REVIEW

Living-donor liver transplantation : present status and future perspective

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Abstract : About 15 years have passed since the first liver transplant from a living donor (living donor liver transplantation : LDLT), and the status of the procedure has since been established as a standard cure for end-stage liver disease in Japan where liver transplantation (LTx) from deceased donors has not yet been accepted. However, the following problems are surfacing with the increase in the number of LDLTs between adults : graft size mismatching, an ABO blood-type incompatible transplantation, the expansion of LDLT indication to hepatocellular carcinoma (HCC), the relapse of hepatitis C after LDLT, marginal donors, and the freedom from immunosuppressive treatment. In this article we outline the present conditions of these problems and the future view of the LDLT. J. Med. Invest. 52 : 22-32, February, 2005

Keywords : *Adult-to-adult living donor liver transplantation, small-for-size graft, large-for-size graft, hepatocellular carcinoma, ABO blood-type incompatible transplantation, marginal donor, hepatitis C, fatty liver, age*

INTRODUCTION

Since the first liver transplant from a living donor (living donor liver transplantation : LDLT) was conducted in Japan, about 15 years have passed. At the beginning, the LDLT was regarded as an emergency procedure until the availability of liver transplantation (LTx) from deceased donors. However, in Japan, the number of deceased donors is also very small since the Organ Transplantation law was enacted in October 1997. The LDLT serves as standard medical treatment of end-stage liver disease in Japan. Since it is transplanted from a living donor, the characteristic advantage to which a liver transplant from a living donor greatly differs from the LTx from deceased donors is that the transplantable liver is of good quality in the first place. The donor livers can be evaluated, and be adequately prepared before transplantation. Furthermore, operations for both the donor and the recipient can be simultaneously performed, therefore, both warm and cold ischemic time can be minimized. As a result, well-suited livers are procured. Secondly, it is being able to choose the time of the transplant operation. Since the donor has determined beforehand, an operation can be on standby-conducted for him in accordance with the state of the recipients. Thirdly, since the donor and recipient are relatives, as one specific donor to one specific recipient, the indications for an LTx may be expanded compared to an LTx from a deceased donor. On the other hand, many problems, such as size mismatching, an ABO-blood type incompatible transplantation, the expansion of indication to hepatocellular carcinoma (HCC), a recurrence of postoperative hepatitis C, and the donor's safety, are surfacing according to the increase in the expansion of indication and number of cases after introduction of the LDLT between an adult donor and an adult recipient. This article describes the present status and future perspective of the LDLT.

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THE HISTORY AND THE PRESENT STATUS OF LDLT (Table 1)

After the world's first LTx was performed by Professor Starzl (Denver, USA) in 1963, the LTx from a non-heart beating donor was performed by Nakayama in Japan in 1964. Although the organ transplantation spread globally through the improvement of immunosuppressants in the 1980s, some patients in Japan went over to the West to receive a LTx. Raia1of Brazil enforced the first LDLT in 1987(1) as a promising method to resolve a chronic organ shortage of potential liver transplants for a child. Since the LTx from deceased donors did not progress in Japan, the first LDLT in Japan was enforced by Nagasue and others in a case involving a boy with biliary atrasia in November 1989 (2). Makuuchi and others (3) succeeded in the world's first LDLT between an adult donor and an adult recipient in November 1993. Although the Organ Transplantation law was enacted in 1997 and the increase in LTx from deceased donors was expected, the number of cases involving LTx remains at 26 cases and about several cases per year till present. Thereafter, the LDLT was the accepted treatment in 2,666 cases in 49 institutions by the end of 2003 in Japan, although at the beginning the LDLT was regarded as an emergency procedure to establish LTx from deceased donors. The demand for LDLT is further expanded due to the serious shortage of donors. Moreover, the LDLT was covered by medical insurance, and the LDLT has also been established as a practical solution to address the organ-shortage in Japan. The LDLT has been rapidly developed also in the West where the shortage of donors is serious. According to the data collected by UNOS

