TOPIC HIGHLIGHT

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Adult to adult living related liver transplantation: Where do we currently stand?

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Abstract

Adult to adult living donor liver transplantation (AALDLT) was first preformed in the United States in 1997. The procedure was rapidly integrated into clinical practice, but in 2002, possibly due to the first widely publicized donor death, the number of living liver donors plummeted. The number of donors has since reached a steady plateau far below its initial peak. In this review we evaluate the current climate of AALDLT. Specifically, we focus on several issues key to the success of AALDLT: determining the optimal indications for AALDLT, balancing graft size and donor safety, assuring adequate outflow, minimizing biliary complications, and maintaining ethical practices. We conclude by offering suggestions for the future of AALDLT in United States transplantation centers.

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INTRODUCTION

At the time of its initial introduction into clinical practice, many believed that adult to adult living donor liver transplantation (AALDLT) would be a panacea for the severe shortage of cadaveric donors that resulted in extensive times on the waiting list and high patient mortality. This belief was illustrated by multiple studies from the late 1990s that suggested that AALDLT was safe and claimed that it would significantly decrease mortality on the transplantation waiting list[1,2]. The first United States AALDLT was performed in 1997, and over the next 3-5 years AALDLT was vigorously embraced by many United States transplantation surgeons. This enthusiasm was obvious in the documented increase from one to 38 United States AALDLT centers and from one to 266 United States AALDLT procedures between 1997 and 2000[3]. However, despite rapid integration of this novel procedure into clinical practice, multiple questions remained unanswered. Little was known regarding the proper indications for AALDLT. Further, there was relatively limited data on how graft size impacted recipient and donor safety. Additionally, techniques to assure adequate outflow and minimize biliary complications

were only in their infancy. Finally, the multitude of ethical issues surrounding AALDLT had not been rigorously addressed. In 2002, possibly due to the first widely publicized death of a living donor, the number of living liver donors plummeted. The current number of annual living liver donors has now reached a relatively static plateau at about 250 donors per year, which is far below the initial peak of 524 donors in 2001(Figure 1)[4].

While there is a current climate of concern in the United States regarding the safety and appropriateness of AALDLT, multiple other countries (mainly Asian countries, Turkey and Egypt) have experienced a continued rise in AALDLT. Presumably, this contrast is the result of societal norms and logistic difficulties that impede cadaveric organ donation in these areas. Review of data from current United States and Asian transplantation centers along with critical review of the literature from United States surgeons who enthusiastically embraced AALDLT in its early years and then altered their practice as increasing risk became apparent, should be undertaken to help us determine how and if AALDLT can safely be reinstated as a more widely utilized procedure in United States transplantation centers. In this review, we draw upon these studies to address the current status of AALDLT. Specifically, we explore issues related to both the technical/scientific aspects of AALDLT as well as the ethical issues that surround AALDLT. We then offer suggestions for the future of AALDLT in the United States.

OPTIMAL INDICATIONS FOR ADULT TO ADULT LIVING DONOR LIVER TRANSPLANTATION HAVE NOT BEEN ESTABLISHED

Extensive efforts have been dedicated to determining the optimal indications for AALDLT. Review of the recent literature identifies two central issues: the appropriateness of AALDLT for patients with acute liver failure (ALF) and whether the Model for End-stage Liver Disease (MELD) score can be utilized to determine the suitability of AALDLT for a given patient. Here, we briefly highlight recent literature regarding these controversial topics.

