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## Guidelines for donor selection and an overview of the donor operation in living related liver transplantation

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**Abstract** Guidelines for donor selection and an overview of the donor operation are reported on the basis of our experience with 120 cases of living related liver transplantation (LRLT) in pediatric patients. Once the parents had clearly expressed their desire to serve as donors, tests were performed to functionally and anatomically screen the donor livers to determine whether or not the parents' general physical condition allowed them to serve as donors. We then evaluated which of the two parental candidates was more suitable as a donor. The wishes of the family as to which parent should serve as donor was considered secondary and taken into account only in a few cases in which certain functional and/or anatomical abnormalities were uncovered that made the prime candidate less suitable. For the 120 LRLTs, 135 candidates were evaluated as potential donors, 15 (11.1%) of whom were rejected for various reasons. The mean volume of blood loss during the donor operation decreased significantly from 489 g in the first 60 LRLTs to 390 g

in the latter 60 LRLTs; this was accompanied by a significant decrease in the mean volume of autologous blood transfused from 449 g to 390 g. Mean cold ischemia time of the graft increased significantly from 71.4 to 128.0 min, while mean operation time conversely decreased from 6.7 to 6.2 h. Bile leakage from the cut surface of the remnant liver, which was the only post-operative surgical complication encountered, was noted in five cases. We conclude that donor candidates should be strictly selected according to basic guidelines, taking into account both the results of preoperative screening and the wishes of the family. With this accumulated experience, we have been able to simplify our LRLT operative procedure, resulting in decreases in blood loss volume, blood transfused, and operation time.

**Key words** Liver transplantation, living related · Living donor, liver transplantation · Donor selection, living donor, liver transplantation

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### Introduction

Living related liver transplantation (LRLT) has come to be performed in institutes worldwide as one of the primary surgical modalities for the treatment of terminal liver disorders in pediatric patients [1–9, 11, 12, 14–16, 19, 21, 22, 25]. LRLT has certain advantages over cadaveric

liver transplantation, such as higher histocompatibility between recipient and donor. It also offers more flexibility since the operation is performed electively. Donor selection therefore becomes a key issue in LRLT when one seeks to procure high viability grafts that can make the most of these advantages. However, since the protocol involves the parents' willingness to donate portions of

their own livers as a gift of life to their stricken child, the wishes of the family must also be taken into account, while at the same time guaranteeing the safety of these donors. Donor selection must, therefore, be carried out discreetly and with the utmost care.

In the present paper, the current guidelines for donor selection employed in our department will be presented, as well as an overview of 120 cases of the donor operation in which the most recent technical improvements in LRLT are demonstrated.

## Patients and methods

### Preoperative evaluation for donor selection

In order to select the best donors for LRLT, routine systemic screenings were preoperatively performed, as previously reported [13]. Figure 1 shows the process of donor selection used by our institute.

#### Functional and systemic screening

Routine liver function tests, complete peripheral blood cell analysis, coagulation tests, serological examination for infectious disease and hepatitis, level of tumor markers, ECG evaluation, chest X-ray and spirometry for cardiopulmonary function test, PSP excretion test for renal function, gynecological examination including a pregnancy test when the candidate is the mother, and routine ultrasonography (US) examination were all included in the screening.

#### Histocompatibility

ABO blood type classification and serological matching were considered, as well as human leukocyte antigen (HLA) matching by DNA typing. The most important and dominant factor is the ABO blood type combination. An identical or compatible ABO combination, or that with a small degree of mismatching as determined by these examinations, is preferable from the standpoint of genetic and immunological histocompatibility [23].

#### Anatomical screening (diagnostic imaging)

Computertomography (CT), magnetic resonance imaging (MRI), and Doppler US were all employed. CT and MRI are performed not only to confirm the absence of anatomical abnormality, but also to evaluate size matching between graft volume and the recipient abdominal cavity by volumetry, as well as the branching pattern of the hepatic veins of the graft liver. Doppler US is done to determine the blood flow of the left portal vein and the diameter and length of the inflow tract to the graft. We no longer perform preoperative angiography of the donor at our institute, primarily out of concern for donor safety. We instead use Doppler US to evaluate the branching pattern of the hepatic arteries to the graft liver.

