Living donor liver transplantation: present status and recent advances

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The first successful living donor liver transplantation (LDLT) was performed in a child in 1989 in Brisbane and in an adult in 1994 by the Shinshu group. Over the past few years, LDLT has increased worldwide and is now an established alternative to deceased donor liver transplantation. The surgical procedures for LDLT are more technically challenging than those for whole liver transplantation. LDLT requires a full understanding of the hepatobiliary anatomy and continuous technical refinement of the procedure. Some of the technical highlights include selective vascular occlusion techniques for donor hepatectomy, hepatic arterial reconstruction under the microscope and the introduction of intraoperative ultrasound, graft volume estimation and hepatic venous reconstruction, all of which have improved the success rate of LDLT over the past few years. This review focuses on recent trends and surgical techniques for LDLT.

Keywords: live donor, hepatitis C virus, hepatocellular carcinoma.

Introduction

The most effective therapy for end-stage liver disease is transplantation. Improved surgical techniques and the introduction of new immunosuppressive agents have enhanced the long-term results of liver transplantation, leading to an increased demand for liver transplantation that exceeds the number of potential donor organs. The disparity has reached a critical level (Fig. 1).

Split liver transplantation [1] has had such a dramatic effect that it has reduced pediatric waiting-list mortality to almost zero [2]. The situation is different, however, among adults. Liver transplantation from living donors (LDLT) is currently the most effective alternative to overcome the problem of organ shortage for adults. In 1987, the first recipients in Brazil failed to survive beyond the early postoperative period [3]. In Australia in 1989, Strong et al. [4] successfully performed LDLT using a left lateral segment from a mother to her son. This success led to a number...
of early reports of this technique in both United States [5] and Japan [6]. The results of LDLT are now comparable with those of whole liver transplantation from deceased donors (DDLT).

In this review, we discuss the surgical procedures and outcomes associated with the recipient and donor. We also describe current trends and controversies in LDLT, including its role in patients with hepatitis C virus (HCV) and in individuals with hepatocellular carcinoma (HCC).

**Current status and trends of LDLT**

The relation between LDLT and DDLT in Eastern versus Western countries is opposite. The most extensive experiences with LDLT were initially made in Asia. In Korea, 985 LDLTs were performed between 2001 and 2003 [7]. In contrast, the number of DDLT was limited to 115 during the period. In Japan, 2667 patients underwent LDLT by the end of 2004 [8]. The organ transplantation law was enacted in 1997, and DDLT is expected to be established soon in Japan; however, there were only 26 DDLT by the end of 2004. At first, LDLT was regarded as a temporary and emergent procedure until DDLT could be established in Japan; however, LDLT is now the major procedure performed for end-stage liver failure. This situation is peculiar and is not the case in Western countries. Since January 2003, most LDLT procedures have been covered by medical insurance, which has also increased the number of LDLTs (Fig. 2).
According to the Japan Liver Transplantation Society, the number of adult patients (≥18 years) has increased annually and reached 300 in 2003. In contrast, the number of pediatric patients (<18 years) was stable at approximately 100–150 cases per year. The 1-, 3- and 5-year survival rates of adult patients were 76, 72 and 69%, respectively. Those of the pediatric patients were 86, 84 and 83%, respectively, which were significantly higher than those of adults. The most common indication for adults was hepatocellular carcinoma (n = 311) followed by primary biliary cirrhosis (n = 255) and HCV-related cirrhosis without carcinoma (n = 113).

In the United States in 2000, there was a high level of enthusiasm for adult LDLT, with 49 centers performing at least one LDLT. The enthusiasm was, however, quickly tempered by the death of a donor in 2002 in the United States [9]. Since 2001, the number of patients who have undergone LDLT has declined [10]. By July 2005, 2734 LDLT cases were performed. The 1-, 3- and 5-year survival rates of adult patients were 89, 80 and 80%, respectively [11]. There were 1761 adult patients, and HCV was the most common indication.

