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Living-donor liver transplantation in adults

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Introduction: The technique of paediatric living-donor liver transplantation (LDLT) has become standardized. In adults, however, there is scope for innovation. Unlike cadaveric whole-size liver transplantation and paediatric LDLT, size matching between the liver graft and the recipient by body weight has been a major challenge in adult LDLT because it is important to provide an adequate graft mass to the recipient while leaving a sufficient mass of remnant liver in the donor to ensure donor safety.

Growing points: In adult LDLT, liver grafts have been selected to meet graft-recipient size-matching requirements. In 1996, the Hong Kong group pioneered the use of the right-lobe grafts vein to overcome the volume insufficiency often encountered with the left-lobe liver grafts. Subsequently, the Asan group introduced modified right-lobe grafting with interposition vein grafts to drain the venous outflow of the anterior sector, thus increasing the functioning hepatocyte mass, and this group initiated dual left-lobe liver grafts to overcome both donor risk and volume insufficiency.

Areas of agreement and controversy: Although the surgical procedures for both donors and recipients are more complex for adult LDLT than for whole-organ deceased donor transplantation, the outcomes in large-volume centers are now similar. Accordingly, the indications for adult LDLT are continually being expanded.

Areas timely for developing research: In performing these procedures, it is crucial to minimize the risks of morbidity and mortality to the healthy live donor. This review focuses on the current technical development and discusses the ethical issues of adult LDLT.

Keywords: living donor liver transplantation in adults

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Introduction

Living-donor liver transplantation (LDLT) in children has become common at numerous transplantation centres around the world and has been shown to have achieved excellent results, with significant decreases in wait-list mortality.[1] The greatest impact of LDLT has been in Asian countries, where cadaveric organ donation has been uncommon or non-existent.[2] LDLT using left-lobe grafts was introduced for adult recipients in 1993,[3] but this procedure did not become widespread owing to the inability of these relatively small-sized grafts to meet the metabolic demands of all adult recipients. To overcome the inadequate graft volume encountered with left-lobe grafts, transplantation with right-lobe liver grafts was introduced for adult recipients in 1996.[4] Although this method rapidly led to the worldwide use of adult LDLT, right-lobe hepatectomies are associated with a greater surgical risk for live donors than left-lobe hepatectomies, and are associated with increased morbidity and mortality rates, owing to the reduced volume of remnant liver in the donor.[5] In LDLT, donor safety is of paramount importance and cannot be compromised regardless of the implication for the intended recipient. Moreover, the absence of hepatic venous drainage to the right anterior sector has led to the right-lobe graft congestion and failure.[6] Although graft size is critical for successful outcomes, the importance of uniformly good venous drainage of the anterior sector of the right-lobe liver graft has been regarded as crucial for maximizing graft function. Not all potential donors can donate their right-liver lobes because safe donation is possible only when the estimated remnant liver volume is more than 30%.[7] If the volume of the right lobe in potential donors is more than 70%, relative to the volume of the whole liver, one alternative may be dual left-lobe graft LDLT, in which smaller left-lobe grafts from two donors are transplanted into one recipient. This technique was first introduced in 2000 to minimize donor risk and alleviate the small-size graft problem.[8] This review assesses current technical innovations, summarizes outcomes and discusses the ethical dilemmas associated with adult LDLT.

Evolution and current status of adult LDLT

In contrast to Western countries, most (90%) organs for liver transplantation in Asian countries come from live donations because cadaveric organ donation rates in this region (below 5 per 1 million population per year) remain among the lowest in the world.[2] The low

