World J. Surg. 27, 356–364, 2003
DOI: 10.1007/s00268-002-6598-8

WORLD
Journal of
SURGERY

Analysis of Failure in Living Donor Liver Transplantation: Differential Outcomes in Children and Adults

Michael J. Goldstein, M.D.,[1] Ephrem Salame, M.D.,[2] Sandip Kapur, M.D.,[1] Milan Kinkhabwala, M.D.,[1] Diane LaPointe-Rudow, N.P.,[1] Patricia Harren, N.P.,[1] Steven J. Lobritto, M.D.,[1] Mark Russo, M.D., M.P.H.,[1] Robert S. Brown, Jr., M.D., M.P.H.,[1] Guellue Cataldegirmen, M.D.,[1] Alan Weinberg, M.S.,[1] John F. Renz, M.D.,[3] Jean C. Emond, M.D.[1]

[1]Liver Center, New York Presbyterian Hospital, 622 W. 168th Street, PH14C, New York, New York 10032, USA
[2]Service de Chirurgie Digestive, CHU Côte de Nacre, 14000 Caen, France
[3]Dumont-UCLA Transplant Center, 10833 Le Conte Avenue, Los Angeles, California 90095, USA

Abstract. Over the past decade we have reported excellent outcomes in pediatric living-donor liver transplantation (LDLT) with recipient survival exceeding 90%. Principles established in these patients were extended to LDLT in adults. To compare outcomes in donors and recipients between adult and pediatric LDLT in a single center, we reviewed patient records of 45 LDLT performed between 1/98 and 2/01: 23 adult LDLT (54 ± 6.5 yr) and 22 pediatric LDLT (33.7 ± 53.5 months). Preoperative liver function was worse in adults (International Normalized Ratio [INR] 1.5 ± 0.4 vs. INR 1.2 ± 0.5; $p = 0.032$). 4 adults (17%) met criteria for status 1 or 2A. Only 1 child was transplanted urgently. Analysis included descriptive statistics and Kaplan-Meier estimation. Donor mortality was 0% with 1 re-exploration, 2.4%. Median hospital stay (LOS) was 6.0 days (range, 4–12 days). Donor morbidity and LOS did not differ by sex, extent of hepatectomy, or adult and pediatric LDLT ($p = 0.49$). In contrast, recipient outcomes were worse for adults. Adult 1 year graft survival was 65% (3 retransplants [ReTx], 5 deaths) vs. 91% for children (1 ReTx, 1 death) $p = 0.02$. Graft losses in adults were due to sepsis (n = 3), small for size (n = 2), suicide, and hepatic artery thrombosis (HAT), whereas in children graft losses were due to portal thrombosis and total parenteral nutrition (TPN) liver failure. Biliary leaks occurred in 22% of adults and 9% of children. Hepatic vein obstruction occurred in 17% of adults and in none of the children. Median LOS was comparable (adult, 16.5 days (range, 7–149 days); child, 17 days (range, 10–56 days), $p = 0.2$). Graft function (total bilirubin (TBili) < 5mg/dl, INR < 1.2, aspartate aminotransferase (AST) < 100 U/l) normalizing by day 4 in children and by day 14 in adults. Adults fared worse, with an array of problems not seen in children, in particular, hepatic vein obstruction and small-for-size syndrome. Biliary leaks were diagnosed later in adults and were lethal in 3 cases; this was later avoided with biliary drainage in adult recipients. Finally, use of LDLT in decompensated adults led to death in 3 of 4 patients, and should be restricted to elective use.

The recent evolution of liver transplantation has been marked by increasing patient demand with a fixed and inadequate donor supply. Over 17,000 patients are awaiting liver transplantation on the United Network for Organ Sharing (UNOS) list, more than a threefold increase compared to just 5 years ago. In 1996 there were 4327 suitable cadaveric donors, compared with 3796 in 2000, a 15% decrease [1]. Living-donor liver transplantation (LDLT) activity during this period tripled, yet contributed only 5% to the donor pool in 2000, though 25% in the State of New York [2]. This inadequacy has mandated the search for safe and reliable alternatives for donor organs.

