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Longterm Outcomes for Whole and Segmental Liver Grafts in Adult and Pediatric Liver Transplant Recipients: A 10-Year Comparative Analysis of 2,988 Cases

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BACKGROUND: Data on longterm outcomes after liver transplantation with partial grafts are limited. We compared 10-year outcomes for liver transplant patients who received whole grafts (WLT), split grafts from deceased donors (SLT), and partial grafts from living donors (LDLT).

STUDY DESIGN: We conducted a single-center analysis of 2,988 liver transplantations performed between August 1993 and May 2006 with median followup of 5 years. Graft types included 2,717 whole-liver, 181 split-liver, and 90 living-donor partial livers. Split-liver grafts included 109 left lateral and 72 extended right partial livers. Living-donor grafts included 49 left lateral and 41 right partial livers.

RESULTS: The 10-year patient survivals for WLT, SLT, and LDLT were 72%, 69%, and 83%, respectively ($p = 0.11$), and those for graft survival were 62%, 55%, and 65%, respectively ($p = 0.088$). There were differences in outcomes between adults and children when compared separately by graft types. In adults, 10-year patient survival was significantly lower for split extended right liver graft compared with adult whole liver and living-donor right liver graft (57% versus 72% versus 75%, respectively, $p = 0.03$). Graft survival for adults was similar for all graft types. Retransplantation, recipient age older than 60 years, donor age older than 45 years, split extended right liver graft, and cold ischemia time > 10 hours were predictors of diminished patient survival outcomes. In children, the 10-year patient and graft survivals were similar for all graft types.

CONCLUSIONS: Longterm graft survival rates in both adults and children for segmental grafts from deceased and living donors are comparable with those in whole organ liver transplantation. In adults, patient survival was lower for split compared with whole grafts when used in retransplantations and in critically ill recipients. Split graft-to-recipient matching is crucial for optimal organ allocation and best use of a scarce and precious resource. (J Am Coll Surg 2009;208:682–691. © 2009 by the American College of Surgeons)

Donor availability is the principal limiting factor for expansion of liver transplantation (LT). In 2007, there were 17,000 candidates on the waiting list; only 6,400 patients received transplants and more than 2,300 patients died for lack of donor organs (2008 Organ Procurement and Transplantation Network/Scientific Resistry of Transplant Recipients). With the scarcity of whole organ grafts, particularly in small children, innovative procedures using partial liver grafts from deceased and living donors have improved the availability of donor organs and lowered mortality on the transplant waiting list.

The ability to use partial hepatic grafts is dependent on the segmental hepatic anatomy (as shown in Figure 1), and regeneration potential of the transplanted graft and the remnant liver. Table 1 summarizes various functional grafts used in liver transplantations for both adults and children. Deceased-donor grafts are of whole organ and split types. Whole organs are used for both pediatric and adult recipients; the conventional split types produce smaller segment

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Abbreviations and Acronyms

LDLT = living-donor segmental graft liver transplantation
LT = liver transplantation
MELD = Model for End-Stage Liver Disease
SL-ER = split extended right liver graft
SLT = split-graft liver transplantation
WLT = whole-organ liver transplantation

II to III grafts for children and larger extended-right grafts for adults. Splitting the liver can also yield functional grafts for two small adults. The full left-right splitting remains experimental because of its inferior outcomes compared with whole-organ LT (WLT).[1,2] There are two methods of splitting the liver. In the ex vivo technique, the whole organ is retrieved and preserved and then divided into two functional grafts on the back table.[3] The in situ method divides the hepatic parenchyma in the heart-beating brain-dead donor before aortic cross-clamping and cold perfusion.[4,5] Ex vivo grafts are subjected to a longer cold ischemia time and graft rewarming, which may have a deleterious effect on graft function after transplantation. Advantages of the in situ method include shorter cold ischemia time, minimal graft rewarming, and easier identification of biliary and arterial systems. Living donors provide segmental grafts including left lateral for pediatric recipients and right or left partial hepatic grafts for adults.