In many Asian centers where socio-cultural norms drastically limit utilization of cadaveric liver donation, AALDLT is being increasingly relied upon to offer expedient transplantation to patients with ALF (Table 1)[5]. Despite relatively widespread use of AALDLT for ALF in many Asian countries, issues regarding graft size and donor safety have prevented widespread acceptance of AALDLT for ALF in the United States. This reluctance to utilize AALDLT in the setting of ALF presumably increases the risk of death due to failure to quickly receive a graft for these critically ill patients. For example, we have found that even when patients with ALF are
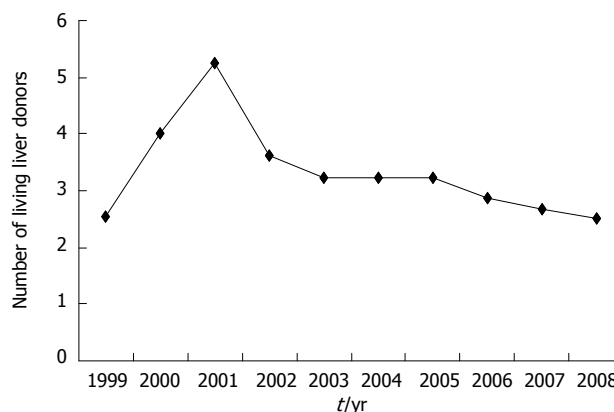

Figure 1 Number of United States living liver donors per year[4].

managed in large-volume, Western liver transplantation centers, the transplantation rate ranges from 41%-72%, and the median waiting time for a deceased donor graft is 3.5-5 d[6]. These statistics clearly indicate the impressive need for more readily available liver grafts.

The issue of AALDLT for ALF also sparks an ethical debate among the transplant community regarding issues such as how to assure adequate informed donor consent in a relatively pressured setting or whether it is appropriate to ask donors to give an organ to a recipient who may not have a successful outcome. Based on our recent analysis of the current ethical issues with AALDLT for ALF, we feel that with adherence to rigorous informed consent efforts mediated by a donor advocate and recognition that most donors rate the experience of donating positively even if the recipient has a poor outcome, AALDLT can be offered to patients with ALF in a way that maintains the highest ethical standards for both the donor and the recipient[5]. Thus, given the extreme need for more liver grafts and the precedent of successful AALDLT outcomes in many Asian centers, United States centers should consider broadening the indication for AALDLT to include ALF.

In addition to efforts to determine whether AALDLT is appropriate for ALF, extensive efforts have also been directed toward determining if the MELD score can help predict the suitability of AALDLT for a given patient. The MELD score, which is based upon creatinine, total bilirubin, and INR, was originally developed by Malinchoc *et al*[7] to predict 3 mo survival in patients undergoing elective transjugular intrahepatic portosystemic shunt procedures. The MELD score has since been shown to be a valuable predictor of pre-transplantation survival, and in 2002 it became a critical tool in assigning priority to patients on the United Network for Organ Sharing (UNOS) transplantation waiting list. At the inception of this policy, little data regarding the predictive value of the MELD score in AALDLT existed thus promoting general concern among transplantation physicians that a higher MELD score (i.e. a sicker patient) may correlate with poor outcomes after AALDLT.

Table 1 Literature review of adult to adult living donor liver transplantation for acute liver failure[5]

Ref.	Year	Location	n	Recipient survival (%)	Lobe utilized	Donor complications (%)	Donor survival (%)
Liu *et al*[38]	2002	China	16	88	Right	25	100
Nishizaki *et al*[39]	2002	Japan	15	80	Left	No comment	100
Wu *et al*[40]	2004	Taiwan, China	8	100	Right	0	100
Lee *et al*[14]	2007	South Korea	57	82	Both	2	100
Kilic *et al*[41]	2007	Turkey	6	83	Right	25	100
Campsen *et al*[42]	2008	United States	10	70	Right	50	100
Ikegami *et al*[43]	2008	Japan	44	80	Both	34	100
Park *et al*[44]	2010	South Korea	40	85	Both	24	100

