10歳以上のB型肝炎ワクチンなどの一部のワクチンを除いて，原則すべてのワクチンが皮下注射である．しかしながら，海外では，生ワクチンを除く全てのワクチンは，原則筋肉内注射である．その理由は，1970年代に大腿四頭筋拘縮症の患者が国内で約3,700名報告され，この原因として，頻回の抗菌薬や解熱剤の筋肉内投与が指摘された．日本小児科学会は，筋肉内注射には安全な場所はないという声明を発表し[10]，それ以来，国内では，全ての医薬品の筋肉内注射の閾値が高くなり，ワクチンにおいても，全て皮下注射となった経緯がある．それから，約40年以上を経過する現在でも，皮下注射で予防接種が実施されている．しかしながら，皮下注射による局所反応は，筋肉内注射に比べ高く[11,12]，また，免疫原性に差はなく，むしろ筋肉内注射の方が高いという報告もある[11]．複数のワクチンを同時に接種する際，または，多くの新しいワクチンが開発され，特に複合ワクチン（複数のワクチンを1本にしたもの），アジュバント入りのワクチンなどは，その局所反応を減らすために筋肉内注射がその標準的投与法である．今後，特に乳幼児早期に多くのワクチンを同時接種し，更には，新しいワクチンが順次導入されていく過程において，筋肉内注射を予防接種の標準的接種法として認める必要があると考える．

3）国策として予防接種制度を考えるワクチン専門集団の欠如

諸外国には，ワクチンの専門家によって構成されるNational Immunization Technical Advisory Group（NITAG）が存在し，それぞれの国の状況に合わせ，新しいワクチンを国のワクチンプログラムに入れるかどうか，そして現行のワクチンの効果，その継続の審議が行われている．その代表的なものは，米国のACIP（Advisory Committee on Immunization Practices）であるが，ACIPには，予防接種を国策として行う米国政府の絶対的な信頼が寄せられており，そこで決定した事項のほぼ全てが国策として反映されている．また，この会議での議論された事項はすべて公開されており，その透明性が示されている[13]．

一方，国内でも，この様な世界的な流れに追いつこうと，厚生労働省内の厚生科学審議会に感染症分科会予防接種部会が2008年より設立され，15名の予防接種に関連する専門家が集まり，また，それぞれのワクチンに関する小委員会が作られ，そこからのファクトシートも作成され，予防接種法の改定作業を勧めてきた．更には，この部会が2013年4月からは，予防接種・ワクチン分科会となり，その下に予防接種基本方針部会，副反応検討部会，研究開発及び生産・流通部会の3つの会が作られ，活発な論議が行われている．これからの活動に注目が集まる．更には，ワクチン関連の14の学会の代表から構成される予防接種推進専門協議会は，予防接種政策を国策として行うための提言を国に対して行い，こちらもワクチンをとりまく専門家の立場からの今後の活動が期待される．

4）限定された複合ワクチン

現在，国内には，異なる病原体のワクチンが一緒になった複合ワクチンは，3種混合ワクチン，2種混合ワクチン，MRワクチン，4種混合ワクチンそして異なる抗原の含まれるインフルエンザワクチン，不活化ポリオワクチンがあるが，国外には，5種混合，6種混合というような多くの複合ワクチンが存在する．その利点は多く，接種率が上昇すること，接種回数が減ることによって患者の痛みに関する負担が減ること，医療従事者の業務が削減できること，保管場所の削減，そして，経済的な効果もあげられる．国内では，同時接種へのハードルが依然高い環境にあるだけに更なる混合ワクチンの国内での普及への期待は高い．

5）接種間隔

国内では，不活化ワクチン接種後，異なる不

トピックス

活化，あるいは生ワクチンを接種する場合，中6日以上あけること，生ワクチン接種後は，異なる不活化，あるいは生ワクチンを接種する場合，中27日以上あけることと規定されている．海外では，生ワクチン接種後は，異なる生ワクチンを接種する場合だけ，中27日以上あけることとなっている[2]．この国内の独特の接種間隔は，接種間隔が短く接種された場合，副反応が起こった場合の責任となるワクチンを明らかにするために規定されたものと思われるが，同時接種が実施されている現在，この規定を支持する科学的根拠は存在しない．接種間隔の規定があることで，接種したくても接種できない時期が作られ，接種時期を逃してしまうことがある．この独特の規定は，可能な限り早期に撤廃されなければならない．

5. 予防接種法の改正

この様な中で，2013年4月には，予防接種法が改正された．その実際の接種における主な変更点は，前述のヒブ，PCV7，HPVワクチンの3ワクチンの定期接種化である．既にヒブ，肺炎球菌の髄膜炎患者数が減少していることが報告されているが[14]，今後，更なる接種率の上昇で，疾患の減少が期待される．また，地方自治体の定期接種ワクチン費用負担が変更され，今までは，定期接種のワクチンは20～30％を地方交付税で，残りを市町村が負担していたのに対して，今回の改訂では，定期接種のワクチンの費用の90％を地方交付税で負担することになり，国の予防接種に対する財源確保が明確となった．更には，医師は，定期接種のワクチン接種後の副反応を厚生労働大臣に報告しなくてはいけないことが義務づけられたこと，そして，BCGの接種が，6カ月までが1歳までとなり，標準的接種期間は5～8カ月未満となったこと，麻しん風しんワクチンのIII期，IV期が中止されたことがあげられる．

おわりに

小児をとりまく予防接種の現状は，大きな変化を遂げている．接種できるワクチンは，大幅に増えたが，接種を実際に行う上での制度は，未だ十分に整備されていない現状がある．このギャップをどう埋めるかが重要であり，今後，継続的な改革のための活動が必要である．

著者のCOI (conflicts of interest) 開示：齋藤昭彦；講演料（MSD，田辺三菱製薬，ファイザー）

文　献

1) Saitoh A, Okabe N : Current issues with the immunization program in Japan : Can we fill the "vaccine gap"? Vaccine 30 : 4752–4756, 2012.
2) Plotkin SA, et al : Vaccines, 5th ed, Saunders/Elsevier, Philadelphia, Pa, 2008.
3) King GE, Hadler SC : Simultaneous administration of childhood vaccinesan important public health policy that is safe and efficacious. Pediatr Infect Dis J 13 : 394–407, 1994.
4) Lewis M, et al : Validating current immunization practice with young infants. Pediatrics 90 : 771–773, 1992.
5) 日本小児科学会ホームページ　http://www.jpeds.or.jp/saisin/saisin_1101182.pdf
6) 日本小児科学会ホームページ　http://www.jpeds.or.jp/saisin/saisin_110427.pdf
7) Yano K, et al : Dynamic epidemiology of acute viral hepatitis in Japan. Intervirology 53 : 70–75, 2010.
8) Arvin A, Gershon A : Control of varicella : why is a two-dose schedule necessary? Pediatr Infect Dis J 25 : 475–476, 2006.
9) 庵原俊昭（分担研究者）：分担研究：ムンプス・水痘の臨床像ならびに今後の対策についての検討，平成23年度厚生労働科学研究費補助金（新型インフルエンザ等新興・再興感染症研究事業）：ワクチン戦略による麻疹および先天性風疹症候群の排除，およびワクチンで予防可能疾患の疫学並びにワクチンの有用性に関する基礎的臨床的研究（班長：岡部信彦）報告書.
10) 筋拘縮症に関する報告書. 日本小児科学会誌　87 : 1067–1105, 1983.
11) Mark A, et al : Subcutaneous versus intramuscular injection for booster DT vaccination of adolescents. Vaccine 17 : 2067–2072, 1999.

12) Carlsson RM, et al : Studies on a Hib-tetanus toxoid conjugate vaccine : effects of co-administered tetanus toxoid vaccine, of administration route and of combined administration with an inactivated polio vaccine. Vaccine 18 : 468–478, 1999.
13) ACIPホームページ　http://www.cdc.gov/vaccines/recs/acip/meetings.htm
14) インフルエンザ菌b型（Hib）ワクチンおよび7価肺炎球菌結合型ワクチン（PCV7）導入が侵襲性細菌感染症に及ぼす効果について．IASR　33 : 71–72, 2012.

LIVER TRANSPLANTATION 19:226-228, 2013

Reducing the Thickness of Left Lateral Segment Grafts in Neonatal Living Donor Liver Transplantation

Mureo Kasahara,[1] Seisuke Sakamoto,[1] Takanobu Shigeta,[1] Hajime Uchida,[1] Ikumi Hamano,[1] Hiroyuki Kanazawa,[1] Megumi Kobayashi,[1] Toshihiro Kitajima,[1] Akinari Fukuda,[1] and Mohamed Rela[2]
[1]*Organ Transplant Center, National Center for Child Health and Development, Tokyo, Japan; and*
[2]*Institute of Liver Studies, King's College Hospital, London, United Kingdom*

Liver transplantation is now an established treatment for children with end-stage liver disease. Left lateral segment (LLS) grafts are most commonly used in split and living donor liver transplantation in children. In very small children, LLS grafts can be too large, and further nonanatomical reduction has recently been introduced to mitigate the problem of large-for-size grafts. However, the implantation of LLS grafts can be a problem in infants and very small children because of the thickness of the grafts, and these techniques do not address problems related to thickness. We herein describe a technique for reducing the thickness of living donor left lateral grafts and successful transplantation in a 2.8-kg infant with acute liver failure. *Liver Transpl 19:226-228, 2013.* © 2012 AASLD.

Received September 24, 2012; accepted October 20, 2012.

The lack of size-matched pediatric liver grafts has led to the development of reduced, split, and living donor liver transplantation. These techniques have expanded the potential donor pool and decreased waiting-list mortality for children.[1] Transplantation in children who weigh less than 5 kg remains a problem because the left lateral segment (LLS) from an adult may be too large when the graft-to-recipient weight ratio is greater than 4.0% and thus may result in a large-for-size graft and its associated morbidity.[2] Further reduced LLS grafts that can be transplanted safely without compromise to patient survival have been introduced for these children to mitigate the problem of large-for-size grafts.[3] In very small children (neonates) who have no portal hypertension, hepatomegaly, or ascites, the abdominal cavity may be small, and the anteroposterior thickness of the graft remains a problem.[4,5] Abdominal closure may require a temporary Silastic mesh, and this is associated with complications. We have developed a modified LLS reduction by which the thickness of the graft is addressed and transplantation is allowed in very small infants. The clinical study protocol was approved by the institutional review committee.

CASE PRESENTATION

A 23-day-old Asian girl weighing 2.8 kg who presented with deteriorated liver function was admitted to our hospital. The laboratory study showed a total bilirubin level of 22.7 mg/dL, a prothrombin time/international normalized ratio of 10.0, an alanine aminotransferase level of 500 U/L, and a serum ammonia level of 217 μmol/L. The investigations for infectious and inherited metabolic pathogenesis were all negative. The patient was diagnosed with neonatal acute

Abbreviations: LHV, left hepatic vein; LLS, left lateral segment; LPV, left portal vein; MHV, middle hepatic vein; P2, segment II portal vein; P3, segment III portal vein; PV, portal vein; RHV, right hepatic vein; RPV, right portal vein.