Deceased and living donors have been complementary in providing grafts for small children and have resulted in a significant decline in mortality in patients on the pediatric waiting list. For adults, the use of segmental grafts from both deceased and living donors has not gained wide application. Split-graft liver transplantation (SLT) in adults is controversial; proponents report outcomes comparable with those with WLT,[6-8] but others argue that the procedure converts an otherwise optimal whole organ to a marginal segmental graft.[9,10] For living-donor segmental graft liver transplantation (LDLT), the risk to the living donor remains a subject of ethical debate, and the annual volume of LDLT in the US has continued to decline for 7 consecutive years, from a total of 520 in 2001 to 266 in 2007.

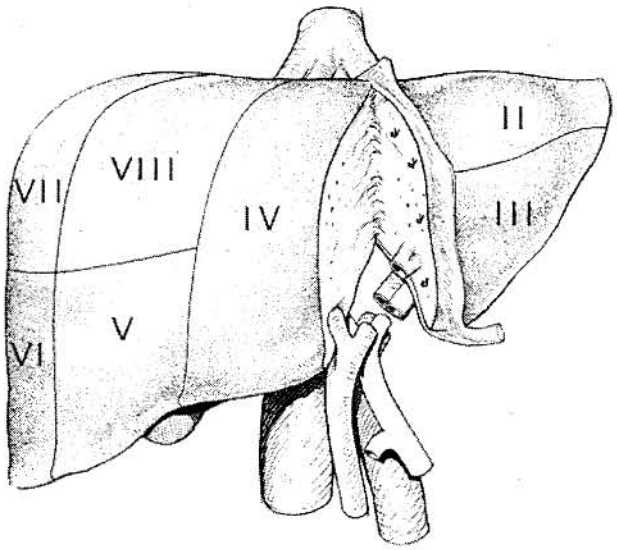

Figure 1. Conventional in situ split technique. The conventional in situ split technique separates the hepatic parenchyma to the right of the falciform ligament and yields a smaller left lateral graft (segments II and III) for a child and a larger extended-right graft (segments I, IV to VIII) for an adult recipient. (From: Yersiz H, Renz JF, Hisatake GM, et al. The conventional technique of in situ split-liver transplantation. J Hepatobiliary Pancreat Surg 2003;10:11–15, Fig. 2, with kind permission of Springer Science & Business Media.)

Although short-term outcomes for segmental grafts have been comparable with those with WLT, few longterm data are reported.[6,7,11] In addition, when data were analyzed separately for pediatric and adult recipients, there were distinct differences in outcomes based on graft types.[10,12] This single center study was undertaken to compare longterm outcomes for whole and segmental liver grafts in adult and pedi-

Table 1. Organ Grafts Used in Liver Transplantation

Donor	Graft	Segments	Common name	Recipient	Abbreviation
Deceased	Whole	I–VIII		Adult	Adult-WL
				Pediatric	Ped-WL
	Split	II–III	Left lateral	Pediatric	SL-LL
		I, IV–VIII	Extended right	Adult	SL-ER
		I–IV	Full left	Adult	SL-FL
		V–VIII	Full right	Adult	SL-FR
Living	Segmental	II–III	Left lateral	Pediatric	LD-LL
		I–IV	Left	Adult	LD-L
		V–VIII	Right	Adult	LD-R

Adult-WL, adult deceased donor whole liver graft; LD-L, living donor left liver graft; LD-LL, living donor left lateral liver graft; LD-R, living donor right liver graft; Ped-WL, pediatric deceased donor whole liver graft; SL-ER, split extended right liver graft; SL-FL, split-extended full left liver graft; SL-FR, split extended full right liver graft; SL-LL, split extended left lateral liver graft.