This concern was based primarily upon the relatively poor early outcomes of AALDLT for critically ill patients. This issue was addressed in work by Testa *et al*[8] that investigated the appropriateness of AALDLT for patients with decompensated end-stage liver disease. The authors highlighted several early studies of AALDLT that described a 1 year survival of about 50% for critically ill patients which was far inferior to the 77%-80% 1 year survival reported for patients with a more favorable clinical status. The authors also cited their own 1 year survival for AALDLT in patients with a MELD score > 30 as 43%, which although relatively low, was considered successful given the high likelihood of patient death before a cadaveric donor graft could be allocated to them[8]. The relatively low survival rates reported in these studies led to a general consensus that critically ill patients should not be candidates for AALDLT. However, Testa el al advocated that rather than abandoning the procedure for these patients, the outcomes of AALDLT in the critically ill could be improved by gaining further experience in appropriate donor selection and working to overcome the technical difficulties of the operation[8]. Recent data from various transplantation centers, especially those in Korea, that heeded this recommendation and continued working to overcome the technical issues that initially contributed to poor outcomes now demonstrate survival in critically ill patients that closely parallels survival of patients who are less ill. Additionally, Hwang *et al*[9] and Bhangui *et al*[10] have recently demonstrated the success of AALDLT for patients with hepatocellular carcinoma. These improvements in outcome across a variety of disease etiologies and recipient clinical status suggest that AALDLT is an appropriate procedure for even the most critically ill patients.

To further understand which critically ill patients would benefit most from AALDLT, several studies have since emerged to specifically investigate the predictive validity of the MELD score in AALDLT. For example, in a retrospective review of 62 AALDLT recipients by Hayashi *et al*[11], MELD score failed to predict 1-year patient or graft survival. To further analyze the predictive capacity the MELD score and 23 other preoperative factors Morioka *et al*[12] conducted a retrospective review of 335 cases of AALDLT in Japan between 1994 and 2003. The authors concluded that lack of pre-transplant encephalopathy, MELD score ≤ 30 (including points

for persistent ascites and low serum sodium), and donor age < 50 were the key factors for obtaining successful outcomes with AALDLT. This work was contrasted by Durand *et al*[13] who conducted a retrospective review of 331 DDLT and 128 AALDLT cases to develop statistical models to determine the most efficacious means of organ allocation. This group determined that AALDLT is most advantageous when performed in patients at high risk of death. More simply, these authors demonstrated that the most critically ill patients will derive the most robust statistical benefit from AALDLT[13]. The studies reviewed here offer slightly conflicting suggestions regarding which patients will benefit most from AALDLT. Further work must be performed to more clearly delineate the indications for the procedure and to establish a meaningful selection criteria for potential recipients.

However, it is our belief that current data generally suggests that the indications for AALDLT should be broadened. Reflection on the drastic improvements in survival for critically ill patients (including those with ALF) in many Asian centers illustrates how diligent refinement of surgical technique and increased procedural experience can result in drastically improved outcomes of AALDLT for even the most critically ill patients. Perhaps United States transplantation centers can call upon the wealth of knowledge generated by these centers to successfully incorporate AALDLT into the routine treatment of United States patients.

DELICATE BALANCE BETWEEN GRAFT SIZE AND DONOR SAFETY

In addition to determining the optimal indications for AALDLT, the transplantation community must advise on the delicate balance of assuring adequate graft size while maintaining donor safety. It is well accepted that AALDLT must be performed in careful balance between recipient needs and donor safety. For example, if acquiring adequate graft volume for the recipient equates to unacceptable risk for the donor, the transplantation must not be performed. Currently, a graft weight to body weight ratio of > 0.8% and a graft size of at least 40% of the standard liver volume is accepted as a minimum requirement for donation[14]. It has been advocated by some that use of a right lobe graft as compared to a

left lateral lobe as is used in pediatric living donor liver transplantation (LDLT) may allow for larger graft size while still maintaining reasonable donor risk. While it is presumed that the increased graft size places donors at a higher risk following a right hepatectomy, no controlled studies substantiate this concern. Further, presumption that donor morbidity or mortality is directly and solely related to the extent of the liver resection is not reasonable given the numerous other factors that may contribute to poor donor outcomes. The Korean experience demonstrates that with increased operative experience, strict donor selection, and an institutional focus on AALDLT, complications and mishaps can be drastically minimized[15].

