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Adult Living-Donor Liver Transplantation

Mary Killackey and Amadeo Marcos

Right-lobe living-donor liver transplantation (LDLT) has emerged as an innovative method to combat the ever-expanding United Network for Organ Sharing waiting list. Although still in its early years of development, certain centers have had extensive experience with outcomes equal to that of traditional cadaveric liver transplantation. As experience is gained, the selection criteria for both donors and recipients have evolved. To combat the unique obstacles of transplanting a segmental graft, various techniques have been proposed and/or refined. The optimal method remains to be determined while taking into consideration that each graft can pose its own unique challenge due to complex anatomical variation. The authors' goal is to review the development of LDLT and to discuss the current issues under debate.

Several donor resections have been safely performed for adult recipients over the years, but the right lobe has emerged as the preferred graft.

Introduction

More than 15,000 patients with end-stage liver disease are listed for transplantation with the United Network for Organ Sharing (UNOS), and countless others are added to the list each year. Unfortunately, fewer than 5000 cadaveric transplants are performed annually, and too many patients succumb to their disease before an organ becomes available. Regrettably, cadaveric donation rates continue to be disappointing, and waiting times are currently measured in years.¹ This discouraging state of affairs has been the driving force behind the development of living-donor liver transplantation (LDLT) for the adult population. Various donor resections have been practiced, but the right lobe clearly has the most utility and has appropriately been the subject of recent attention.

Several years of practical experience have established right-lobe resection as a reasonably safe surgery and transplantation as an effective treatment for liver failure.²⁻⁴ If the established record can be reproduced and long-term results are similarly favorable, the role of LDLT for the adult population will be further solidified. The magnitude and significance of this particular donor surgery are appreciated, and few involved in these endeavors are content to accept "satisfactory" outcomes.

The potential for better patient and graft survival and an improved donor safety profile have been recognized. Refinement in surgical technique, critical evaluation of selection criteria for both donors and recipients, and evidence-based analysis of workup modalities have been the focus in this still-evolving field. This overview summarizes the current status of adult-to-adult LDLT, with particular emphasis on right-lobe resection and transplantation and the issues most likely to impact patient care.

Historical Perspective

LDLT was developed for the pediatric population in response to unacceptable waiting-list mortality. The transplant team at the University of Chicago carefully addressed the ethical issues and went on to advance left lateral segment resection (segments II and III) and transplantation. This group recently summarized its results and the evolution of its surgical techniques and continues to set the standard for pediatric LDLT.⁵ Unfortunately, transplantation of the left lateral segment (200 to 300 ml) is seldom appropriate for adult recipients, but pioneering work in this field removed many of the obstacles to adult LDLT and helped to set the stage for its early success.

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Several donor resections have been safely performed for adult recipients over the years, but the right lobe has emerged as the preferred graft. Brief consideration of other resection options demonstrates some of the advantages of the right lobe and the reasons behind the preferential development of the surgical procedures necessary for its use. Full left lobes (segments II-IV) were the 1st segmental grafts from living donors successfully transplanted into adults. Although these organs are larger than left lateral segments, size mismatch remains an issue. The left lobe is on average only 300 to 500 ml, and these grafts are best suited to recipients who weigh less than 60 kg.^{6,7} The complex biliary and vascular anatomy of segment IV and the challenging anatomical reconstruction required are further disincentives to the routine use of these grafts. The only incentive is the belief that the resection is safer, but the available statistics do not clearly support this conviction.^{3,8}

In an effort to address the inadequate size of a standard left lobe without resorting to right-lobe resection, another group has been practicing extended left-lobe resection—the left lobe plus the caudate lobe. This group summarized its experience with such resections and transplants. Its rate of donor complications was quite low, and its recipient results were remarkable considering recipients' condition at the time of transplant. However, the mean extended left-lobe volume was only 29 ± 3 ml.^{9,10} The caudate lobe does not significantly increase the mass of the graft, and the belief that the donor surgery is safer than right-lobe resection has not been validated. In fact, unfamiliarity with this surgery would likely result in a high initial complication rate in most hands, and it would be surprising if this resection gained popularity.