organ donation rates in Asia are due, at least in part, to deeply rooted cultural beliefs, including the Confucian tenet that respects bodily integrity after death. There is still a lack of understanding and acceptance among the general public of the concept of donating body parts for reuse by transplantation. The need to resort to living-donor liver donation arose as a natural response to the critical shortage of cadaveric organs and the increasing demand for liver transplantation in Asia, where the incidences of hepatitis B virus-related end-stage liver disease and hepatocellular carcinoma (HCC) are quite high.[9,10] The anatomic classification of the liver described by Couinaud has been universally accepted as the reference system for describing grafts for living donation (Fig. 1), with five distinct anatomic grafts used for adult LDLT.[11] These include: the right liver lobe (Couinaud segments V–VIII), comprising 60–70% of the volume of the whole liver; the left liver lobe (Couinaud segments II–IV), comprising 30–35% of the whole liver volume; the left lateral sector (Couinaud segments II–III), comprising 20% of the whole liver volume; the left lobe and caudate lobe (Couinaud segments I–IV); and the posterior sector graft (Couinaud segments VI–VII).[12] The liver is the largest solid organ in the human body, constituting 2% of total body weight. In transplantation or resectional surgery, it is necessary to implant or retain 50% of the volume of the entire liver, a liver mass equivalent to 1% of the body weight, to maintain the basic metabolic functions of the liver during the immediate postoperative period. Either the graft-to-recipient weight ratio (GRWR) or the graft volume as a percentage of the

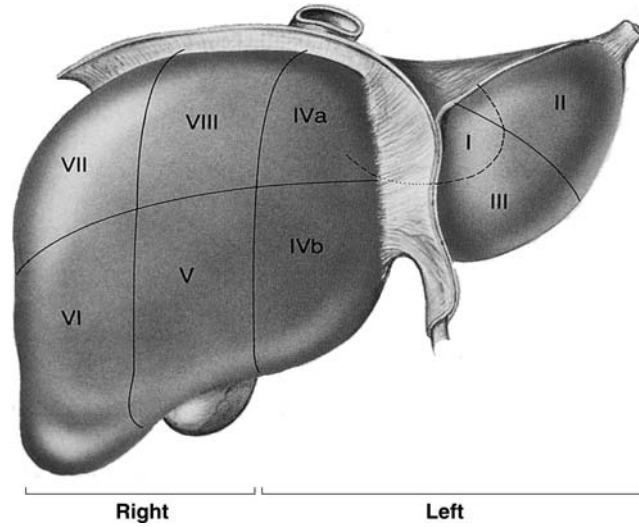


Fig. 1 Anatomic classification of the liver by Couinaud is universally accepted as the reference system for describing grafts created by live-donation techniques.

standard (whole) liver volume for the recipient (GV/SLV) is used to assess the size matching between the liver graft and the recipient. GRWRs of 1.0% and 0.8% are equivalent to GV/SLV ratios of 50% and 40%, respectively.[13] In analysing graft function, a variable degree of post-transplant liver dysfunction has been observed when the GRWR is <1.0% or when GV/SLV is <50%. Early on, it became clear that the left lateral sector, which comprises ~20% of the entire liver volume and is the liver graft used most often for paediatric LDLT, did not provide a hepatocyte mass adequate for successful transplantation in adults. It was therefore necessary to harvest either the left or right liver lobes, which are equivalent to 35–40% and 60–70%, respectively, of donor total liver volume.[1] Thus, right lobe harvesting has significantly increased the extent of donor surgery. The first successful adult LDLT, in Japan in 1993, involved transplanting a left-lobe graft.[3] Initial experience in Western countries with left-lobe LDLT for adult recipients, however, yielded poor results, because the average adult body is not suitable for utilization of the left-lobe grafts, which are largely restricted to recipients weighing <60 kg[11]. If the donor body size is smaller than the recipient body size, the left liver lobe of the donor would likely not provide the recipient with a sufficient liver mass, corresponding to a GV/SLV of more than 40% or a GRWR of more than 0.8%. Many recipients of relatively small partial grafts later developed small-for-size graft syndrome, which is characterized by prolonged cholestasis and increased ascites production.[14] Small-for-size graft syndrome may resolve with supportive care and time, or be irreversible, leading to the patient death. The increasing awareness of the importance of graft volume and deficient graft-recipient weight ratios led to the introduction of successful adult right-lobe LDLT, beginning in May 1996.[4] Right-lobe LDLT enables donations from donors similar in size or smaller than recipients, and has markedly increased the performance of LDLT throughout Asia. In 1997, the first successful right-liver LDLT for adults in Korea was performed at the Asan Medical Center,[15] and in 1998, the first right-liver LDLTs for adults in Japan and Europe were performed at Kyoto University[14] and by the Essen group,[16] respectively. The increasing shortage of cadaveric grafts in the USA has also increased the need for adult LDLT. The first right-liver LDLT in North America was performed at Colorado University in 1998.[17] Although the use of adult LDLT has rapidly increased throughout the world, with encouraging results, the most significant ethical consideration in this procedure is donor risk, which has been associated with the extent of hepatic resection. Donations are regarded as safe when the estimated remnant liver volume exceeds 30% of the whole liver volume.[7] Beyond the safe limit, the remnant liver loses its ability to compensate, regenerate and recover. The latest results on mortality

