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Mini Review

An Overview of Current Status, Recent Techniques and Challenges of Liver Transplantation

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Abstract

A liver transplantation (LT) is a surgical procedure that removes a liver that no longer functions properly and replaces it with a healthy liver from a living or deceased donor. It is a viable treatment option for end-stage liver disease and acute liver failure. The most commonly used technique is orthotopic transplantation or deceased donor liver transplantation (DDLT) in which the native liver is removed and replaced by the donor organ in the same anatomic location as the original liver. Ongoing challenges of LT include those concerning donor organ shortages, recipients with more advanced disease at transplant, growing need for transplantation, side effects associated with long-term immunosuppression, toxicities and obesity. Organ shortage has become the most vexing problem in LT, with 10–25% of patients dying while awaiting transplantation. Different ideas has been evolved like living donor liver transplantation (LDLT), marginal donor liver transplantation (MDLT) and split liver transplantation (SLT) to overcome the growing problem of organ shortage. These techniques are becoming very important in an attempt to narrow the gap between demand and supply of organs. The advances in surgical and anaesthetic techniques, greater understanding of the physiological, haematological, biochemical, microbiological and immunological changes in liver disease and transplantation allowed a multidisciplinary approach that led to better outcomes. These changes, coupled with more effective immunosuppressive and anti-microbial agents and improvements in patient and donor selection, mean that now liver replacement is a routine procedure with excellent long term outcomes.

Keywords: liver; transplantation; challenges; organ shortage; immunosuppression

Introduction

A hepatic transplantation is a surgical procedure of allografting of healthy liver from a living or deceased donor in a liver failure patient. It is a viable treatment option for end-stage liver disease and acute liver failure. The surgical technique is very time demanding and ranges from 4 to 18 hours. Many disconnections and reconnections, anastomoses and suturing of abdominal and liver tissue, must be made for the transplant to succeed. LT is potentially applicable to any acute or chronic condition resulting in irreversible liver dysfunction, provided that the recipient does not have other conditions that will preclude a successful transplant. Most liver transplants are performed for chronic liver diseases that lead to irreversible scarring of the liver, or cirrhosis of the liver. The main indications for liver replacement are alcoholic liver disease, hepatitis C virus (HCV), non-alcoholic liver disease and liver cancer.

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Recent study has shown that selected patients with severe alcoholic hepatitis may also benefit from liver transplant (Neuberger, 2016). Uncontrolled carcinomas outside the liver, active drug or alcohol abuse and active septic infections are absolute contraindications.

The LT is either orthotopic called DDLT or LDLT. Orthotopic transplantation is the most commonly used technique in which the diseased liver is removed and replaced by the healthy donor organ in the same anatomic location as the original liver. The major challenges in these processes are difficulties with donor organ quality, recipient selection, operative and perioperative management, immune suppression and infectious complications. Donor organ shortages, recipients with more advanced disease at transplant, growing need for transplantation, toxicities and adverse effects associated with long-term immune suppression, toxicities and adverse effects associated with long-term immune suppression, obesity and nonalcoholic steatohepatitis (NASH) epidemics, HCV recurrence and the still inscrutable biology of hepatocellular carcinoma are the recent challenges of LT (Zarrinpar & Busuttil, 2013) (Fig.1).

Orthotopic LT recipients experience and succumb to the same afflictions of old age as non-transplant patients, but with greater frequency and at an earlier age (Sethi & Stravitz, 2007). Successful transplant outcomes require optimal patient selection and timing. Currently, the major limitation facing liver transplant centers are the shortage of organs. The limited availability of organs has led to long waiting periods for LT and consequently many patients become seriously ill or die while on the waiting list (Alqahtani, 2012). The recent advances in surgical and anaesthetic techniques, greater understanding of the physiological, haematological, biochemical, microbiological and immunological changes in liver disease and transplantation allowed a multidisciplinary approach that led to better outcomes. These changes, along with more effective immunosuppressive and anti-microbial agents and improvements in patient and donor selection, mean that now liver replacement is a routine procedure with excellent long term outcomes (Neuberger, 2016). This review summarizes the history of LT, current status and challenges for the recipients, transplant surgeons and researchers for making the acceptance or success rate of transplantation high.