#### Patients and operations

From June 1990 to August 1994, 120 LRLTs were performed at the Second Department of Surgery of Kyoto University for the following reasons: biliary atresia ( $n = 102$ ), intrahepatic cholestasis

#### ● Desire of Family Father and/or Mother

#### ● Functional and Systemic Screening

Normal    Abnormality (+) → Eliminated from Selection

#### ● ABO Blood Type

#### ● Desire of Family

Replaced by other Parent

Father or Mother

#### ● Anatomical Screening

#### ● Size Matching

Abnormality (-)    Abnormality (+)

Donor

**Fig. 1** The process of donor selection for living related liver transplantation (LRLT)

( $n = 5$ ), liver cirrhosis ( $n = 3$ ), Wilson's disease ( $n = 3$ ), Budd-Chiari syndrome ( $n = 2$ ), protoporphyria ( $n = 1$ ), fulminant hepatitis ( $n = 1$ ), hypertyrosinemia ( $n = 1$ ), glycogen storage disease ( $n = 1$ ), and chronic rejection after first LRLT ( $n = 1$ ). Recipients of the livers included 36 males and 84 females, ranging in age from 3 months to 17 years (mean 4.2 years).

The donor operation was performed according to our basic principle of avoiding any occlusion of blood flow to either the graft liver or the donor liver [24]. In order to present an overview of the donor operation, a comparison was made between the first 60 LRLTs (cases no. 1–60, performed from June 1990 to March 1992) and the second 60 LRLTs (cases no. 61–120, performed from April 1992 to August 1994) with regard to such factors as mode of operation, operation time, volume of blood loss, volume of autologous blood transfused, ischemia time of the graft, and postoperative surgical complications.

Statistics values are expressed as means  $\pm$  SEM. Statistical significant was analyzed using the Mann-Whitney U-test.

## Results

Table 1 shows the profiles of donors who actually participated in the LRLT protocol. In the first group of LRLTs, about one-third of the donors were paternal, while in the latter LRLTs the percentage of paternal donors increased to about 50%. In total, 43.3% (52/120) were paternal donors, and 56.7% (68/120) were maternal donors. As for the age of the donors, in the first group over 50% of them were in their thirties, while in the latter group those in their twenties and thirties were nearly equal in number. All donors ranged in age from 19 to 51 years, with a mean age of  $33.5 \pm 0.8$  years among the first 60 donors and  $32.1 \pm 0.9$  years in the second 60 donors. There were no significant differences in sex or age between the two groups.

Table 2 shows a summary of the abnormalities and the reasons for rejection of donor candidates. Fifteen (11.1%) of 135 candidates were rejected due to functional and/or anatomical abnormalities. Thirteen candi-

**Table 1** Summary of donor profiles (*P* paternal, *M* maternal)

Age (years)	Cases 1–60 (June 1990–March 1992)			Cases 61–120 (April 1992–August 1994)			Total		
	P	M	Total	P	M	Total	P	M	Total
0–20				1	1		1		1
21–30	6	15	21	11	15	26	17	30	47
31–40	14	20	34	18	8	26	32	28	60
41–50	1	3	4	2	5	7	3	8	11
51		1	1					1	1
Total	21	39	60	31	29	60	52	68	120

**Table 2** Abnormal findings and reasons for rejecting a candidate (*HCV* hepatitis C antibody, *CA* carbohydrate antigen)

Functional	
Fatty liver	12 (6) <sup>a</sup>
High transaminases	12 (3)
Anemia	4 (1)
High alkaline phosphatase	4
High cholinesterase	4 (1)
Hyperbilirubinemia	3 (1)
Low cholinesterase	1
Hypothyroidism	1 (1)
Positive HCV	1 (1)
Asthma	1 (1)
High CA 19-9	1
High CA 125	1
	45 (15)
Anatomical	
Cyst or calcification in the liver	3
Cholecystolithiasis	2
Size matching (too large)	2 (2)
	7 (2)
Total	52 (15) <sup>b</sup>

<sup>a</sup> Values outside parentheses indicate the number of abnormal findings and those inside parentheses indicate the number of cases in which these abnormalities were considered to be sufficient grounds to reject candidates