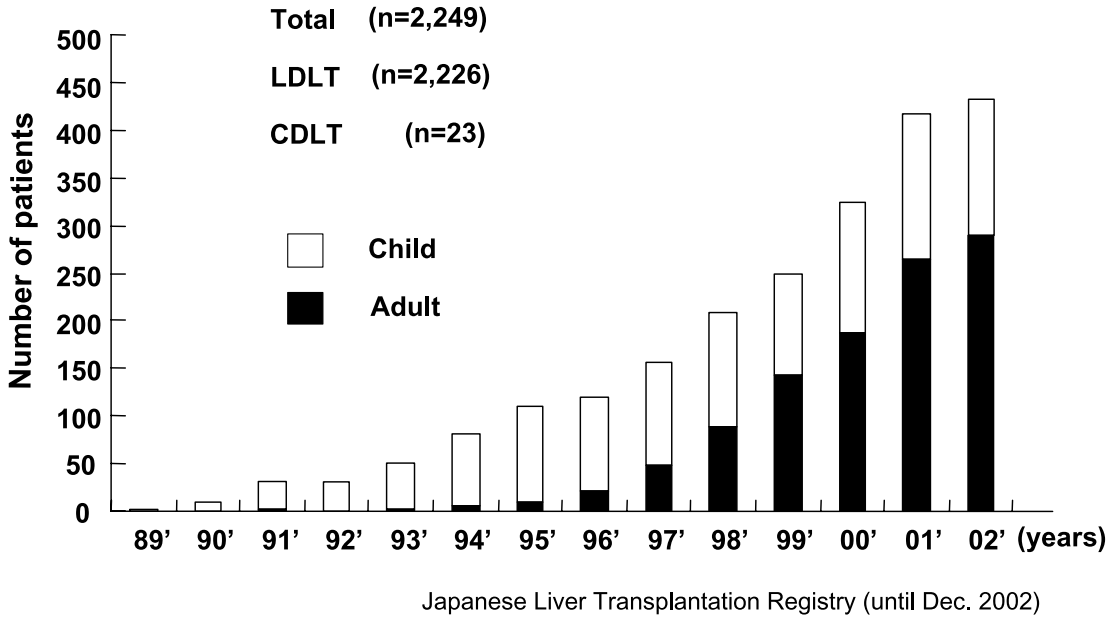

Figure. 1. Annual change in number of liver transplantations in Japan. Registry data of Japanese Liver Transplantation Society until 2002.

Table 1. History of liver transplantation in this country

1963	the first liver transplantation (biliary atrasia)	Starzl TE., Denver, U.S.A.
1964	the first liver transplantation in Japan (biliary atrasia) from non-heart beating donor	Nakayama, Chiba Univ., Japan
1969	the second liver transplantation from non-heart beating donor	Nakayama, Chiba Univ., Japan
1987	the first living donor liver transplantation (Biliary atrasia)	Raia, Brazil
1989	the first living donor liver transplantation (Biliary atrasia)	Nagasue, Shimane Univ., Japan
1993	the first adul-to-adult living donor liver transplantation	Makuuchi, Shinshu Univ., Japan
1997	Organ Transplatation Act in Japan	
1999	the first liver transplantation from deceased donor in Japan	Kawasaki, Shinshu Univ., Japan
2003	the first donor's death in Japan	
2004	the 26th liver transplantation from deceased donor in Japan	

(United Network for Organ Sharing), while the waiting list for LTx in the United States amounts to 17,389 cases, the number of LTx cases in 2003 per year remains at 5,994 cases, including 315 LDLTs. Thus, judging from the present problem concerning global organ shortage, the use of LDLT is expected to increase from now on. According to the data of the Japanese Liver Transplantation Society (4), the adult-to-to-adult LDLT is increasing per year, on the other hand, the child cases have reached a peak aroud 100 cases per years (Fig. 1). The 1, 3, and 5-year survival rates of all recipients are 81.8%, 79.5%, and 77.7%, respectively, while those of child recipients of less than 18 years old in age is 85.6%, 84.1% and 82.6%, respectively. In the adult recipients, the 1, 3, and 5-year survival rates are 75.6%, 71.7%, and 69.1%, and the prognosis of adult recipients is clearly poor (Fig. 2). Therefore, various kinds of treatments are used to improve the outcome of the adult recipients.