Extended right lobectomy (segments IV through VIII including the midhepatic vein) was actually the 1st right-liver donor resection that was purposefully performed. The group that developed these procedures has published its outcomes, and its statistics are remarkable considering the magnitude of the resection and profound decompensation of its recipients.¹¹ Experience is still too limited to demonstrate any real advantage, but the theoretic benefit of these grafts is not the additional mass but rather improved outflow through the midhep-

atic vein.^{12,13} Despite the advantages, few groups have shown any enthusiasm for this approach. The potential for harm to the donor is likely responsible for the lack of acceptance. It involves resection of an average of 70% of the liver, and isolation and sacrifice of the midhepatic vein threatens outflow from the small remnant.¹⁴ Although it makes good sense for the recipient, these disadvantages are compelling.

The 1st right-lobe donor resection (segments V-VIII) was reported in 1994. Interestingly, a left lobectomy was planned but abandoned because the anatomy appeared prohibitive.¹⁵ Despite the initial success, this procedure was not immediately adopted by the reporting group or others. Certainly, donor tolerance of this resection was of concern. Centers in the United States and abroad intermittently performed these procedures, but it was not until 1999 that the outcomes achieved with systematic use of the right lobe were reported.^{16,17} Two independent series demonstrated remarkable safety and efficacy, and right-lobe grafting has since emerged as the preferred technique. More than 40 centers in the United States and abroad have already organized programs.²

A modification to standard right-lobe resection was recently introduced that represents a compromise between the traditional procedure and extended right lobectomy. It recognizes the importance of ensuring adequate venous outflow from the engrafted right lobe. Instead of taking the entire length of the midhepatic vein, the plane of transection is modified to include only the distal portion (with the main trunk as the point of reference).¹⁸ These "outflow-augmented" right lobes derive some of the benefit of the midhepatic vein without subjecting the donor to the dangers of extended right lobectomy. This resection is likely to be more widely accepted and probably represents the best and final compromise.

Donor and Recipient Outcomes

Statistics addressing the safety and efficacy of about 600 right-lobe resections and transplants are available.²⁻⁴ It is difficult to estimate the incidence of minor complications because the definition of "minor" is vague, but the overall complication rate has been 10% to 20%, mirroring the experience with less extensive resections.^{2-4,8} Bile leaks are the

Recipient outcomes have been favorable, and the results rival those achieved with full-sized cadaveric organs.

most common major complication, with an incidence of about 5%. These are of particular concern because invasive intervention or reexploration is often necessary for adequate treatment. Most are simple cut-edge leaks, but injury to the common bile duct and leaks from the stump of the divided ducts have also been reported.^{2,4} The importance of quality preoperative imaging of the biliary tree, optimal surgical protection of the ducts, and careful ligation of cut-edge ducts cannot be overemphasized.

Most other major complications and life-threatening intraoperative events seem to be isolated occurrences, but their significance is not diminished by this fact. One death is known to have been the result of right-lobe donation (mortality about 0.2%).^{2,8} The learning curve is real and the incidence of complications is expected to decrease with time, but active steps toward improvement will accelerate the process. Any event that is the result of a surgical error or that could have been prevented through more restrictive selection or rigorous postoperative care deserves attention. Deep-venous thrombosis is one such example. Pulmonary embolism has been the most commonly reported cause of death in donors for pediatric candidates, and both patients in question had identifiable risk factors.⁸

Overall, recipient outcomes have been favorable, and the results rival those achieved with full-sized cadaveric organs. Most centers have reported patient survival of 80% to more than 90%. Mortality is most often attributable to graft dysfunction or sepsis, as would be expected. Retransplantation has been necessary in 5% to 10% of patients, and biliary complications are common, occurring on average 15% to 20% of the time.²⁻⁴ The relatively high incidence of these events and their associated morbidity has attracted attention. Fortunately, vascular complications have not been as problematic as experience with left lateral segment and left-lobe grafting would have predicted.²⁻⁵ Vascular reconstruction is uniquely challenging, however, particularly when multiple branches must be accommodated. Methods to simplify and perfect the creation of these anastomoses have been reported.¹⁹

