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REVIEW ARTICLE

Living donor liver transplantation: looking back at my 30 years of experience

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Abstract
Since I moved from the National Cancer Center to Shinshu University, I have been performing living donor liver transplantation (LDLT), which is the only way to save the life of patients with end-stage liver disease. In June 1990, we performed the first LDLT that case was the first successful case in Japan. The patient remains healthy and is enjoying a normal life still 28 years after the transplant. In 1993, we successfully performed adult-to-adult LDLT, which was the first successful case in the world. The patient enjoyed a normal life for 17 years until she died at 70 years of age. For small children, the left liver of adult donors is too large to close the abdomen. However, in adolescents or adults, even when the whole right liver is used, the volume of the graft is too small. The concept of the standard liver volume (SLV) has proven very important for this procedure and is calculated as follows: $706.2 \times$ body surface area $+ 2.4$. We proposed a method for evaluating the congestion of the liver by Doppler ultrasound. In addition, we devised the right lateral sector graft. Over the years, we have contributed to LDLT in many ways and published many papers. We feel that our findings are quite useful not only for LDLT but also for other hepatectomy procedures.

Keywords Living donor liver transplantation (LDLT) · Adult living donor liver transplantation · Standard liver volume · Congestion of the liver by Doppler ultrasound · Right lateral sector graft

Introduction

I moved from the National Cancer Center Hospital (NCCH) to Shinshu University as the Professor of the First Department of Surgery at the age of 43. Many around me asked why I was moving from NCCH to Shinshu University, as this transfer gave the impression I was moving away from the center of cancer research. One of the radiologists implied my move was *Miyako Ochi*, a Japanese phrase translated as "moving out of the capital". The move was seen to indicate I was moving away from the center of the "action".

However, I feel that this was a big misunderstanding, as this did not reflect my thinking at all. I decided to change my job in the hopes of achieving a goal, and I could not realize at NCCH. At that time, I was third in line for command of the liver team at NCCH and lacked the authority to do what I wanted to do. With this move, however, I would finally be leading a team and be the decision maker. My aim was to perform living donor liver transplantation (LDLT), and as you all know, by moving to Shinshu University, I was able to realize my dream.

At Shinshu University, I spent 3 months poring over papers on liver transplant and shared my findings with my staff. We then performed experimental studies using pigs and monkeys for the next 3 months. The next task was carrying out internal procedures, such as obtaining approval from the ethics committee. Finally, 8 months and 19 days after my transfer, my team and I were able to successfully perform the first LDLT in a child.

The start of LDLT

Almost 30 years has passed since the introduction of LDLT in Japan. The first LDLT procedure (from a father to his son) was performed by Professor Nagasue's team at Shimane

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University in November 1989. The following year, in June 1990, Professor Ozawa's team at Kyoto University and my team at Shinshu University each performed LDLTs in children, just 4 days apart. While the recipients of the procedures performed at both Shimane and Kyoto passed away soon after the transplant operations, our patient remains alive today. She has been healthy for the last 28 years and is the longest LDLT survivor in Japan.

Our next aim was to successfully perform adult-to-adult LDLT. This procedure was first carried out in Turkey on six patients. Unfortunately, all patients died before being discharged from the hospital [1]. Then in 1993, our team at Shinshu University successfully performed the transplant [2], which became the first successful case anywhere in the world; the recipient survived for 17 years after the operation. In the wake of our success, LDLT between adults is now commonly performed worldwide, especially in Asian countries, where deceased donor availability is low.

Performing LDLT in children

Once we became involved in LDLT, we encountered many unforeseeable new problems not observed with ordinary liver resections. For example, FK (Tacrolimus) was found to induce lymph proliferative disorders, similar to ciclosporin [3]. In addition, liver regeneration speeds appeared to differ between donors and recipients, with the donor's liver regeneration speed slower than the recipient's [4]. This indicated that human liver regeneration was regulated by extrahepatic factors. Evaluating the blood flow in the graft by color Doppler imaging became important [5], and preoperative measurements of the segmental liver volume of the donor are now essential in LDLT [6].