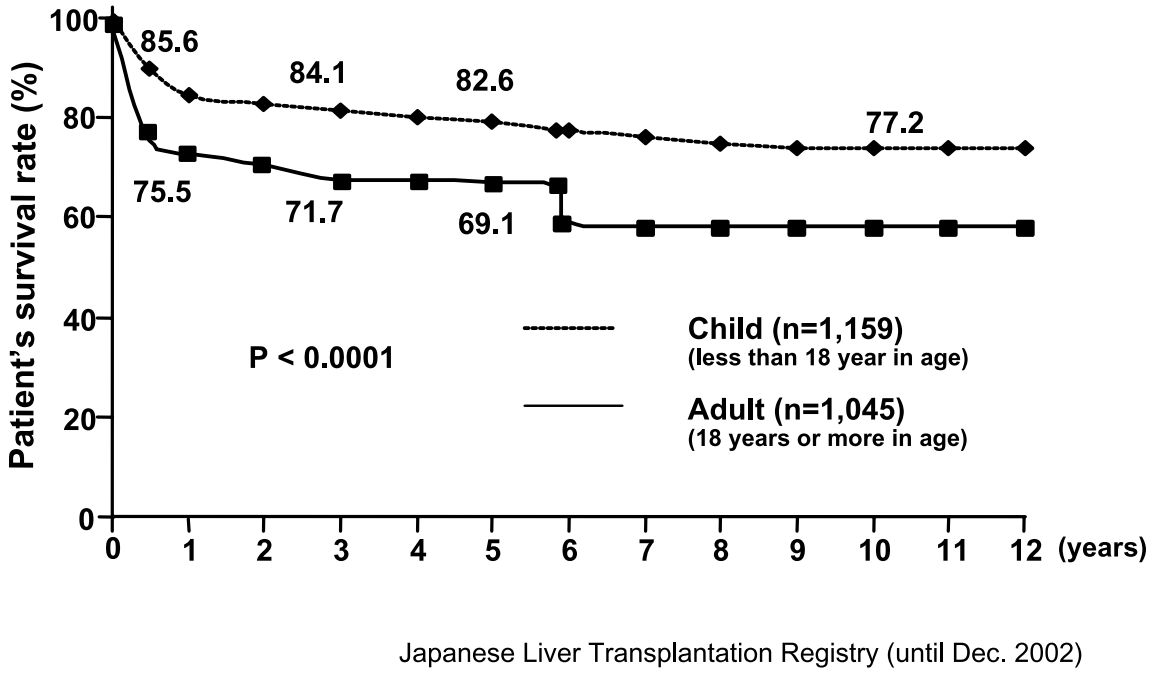

Figure. 2. The cumulative survival rate in living donor liver transplant in Japan. Registry data of Japanese Liver Transplantation Society until 2002. The survival rate in adult cases is significantly worse than that in child cases.

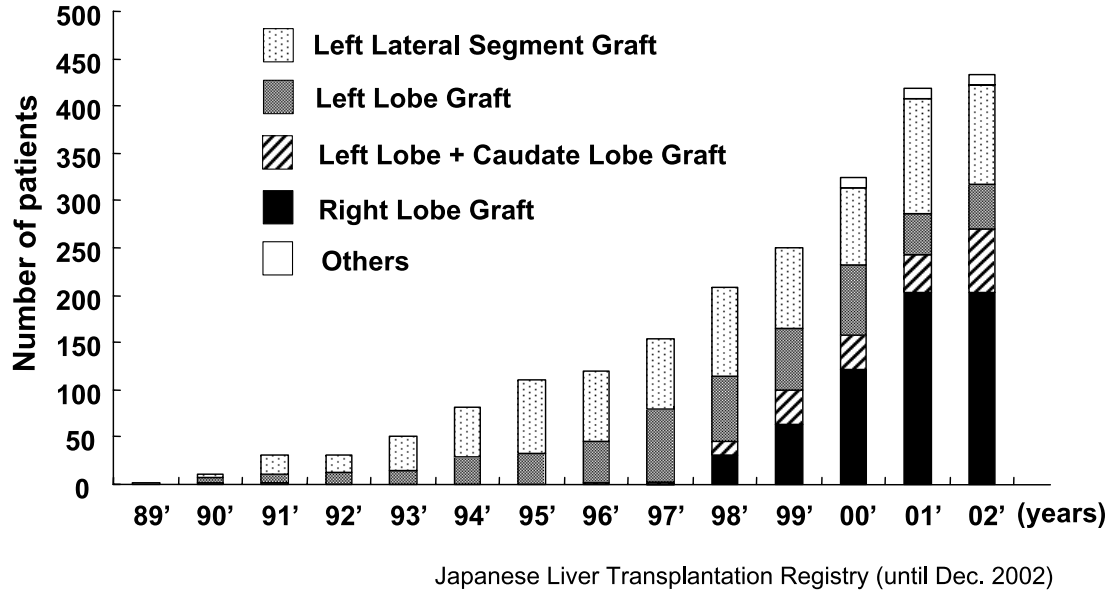

Figure. 3. Annual change of the graft used in the living donor liver transplantation in Japan. Registry data of Japanese Liver Transplantation Society until 2002. The right lobe grafts are getting increased in annual number in proportion to increased number of adult cases.

PROBLEMS TO BE SOLVED

The LDLT is being established as a general medical treatment of various kinds of end-stage liver diseases. On the other hand, it is thought that the original disease recurrence such as hepatitis C and HCC has influenced a significant decline in the survival rate of adult cases. Moreover, the living donor's mortality and need of LTx due to a postoperative hepatic insufficiency raised a critical social concern in Europe and the United States. Also in Japan, a living donor's death was reported in May 2003(5). It is necessary to reevaluate the donor's selection standard and safety anew because of the experience of a donor's morbidity and mortality. The following critical problems remain which should be urgently solved: 1) graft size mismatching, 2) ABO blood-type incompatible transplantation, 3) the expansion of LDLT indication to HCC, 4) the relapse of hepatitis C, 5) marginal donors, and 6) the freedom from the immunosuppressants.