Table 2. Patient and Donor Characteristics by Graft Type

Characteristic	Adult				Children			
	Adult-WL (n = 2,433)	SL-ER (n = 72)	LD-R (n = 41)	p Value	Ped-WL (n = 284)	SL-LL (n = 109)	LD-LL (n = 49)	p Value
Recipient								
Median age, y	52	51	52	0.5019	3.4	1	0.9	<0.0001
Female gender, n (%)	968 (40)	14 (19)	14 (34)	<0.0001	156 (55)	60 (55)	28 (57)	0.9588
History of earlier LT, n (%)	337 (14)	9 (13)	0	0.0357	72 (25)	16 (15)	8 (16)	0.0446
Urgent LT, n (%)	303 (13)	19 (26)	1 (2)	0.0003	83 (29)	47 (43)	15 (31)	0.0251
Donor								
Median age, y	37	20	35	<0.0001	3	18	31	<0.0001
Median hospital stay, d	2	3	n/a	0.2418	3	2	n/a	0.3089
Vasopressor agents ≥ 2, n (%)	388 (17)	22 (31)	n/a	0.0032	75 (26)	35 (32)	n/a	0.785
Graft ischemia								
Median graft cold ischemia, min	402	348	45	<0.0001	468	330	60	<0.0001
Median graft warm ischemia, min	30	41	48	<0.0001	48	66	66	<0.0001

Adult-WL, adult deceased-donor whole-organ graft; LD-LL, living-donor left lateral graft; LD-R, living-donor right graft; LT, liver transplantation; Ped-WL, pediatric deceased-donor whole-organ graft; SL-ER, split extended right graft; SL-LL, split left lateral graft.

atric liver transplant recipients and to determine predictors for patient and graft survival for different graft types.

METHODS

Data collection

Using a prospectively collected transplant database, we performed a retrospective analysis of 2,988 liver transplantations in both adults (18 years or older) and children (18 years or younger) at the Dumont-UCLA Transplant Center, from August 1993 through May 2006. The UCLA Institutional Review Board approved the study. The median followup time was 5 years.

Patient characteristics

All patients with end-stage liver disease were evaluated for LT by a multidisciplinary team, as previously described.[13] Before the year 2002, patients were listed for liver transplant candidacy according to the United Network for Organ Sharing (UNOS) status categories; from 2002 to the present, the current Model for End-Stage Liver Disease (MELD) system has been used.[14] Patient and graft survival outcomes were analyzed by the type of graft received: whole-organ graft from deceased donors and partial hepatic grafts from either deceased or living donors. In addition, results were compared among adult and pediatric transplant recipients.

Operative procedures

Deceased-donor, whole-organ liver transplantation

The surgical procedure for whole-organ orthotopic liver transplantation was performed in a standard manner, with either preservation or replacement of the recipient's inferior vena cava.[15]

Deceased-donor, in situ split-liver transplantation

The in situ split technique was performed on livers from deceased donors that met criteria for splitting, as previously described.[16] Figure 1 demonstrates isolation of the left hepatic artery, left branch of the portal vein, and the extrahepatic portion of the left hepatic vein followed by transection of the parenchyma at about 0.5 cm to 1 cm to the right of the falciform ligament, yielding a left lateral graft (SL-LL; segments II and III) and an extended right graft (SL-ER; segments I, IV to VIII). The left hilar plate and bile ducts were divided sharply with scissors so as not to devascularize the duct. The middle hepatic vein, the entire length of the celiac axis, portal vein, bile duct, and vena cava were retained with the extended right graft.

The recipient operation in children was performed by native hepatectomy with retention of the inferior vena cava, and the left lateral graft was implanted using a piggyback technique in which the venous outflow was anastomosed to the confluence of the recipient hepatic veins. In adults, the extended right graft was prepared in the manner identical to preparation of a whole graft, with the addition of oversewing the left hepatic and portal vein orifices and the left hepatic duct stump. The extended right graft was implanted in the same manner as a whole graft.

Living-donor liver transplantation

The techniques of living-donor partial hepatectomy have been described.[17-19] In adult-to-child LDLT, the left lateral graft (LD-LL; segments II and III) is procured. In adult-

to-adult living-donor liver transplantation, the right lobe (LD-R; segments V to VIII) is procured in the donor with preservation of middle hepatic vein. The living-donor segmental grafts (left lateral and right lobe) were transplanted with recipient caval preservation (piggyback technique) and previously described vascular and biliary reconstruction.[17,18]