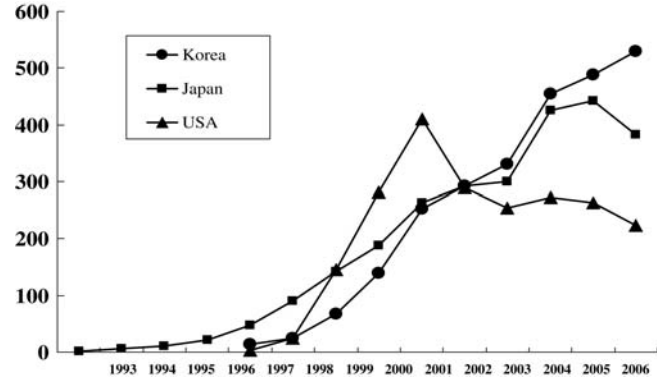


Fig. 2 Number of the changes of adult LDLT in Korea, Japan and the USA.

of live donors from Europe, Asia, and North and South America indicate that donation of a right lobe is associated with an increased risk of mortality.[18] And that liver insufficiency associated with greater extent of resection is the main cause of donor deaths and other serious complications. Since 2002, the number of adult LDLTs has declined rapidly in the USA[19] and Europe[20] due to increased public awareness of the possibility of donor death. In Asia, however, where the supply of cadaveric grafts remains scarce and the necessity of liver transplantation has increased, the demand for adult LDLT has continued. According to the Korean Network of Organ Sharing (KONOS), the number of adult LDLTs (patients aged >18 years) has increased annually, with 502 transplantations performed in Korea in 2006 compared with 383 in Japan and 223 in the USA[18] (Fig. 2). In 2006, the European Liver Transplantation Registry[19] reported that 116 LDLTs, in both children and adults, were recorded, with annual declining trends. Between 1990 and 2003, LDLT was reported to account for ~3% of all total liver transplantations performed throughout Europe.[21] At present, LDLT is thought to account for <5% of all liver transplants in the USA, compared with more than 90% in Asia.[22]

Advantages and disadvantages of adult LDLT compared with cadaveric whole-size liver transplantation

The donor and the recipient surgical procedures involved in adult LDLT are considerably more complex than for whole-organ deceased-donor transplantation. Unlike resectional surgery for liver tumours, the portion of the liver to be removed from the donor must be handled with extreme care. Surgery on the recipient for a partial liver graft,

particularly a right-lobe graft, is quite different and technically more demanding than for standard whole-organ transplantation. Considerable challenges, including multiple biliary and hepatic venous reconstructions, make this procedure particularly difficult.[23,24] Despite these technical complexities, organs from live donors have many potential advantages over those from brain-dead donors. First, organs from live donors enable the optimal timing of transplantation and release patients from the waiting list, especially patients with liver tumours and those with highly urgent conditions such as acute liver failure and acute-on-chronic liver failure. Second, live donors have normal liver function, making the quality of living-donor liver grafts uniformly good. Third, because the donor and the recipient undergo surgery simultaneously in the same operating suite, preservation time of the organ is minimal with significantly less damage to the liver graft. Therefore, primary non-function of the graft is rare, with an incidence of 0.13%. Fourth, LDLT increases the global pool of transplantable organs, allowing more patients to benefit from this life-saving strategy.