<sup>b</sup> Values inside parentheses indicate the number of candidates who were actually rejected as donors due to these abnormalities. Two of the candidates had two different kinds of abnormalities, for a total of 15 cases of rejection

dates were rejected due to functional abnormalities including fatty liver, high transaminase levels, anemia, high cholinesterase, hyperbilirubinemia, hypothyroidism, positive hepatitis C antibody, and asthma. In some candidates, multiple abnormalities were found, such as hypothyroidism and asthma, or high transaminases and fatty liver. In the candidates with high levels of tumor markers, a thorough investigation for malignancy was performed but no evidence of malignancy was found and so they subsequently underwent the donor operation. Two candidates were rejected due to size mismatching, i.e., grafts that were too large for the recipient abdominal cavity. The anatomical abnormalities li-

**Table 3** Comparison of factors associated with donor operation between the first and second 60 cases (*MHV* middle hepatic vein)

	Cases 1–60 (June 1990–March 1992)	Cases 61–120 (April 1992–August 1994)
Lateral segmentectomy	37	46
Left lobectomy		
( $S_2 + S_3 + S_4$ , <i>MHV</i> <sup>a</sup> )	12	7
( $S_2 + S_3$ , partial $S_4$ )	10	7
Right lobectomy	1	0
Operation time (h)	6.7 ± 0.1 <sup>b</sup>	6.2 ± 0.1*
Blood loss (g)	489 ± 37 <sup>b</sup>	346 ± 31*
Autologous blood transfused (g)	449 ± 22 <sup>b</sup>	390 ± 8*
Ischemia time (min)		
Wash-out to put-in	71.4 ± 7.0 <sup>b</sup>	128.0 ± 10.3**
Put-in to reperfusion	52.5 ± 7.8 <sup>b</sup>	46.8 ± 1.6
Postoperative surgical complications (number of cases)		
Bile leakage	1	4
Wound infection	2	0

\*  $P < 0.01$ ; \*\*  $P < 0.001$  compared to the first 60 cases

<sup>a</sup> Left lobectomy including *MHV* in the graft

<sup>b</sup> Except for one case of right lobectomy

ver cyst, calcification, and cholecystolithiasis were not considered to be causes for rejection of a candidate.

Table 3 shows a comparison of the factors associated with the donor operation between the first 60 LRLTs and the second 60 LRLTs. Emergency right lobectomy was performed in one case in which unforeseen anatomical branching of the left hepatic artery was uncovered intraoperatively. Since this mode is no longer scheduled to be performed, the data from the right lobectomy case have been excluded from Table 3. Among the more recent LRLTs, lateral segmentectomies tended to increase in number since the number of patients younger than 1 year old in that group ( $n = 26$ ) was greater than that in the first group ( $n = 14$ ). As a result, the mean age of the recipients was higher (4.34 years) among the first 60 LRLT recipients than among the latter 60 recipients (3.78 years). The operation time became significantly shorter with the second 60 LRLTs than with the first 60 ( $P < 0.01$ ). Blood loss was also significantly less in the latter group ( $P < 0.01$ ). The volume of autologous blood transfused was also smaller in the second 60 LRLTs than in the first 60 ( $P < 0.01$ ). Cold ischemia time was significantly prolonged in the second 60 LRLTs, despite the decrease in operation time ( $P < 0.001$ ). There was no significant difference in ischemia time from put-in to reperfusion of the graft. The most serious postoperative surgical complication was bile leakage from the cut surface. The incidence of bile leakage was higher in the second 60 LRLTs than in the first 60. Wound infection was noted in two cases in the early group, while there was none in the later group.

## Discussion

Since the LRLT protocol initially depends on the parents' willingness to give a part of their own livers to their stricken child, who is usually suffering from an irreversible liver disorder, the desire of the parent to act as donor must be given high priority in the process of donor selection. In cases where both of a child's parents can serve as donor, i. e., neither parent has any functional or anatomical abnormality and both their blood type combinations are identical to or compatible with, that of the child, the family's wishes may become the most dominant factor in selection. In cases where certain functional abnormalities are uncovered, however, the donor must be diagnosed further to determine whether his or her condition is treatable and/or reversible. If treatable or reversible, the candidate is advised to receive specific care [13] and, after a period of management, he or she is then re-evaluated to determine whether there has been any improvement in his or her condition. If there is no improvement, the candidate may have to be replaced by the other parental donor. In any case, if any functional and/or anatomical abnormality is uncovered during the preoperative screening of the donor, the results of the screenings are clearly presented to the family. We then have to take the initiative to select the better donor candidate, giving the medical factor (the results of the preoperative examinations) priority over the social one (the wishes of the family).

