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Chapter 9

Trends and the Current Status of Living Donor Liver Transplant

Ramesh K. Batra and David C. Mulligan

Additional information is available at the end of the chapter

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Abstract

The need for liver transplant and its timely nature are both equally vital for a patient with end stage liver disease. But the ever-growing need for liver transplant across the entire world threatens the two reasons that justify its very existence. The popularity of living donor liver transplant has met great enthusiasm amongst the transplant physicians and surgeons, as it is timely, and also yields superior survival benefit as compared to a deceased donor liver transplant. Living donor liver transplant has been constantly adapting to meet the needs of patients and the expanding wait list. The need for a living donor liver transplant is not the same amongst the various parts of the world, because the population and the disease burden is different. We looked at the trend of living donor liver transplant across the world and also the change in practices over time including a glimpse of what lies ahead for the next decades.

Keywords: living donor liver transplant, deceased donor liver transplant, graft recipient weight ratio, small for size syndrome, United Network for Organ Sharing

1. Introduction

Liver transplant is the gold standard treatment for end stage liver disease (ESLD). This also, being the most viable option for ESLD patients, as there is no bridging dialysis unlike end stage renal disease (ESRD). ESLD patients therefore succumb to their disease in absence of a timely liver transplant. In addition to the disease burden, the expanding list of waitlisted patients and the relative shortage of deceased donor livers have subdued the attempts to bridge the gap between the need v/s availability of deceased donor livers for transplant. Therefore, to alleviate death on liver transplant waiting list, the donor organ pool was expanded by living liver donation in the year 1989. In the decades to follow, the success of

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living donor liver transplantation (LDLT) and the growing burden of the waiting list, boosted a revolutionary momentum amongst transplant physicians around the world, offering living donor liver transplants for their waiting patients. But, the momentum of living donor liver transplant was variable in different regions across the world. There were many factors that contributed to this variability, the main ones being, (1) availability or access to deceased donor organs, (2) etiological factors of liver failure and (3) individual surgical practices. The latter pertains to the evolutionary changes of experience within the LDLT centers. The learning curve of LDLT for the donor operation was relatively short given the previous experience of hepatectomies for liver cancer, yielding an expeditious expansion of the living donor liver pool.

2. History

The revolutionary success of liver transplant at the University of Colorado in 1967, under Dr. Thomas Starzl and colleagues [1] came after seven unsuccessful attempts of the team. Although, this was a considerable technical milestone for transplantation, but the survival after liver transplant at 1 year was dismal, 28.8–50% [1]. But after the discovery of cyclosporine by Sir Roy Calne, its use in liver transplant paved the path for a modern era of liver transplants with survival rates at 1 year rising to 78.6% [1]. The success of whole organ deceased donor liver transplant further led to another technical milestone of split liver transplant from a deceased donor in Germany [2]. Soon to follow was the success of living donor liver transplant at the University of Chicago in 1989, by Christopher Broelsch and colleagues. Around the same time, LDLTs in Australia, Brazil and Japan were successfully performed [2], but as an emergency procedure. But, all these pioneered LDLTs had one thing in common, that they were in-fact pediatric liver transplants utilizing the left lateral segment grafts from the donor liver, and as the LDLT experience grew, various anatomical split liver transplants for LDLT were performed with promising results for both adults and children. As the individual experience of transplant centers grew over the learning curve of at least 15 LDLTs, this allowed to broaden the acceptance of donor candidates for a safer donor surgery, whilst also expanding the acceptance of LDLT to benefit more recipients. Over the years, this has greatly helped reduce death on liver waiting list, whilst also allowing friends and family members to actively participate in the well-being of their loved ones by sharing a section of their healthy liver.

3. Liver transplant wait list mortality and MELD score

Wait-list mortality for liver transplant patients is variable across the world. This is mainly due to the variability in access to organs and etiological factors of liver disease. Wait-list mortality, therefore can be as high as 50% in Asia [3] and about 10% in Australia [4]. In United States, over the last two decades, it has averaged at 10% [5].