The well-established efficacy of LDLT in children has focused the spotlight on LDLT for adult recipients as well [3–5]. This shift to the adult recipient has been hindered by the size constraints of the donor hepatectomy: weighing the risks of extensive resection and liver failure for the donor against the risks of placing a poorly functioning, small-for-size allograft in the recipient. As the use of living-donor organs for adult recipients came into practice, minimal graft weight standards increased the efficacy of LDLT [6]. Some authors have advocated the use of full left lobe grafts and express concern about the safety of more extensive resections in the donor [7]. Yet, others worry about the adequacy of the left lobe for adult recipients and have shown right hepatectomy to provide graft functional outcomes similar to left lateral segments (LLS) in children, with minimal adverse consequences in the donor [8, 9].

In children, large centers have reported patient survival after LDLT to be 80% to 90%, with graft survival ranging from 50% to 70% at 3 years [3, 10–12]. Since the advent of adult LDLT, several series have recently reported patient and graft survival results comparable to those of pediatric recipients [8, 13, 14]. With the maturation of LDLT to adults from a solely pediatric experience in its infancy, one must consider the numerous differences between adults and children, including patient size, age, underlying disease process, systemic manifestations of disease, and urgency of transplant. These factors may significantly contribute to recipient outcome, mandating the more selective use of LDLT. The ongoing debate about the efficacy of left hepatectomy for LDLT in adult

Correspondence to: Jean C. Emond, M.D., Center for Liver Disease and Transplantation, Columbia University College of Physicians and Surgeons, 622 W. 168th Street, PH14C, New York, NY 10032, USA, e-mail: je111@columbia.edu

Table 1. Recipient demographics.

Variable	Adults	Children	*p* value
Total LDLT	23	22	
Age (yr), median (range)	52.2 (42.1–67.5)	1.0 (0.3–17.3)	< 0.0001*
Weight (kg)	63.8 (55.0–130.0)	7.3 (4.8–64.0)	< 0.0001*
Sex (M/F)	1.3	1.2	0.89
Disease process			
Cholestatic	1	16	< 0.0001*
Parenchymal	17	6	
Carcinoma	5	0	
Medical urgency (UNOS)			
1	1	1	
2A	1	0	0.037*
2B	9	8	
3	8	3	
NL	1	10	

LDLT: living donor liver transplantation; UNOS: United Network for Organ Sharing.

*Indicates statistical significance for values of $p \leq 0.05$.

Table 2. Donor demographics.

Variable	Adults	Children	*p* value
Age (yr), median (range)	36.1 (19.3–53.4)	29.9 (21.4–57.5)	0.178
Relationship			
Parent	0	21	< 0.0001*
Sibling	3	0	
Son/daughter	12	0	
Other relative	1	0	
Spouse	4	0	
Unrelated	3	1	
Extent of resection			
RL	14	1	< 0.0001*
LL	8	1	
LLS	1	20	

RL: right lobectomy; LL: left lobectomy; LLS: left lateral segmentectomy.

*Indicates statistical significance for values of $p \leq 0.05$.

recipients, spurred by recent awareness of three donor deaths after right hepatectomy commands further investigation of the safety and efficacy of these procedures for both donors and recipients [15].

Our longstanding experience in pediatric LDLT, as well as our concurrent activity in both adults and children, permitted us to compare adult and pediatric outcomes within the consistent framework of a single team. The goal of this study has to critically assess LDLT to characterize differences between adult and pediatric practice, and identify technical and strategic principles that affect outcomes and the opportunities for improvement.

Patients and Methods

Recipients

The medical records and computer database were reviewed for 45 consecutive patients who underwent LDLT by a single surgical team in our center from January 1998 to February 2001. Of the 45 patients, there were 23 adult and 22 pediatric recipients. The median age of the adult recipients was 52 years, ranging from 42 to 67 years. The median age of the pediatric recipients was 12 months, ranging from 3 to 207 months. The underlying adult diseases necessitating transplantation consisted mainly of cirrhosis from hepatitis C, with or without hepatocellular carcinoma, and alcoholic cirrhosis. In the pediatric group, cholestatic disease predominated, with the majority of children suffering from biliary atresia. Of the 23 adults, 5 met the criteria for status 1 or 2A. Of the 22 children, only 1 was transplanted urgently (Table 1). Adults received 14 right lobe grafts, 8 left lobe grafts, and 1 left lateral segment auxiliary graft. Children received 20 left lateral segment grafts, 1 right lobe graft, and 1 left lobe graft (Table 2).

