Living donor liver transplantation

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Purpose of review
As experience grows, living donor liver transplantation (LDLT) has become an effective treatment option to overcome the deceased donor organ shortage.

Recent findings
Donor safety is the highest priority in LDLT. Strict donor selection according to structured protocols and center experience are the main factors that determine donor safety. However, with increased experience, many centers have explored increasing organ availability within living donation by means of ABO incompatible LDLT, dual graft LDLT, and anonymous living donation. Also, this growing experience in LDLT has allowed the transplant community to cautiously explore the role of liver transplantation for hepatocellular carcinoma outside of Milan criteria and patients with unresectable colorectal liver metastases.

Summary
LDLT has become established as a viable strategy to ameliorate the organ shortage experienced by centers around the world. Improved understanding of this technique has allowed the improved utilization of live donor graft resources, without compromising donor safety. Moreover, LDLT may offer some advantages over deceased donor liver transplantation and a unique opportunity to assess the broader applicability of liver transplantation.

Keywords
expanding indications, liver transplantation, living donor, organ shortage

INTRODUCTION

Living donor liver transplantation (LDLT) was developed and later further expanded to mitigate deceased donor organ shortages and reduce mortality on liver transplant waiting lists around the world [1–3]. This technique, although first described in the Western world, has had a greater impact in Asian countries where deceased donation rates are very low [4–6].

LDLT has proven to have several advantages over deceased donor liver transplantation (DDLT) [7–12]. Chief among these is a faster route to transplantation. Therefore, LDLT has the potential to reduce disease progression and ultimately waiting lists mortality. In addition, living donation allows expansion of the boundaries of liver transplantation to settings in which liver transplantation is currently limited by organ shortages [i.e., intrahepatic cholangiocarcinoma, unresectable colorectal liver metastasis (CRLM), etc.] [13–15,16▪▪].

Although LDLT has progressed significantly over the last 3 decades, there have been restrictions in continued growth of this technique, particularly in the West [17,18]. LDLT is inherently a more complex procedure and comes with the ethical dilemma of putting a healthy individual through a major operation [18–20]. In addition, there has been reluctance to promote LDLT for high acuity recipients. However, in regions with low deceased donor rates, living donation centers have been exploring novel ways of increasing organ availability within living donation, without increasing donor risk. In this regard, transplant centers with significant living donation experience have expanded their donor selection criteria (i.e., older donor age, high BMI, anonymous donation, dual grafts, ABO incompatible) [21,22▪,23,24▪▪,25].

The importance of LDLT has arguably never been higher, considering the marginal improvements in deceased organ availability [26]. Therefore, focusing on the most recent literature, this review will cover

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KEY POINTS

- LDLT has emerged to overcome the organ shortage experienced around the world.
- Donor safety is the main priority of LDLT and is directly related to the centers experience and the ability to follow structure protocols for safe donor selection.
- The organ pool can be expanded within living donation by means of ABO incompatible LDLT, dual-graft LDLT, and anonymous living donation.
- LDLT may offer an opportunity to asses the applicability of liver transplantation for the treatment of patients with increased HCC tumor burden or unresectable colorectal liver metastasis. However, this is matter of debate and additional validations are required.

the following topics: safe donor selection necessary to expand the organ pool within living donation, current recipient outcomes, and the advantages provided by LDLT vs. DDLT. Also, we will discuss recent technical advances within this practice that allow increased graft utilization and the expanding indications of this technique.

DONOR SELECTION AND LIVE DONOR ORGAN POOL EXPANSION

Maintaining donor safety is the highest priority in LDLT. Current morbidity and mortality rates following living liver donation have been reported to be 15–25% and 0.5%, respectively [18–20,27,28]. Therefore, the risks imposed to the donor, although low, are still present. Strict donor selection according to structured protocols and center annual volume/experience are the primary factors that determine donor safety [20,27].