In US, with the introduction of model for end-stage liver disease (MELD) by United Network for Organ Sharing (UNOS) in 2002, livers are allocated based on MELD score using serum

bilirubin, creatinine, sodium, and INR. According to the policies set forth by UNOS, certain subsets of the wait-listed patients qualify for exception points to this calculated physiologic MELD score. This allows for a preferential access to the allocated liver allografts. This helps minimize death on waiting list for patients who are much sicker than it is captured with their calculated physiologic MELD score or have disease processes that will progress but not cause immediate mortality, which includes patients with hepatocellular carcinoma.

Hepatocellular Carcinoma (HCC) is the leading cause of cancer mortality in the world [6], with overall 1 year survival rates below 50% and five-year survival as low as 10% for advanced disease [7]. Surgical resection definitely improves survival in certain HCC cases. However, many patients have unresectable disease or are cirrhotic, which dampens the survival benefit of resection in such cases [8]. For these subset of patients, liver transplantation has delivered excellent survival benefit, compared to resection [9–11]. Therefore, the survival advantage of liver transplant over other treatment options for HCC patients supported their inclusion to the MELD exception policies of UNOS. The MELD exception points therefore allowed for earlier liver transplantation of the qualified patients, thereby reducing the wait-list mortality to 4.49% for patients listed with MELD exception points. However, the preferential allocation and subsequent liver transplant came at the cost of a significantly higher waiting list mortality of 24.6% for patients without MELD exceptions [12]. This raises an ethical controversy of unequally sharing the public resource of deceased donor organ pool. Although the aim of MELD based allocation, was to objectively quantify the sickness of a cirrhotic patient allowing a better way of resource allocation. However, the disadvantage of certain factors causing immediate mortality that were not measured by the MELD score, like bleeding complications and encephalopathy, unknowingly advantaged the MELD exception group. This led to higher wait-list mortality (24.6 VS 4.49%), higher mean waiting time (180% higher) and a lower transplant rate (40% vs. 79%) for patients without MELD exceptions [12].

4. The need for LDLT

For the western world, LDLT is a viable alternative to bridge the gap between the need for liver transplant and the limited deceased donor liver allografts. It therefore allows for better resource allocation by increasing the total donor organ pool. However, for the eastern world, LDLT serves as the lifeline, as it provides for the majority of liver transplants (**Figure 1**) [13]. This is due to the disproportionately low number of deceased donors in the East vs. the West. In the year 2000, there were 0.07–6.5 deceased donors per million populations in Asia, whereas 35.1 and 25.2 deceased donors per million population in Spain and the US respectively (**Figure 2**) [13]. The lack of deceased donation rates in the eastern world has been largely crippled by the cultural and religious barriers of the public, limiting acceptance of the concept, and therefore practice of organ donation for transplant [14, 15]. Due to these factors, Asia follows a much stricter organ allocation based entirely on MELD score with no exception points. Hence tumor progression due to the longer waiting time rendering a patient non-transplantable has been a grave concern. For these subset of patients, LDLT allows for a timely transplant to limit further spread of HCC and also providing another valuable resource and choice to patients waiting for a liver transplant.