Recipient preoperative hepatic function was assessed for statistical purposes by prothrombin time (PT) and International Normalized Ratio (INR), serum total bilirubin (TBili), and aspartate aminotransferase (AST). Adults had a mean PT 17.4 ± 3.6 s, INR 1.5 ± 0.4; TBili 3.9 ± 3.9; AST 145.5 ± 197.1. Children had a mean PT 14.9 ± 3.3 s, INR 1.2 ± 0.5; TBili 11.7 ± 8.4; AST 175.9 ± 112.0.

Donors

The donor age ranged from 19 to 58 years, median 31 years. Donors included of 25 women and 20 men. Relationship to the recipient included 21 parents, 3 siblings, 4 spouses, 9 sons, 3 daughters, 1 niece, 1 daughter-in-law, and 3 friends (Table 2) Donors underwent preoperative medical and psychosocial evaluation before being accepted as a candidate for liver donation; the chronology of events for donor evaluation has been previously reported [16]. Routine screening blood work included liver function tests, hepatitis panel, and HIV tests. Donors routinely received magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) scanning for evaluation of the hepatic vascular and ductal anatomy. Arteriograms, venograms, and liver biopsy were not routinely performed, unless mandated by abnormalities in routine donor screening exams. Suitable donors were previously healthy individuals without pre-existing hepatic or systemic disease, who were willing to become a donor without coercion.

Surgical Technique

Donor Hepatectomy. The techniques for donor hepatectomy have been elsewhere reported [17, 18]. Key principles concern hepatic vein preparation, selective cholangiography, the management of portal trifurcation, and ultrasound guided parenchymal transection using ultrasonic aspirator technique (CUSA). During right liver mobilization, accessory hepatic veins approaching 1 cm in size are carefully preserved. Cholangiography via the cystic duct is selectively performed for cases in which the MRCP and operative anatomy are either unrevealing or complex. In case of an early bifurcation of the right portal vein, dissection is carried out to encircle each tributary individually, avoiding stenosis of the left portal vein during closure. With intraoperative ultrasound, the middle hepatic vein is identified and the plane of transsection determined to the right of the middle hepatic vein.

During left hepatectomy, cholangiography is more commonly employed to identify right-sided ducts entering posteriorly into the left hepatic ducts. During 2 cases of left hepatectomy, right ducts were unknowingly divided as they entered the left hepatic duct posteriorly, requiring complex biliary repair.

Left lateral segmentectomy for pediatric donation is practiced using classic techniques previously described [17, 18].

Adult Recipient (Current Technique). Important considerations during the transplantation in the recipient include triangulation of the hepatic veins for a generous anastomosis, reimplantation of accessory hepatic veins approaching 1 cm in diameter, and use of post-anastomotic stents for end-to-end biliary reconstruction. Eight of 23 adults, 35%, received Roux-en-Y choledochojejunostomy. The remainder were reconstructed in an end-to-end fashion. Biliary stenting for duct-to-duct anastomoses was not performed in the first 18 adult recipients. Concerns over biliary resistance and free-edge leaks mandated the need for early leak detection. We placed T-tube biliary drains in the last 8 adult LDLT to decrease the resistance of the flow of bile and for early identification of leaks and strictures. We have had no bile leaks since employing this technique.

All but 1 child (95%) received biliary-enteric drainage via Roux-en-Y choledochojejunostomy. Many had separate ducts draining segments II and III, requiring 2 anastomoses.

Pediatric Recipient (Current Technique). The techniques for the pediatric recipient are similar to those used in the adult. The confluence of the three veins of the recipient are used for hepatic vein anastomosis, as previously described [19]. Biliary reconstruction is constructed with Roux-en-Y choledochojejunostomy without stenting. In 10% to 20% of pediatric transplants, the abdomen wall is reconstructed with a temporary Goretex patch to avoid compression.

