DERLEME REVIEW

Adult to Adult Living Donor Liver Transplantation: Review

Canlı Donör Karaciğer Transplantasyonu

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ABSTRACT Since the first liver transplantation performed by Starzl in 1963, this has become the standard therapy for end-stage chronic liver disease and acute hepatic failure and the therapy of choice in selected cases of hepatic malignancy. The clinical outcome in patient and graft survival has increased continuously due to the optimization of intra- and postoperative management, new immunosuppressant drugs and improved organ procurement. The shortage of cadaveric donor organs has led to the development of new surgical techniques and living donor transplantation. Adult to adult living donor transplantation has been evolving over the past decade. Living-donation of the left lobe of the liver has become highly successful in pediatric transplantation whereas some transplant centers perform adult-to-adult right lobe transplantation. Advantages of living donor liver transplantation (LDLT) include thorough donor screening, optimization of timing for transplantation, minimal cold ischemia time, and potentially decreased cost. Careful evaluation and patient selection results in good patient and graft survival after transplantation. However, LDLT poses a risk to the donor.

Key Words: Liver transplantation; living donors; treatment outcome

ÖZET Karaciğer transplantasyonu Starzl tarafından 1963 yılında tanımlandığından bu yana son dönem kronik karaciğer hastalığı, akut karaciğer yetmezliği ve seçilmiş olan karaciğer maligniteli olgularda standart tedavi yöntemi haline gelmiştir. Hastanın kliniği ve greft sağkalımı intra ve postoperatif yönetimin optimizasyonu, yeni immünsüpresan ilaçlar ve organ teminindeki artışla sürekli bir şekilde yükselmektedir. Kadavra organ yetersizliği yeni cerrahi tekniklerin ve canlı donor nakillerinin gelişmesine yol açmıştır. Canlıdan canlıya organ nakli son 10 yıldır gelişmektedir. Pediatrik hastalarda sol lob nakli yüksek oranda başarılı olmakla beraber bazı merkezler canlıdan canlıya sağ lob naklini tercih etmektedirler (LDLT). LDLT'nin avantajları arasında alıcının ayrıntılı değerlendirilmesi, transplantasyon zamanlaması optimizasyonunun sağlanması, minimal soğuk iskemi zamanı elde edilmesi ve maliyetin potansiyel olarak daha az olması sayılabilir. Tüm bu faktörler nakil sonrası hasta ve greft sağkalımının daha iyi olmasını sağlamaktadır. Bununla birlikte LDLT'nin en önemli dezavantajı donör sağlığı için oluşturduğu risktir.

Anahtar Kelimeler: Karaciğer transplantasyonu; canlı verici; tedavi sonuçları

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The limiting factor in liver transplantation is the shortage of donor organs. Adult living donor liver transplantation (LDLT) represents an exciting advance in liver transplantation and provides expanded organ availability. Advantages of LDLT include thorough donor screening, optimization of timing for transplantation, minimal cold ischemia time, and potentially decreased cost.[1] There was a high level of enthusiasm for LDLT in 2000 but it diminished quickly in the following years due to reports of

death of the donors.[2] The median donor complication rate reported in a survey of United States transplant centers was 21%.[3] The estimated risk of donor mortality was reported to range from 0.2% to 0.5%3 and 0.3% to 0.9%.[4] The ethical concerns regarding LDLT are related to the potential for donor morbidity and mortality. Opponents argue that it is unacceptable to place a healthy donor at risk of longterm debility or death.

The above issues and lots of other concerns in adult-to-adult transplantation were considered by the ethics committee of the American Society of Transplant Surgeon, which issued an official position statement (Table 1).[5] The guideline included criteria for donor and recipient selection, for centers performing LDLT, and for informed consent.

In this review, we will discuss the liver transplantation surgical techniques, outcomes and morbidity associated with the recipient and the donor.

