Historical perspective of living donor liver transplantation

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Received: August 21, 2007   Revised: September 28, 2007

Abstract

Living donor liver transplantation (LDLT) has gone through its formative years and established as a legitimate treatment when a deceased donor liver graft is not timely or simply not available at all. Nevertheless, LDLT is characterized by its technical complexity and ethical controversy. These are the consequences of a single organ having to serve two subjects, the donor and the recipient, instantaneously. The transplant community has a common ground on assuring donor safety while achieving predictable recipient success. With this background, a reflection of the development of LDLT may be appropriate to direct future research and patient-care efforts on this life-saving treatment alternative.

INTRODUCTION

Living donor liver transplantation (LDLT) has been rapidly growing and evolving since its debut in 1989[1], while deceased donor liver transplantation (DDLT) had already been a standard procedure for a decade[2,3]. LDLT being the legitimate remedy for the refractory shortage of deceased donor liver grafts is characterized by its technical complexity and ethical controversies.

In 1963, Starzl described in detail three cases of DDLT. The first recipient was a 3-year-old boy with biliary atresia and died from intra-operative hemorrhage. The other two recipients were adult males with primary liver cancer. Both succumbed to pulmonary embolism 7 and 22 d after transplantation. These three cases, though ended up in hospital mortality, established the technical feasibility of liver transplantation in human[4]. Only four years later, long survivals were achieved in four DDLT recipients[5]. To become a reliable treatment modality for end-stage liver diseases of a number of etiologies, DDLT has taken two important steps: the clinical use of calcineurin inhibitor - cyclosporine A[6] and improvement of graft preservation techniques by hypothermic perfusion utilizing University of Wisconsin solution[7].

Soon after DDLT had become a standard clinical practice, it outstripped the supply of deceased donor liver grafts. The shortage of pediatric deceased donor liver grafts was even more marked. To overcome size disparity of the graft and the child recipient, reduced-size liver transplantation was devised by Bismuth in 1984[8]. Through extension of this concept, split-graft liver transplantation was then developed by Pichlmayr in 1988[9]. This enables transplanting one more recipient and circumventing graft size discrepancy in one go. The first series was reported by Broelsch in 1990[10].

BIRTH OF LIVING DONOR LIVER TRANSPLANTATION

Experience gained from in-situ donor hepatectomy in reduced-size and split-graft DDLT paved the way for LDLT, an idea proposed by Smith as early as 1969[11]. When harvesting was performed on the living donor, much more technical ingenuity was required. The first attempt was made by Raia[1] and first success achieved by Strong of Australia[12] in July 1989. Under stringent review and auspices of the internal review board[13], the Chicago group led by Broelsch developed the first adult-to-child LDLT program[10]. Small series of adult-to-child LLDT were then reported from the United States[14] and Europe[15].

The problem of deceased donor liver graft shortage has been particularly severe in Asia[16]. In Japan, where deceased donor graft donation was non-existent[17] and liver surgery already well-developed, LDLT flourished[18,19]. For adult-to-adult LDLT (ALDLT), the left liver was used initially and was reported by the Shinshu group[20]. The left lobe used for adults was very often handicapped by the inadequate graft size. In 1993, Kyoto reported their improvisation of using the right lobe in a case of adult-to-child LDLT for a 9-year old recipient. The intention in this particular case was to avoid precarious arterial anatomy of the donor's left lobe[21]. The first case of right lobe ALDLT was performed at Queen Mary Hospital, the University of Hong Kong on May 10th 1996. *A priori*, the right liver

graft design included the middle hepatic vein (MHV). This was to address the problem of small-for-size syndrome[22]. The first series was reported shortly[23].

Donor right hepatectomy is one of the most major surgical living donor procedures. Subjecting a donor who has no medical indication for surgery to a major surgical operation with attendant risks is an ethical challenge. It was viewed by the medical community and the society with caution and skepticism[24-26]. Such donor procedure could only be partially justified by the benefit on the recipient and exhaustion of alternatives. This view is not universally accepted. Our common ground is the commitment to provide care of the highest standard to the living liver donor. Efforts for the betterment of care for the donors and yet not depriving them of the chance of saving or improving the life of their beloved recipients should worth dedication and ingenuity of the transplant community.

