Liver Transplantation: East versus West

Akash Shukla, Hemant Vadeyar, Mohamed Rela, Samir Shah

Institute of Liver Diseases, HPB Surgery and Transplantation, Global Hospital – Superspeciality and Multiorgan Transplant Centre, 35, Dr. E. Borges Road, Hospital Avenue, Mumbai 400012, Maharashtra, India

Liver transplantation (LT) has evolved rapidly since the first successful liver transplant performed in 1967. Despite a humble beginning, this procedure gained widespread acceptance in the western world as a suitable option for patients with end stage liver disease (ESLD) by the beginning of the 1980s. At present, approximately 25,000 liver transplants are being performed worldwide every year with approximately 90% one year survival. The techniques of living donor liver transplantation (LDLT) developed in East Asia in the 1990s to overcome the shortage of suitable grafts for children and scarcity of deceased donors. While deceased donor liver transplantation (DDLT) constitutes more than 90% of LT in the western world, in India and other Asian countries, most transplants are LDLT. Despite the initial disparity, outcomes following LDLT in eastern countries have been quite satisfactory when compared to the western programs.

The etiologies of liver failure requiring LT vary in different parts of the world. The commonest etiology for acute liver failure (ALF) leading to LT is drugs in the west and acute viral hepatitis in Asia. The most common indication for LT due to ESLD in west is alcoholic cirrhosis and hepatitis C virus (HCV), while hepatitis B virus (HBV) predominates in the east. There is a variation in prognostic models for assessing candidature and prioritizing organ allocation across the world. Model for end-stage liver disease (MELD) is followed in United States and some European centers. Other European countries rely on the Child–Turcotte–Pugh (CTP) score. Some parts of Asia still follow chronological order of listing. The debate regarding the best model for organ allocation is far from over. (J CLIN EXP HEPATOL 2013;3:243–253)

LT has been established as the most effective treatment modality for ESLD over the last five decades. Over the years, this procedure has evolved with

refinement in surgical techniques, improvement in postoperative care, advent of new immunosuppressive drugs and new organ preservation fluids. LDLT has developed as an alternative to DDLT to compensate for critical shortage of cadaveric organ donations, particularly in Asia. Although LDLT was initially described in children, with technical refinement and use of partial grafts, it is being extensively utilized in adults as well. While LDLT quickly became the predominant form of LT in the east, it did not find such widespread acceptance in the west. In the west, non heart beating donor transplantations have been initiated as a measure to increase the donor organ pool.¹ ABO incompatible liver transplants have been attempted, in rare circumstances, especially in acute liver failure and primary graft dysfunction when no other alternative is present.¹ In the East, LDLT is common and DDLT uncommon due to cultural, religious and political reasons. However, recent trends from Asia have shown an encouraging increase in cadaver organ donation.²

The etiologies for LT are different between the west and the east. Additionally, for indications such as hepatocellular carcinoma (HCC), there is a significant difference in the application and selection criteria for LT. Many of the differences in practice between the east and the west stem from the predominance of LDLT in the east as compared to DDLT in the west. However, despite these differences, there are a lot of similarities between the application of LT in the east and the west.

Keywords: liver transplantation, acute liver failure, hepatitis B virus, hepatitis C virus

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Address for correspondence: Samir Shah, Institute of Liver Diseases, HPB Surgery and Transplantation, Global Hospital – Superspeciality and Multiorgan Transplant Centre, 35, Dr. E. Borges Road, Hospital Avenue, Mumbai 400012, Maharashtra, India.

E-mail: drshahsamir@gmail.com

Abbreviations: LT: liver transplantation; ESLD: end stage liver disease; LDLT: living donor liver transplantation; DDLT: deceased donor liver transplantation; ALF: acute liver failure; MELD: model for end-stage liver disease; CTP: Child–Turcotte–Pugh; NASH: nonalcoholic steatohepatitis; HCC: hepatocellular carcinoma; HBIG: Hepatitis B Immunoglobulin; MHV: middle hepatic vein; HCV: hepatitis C virus; HBV: hepatitis B virus; PBC: primary biliary cirrhosis; PSC: primary sclerosing cholangitis; DI-ALF: drug-induced acute liver failure; LAM: Lamivudine; ETV: Entecavir; UCSF: University of California in San Francisco; GRWR: Graft weight to recipient's body weight ratio; LLS: left lateral segment; DCD: donation after cardiac death; EDC: extended criteria; pmp: per million population; NGOs: non-governmental organizations; MOHAN: Multi Organ Harvesting Aid Network; OPO: Organ Procurement Organization; NOTA: National Organ Transplant Act; OPTN: Organ Procurement and Transplantation Network; UNOS: United Network of Organ Sharing; ELTR: European Liver Transplant Registry; ITR: Indian Transplant Registry; RLTL: reduced LT; SLT: split LT

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We write this review in order to highlight the ways in which LT has evolved in different parts of the world and comparing practices in the eastern and the western world.