This work was supported in part by grants from the Scientific Research Fund of the Japanese Ministry of Education; by a Research Grant for Immunology, Allergy, and Organ Transplant from the Japanese Ministry of Health, Labor, and Welfare (21591403, 21-04, and 21-042); and by the Foundation for Growth Science (Japan).

Address reprint requests to Mureo Kasahara, M.D., Ph.D., Organ Transplant Center, National Center for Child Health and Development, 2-10-1 Okura, Setagaya-Ku, Tokyo, Japan 157-8535. Telephone: +81-3-3416-0181; FAX: +81-3-3416-2222; E-mail: kasahara-m@ncchd.go.jp

DOI 10.1002/lt.23572
View this article online at wileyonlinelibrary.com.
LIVER TRANSPLANTATION.DOI 10.1002/lt. *Published on behalf of the American Association for the Study of Liver Diseases*

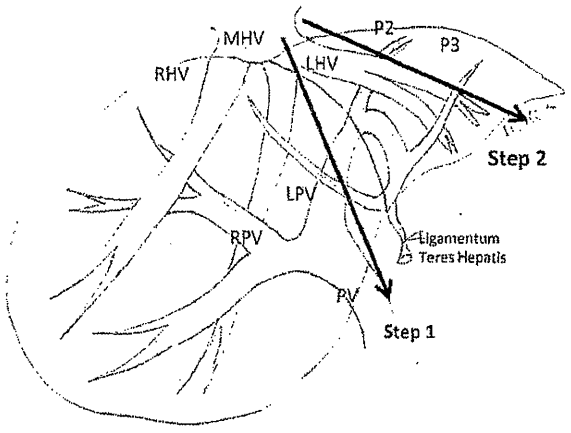

Figure 1. Schema of the cutting lines for left lateral segmentectomy (step 1) and the transection line of the lateral part of the LLS (step 2).

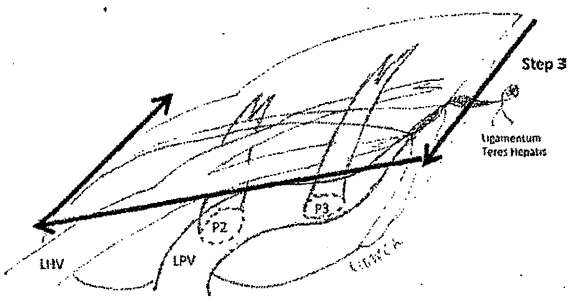

Figure 2. The transection line of the thickness was located horizontally on the level of P3 to thin the graft (step 3).

liver failure of an unknown etiology. The patient, whose liver function had deteriorated despite medical treatment, underwent living donor liver transplantation at the age of 1 month.

The donor was her 31-year-old father, whose blood type was identical. The estimated weight of the LLS according to preoperative computed tomography volumetry was 374 g. This was an extremely large-for-size graft for the child with a graft-to-recipient weight ratio greater than 13%. Hyper-reduction of the LLS graft to remove most of segment II alone seemed inadequate. There was a major anteroposterior size discrepancy between the recipient's abdominal cavity at its maximum (45.6 mm) and the LLS graft of the donor (64.7 mm) according to the preoperative computed tomography evaluation. Therefore, the decision was made to further reduce the anteroposterior thickness of the graft.

In the donor operation, after the isolation of the donor's left hepatic artery and left portal vein (LPV), the hepatic parenchyma was transected 3 mm to the right of the falciform ligament, just as in any standard donor hepatectomy for children (step 1, Fig. 1). The LLS was first reduced by the removal of the lateral aspect of segment II, and care was taken to preserve the segment III branch of the left hepatic vein (LHV;

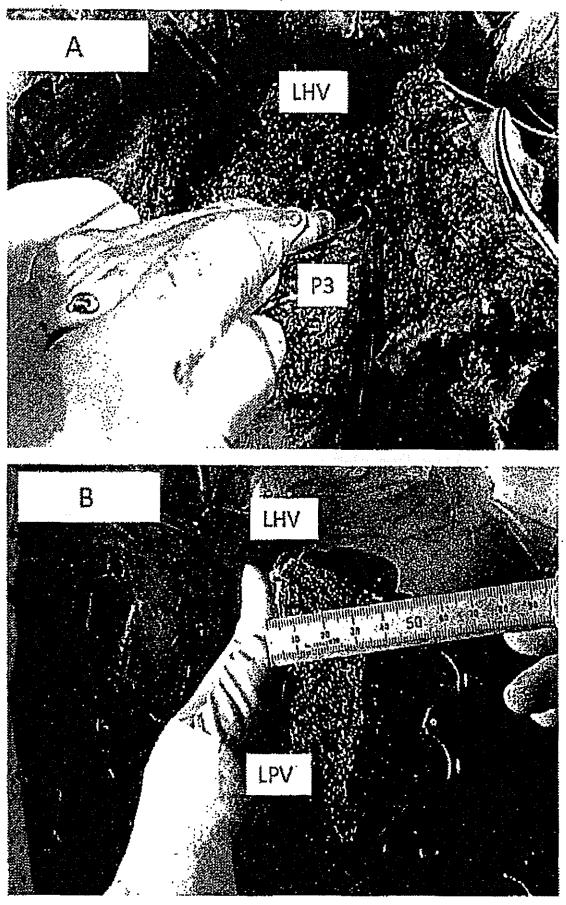

Figure 3. (A) The technique involved the removal of the anterior part of the reduced LLS. This transection line could preserve the drainage vein of the graft, which drained into the inferior vena cava between the segment II and III branches of the PV. This had the potential to reduce the thickness of the LLS graft by more than 40%. (B) The reduced LLS graft weighed 90 g with a thickness of 2.5 cm, so the graft-to-recipient weight ratio was 3.21%.

step 2, Fig. 1).[2,3,4,6] A further reduction of the LLS to reduce the graft thickness was also performed in situ. This technique involved the removal of the anterior part of the reduced LLS (mainly the anterior surface of segment III; step 3, Fig. 2). The transection line for this was located horizontally on the level of the segment III branch of the portal vein (PV). This transection line could preserve the drainage vein of the graft, which drained into the inferior vena cava between the segment II and III branches of the PV. This had the potential to reduce the thickness of the LLS graft by more than 40%. The modified-reduced LLS graft weighed 90 g with a thickness of 2.5 cm and with a graft-to-recipient weight ratio of 3.21% (Fig. 3). The graft was successfully implanted with no major bleeding from the cut surfaces, and primary abdominal closure was achieved. The donor operative time and blood loss were 358 minutes and 50 mL, respectively.

The results of the blood tests performed on days 1 and day 7 for the recipient were as follows: 848 and 57 IU/L for aspartate aminotransferase, 418 and 57 IU/L for alanine aminotransferase, 3.16 and 1.81 mg/dL for total bilirubin, and 3.0 and 1.17 for the prothrombin time/international normalized ratio. The baby was discharged on postoperative day 50. The transplant recipient was doing well with good graft function at the outpatient clinic 3 years after transplantation.

DISCUSSION

Over the past 2 decades, long-term survival has improved significantly for pediatric liver transplant recipients.[5] The disadvantages of using large-for-size grafts include graft compression, the use of Silastic mesh to close the abdomen and associated infections, splinting of the diaphragm, and delayed extubation, all of which contribute to poor outcomes.[7] These complications are amplified by the small recipient size and often associated malnutrition in a patient population that already presents a technical challenge and postoperative complexity.[8] To relieve the problem of large-for-size grafts in small babies, reduced LLS grafts have been introduced.[2,3,4,6] In addition, the size and shape of the LLS of the donor should be taken into consideration. Some LLSs are short and thick, whereas others are thin and long. The second kind poses less of a problem because a further reduction of part of segment II alone may be adequate. However, with short and thick LLSs, the removal of segment II alone is inadequate because the thickness of the graft is the main problem. The technique described herein should be considered for recipients with neonatal/infantile acute liver failure and for children weighing less than 5 kg.

Tailoring the graft size and especially reducing the thickness of the graft might be important for small infants with end-stage liver disease. Although steps 2 and 3 of the procedure presented in this article could be done ex situ to protect the donor from the risk of bleeding and possible air embolisms, prolonged cold ischemia times and rewarming of the graft during back-table surgery have been found to be associated with increased susceptibility to ischemic/reperfusion injury in ex situ split liver transplantation, and it might be postulated that these factors contribute to a higher incidence of graft dysfunction.[9] The procedure is associated with a much higher rate of biliary fistulas, and meticulous surgical technique and pre/intraoperative anatomical evaluations with cholangiography/echography are recommended to prevent compromises to donor and recipient safety. By limiting adhesions in unexpected relaparotomy during follow-up, the use of hemostatic fleeces to protect the cutting edges might be effective.

The modified-reduced LLS has the potential to allow these children to undergo transplantation safely without the associated complications of large-for-size grafts. Although long-term observation should be necessary to establish this technical modification, we hope that increasing experience with the technique and refinements will lead to improved outcomes in liver transplantation for small babies.

REFERENCES

1. Diamond IR, Fecteau A, Millis JM, Losanoff JE, Ng V, Anand R, et al. Impact of graft type on outcome in pediatric liver transplantation: a report from Studies of Pediatric Liver Transplantation (SPLIT). Ann Surg 2007;246: 301-310.
2. Kasahara M, Kaihara S, Oike F, Ito T, Fujimoto Y, Ogura Y, et al. Living donor liver transplantation with monosegments. Transplantation 2003;76:694-696.
3. Srinivasan P, Vilca-Melendez H, Muiesan P, Prachalias A, Heaton ND, Rela M. Liver transplantation with monosegments. Surgery 1999;126:10-12.
4. Kasahara M, Fukuda A, Yokoyama S, Sato S, Tanaka H, Kuroda T, Honna T. Living donor liver transplantation with hyperreduced left lateral segments. J Pediatr Surg 2008;43:1575-1578.
5. McDiarmid SV, Anand R, Martz K, Millis MJ, Mazariegos G, A multivariate analysis of pre-, peri-, and post-transplant factors affecting outcome after pediatric liver transplantation. Ann Surg 2011;254:145-154.
6. Enne M, Pacheco-Moreira L, Balbi E, Cerqueira A, Santalucia G, Martinho JM. Liver transplantation with monosegments. Technical aspects and outcome: a meta-analysis. Liver Transpl 2005;11:564-569.
7. Kiuchi T, Kasahara M, Uryuhara K, Inomata Y, Uemoto S, Asonuma K, et al. Impact of graft size mismatching on graft prognosis in liver transplantation from living donors. Transplantation 1999;67:321-327.
8. McDiarmid SV. Management of the pediatric liver transplant patient. Liver Transpl 2001;7(suppl 1):S77-S86.
9. Busuttil RW, Goss JA. Split liver transplantation. Ann Surg 1999;229:313-321.

Pediatr Transplantation 2013: 17: E25–E28

Pediatric Transplantation
DOI: 10.1111/j.1399-3046.2012.01761.x

Devastating outflow obstruction after pediatric split liver transplantation

Sakamoto S, Nakazawa A, Shigeta T, Uchida H, Kanazawa H, Fukuda A, Karaki C, Nosaka S, Kasahara M. Devastating outflow obstruction after pediatric split liver transplantation.