However, adult LDLT has several disadvantages, which should be considered carefully. A variety of complications can occur after resectional surgery of the liver. A right-lobe hepatectomy, in which 60–70% of the whole liver volume is removed, is a significant undertaking even for the most experienced surgeons. The greater the amount resected, the greater the risks of liver insufficiency and death. The risk of donor mortality after a left lateral sector or a left-lobe donation has been estimated to be ~0.1%, whereas the risk to right-lobe donors has been estimated at ~0.4–0.5%.[25] The morbidity in these healthy donors cannot be regarded as low and death has really occurred even in a few large-volume centres. In large-volume centers, however, donor morbidity rates are surprisingly low and donor mortality rates are zero. Liver functional reserve and the ability to regenerate are adversely affected by many factors, including age >50 years, steatosis >20% and other underlying hepatic pathologies. LDLT is also associated with increased risks to the recipient. It is technically more complex than whole-size cadaveric transplantation because partial grafts have smaller and shorter hepatic arteries and bile ducts. The incidences of biliary complications and hepatic venous outflow obstruction are greater with right versus left lobe grafts, probably due to the higher incidences of multiple bile ducts and hepatic venous openings in the former.[23] Small-for-size graft syndrome is only seen with adult LDLT when a recipient does not receive a sufficient functioning liver volume (Fig. 3). Size matching is a major challenge in adult LDLT. In addition, graft regeneration is most often required in the setting of adult LDLT. By transplanting only 50–60% of the standard (whole) liver volume into an adult recipient, even with a right liver lobe, recipients must rely on

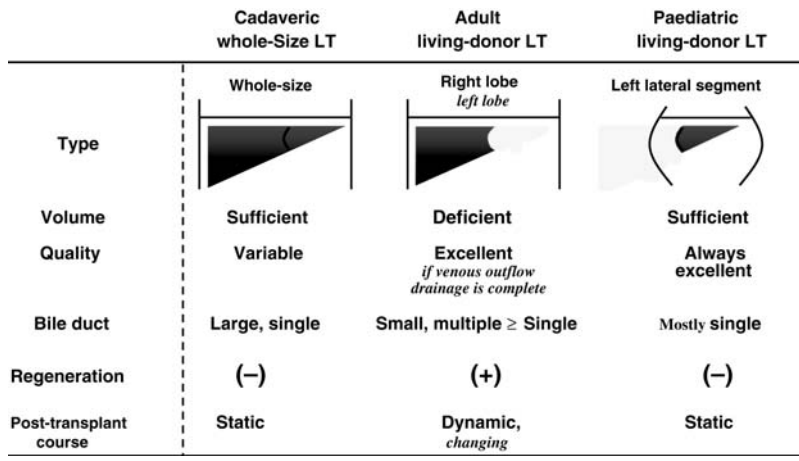


Fig. 3 Unlike cadaveric whole size and paediatric LDLT, size matching and higher incidence of biliary complication are major challenge in adult LDLT.

the rapid repair and regeneration capacity of the implanted partial liver to meet the metabolic demands of operative stress during the immediate postoperative period. There are many unanswered questions relating to the effects of liver regeneration on the risk of recurrence of the recipients' original diseases.[26] The regenerating liver may accelerate viral replication, particularly of hepatitis C virus, or tumour growth of HCC, leading to early and more aggressive recurrence after transplantation. Finally, adult LDLT procedures are more labour-intensive than cadaveric whole-size transplantation; the operation time is longer, and two teams of highly experienced surgeons, working concurrently, are necessary, one to perform the donor and the other to perform the recipient procedures.