THE BEGINNING AND EVOLUTION

In the West

The first LT was attempted in University of Colorado in 1963 by a surgical team led by Dr Thomas Starzl. After 7 unsuccessful attempts, the first successful transplant was performed in July 1967.³ Despite refinement in surgical techniques, LT was not widely accepted and the results remained unacceptable through the next decade. In the pre-cyclosporin era, azathioprine and cyclophosphamide were used widely. In this period, 170 liver replacements took place, with one year survival improving from 28.8% to 50%.³ The turning point in the success of LT was cyclosporine, which was introduced by Sir Roy Calne in 1977.⁴ There was also a Congress hearing in the USA in 1983, where it was concluded that LT was no longer an experimental therapy and approved for general use. Following this decision, LT became recognized as a standard clinical treatment for both adult and pediatric patients with liver failure.

Further advances in surgical techniques led to the first successful split liver transplant in 1988.⁵ Scarcity of cadaver donors led to the concept of living donors. The first reports of successful living donor liver transplants came from Raia in Brazil⁶ and Strong in Australia.⁷ Further technical advances were described by Dr. Christoph Broelsch at the University of Chicago Medical Center.⁸ With better surgical techniques, refinement of immunosuppressive regimen, improved critical care and better knowledge of pathophysiology, some LT centers have shown excellent outcomes, with one year patient survival approaching 90% and 5 year survival 75–80%.¹

In the East

The first liver transplant was done within a year of Starzl by Nakayama at Chiba in Japan.² However, initial transplants were not associated with any long term survivors. The first long term survivor was in Taiwan, where the surgery was performed by Chen et al.² LDLT was first performed in Asia by Nagasue at Shimane University in Japan in 1989; within a year after the first attempt by Raia.⁹ The first successful adult LDLT using a left lobe graft was reported by Makuuchi et al from Japan in 1994.¹⁰ Professor Tanaka and his team from Kyoto have determined the criteria for safe use of a right lobe graft for an adult recipient, notably the minimum volume required for a recipient.¹¹ Use of right liver grafts has had a large impact on the results of adult LDLT. The Hong Kong group was the first to transplant a right liver graft including reconstruction of the middle hepatic vein (MHV) in 1996, terming it an extended right liver graft.¹² Liver transplant programs in Asia have repeatedly made sur-

gical innovations such as left liver grafts with or without the caudate lobe, right liver grafts, right posterior sector grafts, and dual grafts. The University of Tokyo group was the first to design the right posterior sector graft, consisting of segments VI and VII.¹³ Lee et al were the first to devise dual grafts from two living donors, when the calculated residual volume was less than 35% in a proposed right lobe donor.¹⁴

The DDLT program lagged behind the LDLT due to lack of awareness in general public, religious beliefs and lack of proper legislations in Asia. Most Asian countries are struggling to increase DDLT rates with more than 90% of all transplants being LDLT.

In the 1980s and early 1990s, LT in India was more of a dream than reality. The problems were lack of trained doctors in this field, poor understanding of brain death (Indian law only recognizing cardiac death) and the huge cost of the operation.¹⁵ The Transplantation of Human Organs Bill was then passed by Parliament in 1994 and became a law in 1995.

Unfortunately, due to scarce cadaver organ donation, only 131 liver transplants were performed in 15 centers across the country between 1994 and 2004.¹⁶ Most teams had to adopt LDLT in their programs. During 2004 to 2010, there was a significant increase in the number of LT. Currently, approximately 700 - 1000 liver transplants are carried out annually in the country, of which LDLT constitutes about 85%.¹⁶

INDICATIONS

The indications are summarized in Table 1.^{17–22}

Chronic Liver Disease

In the USA, the predominant reasons for liver transplant are cirrhosis due to hepatitis C virus (HCV) infection, followed by HCC, and alcoholic cirrhosis with or without concomitant infection with HCV. Other causes include primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), nonalcoholic steatohepatitis (NASH), and others such as hemochromatosis, alpha-1-antitripsin deficiency, biliary atresia, and hepatitis B virus infection.¹⁷ On the other hand, cirrhosis secondary to alcoholic liver disease is the commonest indication for liver transplant in Europe, followed by Hepatitis C and HCC.¹⁸ A recent review shows rising incidence of NASH as an indication for LT.²³ In Asia, however, the most common indication for LT in adults has been HCC secondary to Hepatitis B, followed by Hepatitis B without HCC, and HCV-related cirrhosis without HCC. In the Far East, Japan is the only exception where HCV is more common than HBV.

Acute Liver Failure

Acute liver failure is an important indication for liver transplantation across the world. Drugs, most commonly

Table 1 Indications for Liver transplantation across the world.