Postoperative Care

Donor. Postoperatively the donor is brought to the Surgical and Anesthesia Intensive Care Unit (SAICU) both for recovery from anesthesia and for close monitoring. Donors receive intravenous 1.5X maintenance fluids, and analgesia is maintained by intravenous infusion of a narcotic dosed by patient-controlled analgesia. Liver function tests, electrolytes, hemoglobin, and prothrombin time are monitored every 8 hours for at least 24 hours. Donors are transferred to the ward after a brief period of observation in the SAICU. Diet is resumed with return of bowel function. Intraperitoneal drainage catheters are removed between days 2 and 4, after patients have resumed a normal diet.

Recipient. Postoperatively the recipient is brought to the SAICU or Pediatric Intensive Care Unit (PICU), both for recovery from anesthesia and for close monitoring. Patients are kept intubated overnight on postoperative day 0-1. Intravenous low dose furosemide in combination with renal-dose dopamine is used to maintain adequate renal perfusion and persistent glomerular filtration. Volume status is monitored by pulmonary arterial catheter monitoring in adults and is maintained with 1.5–2X maintenance isotonic fluids in combination with 5% albumin replacement for ascites drainage, volume per volume. Patients receive perioperative antibiotic prophylaxis against both gram-positive and gram-negative organisms, as well as anti-viral therapy, depending on recipient and donor status. Immunosuppressive induction therapy is initiated generally with a combination of methylprednisolone, cyclosporine, or FK506, and mycophenolate mofetil. Cyclosporine or FK506 levels are monitored daily. Liver function tests, prothrombin time, serum electrolytes, and hemoglobin are monitored every 6 hours for at least 24 hours. Arterial blood gases are monitored with each weaning manipulation of the ventilator. Routine abdominal ultrasound with color flow doppler is performed on postoperative day 1 to identify any signs of arterial or venous thrombosis. Biliary imaging is routinely performed on postoperative day 7 (POD 7) via T-tube cholangiogram. Percutaneous biopsies are used selectively for diagnosis of acute rejection in the presence of rising liver function tests. The first 6 pediatric LDLT patients underwent a planned reexploration on POD 7 for biopsy and early identification of potential problems [20]. This technique was later abandoned.

Data Analysis

Statistical analysis incorporated Cox proportional hazard and Kaplan-Meier estimation. Means were compared using analysis of variance (ANOVA) and standard deviations given to indicate the variance of each group of data; p values of < 0.05 were considered significant. Outcome correlations were made using regression analysis and contingency tables expressed by either regression coefficient, R, or significance, p.

Results

Patient and Graft Survival

Donor operative mortality was 0%. All donors are alive from 1 to 40 months after operation. Recipient operative mortality was 0%. Overall patient survival at 1 year was 82%. Adult and pediatric 1-year survival were 74% and 91%, respectively; $p = 0.08$ (Fig. 1). Three adults died of sepsis, 1 of aspergillosis, 1 of chronic disease 5 months after retransplant for venous outflow obstruction and delayed graft function, and 1 of suicide. Three out of 6 (50%) of the deaths occurred in patients who met the criteria for either UNOS status I or IIA. One child died of total parenteral nutrition cholestasis, and 1 child died of multi-system organ failure 3 days after retransplant for portal vein thrombosis.

Adult 1-year graft survival was 65% (3 retransplant, 5 deaths) with median follow-up of 7 mos (range 2–20 mos) compared with a 91% pediatric 1-year graft survival (1 retransplant, 1 death) and a median follow-up of 21 months (range 1–35 months); $p = 0.02$ (Fig. 2). Adult retransplants were due to primary non-function (PNF), delayed graft function (DGF) secondary to venous outflow obstruction, and to hepatic artery thrombosis (HAT). The one pediatric retransplant, cited above, was due to portal vein thrombosis.

Factors that directly correlated with mortality were preoperative INR value and operative blood loss (Table 3).