DONOR SAFETY AND WELLBEING

Donor safety is central to LDLT. As the application of LDLT extended from children to adults, and from using the left liver graft to the right liver graft, the dilemma between recipient success and donor risk came to the spotlight. The reported overall complication rate of donors is around 20%, but as high as 67% in one review[27]. A unified system of complication reporting[28] may narrow this range. Not only does the complication rate vary amongst different centers, the types of complications reported also vary. The most common complications are wound infection, ileus, and bile leakage. With accumulation of experience, donor morbidity could be lower than 20%. The majority of complications are of Grade I and were wound infections. With careful attention to biliary anatomy and guidance from intraoperative cholangiography, biliary complications are avoidable[29]. While one donor mortality is too many for the transplant community, there are already 14 known donor deaths[30]. Donor right hepatectomy carries a 0.5% donor mortality rate[30]. Similarly, the causes of donor mortality also vary[31]. A widely publicized case is a male donor in New York who succumbed to gas gangrene of *Clostridium perfringens* 3 d after donor right hepatectomy[32]. A hypertensive lady in Japan died from liver failure after right liver donation with a residual left liver with nonalcoholic steatohepatitis 28% of the total liver volume[33]. Fatal pulmonary embolism also occurred in a left liver donor[34]. A donor mother with a history of substance abuse also died from drug overdose 2 mo after donation to her 3 year-old son[35]. In other words, achieving a five-year recipient survival of 80%, it takes one donor life to save 160 recipients. Less tangible is the quality of life changes of the donor in comparison to the predonation state. The long-term biological consequences of donor hepatectomy are not fully known. Nevertheless, there are demonstrable drops in white cell count, platelet counts and elevation of liver transaminases even two years after right liver donation[36]. Quantification of such is mandatory in defining the field strength of LDLT. Detail of the holistic care of living liver donors deserves elaboration in a separate synopsis.

As agreed by the liver transplant community, living liver donors should be of good health[30] and the donor operation performed by experienced centers[37]. There should be no compromise of accepting potential donors with suboptimal physical and mental health. This is the only way to maintain or decrease donor mortality and morbidity.

RECIPIENT SHORT-TERM OUTCOMES

Graft size

Recipient survival is dependent on adequate graft size in relation to recipient body size[38]. Pathophysiology of the small-for-size graft and small-for-size syndrome is then defined[39]. Features include hepatocyte ballooning, steatosis, centrilobular necrosis, and parenchymal cholestasis. Pre-existing portal hypertension of the recipient increases the size requirement of graft[40].

Anecdotal success of using a very small graft for ALDLT 25% of the estimated standard liver weight[41] and even 20% with portosystemic shunting[42] had been reported. The paradigm shift from the left liver to the right liver enables adult recipients to undergo LDLT[43]. With technical maturity, 35% of the estimated standard liver weight remains the minimum requirement of a graft for predictable recipient success[44]. Portal hyperperfusion[45] and portal hypertension[46] are now conceived as possible mechanisms conducive to damage of small-for-size grafts. A battery of techniques for alleviation of portal venous flow was described. This includes superior mesenteric vein to mesocaval shunt[47], hemiportocaval shunting[48], inflow modulation by splenic artery ligation[49]. With portosystemic shunting using a saphenous vein interpositional graft between the right portal vein and right hepatic vein stump, a left lobe 20% of the estimated standard liver mass had been transplanted successfully in one patient[42]. Pharmacological manipulation is on the horizon as well[50].

More basic to these is the accurate assessment of standard liver volume of the recipient and thus the minimum graft size requirements. There have been a number of formulae developed from the west[51,52] and one from Japan[53]. A formula derived from Chinese and for application in Chinese which is also gender dependent has been developed and for validation[54].

Middle hepatic vein

Center to the controversy of right lobe ALDLT is inclusion of the MHV or otherwise. Deleterious effects of no drainage to the segments 5 and 8 include severe venous congestion and necrosis of these segments[55]. Surgical decision of not including the MHV includes demonstration of collaterals between segment 5 and 8 tributaries and the right hepatic vein[56]. Kyoto University devised an algorithm which includes the MHV when the graft is MHV dominant, or the graft to recipient weight ratio less than 1%, and in all cases, remnant left lobe larger than 35%[43]. Chang Gung Memorial Hospital includes the MHV when the graft to estimated standard liver volume is 50% or less, or when segment 5 and 8 hepatic veins are large and the right hepatic vein small[57]. Tokyo University ingeniously observed congestion of segments 5 and 8 of the graft after temporary clamping of the right hepatic artery before determining venous interpositional grafting[58].

We include the MHV in all right liver grafts for simplicity and familiarity of the technique[59]. Irrespective of the venous drainage pattern of segment 4 of the remnant left liver, the segment 4b hepatic vein is preserved. Utmost care is needed for its preservation when it drains into the MHV[60]. The outflow capacity is guaranteed by venoplasty on the back-table of the MHV and right hepatic vein into a single cuff[61]. The venoplasty is further marked by a more expedient hepatic vein to inferior vena cava anastomosis and higher outflow capacity of the right liver graft[62].