Donor Selection

Appropriate donor selection is perhaps the most critical determinant of the outcome of both pa-

tients in question. The pediatric LDLT experience provided a solid outline for adult donor selection, and a staged process was adopted. Many of the details were reported elsewhere.²⁰ Most steps of evaluation are included for obvious reasons, and many decisions about donor candidacy are black and white. Several aspects of selection are not as clear cut, however, and continue to be deliberated. There has also been an inclination to simplify the process and minimize the cost. Biopsy and angiography have been identified as the primary targets of this crusade. The motivation behind this drive for simplicity is not entirely clear, as there has not yet been a complication resulting from these studies. Analysis of the complications and deaths and the problems encountered during the recipient surgery actually support more restrictive selection criteria and the liberal use of imaging studies. Almost every finding necessitating the abortion of a hepatectomy could have been identified through preoperative study, and failure to fully appreciate donor anatomy certainly contributes to major complications (e.g., vascular thrombosis, injury to the common bile duct).² The cost of organ acquisition from living donors can be brought in line with the cost of cadaveric organ procurement, even when biopsy and angiography are performed.^{21,22} Further steps toward cost containment should be instituted only once the incidence of donor complications reaches zero. Rather than trying to eliminate invasive tests, we need to analyze what factors contribute to less than perfect outcomes and do what is necessary to correct those issues. Efforts to develop less invasive means of obtaining the same information should be of priority.

The importance of providing the recipient with a graft of appropriate size has been recognized, but the minimal graft-to-recipient-body-weight (GRBW) ratio has still not been precisely defined. Initially, a GRBW of 1% was believed to be the lower limit, but several years of activity have demonstrated otherwise. A GRBW of 0.8% appears to be adequate for almost any patient, and grafts as small as 0.6% have been successfully transplanted into selected candidates.²³⁻²⁵ The lower limit continues to be tested, but it is still not obvious how much farther it can be pushed and which candidates will thrive with a smaller organ. In countries with limited ca-

cadaveric transplant activity, it is often necessary to accept organs of marginal size for even the sickest of recipients.^{24,26} Suboptimal outcomes under these circumstances are a reflection not only of the mass of the organ but also of the condition of the patient. In the United States, UNOS status IIA patients are generally not considered candidates for LDLT, and most others can afford to wait for an appropriate cadaveric graft. Only status I recipients tend to be challenged with small organs, and this group seems to do very well.²⁷⁻²⁹ A complete explanation for the varied tolerance of small-for-size organs cannot be offered, and there are obviously many variables in the equation for success. Donor anatomy, surgical factors, and recipient characteristics all have a role in determining the fate of these organs. Learning to accurately predict the behavior of a given graft in a particular patient (donor and recipient matching) seems preferable to rigidly defining a lower limit.

Accurate preoperative graft mass estimation will assume even greater importance when the use of smaller grafts becomes commonplace. Regardless of the imaging modality employed, mass estimation depends on identification of the plane of transection. Although radiologists and most surgeons use the midhepatic vein as the landmark for bipartition of the liver, disagreement by even 1 cm can introduce variance of more than 10%.³⁰⁻³⁴ Cooperation with the radiologist will certainly improve the accuracy of these estimates. Those who use inflow control to define the plane of transection rather than the border of the midhepatic vein may find greater variation in the estimated and actual graft volumes.

The routine inclusion of liver biopsy in donor evaluation has been the subject of considerable debate. The controversy is a response not to the problems resulting from the procedure but, rather, to the potential for complications and cost. These concerns are well founded, and it is prudent to critically appraise the value of the information obtained. In interpreting studies addressing the need for biopsy, it is essential to keep in mind that the value of the information depends on how it is used and that changes in selection criteria, imaging modalities, and surgical technique may precipitate the need to revisit the issue.

Biopsy is essential if history, examination, or laboratory or imaging studies raise any question about the health of the donor liver. Obesity, hypercholesterolemia, abnormal transaminases, diffuse parenchymal pathology, or a history of moderate to heavy alcohol use should raise suspicion. For patients at risk, biopsy can actually result in a higher rate of inclusion than exclusion. When a potential donor has no risk factors, biopsy is of lower yield, but there are still patients in whom truly occult pathology (most commonly steatosis) is uncovered.³⁵⁻³⁷ In general, steatosis of less than 30% does not adversely affect the function or regeneration of the graft or remnant, but to conclude that biopsy is always unnecessary based on these data would be incorrect. These results only apply to organs with a GRBW corrected for the degree of steatosis greater than 0.8%.²² Smaller grafts or remnants may not function as well. This point is especially critical as we continue to test the lower size limits. The consequences of overlooking donor pathology are realized by both the donor and recipient and can be far more severe than those attributable to biopsy. Until a noninvasive imaging study can be refined to accurately assess diffuse parenchymal pathology, biopsy should not be dismissed.