1. Graft size mismatching

The minimally required quantity of graft volume has not been fully clarified, which is one of the biggest issues of the adult-to-adult LDLT. The following two methods exist to express the graft volume : 1) the ratio of graft volume (GV) in the standard liver volume (SLV) of recipient, which is calculated by the recipient's height and body weight, and 2) the ratio of graft weight in the recipient's weight (GRWR ; graft to recipient weight ratio). The safe limit of small-for-size graft is reported to be set from 30% to 40% in GV/SLV (6, 7), while from 0.6 to 0.8% in GRWR (8, 9). To increase the graft volume, a left lobe graft with a caudate lobe is often used (10-12). As an alternative, an APOLT (auxiliary partial orthotopic liver transplantation) was applied in those who deviate from this safe limit of the graft volume (13). From the beginning, the APOLT was expected to play a role in providing temporary support for transplant patients with fulminant hepatitis while they were waiting for the regeneration of the native liver. However, this was not generalized from the difficult hepatectomy of a morbid liver and possible disease transmission from the preserved native liver to a new liver graft. In order to conquer this problem (small-for-size graft), the right lobe graft which occupies about two thirds of the liver has been frequently used. Herein, the pathophysiology and cause-oriented strategy are described about a small-for-size graft or a large-for-size graft.

a) Small-for-size graft

The patient, who received a small-for-size graft, exhibited persistent functional hyperbilirubinemia, intractable ascites, graft dysfunction leading to serious conditions such as gastrointestinal bleeding and renal failure. (14-16) The characteristic histological findings are as follows: hepatocellular ballooning, fatty degeneration, hemorrhagic necrosis, and cholestasis around the central vein so called zone 3. We have advocated the following mechanisms for the small-for-size graft : 1) superfluous portal blood flow, 2) insufficient hepatic venous drainage, 3) absolute shortage of functional liver mass, and 4) inappropriate intragraft responses, as shown in Fig.4. Against the superfluous portal flow, which causes sinusoidal endothelial injury immediately after reperfusion (17, 18), the reduction of portal pressure or portal flow by splenectomy, splenic artery ligation (19-21), or a porto-systemic shunting (22, 23) was recommended. To counteract the insufficient hepatic venous outflow, the venoplasty in a left lobe graft or aggressive reconstruction of the venous tributaries from the middle hepatic vein is performed to prevent graft congestion, one of the key factors for a successful outcome (Fig. 5)(11, 24). The 3-dimensional computed tomography(3D-CT) is useful to assess the congestion area in the graft prior to operation (Fig. 6). Against the absolute shortage of functional liver mass, a hyperbaric oxygen treatment or intraportal infusion of drugs (25) has been reported. Recently, as a next-generation strategy, we are developing a bioartificial liver for the period until the transplanted graft obtains sufficient liver volume and function (26, 27). To counteract inappropriate responses, the breakdown of liver tissue reconstitution caused by excessive liver regeneration is considered to be the major cause of the rise of portal pressure, tissue (sinusoidal) congestion, and hepatocellular necrosis. Therefore, it is thought that liver regeneration needs to be adjusted (slowed-down) as a new concept in overcoming a small-for-size-graft. We have also reported the usefulness of geranylgeranylacetone (GGA), which successfully induced the heat shock protein 70, on the hepatic insufficiency after massive hepatectomy in rats (28), and such a heat shock protein inducer may become a new treatment strategy for the small-for-size graft.

b) Large-for-size graft

When a graft size is conversely too large for a recipient such as a newborn infant, the graft necrosis occurred due to insufficient blood inflow into the graft. In the case of the large-for-graft over 5% of GRWR, the graft survival was reported to be worsened due to increased incidence of portal vein thrombosis and an acute cellular rejection by Kiuchi and others (8). Ka-

