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Left-sided grafts for living-donor liver transplantation and split grafts for deceased-donor liver transplantation: Their impact on long-term survival

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Abstract

Background—A small-for-size graft is important in living-donor liver transplantation (LDLT) and deceased-donor liver transplantation (DDLT).

Subjects and methods—First, we confirmed the effect of initial graft volume on survival using a rat model of liver transplantation (LT). We then evaluated the actual long-term survival based on graft type in 1421 LTs (including 1364 LDLTs) at Kyoto University and 2000 DDLTs at the Mayo Clinic, to evaluate donor safety in LDLT and the possibility of shifting to split orthotopic liver transplantation (SOLT) in DDLT.

Results—In the rat model, SOLTs with 40%- and 20%-grafts had a poor survival. A total of 697 pediatric LTs showed good long-term outcomes (survival rate was 0.764 at 21.2 years). The survival rate of 724 adult LTs was 0.664 at 17.8 years. The survival rates of auxiliary partial orthotopic liver transplantation with a left-sided graft (0.421 at 15.0 years) and SOLT with a left-sided graft (0.000 at 0.8 years) need to be improved. Although the survival rate of 1965 adult DDLTs with a whole-liver graft in the Mayo Clinic was 0.727 at 12.8 years, that of adult SOLT was 0.595 at 11.0 years.

Conclusion—From the viewpoint of greater donor safety and expanded donor candidates in LDLT, the choice of a left-sided graft still remains controversial. A shift to SOLT to achieve excellent results should be established to resolve a donor shortage in DDLT.

Background

Use of a small-for-size graft is still controversial in the liver transplantation (LT) field, i.e., living-donor liver transplantation (LDLT) and deceased-donor liver transplantation (DDLT). A small-for-size graft is defined as a graft to recipient weight ratio (GRWR) less than 0.8 or a ratio of graft weight against standard liver volume (SLV) less than 40% [1,2], and these grafts result in a high mortality and morbidity.

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Anatomically, in normal liver, the right and left lobes have hepatic volumes of approximately 60% and 40% against the whole-liver, respectively. Although a right lobectomy is currently a safe procedure because of surgical development, a left lobectomy is safer from the viewpoint of hepatic remnant for the living donor. Moreover, the choice of a left-sided graft for recipients is preferred from the viewpoint of greater donor safety and expanded donor candidates. Additionally, successful split orthotopic liver transplantation (SOLT) [3] for recipients could resolve a donor shortage in DDLT. Although the GRWR and percentage SLV are affected by the recipient's weight or size, the selection of the graft type itself is also crucial for LT to increase donor safety in LDLT and to resolve a donor shortage in DDLT.

In the current study, first, we confirmed the effect of initial graft volume on survival by using an animal model, because many factors may affect the clinical survival after LT. We then retrospectively evaluated the actual long-term survival based on graft type (not GRWR or percentage SLV) in LDLT and DDLT, to evaluate donor safety in LDLT and the possibility of a shift to SOLT in DDLT.

Subjects and methods

Animals

Male Lewis rats (haplotype in major histocompatibility complex: RT-1^l) at eight to 10 weeks of age (body weight of 230–250 g) were used as donors and recipients. The grafts were syngeneic. The study protocol was approved by the institutional ethics review committee (IACUC A19609).

Animal models for orthotopic liver transplantation

An institutional model of rat transplantation has been developed during the last two decades. Operative procedures are described in detail elsewhere for orthotopic liver transplantation (OLT) with a whole-liver graft (100%-OLT) [4] and SOLT [5]. Anatomical findings, surgical materials, graft type and postoperative care are described in detail elsewhere [4,5]. For the SOLT models, we performed SOLTs with graft volumes of 20%, 40% and 60% against the SLV value [5]. Cold ischemic time was two hours in 4 °C of normal Ringer's solution. Each group comprised 10 cases. Previously, we reported that the most important factor for successful OLT was an anhepatic phase less than 15 minutes and that inappropriate samples should be omitted by autopsy findings and histopathological assessment because surgical complications due to technical difficulty will affect the data [4,5]. All recipients in this study fulfilled the criterion of an anhepatic phase less than 15 minutes and there were no surgical complications. This study focused on survival curves, and therefore, we closely monitored survival after surgery (every four hours in 100%-OLT and every one hour in each SOLT).