LDLT CANDIDATE AND DONOR SELECTION

The goal of the donor evaluation is to determine if the donor is medically and psychologically suitable for living donation. Living donors are usually close family members or spouses who are younger than 60 years of age (between 21 to 55 years old), with ABO blood type compatibility preference.[6]

It is of major importance that the donor is well informed of the risks and benefits of the procedure. The surgery team should confirm that consent is informed and ensure that the potential donor has sufficient time to consider the risks of the procedure.[6]

TABLE 1: From the American Society of Transplant Surgeons: Ethics Committee.[5]

Donor Selection and Evaluation
• Potential donors should be healthy individuals who are carefully evaluated and approved by a multidisciplinary team, including hepatologists and surgeons, to ensure that they can tolerate the procedure
• Potential donors should undergo evaluation to ensure that they fully understand the procedure and associated risks
• Potential donors must be of legal age and have sufficient intellectual ability to understand the procedure and give informed consent
• Potential donors who are believed or known to be coerced must be excluded
• Potential donors need to have the ability and willingness to comply with long-term follow-up
Recipient Criteria
• Recipients need to be medically suitable for liver transplantation by standard criteria of the transplant center
• Recipients need to understand and accept that the donation will put the donor at significant risk
• Although it may not be possible to firmly state that adult-to-adult living donor liver transplantation should not be performed in situations in which the recipient has a poor chance of survival, the added risk to the donor must be balanced with a realistic estimate of the chances of success
Center Criteria
Centers should undergo careful institutional planning that shows the following:
• Consideration of the significant risk of the procedure to the donor
• Establishment of an appropriate informed consent process
• Surgical expertise in liver transplantation and hepatobiliary surgery
• An existing need for living donation versus cadaveric donation, shown by insufficient cadaver organs for transplantation resulting in potentially avoidable deaths on the waiting list
• Adequate resources, eg, multiple surgical teams, adequate operating room resources, and institutional support
• Ongoing oversight
Consent
Informed consent for the procedure should contain the following elements:
• The risk for death during or after the operation
• The risk for liver failure resulting in the need for transplantation
• The risk for life-threatening infection resulting from the operation
• The risk for blood-borne infection acquired throuhg transfusion
• The risk for temporary or permanent disability
• The ability to withdraw from participation at any time before surgery
Registry
The American Society of Transplant Surgeons should implement a national registry for all living donor liver transplant procedures

A comprehensive history and physical examination should be performed for the donor with full laboratory examination including testing for hepatitis B, hepatitis C, and human immunodeficiency virus, serum biochemistries, a complete blood count, and liver enzymes. A chest radiograph and an EKG are also performed. Donors should not have liver disease or significant comorbidities like coronary artery disease, kidney disorders or cerebrovascular disease. Obesity is another limiting factor for donation. Donor candidates whose body mass index is more than 35 should e excluded due to high post-operative obesity related morbidity. Obese donors are also more likely to have hepatic steatosis, which would jeopardize the recipients' outcome. Although liver biopsy is an option for such patients, biopsy is an invasive procedure with its own morbidities. Thus, it seems more logical in these patients to rely upon physical examination, risk factors of steatosis like high blood cholesterol and imaging studies.[7]

An accurate estimation of preoperative volumetric measurement of the donor liver is essential in LDLT. A small size graft is a common problem particularly when using left lobe grafts due to the limited volumes associated with the left lobe grafts. Imaging studies provide information to estimate the volume of the left lateral segment or right lobe to assess whether the mass is sufficient to support a particular recipient.[8] Three-dimensional computed tomography (3D-CT) volumetry is useful for size matching in this regard.[9] CT or magnetic resonance imaging (MRI) further serve to identify space-occupying lesions and give an indication for the presence of steatosis. Preoperative evaluation of biliary anatomy with conventional non-enhanced MRI provides a noninvasive method that could minimize postoperative morbidity in the recipient and maximize safety of the donor with a sufficient diagnostic value.[10]

The gold standard to asses the donors abdominal vasculature is the conventional celiac and mesenteric angiography whereas some centers prefer to use a less invasive method which is MRI angiography. Liver biopsy is a routine part of the donor evaluation at some centers, while other programs reserve biopsy for potential donors with elevated liver enzymes or suspected steatosis and rely upon physical examination, risk factors of hepatic steatosis, and imaging studies.[7,11] All living donor candidates should undergo a psychosocial evaluation to ensure that they truly understand the risk of the procedure.