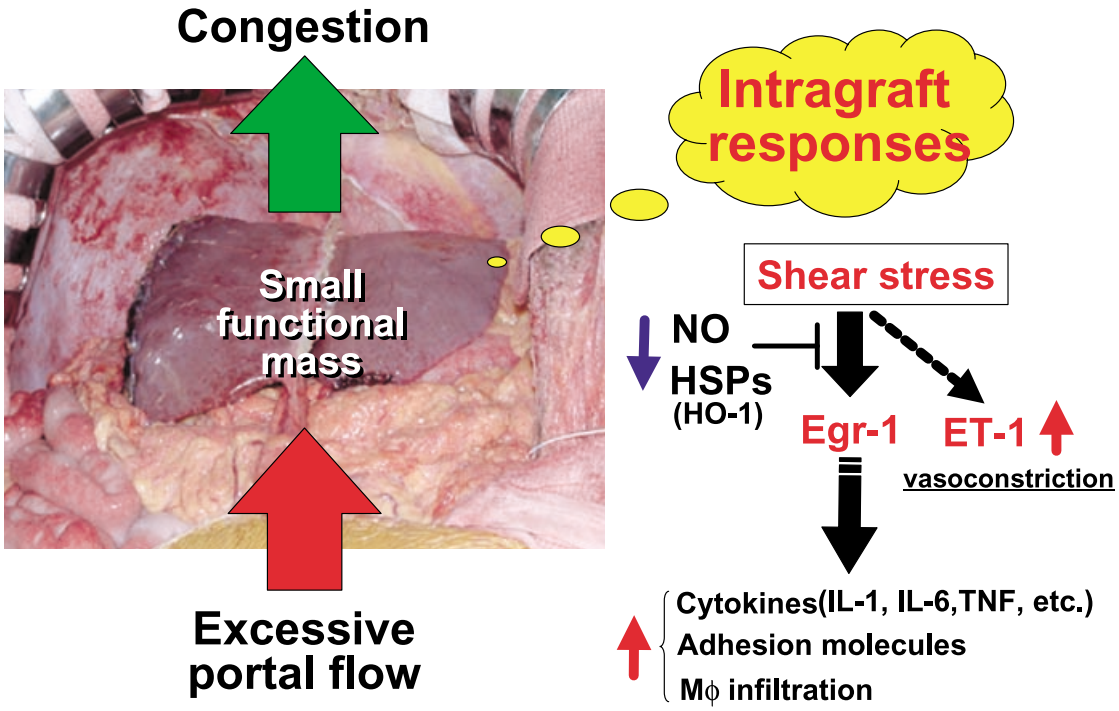

Figure. 4. Pathophysiology of a small-for-size graft

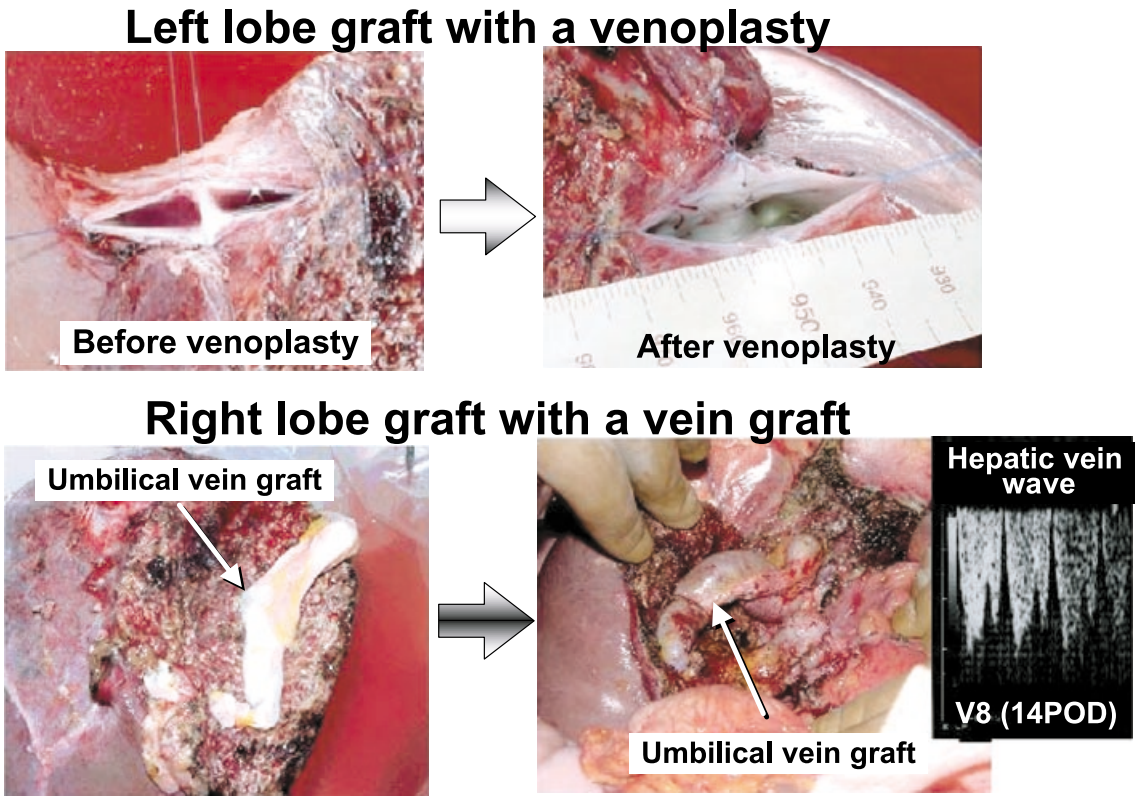

Figure. 5. Venoplasty and reconstruction of venous tributaries of middle hepatic veins. (Upper column)
The multiple hepatic veins in a left lobe graft is made to one lumen (venoplasty).
(Lower column)
The venous tributaries (V5 and V8) were reconstructed using a recipient's umbilical vein. As a result, the venous wave in the ultrasonography maintained well for a long-term period.

