

Living Donor Liver Transplantation: Cumulative Insights from Taiwan

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ABSTRACT: This review portrays the living donor liver transplantation (LDLT) scenario in Asia with emphasis on the role played by Taiwan in meeting the objective of offering LDLT as a life-saving procedure in the treatment of end-stage liver disease. In the West, although LDLT has been offered as a solution to overcome the shortage of organs, in the East, liver transplantation is synonymous with LDLT. Endemic hepatitis B and C viral infections remain the most common indication for transplantation in the East. LDLT helps to leverage maximum benefits in patients with hepatocellular carcinoma by a reduction in waiting time mortality and offering scope for adopting more liberal acceptance criteria. Although several challenges unique to this specialty have been faced time and again, there is no denying that LDLT has offered comparable or even better results than that of deceased donor liver transplantation. Minimizing donor risk and ensuring safe donor surgery should be the objective instead of tunnel vision on benefits to the recipient.

KEYWORDS: living donor liver transplantation, East Asia-Taiwan, evolution experience and outcomes

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Rewinding History

It has been more than five decades since Starzl et al performed the first successful liver transplant in 1967.¹ The initial attempt at living donor liver transplantation (LDLT) was made by Raia et al in 1988.² The first successful LDLT was performed by Strong et al in Australia in 1989.³ Then after several unsuccessful attempts in early 1990s, there was a cascading effect, and serial innovative techniques in LDLT came in vogue due to persistent efforts by surgeons in Asia. It is time for us to step back and have a panoramic view of the LDLT scenario in the whole world with Asia as a nucleus. The first successful liver transplantation in Asia was performed in 1984,⁴ the first LDLT in Taiwan was performed in 1994 by Chen, and as on date the patient is surviving in good health without immunosuppression since 1999. The first split-liver transplantation was performed in Asia in 1997,^{5,6} the first adult LDLT was performed in Taiwan in 1999, and the first dual graft was performed in Taiwan in 2002,⁷ all under the stewardship of Chen. While Makuuchi et al performed the first successful adult-to-adult LDLT in 1993 using a left lobe graft⁸ Lee et al are credited for the first dual grafts⁹ from two living donors in 2000.

Reworking Liver Donation

While deceased donor liver transplantation (DDLT) is widely accepted and practiced in the Western world, LDLT has flourished in East Asia and surgeons in the East have mastered the LDLT.¹⁰ The idea of LDLT was borne from imaginative

conceptualization of reduced-size and split-liver transplantation along with extensive experience in hepatobiliary surgery. Asian countries practiced using living donor, split, domino, and dual grafts as alternatives to overcome the donor shortage and narrow the disparity in demand and supply of organs. Several more innovative modifications were up the sleeve such as whole left lobe grafts with or without caudate lobe, right lobe grafts with or without middle hepatic vein, and right posterior sector grafts. The decision to select a different graft type for LDLT is based not only on liver volume required by the recipient but also more importantly on remnant liver for donor.

Less than optimal results with small size grafts unequivocally implicated that the key to success in adult LDLT was sufficient graft volume, prompting surgeons to develop right lobe liver donation for transplanting larger by weight children, adults, and patients with florid liver disease and high MELD score. The first right liver graft with middle hepatic vein for an adult recipient was performed by Lo et al in 1996.¹¹ Adult-to-adult LDLT involves right lobectomy that carries a higher risk of morbidity and mortality compared with the resection of the left lateral segment for children.¹² There is greater likelihood of insufficient remnant liver in donor and consequent liver failure with a right lobe donation. The greater metabolic demand of recipients with hyperbilirubinemia, portal hypertension, massive ascites, and significant varices need a larger volume graft. With the objective



of contributing maximum functional right lobe graft volume to the recipient, we practice either taking the middle hepatic vein with the graft or reconstructing the venous drainage from anterior segments using conduits in the bench. These procedures ensure adequate drainage of anterior segments in the recipient and segment 4 of the donor. Our center was the first to publish the algorithm for middle hepatic vein (MHV) inclusion in the right graft.¹³ The factors borne while contemplating the inclusion of middle hepatic vein in the right lobe graft include relatively small graft with small right hepatic vein, a significant area of congestion on the anterior segment of the right lobe, and a recipient with a high MELD score or severe portal hypertension. Liver regeneration is central to the success of LDLT. Age of the donor, portal hypertension and disease severity in the recipient, steatosis of graft, and optimum inflow and outflow hemodynamics in graft are the most important factors critical for liver regeneration.¹⁴