Type of transplant	Country	Commonest indication	Other common indications	Less common indications
Elective (chronic liver disease)	USA ¹⁷	Hepatitis C	Alcoholic liver disease and HCC nonalcoholic steatohepatitis (NASH)	Cholestatic liver disease (PBC, PSC)
	Europe ¹⁸	Alcoholic liver disease (19%)	Hepatitis C cirrhosis (13%)	HCC (12%), other cholestatic liver diseases
	Asia ^{21,22}	HCC	Hepatitis B	
Emergency (acute liver failure)	USA ¹⁷	Drug-induced ALF; (mainly paracetamol)	Viral hepatitis	Autoimmune hepatitis or Wilson's disease
	Europe ¹⁸	Drug induced ALF; (mainly paracetamol)	Viral hepatitis Seronegative hepatitis	
	Asia ^{19,20}	Hepatitis B	autoimmune hepatitis Viral hepatitis	

paracetamol are the most common cause of ALF in all western countries including the USA and Europe.^{17,18} According to the 1998–2007 data of the ALF Study Group, acetaminophen was the most common cause of ALF, accounting for 46% of ALF cases among US adults; it was followed by indeterminate causes of ALF (14%) and other drugs (11%).²⁴ In the pediatric population, acetaminophen was the second most common cause of ALF between the ages of 3 and 18 years, and it was followed by autoimmune hepatitis, other, and metabolic causes, whereas other drugs were the sixth most common cause of ALF in that age range.²⁴ Between 1998 and 2007, 26% of the patients who suffered from acetaminophen-induced ALF and 31% of the patients who had ALF due to other drugs died without spontaneous recovery or LT.²⁴ In a UNOS study, recipients who underwent LT for drug-induced acute liver failure (DIALF) from 1987 through 2006 were analyzed.²⁵ A total of 661 patients transplanted for DIALF were included in the analysis. The 4 leading implicated drug groups were acetaminophen ($n = 265$; 40%), antituberculosis drugs ($n = 50$; 8%), antiepileptics ($n = 46$; 7%), and antibiotics ($n = 39$; 6%). One year estimated survival probabilities were 76%, 82%, 52%, 82%, and 79% for acetaminophen, antituberculosis drugs, antiepileptics, antibiotics, and others, respectively.²⁵ In a study from United Kingdom, between 1992 and 2006, 104/469 patients with ALF underwent LT. Acetaminophen was the most common etiology; with LT done in 45/326 patients, While in the non-acetaminophen: 59/143 patients received LT. More patients had contraindications to LT in the acetaminophen cohort (acetaminophen: 99/165, 60%; non-acetaminophen: 21/91, 23.1%; $P < 0.01$), and survival on the LT waiting list was reduced in the acetaminophen cohort (acetaminophen: 45/66, 68.2%; non-acetaminophen: 59/70, 84.3%; $P < 0.05$). Post-LT survival was similar in the 2 groups. An analysis of cohorts admitted in 1993–1996 and 2002–2005 revealed that LT

proceeded less commonly in acetaminophen ALF in the later cohort (1993–1996: 16/99 LT, 16.2%; 2002–2005: 4/81 LT, 5%; $P < 0.01$) in comparison with the non-acetaminophen cohort, in which transplantation proceeded more commonly in the later cohort (1993–1996: 11/34 LT, 32.4%; 2002–2005: 24/49 patients, 49.0%; $P < 0.01$). This was due to an increase in the number of patients with psychiatric contraindications to transplantation (predominantly resistant and severe alcohol dependence). However, in the far east, the commonest indication for liver transplantation for ALF is acute hepatitis B.^{19,20} In India, however, the commonest causes of ALF and hepatitis E and anti-tubercular therapy.²⁶ In most Asian countries, LDLT is the most common form of LT for ALF. Makuuchi reported excellent results following LDLT using a left liver graft. They described end-to-end anastomosis of the hepatic to prevent an outflow occlusion. Wide ostium and sufficient length of the hepatic vein for anastomosis, could be secured by venoplasty of the hepatic veins of the graft and the recipient. A left liver with a caudate lobe graft can overcome the problem of a small graft. Reconstruction of the short hepatic vein of the caudate lobe allows this portion to regenerate at the same rate as the left liver.²⁷ In Japan, LDLT for ALF is associated with patient survival rates of 79%, 74%, and 73% at 1, 5, and 10 years, respectively.²⁸ Patient age was associated with short- and long-term mortality after LT, whereas ABO incompatibility affected short-term mortality, and donor age affected long-term mortality. In a study from Korea, Thirty-six (22.5%) and 124 (77.5%) patients underwent DDLT and adult-to-adult LDLT, respectively for ALF. During a median follow-up period of 38 (range 1–132) months, the DDLT and LDLT groups showed similar patient ($P = 0.99$) and graft ($P = 0.97$) survival rates. The overall 1- and 3-year patient survival rates were 78.8 and 74.6%, respectively. Five predictors of patient survival were identified by bootstrapping and multivariate analysis:

vasopressor requirement, estimated glomerular filtration rate, serum sodium concentration, recipient age, and donor age, at the time of transplant.²⁰ In another study from China, the 1-year and 3-year recipient's survival and graft survival rates were 65% (13 of 20) following LDLT for ALF. Multivariate analysis showed that waiting duration was independently correlated with increased mortality ($P = 0.014$).²⁹