Background

Vittorio Staudacher from Milan, Italy first time reported Orthotopic canine LT in 1952 and C. Stuart Welch performed heterotopic canine LT in 1956. Later in 1957, Jack Cannon performed orthotopic canine LT. Human LT was first attempted by Thomas Starz in 1963. Now liver transplantation is practiced in routine way in over 80 countries.

LT is considered the definitive treatment for patients with terminal liver disease like acute and chronic liver failure, cirrhosis and metabolic derangements, which can be corrected with liver transplant. It is also indicated for hepato-cellular carcinoma (HCC) and other hepatic cancers including hepatoblastoma, epithelioid hemangioendothelioma (EHE), and hilar cholangiocarcinoma (CCA) in highly selected cases (Gores *et al*., 2010; Grossman & Millis, 2010; Alqahtani, 2012). Organ shortage has become the most vexing problem in LT, with 10–25% of patients dying while awaiting transplantation (Korzets *et al*., 2000; Alexander & Vaughn, 1991). In the UK there is currently a mortality of about 6% of patients on the waiting list for LT while another 6% are removed from the waiting list because they become too sick to withstand the process of a transplant (Attia *et al*., 2008). New techniques have been evolved in an attempt to narrow the gap between demand and supply of organs. These techniques include MDLT (Busuttil & Tanaka, 2003), LDLT and SLT. Al Sebayel *et al* (2015) have found no difference between the survival rates of the two groups (DDLT versus LDLT).

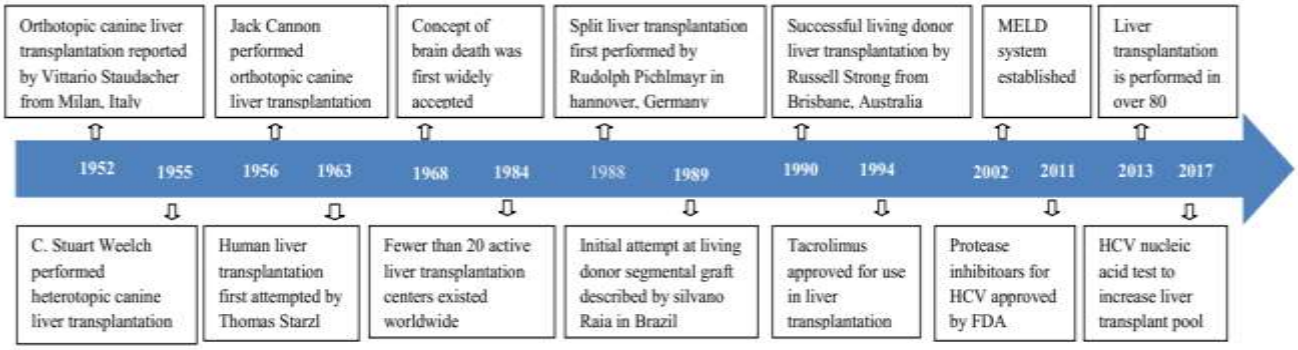

Fig. 1: Selected important activities in liver transplantation; based on Zarrinpar & Busuttil (2013)

Techniques of Liver Transplantation

Deceased Donor Liver Transplantation (DDLT)

Cadaveric LT or DDLT is effective for non resectable early hepatocellular carcinoma (Cheng *et al*., 2001). The conventional technique involves removing the diseased liver combined with the retrohepatic superior vena cava. During this procedure the inferior vena cava is interrupted in its suprahepatic portion. Associated with this, the portal vein ceases its flow to the liver causing infra diaphragmatic venous stasis. Hemodynamic changes are established during this anhepatic phase (when the diseased liver is removed). Cardiac output and mean arterial pressure decrease from the present baseline and may result in intraoperative and postoperative complications. The hemodynamic and metabolic handling of the patient at the moment is a clinical challenge. To avoid the consequences of hemodynamic and metabolic disruption cavo-portal venous, venovenous bypass has been used (Cirilo, 2011). Its use can cause complications such as vascular thrombosis and pulmonary embolism, major or minor vascular injuries, air embolism, hematoma, seroma, nerve damage and wound infection. These complications have the potential to compromise the function of the liver graft and can lead to retransplantation and receptor death.

Some transplantation centers have started to use living donors because of cadaveric organ scarcity, which guarantees transplantation, but may entail a risk to the donor. LDLT is the best strategy, improving life expectancy by 4.5 years compared with cadaveric LT (Cheng *et al*., 2001).