A less publicized debate has surrounded the routine use of visceral angiography. Again, there has not yet been a complication resulting from the execution of this study, and overlooking anatomical variations or subtle pathology (celiac stenosis) can be detrimental to both the donor and the recipient.

Recipient Selection

Recipient selection has not received as much attention as donor selection, but recipient characteristics are also critical determinants of outcome. Several groups have reported dismal results in UNOS status IIA patients, and there is a general consensus that these candidates are best served with a full-sized cadaveric organ.^{27,38-40} A recent report suggests that this is an issue that may be revisited in the future, however. Survival of greater than 70% without the need for retransplantation has been achieved in this population.⁴¹ The postoperative course of these patients is still quite complicated, and the routine use of organs from living donors

for this group cannot yet be advocated. The indications should be expanded cautiously and only with careful attention to the characteristics that distinguish those who do well from those who do not make it. Quite a few patients in the United States deteriorate to status IIA, and unrestricted use of organs from living donors could start a pattern of emergent retransplantation and death of a large number of patients. Needless to say, this would do little to ease the shortage of organs.

UNOS status I patients tend to do very well, and most agree that they should be considered candidates for grafts from living donors. Survival as high as 80% can be expected if an organ is obtained in a timely fashion.^{27,28,42} The process of donor evaluation and informed consent becomes more complicated under these circumstances, but not to the extent that LDLT is contraindicated.^{43,44} UNOS status IIB and III patients do not have to accept the risk associated with waiting for an organ and realize the benefit from living donation as well.^{27,45,46} They are generally in a reasonable state of health and tolerate the challenge of a reduced-sized graft remarkably.

One group of recipients for whom early LDLT should be considered is candidates with hepatocellular carcinoma. As it stands, these patients are given priority for cadaveric organs based on the severity of their cirrhosis rather than the size of their tumor. Long waiting times have a pronounced negative impact on survival under these circumstances, and a significant number must be disqualified before ever receiving an organ.⁴⁷ LDLT offers those with hepatocellular carcinoma the possibility of transplantation almost immediately after diagnosis and would almost certainly offer a survival advantage.^{48,49} These recipients could even be considered for small-size organs.⁵⁰

Technical Considerations

A number of technical modifications have been introduced since the original reports. Most changes have been instituted in response to recipient complications and a greater appreciation for the unique anatomy of the isolated and engrafted right lobe. In general, fewer modifications to the donor surgery have been instituted and the changes have been relatively conservative. In fact, the most radical alter-

ation has been the new plane of transection previously described. Approaching change from the recipient side is consistent with an underlying dedication to donor safety and is most appropriate.

Right-lobe grafts are introduced to the hyperdynamic hemodynamic environment characteristic of end-stage liver disease. Portal and arterial blood flow to right-lobe grafts have been measured before resection and after transplantation. A dramatic increase in portal blood flow with a reciprocal decrease in arterial flow is a consequence of engraftment. Portal flow more than doubles and arterial flow is cut in half in most recipients.⁵¹ Changes of this magnitude would be expected based on the size of the graft compared to the size of the native liver. Although the significance has not been determined in humans, related clinical and experimental evidence suggests that these derangements could be detrimental to the graft.^{52,53} There is no compelling evidence supporting the adoption of radical measures to reverse these changes, but some logical steps can be taken to minimize their impact.

The flood of portal blood into these grafts underscores the importance of adequate venous outflow. Obviously, the method of venous reconstruction chosen should ensure a widely patent anastomosis (cavoplasty), and as many collateral channels and avenues for venous outflow as possible should be preserved.^{18,54} The remaining segments would be expected to see similar increases in portal flow, and steps to augment outflow from the graft cannot be taken at the expense of the remnant. A plane of transection along the right border of the midhepatic vein but deviating to leave the distal portion with the graft makes anatomical sense for both the donor and recipient. Venous drainage from segment IV and collateral channels between the right and midhepatic veins are protected. Preservation and reconstruction of significant inferior hepatic veins and any large tributaries to the midhepatic vein encountered along the plane of transection is also prudent.¹⁸