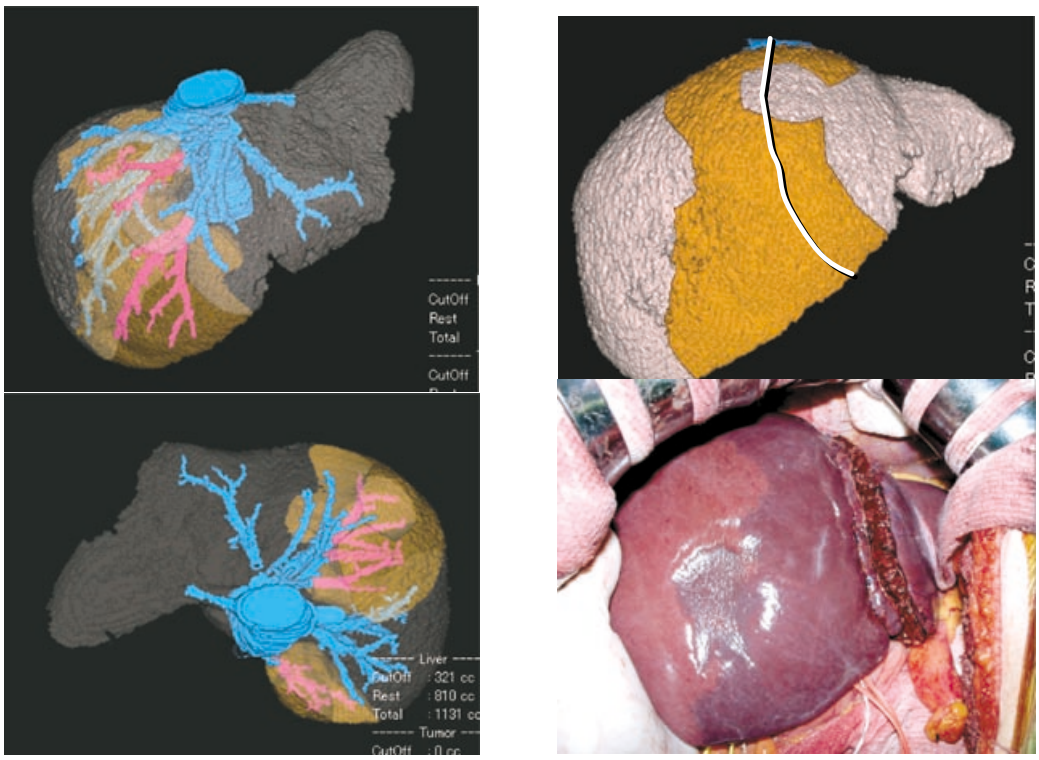

Figure. 6. Three-dimensional computed-tomography (3D-CT) in the graft congenstion. The 3D-CT expressed the congestive area in the liver when significant venous tributaries (V 5 and V 8) are transected. The actual photograph clearly demonstrated the congestive area coincident to the area in 3D-CT.

sahara and others (29) reported obtaining good results using a monosegment graft, when GRWR of a graft exceeds 4.0%.

2. ABO blood-type incompatible transplantation

An ABO blood-type incompatible LTx is known to often need a re-transplant because of the critical complications causing rejection, and, is generally considered to be a contraindication except for urgent cases even in the LTx from deceased donors. However, in the LDLT donor, candidates are restricted to relatives, therefore, the problem of an ABO blood-type incompatible LTx is unavoidable. Because of a serious rejection mainly caused by a pre-existing antibody to a donor blood type antigen, the hepatic insufficiency due to rapid liver necrosis is often seen by less than 1 month after LDLT, and the intractable bile duct damage after 3 months is concurred when the graft overcomes hepatic necrosis. (30-32) In the case of a baby of less than one year of age by whom the immunity function is not established, the result equivalent to the blood-type compatible LTx is acquired. On the other hand, in adult cases, the above-mentioned complications significantly reduce the postoperative probability of survival. According to Egawa and others (33), the overall 5-year survival rate in the ABO blood-type incompatible LDLT was 59%, and was significantly low compared with blood-type compatible LDLT. When this was restricted to adults of 16 years of age or more, the 5-year survival rate was much poorer (22%). Recently, Tanabe and others (34) reported that an intraportal infusion therapy using triple drugs of prostaglandin E1, gabexate mesilate, and steroids was useful to prevent serious complications in the blood-type incompatible LDLT. A big possibility opened up in terms of the improvement in results of an blood-type incompatible LTx. After the introduction of a portal infusion technique, the overall result in the blood-type compatible LDLT improved up to 51.2% of the 5-year survival rate. Furthermore, the Kyoto University group has started a hepatic artery infusion technique and reported further improvement in results (35). They emphasized the following points regarding the merits of using the hepatic artery : 1) direct effect of medication is expected in a thin artery level, 2) main feeder of bile ducts, 3) improvement of drug-distribution due to imbalanced distribution in portal blood flow. Improvement in the results by accumulation of future cases is expected.