Reverent Act of Donor

Patients with chronic liver disease and their families have the options of living donation discussed through family physicians, hospital websites, word of mouth from friends, and print media before they reach for treatment in a liver transplant unit. Fortunately, there is enough preconditioning before reaching hospital, which makes a prospective donor present automatically for evaluation. The donor must be voluntary and altruistic preferably with a compatible blood group with the recipient, free of any major medical and psychiatric illness.¹⁵ Average age of prospective donors and transplanted recipients has increased steadily, essentially to augment the donor pool and with improvement of survival chances of elderly recipients. A computed tomography and magnetic resonance imaging are complimentary in donor graft assessment with regard to quality, volume, vascular, and biliary anatomy. Donor graft type is selected based on volumetric analysis and anatomical feasibility. Liver biopsy is not mandatory as a routine, it is recommended for suspicious pathology, to assess the severity of steatosis and to exclude steatohepatitis. The recipients must satisfy the criteria for liver transplant or meet expanded criteria that are within predefined protocols or clinical trials.

Bird's Eye View of LDLT in Taiwan

Hepatitis B and C are still major causes for liver failure, warranting liver transplantation due to high prevalence rates. In the last decade, there has been an alarming increase in the number of patients with hepatocellular carcinoma (HCC) and alcoholic cirrhosis.¹⁶ With more health conscious society and nationwide active periodic screening programs, the disease diagnosis has increased. In pediatrics, biliary atresia remains the most frequent indication followed by metabolic disorders. In instances of acute-on-chronic liver failure due to viral hepatitis or primary nonfunction of the graft, LDLT had to be performed in short notice as a life-saving measure. LDLT may have been a questionable entity in the past in such

emergencies due to chances of circumstantial coercion, but have become acceptable as deceased donors are hard to come in such situations in this part of the world. Technical innovations in donor hepatectomy, vascular and biliary reconstruction, vibrant interventional radiology for managing complications and perioperative management of transplant patients, and the development of associated specialties have enabled achievement of excellent results after LDLT. The liver transplantation program is well streamlined with sufficient trained health professionals in public and private hospitals, national insurance support from government, and timely proactive policy decision from the ruling dispensation. The spurt in socioeconomic development of Taiwan and universal active nationwide hepatitis B vaccination program, the first of its kind in the world, has also contributed to improvement in the quality of health care.¹⁷ The momentum to legalize brain death gained impetus with performance of first liver transplantation by Chen et al,¹⁸ and Taiwan became the first in Asia to frame legislation for organ donation and brain death as early as 1987. Despite excellent outcomes, the concept of deceased donor organ donation was far less acceptable in Asian countries compared to the West due to different sociocultural religious milieu. Recent trends from Taiwan have shown a marginal increase in deceased organ donation of 9.4 per million population.¹⁹

Universal coverage by the Taiwan National Health Insurance enabled the establishment of rigid and clear protocol-based guidelines for donor selection criteria, along with indications and timing for LT. We have vibrant national registry that regularly publishes transplantation outcomes. Most of the data are placed in the public domain for maintaining quality, transparency, and accountability. Progressive and steady increase in the number of transplants performed is associated with a statistically significant improvement in the survival rates.