Immunosuppression

The primary maintenance immunosuppression regimen consisted of cyclosporine (CyA, Sandimmune or Neoral, Novartis Pharmaceuticals) until 1994 and tacrolimus (Prograf, Astellas Pharmaceutical Inc) thereafter. Most patients received triple immunotherapy with steroids and either azathioprine or mycophenolate mofetil (CellCept, Roche Pharmaceuticals).[13]

Statistical analysis

Patient and graft survival curves were computed using Kaplan-Meier methods and compared using log rank tests. Medians were compared using the Wilcoxon test and proportions using the chi-squared test. Both univariate and multivariate analyses were conducted using Cox's proportional hazard model. The backward stepwise procedure was used for variables selection with retention criteria at a p value of ≤ 0.25 level of significance. In the multivariate analysis, a p value of < 0.05 was considered significant. Statistical analysis was performed using SAS software, version 9.1 (SAS Institute).

RESULTS

Recipient characteristics

Among the 2,988 liver transplantations during the 13-year study period, 2,546 were performed in adults (85%) and 442 in children (15%). Graft types in adults included adult deceased-donor whole liver graft (adult-WL) in 2,433 (95%), SL-ER in 72 (3%), and living-donor right liver graft in 41 (2%). Graft types in children included pediatric deceased-donor whole liver graft (ped-WL) in 284 (64%), SL-LL in 109 (25%), and LD-LL in 49 (11%).

Patient characteristics are compared by graft type in Table 2. In adults, the median recipient ages among the three groups were similar. Although both whole and split grafts were used more often than living-donor grafts for recipients with previous liver transplants, split grafts were frequently used for recipients requiring urgent transplants. The most common liver disease in adult recipients was hepatitis C cirrhosis (32%) followed by alcohol-induced liver disease (15%) and acute liver failure (14%). Comparing indications for LT for all graft types, acute liver failure was more frequent in SLT compared with adult-WLT and LDLT (26% versus 13% versus 2.4%; $p = 0.0003$); primary sclerosing cholangitis was a frequent reason for LDLT. The frequency of hepatitis B, hepatitis C, alcohol-induced liver disease, and cryptogenic cirrhosis were similar for all graft types.

In children, recipients of split and living-donor grafts were smaller children younger than 1 year of age (Table 2). More recipients with previous transplants received whole-organ grafts. Split grafts as with adults, were used more often for urgent transplantation. The most common indications for LT in children were biliary atresia (42%) and acute liver failure (34%). A higher proportion of pediatric recipients with biliary atresia received a split graft compared with a living-donor segmental or deceased-donor whole-organ graft (54% versus 41% versus 34%, respectively, $p = 0.0023$). The distribution of other liver diseases, including neonatal hepatitis, cryptogenic cirrhosis, and malignancy, was similar among all graft types.

Donor characteristics and graft ischemia times

Table 2 compares the donor characteristics and graft ischemia duration for both adults and children. In adults, donors of split grafts were younger than whole-organ and living donors ($p < 0.0001$). There were more deceased donors for split than whole grafts that required two or more vasopressor agent support during organ procurement (31% versus 17%, $p = 0.0032$). The cold ischemia duration for living-donor segmental grafts, as would be expected, was shorter compared with that for deceased-donor grafts. The need for complex microvascular reconstructions in segmental grafts accounted for a longer warm ischemia time compared with whole-organ grafts.

In children, whole-organ donors were younger than deceased and living donors of segmental grafts. The duration of both cold and warm graft ischemia varied between deceased- and living-donor graft types, as in adults (Table 2).

Patient survival

The 10-year patient survival curves for adults and children are shown in Figure 2A. For both adults and children, survival was similar for all graft types. When data were analyzed separately for adult and pediatric recipients, there were distinct differences in outcomes based on graft types. Figure 3A shows that the longterm patient survival curve in adults for SL-ER was significantly lower compared with LD-R and adult-WL (57% versus 73% versus 71%; $p = 0.033$). In contrast to the adults, longterm outcomes for all graft types in children were similar, as shown in Figure 3B.

Multivariate analysis of patient survival in adult recipients is shown in Table 3. Statistically significant independent predictors of diminished survival in adult recipients included recipient age older than 60 years, retransplanta-