Increases in portal flow can also be exacerbated by excessive fluid administration, and operating under the lowest tolerated central venous pressure is a logical principle.^{55,56} Recipients whose cardiac performance or renal function is exquisitely sensitive to relative hypovolemia are probably not optimal

candidates for LDLT unless the GRBW is relatively high and the outflow capacity of the graft is excellent. The consistent use of venovenous bypass minimizes the need for the aggressive fluid administration required for caval clamping. Although it is possible to reconstruct the hepatic veins only with the aid of side-biting clamps, creation of optimal anastomoses is facilitated by extensive cavoplasty.¹⁸

Vascular Reconstruction

Vascular reconstruction of right-lobe grafts is less cumbersome than would be expected based on the experience with left-lobe transplantation. Microvascular anastomosis is not generally necessary, but access to the vasculature can be limited and multiple branches are found in 10% to 20% of patients. Direct in situ reconstruction without the use of vascular conduits is successful in most cases, regardless of the anatomy of the graft, but at times requires a great deal of finesse.⁵⁷ Ex situ reconstruction with the aid of autologous conduits derived from the explanted graft has been suggested as an alternative, and excellent results have been obtained. Ex situ reconstruction provides optimal visualization and access to the vasculature, and it permits precise realignment of the donor and recipient vessels.¹⁹ Ideally, such "standardized" surgical techniques will reduce the level of difficulty associated with vascular reconstruction significantly.

Biliary Reconstruction

Optimal protection and restoration of the integrity of the bile ducts is essential for a successful liver transplant. Management of the bile ducts is more cumbersome with segmental grafts, and the right lobe is no exception. The incidence of biliary complications associated with right-lobe transplantation is testimony to the technical challenges.² Multiple, narrow-caliber ducts are often the products of anatomical variability and protection of the donor biliary tree.⁵⁷ Enteric drainage emerged as the preferred technique because of the experience with left-liver segmental grafts and the complexity of the anatomy. This method of reconstruction is universally applicable and has provided good results, especially when routine stenting is practiced.⁵⁷ The cumbersome nature of creation of the Roux-en-Y limb and/ or creation of multiple anastomoses has

led some groups to attempt alternative methods of reconstruction.

In those instances when a single large-caliber duct results from a safe donor resection, direct duct-to-duct anastomosis over a t-tube has been practiced with good results.⁵⁸⁻⁶¹ It is difficult to estimate the potential applicability of this technique because the presence of a single duct may be somewhat dependent on how the donor resection is executed. Obviously, performing the donor resection with the intent of obtaining a single duct without regard to the integrity of the remnant cannot be advocated. Encroaching on the donor left hepatic or common bile duct is a setup for stricture. The success of duct-to-duct reconstruction is dependent not only on donor anatomy but also on the integrity and health of the recipient common bile duct. If direct reconstruction is planned, aggressive dissection of the recipient hepatic artery should be avoided and arterial reconstruction at the origin of the gastroduodenal artery should probably not be considered.

Creation of a single duct from 2 or more smaller ducts has been practiced as well.^{59,62,63} The reporting group has achieved favorable early results with this technique, but it seems to be a risky practice. Biliary drainage from the entire graft becomes dependent on an unconventional anastomosis of unproven efficacy. Although this seems preferable to cumbersome reconstruction of very small ducts that are likely to stricture, another alternative is probably more prudent. Small ducts that only drain a small part of the graft are better ligated. This practice results in atrophy of the portion in question, but atrophy is preferable to strictures or leaks.⁶⁴

Summary

Experience with right-lobe LDLT is accumulating rapidly, and surgical techniques and donor selection criteria and protocols are evolving in response. As the nuances of right-lobe resection and grafting present themselves, it will become possible to intelligently match donors and recipients to achieve optimal outcomes. The safety of the donor must remain the 1st priority, and altering or eliminating steps in evaluation must be done very cautiously. Changes in resection techniques have been instituted to improve recipient outcomes without compro-

misgiving the record of donor safety. Recipient results are improving, and steps have been taken to simplify this surgery and bring it in line with conventional cadaveric transplantation. Attention to the adequacy of outflow from the right lobe has been recognized as critical, and the donor and recipient surgeries have been modified in response. New techniques for vascular reconstruction have also been introduced that promise to simplify creation of these anastomoses and decrease the incidence of complications.

The optimal method of biliary reconstruction has yet to be determined. There are some situations in which a duct-to-duct anastomosis will work well, but most patients will probably require enteric drainage. Surgical management can be individualized, but any reconstruction that requires too much creativity is probably inadvisable. Long-term outcomes for all management strategies still need to be evaluated.

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