Abstract: HVOO is a rare complication after pediatric LT, which may lead to graft failure. There are various causes of HVOO, such as mechanical anastomotic obstruction and SOS. A 10-month-old female underwent split LT from a deceased donor for ALF. Her postoperative course was uneventful. However, her liver function suddenly deteriorated a month later. A liver biopsy revealed centrilobular injury, and D-US suggested outflow obstruction. Venography was performed to reveal hepatic venous narrowing inside the graft. She received another graft from a living donor because of progressive graft failure in spite of successful venoplasty with stent insertion. The macroscopic findings of the explanted graft did not show an anastomotic stricture of the hepatic vein, although the pathological findings revealed necrosis of the first graft due to SOS. SOS might cause severe consequences with concomitant mechanical outflow obstruction after pediatric LT.

Seisuke Sakamoto[1], Atsuko Nakazawa[2], Takanobu Shigeta[1], Hajime Uchida[1], Hiroyuki Kanazawa[1], Akinari Fukuda[1], Ciaki Karaki[1], Shunsuke Nosaka[3] and Mureo Kasahara[1]

[1]Division of Transplantation, National Center for Child Health and Development, Tokyo, Japan, [2]Division of Pathology, National Center for Child Health and Development, Tokyo, Japan, [3]Division of Radiology, National Center for Child Health and Development, Tokyo, Japan

Key words: hepatic venous outflow obstruction – sinusoidal obstruction syndrome – pediatric split liver transplantation

Seisuke Sakamoto, Department of Transplant Surgery, National Center for Child Health and Development, 2-10-1 Okura, Setagaya, Tokyo 157-8535, Japan
Tel.: +81 3 3416 0181
Fax: +81 3 3416 2222
E-mail: sakamoto-si@ncchd.go.jp

Accepted for publication 24 May 2012

Acute hepatic venous outflow obstruction after LT can present as an acute Budd–Chiari syndrome (1). Mechanical obstruction caused by anastomotic occlusion or stricture of the hepatic vein is often suspected as a common cause. Numerous technical innovations in LT have been achieved to avoid such a vascular complication (2). SOS, previously named VOD, is clinically characterized by jaundice, hepatomegaly, and ascites and occasionally evolves to liver failure in severe cases (3). Although SOS has been reported to occur as a well-known complication after chemo-irradiation conditioning regimens during bone marrow transplantation (4), the incidence of SOS after LT is low, occurring in only 1.9% of cases; however, the outcome is quite poor (5). Prompt management is crucial for the affected patients to survive, although the severe type of SOS presents a devastating clinical course, which may lead to graft failure (6). This report presents a pediatric case with a severe outflow obstruction possibly due to both mechanical obstruction and subclinical SOS after split LT.

Abbreviations: ACR, acute cellular rejection; ALF, acute liver failure; D-US, Doppler ultrasound; GRWR, graft to recipient body weight; HVOO, hepatic venous outflow obstruction; LT, liver transplantation; SOS, sinusoidal obstruction syndrome; TIPS, transjugular intrahepatic portosystemic shunt; VOD, veno-occlusive disease.

Case

A 10-month-old female (body weight: 7.3 kg), with ALF of unknown etiology, underwent split LT by receiving a left lateral segmental graft from a deceased donor. The donor was relatively old, 65 yr, with a mild steatotic liver. The operation was uneventful with cold ischemic time of approximately seven h. The graft weight was 294 g; thus, the GRWR was 4.03%, and partial skin closure was required to close her abdomen. Tacrolimus with an appropriate

trough level and steroids were used for the initial immunosuppression. Her liver function had become stable for a month after her first LT, except one episode of a slight increase of liver enzymes, which was managed with an increased dosage of tacrolimus. D-US, which was routinely performed twice daily for the first two wk and then once every day, did not show any vascular complications, including the documentation of a pulsatile hepatic venous outflow waves. However, her liver enzymes suddenly increased and her clinical condition deteriorated (Table 1). A liver biopsy revealed centrilobular injury (Fig. 1a), and D-US revealed a limited portal venous flow and a flat hepatic venous flow with dilated intrahepatic veins, which indicated hepatic outflow obstruction. Venography was promptly performed to reveal narrowing of the hepatic venous outflow inside the graft close to the hepatic venous anastomosis and required stent insertion (10 mm × 2.5 cm; Boston Scientific, Natick, MA, USA; Fig. 2), which effectively improved portal venous flow (Fig. 3). Although liver support therapy, including continuous hemodiafiltration and plasma exchange, and steroid pulse therapy were immediately initiated after the successful venoplasty, her liver function rapidly deteriorated. She underwent retransplantation by receiving a left lateral segmental graft (GRWR; 2.4%) from her mother. Her explanted graft was 381 g, which was enlarged to approximately 1.3 times larger than the original graft weight. The stent was properly placed at the narrowing site of the left hepatic vein close to the hepatic venous anastomosis, and no macroscopic anastomotic stricture or thrombosis of the hepatic vein was found. The pathological findings showed massive necrosis of hepatocytes, and fibrous obliterative lesions accompanied with organized microthrombi were found in some of the central venules, which were compatible with SOS (Fig. 1b). Her post-transplant course was uneventful, and she was doing well with a stable liver function six months after her second LT.

Table 1. Laboratory data at the onset of acute outflow obstruction

POD after DDLT	AST (IU/L)	ALT (IU/L)	LDH (U/L)	TB (mg/dL)	PT-INR
24	58	49	187	0.79	
26 (on the morning)	468	247	1117	1.38	
26 (after 12 h)	16170	6680	17560	1.81	1.74
27	12420	2640	7520	1.8	2.3
28	2180	1028	918	2.86	1.8
29	675	432	364	6.33	2.21
30	271	291	232	7.03	2.25
31 (before retransplantation)	149	210	243	7.86	2.09

AST, aspartate amino transferase; ALT, alanine transaminase; DDLT, deceased donor liver transplantation; LDH, lactate dehydrogenase; POD, postoperative day; PT-INR, prothrombin time–international normalized ratio; TB, total bilirubin.

Discussion

Hepatic venous outflow obstruction after LT can be caused by mechanical outflow obstruction and SOS, both of which are completely different from each other in pathogenesis. The diagnosis of mechanical outflow obstruction can be made by radiological examinations. In contrast, the diagnosis of SOS can be confirmed histologically on the basis of fibrous obliterative lesions in the hepatic veins, which are accompanied by centrilobular injuries (7), and SOS is often not suspected on clinical grounds. Furthermore, Sebagh et al. (5) noted that the histological diagnosis of SOS may be difficult and hazardous, and liver biopsies may have a large false-negative sampling error, because terminal hepatic veins do not show uniform involvement with SOS. A liver biopsy revealed centrilobular injury in the current case, which might suggest the presence of SOS, although the finding of D-US clearly

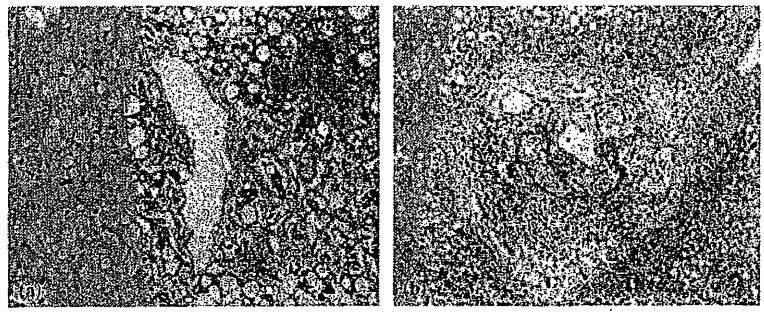

Fig. 1. The pathological findings of a needle liver biopsy (a) showed centrilobular injuries, including severe hepatocyte degeneration and necrosis with steatosis. The pathological findings of the explanted graft (b) showed massive necrosis of hepatocytes with fibrous obliterative lesions in some of the central venules accompanied with organized microthrombi.

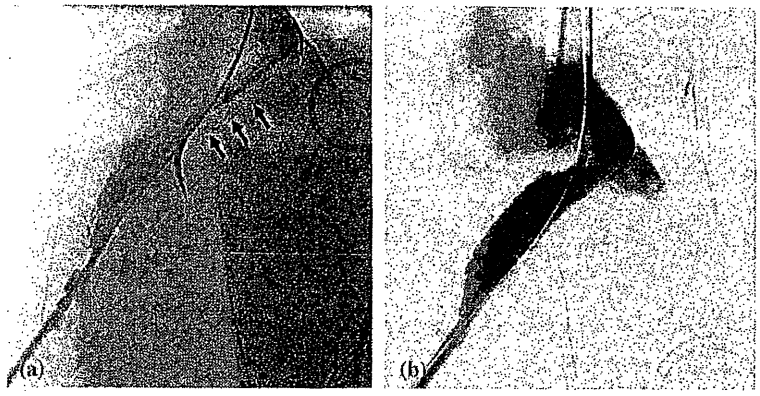

Fig. 2. Venography (a, lateral view) revealed a narrowing of the hepatic venous outflow inside the graft close to the hepatic venous anastomosis (arrow). Stent insertion (b, lateral view) successfully improved the hepatic venous outflow.

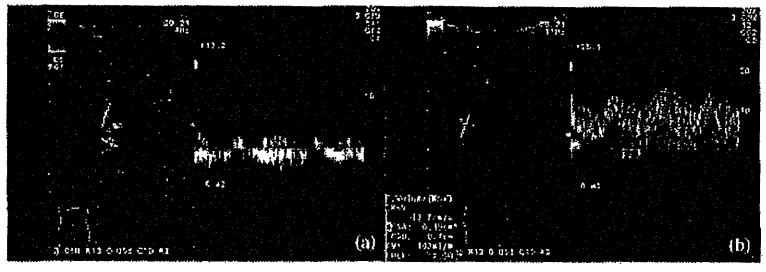

Fig. 3. The findings of D-US before (a) and after (b) the stent insertion revealed the improvement of portal venous flow.

indicated mechanical outflow obstruction, which was confirmed by venography.

Anastomotic occlusion or stricture of the hepatic vein is generally associated with technical issues of hepatic venous reconstruction, although the size, shape, and orientation of the type of graft may predispose kinking of the hepatic venous outflow, especially when using a segmental graft for smaller children (1). Venography showed narrowing of the hepatic venous outflow in the current patient, close to, but not exactly at the anastomotic site. Rapid enlargement of the graft, which was possibly triggered by SOS, may have suddenly induced bending and stretching of the hepatic venous outflow. Moreover, the recipient received a relatively large graft in her small abdominal cavity, which could have compromised the hepatic outflow because of compression.