Between 1990 and 2003, 1473 LDLT cases were recorded in the European Liver Transplantation Registry [12]. LDLT accounts for approximately 3% of the total liver transplantation performed in Europe during the period and is established as an alternative to conventional whole DDLT. Among the 806 cases from October 1991 to December 2001 [13], the overall 5-year graft survival rate was 75%, better for children than for adults (80 versus 66% at 3 years).
Donors

Evaluation and selection

The goal of donor evaluation is to determine whether the donor is medically and psychologically suitable for living donation. All living donor candidates should undergo a psychosocial evaluation to determine whether there is coercion and whether they truly understand the risks of the procedure. According to a recent report [14], for the adult recipients, only 89 (14%) potential donors were considered suitable, with 533 (86%) potential donors rejected. Donors are usually between 20 and 65 years. In the Western countries, the donors can be accepted if they are voluntary to donate the liver. However in Japan and Taiwan, the relation to the recipient is usually limited within the second to third degree of consanguinity. Donors should not have liver disease or significant comorbidities, such as coronary artery disease or cerebrovascular disease. The presence of mild systemic diseases, such as well-controlled mild hypertension or diet-controlled diabetes, is not necessarily a contraindication to donation.

Obese individuals should be excluded as living donors because of possible postoperative complications due to obesity or to the presence of hepatic steatosis. Some centers perform liver biopsies on all donor candidates, while other centers rely upon physical examination, risk factors of hepatic steatosis and imaging studies [15, 16]. In our institution, liver biopsies are performed when body mass index is >25, and Miller et al. [17] suggested that liver biopsy is necessary when body mass index is >28. Indication of liver biopsy for screening steatosis in the donor candidates seems to be controversial. Ryan et al. [18] persuaded that liver biopsy should be routinely performed irrespective of body mass index level or image findings, which are poor indicators for steatosis. However, we must note that liver biopsy can be accompanied with severe complications including intraparenchymal hematomas [19]. The degree of steatosis acceptable for LDLT, however, remains controversial. Marcos et al. [20] reported that function was not impaired in donors or recipients when grafts containing <30% steatosis were used. Fan et al. [21] did not use a right liver graft with steatosis of 20% or more, whereas other groups used liver grafts with steatosis of <50% if the graft volume to standard liver volume (SLV) ratio of the recipient is at least 40%[22].

Evaluation of vascular and biliary anatomy can be achieved noninvasively with computed tomography and magnetic resonance cholangiopancreatography. The approach varies from center to center, but invasive angiography is not generally performed [16]. Less than half of the donors who present for evaluation are suitable candidates that eventually proceed with LDLT [15, 16].
Liver harvesting—left or right?

Determining whether the recipient is receiving an adequate hepatic mass is a key component to LDLT evaluation. In general, a graft to body weight ratio of 0.8% [16] or 40% [21] of the recipient’s SLV is recommended as the minimum cut-off for the recipient. The graft volume is typically determined with computed tomography. In initial LDLT, only a left lateral (segments II and III) or left liver graft (segments II–IV) was used [23]. The results were not satisfactory, however, and some transplant surgeons suggested that the results were due to undersized grafts that might not have met the metabolic demands of the patient [24]. Accordingly, recent reports indicate that left liver grafts for adult patients have now been almost abandoned and right liver grafts (segments V–VIII) are routinely used [25]. We do not agree with the recent tendency to use a right liver graft routinely for almost all adult patients. In our institution, the left liver is considered acceptable as a graft when it is estimated to be >40% of the recipient SLV. Otherwise, right liver harvesting is indicated, provided that the estimated right liver volume is <70% of the donor’s SLV.

Surgical procedure

After cholecystectomy, hilar dissection is performed. For left liver grafts and right liver graft, liver parenchymal transection is conducted along the main portal fissure to the right side of the middle hepatic vein. The transection plane for the extended right liver graft is along the right portal fissure and to the left side of the middle hepatic vein. After completion of the liver parenchymal transection, intraoperative cholangiography is performed through a tube inserted into the cystic duct. The right and left hepatic ducts are identified and divided together with their perivascular connective tissue. When harvesting the graft, the principal portal vein, principal hepatic artery and principal hepatic vein are divided in that order, for each type of graft.

Morbidity

A wide range of complication rates are reported in the literature in donors after LDLT. Overall complication rates range from 0 to 67%, with an overall crude complication rate of 31% [26]. Because of the wide variation in complication rates and lack of uniform criteria used by centers for defining complications, a standardized system for reporting complications should be used. The Clavien system [27] can be applied to complications after LDLT. According to a recent series [28]
of 101 donors who underwent right liver resection, overall morbidity rate was 37%; all complications were either grade 1 or 2 of Clavien’s classification, and the majority occurred during the first 30 days after surgery.