3. LDLT for hepatocellular carcinoma

A liver transplantation is the ultimate treatment in which not only HCC but the liver cirrhosis of the high cancerous state is cured. Until the start of the 1990s, the results of LTx was very poor (36-38), since the LTx in the West was also positively enforced in advanced HCC. Therefore, HCC has been a contraindication of

LTx due to the serious organ shortage late in the 1980s. Mazzaferro and others (39) reported in 1996 a good (acceptable) result of HCC patients (4-year survival rate of 75% and 4-year disease free survival rate of 83%), which is equivalent to the results in other non-HCC patients. Their patient's selection criteria are as follows : no extrahepatic metastasis, no macroscopic vascular invasion, single tumor nodule 5 cm or less in diameter or tumor nodule 3 or less in number and 3 cm or less in diameter. This patient selection criteria is called the Milan standard, it is set to a gold standard of the transplant indication for HCC. Recently, UNOS (United Network for Organ Sharing) changed its policy to reduce the number of HCC patients that drop-out from the waiting list due to HCC progression during the waiting time, in which HCC patients are given a higher MELD (Model of End-stage Liver Disease) score than other liver diseases. As a result, the opportunity for a HCC patient to receive an LTx increases (40).

Also in Japan, a LDLT is carried out positively on HCC patients, and the number of LDLT for HCC was 225 cases by the end of 2002. Since medical insurance covered the LDLT for cirrhotic patients with HCC, which meets the Milan standard, from January 2004, therefore, the LDLT becomes an important option for HCC treatment. At almost all institutions in Japan, the diameter of HCC and the number of HCC nodules are not included in the institutional criteria of LDLT to HCC. Furthermore, a LDLT may produce the possibility of the further expansion of indication to HCC. Because the LDLT can be made on the basis of both recipient's and donor's sufficient understanding of the validity and limit of LDLT, and a fair number of non-recurred survivors are also proven to exist in the cases of deviation from the Milan standard. Furthermore, the LDLT is a special type of transplant, which is performed from a specific donor to a specific recipient. The UCSF (University of California, San Francisco) standard to which the Milan standard was actually expanded is advocated by Yao and others (41) in 2001. Their criteria are as follows : single nodule 6.5 cm or less in diameter, or 3 or less in number and 4.5 cm or less in diameter (8 cm or less in the sum of total maximum diameters of the nodules). They reported a good result of probability of survival as 90% and 75.2% for one year and five years, respectively, in those who satisfied their criteria.

We also reported even those with the Milan standard deviation can be expected to have a good prognosis if their tumor nodule is 5 cm or less in diameter and their des-gamma-carboxy prothrombin value is less than 300 mAU/ml (42). It is considered that this useful marker, which serves as an index of the recurrence and the expansion of indication to HCC patients, is necessary. Furthermore, such apparent risk factors for a recurrence of HCC as 1) the diameter of HCC, 2) the presence of vascular invasion, and 3) the poorly differentiated histological type. Therefore, in the near future, a needle biopsy of HCC should be taken into consideration to clarify the histological type and degree of malignancy of HCC using molecular biological techniques in each patient. Regarding the expansion of the indication of LDLT to HCC, a new standard based on the above-mentioned facts should be made in the near future.

4) Relapse of hepatitis C

Liver cirrhosis due to hepatitis C is now one of the most frequent indications for LTx, occupying 30-50% of all European and American liver transplant patients. While the relapse of hepatitis B can be completely controlled by lamivudine and the anti-hepatitis B virus immunoglobulin (HBIG), the relapse of hepatitis C occurs virologically in about 100% of recipients and histologically in about 20% of cases to advance to liver cirrhosis five years after LTx (43, 44). Furthermore, some patients exhibit a rapid progression to liver cirrhosis as a serious type of hepatitis called fibrosing cholestatic hepatitis, which results in graft loss (45). The risk of graft loss due to a hepatitis C relapse has increased in recent years with an increase in the number of cases, and leading to a decline in the probability of survival is a big problem (46). Although an interferon was used as a method of preventing hepatitis C recurrence before, and normalization (biochemical effect) of alanine aminotransferase value is obtained, but the virological effect on hepatitis C is seldom seen (47). The anti-virus treatment of a combination of interferon and ribavirin results in a continuous virological response of 40% or more in patients (48, 49). However, while it is expected as an effective cure, the side effects (hemolytic anemia, etc.) are also strong, and there are also many patients dropping-out from the treatment regimen. Pegylated-interferon having the same anti-viral effects and few adverse effects, which is administered only once a week, is more attractive than conventional interferon, and recently the expectation is growing in the combined use of treatment with rivabirin. Moreover, a recent report raised the following risk factors for a hepatitis C relapse : short-term use of steroids, an elderly donor's age, the use of azathiopurine, steroids and use of purine-metabolic antagonist of mycophenolate mofetil (50).Cyclosporine A, one of the calcineurin inhibitors, was recently reported to suppress the viral replication of the hepatitis C virus (51). The prevention of hepatitis C is a growing issue

in LDLT.