Usually, one of the parents is chosen as the donor on the basis of both ABO blood type combination and the wishes of the family, although these two factors may not be the only ones that determine the final selection. Generally, an identical or compatible ABO blood type combination is preferred. Thus, unless anatomical abnormality or size mismatching is subsequently uncovered, the donor candidate will be selected on this basis. In cases involving small-sized recipients, maternal donors may be preferable for one of the following reasons: (1) the greater ease of size matching or (2) the potential use of the ovarian vein of the donor as the vein graft in portal vein reconstruction since, in most cases of biliary atresia, the portal vein of the recipient is constricted and must be replaced [20].

As for the incidence of rejection of donor candidates during selection, we have recently reported an analysis of functional abnormalities of donor candidates uncovered during the preoperative evaluation. It showed that 8.3% (9/109) of the candidates were rejected as donors due to certain functional abnormalities [13]. In our series of 120 LRLT cases, 135 candidates were preoperatively evaluated, of whom (11.1%) were subsequently rejected due to certain functional abnormalities or anatomical mismatching uncovered during the examination period. However, reports from other institutes abroad where LRLT has been actively performed have shown

that as much as 33% of the candidates were rejected as unsuitable, due not only to functional and/or psychological factors, but also to anatomical variations of accessory hepatic arteries [17]. By contrast, at our institute, ever since we began using microvascular surgical techniques for hepatic arterial reconstruction in recipients [10], our new policy has been never to reject those cases with anatomical variations in the hepatic artery since they no longer pose a problem surgically.

Another possible explanation for the great difference in the percentage of potential donors who are rejected may be the racial differences between oriental and western people, in terms of physique, nutritional status, and the like. Since LRLT is, at the moment, mainly performed on pediatric patients, the graft volume required for the recipient is not so large, i. e., the lateral segment is sufficient in most cases, even in western countries. However, the body weight of the donor in western countries is generally greater than that in oriental ones, resulting in a large liver volume, even in cases in which only the lateral segment would be harvested as the graft. Furthermore, the nutritional status in western people tends to be more fatty due to dietary differences, resulting in a higher incidence of abnormal fat metabolism, such as fatty liver, in that population than in an oriental one. Although there may be cases in which recipient body weight is relatively high, thus requiring a larger graft, oriental people tend to be more suitable LRLT donor candidates due to their relatively smaller physique and their less deteriorated fatty metabolism function. Therefore, from the standpoint of the donor, it is conjectured that the LRLT program may have greater advantages in oriental countries than in western countries. In the future, however, if the dietary patterns in oriental countries begin to resemble those in western countries, the problem of donors with fatty change of the graft liver will likely become manifest in these countries as well. This will then require preoperative management of the donor as well as of the recipient. Donors with fatty liver should be managed preoperatively with regard to their caloric intake, alcohol consumption, and all other forms of nourishment. Indeed, when two candidates in our series (35- and 37-year-old fathers) were diagnosed with fatty liver on their first visit to our hospital, their efforts to reduce caloric intake resulted in successful normalization of these abnormalities within 2 and 4 months, respectively, during which time the recipient children were fortunately faring well [13].

Our comparison of factors associated with the donor operation shows an improvement in the overall management of the donor operation, i. e., in the operation time, volume of intraoperative blood loss, and volume of blood transfused. In the latter group, the number of cases of lateral segmentectomy increased. This was most likely due to the facts that (1) the recipient age tended to decrease and (2) the advantages and safety of lat-