In summary, adequate graft size and quality, excellent venous outflow, and moderate portal inflow are keys to success of ALDLT[63].

High urgency LDLT

ALDLT under high urgency was impetus to development of liver transplant in our center[23]. Early experience of a number of centers showed inferior surgical outcomes of ALDLT in the high urgency situation[64-66]. With accumulation of experience and right liver graft incorporating the MHV, surgical outcomes of ALDLT is not compromised[67]. We also showed that ALDLT improves the survival of potential recipients[68]. The question of when a patient becomes too sick for liver transplantation is to be answered[69]. To justify ALDLT, good recipient outcome and acceptable donor morbidity, and voluntarism of the donor are the least that could be expected. The Live Organ Donor Consensus Group has largely supported this viewpoint[70]. The Model for End-Stage Liver Disease score has been validated as a factor predictive of recipient short-term survival in DDLT[71]. Data from ALDLT in North America[72] and Europe[73], however, do not support this view. Outside Asia, ALDLT is gradually considered a standard treatment for acute liver failure.

Biliary reconstruction

Biliary complication justifies itself the Achilles' heel of DDLT and is even more convincing in ALDLT[67]. Hepaticojejunostomy and duct-to-duct anastomosis have no substantial difference in the incidence of biliary complications. Nonetheless, duct-to-duct anastomosis reduces the operating time and avoids contamination of the operation field, expedites return of bowel functions, and avoids internal herniation of bowel loops. It also allows subsequent intervention by endoscopic retrograde cholangio pancreatography. In some centers, duct-to-duct anastomosis is stented to minimize the chance of stensosis and leakage. Whether the stent plays a role in the postoperative period, or in facilitating anastomosis, or both, has not been validated. Furthermore, whether continuous or interrupted sutures makes a difference is unknown. A study on DDLT which showed no difference[74] may not be applicable to ALDLT. Randomized controlled trials of recipients allocated to both arms may answer these questions.

RECIPIENT LONG-TERM OUTCOMES

Hepatocellular carcinoma

Early efforts of transplanting patients with advanced unresectable primary liver cancers were tempered by invariable relapse of malignancy[75]. Further work of the same group established the correlation between poor prognosis and high pathological tumor-node-metastasis staging[76]. Vascular invasion by tumor is the single most important factor in treatment failure of ALDLT for unresectable small hepatocellular carcinoma (HCC). Major vascular invasions though apparent for large tumors, may not be so for the small ones. Now called the Milan Criteria[77] and the University College of San Francisco Criteria (UCSF)[78], the tumor size and number are used as surrogate parameters for likelihood of vascular invasion. The Milan criteria are based on pretreatment imaging, whereas the UCSF criteria on liver explant histopathology. Accuracy of preoperative imaging in staging is inadequate[79]. The tendency is toward underestimation of tumor load. Even in studies with good image to histopathology correlation, underestimation is common. Tumor grade[80] and tumor size[81,82] are predictors of vascular invasion. Tumor size itself is also a predictor of tumor grade[81,82].

In our own series of ALDLT for HCC, there is a tendency of a higher recurrence rate compared with DDLT. It is postulated that the higher regeneration rate and reperfusion injury of small grafts in ALDLT provides an environment favorable for HCC cell implantation and growth in the graft[83]. It is also possible that in ALDLT, for preservation of the inferior vena cava, more liver manipulation is required leading to tumor compression and cancer cell dissemination. However, it is not unlikely that patients who have received DDLT are the self-selected patients because only candidates with slowly growing HCC who could wait for deceased donor liver grafts could receive the transplantation as the cancer cells are less aggressive. In fact, fast-tracking ALDLT for HCC had a higher recurrence rate[84]. Further studies on patient selection criteria and innovation of surgical technique are required to improve the long-term outcome of ALDLT for HCC. A recent series from Korea, nonetheless, has comparable results as DDLT[85].

In a series of 316 recipients with HCC who underwent ALDLT in Japan, the patient and recurrence-free survival rates were significantly worse if the Milan's criteria were not met. However, within this series, 171 (54.1%) of the recipients did not fulfill the Milan's criteria, and 176 were staged IVa. The alpha-fetoprotein level, tumor size, vascular invasion, and bilobar distribution were independent risk factors for HCC recurrence. The grade of histological differentiation of HCC showed close correlation with tumor characteristics and recurrence. Multifocal HCC verified by histopathology after transplantation with no recurrence was reported[86]. A policy of extended indication beyond the Milan and UCSF criteria is being validated[87].