5) Marginal donors

In order to improve the results in adult-to-adult LDLT, a right lobe graft, approximately two thirds of the liver, was introduced and is now frequently used, instead of a left lobe graft or a left lateral segment graft in chi recipients. Recently, a mortality of the living donor was reported in the West (52-55). Furthermore, in Japan, in proportion to an increase of a right lobe graft, donor's complications have increased due to the small residual liver volume in donors. A donor's death was finally reported in Japan May 2003(5). Now, the donor's safety is again a top priority. From the viewpoint of both the donor's safety and the recipient's outcome, the interests in marginal donors are rapidly increasing. The selection standard and evaluation basis of marginal donors are herein discussed.

a) Fatty liver

A fatty liver is known to be unsuitable as a transplant graft, which has been pointed out from experiences of LTx from deceased donors. During a cold preservation of the fatty liver graft, the fusion and expansion of fats is made to press sinusoids and hepatocytes, leading to the circulation disturbance in the sinusoids ad graft injury (56). Since such a cold preservation period can be minimized in a LDLT, the graft with a certain degree of fatty infiltration is usable. However, there are little clear parameters to demonstrate the limits of the fatty liver. We previously reported that in the LDLT the fatty liver was acceptable to the moderate grade of macrovesicular steatosis (20 to 50% of macrovesicular steatosis) (57). However, our recent research showed that the breakdown of sinusoidal reconstitution occurs in the liver regeneration process of a fatty liver (58), therefore, the fatty liver donor should be avoided in the case of the small-for-size graft. In such a case, since a LDLT is a scheduled operation, diet control and/or daily exercise are recommended before an operation to improve the degree of fatty liver. Moreover, NASH (non-alcoholic steatohepatitis) has attracted attention because of the first donor's death in Japan in 2003. Especially, in the case of metabolic syndrome exhibiting the following symptoms and signs of high blood pressure, hyperlipidemia, diabetes, and obesity, the NASH should be ruled out using an ultrasonography and abdominal CT, furthermore and sometimes liver biopsy.

b) Age

There are many institutions, which specify the maximum living-donor's age to be 65 years old for the LDLT. An advanced age donor's problem in LDLT is firstly the increase in a risk of hepatectomy. Due to improvements in surgical techniques and the perioperative management, the rate of postoperative complications is low (nearly zero) compared with overseas. However, since the donor's hepatectomy is an operation conducted on a healthy donor, in order to avoid postoperative complications, an evaluation of the whole body state (operability) or estimation of residual liver volume before an operation takes precedence. Secondly, it is an increase in the risk to the recipient due to a reduced functional reserve of the transplant graft based on an advanced age. It is thought that elderly people's liver function is greatly influenced by the ischemia and reperfusion injury compared to young livers, although it seems practically equal compared with a young liver. For this reason, when a transplant graft is small-for-size, an aged liver graft should be avoided. Technetium-99m-galactosyl-human serum albumin (GSA) scintigraphy, which expresses the binding ability of asialoglycoprotein of the liver, was suggested to be useful in the evaluation of potential graft quality in LDLT(59).

6) Freedom from immunosuppressants

The immunosuppression after a liver transplantation is in principle based on the combination of a calcineurin inhibitor such as cyclosporine A and taclorimus, and steroids. Recent trends in immunosuppression after LTx is an early cessation of steroids and dose-reduction of calcinneurin inhibitors to decrease the incidence of adverse effects. A big theme in immunosuppression after LDLT is the complete freedom from the immunosuppression. The Kyoto University group advocated the following conditions to reduce or stop immunosuppression : 1) 2 years or more passed after LDLT; 2) normal liver function, 3) no history of acute cellular rejection within one year ; and 4) no evidence of progressive bile duct damage in a liver biopsy specimen. They succeeded in creating operational immune tolerance in 35 children out of 67(10^{th} ILTS). A future aim is an operational immune tolerance in adult recipients.

IN CONCLUSION

In this article we outlined the historical background of a LDLT, and its present status and future perspective. In the present time, beyond all doubt, a LDLT is an important treatment option for end-stage liver diseases in Japan, where a LTx form deceased donors has not been yet accepted. However, the LDLT is a medical treatment with a relatively short history, and there are

also many problems to be solved. Now in Japan, viral liver cirrhosis and HCC within the Milan criteria has been covered by medical insurance from January 2004. The number of LDLT is expected to increase from now on. Under these circumstances, although an improvement in the results of LDLT is the aim, the donor's safety must be a priority. Obviously critical complications and accidental death must be avoided by only operating on healthy patients. Anyway, from now on it is expected that there will be an increase in the number of LTx from deceased donors which currently amounts to about several cases per year.

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