Living liver donors should be healthy individuals with no comorbidities. In this manner, they should undergo a thorough assessment of their past and current health status. In general, most centers restrict donation to individuals who are 18–60 years old with minimal liver steatosis, who are blood group compatible and can provide an adequate graft to recipient weight ratio (GRWR) while maintaining an adequate remnant liver volume (i.e., >30%) [20,29–31]. Anatomical suitability is usually assessed with computed tomography scan and magnetic resonance cholangiopancreatography, and liver volumes evaluated with volumetric software.

The type of graft donated, and therefore the amount of liver parenchyma removed from the donor, has been matter of debate in terms of impacting donor morbidity. Although right lobe (RL) grafts are most commonly used in adult-to-adult LDLT, several centers advocate for the expanded use of left lobe grafts, citing improved donor safety with the increased residual volume [32,33]. Thus far, outcomes of appropriately selected left lobe grafts appear to be equivalent to right lobe grafts. The main limitation associated with left lobe grafts is an inadequate GRWR for larger recipients.

High donor BMI and consequent hepatic steatosis has limited donor selection and living donation organ resource utilization. Many transplant centers routinely decline living donation based on obesity, defined by a BMI more than 30 [34,35]. However, recent data has suggested that living donation can be performed safely in selected patients with BMI more than 30 and minimal hepatic steatosis (<10%) [22▪]. This study demonstrated a similar complication rate in this population, including wound dehiscence, lung infections, and venous thrombotic events. It is crucial that in such patients steatohepatitis is ruled out and adequate remnant liver volume maintained. Similarly, other centers have safely proposed consideration of living donation with up to 30% macrosteatosis as long as their BMI is less than 30, are young (i.e., <35 years old), and have a remnant liver volume more than 35% [2].

Currently, many donors are also declined due to inadequate GRWR (GRWR < 0.8) or because their residual liver volume (RLV) is less than 30%. Driven by organ scarcity and the commitment to improve utilization of living donors, the Asan medical group have successfully introduced dual graft adult-to-adult LDLT [36]. In this innovative and challenging technique, the group led by Dr Sung-Gyu Lee has been able to optimize living donation utilization by utilizing donors that would otherwise provide insufficient GRWR or have insufficient RLV with right lobe donation. Specifically, two grafts from different living donations are combined to provide a sufficient and safe graft volume to a single recipient. The authors recently reported their impressive experience with more than 400 cases and demonstrate comparable patient survival between dual and single graft LDLT [24▪▪]. Not surprisingly, recipient hospital mortality and surgical complication rates were significantly higher than with single graft LDLT due to the increased technical complexity of this technique. However, these challenges are likely offset by the benefits of reducing waiting lists mortality. Using this novel approach, the authors were able to expand the living donation pool by 12% [37]. Although two donors are at risk for each recipient case, the donor risk per individual did not change [24▪▪]. Moreover, donor risk of postoperative liver failure is likely to actually be lower, given that less extensive hepatectomy is performed when

combining two left lateral section (LLS) grafts. living donation programs around the world should be cautious in the implementation of this technique as the excellent outcomes reported by the Asan Medical Group derive from their extensive living donation experience (>400 LDLT cases/year), center resources, and the need of technical innovation to overcome donor scarcity and high waiting lists mortality.