LT for HBV

Liver transplantation for hepatitis B was a relative contraindication until the introduction of Hepatitis B Immunoglobulin (HBIG) in liver transplant, which had a significant impact on the prevention of HBV recurrence in the graft. HBIG is a polyclonal antibody to HbsAg, derived from pooled human plasma. It acts by preventing hepatocyte infection, binding to and neutralizing virions and inciting lyses of infected cells.³⁰

Todo et al from the UPMC group, Pittsburgh, USA were the first ones to suggest improved long term survival of the graft with use of HBIG.³¹ This was reinforced by Samuel D et al from France who demonstrated that use of HBIG improved 1 year survival to 83.6% and reduced HBsAg recurrence to 29% at 2 years amongst patients with HBV undergoing LT.³²

The pivotal European multicenter trial published in 1993 showed use of HBIG was associated with improved graft and patient survival.³³ However, the treatment was costly with the estimated cost for the high dose regimen at the time being \$50000–70000 for the first year and \$25000–40000 for every subsequent year.³⁴ Angus et al from Australia showed excellent outcome with use of low dose HBIG and Lamivudine with HBV recurrence rate of only 3.1% at 1 ½ years.³⁵ A multicentre trial in USA and Canada evaluated the use of Lamivudine as monotherapy and demonstrated HBsAg negative rates were comparable to long term HBIG monotherapy.³⁶ Yoshidan et al from Miami, USA found that there was no difference in recurrence rate of HBV in those treated with Lamivudine monotherapy (15%) and Lamivudine + HBIG (18%) after 5 years median follow-up.³⁷ However, the long term resistance with Lamivudine was a problem. Now, with the widespread use of newer antiviral agent Entecavir and Tenofovir, results are expected to be superior to those reported earlier. In a retrospective cohort study by Xi et al from China, none of the 30 patients treated with low dose IM HBIG and Entecavir had HBV recurrence as opposed to 11% with Lamivudine + IM HBIG.³⁸

Wadhawan et al from New Delhi reported preliminary data on 56 patients who received Lamivudine + Adefovir ($n = 17$), Entecavir ($n = 25$), Tenofovir ($n = 8$) or Entecavir + Tenofovir ($n = 2$) prior to LT. 47 of these patients had HBV DNA < 2000 IU/ml pre-transplant and

none were given HBIG. At a follow of 20 months, all were HBsAg negative.³⁹

Similarly Fung from Hong Kong found that the HBsAg clearance rate was 90% at 1 year with Entecavir monotherapy.⁴⁰ Of the 362 patients who were managed without Hepatitis B Immunoglobulin, 176 (49%), 142 (39%), and 44 (12%) were on Lamivudine (LAM), Entecavir (ETV), and combination therapy (predominantly LAM + Adefovir), respectively, at the time of transplant. The rate of hepatitis B surface antigen seronegativity and hepatitis B virus DNA suppression to undetectable levels at 8 years was 88 and 98%, respectively. The virological relapse rates (>1 log increase IU/ml) at 1, 3, 5, and 8 years was 5, 10, 13 and 16%, respectively. The virological relapse rate at 3 years for LAM, ETV, and combination group was 17, 0, and 7%, respectively ($P < 0.001$). Forty-two patients had virological relapse, of which 36 had YMDD mutation (31 in the LAM group and 5 in the combination group). The overall 8-year survival was 83%, with no difference between the three treatment groups ($P = 0.94$). No mortality from HBV recurrence occurred in the 362 patients.

These HBIG free regimens bring down the cost significantly and are becoming increasingly popular in most centers.

LT for HCC (Table 2)^{41–46}

In 1996, Mazzaferro et al introduced the Milan criteria (solitary tumor not exceeding 5 cm or no more than three tumors, each measuring less than 3 cm) based on a retrospective study of 48 patients who had undergone OLT for HCC.⁴¹ In that study, the 4-year overall and recurrence-free survival rates were 75 and 83% respectively. The University of California in San Francisco (UCSF) criteria proposed that the indication for LT can be expanded to include only solitary tumor up to 6.5 cm or ≤ 3 nodules with largest <4.5 cm and total < 8 cm.⁴² Most of the western countries follow either one of the above criteria.

The Milan and UCSF criteria have been designed mainly for cadaveric organ donation and take into account the organ allocation system to maximize organ utilization. However, the organ from a living donor is not a public resource, but a private gift to the patient. Hence, the Milan and the UCSF criteria may be too restrictive for LDLT. Many centers performing predominantly LDLT have proposed expanded criteria, and have shown outcomes comparable to the Milan or the UCSF criteria. On the basis of these results, some make a strong plea for relaxing the selection criteria for HCC beyond Milan and UCSF. However, there is a risk of morbidity and mortality to the donor and hence it is imperative that care be taken while relaxing these criteria. This is important for protection of the donor and avoiding futile transplantation.