Living Donor Liver Transplantation (LDLT)

In LDLT, diseased liver of recipient is entirely removed and replaced with a piece of healthy liver from a living person. The concept of LDLT is evolved from (1) the remarkable regenerative capacities of the human liver (Pomfret *et al*., 2001) and (2) the widespread shortage of cadaveric livers for patients awaiting transplant (Jeon & Lee, 2010). LDLT is budding as an important surgical option for patients with end stage liver disease, such as cirrhosis, hepatocellular carcinoma often attributable to long-term alcohol abuse, long-term untreated hepatitis C infection, and long-term untreated hepatitis B infection. The potential benefit of LDLT include the superior quality of the allograft despite the smaller size, selection of proper timing for transplantation and a reduced waiting time, which prevents waiting list mortality (Jeon & Lee, 2010). It serves as a best alternative of life saving procedure when a deceased donor liver is not available. Unfortunately, LDLT is a more complicated procedure than DDLT, mainly because of its technical complexity and different physiological requirements resulting from regeneration of a partial graft. Moreover, donor safety continues to be a major hurdle in LDLT (Broering *et al*., 2003; Song & Lee, 2014).

Rapid hepatic regeneration occurs both in donor and recipients due to high regenerating capacity of hepatic cells. Three phases of liver regeneration after massive hepatic resection describe an early phase of rapid regeneration occurring in the first 2 weeks postoperatively which is associated with vascular engorgement. The second phase takes place 1–2 months postoperatively, and is characterized by a decrease in liver volume that is thought to be associated with the normalization of the vascular engorgement and resolution of tissue edema. In the final phase, there is a slow increase in volume until the liver volume reaches a constant level. Liver regeneration has been reported to halt after the liver achieves 75–95% of its original liver volume (Pomfret *et al*., 2001). Young and very sick children may benefit more from this technique because the number of available full size cadaveric organs is limited with following high mortality on the waiting list. The graft survival rate found to be more than 80% in most transplant centers (Broering *et al*., 2003).

In a typical adult recipient LDLT, 55 to 70% of the liver (the right lobe) is removed from a healthy living donor. The donor's liver will rejuvenate approaching full function within one to one and half month, and will almost reach full volumetric size with recapitulation of the normal structure. It may be possible to remove up to 70% of the liver from a healthy living donor without harm in most cases. The transplanted portion will attain 100 % function and the proper size in the recipient as well, although it will take longer than for the donor. Very few individuals require blood transfusions during or after surgery. All potential donors should know there is a 0.5 to 1.0 percent chance of death. Other risks of donating a liver include bleeding, infection, and painful incision, possibility of blood clots, prolonged recovery and portal thrombosis because of the large use of cryopreserved venous segments to enlarge the portal vein. The vast majority of donors enjoy complete and full recovery within 2–3 months.

Liver Donor Requirements

Any member of the family, parent, sibling, child, spouse or a volunteer in a good health condition having a charitable desire of donation without financial motivation of the age between18 and 60 years old can donate their liver. Before one becomes a living donor, the donor must undergo testing to ensure that the individual is physically fit. Sometimes CT scans or MRIs are done to image the liver. In most cases, the work up is done in 2–3 weeks. The donor's blood group must be compatible with the recipient's, although some centers now perform blood group incompatible transplants with special immune suppression protocols. There are several advantages of LDLT over cadaveric donor transplantation because transplant can be done on an elective basis because the donor is readily available and the possibilities for complications and death are fewer than there would be while waiting for a cadaveric organ donor.

Marginal Donor Liver Transplantation (MDLT)

A marginal graft could be defined as an organ with an increased risk for poor function or failure that may subject the recipient to greater risks of morbidity or mortality. The liver is a `privileged' organ, with a dual blood supply, rarely involved by atherosclerosis, and with relatively preserved function at old age. Therefore, the concept of marginal donors for LT is very important to face the growing problem of organ shortage. The patients which die from acute cerebrovascular disease, intracranial hemorrhages, and chronic liver failure can be considered as potential liver donors called marginal donors, especially if they are free of known liver diseases (Korzets *et al*., 2000).