There are 26 liver transplant programs approved by the Ministry of Health and Welfare, which performed 3,017 liver transplants in Taiwan between 2003 and 2012, with an overall three-year survival rate of 82%.¹⁹ Kaohsiung Chang Gung Center is the highest volume center with the best three-year survival rate of 91%. The one- and five-year survival rates for pediatric LDLT for biliary atresia at this center (98%) were among the highest in the world.²⁰

Taiwan National Health Insurance covers management guidelines of HBV recipients undergoing liver transplantation. Aggressive long-term immunoprophylactic strategy led to prevention of HBV recurrence in graft and helped to achieve improved long-term survivals. Continued immunoprophylaxis using HBIG has improved the HBV recurrence, the National Health Insurance regime prescribed the dosing as 10,000 IU of HBIG during anhepatic phase followed by 2,000 IU once a day for one week to maintain anti-HBs titers >100 mIU/mL and to continue nucleotide analogs indefinitely. In our series of 115 patients using entecavir and low-dose on-demand HBIG had an HBV recurrence

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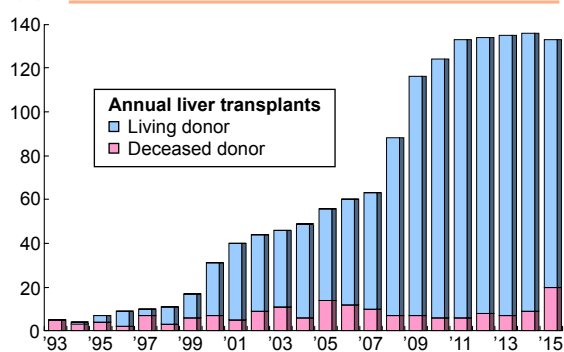


Figure 1. Annual liver transplant statistics at our center in the last two decades.

rate of only 1.7% as compared to 6.4% in a previous series of 171 patients using lamivudine.²¹

With the objective of expanding the donor pool, HBcAb-positive donors are accepted for donation. Pretransplant HBV vaccination with resultant titers >1,000 IU/L prevents de novo hepatitis B in HBsAg(-) pediatric recipients accepting HBcAb(+) grafts. For pediatric recipients with pretransplant HBsAb titers >1,000 IU/L, only booster vaccination after steroid withdrawal is required following a drop in titers. However, recipients with HBsAb titers <1,000 IU/L require prophylaxis with nucleos(t)ide analogs, in addition to booster HBV vaccinations after steroid withdrawal.^{22,23} These strategies of vaccination markedly reduced the de novo HBV infection from 37.5% to 3.4%.²⁴

Hepatitis C virus recurrence in recipients who are viremic at the time of liver transplant is pervasive and carries a poor prognosis. A careful analysis of the literature confirms that long-term survival of patients transplanted for HCV-related liver diseases takes a downturn, few years after transplant, mainly as a result of disease recurrence. Pretransplant, short-term antiviral therapy with fixed dosage of Peg-IFN-[alpha]2a (135 µg/week) plus Ribavirin (10 mg/kg per day) for four weeks lowers HCV genotype-2 recurrence by 28% at six months after transplantation. Short course limits side effects and increases tolerability in patients with advanced liver cirrhosis.²⁵

The guidelines mandated by the Taiwan National Health Insurance for accepting HCC patients were expanded in 2006 to UCSF criteria from the Milan criteria. High burden of locally advanced HCC and predominantly living donor-based transplantation program are unique to East Asia. Downstaging HCC helps to meet the criteria mandated by National Health Insurance. Unlike in USA, organ allocation system in Taiwan offers no scoring benefit to patients with HCC. Existence of nonpreferential model, in spite of having high burden of HCC in Taiwan population, has made us to aggressively treat with locoregional therapy (LRT) before transplantation. TAE using drug-eluting bead is the best downstage method before transplant. DC beads of different dimensions are used according to

tumor size. It offers less systemic side effects with an enhanced local response. HepaSphere with better penetration into the hepatic microcirculation ensures extensive tumor necrosis. TAE has been the predominant downstaging method with 84% disease-free survival rates at five years after transplant.²⁶ TAE and RFA/PEI are offered to patients beyond UCSF criteria to downstage them prior to transplant or with curative intent to patients within criteria,²⁷ when resection is not feasible due to inadequate functional reserve or anatomical reasons.