For LDLT, calculating the standard liver volume (SLV) is crucial [7], as the concept of the "standard volume" has become particularly important in LDLT. The human liver volume is affected by the progress of liver disease; given that the equation to estimate the SLV was established based on the CT volumetry of patients without liver diseases, the same equation cannot be used to estimate the SLV of the LDLT recipient. However, the liver volume of patients may be influenced by their disease. Soon after hepatitis viral infection, the liver volume increases and then later decreases in response to the progress of fibrosis or cirrhosis. Therefore, a CT volumetric analysis of an LDLT recipient is useless.

Problems in pediatric LDLT

In pediatric patients whose abdominal cavity is too small to accommodate the donors' left liver (SII + SIII), the abdominal wall cannot be closed. Therefore, the muscle layer and skin are closed separately, with or without Gore-tex mesh.

In LDLT, the donor's own blood is deposited and used to prevent disease transmission from blood transfusion. The liver is transected under warm ischemia. Warm ischemia is forbidden in cases of brain-dead donors' operations, because the graft liver is already damaged by the processes of brain death and organ preservation. In LDLT, however, we are able to keep the liver damage to a minimum. Therefore, intermittent warm ischemia, routinely performed in ordinary hepatectomies, is a safe procedure [8]. This procedure would never have been considered by doctors trained in liver transplantation in the US or Europe.

Small-for-size graft problems can also occur in children. For example, when a boy who received a graft from his mother as a child becomes a teenager, he might outgrow his mother in body size. In such cases, the mother's total left liver volume with the left caudate lobe will not be sufficient to support his needs, resulting in the inevitable need to harvest the mother's right liver as well.

Outflow blockade due to obstruction of the inferior vena cava (IVC)

Our fourth patient was a 9-month-old female. The left lobe (SII + SIII) was resected from her father and transplanted. The left hepatic vein orifices of the graft were much larger than the IVC of the recipient. To overcome the size mismatch, the hepatic veins of the graft were sutured longitudinally to the recipient IVC from the left cranial side to the right caudal side. Initially, it seemed to have worked quite successfully. However, when the portal vein was reconstructed end to end and reperfusion of the graft was carried out, the IVC became extremely swollen, and a large amount of bleeding was observed from the transected surface of the graft. The venous wall had stretched in the horizontal direction, and the dorsal side of the IVC wall had become tightly attached to the suture line of the two left hepatic venous walls, causing massive bleeding from the graft [9]. We, therefore, immediately transected the IVC 2 cm below the liver. The right dorsal flap of the IVC was fixed at the right lateral side of the IVC near the suture line of the left hepatic vein (LHV). The opened IVC was then closed completely with running sutures. When declamped, the graft returned to its normal color and size and soon became soft. No bleeding was observed thereafter from the liver stump. The IVC was then reconstructed below the liver, end to end [9], and ultrasound indicated the graft had an almost normal blood flow.

Reconstruction of hepatic veins after transplantation

We have developed several methods for preventing constriction of the hepatic veins. We herein report the two most common procedures.

An infant under 2 years of age received a venoplasty using three veins from the recipient [10]. For children under 10 years, the left and middle hepatic veins are plastied into a single vessel [11] that resembles the bell of a trumpet; this means that the orifice is larger than the IVC [11]. Outflow blocking can occur at any time in the first 2 years after transplantation and can easily be released by balloon dilatation. However, when stenosis continued in this patient and the orifice could not be enlarged sufficiently, surgical intervention was required. This operation is difficult, as the graft is sometimes tightly adhered to the surrounding organs, and dissection at the hepatic hilus and near the supra- and infra-hepatic IVC requires meticulous attention.