Expanded indications for adult LDLT

LDLT has undergone an evolution from paediatric transplantation using left lateral sector grafts to adult transplantation mainly using right-lobe grafts. Naturally, the major indications for LDLT have expanded from biliary atresia and certain metabolic disorders to a variety of adult liver diseases, particularly hepatitis virus-related liver diseases with or without HCC. LDLT has also affected the timing of surgery, allowing urgent transplantation for acute (fulminant) liver failure or acute deterioration of chronic end-stage liver disease (acute-on-chronic liver failure). The encouraging outcomes of both donors and recipients are important to the expansion and overall success of this procedure. The current survival statistics for adult LDLT

are satisfactory for right-lobe grafts. Overall 1-year graft survival rates were 81% for the A2ALL Study Group in the USA[27] and 93.3% for both the Hong Kong[28] and Asan Groups, although these high rates may, at least in part, be due to the selection of recipients considered most likely to experience favourable outcomes.

LDLT in high-urgency situations in adults

Acute liver failure and acute-on-chronic liver failure are considered to be highly urgent conditions for liver transplantation. Owing to the scarcity of cadaveric liver grafts, the mortality rate for these patients on the waiting list for cadaveric grafts often exceeds 90%, especially in Asian countries. The results of emergency LDLT have been considered inferior to those of elective transplants, owing to the small size of partial liver grafts and the poor premorbid status of patients.[29] Nonetheless, since the first such procedure in 1999,[30] LDLT has emerged as a life-saving procedure in adult patients in high-urgency situations. Although emergency LDLT using right-lobe grafts for patients with acute liver failure who had a healthy liver before deterioration results in satisfactory survival, poorer survival outcomes have been reported for patients listed as status 2a according to the United Network for Organ Sharing classification system (i.e. acute-on-chronic liver failure) because these patients are chronically ill, with many having severe cirrhosis with portal hypertension. The reported 1-year survival rate of these patients was ~50% in Western countries, which is far inferior to the rates of 73–88% reported for patients undergoing elective LDLT.[31] The main argument against urgent LDLT for patients with acute-on-chronic liver failure is that risks taken by the donor are not justified owing to the poor graft and patient survival results. However, experiences of the Hong Kong and Asan groups have indicated that size matching, near 1.0% GRWR or 50% GV/SLV, and adequate hepatic venous drainage of the liver graft can result in survival rates for these critically ill patients that are similar to those observed after deceased donor liver transplantation.[21,30] The use of LDLT in high-urgency situations in our institution increased the transplantation rate from 5% to 75% and the patient survival rate from 5% to 85%, compared with rates in patients who did not opt for LDLT.[32] The average times from listing to donor evaluation (1 day) and from donor evaluation to transplantation (2 days) also showed that LDLT could reduce waiting times and provide optimal timing for transplantation. In emergency cases, donor work-ups, including liver biopsy, can be completed in half a day. Urgent LDLT is justified for these seriously ill patients if donor surgery can be performed with minimum risk, donors provide voluntary informed consent, the timing of

transplantation is not too early or too late, and recipient outcomes at that centre for emergency LDLT are similar to those for cadaveric whole-organ transplants.

Expanding indication of HCC for LDLT

HCC is one of the top five causes of cancer deaths in Asian countries, and more than 80% of cases develop in cirrhotic livers. Liver replacement in patients with HCC is theoretically ideal, removing the entire liver, which is at risk for synchronous or metachronous HCC, and restoring liver function. Early experiences in transplanting patients with HCC often resulted in poor outcomes owing to the inclusion of patients with advanced tumours. Applying restrictive selection criteria, the so-called 'Milan criteria', which limit transplantation to patients presenting with a single HCC <5 cm in diameter or 2–3 lesions <3 cm in diameter, resulted in a 4-year survival rate of 75%.[33] These results have been validated by many other centres and are the basis for current cadaveric organ allocation policies, affording priority to patients with HCC who are on the liver transplantation waiting list in the USA. However, many HCC patients who would be excluded because they do not meet the Milan criteria could survive for long periods of time after transplantation. Many have argued that the Milan criteria are too restrictive and that they can be expanded without increasing HCC recurrence or decreasing patient survival rates. The application of the Milan criteria in selecting patients at low risk for tumour recurrence was predicated on cadaveric organ donation, where the timing of transplantation cannot be controlled by restricted graft allocation. If we strictly applied the Milan criteria to our patients, we would have excluded many patients who remained alive after transplantation. With LDLT, liver grafts can be considered as private gifts instead of a public resource. Expanded criteria for patient selection are, therefore, acceptable and necessary in LDLT. A group from the University of California at San Francisco (UCSF) retrospectively analysed 70 patients presenting with a single tumour <6.5 cm in diameter, or two lesions each <4.5 cm in diameter and with a total tumour diameter <8 cm[34]. They reported a 5-year patient survival rate of 75%, although the number of patients who did not meet the Milan criteria but were within these new criteria was not reported. On the basis of a retrospective analysis of 221 LDLT patients with HCC, the Asan group indicated that the minimal criteria for transplantation could be expanded to £6 nodules with the largest tumour diameter £5 cm and the absence of gross vascular invasion.[35] Of these 221 patients, 186 met these criteria, with an actuarial 5-year survival rate of 76.3%. In