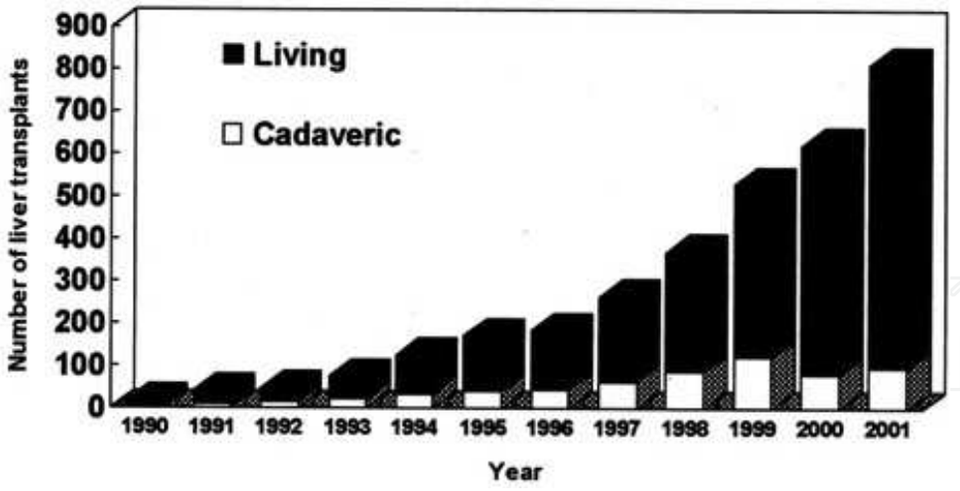


Figure 1. Comparison of annual deceased (cadaveric) and living-donor liver transplantation rates in Hong Kong, Japan, Korea, and Taiwan (pooled data) [13].

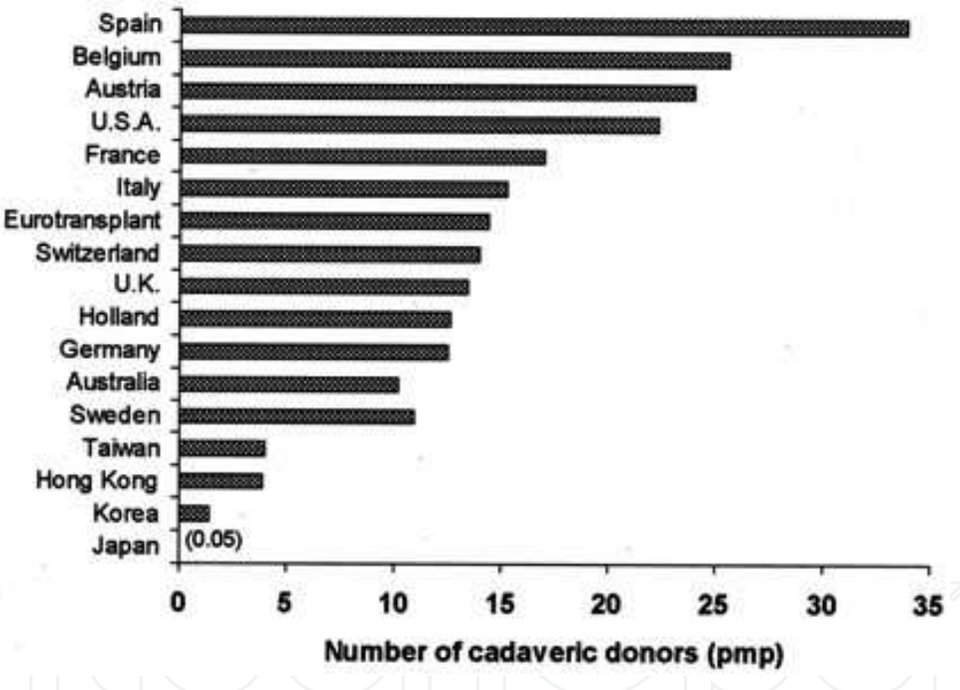


Figure 2. Number of deceased (cadaveric) donors per 1 million population (pmp) in different countries in the year 2000 [13].

5. Living donor liver transplant: statistics

In United States, until 1991, LDLT, an alternative to deceased donor liver transplant (DDLT) was offered at only one center. But by 2001, 67 transplant centers were offering LDLT for their patients. Its contribution to the US donor organ pool for livers started slow, but expanded

exponentially within a decade. In 1991, the 22 LDLTs (0.75% of all liver transplants) at only one center in United States, rose to 524 total LDLTs (10% of all liver transplants) by the year 2001 [16]. This opportunity to offer LDLT for patients was met with much greater enthusiasm in Asian transplant centers, who had been suffering with low deceased donation rates due to the earlier discussed barriers. Asian transplant centers (comprising of Japan, Hong Kong, Korea and Taiwan) started with about 50 LDLT cases in 1999, but in less than a decade, rose to 1387 (>90% of all liver transplants) by 2005 [17], a much greater rise when compared to United States.