LDLT using ABO incompatible (ABOi) grafts is another strategy to increase organ availability and resource utilization within living donation. In general, ABO compatibility (ABOc) has been a standard selection criteria outside of a small minority of ABOi cases performed for fulminant hepatic failure [38,39]. Concerns for increased rates of rejection, hepatic artery thrombosis, and diffuse intrahepatic biliary strictures have traditionally restricted more broad application of ABOi liver transplantation. However, Asian centers with limited deceased donor organ access and significant LDLT experience have explored LDLT with ABOi grafts out of necessity [25,40▪,41–44]. With refinements in approach, centers offering this technique have achieved similar outcomes that with ABOc grafts. These excellent outcomes have derived from improved desensitization protocols including the use of rituximab [45]. LDLT centers have continued to explore desensitization protocols including rituximab in combination with one or more of the following: plasmapheresis, local infusion of prostaglandins, intravenous immunoglobulin (IVIg), and splenectomy [25,41,40▪,46]. More recently, transplant centers have implemented simpler desensitization protocols with promising results. In 2018, Yamamoto *et al.* [40▪] reported their experience with monotherapy with rituximab for ABOi LDLT. In this study, the outcome of 20 patients undergoing ABOi LDLT with rituximab alone were compared with 20 patients undergoing a desensitization protocol that included plasmapheresis (pretransplant) and local infusion therapy (postransplant) in addition to rituximab. No difference was observed between groups regarding rejection rates or biliary and vascular complications. Moreover, patient survival was not different between groups and there was a tendency to lower fungal and viral infections in the rituximab-only treatment group. Likewise, Kim *et al.* [25] reported the outcome of 43 patients undergoing ABOi LDLT with a simplified desensitization protocol. In this study, patients received preoperative rituximab followed by two postoperative doses of IVIg on days 1 and 4. Of note, this group of patients had iso-agglutinin titers not higher than 1 : 64, and none underwent plasmapheresis, splenectomy or local infusion therapy following transplantation. A propensity score match was conducted to compare outcomes of the ABOi LDLT group ($n = 43$) to 86 patients undergoing ABOc LDLT at the same institution (2 : 1 match ratio). None of the patients in the ABOi LDLT group developed antibody mediated (AMR) or acute cellular rejection (ACR). Biliary strictures were the most common complication in the ABOi group; however, all strictures (30.2% incidence) were anastomotic and no cases of diffuse intrahepatic biliary strictures occurred in the entire series. No difference was observed in the incidence of biliary complications (30.2 vs. 27.9%; $P = 0.783$), hepatic artery thrombosis (4.6 vs. 1.2%; $P = 0.258$), and postoperative infections (4.6 vs. 5.8%; $P = 1$) when compared with the ABOc LDLT group. No patient in either group underwent retransplantation and patient survival at 1, 2, and 3 years were similar between groups (ABOi LDLT: 87.9, 82.4, and 82.4% vs. ABOc LDLT: 96.9, 93.7, and 85.9%; $P = 0.115$). The Asan Medical Center group has pushed the envelope even further and recently published excellent outcomes with dual-graft LDLT using ABOi grafts [43]. In this series of 28 ABOi dual grafts, LDLT recipients received the same desensitization protocol of preoperative rituximab and plasmapheresis and results were compared with the outcome of 145 patients undergoing ABOc dual-graft LDLT during the same time period. No cases of AMR occurred and no difference was observed in the incidence of ACR between both groups (3.6 vs. 7.6; $P = 0.693$). Biliary complications (7.9 vs. 22.2; $P = 0.195$) and infection rate (17.9 vs. 16.6; $P = 0.789$) were similar between the ABOi and ABOc dual-graft LDLT groups. The 1-year, 3-year, and 5-year graft survival rate was 96.4, 94.2, and 92.0%, respectively, similar to the ABOc group ($P = 0.145$) [43]. Another limitation of wider application of ABOi LDLT has been the concern for higher rates of hepatocellular carcinoma (HCC) recurrence due to the more aggressive immunosuppression applied in this approach [47]. However, recent reports from two Korean centers failed to demonstrate a difference in HCC recurrence-free survival and long-term survival between patients receiving an ABOi or ABOc LDLT [44,48].

Anonymous living donation is another approach to increase the LDLT donor pool, although it comes with unique ethical considerations. In anonymous donation, a healthy individual with limited or no previous relationship with the recipient steps forward and donates without recipient knowledge of their identity. To date, the University of Toronto has the largest experience with anonymous living liver donation. Since the report of the first case in 2005 [23,49], Toronto has performed more than 50 cases, representing more than 7% of the LDLT transplant activity to date (unpublished data). With regard to donor characteristics, most

had a university education, a middle-class income, and a history of altruism. The vast majority (70%) learned of the anonymous donation opportunity through social media. Twenty-eight grafts were allocated to a pediatric recipient and 22 to adult recipients. Almost 90% (44/50) of these donors maintained their anonymity and none expressed regret after donation (unpublished data). The favorable outcomes experienced by the Toronto group should encourage other transplant centers performing LDLT to consider this type of donation, provided strict ethical guidelines are in place.