contrast, the 35 patients who were outside of these criteria had a 5-year survival rate of only 18.9%. By expanding the Milan criteria, 22 (10%) patients benefited from long-term survival, which is similar to the rate of patients who met the Milan criteria. Because many patients who did not meet the Milan criteria survived without tumour recurrence after transplantation, different patient selection criteria are necessary in LDLT to save those patients with advanced HCC.

Guidelines for safe donor selection

The practice of adult LDLT is self-perpetuated because, as outcomes improve, more people become aware of the feasibility of this treatment option, which encourages donors to volunteer. Donor risk, however, has not yet been eliminated completely, and the main issue is the justification of donor risk relative to recipient benefit.[36] Therefore, strict donor selection criteria are required for successful LDLT in adult patients.[37] Potential donors for right-lobe hepatectomy must be healthy volunteers between the ages of 18 and 55 years. Older donors have an increased risk of occult medical problems, and their livers may have reduced regenerative capacity, which can affect both the donor and recipient outcomes. Donors should have normal liver function and no medical comorbidities. In paediatric LDLT, there is essentially no concern with regard to the donor's remnant size because left lateral sector grafts (Couinaud segments II and III) generally constitute 20% of the donor's whole liver volume. There have been occasional recipient deaths from the use of left-lobe grafts, due to small-for-size graft complications; therefore, many centres now routinely use right-lobe grafts to provide more actual graft mass for the recipient. Exclusion criteria for right-lobe liver donations for adult recipients are remnant liver volume $<30\%$ of the entire liver volume, $>10\%$ fatty changes in the liver, and BMI >30 kg/m^2.[25] In analysing the reasons for donor death after adult LDLT, liver insufficiency due to large resection was found to be the main cause of complications. Therefore, preoperative volumetric measurements of the future remnant liver, combined with estimations of liver quality, especially fatty changes, by preoperative ultrasound-guided liver biopsy, must be assessed prior to the right-lobe donation. Even minor fatty changes of the liver ($<30\%$ steatosis) have been shown to have significant adverse effects for the donors after right-lobe grafting, especially if the remnant liver volume is between 30% and 35%.[38] Donor morbidity and mortality are significant issues for all concerned with adult LDLT. In our institute, which has performed more adult LDLTs than any other single centre in the world, the high donor morbidity rate recorded during the learning period has

been substantially reduced with increased experience. Since 2002, the perioperative annual major morbidity rate (>Claviens classification grades III and IV) has declined from 6.7% to 1.3%.[37] There have been no donor deaths from any of the 1750 adult LDLTs performed. The low morbidity rate and 0% mortality rate of donors were likely due to our extensive experience in hepatobiliary surgery. In Asia, where the incidence of HCC in cirrhotic livers is high, most liver transplant teams benefit from prior and continuing experience in liver resections, which has helped consolidate their expertise.