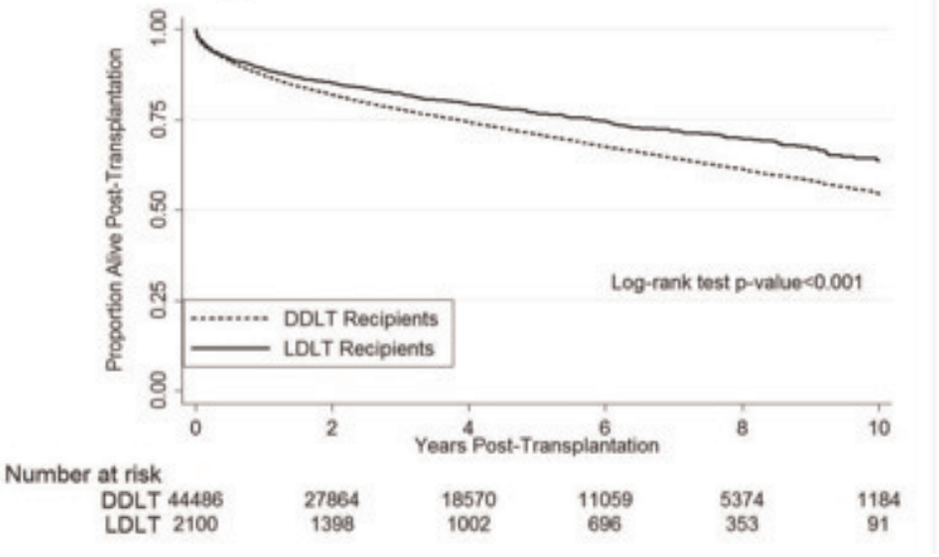


Figure 3. Post-transplant patient survival [18].

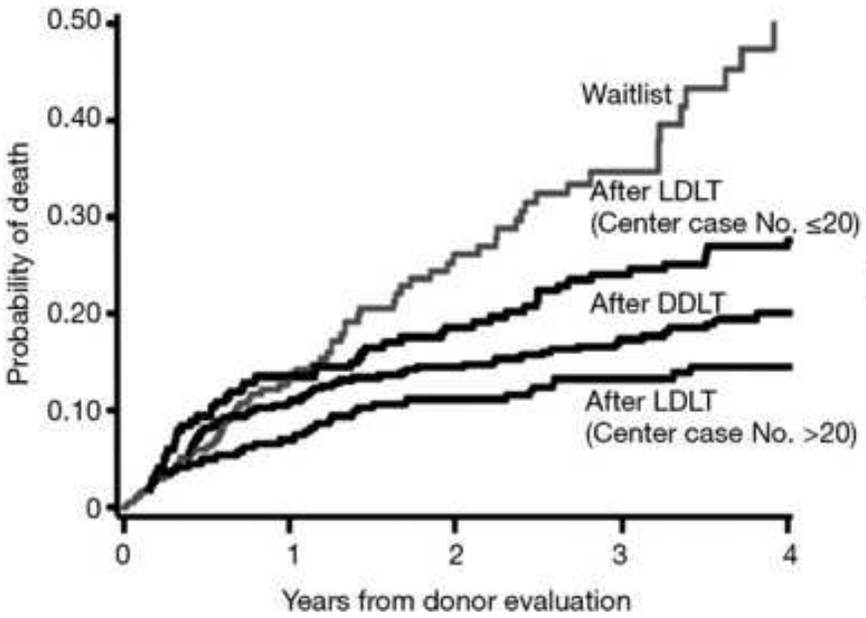


Figure 4. Cumulative risk of death whilst waiting for a liver transplant, compared to LDLT based on center experience and DDLT [19].

The encouraging growth in LDLT volume and its timed elective nature, yielded superior graft and patient survival when compared to DDLT (**Figure 3**) [18]. But it is noteworthy, the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) group in United States showed that a low volume LDLT transplant center (center case no. <20) had far poorer outcomes when compared to DDLT (**Figure 4**) [19]. This echoes the learning curve that follows a novel surgical technique but also the updation of the infrastructure that a transplant center needs during the initial experience.

6. Trend of living liver donors

As the experience grew with LDLT amongst the transplant surgeons, there was constant fine tuning of the technique for both the donor and recipient operations. The refinement of technique allowed for the donors who were once considered anatomically unfeasible to be much more openly accepted, further increasing the living liver donor pool available for transplant.