Complete tumor necrosis is beneficial for recurrence-free survival. Patients achieving 100% pathological response in the form of complete tumor necrosis in the explant liver with neoadjuvant LRT prior to LDLT had 100% disease-free survival rates at three years. Whereas patients without viable tumor following primary resection and sequential LDLT because of unfavorable pathology had 1.2% recurrence rate and patients with residual viable tumor at the time of LDLT in spite of LRT had 12.6% HCC recurrence rate at three years.²⁶

The Milan and the UCSF criteria are too limiting and restrictive for LDLT programs. Survival rates of LDLT for locally advanced HCC when downstaged to fit UCSF/Milan criteria compare favorably to other reported experiences from around the world.²⁸ Our first reported series of LDLT for HCC with pretransplant downstaging was encouraging, with a one-year survival rate of 98% and a five-year survival rate of 90%.²⁷ The updated overall survival rates at 1, 5, and 10 years are 92.9%, 84.1%, and 77.6%, respectively, for LDLT ($n = 525$) and 84%, 65%, and 65%, respectively, for patients undergoing DDLT ($n = 29$) for HCC.

Unlike DDLT where timing of transplant is difficult to anticipate, we are at liberty in LDLT to optimize pretransplant downstaging protocol and time the transplant accordingly. Pre-transplant downstaging has a number of advantages, namely, it spares patients from adverse effects of earlier immunosuppression when tumor burden is high, is cost effective, and is a low-risk procedure; at the same time, it prevents tumor progression during waiting time. Altruistic donor is subjected to surgical risk for a recipient with malignant disease; hence, it is ethically and morally of paramount importance for surgeons to ensure improved survival rates for the recipient.

To summarize the management protocol for HCC in our center: for patients with Child's A liver function and HCC—resection and subsequent salvage LDLT on recurrence seems to be a good choice; for patients with early Child B and HCC but leading on to a decompensated status of liver failure at any point of time, they will benefit from LDLT; and for patients with Child C and HCC due to poor liver functional reserve, there is no scope for resection but LRT can be considered with biopsy done during RFA. AFP values >200 ng/mL at the time of transplant predict high rates of HCC recurrence.²⁷

Immunosuppression protocol with calcineurin inhibitors forms the mainstay. Immunosuppression should be maintained at the lowest effective dose. Multidrug combination boosts immunosuppression with synergistic action and helps



reduce the toxicity of calcineurin inhibitors. mTOR inhibitors are supplemented for adult recipients at risk of HCC recurrence or renal insufficiency, considering its antineoplastic and renal-sparing effects.

Infections in recipients are more common in the settings of allograft dysfunction, graft rejection, and the presence of vascular and biliary complications. The infections with extended-spectrum beta-lactamases, carbapenem-resistant enterobacteriaceae, and vancomycin-resistant enterococci are quite common, and treatment of these resistant bugs place sizeable burden on the medical system. As a policy, we hit these infections hard with high-end cephamycins and carbapenems on earliest sign of sepsis and de-escalate on clinical improvement and negative cultures.

Survival rates have improved year after year due to innovations in surgical techniques, advances in anesthesia, comprehensive postoperative management, and better immunosuppressive therapy. Most of the technical complications arise in the first postoperative year. Predominant causes of graft loss included vascular complications, recurrence of the original disease, malignancies, rejection, and very rarely, primary graft non-function as reported in literature by series. Main causes of death in recipients were recurrence of primary disease, namely, HCC and HCV; multiorgan failure and cerebrovascular, cardiovascular, pulmonary, and renal complications; sepsis; and rarely chronic rejection.