SOS after solid organ transplantation is a recognized condition in the context of azathioprine toxicity (8). In the report of the largest series of SOS after LT, most of the patients with SOS had an episode of ACR before or at the time of SOS, and the authors suggested that SOS might have an association with cellular rejection with an endothelialitis-induced damage to the centrilobular venous wall (5). The current patient had an episode of a slight increase of liver enzymes a wk before a rapid deterioration of her clinical conditions. Although a liver biopsy was not performed, it is speculated that ACR or a pathological feature indicative of SOS, such as centrilobular endothelialitis, might have already occurred at that point. On the other hand, the etiology of ALF in the current patient remains unknown in spite of precise pretransplant examinations. The outcome of LT for ALF of unknown etiology in smaller children is poor, and centrilobular injuries have often been simultaneously observed with ACR in the liver biopsy specimens at the time of rapid deterioration of liver functions after LT (9). Although these pathological findings might be recognized as a manifestation of rejection, the recurrence of the original disease after LT could not be ruled out as a cause of graft failure. Shimojima et al. (10) described that unique vascular obstructive changes like SOS occurred in native livers and transplanted allografts in infants after LDLT for cryptogenic fulminant hepatic failure. The pathological findings compatible with SOS in the current patient might be similar to their findings, although the pathogenesis of centrilobular injuries remains unknown.

The effectiveness of medical and/or radiological treatment has been previously reported for severe type of SOS. Defibrotide, a polydeoxyribonucleic acid with pro-fibrinolytic and antithrombotic properties, can provide promising results, although the response rate is only about 40% (11). A TIPS is another therapeutic option (12). Campos-Varela et al. (13) summarized seven LT recipients of TIPS-treated SOS and showed that all but one recipient survived, although two required retransplantation and histological resolution of SOS was observed in only one case. In addition, all of the TIPS-treated recipients were adults, and TIPS is technically difficult in small children, as was the situation in the aforementioned case.

Most of the previously reported cases with SOS after LT were adults (5, 6, 12, 13, 14, 15). To the best of our knowledge, only one case demonstrating SOS to occur after LT in a small child has been previously reported (16). Adult patients with SOS tend to show a gradual deterioration over a couple of months. In contrast, the pediatric case with SOS presented with early graft failure several days after undergoing the first LT (16). This case demonstrated a number of similarities with our current case, such as a high GRWR (3.9%), an enlarged explanted graft (1.7 times larger than the original graft weight), and a decreased portal vein flow during the clinical course. As a matter of speculation, rapid enlargement of the graft due to SOS might therefore compromise the hepatic blood flow because of compression, and this phenomenon may be one of the characteristic findings of small children with SOS after LT.

It is worthy of note that both mechanical outflow obstruction and SOS occurred concomitantly in the current case, and the persistent severe type of SOS consequently led to graft failure in spite of prompt management of the mechanical outflow obstruction. SOS should be considered for the cases with acute hepatic venous outflow obstruction after LT.

Authors' contributions

S.S.: study design and writing of the article; A.N.: critically revising the article for pathological content; T.S., H.U., H.K., A.F., and C.K.: collection of data; S.N.: critically revising the article for radiological content; M.K.: study design and critically revising the article for surgical content.

Source of funding

This work was supported in part by grants from the Scientific Research Fund of the Ministry of Education and by a Research Grant for Immunology, Allergy and Organ Transplant from the Ministry of Health, Labor and Welfare, Japan and Foundation for Growth Science, Japan.

References

1. Mazariegos GV, Garrido V, Jaskowski-Phillips S, Towbin R, Pigula F, Reyes J. Management of hepatic venous obstruction after split-liver transplantation. Pediatr Transplant 2000; 4: 322–327.
2. Sakamoto S, Egawa H, Kanazawa H, et al. Hepatic venous outflow obstruction in pediatric living donor liver transplantation using left-sided lobe grafts: Kyoto University experience. Liver Transpl 2010; 16: 1207–1214.
3. DeLeve LD, Shulman HM, McDonald GB. Toxic injury to hepatic sinusoids: Sinusoidal obstruction syndrome (veno-occlusive disease). Semin Liver Dis 2002; 22: 27–42.
4. Liatsos C, Mehta AB, Potter M, Burroughs AK. The hepatologist in the haematologists' camp. Br J Haematol 2001; 113: 567–578.
5. Sebagh M, Debette M, Samuel D, et al. "Silent" presentation of veno-occlusive disease after liver transplantation as part of the process of cellular rejection with endothelialpredilection. Hepatology 1999; 30: 1144–1150.
6. Nakazawa Y, Chisuwa H, Mita A, et al. Life-threatening veno-occlusive disease after living-related liver transplantation. Transplantation 2003; 75: 727–730.
7. Shulman HM, Fisher LB, Schoch HG, Henne KW, McDonald GB. Veno-occlusive disease of the liver after marrow transplantation: Histological correlates of clinical signs and symptoms. Hepatology 1994; 19: 1171–1181.
8. Sterneck M, Wiesner R, Ascher N, et al. Azathioprine hepatotoxicity after liver transplantation. Hepatology 1991; 14: 806–810.
9. Sakamoto S, Haga H, Egawa H, et al. Living donor liver transplantation for acute liver failure in infants: The impact of unknown etiology. Pediatr Transplant 2008; 12: 167–173.
10. Shimojima N, Shibata R, Hoshino K, et al. Cryptogenic fulminant hepatic failure in infancy: Report of 2 cases with unique vascular obstructive changes in native livers. Liver Transpl 2006; 12: 1418–1422.
11. Richardson PG, Soiffer RJ, Antin JH, et al. Defibrotide for the treatment of severe hepatic veno-occlusive disease and multiorgan failure after stem cell transplantation: A multicenter, randomized, dose-finding trial. Biol Blood Marrow Transplant 2010; 16: 1005–1017.
12. Senzolo M, Patch D, Cholongitas E, et al. Severe venoocclusive disease after liver transplantation treated with transjugular intrahepatic portosystemic shunt. Transplantation 2006; 82: 132–135.
13. Campos-Varela I, Castells L, Dopazo C, et al. Transjugular intrahepatic portosystemic shunt for the treatment of sinusoidal obstruction syndrome in a liver transplant recipient and review of the literature. Liver Transpl 2012; 18: 201–205.
14. Mor E, Pappo O, Bar-Nathan N, et al. Defibrotide for the treatment of veno-occlusive disease after liver transplantation. Transplantation 2001; 72: 1237–1240.
15. Kitajima K, Vaillant JC, Charlotte F, Eyraud D, Hannoun L. Intractable ascites without mechanical vascular obstruction after orthotopic liver transplantation: Etiology and clinical outcome of sinusoidal obstruction syndrome. Clin Transplant 2010; 24: 139–148.
16. Izaki T, Inomata Y, Asonuma K, et al. Early graft failure due to a veno-occlusive disease after a pediatric living donor liver transplantation. Pediatr Transplant 2004; 8: 301–304.

Living-Donor Liver Transplantation With Hyperreduced Left Lateral Segment Grafts: A Single-Center Experience

Hiroyuki Kanazawa,[1,2] Seisuke Sakamoto,[1] Akinari Fukuda,[1] Hajime Uchida,[1] Ikumi Hamano,[1] Takanobu Shigeta,[1] Megumi Kobayashi,[1] Chiaki Karaki,[1] Hideaki Tanaka,[1] and Mureo Kasahara[1]

Background. In the setting of liver transplantation in small infants who receive left lateral segment (LLS) grafts, problems are encountered related to graft-size mismatching in the form of so-called "large-for-size" grafts. To address these problems, the feasibility of further reducing the size of LLS grafts to form hyperreduced LLS (HRLLS) grafts was investigated.

Methods. Of the 175 pediatric living-donor liver transplantations performed between November 2005 and December 2011 at our institute, 31 cases were performed using HRLLS grafts. The medical records were reviewed and data were collected retrospectively.

Results. The graft-to-recipient body weight ratio was successfully reduced from 5.2%±2.0% to 2.9%±0.5%. Portal vein thrombosis was observed in one case, and biliary stenosis was seen in two cases. No hepatic artery thrombosis was encountered. The graft and patient 2-year survival rate was 87%. When the results categorized according to the original disease were verified, patients with fulminant hepatic failure (FHF) weighed less and had smaller abdominal cavities compared with patients with cholestatic or metabolic disease. Patients with FHF frequently required skin or partial skin closure to avoid graft compression. For this reason, the anteroposterior diameters in the recipients' abdominal cavities were not adequately large to accommodate the graft thickness, especially in patients with FHF.

Conclusions. In conclusion, living-donor liver transplantation using HRLLS grafts offers a safe and useful option for treating smaller infants.

Keywords: Hyperreduced left lateral segment graft, Liver transplantation, Living donor, Large-for-size graft.

(*Transplantation* 2013;95: 750–754)

In most pediatric patients undergoing living-donor liver transplantation (LDLT), the transplant comprises a left-side partial graft from an adult living donor. Reduced-size, split-liver, and living-donor transplants are all capable of reducing the shortage of organs for pediatric patients (*1*). In small infants receiving left lateral segment (LLS) grafts, problems related to size mismatching between the recipient and the graft are encountered in the form of so-called "large-for-size" grafts. Further reducing the size of the LLS graft may thus be necessary to optimize the graft to match the abdominal cavity of the recipient.

The small sample sizes in the reported studies of liver transplantation using monosegment or hyperreduced LLS (HRLLS) grafts make it difficult to draw conclusions about indications and outcomes (*2–6*). The authors of a previous meta-analysis of data for reduced grafts suggested that the frequencies of vascular complications and retransplantation in patients undergoing liver transplantations may be lower in those with reduced grafts than in those with LLS grafts and concluded that reduced grafts appear to represent a satisfactory option (*3*).

However, if the recipient is a much smaller infant, HRLLS may not fit within the abdominal cavity. In much smaller infants, graft thickness rather than graft volume can become more important.

The present study analyzed 31 cases of LDLT using HRLLS grafts in a single center to clarify the remaining issues related to large-for-size grafts and highlight

This work was supported in part by grants from the Scientific Research Fund of the Ministry of Education and by a research grant for immunology, allergy, and organ transplant from the Ministry of Health, Labor and Welfare, Japan and the Foundation for Growth Science, Japan.

The authors declare no conflicts of interest.

[1]Department of Transplant Surgery, National Center for Child Health and Development, Tokyo, Japan.

[2]Address correspondence to: Hiroyuki Kanazawa, M.D., Department of Transplant Surgery, National Center for Child Health and Development, 2-10-1 Okura, Setagaya-ku, Tokyo 157-8535, Japan.

E-mail: kanazawa-hr@ncchd.go.jp

H.K. participated in the research design, writing of the article, performance of the research, reagents of analytic tools, and data analysis. S.S. participated in the research design, writing of the article, and performance of the research. A.F. and M.K. participated in the research design and performance of the research. H.U., I.H., T.S., M.K., C.K., and H.T. participated in the performance of the research.

Received 20 July 2012. Revision requested 6 August 2012.

Accepted 22 October 2012.

ISSN: 0041-1337/13/955-750

DOI: 10.1097/TP.0b013e31827a93b4

problems arising from HRLLS grafts, indicating directions for further improvement.

