafts for patients with hepatocellular carcinoma? Ethical considerations. *Liver Transpl*. 2011;17 Suppl 2:S128-S132.

Living-donor liver transplantation (LDLT) is a relatively recent surgical innovation that was developed to alleviate the severe shortage of transplantable organs for patients suffering from end-stage liver disease (ESLD). Living donation seriously challenges the medical dictum to "do no harm" because donors are subjected to the risks of surgery for no physical benefit to themselves.

The first successful LDLT was performed in 1987, when a child with ESLD received a left-lateral segment from his parent. Due to the success of LDLT in children it was subsequently extended to adults [1]. In adults, right-lobe grafts are commonly used because they have the larger hepatocyte volume necessary for successful LDLT.

The initial enthusiasm for and success of LDLT in the 1990s led to a proliferation of programs offering living-donor liver transplants, but that number quickly waned due to technical challenges and ethical concerns after a highly publicized donor death in 2002 [2]. The number of LDLT procedures peaked at around 500 cases per year but quickly dropped after 2002 and then stabilized at around 250 cases per year [3]. The risk of donor death after right lobe LDLT has been estimated to be around 0.2-0.5 percent and does not seem to be associated with the transplant center's level of experience [4].

The benefit of living donation is obvious in countries with limited access to deceased-donor grafts (due to cultural or religious beliefs), but in countries like the United States where this is not an issue, living donation offers patients the possibility of transplantation before they become too sick to benefit or die on the waiting list. While most deceased-donor donations are nondirected, most living-donor donations are directed, so LDLT does not disadvantage patients on the waiting list, and the argument can be made that LDLT should be extended to patients who are not eligible for transplants from deceased donors according to standard allocation criteria.

Since its inception, LDLT has generated extensive ethical discussion because of concerns for donor safety. LDLT as a treatment for hepatocellular carcinoma (HCC) in particular is the subject of some controversy. The ethical principle of respect for patient autonomy coupled with the poor outcomes observed after transplantation in

patients with advanced HCC engendered debate about the utility of LDLT in that case.

In their article "Should We Use Living Donor Graft for Patients with Hepatocellular Carcinoma? Ethical Considerations" [5], Pomfret and colleagues examine three important questions: why is living donation necessary and is it different for patients with hepatocellular carcinoma (HCC)? What is double equipoise, and how is it affected by the diagnosis of HCC? Is paired exchange appropriate if one or both recipients have HCC?

Living Donation and HCC

The authors suggest that since a case of HCC that is within Milan criteria—a single tumor less than 5 cm in diameter or 2-3 lesions with individual diameters less than 3 cm—is an acceptable indication for receiving a deceased-donor liver transplantation, it should also be an acceptable indication for LDLT [6]. Moreover, almost all patients with HCC who receive liver transplants have cirrhosis, and patient with cirrhosis are excellent candidates for LDLT because they often have well-preserved liver function and low natural MELD (model for end-stage liver disease) scores.

The wide regional variability in MELD score-based liver allocation supports the authors' argument that acceptable risks for donors and recipients may exist in certain areas of the country where the availability of deceased-donor organs is limited. For example, in New England, New York, and California, patients who receive transplants have much higher MELD scores than patients in other areas within the same time zone. This often results in patients "chasing the organ," moving to different parts of the country in search of liver transplants. The most notable example of this was the late Steve Jobs who temporarily moved from his home in California to a more favorable location for his MELD score in Tennessee.

Because their mortality risk from cancer is greater than from liver failure, patients with HCC receive a priority MELD score that is increased every 3 months as long as their disease remains within Milan criteria limits. In many regions, patients with HCC can receive a deceased-donor liver transplant within 3 months of listing, but in other regions they may wait as long as 9 to 12 months, facing the risk of disease progression and death on the waiting list.

The ethical question is whether it is justifiable to subject a healthy donor to the risk of right-lobe donation if the recipient has a reasonable chance of receiving a deceased-donor organ within a reasonable time frame. Hence, the decision to offer LDLT must be individualized and weighed against regional differences such as waiting time for transplant and risk of the patient's "dropping out," which is an euphemism for dying while on the waiting list. For example, a patient with a 2.1-cm lesion who can receive ablative therapy in the form of radiofrequency ablation or transarterial chemoembolization as a bridge to transplantation has a reasonably good chance of receiving a deceased-donor liver transplant (DDLT), even in regions of the country where the wait for it is longer, with minimal risk of dropping out. It can be

argued that it is not reasonable to subject the donor to a 0.2-0.5 percent mortality risk if the recipient has a high probability of receiving a DDLT.

As physicians, however, it is our responsibility to present both the risks and benefits of the procedure and help patients make informed decisions. Some donor-recipient pairs may choose to proceed since uncertainty about disease progression becomes incapacitating, while others are perfectly comfortable waiting. On the other hand, a patient with more advanced disease who is at risk for exceeding Milan criteria may not have the luxury of waiting and may benefit from a LDLT performed earlier, especially in regions where the wait for DDLT is long.