6.1. Donor age

The majority of living liver donors in United States are <50 year old patients. But in the three decades since the first successful LDLT in Chicago, the living liver donor pool for donors >50 years and also for >65 year old, has doubled (**Figure 5**), whilst reducing the percentage share of the living donor pool from <50 year old donors. This is largely due to the reduced no. of <50 year old live liver donors available, further complicating the increased burden on the liver transplant waiting list in United States. Therefore, this increased demand has somewhat driven the acceptance of extended age spectrum for living liver donors.

Increased donor age, i.e., above 50 years has profound negative impact on long term patient survival after a Deceased Donor Liver Transplant (DDLT) [21]. This is thought to be largely due to the poor tolerance of such liver allografts to longer cold ischemic times and the ischemia-reperfusion injury that follows. In LDLT too, donor age > 50 years negatively impacts recipient survival [22, 23], but not at a significant rate when compared to the DDLT experience with older donors. But the reduced patient survival is hard to explain, especially when LDLT has much shorter cold ischemic times which are significantly higher in a DDLT.

Liver allograft regeneration in LDLT has been shown to be impaired in older liver donor allografts [22], however this effect seems to disappear in a prospective study [24]. At a molecular level, activation of phosphorylated-Signal Transducer and Activator of Transcription 3 (p-STAT3) gene through signal transduction of cytokines protects hepatocytes from apoptosis and oxidative stress [25] and p-STAT 3 is under-expressed in LDLT from donors>50 years [25]. This imbalance of anti-apoptotic and anti-oxidative functions at the cellular level could explain the reduced graft and patient survival in living donor liver transplant from older donors.

Therefore, although LDLT is preferable from a younger donor, but LDLT from older donors, still confers a far superior survival advantage in comparison to waiting on the liver transplant wait-list.

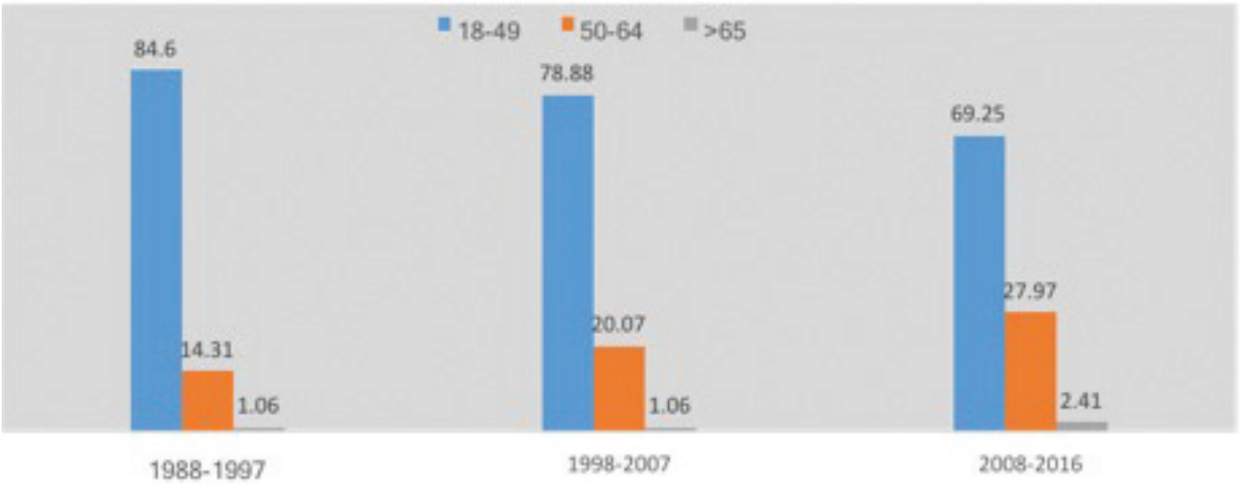


Figure 5. Age distribution of living liver donors in the last three decades in the US [20].