Morbidity in Donors

Donor morbidity consisted mainly of minor wound complications, with the exception of 1 patient who required reoperation for an incarcerated incisional hernia causing a small bowel obstruction on POD 7. Four patients presented as outpatients with incisional hernias (Table 4). The high incidence of hernias has been attributed to use of absorbable suture for fascial closure. Since changing to a nonabsorbable suture for fascial closure we have had a zero incidence of hernias. Length of hospital stay (LOS) ranged from 4 to 12 days with median of 6 days. LOS did not differ by sex, graft type, or

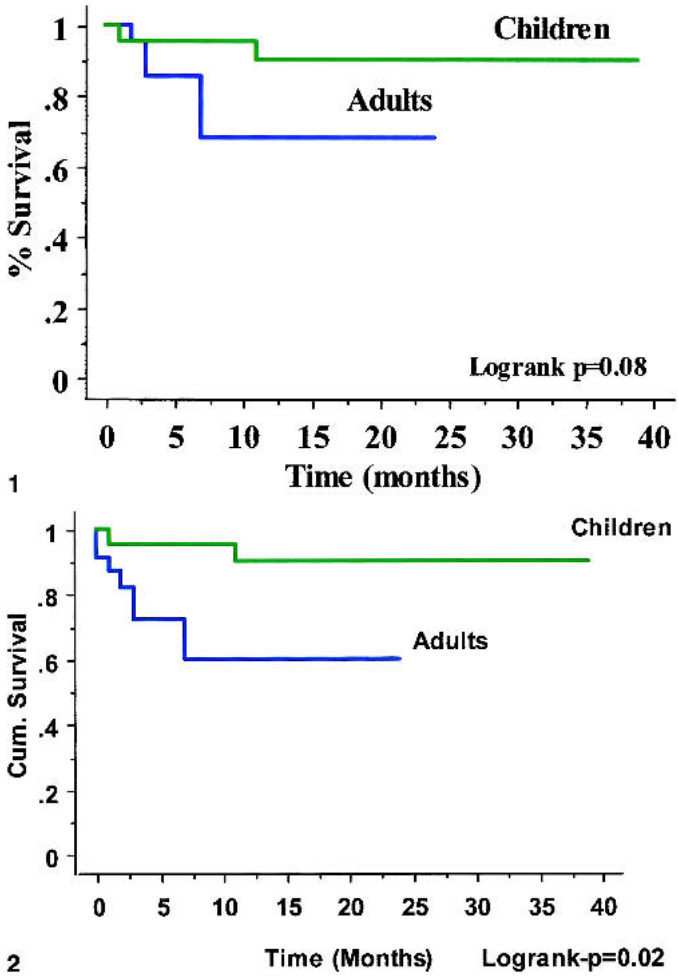

Fig. 1. Kaplan-Meier limit estimate for patient survival.

Fig. 2. Kaplan-Meier limit estimate for graft survival. Cum.: cumulative.

adult vs. child recipient ($p = 0.21$, $p = 0.20$–1.0, $p = 0.50$, respectively).

Morbidity in Recipients

In contrast to donor morbidity, recipient complications were substantial. Up to 50% of recipients had at least one major complication. Major complications included HAT, portal venous thrombosis (PVT), hepatic vein obstruction, bile leak, bowel injury, intra-abdominal abscess, systemic sepsis, PNF, DGF, major hemorrhage, and rejection. Minor complications included incisional hernias and wound infections. 60% of adult recipients suffered at least one of the complications listed above, whereas, 41% of pediatric recipients had complications. In comparison, the majority of pediatric complications were bowel injuries during adhesiolysis; whereas, adult grafts functioned worse and suffered more hepatic vein outflow obstruction, biliary leaks, and infectious complications (Table 5). There was no statistical difference in LOS between adults and children. LOS in adults ranged from 7 to 149 days, with median of 16.5 days compared with the LOS in children that ranged from 10 to 56 days, with median of 17 days ($p = 0.23$).