Technical refinement for liver graft

Overall, for adult LDLT, better results have been obtained with right versus left-lobe grafts because right-liver grafts can help alleviate the problem of graft size insufficiency in adult patients. Even with larger right-lobe grafts, however, the small-for-size graft syndrome may still occur. The unexpected occurrence of this syndrome, despite adequate actual graft volume, led to our understanding of the critical importance of the venous outflow drainage of the liver graft in the determination of functional graft size.[6] Adequate hepatic venous outflow is essential for both the function and regeneration of the liver graft. Although graft size is critical for successful outcomes, a uniformly good venous drainage of the anterior sector (segment) of the right hemiliver graft is important for maximizing the functioning liver graft mass. An extended right-lobe graft, which includes the trunk of the middle hepatic vein, has been found to enhance venous drainage of the graft because the middle hepatic vein is the major drainage vein of the anterior sector (Fig. 4).[4] Because this procedure was thought to increase the extent of donor surgery by introducing some congestion to the remnant liver, a right-liver graft without the middle hepatic vein trunk was commonly used (Fig. 4). In the absence of hepatic venous drainage to the right anterior sector, however, graft congestion and failure occurred in the right-lobe graft. Therefore, hepatic venous drainage of the anterior sector can be reconstructed using an interposition vein graft[6] (Fig. 4). Approximately 85% of the right-lobe grafts performed by the Asan group involved reconstruction of the hepatic venous tributaries of the anterior sector. Transplantations of right-lobe grafts with the appropriate middle hepatic vein drainage, by retaining the middle hepatic vein trunk (extended right-lobe graft) or using a jumping interposition graft (modified right-lobe graft) from live donors, has resulted in graft survival rates similar to those observed with cadaveric whole-size liver grafting.[28] This is particularly crucial for patients with acute-on-chronic liver failure with poor functional reserve, as it provides sufficient functioning liver

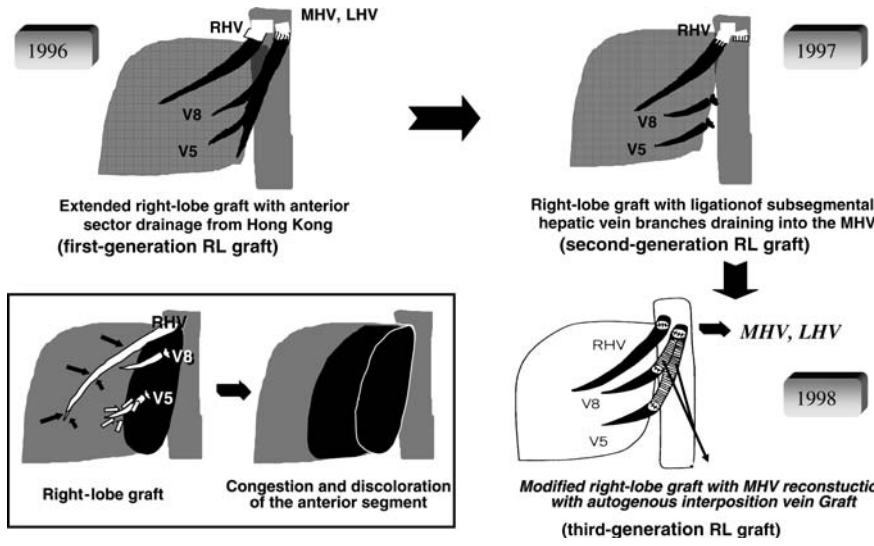


Fig. 4 Evolution of a right-lobe liver graft concerning hepatic venous outflow drainage of anterior sector. RHV, right hepatic vein; MHV, middle hepatic vein; LHV, left hepatic vein; RL, right lobe; V8, segment 8 hepatic vein; V5, segment 5 hepatic vein.