The foremost concern in LDLT is donor safety.²⁹ Highly concerted efforts through intensive preoperative workup have been made to ensure donor safety. The risk to donor should not be overlooked or underestimated. LDLT is more complex and technically challenging than DDLT. Specific issues inherent to LDLT lead to a spectrum of complications. Worldwide mortality risk to the donor is approximately 0.2%–0.5%³⁰ and the morbidity risk is 20%.³¹ However minimal these rates may be, donor mortality for an act of altruism is highly disturbing. With gaining experience and perfection of technique, the morbidity and mortality rates are less, and the risk of the donor can be balanced against the benefits to the recipient.³² Biliary complications and infections were the most commonly reported donor morbidities with median frequencies of 6.2% and 5.8%, respectively. The other drawback is the chance of a smaller graft volume in LDLT than DDLT. A graft-to-recipient ratio of greater than 0.8 in LDLT with measures to ensure adequate outflow of anterior segments in the right lobe graft leads to better function.

The main advantage of LDLT is ready availability at short notice with substantial reduction in waiting time, quite often allowing the luxury of optimal timing, particularly in patients with HCC and acute-on-chronic liver failure. It also has the added advantage of pursuing more liberal expanded criteria for HCC compared with those for DDLT recipient. The cold ischemia time is shorter, with possibilities of closer HLA matching, reducing the chances of rejection and minimizing the requirement of immunosuppressant.

Valuable Technical Tips and Strategies for Surgical Predicaments

Living donor hepatectomy is done through a midline incision with right subcostal extension. After mobilization of liver lobes, hilar dissection is performed on right portal vein and working further in a meticulous way exhibiting enough caution to free the delicate hepatic artery. For left lobe graft to begin with, proper hepatic artery is dissected free followed by left portal vein. Trick of the trade is fine dissection to skeletonize artery in small steps ligating and dividing the fibroareolar lymphatic connective tissue, avoiding energy source and using fine silk ties to gently retract and visualize the artery. The portal vein and hepatic artery are skeletonized, leaving the hepatic duct encased in hilar plate undisturbed until inferior surface of liver is transected close to the confluence of hepatic ducts.

The technique to ensure safe and precise division of hilar plate using a radiopaque marker filament and C-arm cholangiography is routinely used by us. Intraoperative cholangiogram is done for all right lobe graft, left lobe graft with a trifurcation of the common hepatic duct, right posterior segmental duct draining to left hepatic duct or common hepatic ducts and in patients with history of previous biliary procedure, nevertheless preoperative evaluation of biliary anatomy is performed in all donors with magnetic resonance imaging. Prior to hilar dissection, the gall bladder is detached from the liver bed, the hepatic artery and portal branch are fully defined and isolated from the hilar plate. Particular attention is paid to retaining the surrounding tissue of the hilar plate without exposing the bile duct; it is encircled with a radiopaque marker filament. The incidence of multiple bile ducts in the graft was significantly reduced by this method. A large, single bile duct orifice reduces the risk of postsurgical biliary complications.³³ Parenchymal transaction is performed on the plane determined by the line of demarcation using a combination of CUSA and Kelly fracture technique. All the tributaries of right inferior and middle hepatic veins >5 mm are preserved for reconstruction. The posterior surface of the liver is transected with the aid of Belghiti sling.

Regarding the recipient its no longer privy that redo arterial reconstructions using right gastroepiploic artery, left gastric artery and radial artery interposition graft can salvage the liver graft following initial dissection and thrombosis of hepatic artery.³⁴ With microsurgical biliary reconstruction, the complication rates in our series had been 6%, 12%, and 18% for one-, two-, and three-duct anastomoses, respectively.³⁵ The comparable complication rates in other centers is 12–47%. In the published series from our center of nearly 800 consecutive microsurgical biliary reconstructions, 24% had multiple ducts. The overall complication rate was about 7%, which included 4% biliary strictures, 3% bile leaks, and 5% required intervention.³⁶ Thus, technical anastomotic constraints of small-size multiple ducts are no longer in vogue with the use of microsurgical reconstruction. The lower complication rates were achievable due to novel technique of complete hilar plate

encircling³⁷ during donor hepatectomy, intraoperative cholangiogram prior to division of hilar plate in situations where anatomy of confluence is complex and deceptive and recipient bile duct bonded to hepatic artery is safeguarded, preserving the axial arterial supply. The technique to minimize biliary complications while harvesting the left lobe is to move behind the left portal vein taking the left hilar plate in en bloc, thus preserving and sometimes sparing segment IV bile duct and artery, exhibiting caution against leaving undrained segments and careful oversewing of the stump of the entire hilar plate to prevent postoperative bile leaks.