6.2. BMI and macrosteatosis

Hepatic steatosis marginalizes the quality of the allograft by compromising graft and patient survival in short and also long term [26, 27]. It is also associated with higher incidences of Primary Non-Function (PNF) [27] in DDLT. The positive predictive value of PNF after a DDLT based on a deceased donor liver biopsy can be as high as 90% [28], therefore transplant centers when accepting donor livers>30% macrosteatosis on liver biopsy are cautious, and control other variables that can jeopardize the outcomes, like cold ischemic time and warm ischemic time [29]. But, such detailed causal relationship of hepatic steatosis with PNF has not been well studied in LDLT. Furthermore, to establish the true level of hepatic steatosis, a liver biopsy is needed which carries although low but un-needed risks for the living donor, i.e. 5% risk of serious complication and 1% risk of significant bleeding and 1 in 10,000 risk of a fatality [30, 31]. Therefore, transplant centers tend to avoid routine liver biopsies in living liver donors during evaluation, but some, instead rely on the BMI as an indicator of hepatic steatosis [32]. But obesity has been rising in the last two decades across the world. In 2012, in United States, 69% people were overweight (BMI > 25) and 35% obese (BMI > 30) [33]. Therefore, in presence of the obesity epidemic, and the rising liver transplant waiting list, should transplant centers be selective in choosing living liver donors with BMI > 30, especially when it has been demonstrated that BMI > 30 is not a contraindication for live liver donation [34]. The yield of such a donation also had comparable results for donor safety and donor complications in both short and long term when compared with live liver donors with BMI < 30. Furthermore, the recipients also enjoy similar graft/patient survival both in short and long term (**Figure 6**) [34]. Therefore, when considering obese live liver donors, accepting Graft Recipient Weight Ratio (GRWR) of a higher value (1.42 vs. 1.17, p = 0.0001) can yield the desired donor safety and comparable recipient outcomes [34]. However, there is no ideal GRWR, that is considered optimal in an obese live liver donor, because values as low as 0.74 have successfully achieved comparable and good recipient outcomes [35]. It is also thought that various techniques for Graft Inflow Modulation (GIM) allows for accepting and safely transplanting a lower GRWR liver allograft in LDLT to minimize Small For Size Syndrome (SFSS) [36], whereas others are of

the belief that higher portal pressures on the contrary help in liver regeneration [35, 37] thereby avoiding the need for GIM.

6.3. The debate of right vs. left lobe donor hepatectomy

The very first few LDLTs performed were in pediatric patients, utilizing Left Lateral Segment (LLS) liver grafts. This was technically easier for the recipients, whilst offering higher level of donor safety. Both these factors were paramount in gaining the needed success and popularity of LDLT across the world. Meanwhile in adult recipients, right lobe versus left lobe LDLT was debated heavily for two decades. The debate aimed at balancing donor safety and recipient outcomes. Although, logic and ethics favored donor safety, but the recipient risks and outcome were equally important, thus feeding the debate. Normally, the right lobe of the liver is larger and denser than the left lobe, which is much smaller and flatter. Therefore, a left lobe hepatectomy generates a smaller allograft providing higher safety for the donor but limiting the choice of recipient. This blunted the popularity of LDLT in adult patients. But in 1997, the feasibility of using a right lobe liver graft safely in adults by overcoming the graft size matching, opened the gateway for adult LDLTs [38, 39].

In United States, right lobe living donor hepatectomy remained the choice for 95% adult LDLTs, between 1998 and 2009 [40]. Although the number of left lobe living liver donors were smaller for statistical inference, nonetheless, A2ALL consortium concluded, a higher rate of donor complications with left lobe donation. The Turkish group also noted similar findings, whereby performing 91% right lobe LDLTs between 2007 and 2011, they experienced higher donor complications for left lobe liver donation [41]. Arguably both in the US and Turkey, the number of left lobe liver donation was far smaller for a meaningful covariate analysis, instead, it hinted towards the importance of individual surgeon experience in right or left lobe donor hepatectomy.