RESULTS

Recipient Outcomes

The profiles of the recipients undergoing LDLT using HRLLS grafts are summarized in Table 1. The median (range) operative time and bleeding volume for the recipients were 515 (352–1558) min and 927 (135–5380) mL, respectively. In terms of vascular complications, portal vein thrombosis occurred in 1 (3.2%) case, and no cases of hepatic arterial thrombosis were encountered. Biliary stenosis occurred in 2 (6.5%) cases. Bowel perforation was seen in three cases, diaphragmatic hernia occurred in two cases (7), intraabdominal abscesses developed in two cases, and intraabdominal bleeding was observed in one case. No complications associated with the HRLLS graft procedures were observed such as hemorrhage or bile leakage from the cut surface of the lateral and caudal reductions. Relaparotomy to address these complications was performed in 13 (42%) cases, and no retransplantations were required. Primary closure using abdominal closure, including fascia closure, was achieved in 19 (61%) cases. Skin or partial skin closure was performed in the remaining cases (39%), including five patients with fulminant hepatic failure (FHF), five patients with cholestatic disease, and two patients with metabolic disease. Skin or partial skin closure was performed significantly more often in patients with FHF than in those with cholestatic disease (71% vs. 25%; $P<0.03$). At the time of reoperation, two patients required secondary closure using prosthetic mesh. The overall patient survival rate was 87% at 2 years.

TABLE 1. Profiles for recipients of LDLT using HRLLS grafts

Patient characteristics (n=31)	
Age, mo	7 (1–17)
Sex, male/female	6/25
Body weight (kg)	5.8 (2.8–8.5)
Pediatric end-stage liver disease score	20 (0–52)
Original disease	
FHF	
Cryptogenic etiology	4
Cytomegalovirus infection	1
Echovirus 3 infection	1
Herpes simplex virus infection	1
Cholestatic liver disease	
Biliary atresia	18
Alagille syndrome	1
Progressive familial intrahepatic cholestasis	1
Metabolic disease	
Oxysterol 7-a-hydroxylase deficiency	1
Propionic acidemia	1
Carbamyl phosphate synthetase 1 deficiency	1
Ornithine transcarbamylase deficiency	1
Abdominal wall closure	
Skin or partial skin/primary	12/19
Postoperative complications, n (%)	
Vascular complication	1 (3)[a]
Biliary complication	2 (6)[b]
Diaphragmatic hernia	2 (6)
Intraabdominal abscess	2 (6)
Intraabdominal bleeding	3 (10)
Bowel perforation	3 (10)
Reoperation	13 (42)
Intubation period >7 days	15 (48.4)
2-yr graft survival rate, %	87

[a] Portal vein thrombosis.
[b] Biliary stenosis.
FHF, fulminant hepatic failure; HRLLS, hyperreduced left lateral segment; LDLT, living-donor liver transplantation.

Data for the Hyperreduced Left Lateral Segment Grafts

The data for the HRLLS grafts are summarized in Table 2. The median (range) graft weights before and after reduction were 280 (205–464) and 172 (72–245) g, respectively. The median (range) graft-to-recipient body weight ratio (GRWR) before reduction was 4.8% (3.4%–11.3%). The median (range) GRWR after reduction was 2.8% (2.0%–3.8%). The median (range) weights of the lateral and caudal reductions were 56 (21–259) and 36 (12–111) g, respectively. The mean rate of volume reduction in the LLS grafts was 39%. The median (range) HRLLS graft thickness was 61 (36–85) mm. The median (range) graft thickness-to-anteroposterior diameter in the recipient's abdominal cavity ratio was 1.0 (0.6–1.7).

The data categorized according to the original diseases are shown in Table 3. Patients with FHF were significantly younger than those with cholestatic disease ($P<0.01$). The body weights were significantly smaller in patients with FHF than in those with cholestatic ($P<0.01$) or metabolic diseases ($P<0.03$). No significant differences between underlying diseases were seen in terms of GRWR after reduction, portal flow velocity before or after abdominal closure, or graft thickness. GRWR before reduction was significantly larger in patients with FHF than in those with cholestatic disease ($P<0.01$) or metabolic disease ($P<0.05$). The HRLLS graft weight-to-recipient's native liver weight ratios were significantly lower in patients with FHF than in those with cholestatic disease ($P<0.01$) or metabolic disease ($P<0.05$). The graft thickness-to-anteroposterior diameter in the recipient's abdominal cavity ratios were significantly higher in patients with FHF than in those with cholestatic disease ($P<0.03$). The frequency of skin or partial skin abdominal closure was significantly higher in patients with FHF than in those with cholestatic disease ($P<0.03$).

The data of the nonsurvivors are shown in Table 4. The original disease in the four nonsurvivors was cholestatic disease in three cases and FHF in one case. The median (range) age was 9.5 (1–14) months. The median (range) body weight was 5.9 (3.5–6.5) kg. The median (range) portal flow velocity after abdominal closure was 11.2 (8.7–49.6) cm/s. The median (range) graft thickness was 71.5 (60–83) mm. The median graft thickness-to-anteroposterior diameter ratio was 1.07 (0.94–1.63). Three of four nonsurvivors

TABLE 2. HRLLS graft

Graft weight before reduction, g	280 (205–464)
Graft weight after reduction, g	172 (72–245)
GRWR before reduction, %	4.8 (3.4–11.3)
GRWR after reduction, %	2.8 (2.0–3.8)
Lateral part reduction weight, g	56 (21–259)
Caudal part reduction weight, g	36 (12–111)
HRLLS graft weight/native liver weight[a]	0.67 (0.18–0.85)
Graft thickness, mm	61 (36–85)
Graft thickness/anteroposterior diameter[b]	1.0 (0.6–1.7)

[a] HRLLS graft weight-to-recipient's native liver weight ratios.
[b] Graft thickness-to-anteroposterior diameter in the recipient's abdominal cavity ratio. Anteroposterior diameter is identified as length from the inside abdominal wall to the front of the vertebra on axial computed tomographic images.
GRWR, graft-to-recipient body weight ratio; HRLLS, hyperreduced left lateral segment.

underwent relaparotomy. Three patients died due to sepsis-related intraabdominal infection, bowel perforation, and *Escherichia coli* bacteremia, respectively. One patient died due to pulmonary hemorrhage related to graft failure.

DISCUSSION

Over the past two decades, long-term survival in pediatric recipients of liver transplants has improved significantly (*8*). Finding solutions to the problems related to large-for-size grafts represents the biggest remaining challenge in the field of small infantile liver transplantation. The main problems of large-for-size grafts include the risk of abdominal compartment syndrome due to the small size of the recipient abdominal cavity, size discrepancies in vascular caliber, and insufficient portal circulation and tissue oxygenation (*9–11*). Reducing the size of the graft to that of a monosegment or HRLLS graft is thus necessary. The concept of monosegment liver transplantation was first described in 1992 (*12*). We have reported previously that LDLT using HRLLS grafts is feasible and efficacious in recipients with problems associated with large-for-size grafts (*4, 10, 13*). Both monosegment and HRLLS grafts might overcome the problems associated with large-for-size grafts simply by reducing the volume of the LLS graft.

When the estimated GRWR was more than 4% on preoperative evaluations, we approved the use of reduced grafts for LDLT (*9*). Creating a monosegment graft in situ requires identification and preservation of Glisson's capsule, leading to hazardous dissection at the base of the umbilical fissure (*14*). In situ reduction of an LLS graft to create an HRLLS graft is technically easier than monosegmentectomy due to the use of nonanatomical resection. After reduction of LLS to HRLLS grafts, the median GRWR was successfully reduced from 4.8% to 2.8%.

The recipients with lower body weights showed a tendency toward requiring skin or partial skin closure. Although the HRLLS graft weight-to-recipient's native liver weight ratios were as low as 0.67, up to 39% of the cases required skin or partial skin closure of the abdominal incision to avoid graft compression. This indicates that not only GRWR but also the shape of the graft are more important factors in recipients with much lower body weights, particularly in those with FHF, compared with patients with cholestatic liver disease who usually have ample capacity in the abdominal cavity after ascites retention. Graft shape was evaluated using the graft thickness-to-anteroposterior diameter in the recipient's abdominal cavity ratio. This ratio was found to be negatively correlated with the age and body weights of the recipients ($P<0.01$; data not shown). Patients with a larger ratio more often required skin or partial skin closure to avoid graft compression

TABLE 3. Data categorized according to original disease in recipients of LDLT using HRLLS graft

	FHF (n=7)	Cholestatic (n=20)	Metabolic (n=4)
Age, mo[a]	1 (1–10)	7.5 (4–17)	5.5 (3–8)
Sex, male/female	1/6	4/16	1/3
Body weight, kg[b]	3.7 (2.9–8.0)	5.9 (5.2–8.5)	6.8 (5.8–8.0)
GRWR before reduction, %[c]	6.43 (4.26–11.34)	4.51 (3.51–7.17)	3.85 (3.46–4.06)
GRWR after reduction, %	2.64 (1.80–4.00)	3.00 (2.27–3.73)	2.89 (2.65–2.92)
Portal flow velocity before abdominal closure, cm/s	30.1 (12.7–48.2)	37.6 (14.5–109.2)	44.6 (35.2–57.0)
Portal flow velocity after abdominal closure, cm/s	19.2 (6.8–58.5)	32.25 (11.1–90.4)	44.4 (28.9–57.0)
HRLLS graft weight/native liver weight[d]	0.48 (0.18–0.69)	0.67 (0.48–0.85)	0.71 (0.68–0.74)
Graft thickness, mm	64 (36–78)	60 (44–85)	67 (62–76)
Graft thickness/anteroposterior diameter[e]	1.26 (0.61–1.73)	0.94 (0.64–1.6)	1.23 (1.11–1.43)
Skin or partial skin abdominal closure, n (%)[f]	5 (71)	5 (25)	2 (50)
Intubation period >7 days, n (%)	5 (71)	10 (50)	0 (0)

[a] FHF vs. cholestatic disease with age ($P<0.01$).
[b] FHF vs. cholestatic disease with body weight ($P<0.01$). FHF vs. metabolic disease with body weight ($P<0.03$).
[c] FHF vs. cholestatic disease with GRWR before reduction ($P<0.01$). FHF vs. metabolic disease ($P<0.05$).
[d] FHF vs. cholestatic disease with HRLLS graft weight-to-recipient's native liver weight ratio ($P<0.01$). FHF vs. metabolic disease ($P<0.05$).
[e] FHF vs. cholestatic disease with graft thickness-to-anteroposterior diameter in the recipient's abdominal cavity ratio ($P<0.03$). Cholestatic disease vs. metabolic disease ($P<0.01$).
[f] FHF vs. cholestatic disease with skin or partial skin closure ($P<0.03$).
FHF, fulminant hepatic failure; GRWR, graft-to-recipient body weight ratio; HRLLS, hyperreduced left lateral segment; LDLT, living-donor liver transplantation.

TABLE 4. Nonsurvivors of LDLT using HRLLS graft

	Case 1	Case 2	Case 3	Case 4
Original disease	Cholestatic	FHF	Cholestatic	Cholestatic
Age, mo	10	1	14	9
Body weight, kg	6.5	3.5	6.0	5.7
GRWR after reduction, %	3.37	2.06	2.31	3.54
Portal flow velocity before abdominal closure, cm/s	20.2	12.7	14.5	16.1
Portal flow velocity after abdominal closure, cm/s	49.6	8.7	11.3	11.1
Graft thickness, mm	65	78	60	83
Graft thickness-to-anteroposterior diameter ratio	0.94	1.63	1.00	1.14
Abdominal wall closure	Primary	Partial skin	Partial skin	Primary
Relaparotomy (POD)	Yes (7)	Yes (13)	Yes (7)	No
Cause of death	Sepsis	Pulmonary hemorrhage	Sepsis	Sepsis

FHF, fulminant hepatic failure; GRWR, graft-to-recipient body weight ratio; HRLLS, hyperreduced left lateral segment; LDLT, living-donor liver transplantation; POD, postoperative day.