Biliary complications are reported in 0–7% of donors, including bile leaks and strictures. Complications related to major abdominal surgery occur in 9–19% of donors, including wound infections, small bowel obstruction, pneumonia and incisional hernia. According to a national survey in Japan [29], 244 postoperative complications were reported in 12% of donors (228/1853). The frequency of complications was significantly higher in donors of the right liver graft than in those of left-sided grafts. Re-operation was performed in 1% of the donors.

**Mortality**

In 1999, Strong [30] reported that six persons died because of liver donation but did not specify the causes. In the United States, at least three deaths were confirmed. One donor died from complications of aspiration pneumonia [9]. One donor died of recreational drug use or suicide 23 months after donation [31]. The other was not reported in detail [2]. Another three deaths in Europe [32, 33] and one [34] in Japan have been reported. Although three of the seven deaths might have also been reported in Strong’s report [30], at least 10 donors have died, resulting in a mortality of 0.15% (10/6450).

**Regeneration**

It is well known that liver regeneration can be expected after right liver harvesting. Marcos et al. [20] assessed the regeneration prospectively by volumetric magnetic resonance imaging in living right liver donors and showed that the regeneration occurs in the first week after resection. More recently, it was suggested that the functional recovery occurs much more gradually than the recovery of volume and liver biochemistries [35].

Regeneration occurs also in the recipient postoperatively. Initial reports suggested that over 85% of hepatic volume was restored 1 week after transplantation [20]. Based on magnetic resonance imaging of the abdomen, the left liver increases in mass by 100% in the donor and the right liver increases by 87% in the recipient, but subsequent studies suggest that regeneration continues over 6 months [36]. Liver regeneration is rapid and might be affected by the severity of liver disease prior to transplantation and the type of reconstruction performed with the middle hepatic vein.
Quality of life

Studies assessing donor quality of life after LDLT demonstrate no evidence of significant psychologic impairment after donation [37]. More positively, donors did not regret their decision to donate; several felt the experience had changed their lives for the better [38], they would donate again, irrespective of recipient outcome [39]. Ninety-six percent of donors were able to return to work 10 weeks (mean) after surgery. Seventy-one percent of donors reported abdominal symptoms several months after surgery, which they attributed to the surgery [37].

Recipients

Indications

In areas with low deceased donor organ availability, the indications for LDLT should be similar to those for deceased donor transplantation. In contrast, in Western countries, LDLT is conducted in an attempt to alleviate the shortage of donor organs and to decrease the mortality among the patients awaiting transplants. That is, a balance needs to be achieved between the candidate’s liver disease severity and the adequacy of a partial graft for transplantation. The candidate’s liver disease should be advanced so that transplantation is justified, but the liver disease cannot be too advanced so that a partial graft will not provide adequate hepatic mass.

According to Russo and Brown’s report [40], a substantial proportion of patients were United Network for Organ Sharing (UNOS) status 3 at the time of LDLT (43%). The policy at their centers prior to the implementation of model for end-stage liver disease (MELD)-based allocation was not to proceed with LDLT in patients meeting UNOS status 2A criteria. Their patient survival rate was 57%, with an average stay of 23 days in the intensive care unit. In comparison, 1-year patient survival rate was 82% in DDLT recipients who were UNOS status 2A at the time of transplant [41].

The waiting-list mortality increases in patients with advanced liver disease, and patients with an MELD score of 25 have a 20% 3-month mortality [42]. In general, it is uncommon to proceed with LDLT in patients with MELD scores >25. Thus, depending on the region of the country and the average MELD score at the time of transplant within the area served by the organ procurement organization, LDLT might offer patients transplantation before they die waiting for a deceased donor liver. The lower MELD score limit with LDLT is more controversial and varies from center to center. Russo and Brown [40] commented that they did not proceed with LDLT in candidates with MELD scores <11.
The surgical technique for recipients is based on whole liver resection, with preservation of the inferior vena cava used for whole DDLT [43]. We believe that it is important to make a large and long opening along the sides of the hepatic veins and important to maintain satisfactory portal, biliary and hepatic arterial sources for the reconstruction. Right and left hepatic arteries should be dissected out as distally as possible, and the left portal vein should be dissected up to the umbilical portion, just distal to the point of origin of the branch to segment II, and the right portal vein up to its bifurcation into the anterior and posterior branches.