Broadly, there are two categories of marginal grafts. Firstly, there are grafts, which carry a high risk of technical complications and impaired function, examples of which are steatotic livers, non-heart beating donors (NHBD), elderly donors, and split livers, donors with high inotrope requirement or long ischaemia times. Secondly, grafts will be considered marginal if they carry a risk of transmission infection or malignancy to the recipient. This increased use of marginal grafts has been driven primarily by two factors: the critical shortage of donor organs for transplantation and data demonstrating that marginal grafts may be used with favorable outcomes (Busuttil & Tanaka, 2003). Tisone *et al* (2004) have reported that there is no difference between marginal and standard donors, even in sick patients, with the exception of donor age.

Reduced Size Liver Transplantation (RSLT)

RSLT was first reported in 1984 by Bismuth, and involves *ex vivo* resection of an adult cadaveric liver in order to create an appropriate sized liver graft for an infant or small child. It is introduced as a surgical solution for decreasing the pediatric liver transplant waiting list mortality which uses organs from donors much larger than the recipient, but does not increase the total number of livers available for transplantation. This is because the reduced-sized portion is not used and discarded (Pomfret *et al*., 2001). Reduced-size LT diverts the limited organ supply from adult to pediatric patients without increasing the absolute number of available grafts. Since this technique resulted in discarding the remaining portion of liver, it clearly had a negative impact on the adult population awaiting LT, and for that reason, is rarely used today. Unlike RSLT, SLT resulted in an increased number of organs in the donor pool with each cadaveric liver giving rise to two functioning allografts.

Split Liver Transplantation (SLT)

According to the report of Organ Procurement and Transplantation Network in January 2017, 14,450 patients were awaiting a liver transplant (Hashimoto *et al*., 2014). Many patients continue to die while awaiting a life-saving transplant. The shortage of available organs was previously most acute for pediatric patients. The mortality rate among patients on the wait list was commonly high when only whole-organ transplantation was performed because of the small number of pediatric donors. RSLT, in which infants and children receive a portion of the adult liver, was introduced in 1984. Although RSLT decreased the waiting list mortality of nearly 50% among children, it increased the number of adult patients on the waiting list, since the organs were withdrawn from the adult organ pool. This problem was addressed by SLT, in which a deceased donor liver is divided into two parts for two recipients. The technique was first described by Pichlmayr in 1988. The split-LT offers the attractive concept of transplanting two patients with one donor liver, only children, or occasionally, small adult patients benefit from the additional left lateral segment graft provided by splitting (Lo *et al*., 1997). As most commonly performed, SLT involves the division of donor liver from a deceased adult between a pediatric recipient and an adult recipient to maximize the benefit of each available donor organ. However, living-donor partial liver grafts are also used. It allowed the preparation of two split grafts by dividing all vascular and biliary structures and parenchyma for the benefit of two recipients, one receiving a right lobe graft and the other receiving a left lobe (2-4 segments) or left lateral one (2-3 segments) (Nadalin *et al*., 2006).

Contraindication for Liver Transplantation

Relative contraindications to liver transplant are those that may prevent optimal allograft and patient outcome but may be correctable prior to transplantation (Table 1). Absolute contraindications consistently lead to poor post-transplant outcome and should prevent LT outcome and should prevent LT in all circumstances (Table 2) (Alqahtani, 2012).

Complications after Liver Transplantation

Bleeding, hepatic artery thrombosis and primary non-function are the immediate surgical complications after LT. The delayed surgical complications after LT are hepatic artery thrombosis, bile leak, biliary stricture, rejection and infection caused by microorganisms.

Challenges

Organ shortage

Despite of the advances in donor selection, surgical technique, immunosuppression, and peri-operative management, the need for liver replacement exceeds organ availability. A variety of approaches have been implemented to expand the organ donor pool including live donation, a national effort to expand deceased donor donation, split organ donation, paired donor exchange, national sharing models and greater utilization of expanded criteria donors (Saidi & Kenari, 2014). This ongoing shortage of organs has led surgeons to develop innovative techniques in an attempt to expand the donor pool, and clinicians are continually modifying criteria to accept organs. The appropriate donor-recipient match allows the use of grafts that otherwise would be discarded due to

anatomic anomalies. The organ scarcity becomes more challenging in the state of re-transplantation where the use of a limited resource such as a liver graft must be weighed against the risk of a more difficult surgery (Gruttadauria *et al*., 2010).