Unfortunately, only a minority of potential donors which is reported to be between 15% and 45% end up being suitable candidates that eventually proceed with LDLT after the above evaluation.[2,11] The lowest rate for suitable candidates after evaluation was reported by Valentin-Gamazo et al as 14% in 700 potential donors.[12]

SURGICAL TECHNIQUES

As mentioned above, the left and the right lobes of the liver can be used for transplantation depending upon anatomic considerations, the volume of the donor liver, and the size of the recipient.

LEFT LOBE TRANSPLANTATION

In the initial adult LDLT procedures, only a left liver graft was used. In 1998, the Shinshu group reported satisfactory results using a left liver graft in 13 patients.[13] The donor was selected based on computed tomography volume examination where the calculated size of the liver graft was larger than 30% of the recipient's standard liver volume. By January, 2004, the group had performed 95 adult LDLTs using left liver grafts. The 5-year graft and patient survival rates were 81% and 82%, respectively. Graft survival did not appear to be related to the graft volume/patient standard liver volume ratio.

Their data indicate that left liver graft provides satisfactory results for appropriately selected recipients.

Miyagawa et al reported on LDLT using the left liver grafts including the left-side caudate lobe (the Spiegel lobe and the left side of the paracaval portion of the caudate lobe). Takayama et al designed a similar procedure with direct anastomosis to the vena cava of the hepatic vein from the caudate lobe.[14,15] The caudate lobe corresponds to only 3% to 4% of the whole liver volume. In conjunction

with a left liver graft, however, the caudate lobe increases the graft weight by 8% to 12%.

The strategy for selection of left or right liver graft, is influenced by the patient's preoperative condition, as patients with advanced liver disease require a larger liver mass.[16] The model for end-stage liver disease score could become a satisfactory criterion for differentiating between high- and low-risk patients and therefore to determine the type of graft to use.

The left lobe harvest operation starts by exposing the liver and dividing the peritoneal attachments to the left lobe. The left and middle hepatic veins are dissected, as are the left hepatic artery and left portal vein. Small portal vein branches are ligated. The left bile duct is divided cautiously avoiding the injury to the common bile duct. Vascular and biliary structures entering segment 4 are divided or left intact depending upon whether the left lateral segment or full left lobe is required. The parenchyma is transected and then the left hepatic artery and left portal vein are divided, releasing the graft. The middle hepatic vein is removed with the graft when a full lobectomy is performed. The graft is flushed with preservation solution in preparation for implantation. A portion of the saphenous vein may be harvested from the donor to provide the for extension of the hepatic artery (Figure 1).[17,18]

Critical parts of the recipient operation include the vascular and biliary anastomoses. Unlike the situation in cadaveric grafts, the living donor's vena cava is preserved, so the donor hepatic vein is anastomosed directly to the recipient vena cava or hepatic vein. The graft is rotated approximately 45 degrees to protect venous outflow. A low rate of arterial thrombosis has been achieved by using microvascular techniques to perform an end-to-end arterial anastomoses.[19] Portal vein reconstruction may include an interposition vein graft and/or branch patch depending on portal vein length and diameter mismatch.[20] The left hepatic duct is anastomosed to a Roux en Y loop to complete the biliary reconstruction (Figure 2).

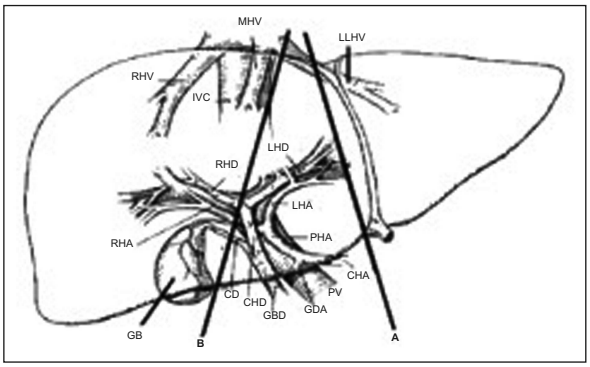

FIGURE 1: Donor operation (for left graft).
The relationships of anatomic structures are shown. Planes A and B parenchimal transection are presented for the creation of A: segment 2 and 3 graft and B: full left lobe graft
LLHV: left hepatic vein, MHV: Middle hepatic vein, IVC: Inferior vena cava, RHV: Right hepatic vein, RHA: Right hepatic artery, RHD: Right hepatic duct, LHD: Left hepatic duct, LHA: Left hepatic artery, PHA: Proper hepatic artery, CD: Cystic duct, CHD: Common bile duct, GB: Gall Bladder, GDA: Gastroduedenal artery, CHD: Common hepatic artery, PV: Portal vein.