Anastomosis is performed in the following order: hepatic vein, portal vein and then hepatic artery. The provision of adequate outflow is indispensable for graft function; thus, it is necessary to obtain a wide ostium and a sufficient length of the hepatic vein for anastomosis. An extended right liver graft is beneficial with regard to venous drainage of the graft because the middle hepatic vein is the major draining vein of the right paramedian sector, and its role in the left paramedian sector is limited [42]. On the other hand, a right liver graft without the trunk of the middle hepatic vein can cause severe congestion of the right paramedian sector (segments V and VIII) without middle hepatic vein reconstruction. To provide a functioning liver mass comparable to an extended right liver, several methods have been devised for middle hepatic vein reconstruction [44].

Portal venous thrombosis, sclerosis and size discrepancy between the graft and recipient’s portal vein are other issues that make it difficult or impossible to perform standard end-to-end anastomosis. These problems are usually overcome by the use of an interposition vascular graft, vascular patch graft or portal venoplasty. Hepatic arterial reconstruction in LDLT is technically difficult due to the existence of short and thin hepatic arteries on the liver graft. The Kyoto group [45] reported the introduction of microvascular surgery to hepatic artery reconstruction in LDLT, although Marcos et al. commented that anastomosis under a microscope is usually unnecessary in adult recipients, especially with a right liver graft [12].

Bile duct reconstruction is usually performed last. The preferred technique in adult LDLT is currently shifting from hepaticojejunostomy to duct-to-duct anastomosis. The procedure might preserve physiologic biloenteric and bowel continuity, thus preventing delayed bowel movement. Duct-to-duct reconstruction allows for endoscopic access to the biliary tree for diagnostic and therapeutic instrumentation and management and prevents ascending cholangitis. Long-term postoperative observations and technical modification are still necessary [46].
Morbidity

Vascular complications, including thrombosis of the hepatic artery and portal vein, might be more frequent than those after whole liver transplantation because of the small size of the vessels anastomosed. The Achilles’ heel of LDLT is biliary complications. Biliary complications, either bile leak or stricture at the anastomotic site or cut edge of the transected liver, are reported in 15–60% of recipients [46, 47]. Stenting of the biliary anastomosis has been used in an attempt to reduce the rate of bile leaks and strictures, but it is of unproven benefit. Complications are probably underreported, and a standardized reporting system has been recommended for LDLT.

HCV

One of the hottest debates is the possibility of increased severity of recurrent HCV infection in LDLT. The association between liver graft from living donors and early HCV recurrence remains to be determined [48], although most of the recent reports suggest that living donor graft has no effect on short-term outcome or severity of virus recurrence. Reports from New York-Presbyterian Hospital [49] indicate that the time to diagnosis of recurrent HCV is significantly shorter in LDLT. Other data indicate that the 5-year survival rate of HCV patients (n = 69) who undergo LDLT is 64%, which is comparable with that of DDLT patients (n = 202, 69%). One study in which protocol biopsies were performed demonstrated no difference in recurrent hepatitis C and graft survival in LDLT recipients compared with a deceased donor control group [50]. An analysis of 279 LDLT recipients with HCV in the UNOS database demonstrated similar patient and graft survival rates compared with deceased donor recipients with chronic HCV [40]. Rapidly progressive, cholestatic HCV reinfection of living donor grafts was known [51], but the risk factor is remained to be examined.

We have performed preemptive therapy for LDLT patients for HCV [52]. From July 1996 to July 2002, 23 patients underwent LDLT for HCV cirrhosis at the University of Tokyo Hospital. All the patients preemptively received antiviral therapy consisting of interferon-alpha2b and ribavirin, which was started ~1 month after the operation. The therapy continued for 12 months after the first negative HCV-RNA test. The subjects were removed from the protocol if they could not continue the therapy for 12 months due to adverse effects or could not start the therapy due to early death. Eight patients were removed from the protocol. The sustained virologic response ratio was 39% (9/16). The ratio of
genotype 1b patients was 32% and that of non-1b was 75%. The cumulative 3-year survival rate of the HCV-positive patients was 85%, comparable with that of patients negative for HCV (n = 93, 90%). The present study is preliminary, but the results warrant a randomized protocol to examine the feasibility of preemptive therapy for LDLT.

The significance of preoperative regimen for HCV has remained unclear. Everson and colleagues [53] reported the result of preoperative low-dose regimen for HCV. The regimen consisted of either interferon alfa-2b (1.5 MU three times a week) or peginterferon alfa-2b (0.5 μg kg⁻¹ week⁻¹) plus ribavirin (600 mg day⁻¹). One hundred and twenty-four patients (70% genotype 1) were treated with the regimen. The mean Child Turcotte Pugh score was 7.4, and 23 of them were Child class C. Of these, 15 patients (12%) were negative for HCV at liver transplantation among which 12 remained (six of them received LDLT) negative 6 months or more after liver transplantation.