Table 2 Criteria for liver transplantation in patients with HCC.

Center	Criteria	Type of donor	Recurrence-free survival
Milan, Italy ⁴¹	<ul style="list-style-type: none"> • Diameter $\leq$ 5 cm if single lesion • Diameter $\leq$ 3 cm if multiple lesions and number of lesions $\leq$ 3 	DDLT 100%	75% 4 yr survival
UCSF, USA ⁴²	<ul style="list-style-type: none"> • Diameter $\leq$ 6.5 cm if single lesion or • Diameter $\leq$ 4.5 cm if $\leq$ 3 lesions if total diameter $\leq$ 8 cm 	DDLT 93% LDLT 7%	75% 5 yr survival
Asan, Korea ⁴³	<ul style="list-style-type: none"> • Diameter $\leq$ 5 cm • No. of lesions $\leq$ 6 • No gross vascular invasion 	LDLT 100%	76.3% 5 yr survival
Kyoto, Japan ⁴⁴	<ul style="list-style-type: none"> • Diameter $\leq$ 5 cm • No. of lesions $\leq$ 10 • PIVKA-II $\leq$ 400 mAU/ml 	LDLT 100%	86.7% 5 yr survival
Fukuoka, Japan ⁴⁵	<ul style="list-style-type: none"> • Diameter or number not limited • No gross vascular invasion or extrahepatic disease 	LDLT 100%	74% 3 yr survival
Tokyo, Japan ⁴⁶	<ul style="list-style-type: none"> • Diameter $\leq$ 5 cm • No of lesions $\leq$ 5 	LDLT 100%	94% 3 yr survival

CONTRAINDICATIONS

Absolute contraindications should be situations where the outcomes of liver transplantation are so poor that it must not be offered. Relative contraindications would be conditions that have poor survival, but not to the extent that they should be categorically withheld. Ongoing uncontrolled sepsis, severe cardiovascular or pulmonary disease multisystem organ failure, active substance abuse, metastatic HCC, co-existing extra-hepatic malignancy, macrovascular invasion by HCC, anatomic abnormalities that preclude performing the surgical procedure of liver transplantation, severe co-morbid illness(es), active alcoholism and morbid obesity are considered as contraindications to liver transplant.

TECHNICAL ASPECTS OF LIVER TRANSPLANTATION

The indications for liver transplantation have widened resulting in an increasing number of patients being listed for liver transplantation. As a result, increasing the donor pool is a challenge in all the countries of the world. While the

eastern countries have tried to meet this challenge by innovations in the use of LDLT, the countries in the west have sought to overcome this challenge by pushing the boundaries of DDLT.

There are a number of different grafts that are used for LDLT. The decision is based on the volume of liver required by the recipient. For patients with advanced liver disease, a graft volume of greater than 40% of the recipient standard liver volume is necessary,⁴⁷ while for the living donor the remnant liver must be more than 30% of the volume of the whole liver.⁴⁸ It is generally believed that the ideal graft size is 0.8% of GRWR (Graft weight to recipient's body weight ratio).¹¹ However, in recent years, it has become evident that the ideal graft size varies from patient to patient and is dependent on other factors such as the condition of the recipient and the steatosis in the graft.⁴⁹

DIFFERENT TYPES OF LIVING DONOR GRAFTS

The different types of grafts currently used in LDLT are summarized in Table 3.^{7,9,10,12,14,50}

Table 3 Different types of living donor grafts.

Type of graft	Couinaud segments	Reference	Advantages	Limitations
Left lateral Segment graft	II, III	Strong et al ⁷	Minimal risk to donor. Ideal for small children	Volume of graft is low Only suitable for small children
Left lobe graft	II, III, IV	Sugawara et al, ⁹ Kawasaki et al ¹⁰	Lower risk to donor compared to right lobe donation	Suitable only for large children and small adults
Right lobe graft	V, VI, VII, VIII	Lo et al ¹²	Suitable for adult recipients	Increased donor risk technically more challenging
Right posterior sector graft	VI, VII	Sugawara et al ⁵⁰	Lesser donor risk	Technically difficult only few patients suitable
Dual grafts	Either 2 left lateral segments or 2 left lobes or a right and left graft	Lee et al ¹⁴	Minimizes risk to donor More recipients may be suitable	Needs two living donors Technically more challenging

Left Lateral Segment Graft and Left Lobe Graft

The first LDLT was done with the left lateral segment (LLS) graft. This graft uses segments II and III. It is mainly used in children and is safest for the donor. As a result of the use of this graft, the pediatric waiting lists in the western world have reduced significantly. The left lobe graft (segments II, III and IV) is used for large children and for some small adults. In order to increase the available liver volume for the recipient, innovations like inclusion of the caudate lobe with the left lobe have been introduced.⁵¹