Table 1: Relative contraindications in LT (adapted from Alqahtani, 2012)

Contraindication	Comment
Age >65 years	If otherwise healthy, older patients do well, but overall long-term survival is decreased compared to younger patients.
	10% of liver transplants performed in the United States in 2008 were in patients >65 years old.
Severe malnutrition	Survival decreases when BMI is <19–20 at time of transplantation. Malnutrition may be reversible with vigorous therapy.
Other organ failure	Can organ failure (i.e., ischemic heart disease) be corrected such that transplantation is possible?
Previous upper abdominal surgery	Will the transplant be technically feasible?
Poor functional status	Does the patient have the strength to survive the operation and recover postoperatively
Poor medical compliance	Poor compliance with the medical regimen may lead to graft failure and poor outcome post-transplant.

Table 2: Absolute contraindications to LT (adapted from Alqahtani, 2012)

Contraindication	Comment
Severe cardiopulmonary disease	In this setting, the heart or lung disease would prevent successful operation.
Irreversible cerebral injury	In patients with acute liver failure, elevated intracranial pressure leads to cerebral edema and ultimately brainstem herniation. If intracranial pressures are elevated and unresponsive to treatment, patients fail to regain mental function post transplant.
Sepsis or active infection	This would portend a poor outcome after surgery, especially in the context of immunosuppression.
HIV/AIDS	AIDS-defining illness or HIV unresponsive to highly active antiretroviral therapy carries a poor survival outcome making LT futile.
Extra-hepatic malignancy	Including hepatic malignancies with loco-regional or distant metastases If a patient has history of malignancy, the disease-free period should be 2–5 years, depending on the type of malignancy
Vascular	An anatomic anomaly (such as in the hepatic artery) or extensive portal and mesenteric vein thromboses may preclude transplantation due to technical difficulty.
Active alcohol or drug usage	Patients must be abstinent of alcohol and illicit drugs (and in some institutions, tobacco) for a minimum of 3–6 months.
Psychosocial issues	Inability to understand the procedure and the lifetime commitment it entails severe psychological disorders which will prevent medical compliance; or Lack of social support.

Inadequate donor procurement, the risk/benefit ratio in transplantation, the time needed for diagnosing and certifying death coupled with the necessity of shortening ischemia time for retrieved organs have a strong impact on terms and timing of suitability evaluation of the potential donor. Despite such limits and the fact that even good clinical practice behavior cannot eliminate the risk of transmission of infectious or neoplastic pathologies, any retrieved organ should have an acceptable quality and should not expose the recipient to unacceptable risks. In hepatitis C, new drug combinations may improve the disease control, reducing the progression to cirrhosis and also the risk of post-transplant re-infection allowing to anticipate a future decrease in the indications for transplantation and re-transplantation in these patients (Lucidi *et al*., 2015). In hepatocellular carcinoma patients, surgical resection or radiofrequency destruction has now appeared as an alternative to liver transplant.

Immunosuppressive Management

A liver transplant will be unsuccessful like most other allografts unless immunosuppressive drugs are used. Immunosuppressive regimens include calcineurin inhibitors (CNIs), anti-metabolites, mammalian target of rapamycin (mTOR) inhibitors, steroids and antibody-based therapies. These agents act at different sites in the T-cell activation cascade and cause inhibition of activation or depletion of T-cell (Pillai & Levitsky, 2009). The use of CNIs (tacrolimus, TAC and cyclosporine, CsA) was reported in 97% of patients discharged from the hospital after OLT in the United States in 2004. Corticosteroid is the most reported immunosuppressive drug prescribed at the time of patient's discharge followed by mycophenolate mofetil (MMF) and azathioprine (AZA). Sirolimus (SRL) use was noted in nearly 5% of OLT patients at discharge (Eghtesad *et al*., 2010).

CNIs and corticosteroids are the primary immunosuppressant used in LT. The anti-proliferative agents MMF, AZA, and SRL are generally prescribed as an adjunctive medication in addition to CNIs. Antibody induction therapy has been limited to the perioperative period as a means to reduce early exposure to CNIs or to obviate the need for large doses of perioperative corticosteroids. Most liver transplant recipients receive corticosteroids plus a calcineurin inhibitor such as TAC or CsA plus a purine antagonist such as MMF. Side effects of immunosuppressive drug induced nephrotoxicity, diabetes, hypertension, hyperlipidaemia, osteoporosis and neuropathy play an essential role in long term allograft and patient survival (Encke *et al*., 2004; Mukherjee & Mukherjee, 2009). The adverse side effects of CNIs, the main class of immunosuppressive agents used in LT, has led to consideration of the use of antibody induction therapies for patients at higher risk of developing adverse side effects (Moini *et al*., 2015). The risk of chronic rejection in the liver transplant recipients decreases over time, although the great majority of recipients need to take immunosuppressive drugs for the rest of their lives. It is possible to be slowly taken off anti-rejection medication but only in certain cases.