LDLT would be deemed successful not only by ensuring safe donor surgery but also by tackling the intricacies in recipient surgery. We devised several techniques to minimize these complexities in recipients as well. In line with various recommendations for venoplasty, our modified triple venoplasty technique in left side graft³⁸ involves cross-clamping the IVC, creating a single wide orifice, coapting the redundant edges facilitating anastomosis by eversion technique. This technique has added benefits of creating a short outflow trunk, safeguarding from twisting or kinking. Cross-clamping of IVC offers immunity against bunching and malorientation, which can happen with individual clamping of the hepatic veins.³⁹

Portal vein size <4 mm, GRWR greater than 3, and portal vein flow velocity less than 7 cm/second at pretransplant evaluation are predictors of intraoperative PV thrombosis.⁴⁰ The P4 stump approach for intraoperative PV stenting was propagated to secure adequate portal flow in the hypoplastic portal vein in children, particularly with biliary atresia.^{41,42}

Routine use of microsurgical arterial and biliary surgical reconstruction reduced the complication rates markedly. Multiple small-sized ducts are better anastomosed under microscope.^{37,43} We formulated oblique trimming of hepatic artery to prevent kinking and intimal dissection along with microsurgical anastomotic technique⁴⁴ of combined-continuous suture and interrupted tie with the posterior wall first approach.⁴⁵ Similarly, the most feared hepatic artery thrombosis can lead on to graft loss and retransplantation. Microsurgical reconstructions using right gastroepiploic artery, left gastric artery, and radial artery interposition grafts serve as a reliable replacement of severely diseased native hepatic artery and aid in salvage of failing graft following hepatic artery thrombosis.

Techniques to minimize blood loss during donor hepatectomy⁴⁶ and importance of diminished transfusion during recipient surgery were emphasized as multiple transfusions were detrimental to host immune mechanisms and increased the possibility of late complications.⁴⁷

We proposed and practiced maneuvers such as fixation of falciform ligament, tissue expanders, and inflated Foley catheter balloon to support the graft, effectively preventing mechanical and torsional outflow obstruction. All the expanders and catheters are removed by three to eight weeks, once adhesions develop, to retain the graft in position.⁴⁸

Gore-Tex, Silastic mesh was used for tension-free approximation of anterior abdominal fascia in situations like GRWR > 4%, where abdominal compartment syndrome is very much a possibility. Using segment 2 monosegment¹⁶ graft has effectively reduced complications associated with larger grafts.

Conclusion

The number of DDLT has been dismal in Asian countries, and for all practical purposes, LDLT has been the main option for treatment. The donor has a unique opportunity to restore good health to a family member. Because the liver regenerates in three weeks to three months,^{49,50} long-term liver function is normal, and there are not many undue late physical or psychological problems in both the donor and the recipient.

LDLT has progressed, despite initial skepticism, and plays a major role since the shortage of organs has been perennial and is likely to remain same for some more years. The concerns about donor safety have been well received and are evident with declining morbidity due to improvement in the quality of health care and standardization of techniques by experienced surgeons. Aggressive social reforms and changes in outdated orthodox perceptions are necessary to alleviate the critical shortage of deceased organ donation.

Author Contributions

Conceived and designed the article: C-LC, NP. Analyzed the data: C-LC, NP. Wrote the first draft of the manuscript: NP. Contributed to the writing of the manuscript: C-LC, NP. Agree with manuscript results and conclusions: C-LC. Jointly developed the structure and arguments for the paper: C-LC, NP. Made critical revisions and approved final version: C-LC. All authors reviewed and approved of the final manuscript.

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