Right Liver Graft Including Right Posterior Sector Graft

The volume of the left lobe may be inadequate to meet the metabolic demands in most adult patients. The right lobe is larger than the left lobe and forms approximately 60–70% of the total liver volume and is used for most adult to adult LDLTs. Couinaud segments V, VI, VII and VIII are used in this graft. The main difference between centers using this graft is regarding utilizing the graft with or without the middle hepatic vein. The right lobe graft involves resection of at least 60% of the donor's liver volume. Hence, the risk for the donor is greater in this procedure compared to other forms of living donation. In very selected patients, where the right lobe volume is greater than 70% of the total liver volume of the donor and the right posterior sector is at least 40% of the estimated liver volume of the recipient, the use of the right posterior sector alone (segments VI and VII) has been advocated.⁵⁰ This is however, technically more challenging and applicable in only a few selected situations.

Dual Donor Grafts

In situations where the donor volumes of a single donor may not be sufficient for the recipient, the Korean group advocates the use of two donors, so as to increase the margin of safety for both donor and recipients, if the estimated remnant volume was less than 30%. Typically, both donors donate the left liver or the left lateral segment, with one graft positioned in the normal anatomical position, and the other one placed in a reversed position.¹⁴ This is technically challenging and quite resource intensive, requiring three operation theaters and three operating teams. However, satisfactory outcomes are being achieved using these variations.^{14,50}

Middle Hepatic Vein Reconstruction

The decision to either take the MHV with the graft or leave it behind for the donor is widely debated. A right lobe graft without middle hepatic drainage can cause severe congestion of the right anterior sector of the liver. The MHV is also necessary to ensure drainage of segment IV in the donor.

In the east, due to poor cadaveric organ donation, right lobe LDLT is the only option for most patients, and ensuring maximum available functional volume to the recipient is an important goal. In most instances, this is achieved by providing adequate venous drainage to the right anterior sector, either by taking the MHV with the graft as practiced by the Hong Kong group or reconstructing the venous drainage on the bench,⁵² as practiced by the Korean group.⁵³ Most teams in the west advocate use of right lobe grafts without MHV drainage. In this situation, there is a possibility that the available functional liver for the recipient may be less than optimal. This policy may dictate use of cadaveric whole organ grafts for poor-risk patients, while right lobe grafts from living donors could be used for good-risk recipients, who can tolerate a potentially lesser parenchymal liver mass.⁵⁴

Donor Shortage in the West

The success of LT resulted in donor shortage even in western countries; both in children because of the paucity of size matched pediatric donors for use of the whole organ for transplant and in adults, due to increasing number of patients being listed for LT. The western countries are seeking to overcome this problem by the use of extended criteria donors and evolution of techniques in DDLT, such as using partial liver grafts including reduced LT (RLT) or split LT (SLT) and the use of donation after cardiac death (DCD).

Partial liver grafts

Partial-liver allografts from cadaver donors may be either RLT or SLT. RLT is the surgical reduction of a whole cadaver allograft to yield a single cadaver allograft of smaller size. This technique was initially reported by Bismuth⁵⁵ and Broelsch⁵⁶ to create allografts for children from adult cadaver donors. The shortcomings of RLT, namely the discarding of a right hemi-liver and the increased competition between adult and pediatric candidates for the same donor pool, make the procedure impractical. Currently, RLT is rarely performed. Sparse data exists on RLT outcomes because of the tremendous heterogeneity in allograft creation. Split-liver transplantation is a procedure in which one cadaver liver is divided to provide for two recipients.⁵⁷ The principle beneficiaries of SLT have been adult-pediatric recipient pairs⁵⁸; however, continued scarcity of cadaver organs has renewed interest in expanding these techniques to include two adult recipients for one adult cadaver donor.

Technical challenges in partial liver transplantation include the creation of sufficient liver volume to meet the metabolic demands of the recipient, graft positioning to optimize vascular flow and biliary drainage, and an appreciation of anatomic variations that necessitate complex biliary or vascular reconstruction. Although initial reports

suggested a possible increased risk of complications among partial-liver allograft recipients, results have improved significantly in recent years.⁵⁹

Extended Criteria Donors

A reference (or ideal) donor was defined according to the following criteria: age below 40 years, trauma as the cause of death, donation after brain death, hemodynamic stability at the time of procurement, no steatosis or any other underlying chronic liver disease, and no transmissible disease.⁶⁰ An 'ideal' donor implies a very low risk of initial poor function or early allograft failure leading to death or requiring retransplantation. Any donor who does not fit these criteria of 'ideal' donor would be considered as an "extended criteria (EDC)" or "marginal" donor. Increasing organ scarcity has motivated transplant centers to relax customary restrictions to donation and use marginal donors. However, precise definitions of these terms have not been widely accepted. An extended criteria donor implies higher risk in comparison with an 'ideal' donor. The risk may manifest as increased incidence of poor allograft function, allograft failure, or transmission of a donor-derived disease.