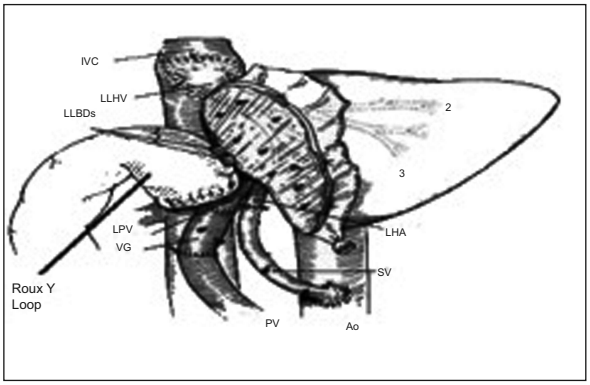

FIGURE 2: Complete recipients' left lobe implantation. Interposition grafts are used for both hepatic artery and portal vein to assure adequate length.
LLBDS: Segment 2 and 3 bile ducts, LPV: Left portal vein, VG: Vein graft, SV: Saphenous vein, Ao: Aorta.

RIGHT LOBE TRANSPLANTATION

Techniques for right lobe transplantation have many variations and modifications but the following represents a standard approach. Following cholecystectomy, intraoperative ultrasound may be used to delineate the position of the hepatic veins and portal branches.[22-24] The right hepatic artery and right portal vein are dissected followed by the retrohepatic vena cava, isolating the origin of the right hepatic vein. The middle hepatic vein is not dissected at most centers, although accessory hepatic veins greater than 5 mm may be preserved to improve outflow from the graft.[23] The right bile duct is isolated, completing mobilization of the

right lobe. The liver parenchyma is transected using an ultrasonic scalpel (Cavitron). Doppler may be used to assess inflow to the remaining left lobe. The main vessels are then divided and the isolated right lobe is flushed with preservative solution in preparation for implantation. Any bleeding of the donor's left lobe is controlled with sutures and fibrin glue is applied to the cut surface prior to closure (Figure 3).

Implantation of the graft starts with end-to-end anastomosis of the donor and recipient right he-patic vein. The hepatic artery anastomoses are completed using microvascular techniques. Next, an end-to-side hepaticojejunostomy (and less commonly duct-to-duct anastomosis) is performed with internal stent replacement followed by abdominal closure (Figure 4). Doppler ultrasound is performed in the postoperative period.

ADULT-TO-ADULT LIVER TRANSPLANTATION

The success of LDLT in children prompted attempts for LDLT in adults. Multiple series demonstrated favorable results with living donor trans-plantation; successful results often exceeded those with cadaveric grafts.[22,25-27] However, these out-comes may not be directly comparable since most recipients who received a living donor graft were far less sick than patients who received a cadaveric graft. Furthermore, right lobe grafts may be prone to a variety of technical complications. Thus, the major advantages to the recipient are the warranty that a transplant will be performed and minimization of waiting time with its associated clinical deterioration.

Using the left hemiliver, which was the initial approach in LDLT history could only provide approximately 30% to 50% of the estimated liver volume in an adult recipient. Emond and col-leagues studied the results of small graft size and found significant functional impairment, as evidenced by prolonged cholestasis, intractable ascites, coagulopathy, and encephalopathy. The histology of the graft showed changes that were typical of ischemia and were probably related to portal hyperperfusion; thus, the small-for-size syndrome is most likely to occur in the patient with pretrans-plant cirrhosis and portal hypertension. Kawasaki et al[13] reported their successful results using a left hemiliver graft in 13 adults, and subsequently, in 2004, found that the 5-year patient and graft survivals were 82% and 81%, respectively in 95 patients who received left hemiliver grafts from living donors.[13,29] When the graft volume/patient standard liver volume ratio was less than 50%, the 1-year graft survival was 83%, compared to a survival of 100% when the ratio was greater than 50%. Similar results were achieved in Tokyo, using the left hemiliver with or without inclusion of the cau-