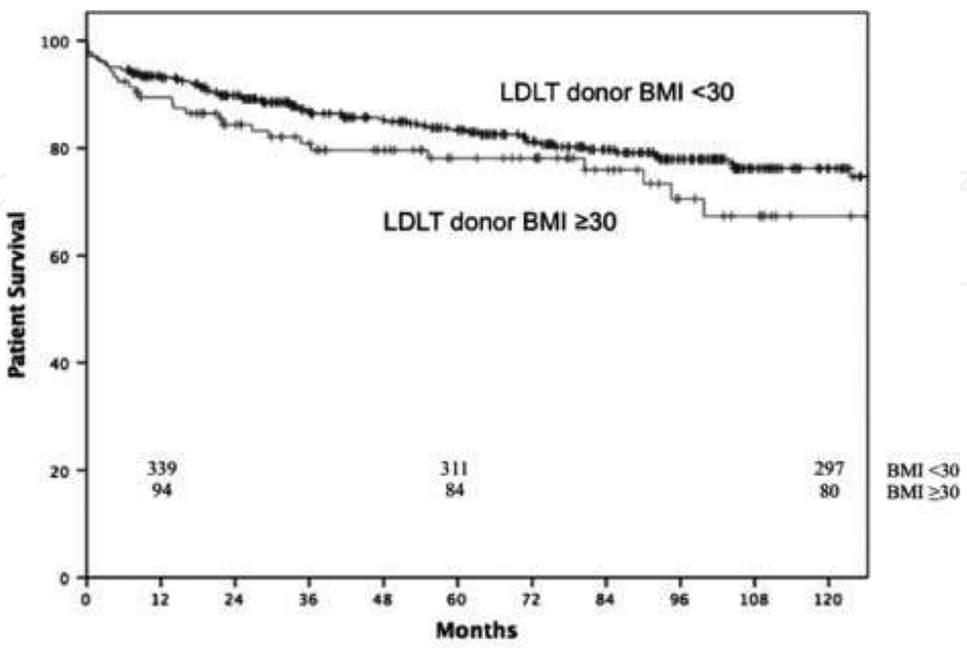


Figure 6. LDLT patient survival based on BMI [34].

The experience in the east was entirely different at the five-large volume Asian transplant centers (Seoul, Hong Kong, Taiwan, Kyoto and Tokyo), wherein 38% were left hepatic lobe donation versus 62% right lobe between 1990 and 2001, with lower complication rates for left lobe donation 7.5 vs. 28% [42]. Furthermore, when the transplant centers performed more left lobe hepatectomy as compared to the right (762 vs. 500), the lower donor complication rates for the left lobe liver allografts even reached statistical significance (18.8 vs. 44.2%, $p < 0.05$) [43].

In summation, the combined experience of living donor hepatectomy across the eastern and western world resonates, that the success of surgery with lower donor complication rates is heavily dependent on the experience of surgeons and their individual practice, than just the laterality of the hepatic lobectomy. Inherently, a living donor transplant carries high stakes, as a donor death or higher complication rate can significantly impact the LDLT practice of an entire nation. In 2001, United States performed a record no. of LDLTs, i.e., 524. But the infamous living liver donor death later that year, crippled the LDLT practice of US to this date, annually averaging to only about 300 LDLTs.

7. Advances in LDLT

7.1. Dual lobe liver transplant

Donor Safety is paramount to the success of LDLT and also for the transplant program. Therefore, inadequate graft size is a major obstacle, considering the low number of donors willing and suitable to donate. Inadequate graft size along with portal hyper-perfusion can lead to Small For Size Syndrome (SFSS), a clinical syndrome characterized by postoperative coagulopathy and liver dysfunction. Various modes of GIM have been proposed to minimize the portal hyper-perfusion and also minimize congestion, but little focus has been on how to encompass the low GRWR. Therefore, dual lobe liver transplant, a technical advancement to the standard LDLT has been described and safely practiced [44] by certain centers. Herein, dual allografts from two separate donors are transplanted heterotopically and orthotopically in one recipient; yielding higher liver volume for better recipient outcome and at the same time, be safer for the living donor(s) (**Figure 7**). Besides being a technically complex operation, it comes with immunological challenges of acute rejection between the two grafts and the recipient, and also between the grafts itself, including the risk of Graft Versus Host Disease (GVHD).