Numerous studies have also been conducted in an effort to determine the safest selection criteria for donors. Authors at a prominent United States transplantation center reviewed the screening of 66 potential donors for 15 eventual AALDLT procedures[16]. The group relied upon 3D helical imaging including hepatic lobe volume renderings, vascular anatomy, virtual resection planes, preoperative arteriography, and medical/psychological examination, and found that even with robust preoperative donor screening in an experienced hepatobiliary center, morbidity occurred in 67% of donors[16]. A slightly more recent study of 893 AALDLT cases between 1994 and 2005 in Korea demonstrates how modification of graft size and careful donor selection can result in marked reduction in donor morbidity[15]. Specifically, until 2001, this group reported an AALDLT donor complication rate of 6.7% which was predominantly due to complications in right lobe liver donors. In 2002, authors changed their donor selection procedure such that liver resection exceeding 65% of total liver volume was avoided except in young donors with no evidence of hepatic steatosis. This change resulted in a reduction of donor morbidity to 1.3% and prompted authors to conclude that a majority of major living donor complications are avoidable through strict selection of living donor/graft type (with cautious selection of the donor right liver if it appears to be larger than 65% total liver volume), intensive postoperative surveillance, and prompt feedback regarding surgical technique. Perhaps most interestingly the authors commented that the experience that they gained from implementation of AALDLT has actually optimized all hepatobiliary surgery practices at their institution[15]. There is also an interesting body of work evaluating the accuracy of preoperative assessment of graft volume *via* 3D-CT volumetry in AALDLT. Both Hiroshige *et al*[17] and Kayashima *et al*[18] have demonstrated that 3D-CT volumetry may overestimate graft volume by as much as 13%, especially in donors under 30 yr old. Authors suggest that this may be due to graft dehydration secondary to University of Wisconsin solution. Studies such as these illustrate the difficulty in assuring accurate pre-operative assessment of graft volume. Given the obvious importance of assuring adequate graft

size, future work to further optimize pre-operative assessment of graft volume is certainly warranted. Clearly, the transplantation community will benefit from further study regarding how to safely balance donor safety and graft size; however, studies such as those discussed here suggest that we are beginning to develop a more robust understanding of how to address this critical issue. We suggest that implementation of strict policies regarding acceptable graft size is the best method for avoiding complications related to small for size grafts or resection of an unsafe donor graft volume.

However, surgical technique alone, even that delivered by expert surgeons, cannot substitute for the institutional organization at all levels of patient care that is mandatory to minimize complications. Any institution willing to offer AALDLT to its patients must invest in AALDLT. Specifically, in order to replicate the results of the best transplantation centers in the world, United States centers should focus on how the entirety of the operative experience, ranging from pre-operative donor evaluation to the number of capable transplant surgeons to the coordinated management of post-operative care, can be structured to provide the highest levels of success.

ISSUE OF OUTFLOW

The right lobe of the liver is increasingly being utilized to assure adequate graft volume in AALDLT. However, use of the right lobe brings with it a heightened risk of impaired graft outflow. Specifically, the right lobe graft carries an increased risk of early post-operative congestion of the paramedian segments 5 and 8 due to interruption of the venous drainage of the middle hepatic vein (MHV). Post-operative congestion has been shown to lead to congestive necrosis which has been reported to incite early post-operative graft failure and recipient death[19-21]. Harvest of an extended right lobe graft with inclusion of the entire donor MHV is an effective means of preventing outflow obstruction: however, the larger graft size may increase the donor's risk of morbidity and mortality. The surgeon's decision to resect or not resect the donor MHV is thus a complicated one that rests upon several key factors. Donor residual liver volume, the importance of MHV in right lobe drainage, the ratio of graft weight to recipient body weight, and the MELD score must all be carefully evaluated prior to determining whether resection of the MHV is appropriate. Generally, it seems prudent to suggest that if the donor residual liver volume is marginal (ratio < 0.6) or the rest volume is < 30%, the MHV should remain with the donor and segments 8 and 5 should be re-anastomosed.