The hilar structures were taped as one, and the supra-hepatic and infra-hepatic IVC were also taped. The IVC above and below the liver and of hilar vessels all in one were all clamped, and the IVC was incised from the cranial clamp to the left hepatic vein and the middle hepatic vein. The IVC incision was then extended to the caudal side at the same level as the middle hepatic vein (MHV) [12]. The right dorsal wall of the MHV and the left side wall of the IVC were then sutured together longitudinally, thereby creating a large opening orifice. Patch plasty was performed using a cryopreserved venous wall that was almost twice as large as the orifice, consisting of the IVC, LHV, and MHV. The venous patch showed bulging to the right lateral side and fluttered with the heart beat after reconstruction was completed.

Controversy with Prof. Ozawa

When multiple hepatic arteries were identified in the left liver graft, whether all these hepatic arteries should be reconstructed became a point of discussion. Professor Ozawa of Kyoto University insisted that all left hepatic arteries should be reconstructed. This may have originated from Professor Thomas Starzl, as almost all of Professor Starzl's pupils have insisted on all hepatic arteries being reconstructed. This may be acceptable in cadaveric liver transplantation, where all hepatic arteries can be resected near their origin during liver graft donation, and reconstruction of the hepatic artery or arteries is not difficult. However, in LDLT, obtaining long hepatic arteries is difficult, the vessels are small in caliber, and reconstruction of all arteries takes a rather long time under the microscope.

However, hepatic arteries, especially those in the left-sided liver, have mutual communications. If many communications are present, reconstruction of the left hepatic arteries may not be required. To assess the degree of mutual communications among hepatic arteries, clamp tests are performed. During donor hepatectomy, arterial clamp tests are performed after liver transection has been finished. The right hepatic artery is clamped first, and then the smallest left hepatic artery. Pulsation of the artery is evaluated by Doppler ultrasound. If pulsatile blood flow is observed at the liver side of the clamp, reconstruction is unnecessary. The middle sized artery is clamped next, and if arterial signals are detected at the distal side from the clamp, reconstruction is again unnecessary. The main (largest) left hepatic artery is not clamped, and the smallest left hepatic arterial branch is cut after ligation of the artery near the branching site. If pulsatile bleeding is observed, a vascular clamp is placed. The second thickest artery is then cut after ligation of the artery, and if pulsatile bleeding is observed, a small vessel clamp is placed, and the graft is removed after the largest left hepatic artery has been ligated and divided. Saline is then injected via the largest left hepatic artery and drained from other arterial branches at the back table; in such cases, smaller arteries need not be reconstructed. After reconstruction of the largest left hepatic artery, the vascular clamps are released one by one, and when pulsatile blood regurgitation is identified, the vessel is ligated.

Using this method, single hepatic artery reconstruction is sufficient, and in our experience, 92% out of 66 patients with multiple hepatic arteries were able to receive only single hepatic artery reconstruction without experiencing arterial ischemia [13–16].

Reconstruction of the left caudate lobe vein

In 1998, Miyagawa et al. reported the use of the left caudate lobe for LDLT to increase the volume of the left liver graft [17]. Under this procedure, the weight of the left liver graft increased by about 7%. We later performed reconstruction of the caudate hepatic vein [18]. The need for caudate vein reconstruction had not yet been clarified, but we forged ahead with its reconstruction, because a thick caudate vein was often found when the left caudate lobe was dissected from the IVC, prompting concerns that this might affect the caudate lobe regeneration. Outflow blocking of the LHV and MHV occurred in one recipient with caudate hepatic vein reconstruction. Segments II–IV were not deeply stained with contrast material, whereas the caudate lobe was, underscoring the usefulness of caudate vein reconstruction. When the caudate vein was distant from the LHV and MHV orifices, it was directly anastomosed to the IVC; however, when it was close to the LHV and MHV, they were sutured together, or the interposed hepatic vein was placed between them. After revascularization of the graft, the color of the caudate lobe should be the same as that of other parts of the liver.