Overall long-term survival in a large number of living-donor liver transplantations

Although Kyoto University started an LT program from 1990, LDLT is still mainly used. Institutional graft selection and surgical procedures in LDLT are described in detail elsewhere [6]. A total of 1421 recipients who underwent LT from 1990 to 2009 (1364 LDLTs, 31 auxiliary partial orthotopic liver transplantations [APOLTs], 18 OLTs with a whole-liver graft in DDLT or domino liver transplantation [DLT] and eight SOLTs in DDLT or DLT) were evaluated. The follow-up period was 7.76 ± 5.61 years. Overall survivals were separately evaluated in pediatric and adult recipients. Moreover, survivals were separately assessed according to LT type and graft type. The study protocol was approved by institutional ethics review committees (C-279).

A total of 697 LTs at Kyoto University were pediatric recipients. Pediatric recipients were divided into DDLT (OLT) with a whole-liver graft ($n = 1$), LDLT with a right-lobe graft without the middle hepatic vein (MHV) ($n = 13$), LDLT with a left-lobe graft ($n = 83$), LDLT with an extended lateral-segment, lateral-segment, mono-segment or reduced mono-segment graft ($n = 587$), APOLT with an extended lateral-segment or lateral-segment graft ($n = 9$) and DDLT or DLT (SOLT) with an extended lateral-segment, lateral-segment or left-lobe graft ($n = 4$).

A total of 724 LTs at Kyoto University were adult recipients. Adult recipients were divided into DDLT or DLT (OLT) with a whole-liver graft ($n = 17$), LDLT with a right-lobe graft (with or without MHV) ($n = 555$), LDLT with an extended lateral-segment, posterior segment or left-lobe graft ($n = 126$), APOLT with a right-lobe graft ($n = 3$), APOLT with an extended lateral-segment or left-lobe graft ($n = 19$), DDLT (SOLT) with a right-lobe graft ($n = 2$) and DDLT or DLT (SOLT) with a left-lobe graft ($n = 2$).

Overall long-term survival in a large number of deceased-donor liver transplantations

DDLT is the main LT used in the USA, and a total of 2000 recipients who underwent LT in the Mayo Clinic from 1998 to 2011 were evaluated. All recipients were adults, and recipients were divided into DDLT (OLT) with a whole-liver graft ($n = 1965$), DDLT (SOLT) with a right-lobe graft ($n = 18$) and DDLT (SOLT) with a left-lobe graft ($n = 17$). The follow-up period was 4.82 ± 3.21 years. Institutional graft selection and surgical procedures in DDLT are described in detail elsewhere [7–9]. Survivals were separately evaluated according to graft type. The study protocol was approved by institutional ethics review committees (IRB 09-003057).

Statistical analysis

Data are presented as mean $\pm$ standard deviation. The Kaplan-Meier method (the log-rank test) was used for survival curves and survival rate analysis. Statistical calculations were performed by SPSS Version 16.0 (SPSS Software Version 16.0; SPSS Inc., Chicago, IL, USA). A P value less than 0.05 was considered statistically significant, and a P value greater or equal to 0.05 was considered as not significant.

Results

Survival curves in the animal model

Actual survival curves are shown in Fig. 1. Both 40%-SOLT and 20%-SOLT were significantly worse compared with 100%-OLT ($P < 0.0001$), but 60%-SOLT did not reach statistical difference ($P = 0.5006$).