HCC

At present, there are no well-defined or universally adopted criteria for potential candidates for LDLT. Because deceased donor grafts are a public resource, while LDLT is a private family matter, the inclusion criteria for LDLT should not be as strict as that for cadaveric liver transplantation. From a medical perspective, if patient or graft survival rates are markedly lower compared with DDLT, then LDLT might be perceived as a failure. Some exclusion criteria, however, regarding the number and maximum size of the tumors might be necessary to obtain satisfactory results after LDLT. In the University Hospital Essen [54], patients with a single tumor not larger than 8–10 cm, or not more than five tumors, none >5 cm in size, and no tumor thrombosis are considered as acceptable. The Barcelona Clinic Liver Cancer Group [55] has proposed expanding the criteria to single tumors <7 cm or, in the case of multinodular disease, three nodules <5 cm or five nodules <3 cm.

According to Todo and Furukawa [56], by the end of 2003, 316 adult patients (246 men and 70 women; median age of 55 years) underwent LDLT in Japan. The median follow-up period was 16 months. Patient survival rate at 1 and 3 years was 78 and 69%, respectively. MELD score and preoperative serum alpha-fetoprotein level were independent risk factors for patient survival. Recurrence-free survival at 1 and 3 years was 73 and 65%, respectively. Serum alpha-fetoprotein level, tumor size, vascular invasion and bilobar distribution were independent risk factors for HCC recurrence. The grade of histologic differentiation of HCC was closely correlated with tumor characteristics and recurrence. Patient survival and disease-free survival at 3 years were both
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Fig. 3 Survival of patients stratified by the Milan criteria who underwent LDLT for HCC in Japan. Black line, within Milan ($n = 138$); gray, beyond Milan ($n = 171$). HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation.

79% in patients who met the criteria and 60 and 53%, respectively, in those who did not (Fig. 3). Similarly, Mt. Sinai Hospital [57] has reported that 36 patients received LDLT for HCC, with a median follow-up of 470 days. Half of the patients exceeded Milan criteria. Intra- and postoperative chemotherapy with doxorubicin was used for tumors $>5$ cm. Two-year recurrence-free survival was 74%. Bilobar distribution was the only significant risk factor for recurrence.

In our estimation, these results failed to justify the present use of expanded criteria for LDLT [58]. At the University of Tokyo, patients were selected based on a tumor number of five or fewer and a maximum diameter of $<5$ cm. Between 1996 and 2004, 235 patients underwent LDLT; of these, 61 had HCC and satisfied our criteria (51 men and 10 women; median age of 54 years). MELD scores ranged from 2 to 34 (median, 13). In explanted specimens, median tumor number was 2.8 and median size was 2.6 cm. During the median observation period of 25 months, two patients died with HCC recurrence and another six died without recurrence. Patient survival rate at 1 and 3 years was 91 and 82%, respectively, which was comparable to that of patients without HCC ($n = 168$, 90% in both, $P = 0.73$).

Ethical issues

Ethicists will undoubtedly debate the risks and benefits to the donors. Major complications and deaths related to an innovative procedure—
especially one involving living, healthy donors—should be reported in
detail in a timely fashion in peer-reviewed journals and ideally to a regis-
try. The establishment of a national registry for LDLT is ongoing as is a
National Institutes of Health sponsored multi-center prospective study
of LDLT at nine centers in the United States.

**Conclusions**

LDLT offers hope to patients with end-stage liver disease in areas where
waiting-time mortality is high and the availability of deceased donor
organs falls short of the population need. There are significant risks to
the living donor, including the risk of death and substantial morbidity,
which must be taken into account before patients, physicians and trans-
plant programs embark in LDLT. There have been significant improve-
mements in outcome over recent years.

**Acknowledgements**

This study was supported by a grant-in-aid for Scientific Research from the
Ministry of Education, Culture, Sports, Science and Technology of Japan
and grants-in-aid for Research on HIV/AIDS, a multicenter pilot clinical
study to compare the safety and efficacy of a steroid-free immunosuppres-
sion protocol with monoclonal anti-IL2R antibody in HCV-positive living
donor liver transplantation and Research on Measures for Intractable Dis-
eases from the Ministry of Health, Labor and Welfare of Japan.

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