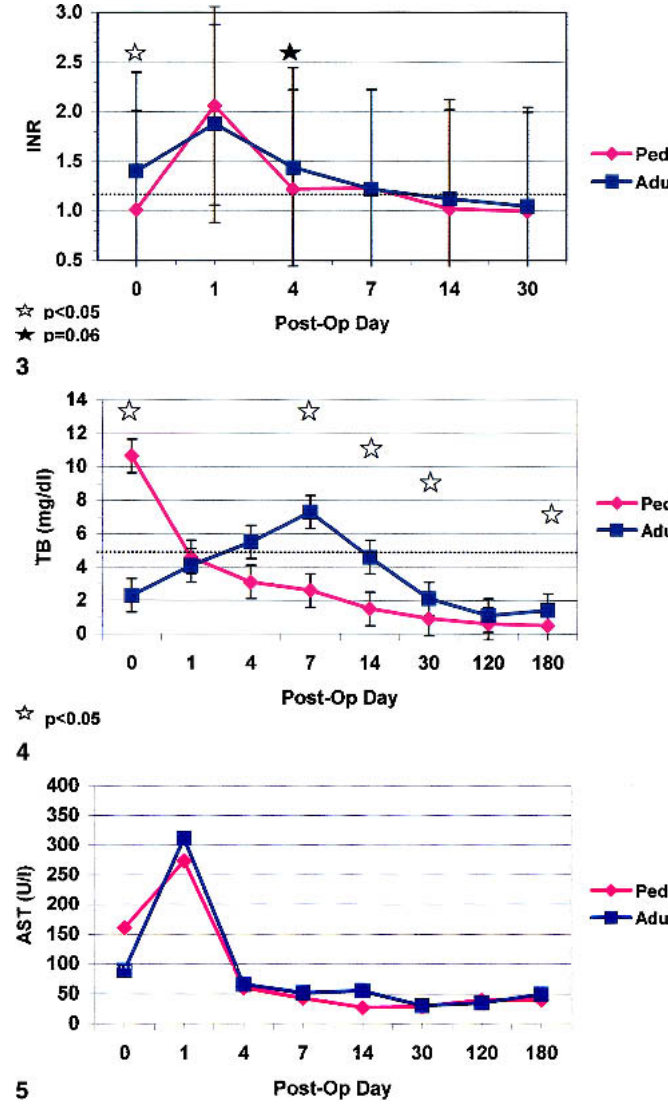

Fig. 3. Postoperative international normalized ratio (INR) as a function of time is shown as an indicator of graft function. Adults (blue) suffered a delay in normalization of INR below a value of 1.2 for up to 7 days after transplantation when compared to children (red). This difference approached significance on post-op day 4 ($p = 0.06$). Ped: children; Post-Op: postoperative.

Fig. 4. Postoperative total bilirubin (TB) as a function of time is shown as an indicator of graft function. Adults (blue) suffered a delay in clearance of total bilirubin below a value of 5 mg/dl for up to 14 days after transplantation when compared to children (red). This difference was significant on postoperative day 7 ($p < 0.05$).

Fig. 5. Postoperative aspartate aminotransferase (AST) as a function of time is shown as an indicator of graft function. There was no difference in postoperative AST between adults (blue) and children (red).

Analysis of Graft Function

A regression analysis was conducted to identify variables correlated with recovery of graft function. Age, weight, and preoperative INR individually correlated with the increased likelihood of postoperative hyperbilirubinemia (Table 6). This reaffirms the observation that postoperative cholestatic dysfunction is a consequence of the small-for-size graft, which is seen more frequently in adults than

Table 3. Mortality correlation analysis.

Variable	Alive	Expired	*p* value
Pre-op INR*	1.24 ± 0.35	1.84 ± 0.56	0.0006*
Blood loss* (ml/kg)	31.1 ± 18.4	66.9 ± 49.1	0.0015*
Age (yr)	43.9 ± 41.6	44.8 ± 22.3	0.109
Adult/child	0.85	3.0	0.136
Small-for-size syndrome	3/37	2/8	0.168
Pre-op Tbili	7.1 ± 6.6	9.9 ± 11.9	0.387
Operative time (min)	503 ± 91	533 ± 11	0.669
Weight (kg)	42.8 ± 41.0	30.8 ± 36.8	0.695
Sex (M/F)	1.31	1.0	0.727
Graft type			
RL	12	3	0.840
LL	7	2	
LLS	18	3	
Rejection	5/37	1/8	0.940

INR: international normalized ratio; pre-op TBili: preoperative total bilirubin.

*Indicates statistical significance for values of $p \leq 0.05$.

Table 4. Donor complications.

Variable	Adults	Children
Bile leak	0	0
Major hemorrhage	0	0
Wound infection	0	1
IP fluid collection	2	0
Incisional hernia	4	1[a]
UTI	0	1
Superficial phlebitis	1	0
Total	7/23	3/22
Percent	30%	14%

IP: intraperitoneal; UTI: urinary tract infection.

[a]Incarceration presenting as small bowel obstruction on postoperative day (POD) 7.