($P<0.01$; data not shown). Even when the ratio was large, we made an in-principle decision not to use prosthetic mesh for abdominal closure due to the risk of infection, except in cases requiring relaparotomy. To date, we have been able to close abdominal incisions without using prosthetic mesh by measuring portal flow velocity during abdominal closure. In the present 31 cases, portal flow velocity was sufficient both before (median, 35.2 cm/s) and after (median, 34.0 cm/s) abdominal closure. The former value indicates that the vascular bed of the graft was reasonably well adjusted with graft reduction, whereas the latter indicates that abdominal closure was possible without graft compression. Recipients requiring HRLLS grafts are likely to develop abdominal compartment syndrome after relaparotomy due to severely edematous intestines that do not fit into the small size of the abdominal cavity. In this study, the frequency of relaparotomy to address postoperative complications was high (42%). Two relaparotomies to treat posttransplantation complications required the use of prosthetic mesh during abdominal wall closure, and all of these patients suffered from sepsis afterward.

Then again, intraabdominal pressure elevation has a direct effect on the pulmonary function (*15*), and the functional residual capacity is lower in smaller infants. In this study, 15 (48.4%) patients required ventilator assistance for more than 7 days after undergoing liver transplantation. Among them, patients with FHF did at a high rate (71%) because they were smaller and tended to have prolonged encephalopathy due to the development of FHF after liver transplantation.

When the data of our 31 patients were categorized according to the original diseases, patients with FHF experienced most of the adverse conditions that were prone to causing

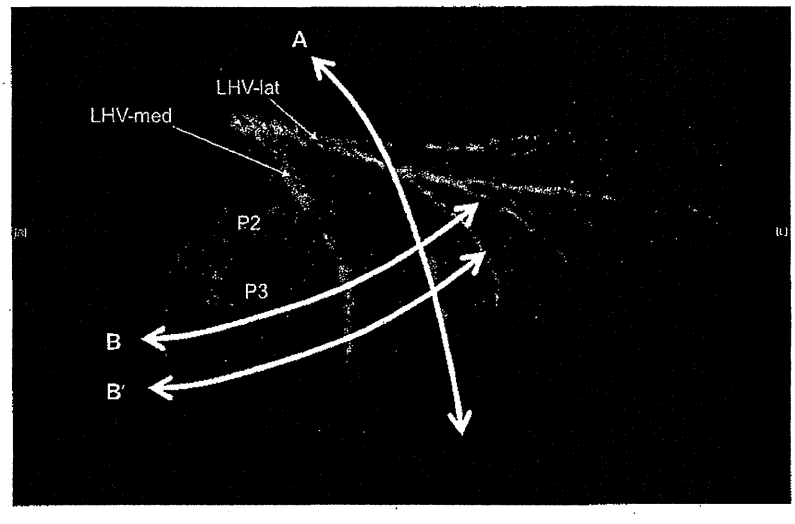

FIGURE 1. The method of caudal reduction was performed while preserving Glisson's capsule of segment 3. The amount of caudal reduction was determined according to the weight of the lateral segment reduction (A). The cutting surface was often the transverse plane. It is possible to adjust the amount of caudal reduction by changing the cutting plane (B or B'). P2, portal vein in segment 2; P3, portal vein in segment 3; LHV-lat, lateral tributary of the left hepatic vein; LHV-med, medial tributary of the left hepatic vein.

abdominal compartment syndrome, such as having much lower body weights, higher graft thickness-to-anteroposterior diameter in the recipient's abdominal cavity ratios, and lower portal flow velocities before and after abdominal closure. Patients with FHF, required skin or partial skin closure frequently due to limited abdominal cavities. Therefore, once postoperative complications occurred, patients were vulnerable to developing abdominal compartment syndrome. Then again, patients with cholestatic disease tended to develop bacterial cholangitis or severe intraabdominal adhesions due to hepaticojejunostomy. Therefore, they had high risks of infection and bowel perforation after liver transplantation.

We made an in-principle prohibition against mothers becoming living donors for 3 months after childbirth. Fathers generally have large livers in comparison with mothers and were common living donors in the present cases. The median thickness of the grafts obtained from fathers was 67 mm compared with 55 mm for grafts obtained from mothers ($P<0.01$). Donor weight was found to be positively correlated with graft thickness ($P<0.01$; data not shown). Particularly in cases of FHF, it is common to face the dilemma of a father with a blowfish-shaped LLS graft becoming the living donor for a small recipient requiring a flatfish-shaped graft. The liver volume can be reduced, whereas the graft thickness cannot (*16*). As a next step toward achieving a promising solution, patients with FHF might require even lower GRWR and HRLLS grafts should be made thinner with further innovation.

In conclusion, LDLT using HRLLS grafts represents a safe and useful option for treating smaller infants. However, problems related to large-for-size grafts, particularly in terms of graft thickness, remain for much smaller infants.

MATERIALS AND METHODS

The medical records were reviewed and data were collected retrospectively. Between November 2005 and December 2011, 175 LDLTs were performed at the National Center for Child Health and Development (Tokyo, Japan). We enrolled 31 patients who received HRLLS grafts from living donors.

Recipients

The recipient characteristics are listed in Table 1. The median (range) age of the recipients was 7.0 (1–17) months. The median (range) weight was 5.8 (2.9–8.5) kg, with 17 (55%) patients weighing less than 6 kg. The indications for LDLT included FHF in 7 recipients, cholestatic liver disease in 20 recipients, and metabolic liver disease in 4 recipients. The median (range) pediatric end-stage liver disease score was 20 (0–52).

Donors

The donor's relationship to the recipient was father in 15 cases, mother in 14 cases, and aunt in two cases. The median (range) donor age and weight were 32 (20–42) years and 62 (38–80) kg, respectively. The median (range) operative time and bleeding volume in the donors were 347 (206–470) min and 200 (10–815) mL, respectively. All donors were discharged without any postoperative complications.

Graft Type Selection and Surgical Procedures

The selection of graft type was made based on the estimated GRWR using computed tomography volumetry. If the estimated GRWR of an LLS graft was more than 4%, an HRLLS graft was selected.

Our surgical techniques were standardized, and both the preoperative evaluation and the surgical techniques have been reported previously (*17, 18*). In each case, the transection line was dependent on the anatomical variation of the hepatic venous system rather than the portal venous system. The caudal and lateral portions of the LLS grafts were transected in situ while preserving the medial branch of the left hepatic vein (*19*). The first step was to transect and weigh the lateral portion of the LLS graft. The second step was to further transect the caudal portion of the LLS in consideration of the weight of the lateral portion (Fig. 1). A cavitron ultrasonic surgical aspirator (Tyco Healthcare, Mansfield, MA) and irrigating bipolar cautery were used for graft reduction without inflow occlusion. The cut surface was cauterized with bipolar cautery, and the clearly exposed vessels were either ligated or sutured according to their size.

Intraoperative color Doppler ultrasonography was performed to assess the blood flow velocity and pattern after vascular reconstruction and during abdominal wall closure.

Immunosuppressive Therapy

The immunosuppressive therapy consisted of tacrolimus and low-dose steroids. Patients were weaned off the steroids during the first 3 months (*20*).

Statistical Analysis

The results are expressed as the median (range). All statistical analyses were performed using SPSS version 19.0 software (SPSS, Chicago, IL). *t* test was used to compare continuous variables. $P<0.05$ was considered statistically significant. The survival rates were determined using the Kaplan-Meier method.

REFERENCES

1. Broelsch CE, Emond JC, Whichington PF, et al. Application of reduced-size liver transplantation as split grafts, auxiliary orthotopic grafts, and living related segmental transplants. *Ann Surg* 1990; 212: 368.
2. Kasahara M, Kaihara S, Oike F, et al. Living-donor liver transplantation with monosegments. *Transplantation* 2003; 76: 694.
3. Enne M, Pacheo-Moreira L, Balbi E, et al. Liver transplantation with monosegments. Technical aspects and outcome: a meta-analysis. *Liver Transpl* 2005; 11: 564.
4. Ogawa K, Kasahara M, Sakamoto S, et al. Living donor liver transplantation with reduced monosegment for neonates and small infants. *Transplantation* 2007; 83: 1337.
5. Srinviasan P, Vilca-Melendez H, Muiesan P, et al. Liver transplantation with monosegments. *Surgery* 1999; 126: 10.
6. Mizuta K, Yasuda Y, Egami S, et al. Living donor liver transplantation for neonates using segment 2 monosubsegment graft. *Am J Transplant* 2010; 10: 2547.
7. Shigeta T, Sakamoto S, Kanazawa H, et al. Diaphragmatic hernia in infants following living donor liver transplantation: report of three cases and a review o the literature. *Pediatr Transplant* 2012; 16: 496.
8. Jain A, Mazariegos G, Kashyap R, et al. Pediatric liver transplantation. A single center experience spanning 20 years. *Transplantation* 2002; 73: 941.
9. Kiuchi T, Kasahara M, Uryuhara K, et al. Impact of graft size mismatching on graft prognosis in liver transplantation from living donors. *Transplantation* 1999; 67: 321.
10. Kasahara M, Fukuda A, Yokoyama S, et al. Living donor liver transplantation with hyperreduced left lateral segments. *J Pediatr Surg* 2008; 43: 1575.
11. Vanatta JM, Esquivel CO. Status of liver transplantation in infants <5 kg. *Pediatr transplant* 2007; 11: 5.
12. Houssin D, Soubrane O, Boillot O, et al. Orthotopic liver transplantation with a reduced-size graft: an ideal compromise in pediatrics? *Surgery* 1992; 111: 532.
13. Bustill RW, Goss JA. Split liver transplantation. *Ann Surg* 1999; 229: 313.
14. Thomas N, Thomas G, Verran D, et al. Liver transplantation in children with hyper-reduced grafts—a single-center experience. *Pediatr transplant* 2010; 14: 426.
15. Bailey J, Shapiro MJ. Abdominal compartment syndrome. *Crit Care* 2000; 4: 23.
16. Fan ST. Commentary on living donor liver transplantation with reduced monosegments for neonates and small infants. *Transplantation* 2007; 83:1299.
17. Tanaka K, Uemoto S, Tokunaga Y, et al. Surgical techniques and innovations in living related liver transplantation. *Ann Surg* 1993; 217: 82.
18. Egawa H, Inomata Y, Uemoto S, et al. Biliary anastomotic complications in 400 living related liver transplantation. *World J Surg* 2001; 25: 1300.
19. Sakamoto S, Shigeta T, Hamano I, et al. Graft outflow venoplasty on reduced left lateral segments in living donor liver transplantation for small babies. *Transplantation* 2011; 91: e38.
20. Inomata Y, Tanaka K, Egawa H, et al. The evolution of immunosuppression with FK506 in pediatric living-related liver transplantation. *Transplantation* 1996; 61: 247.