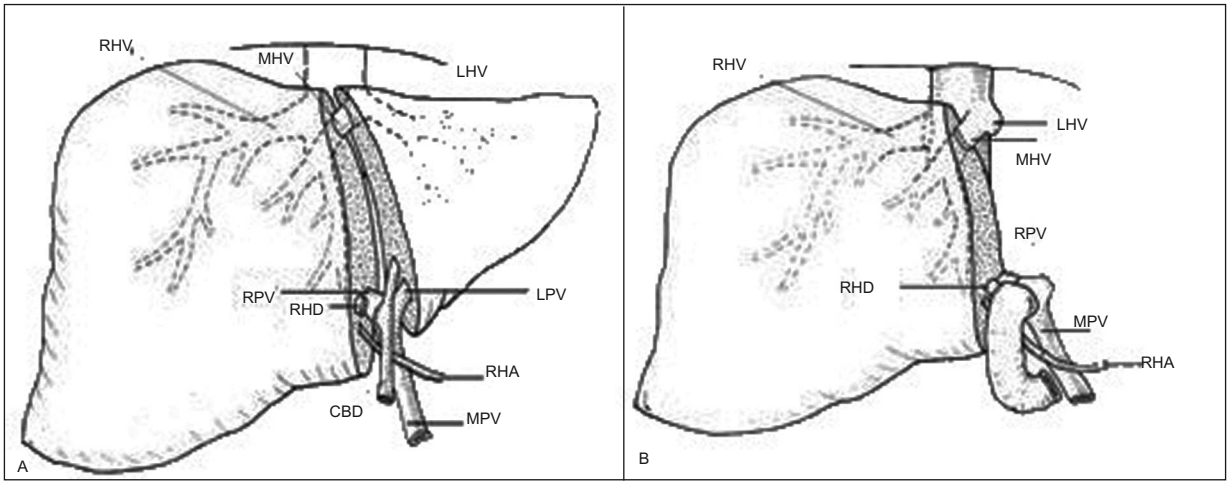

FIGURE 3: (A) Donor operation. (B) Implantation of the graft.

RHV: Right hepatic vein, MHV: Middle hepatic vein, LHV: Left hepatic vein, MPV: Main portal vein, RPV: Right portal vein, LPV: Left portal vein, RHA: Right hepatic artery, RHD: Right hepatic duct, CBD: Common bile duct.

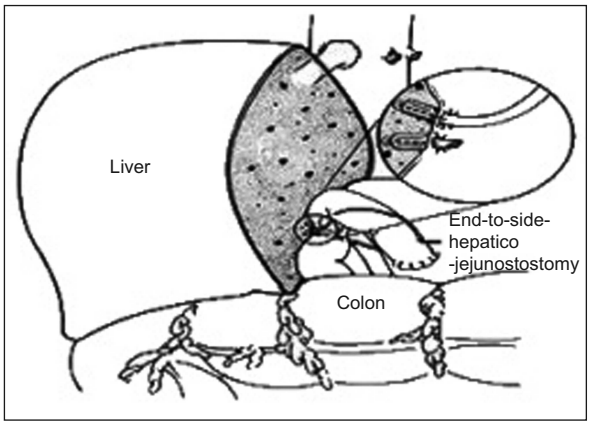

FIGURE 4: Right lobe transplantation: anastamoses in the recipient.

date lobe.[29] The beneficial inclusion of the caudate has been confirmed in a study by Soejima et al[30] The pretransplant disease severity of recipients is one of the major factors in developing the small-for-size syndrome.[16] Hwang et al proposed a graft volume/standard liver volume ratio of more than 30% for those without cirrhosis and a ratio of more than 45% for patients with cirrhosis.[31]