The first use of sirolimus in liver transplantation was in patients with liver cancer, using the reported antitumor effects of the drug[88]. Subsequent work has shown efficacy of the drug in the inhibition of hepatocellular tumor cell lines[89,90]. Recipients transplanted for HCC and received sirolimus and low dose tacrolimus survived longer[91].

Sequelae of long-term immunosuppression

Calcineurin inhibitors greatly improve graft and recipient

Table 1 Landmark publications of liver transplantation in chronological order

Author	Discovery and application	Year of publication
Starzl[4]	First attempts of DDLT in human (1963)	1963
Starzl[5]	First long survival DDLT recipients (1967-1968)	1968
Smith[11]	Conceptualization of LDLT (1969)	1969
Calne[6]	Cyclosporin A used in solid organ transplantation	1979
Bismuth[8]	First adult-to-child reduced-size DDLT (1981)	1984
Pichlmayr[9]	Split-graft DDLT for 2 recipients (1988)	1988
Belzer[7]	Clinical use of University of Wisconsin Solution	1990
Raia[1]	First attempt of LDLT (December 1988)	1989
Strong[12]	First successful LDLT from adult to child (July 1989)	1990
Yamaoka[21]	First report of right liver graft from adult to child (1992)	1994
Hashikura[20]	First successful left liver adult-to-adult LDLT (November 1993)	1994
Lo[22]	First right liver adult-to-adult LDLT using right liver (May 1996)	1997

survivals. The lowest permissible serum drug level is employed to minimize the side effects. Nonetheless, two undesirable results still occur in recipients, i.e. renal impairment and tendency toward diabetes. A trend toward steroid-sparing immunosuppression seems workable[92]. The added benefit of the potential antineoplastic property of sirolimus makes it very attractive for recipients with renal impairment transplanted for resectable HCC[93].

Prompted by development of immune tolerance of noncompliant liver recipient after cessation of immunosuppressant therapy, weaning programs were incorporated into a long-term strategy of liver transplant programs. Drug-free tolerance was observed more frequently in humans after transplantation of the liver than of any other organs. Clinical application of cyclosporine[6] and then tacrolimus[94] dramatically prevented acute rejection of transplanted organs. However, drug-free tolerance became rare with the dominance of multiagent prophylactic immunosuppression[95].

Development of tolerance to the graft obviates the use of immunosuppressant with the side effects. The equivalence of solid organ and bone marrow transplantation is substantiated by documentation of systemic microchimerism[96]. Liver cells were identified in distant organs and host cells were also identified in liver grafts. The mirror image of solid organ and bone marrow transplantation envisioned by Starzl brings to light the practicality of long-term donor specific tolerance. The liver as a privileged graft[97] is a constant source of donor leukocyte, thus facilitates the process of clonal exhaustion-deletion especially in the early post-transplant phase under low immunosuppression pretransplant by antilymphocyte globulin. The concept of prope tolerance is also proposed as a means to a similar condition at a lesser degree[98]. Utilizing a powerful lymphocyte-depleting antibody, Campath 1H, half-dose cyclosporine monotherapy became workable. During a window of opportunity for immunologic engagement (WOFIE), it is hypothesized that there is engagement of donor and recipient marrow cells. Not until the availability of transgenic xenografts, effective and specific immunosuppression remains the practical way to graft maintenance. Nonetheless, continual assessment of the risk of chronic subclinical rejection is necessary[99].

CONCLUSION

At a minimum, recipient success is high and donor risk low. This brings donor and recipient issues into a close relationship. Conceptually, it would be inappropriate to accept a higher risk for the donor simply because of the improvement of recipient outcome. It is nonetheless our common goal to improve the standard of recipient and donor operations. What the public should change is, however, the better acceptance of ALDLT in the face of better safety and success, while the effort to make more deceased donor grafts available is never be forgotten.

Now we have near perfect graft harvesting and implantation techniques. Excluding patients with prohibitive conditions, e.g. uncontrolled sepsis and poor cardiac conditions, the short-term success is predictable. We still require selecting patients with a low recurrence rate of HCC and hepatitis C after transplantation. A lower biliary complication rate is welcome and could only be reduced by better preservation of biliary vasculature on the donor and the recipient and careful anastomotic techniques.

Donor safety and recipient success are inseparable. While donor mortality is a reality, it is by lowering donor mortality and improving recipient survival the justification of LDLT becomes stronger.

Although the major interest of the liver transplant community was in ALDLT in the last decade, the success of ALDLT has been a result of the ground works laid since the sixties. Key publications documenting the major achievements in liver transplantation leading to the ever improving results of ALDLT are listed in chronological order in Table 1.

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