RECIPIENT OUTCOMES

As experience has grown, LDLT has matched DDLT with respect to recipient outcomes. The improvements in graft and patient survival are the result of refined patient selection and the technical experience gained throughout the years [2,3].

A right lobe graft without the middle hepatic vein (MHV) has become the most widely used graft type for adult-to-adult LDLT [2,50,51]. The primary rationale for excluding the MHV is to improve outflow of the residual liver and thus reduce donor risk [2,52▪,53]. However, when this type of graft is utilized, there has been debate about the utility of reconstructing the segments 5 and 8 outflow to avoid anterior sector congestion, facilitate liver regeneration, and improve graft function. Although some centers are inclined to reconstruct these veins on a case-by-case basis, others suggest that all tributaries should be reconstructed if more than 5 mm in diameter [54]. Recently, Goja *et al.* [52▪] from the Medanta group in India reported their experience with 665 RL grafts in a 2.5-year period. In this study, they propose an algorithm to determine the type of outflow reconstruction to utilize based on donor anatomy [52▪]. Specifically, if segments 5 and 8 tributaries were more than 5 mm in size they opted to leave the MHV in the donor as these vessels are simpler to reconstruct in the recipient. On the other hand, if the tributaries were between 3 and 5 mm, these veins were reconstructed if there were multiple in close proximity and they drained segment 5 [52▪]. In these cases, a patch venoplasty was used for reconstruction. In cases in which the GRWR was less than 0.8 and the recipient had more advanced disease (higher model for end stage liver disease + portal hypertension), the authors also were inclined to reconstruct vessels less than 5 mm. With this approach, the authors reported similar outcomes independent of the type of RL graft utilized. Incidence of overall complications, biliary complications, and number of patients developing small for size syndrome was similar amongst all graft types.

Despite the advances in LDLT, biliary complications continue to be the Achilles heel of this procedure. Biliary complications in LDLT have been reported to be anywhere between 15 and 60% [2,55,56]. Numerous risk factors for the development of biliary complications have been studied [57]. The occurrence of this complication is likely the result of multiple variables including the presence of multiple and/or small bile ducts, poor bile duct blood supply due to excessive hilar dissection, portal hypertension and consequent arterial hypoperfusion, and bowel edema in Roux-Y reconstructions. Among these risk factors, studies have suggested that LDLT biliary complications are most likely associated with the presence of multiple ducts [58,59]. However, Kollmann *et al.* [56] from the University of Toronto recently reported their experience with LDLT using grafts with more than two ducts. In this study, the outcome of patients receiving grafts with two bile duct ($n = 169$) was compared with those patients receiving a graft with a single bile duct ($n = 320$). Significantly, there was no difference in the incidence of biliary complication (either stricture or leak) within 1-year following liver transplantation between both type of grafts (one bile duct: 18% vs. two bile duct: 21%, $P = 0.46$). As expected, Roux-en-Y-reconstruction was more common in the two bile duct-group (77 vs. 39%, $P < 0.001$) and 50% of patients in the two bile duct-group, had their bile duct reconstructed with two anastomoses. However, on multivariable cox regression analysis, the number of anastomoses did not negatively impact biliary complication rates. Regardless of the number and size of the bile duct to be reconstructed, there are some principles that should be followed to minimize the occurrence of this complication. Amongst them, avoiding unnecessary dissection around the donor biliary plate during donor hepatectomy, keeping as much connective tissue around the recipient common bile duct to preserve blood supply, avoiding tension on the biliary anastomosis with appropriate approximation of the bile duct mucosa and avoiding trauma to the biliary epithelium will optimize outcomes.