LDLT for adults

On November 2, 1993, we performed adult-to-adult LDLT from a son to his mother, who had primary biliary cirrhosis. The postoperative course was difficult, with pleural effusion and ascites amounting to more than 10 l/day. Fortunately, the pleural effusion and ascites gradually subsided [2]. The patient was followed up by a referral doctor for 17 years until she passed away at 70 years of age. Before this case in an adult was successfully performed, six other cases of adult-to-adult LDLT had been reported in Turkey [1]. However, all six patients died soon after the procedure, making ours the first successful case of adult-to-adult LDLT in the world.

Concept of SLV

The liver volume in humans varies, differing by age as well as by the growth of an individual's body. Disease can also be a factor influencing the volume.

Hepatitis virus infection induces hepatitis, which increases the liver volume. However, once the infection settles, the liver becomes fibrotic, and cirrhosis develops, which causes the liver volume to gradually decrease. These findings indicate that the human liver volume not only varies but also changes. We must, therefore, estimate the volume of the liver in patients without liver diseases [7]. The concept of the SLV is very important, as it reflects the volume of the liver under normal conditions [7]. For example, if the SLV is not fixed, we cannot estimate how much amount of the liver needs to be transplanted. For this reason, we perform volumetric estimations from infants to old men's volumetry with CT and devised a formula that takes into account a given patient's height and weight, as follows: $706.2 \times$ body surface area $+ 2.4$ [2].

Following our initial success in performing adult-to-adult LDLT, we carried out the procedure for a husband to his wife [19], a case of fulminant hepatic failure (adolescent) [20], and a case of familial amyloidosis [21]. These results were published in *Ann Surg* 1998 [19]. The shortage of cadaveric donors is a common problem around the world, and our success in adult-to-adult LDLT has given hopes to millions who have been searching for a new treatment option.

Problems of small-for-size grafts

The advent of adult-to-adult LDLT has given rise to new problems, and the first, we encountered was that of small-for-size graft. For cases of LDLT performed in adolescents as well as in adults, we compared the SLV of the recipients and the volume of the transplanted graft and noted the following pattern: if the graft volume (≒weight) exceeded 40% of the SLV of the recipient, the post-transplant course was uneventful.

To overcome the small-for-size graft problem, several methods have been proposed. Lo of Hong Kong proposed the right liver graft with the MHV be used as the standard operative procedure in cases of adult-to-adult LDLT [22]. With this method, the graft is quite large, so the procedure affords the decrease in the rate of liver disfunction in recipient caused by the small-for-size syndrome. However, in the donor, the draining area by the MHV of the Segment 4, i.e., the medio-caudal side will be congested. The volume of the drainage area of Segment 4 by this procedure may be small but for donors with large Segment 4 and small left lateral lobe, liver disfunction may occur. In such instances, we reconstructed these venous tributaries using cryopreserved veins.

Methods for overcoming small-for-size syndrome

Prof. Miyagawa proposed the use of the left caudate lobe with a left liver graft [17]. With this procedure, the graft liver volume increased by 8–12% [17]. We have also incorporated the reconstruction of the caudate hepatic vein, as previously mentioned [18].

However, Lee et al. [23] published a method describing a dual liver graft, where liver grafts are donated from two donors. This approach resolved the small-for-size graft problem but has not been performed in many countries aside from South Korea. The reason for this is that the procedure requires donations from two family members, despite one liver graft seeming sufficient. I personally feel that the reason this method became particularly popular in Korea may lie in the Confucianism cultural background. In Korea, if a family included two sons, both might express their will to donate to save a parent's life; doctors might then have difficulty selecting one donor over the other. Another reason why this method failed to gain traction in other countries is that it was too resource intensive, as extra operation rooms would also be required to harvest the second graft, and the entire procedure might also take much longer time than a single-graft harvest would.