Several procedural modifications have been proposed to generate improved outflow in cases where the MVH must be interrupted. For example, in a review of 74 AALDLT patients, Malago *et al*[22] observed that rapid regeneration of the graft in the first 10 post-operative days

resulted in medial displacement of the graft such that kinking, torsion, and compression/occlusion of the outflow tract resulted. By using a cadaveric iliac vein graft to create an interposition conduit that allowed drainage of all intrahepatic veins (diameter > 5 mm) draining segments 5 and 8 into the MHV, the authors devised a modification of the outflow tract that enlarged the caval orifice and assured better outflow[22]. Successful use of this cadaveric vein outflow reconstruction procedure in patients undergoing AALDLT was also demonstrated by Dong *et al*[19]. Continued efforts to develop procedural modifications that assure successful outcomes in recipients of AALDLT while maximizing donor safety are imperative. Additionally, it is good practice to remember that every donor-recipient pair presents a unique set of anatomical challenges, however, these challenges should not be considered separately. Favorable outcomes are a result of the safest and most feasible combination of donor and recipient need. Any compromise at the expense of either may result in serious complications and poorer outcomes. Procedural flexibility is ultimately the best policy to protect the donor and assure prompt, successful graft functioning in the recipient.

BILIARY COMPLICATIONS

In addition to issues of impaired outflow, reliance on right lobe grafts for AALDLT has brought with it an increased rate of biliary complications. Overall, since the introduction of AALDLT with right lobe grafts, biliary complications have been the leading cause of post operative complication and re-operation[23-27]. The reported incidence of biliary complication in AALDLT ranges from 15%-60%[25,28-31], which is substantially greater than that of cadaveric full-liver transplantation 5%-15%[29,32,33], and pediatric LDLT with the left lateral lobe of 4%-6%[34]. Presumably, anatomic differences between the left and right hepatic biliary systems are responsible for this differential complication rate. Specifically, reliance upon the left hepatic duct usually allows a relatively easy dissection due to straightforward ductal anatomy. However, use of the right lobe hepatic system is markedly complicated by the numerous anatomic variations of the right duct. Multiple technical modifications for biliary reconstruction have been published over the past decade (use of recipients right and left hepatic ducts, end-side reconstruction of donor ducts to native common hepatic bile duct, donor ductoplasty, stents, T-tubes, *etc*.), however none has provided a standardized, replicable method that consistently decreases the incidence of biliary complications[24,30].

Although, biliary complications result in high recipient morbidity and occasionally mortality, early detection and prompt treatment offers a favorable rate of recovery in these patients. Perhaps most importantly, a high rate of success in non-operative management of biliary complications has been consistently demonstrated in the literature. For example, in a review of 429 patients that underwent liver transplantation, the success rates for treatment of biliary complications by endoscopic retrograde cholangiopancreatography and percutaneous transhepatic radiologic procedures were 100% and 78% respectively[35]. Given the consistently high rate of biliary complications despite over a decade of efforts to perfect the biliary anastomosis, assurance of robust non-operative treatment modalities is imperative. Thus while continued refinement of technique is critical, we have limited expectation of an easy fix for biliary complications in AALDLT. It is generally clear that while most of the other technical obstacles to AALDLT have found favorable solutions, we are still far from having developed a biliary anastomosis technique that will provide consistently positive results. While relying on continued advancement in minimally invasive procedures to remedy these frequent complications is currently an acceptable compromise, it is imperative that we continue significant efforts to construct a biliary anastomosis with equivalent or lower complication rates than that of deceased donor liver transplant.

ETHICAL ISSUES

The ethical issues surrounding AALDLT are complex and warrant thoughtful discussion prior to widespread implementation of the procedure. Overall, the majority of regulations on liver transplantation are guided by a simple reality: liver grafts are provided by a public supply, and the supply is insufficient to meet current societal demands. The introduction of AALDLT presumably alters this climate by increasing the available supply of grafts. This increase in supply offers the opportunity of transplantation to patients who previously had relatively minimal chances of obtaining a graft given that their clinical status was not critical enough to assure high priority listing on the transplantation waiting list or because the etiology of their disease precluded them from being a transplant candidate (hepatocellular carcinoma, polycystic liver disease, *etc*. While introduction of AALDLT clearly expands the opportunity for many patients awaiting transplantation it carries with it multiple ethical questions.