EXPANDING INDICATIONS OF LIVING DONOR LIVER TRANSPLANTATION FOR THE MANAGEMENT OF CANCER

In the HCC arena, the optimal utilization of LDLT has been matter of debate [9,60,61]. The primary theoretical benefit of LDLT over DDLT for HCC is a significant reduction in waiting time. However, some have suggested that expediting transplantation in HCC patients precludes a period of observation of disease biology and thus might increase risk

of early tumor recurrence/progression (fast track effect) [60]. At present, there is no clear evidence supporting higher recurrence rates in LDLT compared with DDLT. Moreover, in many patients with more extended tumor criteria (i.e., beyond Milan and University of California, San Francisco – UCSF – criteria) that would not have access to DDLT, LDLT offers a substantial survival benefit [62,63]. At the University of Toronto, patients are eligible for DDLT if their total tumor volume is 115 cm^3 or less and their serum alpha-fetoprotein of 400 ng/ml or less. However, patients beyond those criteria but within the extended Toronto criteria (ETC) (any size and number of HCC lesions without vascular invasion, extrahepatic disease, or cancer-related symptoms, and a biopsy ruling out poor differentiation) can be transplanted with a living donation [64]. For this patient population (beyond UCSF but within ETC) the University of Toronto has achieved a 1-year, 3-year, and 5-year overall survival from the time of listing of 86, 65, and 60%, respectively, ($n = 57$) compared with 82, 61, and 56% in those patients receiving a DDLT ($n = 119$), $P = 0.72$ [65▪▪].

The experience with the use of LDLT for extended criteria HCC tumors has stimulated the transplant community to explore liver transplantation for other types of advanced tumors that are not currently considered eligible for DDLT [66]. The encouraging results published by the Norway group [67,68] on the use of liver transplantation for the treatment of unresectable CRLM has prompted other centers to explore LDLT in this setting. Recently, Konigsrainer *et al.* [16▪▪] reported a case in which a two staged hepatectomy was combined with a LDLT using LLS graft for unresectable CRLM. In this strategy, the authors performed a first stage operation consisting of a left hepatectomy and a LDLT with a LLS graft. The implantation of the living donation graft was performed similarly to auxiliary liver transplantation or dual graft LDLT [24▪▪,69]. The graft hepatic vein was anastomosed to the ostium of the middle/left HV of the recipient, the donor portal vein and hepatic artery were anastomosed to the recipient left portal vein and left hepatic artery stumps. In that same procedure a ligation of the recipient right portal vein was performed to induce hypertrophy of the living donation LLS graft. Following hypertrophy of the LLS graft, the second stage of the procedure was carried out 10 days after the initial intervention. In this procedure, a completion right hepatectomy was performed, similar in concept to the associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure [16▪▪,70]. Although the oncological benefit of this novel approach has not been proven, it introduces another potential treatment option for unresectable CRLM. This approach may offer the opportunity to overcome the limitations of the current treatment options of unresectable CRLM without compromising the deceased donor organ pool. Also, donor risk is reduced as it involves donation of a LLS graft. However, it should be taken into account that approaches, as the one described, should only be performed in highly specialized centers under approved clinical trial protocols.

CONCLUSION

As experience grows, LDLT has become an effective treatment option to overcome the current deceased donor organ shortage experienced around the world. Moreover, improved understanding of this technique together with the technical advances achieved throughout the years has demonstrated that LDLT may offer some advantages over DDLT. Although the expansion of LDLT to other diseases or to more advanced HCC are still matter of debate, there is no doubt that LDLT offers a unique opportunity to increase access to transplantation and demonstrate the potential benefit of liver transplantation. However, living donation morbidity remains a major concern following living donation hepatectomy. Therefore, as indications for LDLT are expanded, donor safety still remains the main priority of LDLT.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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