American Journal of Transplantation 2013; XX: 1–10
Wiley Periodicals Inc.

doi: 10.1002/ajt.12276

Long-Term Outcomes of Pediatric Living Donor Liver Transplantation in Japan: An Analysis of More Than 2200 Cases Listed in the Registry of the Japanese Liver Transplantation Society

M. Kasahara[1,*], K. Umeshita[2], Y. Inomata[3], S. Uemoto[4] and Japanese Liver Transplantation Society

[1]*Transplantation Center, National Center for Child Health and Development, Tokyo, Japan*
[2]*Department of Surgery, Osaka University, Osaka, Japan*
[3]*Department of Transplant Surgery, Kumamoto University, Kumamoto, Japan*
[4]*Department of Surgery, Kyoto University, Kyoto, Japan*
**Corresponding author: Mureo Kasahara, kasahara-m@ncchd.go.jp*

The Japanese Liver Transplantation Society (JLTS) was established in 1980 in order to characterize and follow trends in patient characteristics and graft survival among all liver transplant patients in Japan. This study analyzed the comprehensive factors that may influence the outcomes of pediatric patients who undergo living donor liver transplantation (LDLT) by evaluating the largest cohort in the world. Between November 1989 and December 2010, 2224 pediatric patients underwent LDLT in Japan. There were 998 male (44.9%) and 1226 female donors (55.1%) without donor mortalities related to transplant surgery. There were 946 male (42.5%) and 1278 female (57.5%) recipients with a median age of 4.0 years (range: 13 days to 17.9 years). Cholestatic liver disease was the leading indication for LDLT (n = 1649; 76.2%), followed by metabolic disorders (n = 194; 8.7%), acute liver failure (n = 192; 8.6%) and neoplastic liver disease (n = 66; 3.0%). The 1-, 5-, 10- and 20-year patient survival rates were 88.3%, 85.4%, 82.8% and 79.6%, respectively. Blood-type incompatibility, recipient age, etiology of liver disease and transplant era were found to be significant predictors of overall survival. We are able to achieve satisfactory long-term pediatric patient survival outcomes in the JLTS series without compromising the living donors.

Key words: Liver transplantation, living donor, living donor liver transplantation, pediatric liver transplantation

Abbreviations: GRWR, graft-to-recipient body weight; JLTS, Japanese Liver Transplantation Society; LDLT, living donor liver transplantation; LLS, left lateral segment; LT, liver transplantation

Received 08 February 2013, revised 10 March 2013 and accepted 29 March 2013

Introduction

Living donor liver transplantation (LDLT) was introduced in Japan in 1989 as a life-saving procedure for a patient with biliary atresia due to the absolute scarcity of organs available for deceased donor transplantation (1). The shortage of deceased organ donors led to the development of unique technical, physiological and logistical innovations in LDLT (2,3). Experience with and technical improvements in living donor surgery have led to the generalization of pediatric LDLT with excellent patient and graft survival outcomes. These techniques have expanded the potential donor pool and decreased waiting list mortality in the setting of pediatric liver transplantation (LT) (4).

Recently, there have been technical and immunological refinements in the Japanese pediatric LDLT program, such as resolving graft size matching and overcoming blood-type mismatches. The Kyoto group reported that ideal grafts, defined as grafts with a graft-to-recipient body weight ratio (GRWR) of 0.8–4.0%, are associated with small- and large-for-size syndrome, which results in poor patient survival (5,6). ABO-incompatible LDLT was introduced in Japan to overcome the potential donor shortage. It has been reported that, despite the application of preoperative plasma exchange, splenectomy and enhanced immunosuppression, the 5-year graft survival rate is less than 70% in the pediatric population (7,8). Specific diseases and preoperative patient conditions are associated with transplantation outcomes (9–11).

The JLTS, the Japanese Liver Transplantation Society, a cooperative research consortium, was established in 1980 in order to characterize and follow trends in patient characteristics and graft survival outcomes at all liver transplant centers in Japan. The JLTS is a mandatory data registry, and 100% of the LDLT cases were enrolled in this

study. All data were validated by cross-checking the information with the national registry of the Japanese Transplantation Society and the national clinical database of the Japan Surgical Society. The aim of this preliminary study was to evaluate the largest cohort of pediatric patients who have undergone LDLT in the world. The use of annual LT registry data was approved by the ethical committee of the JLTS.

Patients and Methods

Study design

We analyzed data for all living donors and recipients who underwent isolated LDLT and were enrolled in the JLTS between the registry's inception in November 1989 and December 2010. The study patients were followed before LDLT, then yearly after transplantation. The following donor data were obtained from the JLTS database: age, sex, blood type, relationship to the recipient and graft type. The following recipient data were collected: age, sex, blood type, original liver disease and outcome at last follow-up (survival or death). Data regarding perioperative patient conditions, immunosuppression protocols, postoperative complications and cause of death were not available due to limitations in the information contained within the JLTS database.

The number of LDLTs performed in Japan showed an initial increase to a maximum of 562 in 2005 followed by a decrease and return to the status quo of approximately 450 annually (Figure 1). During the study period (November 1989 to December 2010), 6097 LDLTs were performed in Japan with a minimum follow-up of 2 years. Of these cases, 2224 involved children less than 18 years of age (36.5%) who were enrolled in the present study. The annual number of pediatric LDLT cases has been 130–140 over the past 5 years. During the same study period, 96 deceased LTs, including 13 split LTs in pediatric patients were performed, and these patients were excluded from the present study.

Statistical analysis

Continuous variables are reported as medians and interquartile ranges, and categorical variables are reported as proportions. The cumulative survival is shown with Kaplan–Meier curves, and differences in survival between groups were analyzed using the log-rank test. Medians were compared using the Wilcoxon test and proportions were compared using the chi-square test. Factors associated with long-term patient survival were analyzed with Cox regression analyses. The backward stepwise procedure was used for variable selection with retention criteria at a p value of <0.1 level of significance. Variables with $p < 0.1$ in the univariate analysis were included in the multivariate analysis. All recipients were followed until death and/or graft loss or until December 2010. The median follow-up period was 10.6 years (range: 2.0–21.1 years). All statistical tests were two-sided, and $p < 0.05$ was considered to be significant. The statistical analyses were performed with the SPSS version19.0 software program.

Results

Donor characteristics

The characteristics of the 2224 donors and recipients are summarized in Table 1. The potential donors were evaluated using liver function tests, and blood type, anatomical variations and graft size were evaluated with computed tomography (CT) volumetry. All patients received grafts from family members. There were 998 male (44.9%) and 1226 female donors (55.1%) with a median age of 35.2 years (range: 17–70 years) and a median body weight of 59 kg (range: 36–103 kg). The donors were parents in 95.3% cases, including fathers and mothers in 42.9% and 52.4% of cases, respectively, followed by grandparents in 2.7% of cases. The blood-type combination was identical in 1484 (66.7%) cases and compatible in 446 (20.1%) cases, while 294 (13.2%) recipients received ABO-incompatible grafts. The graft types included reduced left lateral segment (LLS; n = 96; 4.3%), LLS (n = 1549; 69.6%), left lobe (n = 500; 22.5%), posterior segment (n = 3; 0.1%) and right lobe grafts (n = 76; 3.4%). There were no donor mortalities related to surgery in this study population.

Recipient characteristics

There were 946 male (42.5%) and 1278 female (57.5%) recipients with a median age of 4.0 years (range: 13 days to 17.9 years) and a median body weight of 16.6 kg (range:

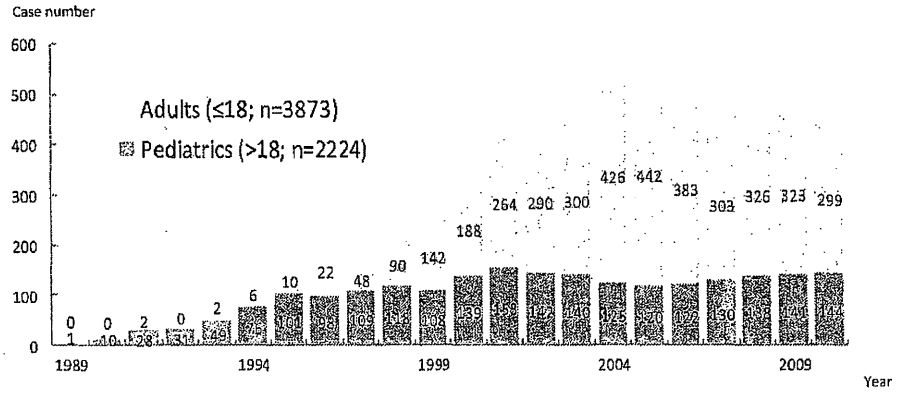

Figure 1: Number of cases of living donor liver transplantation in Japan (n = 6097).

Table 1: Characteristics of patients undergoing pediatric living donor liver transplantation in Japan

Donor	Median	Range
Age (years)	35.2	17–70
Body weight (kg)	59.0	36.0–103.4
Male sex (n [%])	998	44.9%
	n	%
Relationship to recipient		
Father	954	42.9
Mother	1166	52.4
Grand father	19	0.9
Grand mother	41	1.8
Sibling	13	0.6
Uncle/aunt	26	1.2
Cousin	2	0.1
Others	3	0.1
Blood-type combination		
Identical	1484	66.7
Compatible	446	20.1
Incompatible	294	13.2
Type of graft		
Reduced left lateral segment	96	4.3
Left lateral segment	1549	69.6
Left lobe	500	22.5
Posterior segment	3	0.1
Right lobe	76	3.4
Recipient	Median	Range
Age	4.0 years	13 days–17.9 years
Body weight (kg)	16.6	2.6–90.0
Male sex (n [%])	946	42.5%

2.6–90 kg). Table 2 lists the indications for LDLT observed in the present study. Cholestatic liver disease was the leading indication for LDLT (n = 1649; 76.2%), followed by metabolic disorders (n = 194; 8.7%), acute liver failure (n = 192; 8.6%) and neoplastic liver disease (n = 66; 3.0%). Biliary atresia (n = 1471; 66.1%) was the most common indication in patients with cholestatic liver disease, followed by Alagille syndrome (n = 70; 3.1%). Wilson's disease (n = 59; 2.6%) was the most common indication in patients with metabolic liver disease, followed by Ornithine transcarbamylase deficiency (n = 40; 1.8%) and Methylmalonic academia (n = 20, 0.9%). Nearly 85% of the children who underwent LDLT for acute liver failure had disease of unknown etiology (163 out of 192 cases). Hepatoblastoma (n = 52, 2.3%) was the most common indication in patients with neoplastic liver disease. Retransplantation using living donors was indicated in 76 patients (3.4%), including two cases of third LDLT.

Patient survival

The 1-, 5-, 10- and 15-year survival rates for adult and pediatric patients undergoing LDLT were 80.7%, 71.9%, 65.5% and 56.9% and 88.3%, 85.4%, 82.8% and 80.0%, respectively. There were significant differences in survival between the adult and pediatric patients ($p < 0.0001$).