Overall, the issue of whether AALDLT is ethically appropriate requires careful assessment of the risks and benefits to the individual donor-recipient pair. The benefits to the potential recipient are relatively obvious. AALDLT offers potential recipients decreased time on the waiting list or, in some cases, the opportunity to completely bypass the waiting list. Further, with AALDLT potential recipients are able to undergo transplantation as an elective rather than urgent surgery thereby allowing increased control of variables such as graft ischemic time. However, given the healthy status of the donor, the age old vow of physicians, "primum non nocere" (first do no harm), mandates that the risks and

benefits to the donor be the primary focus of a discussion of transplantation ethics. In our brief review of the literature, it is evident that donors experience a relatively high risk of morbidity and a realistic risk of mortality in even the most well-qualified transplantation centers with the most experienced transplantation surgeons. The risk of short and long-term medical morbidity is compounded by the financial burdens that may result due to ongoing medical bills and time lost from work. Currently, no system is in place to assure that donors are not excessively burdened by such issues. However, one must remember that while this risk may be of high concern for United States donors, it may be less of an issue in European countries where public health insurance typically covers all donor expenses. While substantial health and financial risk is obvious for the donor, great benefits may also be incurred by consenting to living liver donation. The psychological benefit from this altruistic decision is one of the primary benefits to donors. A vast body of literature exists that consistently supports the finding that even in cases of poor recipient outcome, undergoing donation helps donors feel as if they have done everything possible to help save the life of their loved one[36]. Donation may also bring with it a decreased caregiver burden and increased participation of the recipient in subsequent household matters.

Several other issues are central to a thorough discussion of the ethics of AALDLT. First, there is great concern among the transplantation community that critical recipient status (especially in the setting of ALF) or familial pressure may limit the ability of potential donors to fully engage in an informed consent discussion. Many worry that donors may feel pressured to donate, and they encourage a robust donor evaluation process with inclusion of a donor advocate who assures donors the opportunity to make their decision with minimal pressure from family or members of the health care team. Additionally, many worry that performing an AALDLT in a setting in which recipients may have a poor outcome (*e.g.*, ALF) may not be appropriate. However, multiple authors have determined that even in settings in which recipients die or suffer significant morbidity, most donors rate the donation experience positively as they feel as if it has allowed them to do all they can to help save the life of their loved one[36]. Clearly, the ethical issues involved with AALDLT are complex and deserving of further discussion to assure the highest ethical standards are maintained when caring for the donor-recipient pair.

HAVE WE IMPROVED SINCE 1997?

Critical review of the success and failure of AALDLT over the past decade is imperative in assessing our current status. Improved transparency in outcomes reporting, development of uniform regulations, an increasing number of National Institutes of Health funded studies, and increasing procedural experience all suggest that our ability to safely and successfully perform AALDLT has improved since the initial introduction of the procedure in 1997.

MOVING FORWARD

Critical review of AALDLT suggests that the Western world both embraced and dismissed AALDLT too quickly[37]. A new framework for integration of AALDLT into United States medical practice that is rooted in clinical expertise, genuine need, and accurate reporting should be developed to create a new starting point for AALDLT in the United States. Focus upon the key factors of determining the appropriate indications, balancing graft size with donor safety, assuring adequate outflow, minimizing biliary complications, and mandating ethical rigor is imperative. Additionally, we offer several suggestions that we believe will assure thoughtful integration of AALDLT into United States practice. First, all AALDLT activity should be concentrated in centers with dedicated AALDLT staff and adequate field strength (capacity of surgical team to meet the technical demands of a relatively innovative procedure, proven success with all facets of hepatobiliary surgery, *etc.*). Next, we believe that proper training programs for staff along with validated criteria to demonstrate clinical competency should be developed. Further, incorporating knowledge from centers that are already world leaders in AALDLT to establish patient and graft survival that is superior to deceased donor liver transplantation must be the ultimate goal. Finally, working to improve the societal image of AALDLT is critical for assuring integration into current United States medical practice. It is our belief that careful attention to these key factors will help redefine the role of AALDLT in United States transplantation centers. And while this may not provide the panacea for long wait times and high recipient mortality that was originally assumed, we believe that robust integration of AALDLT into United States practice will offer significant improvements for patients awaiting liver transplantation.

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