eral segmentectomy have improved with the accumulated experience from the earlier cases. Generally, of the anatomically important factors surrounding the LRLT procedure, the size and volume matching of the graft liver to the recipient are the most essential. Whenever we preoperatively discuss volume matching of the graft, we determine the ratio of graft weight to recipient body weight, i. e., the ratio of graft volume ( $\text{cm}^3$ ) as calculated by CT volumetry to the recipient body weight ( $\text{kg}$ )  $\times 100$ . The ratio of graft weight to recipient body weight ranged from 0.61 to 6.00 in our series. From our experience, we have determined that the lower safety limit of this ratio is 1.00. Ten recipients with ratios lower than 1.00 were over 10 years of age and their body weight exceeded 25 kg (25.2–58.0 kg), even though the left hepatic lobe was donated for the graft. By contrast, recipients with ratios higher than 5.00 were younger than 1 year old and weighed less than 5.0 kg, even though only the lateral segment was harvested. In normal Japanese children without any developmental retardation, body weight ranges from 14 to 21 kg in the 3- to 6-year-old age range. On the other hand, the average weight of the lateral segment harvested as the donor graft was about 240 g [14], the volume of which is calculated to be about  $230 \text{ cm}^3$ . From these facts it is possible to calculate that when recipient age ranges from 3 to 6 years and the lateral segment is harvested, the ratio of graft weight to recipient body weight should be at least 1.2, a value that is well over the lower safety limit of 1.00. This is the other major reason why we have predominantly selected lateral segmentectomy as the standard harvesting procedure in our LRLT protocol. In our series, the body weight of the recipient and the ratio of the graft volume to body weight for recipients of lateral segments were  $8.99 \pm 0.44 \text{ kg}$  and  $3.09 \pm 0.12$ , respectively.

Furthermore, the increasing familiarity of our surgeons with the operative procedures used in the donor operation has resulted in decreased values for these factors, especially the volume of intraoperative blood loss. In all cases, at least 400 g of autologous blood was obtained from the donor 1 week prior to operation; all of this blood was transfused back into the donor during the operation without exception, regardless of the volume of intraoperative blood loss. In several of the first 60 donors, by contrast, 600 g or 800 g of autologous blood was obtained preoperatively, while only 400 g was procured in all of the latter 60 donors. This is the main reason for the differences in the volume of blood transfused between the two groups of donors studied.

In our early experience, we made every effort to minimize the total ischemia time of the graft by adjusting the process of the donor operation to the pace of the recipient operation; the result was a total ischemia time of around 120 min. In the second 60 LRLTs, however, we

were less concerned with the cold ischemia time of the graft, especially in cases with identical and compatible ABO blood type combinations. Since the duration of ischemia time, i. e., the period in which the graft has to be preserved in the backtable basin, usually does not exceed 3 h in our LRLT protocol, and since the prolongation of cold ischemia time seems to have no influence on the postoperative clinical features of the recipients (data not shown), we now assume that as long as the total ischemia time is kept under 3 h, it will have no adverse effect on graft viability. Generally speaking, the shorter the duration of the overall donor operation, the greater the donor safety. Hence, the donor operation time should take priority over the ischemia time of the graft. Therefore, nowadays, we generally do not adjust the process of the donor operation to the pace of the recipient operation but rather proceed to harvest the graft independently of the recipient operation, resulting in a shortening of the donor operation time and a prolongation of cold ischemia time of the graft. However, in donors with incompatible ABO blood type combinations, the ischemia time should be kept to a minimum since it is essential to avoid any risk that may adversely affect the viability of the graft [18].

The most prevalent postoperative surgical complication in our experience has been bile leakage. In the early cases with this complication, conservative therapy was sufficient to correct the condition, and spontaneous remission occurred within a month [14]. However, in one of the recent cases, after removal of the drainage tube inserted along the cut surface of the remnant liver, bile leakage and fluid collection on the cut surface were detected by US and CT at 2 weeks after operation. The donor returned home (to a place somewhat far from our institute) soon after the recipient had been discharged, and this resulted in less intensive management of the physical condition of the donor. While this may have been one of the reasons for the late detection of the bile leakage, we learned from this episode that the dissection procedure of the donor liver has to be performed with the utmost care, and that the donor should be managed more intensively for at least the first 2 weeks after operation.

We conclude that donor candidates should be selected according to basic guidelines that take into account both the results of preoperative screening and the wishes of the family. Our accumulated experience has enabled us to simplify our LRLT operative procedure, with a resultant decrease in blood loss volume, blood transfusion volume, and donor operation time. However, we must also emphasize that every effort must be made to avoid postoperative surgical complications in the donor, even after achieving such technical improvements in the donor operation.

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