Survival curves of pediatric living-donor liver transplantations

Survival curves for each graft type are shown in Fig. 2. Although the survival rate at 21 years after LDLT was 0.692 in LDLT with a right-lobe graft, the survival rate at 19.5 years after LDLT was 0.0609, even in LDLT with a left-lobe graft, which appeared to have the worst long-term survival. Overall, pediatric LT showed good long-term outcomes (survival rate in all 697 cases at 21.2 years after LT was 0.764).

Survival curves of adult living-donor liver transplantations

Survival curves for each graft type are shown in Fig. 3. The survival rate in all 724 cases at 17.8 years after LT was 0.664. Overall, APOLT with a left-sided graft (survival rate at 15.0 years after LDLT was 0.421) and SOLT with a left-sided graft (survival rate at 0.8 years after LDLT was 0.000) need to have improved long-term outcomes, even if LDLT with left-

sided grafts is considered acceptable (survival rate at 17.8 years after LDLT was 0.629). Overall, survival needs to be improved in LTs with left-sided grafts.

Survival curves of adult deceased-donor liver transplantations

Survival curves for each graft type are shown in Fig. 4. Survival rates were 0.727 at 12.8 years after OLT, 0.637 at 10.8 years after SOLT with a left-lobe graft and 0.556 at 11.0 years after SOLT with a right-lobe graft. Overall, unexpectedly, it appeared that DDLT (SOLT) with a left-lobe graft showed a better survival curve than that with a right-lobe graft, but this was not significantly different ($P = 0.6599$). The SOLT survivals appeared to be poor compared with those for OLT with a whole-liver graft, but there were no significant differences with SOLT ($P = 0.8161$ in a left-lobe graft and $P = 0.3007$ in a right-lobe graft). The SOLT survival rate needs to be improved (survival rate was 0.595 at 11.0 years after SOLT).

Discussion

After LT, liver regeneration occurs even if the initial graft volume is insufficient, and there is still immunological tolerance with implantation of allogeneic antigens. Organically and geometrically, many factors have mutual effects on the postoperative course and outcome of LT. Many clinical studies have already documented important risk factors or reliable predictors of postoperative course or outcome after LT, such as recipient age, donor age, original disease, Model for End-Stage Liver Disease or Pediatric End-Stage Liver Disease score, cold ischemic time, GRWR, percentage SLV, operative time, blood loss, ABO compatibility and lymphocyte cross-match [10–16]. It is difficult to determine how graft type affects outcome. Therefore, at first, we confirmed the effect of initial graft volume on survivals using an animal model using syngeneic grafts. According to the definition of a small-for-size graft, SOLTs with a graft volume less than 40% showed poor outcomes.

In pediatric LT, even smaller sized grafts can provide sufficient GRWR or percentage SLV, because the recipient body is also small. Paradoxically, a large-for-size graft is problematic in the pediatric LT field. Mono-segment or reduced mono-segment grafts have already been introduced [17], and then this issue was resolved from the viewpoint of graft volume. Similar to previous studies, we showed that pediatric LT usually showed good outcomes, although a poor outcome in LT for newborns or infants still remains a problem [18].

On the other hand, insufficient graft volume is predestinate in adult LDLT. The minimum graft size required for LDLT to provide adequate hepatic function has been reported to be a SLV of 40% or GRWR of 0.8 [2]. For insufficient graft volume, APOLT was established to increase liver volume after LT [19], although there are some limitations in the choice of recipients. From the viewpoint of graft size, a right-lobe graft with or without the MHV has been introduced in adult LDLT [20,21]. From the viewpoint of the donor safety, the major concern in adult LDLT is the selection of right-lobe graft, with or without the MHV. In our institution, an algorithm of graft selection based on the congestion volume in each segment (i.e., the segmental drainage of MHV) is well worked in adult LDLT [22–24]. Preoperative careful evaluation of the donor anatomy is crucial for the donor safety, especially in the adult LSLT using a right-lobe graft with the MHV. The right-lobe graft has become the standard graft type for adult LDLT, although the harvest of a larger graft has a high risk in some donors. Therefore, donor safety and graft volume conflict with each other. This is an ironic dilemma. A smaller sized graft is safer for living donors, but satisfactory results still need to be achieved for these grafts.