There is wide variation in the allocation of and use of extended criteria donors. An analysis of the Scientific Registry of Transplant Recipients of the United Network for Organ Sharing indicates increased allograft utilization from elderly donors, DCD, and donors with positive markers for hepatitis B and hepatitis C.⁶¹ There is no uniformity or defined criteria for use of extended criteria donor livers. Hence, there is no comprehensive database that will allow us to reliably compare results using EDC donors against the 'ideal' donors.

Donation after Cardiac Death

Liver transplantation from non-heart-beating donors, now termed donation after cardiac death (DCD), is a promising way to increase the supply of organs.⁶² In controlled circumstances, the organs are retrieved after a standoff period of 5 min after death is certified. In DCD situations, the organs are subjected to a variable period of warm ischemia, which predisposes them to primary nonfunction, delayed graft function, or irreversible ischemia like diffuse cholangiopathy.⁶³ In early reports, the prolonged period of warm ischemia resulted in markedly increased early graft dysfunction in comparison with donation after brain death donors. It has been possible to achieve good results with an incidence of primary nonfunction below 15% and a lower incidence of biliary complications with specific measures.^{64,65} These measures include judicious donor selection, including donor age below 40 years and no steatosis, use of heparinized perfusate, the use of extracorporeal oxygenation, a short warm ischemia time (less than 15 min), and a short CIT (less than 10 h).^{66,67} Although

this procedure is limited to selected centers in the west with specific protocols, DCD has the potential to increase the donor pool by 10%–20%.⁶²

ORGANIZATIONAL ISSUES

Organ Donation

Deceased Organ Donation

Deceased organ donation rates vary across the world. UK and the USA have an organ donation rate of 14.7 and 26.3 per million population (pmp) respectively. Spain has the highest organ donation rate of 34.2 per million population in the world.¹⁷ This could be due to the following reasons. Firstly, Spain uses the principle of active detection whereby transplant coordinators visit emergency rooms and the ICU on a daily basis, checking the status of patients. In addition, Spain adopted the approach of "opting-out"/presumed consent, which permits organ and tissue removal unless the donor had opposed donation during his lifetime. Countries such as, Poland, Singapore have also adopted the same 'opt out' approach. USA uses the policy of voluntary "opting-in"/family consent to govern organ donation and individuals had to specify their intention to donate. Some nations like Austria, have considered a third policy; "pure presumed consent" which means that a person must register at a courthouse to express their desire or opposition to be an organ donor. Also, if a person who refused to be a donor, ever needs a transplant, he would automatically be placed at the end of the list working on the principle, those who wish to receive an organ must be willing to give one.

Due to cultural, religious and political reasons, the DDLT rates are dismal in Asia although the recent trends are encouraging, especially in China, where the recent trends suggest that more than 90% of all LT are DDLT. The rest of Asia is also slowly picking up although the donation rates are far from satisfactory. India despite a population of 1.2 billion, has an organ donation rate at a miniscule 0.08 pmp.²³ This is despite India having highest number of deaths from road traffic accidents in the world. Poor organ donation rates in India could be explained by multiple reasons. There is lack of awareness and education regarding organ donation. There is also an inadequate coordination and implementation of governmental policies across all the states of India. There is a need for better understanding of brain stem death amongst medical professionals and motivation to identify potential donors. There is an attempt to address these issues by a number of non-governmental organizations (NGOs) like Multi Organ Harvesting Aid Network (MOHAN) foundation.

Brain stem death can only be diagnosed in hospitals with license for organ transplantation. To confirm the diagnosis, two separate sets of tests should be performed at a minimum interval of 6 h and by 4 doctors. In India,

the law is not clear about whether the patient can be taken off life support once brain stem death has been confirmed if the family refuses organ donation. As a result of this ambiguity, both intensivists and physicians are reluctant to ask family members for organ donation. Another social hurdle is the discrepancy in the socioeconomic class of the donors and the recipients, and that financial constraints would never permit the donors to be recipients. This may lead to a feeling of disenfranchisement and poor attitude to donation and transplantation.

Living Liver Donation

Despite all the efforts to increase cadaver organ donation, this is unlikely to completely meet the demands for all patients on waiting list for LT. LDLT has developed to bridge this gap in most western countries. However due to poor organ donation rates, it has emerged as the predominant form of LT in India and most of Asia. Timing of LT for patients who have a living donor remains a critical issue. The patient survival for 5 years is similar following DDLT and LDLT.⁶⁸ The main argument against LDLT is donor safety. The mortality risk to the donor is approximately 1 in 500 (0.2%) and the morbidity risk is 24% from data pooled from various centers.⁶⁹ The main advantage for LDLT is reduction in waiting time, and optimization of the timing of surgery.