Congestion of the liver

During hepatectomies and/or liver transplantations, we very commonly encounter liver congestion. In such instances, we must decide whether or not reconstruction of the vein is necessary. In ordinary clinical practice, liver congestion is difficult to detect, but one easy way of doing so is to clamp the hepatic artery. If liver congestion is present, a discolored area will appear on the liver surface. In such instances, we can be certain that there is congestion. However, congestion of a limited part of the liver is much difficult to detect. Communication among hepatic venous tributaries and sinusoid of the liver makes it difficult to identify minimal congestion. The latter case would be very difficult to determine because of the arterial blood and portal blood entering into the sinusoid and thus becoming mixed together. When congestion develops in a limited area, the color of the liver surface does not change until the hepatic artery or arterial branches have been obliterated. Whether or not the hepatic vein or tributaries can be transected (i.e., whether or not congestion has occurred) can be determined by clamping the hepatic vein or its tributaries or clamping the hepatic artery to produce a color change at the liver surface. If the liver surface becomes dark, there is congestion. Mutual communication among hepatic venous tributaries may be found, but that is of no problem when you ligate the hepatic vein or its tributaries. However, if congestion happens, it is always the problem.

In January 2000, the 10th Anniversary of the Ulsan College of Medicine was held in Seoul, chaired by Professor Lee, and he presented a paper titled, “Congestion of right liver graft in living donor liver transplantation” in which the MHV was ligated [24]. In response, Professor Tanaka of Kyoto University claimed that the liver abscess mentioned in the paper was not caused by congestion. This discussion was brought up again later at the reception following the meeting. Lee insisted that the liver abscess was indeed due to congestion, and therefore, the MHV should be reconstructed in all patients [25]. Tanaka was, at that time, performing right liver graft transplantation without reconstructing the MHV in every patient. Therefore, during the farewell party, I proposed clear criteria be established to indicate MHV reconstruction. Thirteen months later, we completed our study and submitted our paper to *Ann. Surg*, where it was accepted and published [26] 25 months after the party.

The paper clearly explains that (1) the congested area appears on the liver surface as a dark blot after clamping the hepatic vein and/or the hepatic artery; (2) after clamping the hepatic vein, the congested area is demonstrated as the portal vein blood regurgitating; and (3) under color Doppler ultrasonography, the delineated portal vein color changes from red to blue by clamping the hepatic vein, a definite sign of portal vein regurgitation. These findings were obtained by using the ultrasound technique during LDLT operations.

Right lateral sector used as a graft

Right lateral sector resection is rare. Therefore, doctors only involved in liver transplantation may find such resection difficult. The same may be said with left trisectoriectomy, even for well-experienced hepatic surgeons. During an operative demonstration at Torino, one surgeon performed left trisectoriectomy in a patient with a liver tumor. The moment he removed roughly 4 cm of the right hepatic vein (RHV) with the left trisectors. I understood the situation, went straight to the operating theater, washed my hands, and joined the operation. Fortunately, the resected specimen was placed on the table right in front of the scrubbed nurse. I explained to the nurse and surgeon that I was going to remove the RHV from the resected specimen. The RHV was dug out and the side holes sutured, at which point I advised the surgeon to interpose the RHV between the IVC and its cranial stump. The operation was successful, and the patient was discharged from the hospital without further complications.

A similar incident happened during right lateral sectoriectomy of a donor, where the proximal RHV was left in the donor liver with several branches of the RHV observed on the graft. It was obvious that the surgeon had lacked the necessary training in intraoperative ultrasonography. This should never have happened, and such a surgeon should never have been allowed to perform donor hepatectomy, which can affect the outcome of the whole operation and so influence the recipient’s life. Another important factor that should be considered when training surgeons in liver transplant operations is the ability to maneuver intraoperative ultrasound equipment. Surgeons familiar with ultrasound equipment would never have performed such a clumsy procedure.

The right lateral sector (S6 + S7) makes up approximately one-third of the total liver parenchyma, but there are individual variations, and in only 19% of cases do, we find a right lateral sector larger than the left liver + left caudate lobe. However, when donors whose left liver + left caudate lobe is smaller than 1/3 of the total liver volume, it is possible that left liver + caudate lobe volume is smaller than right lateral sector. Therefore, when the left liver + the caudate lobe is smaller than 30% of the total liver volume, we also need to check the volume of the right lateral sector to determine whether or not it exceeds 40% of the recipient’s SLV.