As the limitations of LDLT using the left hemiliver became apparent, the natural sequence was to use the right hemiliver, which has been used successfully in split-liver transplantation from deceased donors (DDs). The right lobe accounts for approximately two-thirds of the liver mass and provides adequate tissue to support the metabolic needs of an adult recipient. The right lobe also fits correctly into the right subphrenic space, making the vascular anastomoses easier to perform. However, the extent of the resection may put the donor at increased risk for complications compared with donation of smaller segments. The Hong Kong team was the first to embark on a program of adult-to-adult LDLT using the right-side graft.[22] Their early experience was accompanied by significant donor and recipient complications, which were markedly reduced with increasing experience. Their inclusion of the donor MHV in the graft (termed the extended right liver graft) was deemed necessary because of congestion in the anterior sector of the graft in their first case, which did not include the MHV. Lee et al, from Korea, rec-ommended routine reconstruction of MHV tributaries.[32] On the other hand, Kam and his colleagues in Denver, after losing three of their first ten grafts, moved the transaction plane to the right border of the MHV, preserving the MHV branches and their connections to the RHV.[33] Only two of the subsequent 70 transplants required reconstruction of the MHV tributaries when the RHV of the graft was small. It seems that there is no clear answer as to the necessity of routinely obtaining venous drainage of the MHV.

One of the largest reports summarized outcomes of 385 transplants performed at nine centers.[34] Ninety-day and one-year graft survival rates were 87 and 81%, respectively. Graft failure within 90 days occurred in 51 transplants, primarily because of vascular thrombosis, primary nonfunction, and sepsis. Biliary complications were common (30% early and 11% late). Older recipient age and longer cold ischemia time were significant predictors of graft failure. Center experience with more than 20 transplants was associated with a significantly lower risk of graft failure.

DONOR OUTCOMES

The available evidence for the donor mortality and morbidity suggests that while right lobe donation appears to be safe, it may be associated with significant morbidity and may affect quality of life.[35] Donor deaths were also reported.[35,36] A systematic review of 214 published reports estimated that donor mortality was approximately 0.2 percent (0.3 to 0.5 percent for right lobe donation).[37] The most common donor complications were biliary and infectious. Nearly all donors had returned to normal function by 3 to 6 months.

Major complications were observed in 3.2% of donors in a single center study involving 1162 transplants (of which 588 were right lobe) between 1994 and 2005.[38] The rate of serious complications decreased in more recent years (to 1.3%) when resections exceeding 65% of whole liver volumes were avoided except for young donors without steatosis. The authors noted that complications were also reduced by intensive postoperative surveillance and improvement in surgical techniques.

Liver regeneration is rapid following LDLT. In one report, the volume of small-for-size left lateral segment grafts increased by 60 to 200% within 1 month and approximated standard liver volume by about 2 months post-transplant.[39] Substantial hepatic growth also occurs in the donor during the first month, although full restoration of liver volume seems to occur more slowly in the donor than in the recipient.[39]

CONCLUSIONS

Adult living donor transplantation offers hope to patients with end stage liver disease in areas where waiting time mortality is high and availability of DD organ falls short of the need of the population. There are significant risks to the living donor including risk of death and substantial morbidity, that must be taken into account before patients, physicians and transplant programs embark in LDLT.

It is now 16 years since the first successful LDLT from a parent to child was performed. LDLT has become an accepted practice in pediatric transplantation. Improvements in surgical techniques have minimized the risks of left lateral segmentectomy to the donor and recipient outcomes are now excellent. The overall results, with very acceptable patient and graft survival in recipients, coupled with a relatively low morbidity and minimal mortality in donors, has established the procedure to be relatively common.

Adult-to-adult LDLT is a much more recent improvement and it is still developing. The marked improvement in patient and graft survival by units that are now considered to be experienced and established is a manifestation of a quite precipitous learning curve. However, despite the selection of better-risk patients, the overall results of patient and graft survival could only be described as disappointing and combined with the high morbidity and considerably high mortality in donors makes the rapid and extensive expansion of adult-to-adult LDLT somewhat questionable. However, the major benefit of LDLT in adults is that it warrants a transplant will be performed and minimizes morbidity associated with clinical deterioration as potential recipients await a cadaveric graft.

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