Donor Organ Distribution

Due to the relative shortage of organ donors and need to accurately select the candidates who will benefit from LT, it is imperative to have allocation algorithms of organs. It is also important to define the geographic distribution of organs as there is evidence to suggest that prolonged preservation of liver grafts results in increasing rates of graft failure. In USA, there are defined donor service areas of a given Organ Procurement Organization (OPO). UNOS maintains a centralized computer network which links all OPO's. This network is accessible 24 h a day and provides support to transplant centers, helping them with donor recipient matching process, transportation of organs and organ sharing policies. In the UK, when an organ becomes available anywhere in the country, UK Transplant is notified immediately. In the rare situation when there is no suitable patient anywhere in the UK, there is a reciprocal relation with the European Union, which allows the donor organs to be offered to other European countries.

The selection and allocation policies vary in different health care systems. Most policies work on following principles such as assessing medical urgency, utility and benefit in order to streamline the process of prioritization of LT. Although USA has adopted the MELD system, most parts of Europe use the CTP scoring system. Recently, UK has been working on the UKELD score for their patients,

which includes the following parameters, INR, creatinine, bilirubin and sodium.

In Asia, most centers use MELD and CTP scoring system, however with 90% of LTs being living related, the score will not affect the waiting time for LT but certainly help with candidate selection. In India, there is no uniform policy for organ sharing. As health is a state matter in India, any policy related to health must be approved by individual state assemblies.

Liver Transplant Registry

In USA in 1984, the National Organ Transplant Act (NOTA) allowed for Organ Procurement and Transplantation Network (OPTN) to be created and run by United Network of Organ Sharing (UNOS) which is a private non-profit organization under federal contract. This organization has helped to streamline the process of LT by maintaining region-wise procurement, allotment and registry data across USA.^{8,9} Similarly, the idea of European Liver Transplant Registry (ELTR) was first proposed by Prof Henri Bismuth in 1985. This registry has data on all LTs performed in Europe from 1968 to present. Currently, nearly 145 centers in 25 countries of Europe are contributing to ELTR. Similar registries are being maintained in Japan, Korea and China.

Due to increasing number of solid organ transplants in India, efforts are in place to establish an Indian Transplant Registry (ITR) with the help of Indian Society of organ transplant (ISOT).

FUTURE DIRECTIONS

The challenges facing the international transplant community are similar across the world. Improved results have widened the indications for liver transplantation. Increasing numbers of recipients are being listed for LT. In countries where LDLT forms the cornerstone of LT, many recipients are denied the opportunity for an LT because of the lack of a suitable donor. These countries need to increase awareness of and improve rates of cadaveric organ donation. There are encouraging trends from some countries such as South Korea and China, but other countries such as Japan and India have not made any significant progress in this direction.

The countries in the west face the challenge of minimizing their waiting list mortality, which currently stands at an average of 10–15%.^{70–72} The waiting times for a liver transplant are increasing year on year. In the USA, there are 16,000 patients on the waiting list and only about 6000 transplants are done every year. The situation is similar across most of the western world. These countries have been slow in adopting LDLT and may need to make renewed efforts towards introducing adult to adult LDLT. At the same time, improving cadaveric organ donation and maximal utilization of available organs is

also an important goal. Although a lot of effort has been made to use DCD livers, the results are still suboptimal. This is an area of continued research and if outcomes could be improved, this will go a long way towards increasing the availability of cadaveric donors. ABO incompatible LT have been done both in the east and the west, but the results are still not optimal. There may be some merit in using them in desperate situations.

Although LDLT has been shown to have similar outcomes to DDLT in terms of survival, biliary complications after LDLT are higher than after DDLT and contribute significantly to the morbidity after LDLT. These complications, reported to be between 25–30%,^{73,74} are the Achilles heel of LDLT, and have more or less remained constant. Improved understanding of the blood supply of the biliary tree and technical refinement at all stages of the donor and recipient operation may be needed to minimize this risk.

Hepatitis C recurrence is also a common and difficult problem to deal with in the months to years after LT, and has the potential to significantly impact on the long term results. Newer drugs for the treatment of Hepatitis C, which may be in clinical use in the near future will significantly benefit these patients and improve outcomes. There are also many complications associated with long term use of immunosuppressive drugs. The challenge is to reduce long term complications by judicious use of the available immunosuppressants or eventually eliminate their use by innovative methods to induce immune tolerance.

In addition, India faces some unique additional challenges. The most important is the accessibility to LT, which at the moment is primarily available in large private hospitals. As a result, a large number of patients with ESLD who cannot afford the high costs of the procedure, cannot have a liver transplant. The national cadaveric organ donation rate at the moment in India is only about 0.08 per million population.⁷⁵ The organ donation rates in some states, such as Tamil Nadu, have shown encouraging improvement, but this needs to be replicated in other parts of the country. In addition, we need to have a network for an equitable distribution of cadaveric organs, and the mechanisms to make them available in all parts of the country.

In conclusion, although LT as a therapeutic modality is now 50 years old, it is still evolving with newer indications, newer techniques and newer medications, all of which aim to make this procedure safer and more accessible.

CONFLICTS OF INTEREST

All authors have none to declare.

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