Donor shortage is problematic in DDLT. Although DDLT is still not widespread in Japan according to the concept of death (e.g., being brain-dead is not always considered as being

dead), donor shortage is severe even in the USA and Europe. If whole-liver allografts from cadaveric donors can always be split, a cadaver donor can provide liver allografts to more DDLT recipients. It is also preferred that OLT with a whole-liver graft eventually shifts to SOLT with a guarantee of excellent results in DDLT recipients who receive smaller sized grafts. Even though it unexpectedly appeared that DDLT (SOLT) with a left-lobe graft showed a better survival curve than that with a right-lobe graft in our study, the survival rate of SOLT is still not acceptable.

Problems in the LT field such as ABO incompatibility may be resolved on a daily basis [14]. Since we recognized that intentional modulation of portal pressure during LDLT prevents small-for-size syndrome [1,25,26], the acceptable minimum graft size at Kyoto University is currently a GRWR greater than 0.7 at graft selection [1]. The GRWR value already became to never reflect clinical course and outcome [27], and the smallest GRWR with a successful LDLT is 0.49 [1]. Graft types clearly shifted from left-sided grafts to right-lobe grafts after this surgical strategy was reported [27]. However, it appears that more advanced strategies using the approach of developments in pretransplant evaluations, immunological tolerance, treatments for original diseases, postoperative infectious controls and methodologies for excellent liver regeneration are also crucial in the LT field.

Many basic researchers focus on severe small-for-size grafts such as the 20%-graft, because the results are more drastic, and differences are obvious if their hypotheses are correct. In adult recipients of LDLT or DDLT (SOLT), we often experience the fulfilment of small-for-size grafts ($GRWR < 0.8$ or $SLV < 40\%$), especially in the choice of a left-sided graft rather than a right-lobe graft, although graft selection of SLV less than 20% is impossible. Although GRWR and percentage SLV are affected by factors of the recipient, a stable graft selection of a left-sided graft has an advantage in LDLT and DDLT (SOLT). Based on the current status of long-term survivals, to overcome a smaller sized graft, use of an approximately 40%-graft appeared to have a reasonable effect and an actual advantage for LT, even though in our study, it unexpectedly appeared that DDLT (SOLT) with a left-lobe graft showed a better survival curve than that with a right-lobe graft. Establishment of excellent results with a 40%-graft will ultimately provide the selection of smaller sized grafts with greater donor safety and a good result for the recipient in LDLT. Establishment of excellent results with a split liver graft will also provide the resolution of a donor shortage with good SOLT results in DDLT.

From the viewpoint of greater donor safety and expanded donor candidates in LDLT, a stable choice of a left-sided graft still remains controversial. A shift to SOLT with excellent results should be established to resolve a donor shortage in DDLT. Although splitting a liver maximizes the number of transplanted recipients, it may increase the morbidity and mortality for the individual recipient. Also, specific regulations for splitting liver graft and ethical policies for SOLT were still not established in some countries. Advanced technological developments in the SOLT have resulted in these ethical dilemmas. The SOLT must be improved all around the world. The transplant surgeons all around the world should explore these difficult issues and propose a general ethical policy for SOLT. The question can be asked: "Where should liver transplant surgeons head in the next decade?" We consider that it is important to focus on improving split liver grafts including approximately 40%-grafts.

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Figure 1.

Survival curves of each graft volume in rats. Syngeneic grafts were used in this study. NS: not significant ($P > 0.05$).

Figure 2.
Survival curves of pediatric living-donor liver transplantation.

Figure 3.
Survival curves of adult living-donor liver transplantation.

Figure 4.
Survival curves of adult deceased-donor liver transplantation.