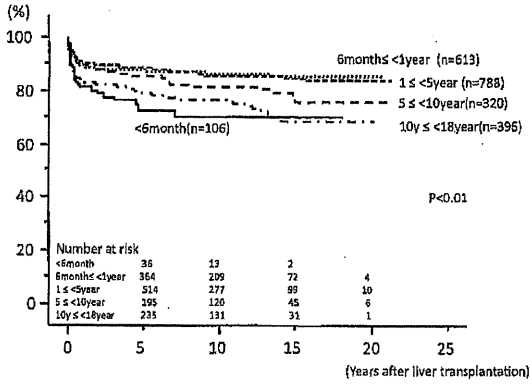

Figure 2: Recipient survival curves according to the recipient age.

Recipient and donor factors were analyzed for overall recipient survival. The results of the univariate and multivariate analyses are shown in Table 3. According to the univariate analysis, donor age, ABO incompatibility, recipient age, etiology of liver disease and transplant era were significant predictors of survival. The univariate analysis of the factors predicting patient survival showed no significant associations between survival and donor sex, gender combination, relationship of the donor, graft type or recipient sex. Factors with $p < 0.1$ were included in the multivariate analysis, and ABO incompatibility, recipient age, etiology of liver disease and transplant era were found to be significant predictors of overall survival.

When the data were analyzed separately, there were distinct differences in outcomes based on graft-type and blood-type combination. In this study, patients with reduced LLS and left lobe grafts exhibited a trend toward lower patient survival than those who received LLS and right lobe grafts over the long term. Similarly, the age of the recipient was found to be a predicting factor for patient survival, and recipients less than 6 months or older than 10 years of age demonstrated significantly worse patient survival, with 15-year survival rates of 70.5% and 68.4%, respectively (Figure 2).

ABO compatibility had a significant impact on overall patient survival, with a 15-year survival rate of 68.5% among patients who received ABO-incompatible grafts (Figure 3). When the cumulative patient survival in patients with ABO-incompatible grafts (n = 294) was analyzed according to the recipient age at LDLT, a significantly better 20-year patient survival rate of 81.4% was achieved in the recipients less than 2 years of age ($p < 0.01$).

When the survival rates were analyzed according to the original liver disease, patients with cholestatic liver disease showed a significantly better patient survival rate than those with metabolic disease, neoplastic disease or acute

Table 2: Indications for pediatric living donor liver transplantation in Japan

	n	%
Cholestatic liver disease	1649	76.2
Biliary atresia	1471	66.1
Alagille syndrome	70	3.1
Bayler disease	33	1.5
Cryptogenic cirrhosis	27	1.2
Primary sclerosing cholangitis	20	0.9
Congenital bile duct dilatation	5	0.2
Caroli disease	3	0.1
Autoimmune hepatitis	3	0.1
Non-alcoholic steatohepatitis	2	0.1
Others	15	6.7
Metabolic liver disease	194	8.7
Wilson's disease	59	2.6
Ornithine transcarbamylase deficiency	40	1.8
Carbamoyl phosphate synthetase 1 deficiency	9	0.4
Argininosuccinic aciduria	2	0.1
Methylmalonic academia	20	0.9
Propionic academia	9	0.4
Citrullinemia	6	0.3
Tyrosinemia	13	0.6
Glycogen storage disease	15	0.7
Primary hyperoxaluria type 1	9	0.4
Others	12	0.5
Acute liver failure	192	8.6
Hepatitis B	9	0.4
Drug induced	2	0.1
Auto immune hepatitis	2	0.1
Unknown	163	7.3
Others	16	0.7
Neoplastic disease	66	3.0
Hepatoblastoma	52	2.3
Hepatocellular carcinoma	6	0.3
Others	8	0.4
Vascular disease	32	1.4
Congenital absence of portal vein	21	0.9
Budd-Chiari syndrome	7	0.3
Others	4	0.2
Re-transplantation	76	3.4
2nd transplantation	74	3.3
3rd transplantation	2	0.1
Others	15	0.7
Total	2224	100

liver failure, with a 20-year survival rate of 84% (Figure 4). After assessing the patient survival rate of the patients with biliary atresia, the leading indication for LT, according to the age at LDLT, a significantly worse 15-year survival rate of 68.4% was seen in the patients over 10 years of age. The patients with metabolic liver disease, Wilson's disease and urea cycle disorders showed significantly better patient survival than patients with other metabolic liver diseases, with 15-year survival rates of 73.4% and 95.9%, respectively. Among the acute liver failure patients, who showed a 15-year survival rate of 67.0%, those under 1 year of age exhibited a decreased 15-year survival rate of 54.2% (Table 4).

Retransplantation with living donors remains a controversial undertaking, given the scarcity of organs from relatives. In the present series, retransplantation with living donors accounted for 3.3% of cases, and third transplantation accounted for 0.2% of cases. Patient survival was significantly worse in the retransplant recipients compared with that observed in children receiving single grafts (48.1% and 84.0% at 10 years, respectively).

Liver transplant centers can be categorized as low- or high-volume. The overall number of liver transplants is less than 50 for low-volume centers (26 centers) and greater than 50 for high-volume centers (23 centers). There were no significant differences between the low- and high-volume centers with regard to patient survival ($p = 0.2584$).

The number of pediatric LDLTs has remained static, with 130–140 transplants performed annually. The two decades comprising the study period can be categorized into four eras. Although there were no significant differences, the proportions of recipients with ABO-incompatible grafts and those less than 6 months of age increased from 13.5% to 16.0% and 4.7% to 12.2% over the past two decades, respectively. Significant improvements in patient survival were obtained within the most recent 5 years, with a 5-year patient survival rate of 91.8% (Figure 5). Comparing the recipient 1- and 3-year survival rates according to the two dominant graft types (LLS grafts and left lobe grafts) by transplant era reveals significant improvements within the past 5 years (93.9% and 92.9% for 1- and 3-year survival in patients with LLS grafts and 90.8% and 89.9% for 1- and 3-year survival in patients with left lobe grafts; $p < 0.01$). The survival rates over the past 5 years among patients with ABO-incompatible grafts demonstrate significantly superior survival, with rates of 87.9% and 87.9% at 1 and 3 years, respectively ($p < 0.01$). There were significant differences in the 1- and 3-year survival rates for recipients according to age (less than 6 months and over 10 years) and transplant era. Among the patients who received LDLT within the past 5 years, the 1- and 3-year survival rates were 91.8% and 88.7% among the patients less than 6 months of age and 88.7% and 86.7% among the patients over 10 years of age ($p < 0.01$).

Discussion

We reviewed the outcomes of 2224 pediatric LDLT recipients, the largest pediatric LDLT cohort in the world. The survival rates observed in the Japanese pediatric LDLT series were excellent, approaching 88.3%, 85.4%, 82.8% and 79.6% for patients at 1, 5, 10 and 20 years post-LDLT, respectively. The present results compare favorably with recently published data from an outstanding series regarding deceased LT (10,11). In this study, ABO incompatibility, recipient age, etiology of liver disease and the transplant era were found to be significant predictors of overall survival. Liver graft size matching is one of the major

Table 3: Factors associated with survival after pediatric living donor liver transplantation in Japan

	Hazard ratio	95% Confidence Interval		p-value
Univariate analysis				
Donor age: ≥40 years vs. <40 years	1.015	1.003	1.027	0.013
Donor sex: male vs. female	1.086	0.884	1.334	0.433
Gender combination: male to male vs. male to female vs. female to male vs. female to female	0.990	0.970	1.011	0.343
Donor relationship	0.996	0.957	1.038	0.864
ABO compatibility: identical vs. compatible vs. incompatible	0.748	0.656	0.853	<0.001
Graft type: monosegment vs. left lateral segment vs. left lobe vs. left with caudate lobe vs. right lobe	1.064	0.935	1.210	0.346
Recipient age: <6 months vs. ≤6 months, <1 year vs. 1–5 years vs. 6–10 years vs. ≤11 years, <18 years	1.146	1.044	1.257	0.004
Recipient age: ≥1 years vs. <1 years	1.100	0.879	1.378	0.405
Recipient sex: male vs. female	0.914	0.825	1.013	0.087
Etiology of liver disease	1.040	0.948	1.141	0.404
Cholestatic liver disease vs. others	0.453	0.367	0.558	<0.001
Acute liver failure vs. others	2.405	1.823	3.173	<0.001
Metabolic disease vs. others	0.851	0.575	1.260	0.422
Neoplastic disease vs. others	1.747	1.073	2.843	0.025
Vascular disease vs. others	0.787	0.294	2.109	0.634
Re-transplantation vs. others	4.433	3.152	6.235	<0.001
Transplant era: 1989–1995 vs. 1996–2000 vs. 2001–2005 vs. 2006–2010	0.698	0.629	0.775	<0.001
Multivariate analysis				
Donor age: ≥40 years vs. <40 years	1.003	0.989	1.017	0.675
ABO compatibility: identical vs. compatible vs. incompatible	0.776	0.677	0.890	<0.001
Recipient age: <6 months vs. ≤6 months, <1 year vs. 1–5 years vs. 6–10 years vs. ≤11 years, <18 years	0.562	0.387	0.816	0.002
Recipient sex: male vs. female	0.921	0.745	1.137	0.344
Etiology of liver disease	0.661	0.462	0.945	0.395
Cholestatic liver disease vs. others	0.273	0.173	0.433	0.348
Acute liver failure vs. others	3.063	2.304	4.071	<0.001
Neoplastic disease vs. others	2.634	1.598	4.339	<0.001
Re-transplantation vs. others	5.746	3.978	8.299	<0.001
Transplant era: 1989–1995 vs. 1996–2000 vs. 2001–2005 vs. 2006–2010	0.651	0.584	0.726	<0.001

factors determining a successful outcome. Relative to older pediatric recipients, infants had worse overall patient survival rates in the present study. The use of small-for-size grafts leads to lower graft survival due to insufficient metabolic and synthetic functions and portal hypertension in older recipients 5). Although the patients with left lobe grafts showed significantly lower survival rates in the present study, there might be considerable historical perspectives. For example, the success of pediatric LDLT using LLS for children led to the use of the same procedure in adolescent recipients in the early 1990s. With occasional patient mortalities from small-for-size grafts impeding the wider use of LDLT in adolescents, many centers began to use the right lobe from the donor to provide a greater amount of actual graft mass for the recipient in order to achieve a better outcome without compromising the living donor (12). It has been reported nonadherence with recommended immunosuppressant medication is associated with poor medical outcomes in adolescent transplant recipients in the world (13,14). Nonadherence might not be a common cause of graft failure in Japan, in part due to national healthcare coverage for all pediatric patients who become adults, although prospective investigations of transition process might be necessary.

On the other hand, the disadvantage of using large-for-size grafts in infants is that insufficient tissue oxygenation and graft compression are observed in association with a relatively high incidence of vascular complications that result in poor outcomes (15). To address the problems of large-for-size grafts in small babies, the use of reduced LLS was introduced with acceptable results, including a 10-year survival rate of 74.2% in the present series. The proportion of recipients less than 6 months of age, who may potentially receive large-for size grafts has increased to 12.2% over the past 5 years. Tailoring the graft size is essential for obtaining better outcomes in small infants and large adolescents with end-stage liver disease. Children with liver disease are particularly susceptible to malnutrition, which is reported to be one of the few pretransplantation variables with a known detrimental