7.2. ABO-i liver transplant and paired exchange

ABO-incompatible (ABO-i) living donor liver transplants have been in discussion and sparse use for almost three decades, and is reserved for urgent cases only. This is because the five-year patient survival rates in adults are abysmally low at 22% [45]. Therefore, ABO-i LDLT has unpopular amongst transplant surgeons. But in 2003, Rituximab, an anti-CD20 monoclonal antibody was introduced in liver transplantation with excellent graft and patient survival rates for ABO-i LDLT [46]. Since then, there have been various immune-modifications by adding plasmapheresis, splenectomy or immunoadsorption columns to Rituximab therapy, in order to successfully cross the blood group incompatibility barrier.

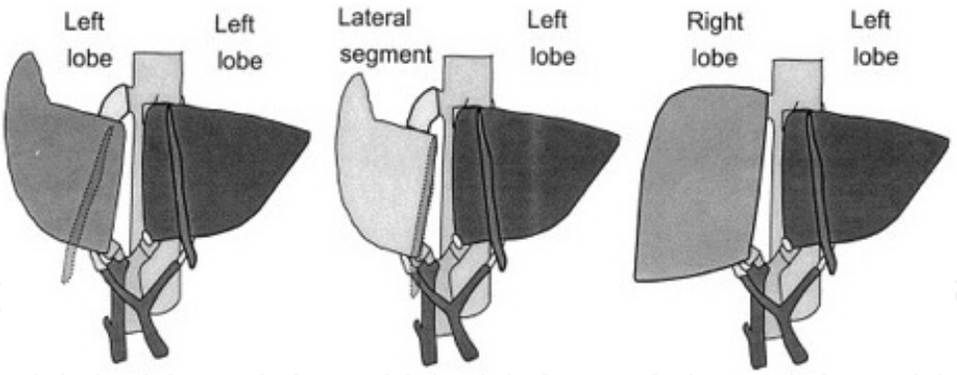


Figure 7. Adult to adult living donor liver transplant, using dual grafts [44].

The other alternative to blood group incompatible liver transplant is liver paired exchange. This requires a very high level of coordination between multiple transplant teams as it can be a logistical puzzle. A paired exchange liver transplant in essence, offers superior survival advantage over an ABO-i liver transplant, but the level of communication can strain the system to fail. There are also socio-cultural issues amongst patients in accepting someone else's organ, therefore the success rate of liver exchange matching can be as low as <10% [47]. But its conceptual possibility has been well established with excellent outcomes.

ABO-i liver transplants have a valuable role in patients where socio-cultural barriers deter them from participating in the exchange program. At the same time, certain patients cannot tolerate higher level of immunosuppression and therefore will not be suitable for an ABO-i liver transplant, requiring higher levels of immunosuppression and immune-modulation. But, the availability of multiple options offer valuable and real choices for patients, that meet their individual needs and agrees with their beliefs.

7.3. Tolerance in liver transplant

The liver has been considered very tolerant in solid organ transplantation, but its mechanism is still unclear. Application of regulatory T (T-reg) cells are in experimental stages, but have offered promising early results in solid organ transplantation including LDLT. However, most studies have focused on the applicability and short-term success as of now, but there is a real concern of chronic rejection with auto-antigens in T-reg therapies.

8. Summary

After the first decade following the inception of LDLT, there were refinements to the surgical technique and in the process of evaluation to select a suitable donor. There were also lessons learnt on how best to select a suitable recipient for LDLT. After being surgically refined, the second decade offered advancements to the learnt lessons on how to extend the donor acceptance boundaries, and at the same time, how best to match the extended spectrum donor to the

most appropriate recipient. This benefitted the growing need for liver transplant versus the sparse availability and poor access to deceased donor livers.

The current decade has been focused on entertaining further advancements not just in technique, but in immunosuppression and disease control i.e. hepatitis C treatment.

LDLT in summary has come a long way since 1989, and the future progress is yet to be seen in the direction of 3D-bioprinting, cell therapy and crossing the barrier into successful xenotransplantation.

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