Graft Rejection

Klintmalm *et al* (1989) reported that 39.4% of the patients never experienced acute rejection, and 60.6% had at least one episode of acute rejection. After a LT, there are three types of graft rejection that may occur. They include hyper-acute rejection, acute rejection and chronic rejection. Hyper-acute rejection may occur a few minutes after the transplant when the antigens are completely unmatched. It is characterized by the binding of these antibodies to antigens on vascular endothelial cells. Complement activation is involved and the effect is usually profound. Unlike hyper-acute rejection, which is B cell mediated, acute rejection is mediated by T-cells. It involves direct cytotoxicity and cytokine mediated pathways. Acute rejection may occur any time from the first week after the transplant to 3 months afterward. All recipients have some amount of acute rejection. Acute rejection is the most common and the primary target of immunosuppressive agents. Chronic rejection may occur over many years. The constant immune response of body against the new organ slowly damages the transplanted tissues or organ. The cause of chronic rejection is still unknown but an acute rejection is a strong predictor of chronic rejections. Liver rejection may happen any time after the transplant. Lab findings of a liver rejection include abnormal level of liver enzymes and values such as prothrombin time, ammonia level, bilirubin level, albumin concentration, and blood glucose. Physical findings include encephalopathy, jaundice, bruising and bleeding tendency.

Preservation of the liver before transplantation

It is necessary to maintain organ viability after donation till transplantation for optimal graft function and survival. In the clinical practice, static cold storage is the most widely used form of preservation. However, ischemic damage present in donation after circulatory death (DCD) grafts jeopardizes organ viability during cold storage. A hypothermic machine perfusion (HMP) technique has recently been developed to prevent ischemia-reperfusion injury in DCD liver grafts and may be superior to static cold preservation (Henry *et al*., 2012).

Medical Management of the Liver Transplant Recipient

The life expectancy of orthotopic liver transplant (OLT) recipients continues to increase with improvements in preoperative management and immunosuppression (Robert *et al*., 2004).

Table 3: Adverse metabolic effects of common immunosuppressive agents in OLT recipients: relative risk (adapted from Sethi & Stravitz, 2007)

Adverse effect	Ciclosporin A	Ciclosporin A	Ciclosporin A	MMF	Corticosteroids
Hypertension	+++	+++	-	-	++
Renal insufficiency	+++	++*	-	-	+┼
Diabetes mellitus	-	+	-	-	++
Diabetes mellitus	+	-	++	-	+
Diabetes mellitus	+	+/-	+++	-	+
Osteoporosis	++	+	-	-	+++

***** Lower nephrotoxicity of TAC compared with CsA has been reported in several series but remains controversial. ┼ Corticosteroids may exacerbate calcineurin-induced renal insufficiency by increasing hypertension, but do not have direct nephrotoxic effects.OLT, orthotopic liver transplant; MMF, mycophenolate mofetil.

Hypertension develops within the first 6 months of transplantation in 50% of OLT recipients, and up to 75% in long-term follow-up (Table 3). The declining post OLT hypertension may be due to advances in immunosuppression regimens, such as avoidance or early withdrawal of corticosteroids and the use of less nephrotoxic CNIs.

Conclusion

Ongoing challenges of LT include those concerning donor organ shortages, recipients with more advanced disease at transplant, growing need for transplantation, toxicities and adverse effects associated with long-term immunosuppression. Organ shortage has become the most vexing problem in LT, with 10–25% of patients dying while awaiting transplantation. Different ideas have been evolved such as LDLT, MDLT, RSLT and SLT to overcome the growing problem of organ shortage. Refinements of surgical techniques, improved patient selection and management, better organ preservation and improved immunosuppressive medications have improved results with LT. Now, LT is practiced in routine way in different transplantation centers over 80 countries.

Conflict of Interests

The authors declare that they do not have any conflict of interests.

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