Because of the inherent donor risk associated with LDLT, there is further debate on whether to proceed with LDLT in patients with advanced HCC that puts them beyond Milan criteria. Pomfret et al. [6] explore why LDLT is a reasonable treatment option for patients whose tumors are slightly beyond Milan criteria. Using the University of California San Francisco (UCSF) criteria, which are more liberal (allowing larger tumors) than Milan criteria, liver transplant recipients did not experience significant increases in recurrence rates or decreases in long-term survival [7]. In many parts of the country, patients whose tumors are only slightly too large for them to qualify under Milan criteria do not receive MELD priority points, and LDLT represents the only realistic option. Expansion of the criteria beyond UCSF's significantly increases the recurrence risk and reduces the likelihood of long-term survival [8]; it is therefore ethically uncertain. The authors explain [6] that in these situations defining what is an acceptable recurrence risk to justify donor risk proved to be more challenging.

A more difficult ethical dilemma arises if a recipient who received a LDLT develops complications that cause graft loss (e.g. hepatic artery thrombosis or small-for-size syndrome) and is in urgent need of a deceased-donor graft for which he or she is not eligible. The authors rightly recommend that "Until extended criteria are adequately defined and accepted, indications for LDLT should be individualized" to minimize the likelihood of this set of circumstances occurring [6].

The current liver organ allocation system for patients with ESLD and HCC, which provides fixed priority points for HCC, does not accurately predict the risk of dropout and advantages HCC patients over non-HCC patients, who are prioritized using a continuous system that is revised over time. Development of a continuous system for HCC patients that incorporates tumor size, grade, alpha-fetoprotein levels, and natural MELD scores that would more accurately predict the drop-out risk and not disadvantage non-HCC patients has been suggested [9]. Such a system would not only be valuable for allocation of deceased donors but also helpful in selection of recipients for LDLT as well.

Double Equipoise and Paired Exchange

The authors offer an incisive analysis of the concept of double equipoise, which refers to the balance between the recipient's survival benefit and the risk of donor

death, and apply it to patients with HCC outside of Milan criteria. Unlike DDLT, in which the risk benefit analysis is restricted to the recipient, double equipoise evaluates the relationship between the recipient's need, the donor's risk, and the recipient's outcome. The authors affirm that these areas need to be explicitly defined and accepted by the donor, the recipient, and the medical and surgical teams [10]. In this model, ethical unacceptability occurs when the risk to the donor is not justified by the predicted minimal benefit to the recipient.

For example, if the recipient has multifocal HCC outside UCSF criteria or has extrahepatic disease in which the recurrence rate is high and long-term survival tends to be poor, risking a donor's life does not seem justified. Currently, there is no consensus on what constitutes an acceptable recurrence rate for advanced HCC or an acceptable donor risk.

The concept of double equipoise calculation means that reducing the risk to the donor may make greater risk to the recipient (of HCC recurrence and lower long-term survival) ethically acceptable. This could conceivably be achieved by using left-lobe grafts, which are smaller than right-lobe grafts, since the donor's risk is proportional to the amount of liver tissue removed. The removal of the left lobes confers significantly lower mortality and morbidity on donors, but left-lobe grafts are more challenging to the recipients because they increase the risk of graft loss due to small-for-size syndrome.

Interestingly, the concept of double equipoise considers each donor-recipient pair as a unit, analyzing whether the specific recipient's benefit justifies the specific donor's risk. Paired exchange, as eloquently suggested by the authors, could swing the pendulum towards ethical acceptability if one member of the recipient-donor pair is exchanged for reasons such as ABO (blood-type) incompatibility [10] or size mismatch. The complexity and logistics of LDLT prevent paired exchange from becoming as widespread as it is in kidney transplantation.

As transplant physicians and surgeons we must judge each case individually and reconcile donor risk and recipient gain. The answers are not always straightforward. When faced with a patient with advanced HCC, the physician's instinctive response is that the likelihood of recurrence poses an unacceptable risk to the living donor. But there are situations in which the benefit derived may justify the risk to a given donor. The case cited by the authors—of a mother of three young children with advanced HCC whose husband is aware of the risks but still committed to providing a graft [10]—is such a situation. To their family, even a short prolongation of survival is beneficial. After being presented with the risks and the potential benefits, donor and recipient should be granted the right to exercise autonomy in making an independent decision.

Conclusion

LDLT is an ethically viable treatment option for patients with ESLD and HCC. This is especially true with the current organ allocation system and the regional

differences in terms of MELD score and waiting times. If and when the organ allocation system becomes more uniform and the regional differences are eliminated, the impetus to perform LDLT will be reduced. Decisions regarding LDLT for advanced HCC should carefully balance donor's risks and recipient's probable outcome. Only when suitable organ substitutes can be generated in the form of xenografts from animals or artificial organ equivalents bioengineered in the lab will LDLT be relegated to surgical history.

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