There are two types in bile ducts exiting the right lateral sector. One independently branches out from the common hepatic duct, and the other originates from the right hepatic duct. During cholecystectomy, if a bile duct-like structure is observed, it should be carefully followed to determine whether or not it becomes confluent with the cystic duct. If no such confluence is observed, this means that it will enter into the common bile duct. The entire bile duct map should be identified by inserting a tube via the cystic duct. When the posterior bile duct originates from the right hepatic duct (sometimes from the left hepatic duct), the bile duct should be followed from the caudal side after completing liver parenchyma division. It can be identified as a yellow line from the caudal side behind the right portal veins. The posterior bile duct is identified by pulling the vessel loop to the medioventral side, then the tape on the right posterior portal vein pulled to the medi-odorsal side, and posterior bile duct can be identified from the right caudal side. The lateral perivascular connective tissue is then ligated and divided to the posterior bile duct. The tape on the posterior portal branch is pulled toward the lateral side, and the perivascular connective tissue can also be divided. Both tapes are pulled to the dorsal side, and the bile duct is ligated at the ventral side and divided. Through this procedure, the right lateral sector can be removed without any difficulty.

Graft regeneration occurs in three steps, so blood flow through the right hepatic vein also increases three times. As a result, the RHV will pour out about three times of blood but expansion of the RHV may be limited. Therefore, a large venous patch is anastomosed to the anterior wall of the RHV, which is protuberated to the ventral side and facilitates to decrease the hepatic venous pressure [27].

Regarding variation in the liver itself, the right caudal tributary of the MHV draining segment 6 may be observed. In such cases, to decrease the venous pressure, the tributary should be reconstructed using a cryopreserved vein homograft [28]. Since the volume of the graft is near the small limit, the congesting part of the liver should be eliminated as possible.

Transplant using a right lateral sector graft has been considered to have a higher complication rate than procedures using other grafts. However, in our experiences, no marked difference in the complication rate was observed compared to other procedures [29]. I have performed 26 LDLTs using a right lateral sector graft, and the 5-year-survival rate has been 87%, which is actually higher than those of left liver graft (86%) and right liver graft (82%), without significant differences.

Final remarks

LDLT is tough, intensive work that can sometimes last multiple days. The longest liver transplant operation I have experienced started from Wednesday morning and finished on Friday afternoon. However, accomplishing such work brings surgeons a sense of satisfaction. Furthermore, most of my patients (85%) have survived and were able to enjoy a long life once they made it through the first 2–3 years, which is priceless and precious. Simply seeing a smile on the once-devastated face of a patient is truly rewarding.

These days, with great disappointment and dismay, I find that most young doctors in Japan tend to avoid such mentally and physically taxing work. Perhaps their ethic alone is not to blame; perhaps the system is failing them, or perhaps what people and society value in life has changed. Whatever the reason for this change in mentality, the fact remains that operations such as LDLT can only be performed by an outstanding and dedicated team of surgeons. Surgeons who understand and value the meaning of life, who are prepared for hard work, who are not afraid to dedicate their lives to a truly meaningful mission and who find great joy in contributing their skills to the society. Nothing comes easily. Rome was not built in a day, and the skills for demanding operations can only be obtained through dedication and hours and hours of training. I am increasingly alarmed at the current situation, but I feel like my anxiety is not reaching the next generations, and I cannot help but worry for the future ahead. I have come a long way as a surgeon, and I have travelled around the world, meeting, teaching, demonstrating live operations and lecturing enthusiastic young surgeons in the hopes of encountering my successors. I only pray that my efforts are not futile and that young surgeons will come to their senses and follow their predecessors' footsteps to defend the hopes of many who are fighting for their lives.

Compliance with ethical standards

Conflict of interest Masatoshi Makuuchi has no conflicts of interest.

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