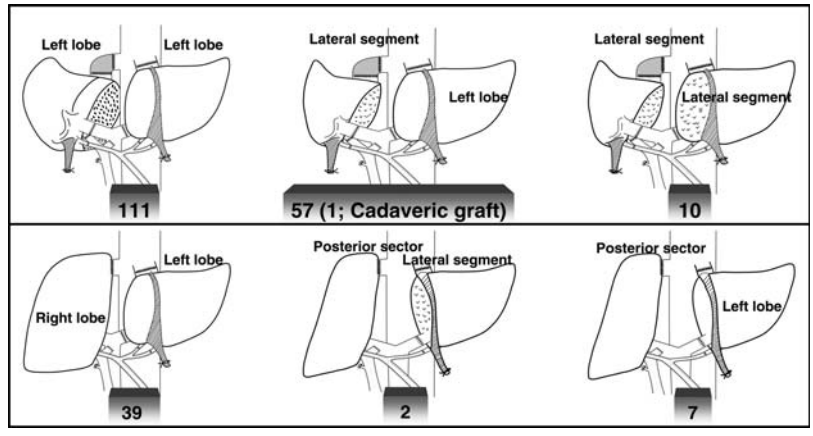
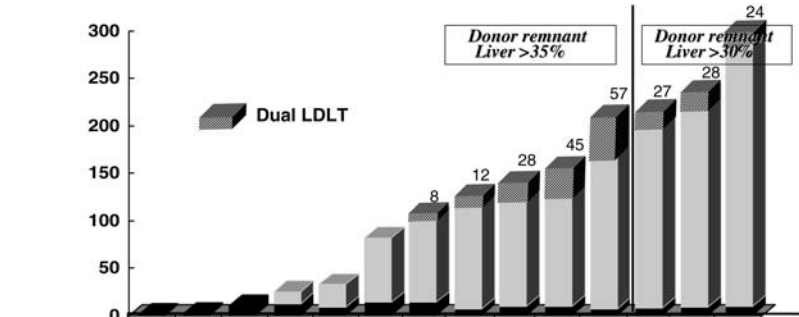


Fig. 5 From March 2000 to December 2007 at the Asan Medical Center, 226 dual adult LDLTs were performed. One recipient received a left lobe from a live donor and a split lateral segment from a deceased donor in June, 2000. A right lobe (from a spouse) and a left lobe (from a cousin) dual LDLT for a large recipient was successfully performed in April 2001.

volume with good venous drainage to meet the high metabolic demands of the recipients. Size matching is a major challenge in adult LDLT, and the goal is to provide adequate graft mass to the recipient while leaving sufficient remnant liver in the donor for donor safety. Grafts can be designed to meet the graft-recipient size matching. In a study by the Tokyo group, 25% of the potential donors had a large right lobe, which



Year	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	Total
Adult to adult	0	0	0	12	24	68	91	116	127	142	203	206	225	276	1494
Paediatric	2	3	11	13	9	14	14	7	10	10	7	8	9	10	122

Fig. 6 Annual number of LDLTs at the Asan Medical Center, Ulsan University College of Medicine. Until 2004, the accepted remnant liver volume was >35% of the total liver volume of the donor, which was changed to >30% in 2005.

accounted for more than 70% of the whole liver volume.[39] Safe donation is possible only when the estimated remnant liver volume is over 30%; hence, right-lobe donation would be dangerous in this donor population. Dual-graft LDLT, or transplantation from two donors into one recipient, was initiated to overcome graft-size insufficiency and to minimize donor risk. Two left-lobe grafts are usually implanted, although various other combinations have been transplanted[40] (Fig. 5). Indications and survival outcomes of dual LDLT are similar to those of single right-lobe LDLT. Although these surgeries are complex, they can provide an adequate graft mass for larger recipients who would otherwise be ineligible if only one donor was considered. By using a dual-transplantation programme, a 20% increase in the number of adult LDLTs can be anticipated (Fig. 6).

Conclusions

Over the past 16 years, adult LDLT has evolved to become an indispensable surgical strategy to minimize the mortality of patients awaiting transplantation. The crucial prerequisite to performing this procedure is minimal morbidity and zero mortality risk to the healthy live donors. Recipient outcome is a strong determinant of the donor's well-being. Because donor surgery can now be performed with minimum risk, and because patient outcomes have improved and public awareness increased, live liver donation is increasingly feasible. Until more cadaveric grafts become available, adult LDLT will

continue to be a relevant therapy for patients with irreversible end-stage liver disease.

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