Table 5. Recipient complications.

Variable	Adults	Children	*p* value
Bile leak	5 (22%)	2 (9%)	0.24
Biliary stricture	2 (9%)	8 (36%)	0.03*
Vascular			
HAT	1 (4%)	0	0.32
PVT	0	2 (9%)	0.14
HV outflow obstruction	4 (17%)	0	0.08
Sepsis	3 (13%)	1 (4.5%)	0.32
Abscess	2 (9%)	0	0.16
Rejection	3 (13%)	7 (32%)	0.13
SSS	5 (22%)	0	0.02*
PNF	1 (4%)	0	0.32
Hernia	3 (13%)	0	0.08
Bowel	1 (4%)	4 (18%)	0.14
Major hemorrhage	1 (4%)	2 (9%)	0.52

HAT: hepatic artery thrombosis; PVT: portal vein thrombosis; HV: hepatic vein; SSS: small for size syndrome; PNF: primary nonfunction.

*Indicates statistical significance for values of $p \leq 0.05$.

children. Five of the 23 adult patients had significantly delayed functional recovery, defined as 14 or more days for normalization of INR and TBili to predefined levels or 1.2 and 5 mg/dl or less, respectively, compatible with our original description of the small-for-size syndrome (SSS) [6]. Four of 5 patients with SSS had received left lobe grafts. This observation is highly significant when compared with right lobe and left lateral segment LDLT ($p = 0.0022$, $p = 0002$, respectively).

Table 6. Graft function analysis.

	INR-POD 7			TBili-POD 7	
Variable	*r*	*p*	Variable	*r*	*p*
Weight	0.311	0.16	Weight	0.478*	0.02*
Age	0.195	0.23	Age	0.496*	0.0008*
Adult/child		0.32	Adult/child		0.002*
Sex		0.39	Sex		0.83
Graft type		0.42	Graft type		
Pre-op Tbili	0.117	0.47	LLS to RL		0.01*
Blood loss	0.068	0.69	LLS to LL		0.03*
Rejection	0.055	0.74	LL to RL		0.96
Pre-op INR	0.039	0.81	Pre-op Tbili	0.039	0.81
OR time	0.014	0.95	Blood loss	0.151	0.37
			Rejection	0.058	0.71
			Pre-op INR	0.335*	0.03*
			OR time	0.238	0.28

RL: right lobe; LL: left lobe; LLS: left lateral segment; OR: operating room.

*Indicates statistical significance for values of $p \leq 0.05$.

Figures 3, 4, and 5 display graphically the restoration of liver function with highly significant differences between adults and children. Comparing the 2 groups on POD 7, adults with children, median INR 1.2 and 1.2, respectively ($p = 0.30$), median TBili 8.1 and 2.6 mg/dl, respectively ($p = 0.002$), and median AST 49 and 42 U/l, respectively ($p = 0.94$).

Operative Data

Implanting adult livers is technically more challenging than pediatric livers because of the biliary and vascular complexities (Table 7). Consequences of these differences were manifested in operative time. Adult recipient surgery lasted from 480 to 630 mins, with a median of 570 min. Pediatric recipient surgery lasted from 285 to 600 min, with a median of 457 mins ($p = 0.0015$). Left lateral segment (LLS) grafts took less time to transplant (446 ± 78 min) than either right lobe (RL) (567 ± 37 min, $p = 0.0025$) or left lobe (LL) (565 ± 56 min, $p = 0.001$) grafts. Blood loss for LLS grafts (414 ± 387 ml) was significantly less than for both RL (2520 ± 1423 ml, $p < 0.001$) and LL (1922 ± 1420 ml, $p = 0.0022$). There was no difference in either anesthesia time or blood loss between RL and LL LDLT.

Technical Complications

Vascular. One HAT was noted in the entire series, occurring in an adult recipient (4%). Tension on the arterial anastomosis created by an underlying portal anastomosis was believed to be the causative factor. We believe that use of a microvascular technique for anastomosis has kept the incidence of HAT low.

Two PVTs occurred in small babies. Both had veins smaller than 5 mm. One of these was repaired successfully; however, the other led to graft failure. We now recommend interposition grafting for small-caliber portal veins.

The most important difference between adult and child recipients was the high incidence of outflow complications in adults (17%). We identified venous outflow resistance or obstruction in 4 of the 23 adult recipients. Seven of the 23 adult recipients (30%) had received grafts with accessory right hepatic veins requiring re-

Table 7. Operative data.

Donors	Adults	Children	*p* value
Graft type			
RL	14	1	
			< 0.0001*
LL	8	1	
LLS	1	20	
Hepatic veins			
1 Accessory R	5	0	
2 Accessory R	3	0	
> 2 Accessory R	1	0	
Interposition graft	1	0	
Portal veins			
2 veins	1	0	
Arteries			
Interposition graft	2	0	
Bile ducts			
Duct-to-duct			
1 duct	10	1	
2 ducts	5	0	
Choledochojejunostomy			
1 duct	6	16	
2 ducts	2	5	
T-tube stent	5	0	

*Indicates statistical significance for values of $p \leq 0.05$.
R: right.

implantation. Most of these accessory veins were reimplanted into the cava in an end-to-side fashion. In 2 cases, the stump of the recipient's middle hepatic vein was used for anastomosis, one incorporating the recipient's inferior mesenteric vein as an interposition graft.

A bile leak with biloma compressing the cava and long hepatic vein creating outflow resistance contributed to delayed graft function and ultimately to retransplantation in 1 patient. A second patient presented with graft congestion after intraoperative reperfusion and required reimplantation of 2 of 4 accessory right hepatic veins. Subsequently, this graft did not function well and required retransplantation as well. Many months after transplant, 2 patients developed hepatic outflow stenosis. One developed ascites 8 months after receiving a RL graft. Work-up revealed a tight stenosis at the caval-hepatic vein junction. It was postulated that the weight of the regenerated liver created tension and rotation on the anastomosis leading to this late-presenting stenosis. The stenosis was treated successfully with balloon dilatation and stenting. During a work-up for failure to thrive, the other patient was found to have a moderate stenosis 5 months after RL LDLT. A 6-mm systemic/portal gradient was identified and a percutaneous stent was placed to relieve this resistance.

Biliary Complications. Bile leaks occurred more frequently in adults, whereas, late strictures were more common in children. Five adults suffered bile leaks (22%). Four of these required repair either by percutaneous stenting or reoperation. The fifth was an incidental liver edge leak that did not require treatment. Only two children suffered leaks (9%). Both were leaks from small biliary radicals requiring operative repair. The second child, interestingly, was 17 years old and received the only pediatric right lobe LDLT.

Strictures occurred in 8 child recipients (36%). Three strictures were treatable with percutaneous stenting, whereas the other 5 required operative biliary reconstruction. In adults, 2 strictures occurred (9%). One occurred in an adult who previously had undergone biliary reconstruction for a biliary dehiscence. Both were treated with percutaneous stenting.

Rejection

Ten of the 23 adult recipients required percutaneous liver biopsy for either persistent or newly elevated liver function tests (LFTs) in the first 2 weeks after transplantation. Three of 23 (13%) exhibited histologic criteria for acute rejection requiring treatment. Seventeen of the 22 children received liver biopsies for either routine monitoring or elevation in LFTs. Most of the first 15 children receiving LDLT at our center received routine biopsy either at planned second-look operations or percutaneously at 1 week postoperatively. Seven of the 22 (32%) exhibited signs of acute rejection and were treated.

Episodes of acute rejection requiring treatment in the immediate postoperative period did not correlate with short-term functional outcome of the graft or with patient survival. Episodes of rejection did not differ by lobe ($p = 0.916$) or adult vs. child ($p = 0.92$).

Discussion

This is the first large series to compare outcomes of adults and children receiving right lobe, left lobe, and left lateral segment grafts. The disappointing outcomes in our initial series of adult LDLT indicate that some lessons learned from over a decade of pediatric LDLT do not apply to adult recipients. Broadly considered, adult LDLT differs from pediatric LDLT in three principal areas: patient selection, graft function, and technical morbidity, specifically, the increased frequency of hepatic venous and biliary complications. Review of national data on the need for liver transplantation and the progressive decline in cadaveric donation make it clear that abandonment of LDLT will not be an option in the near future. This analysis has been useful in identifying strategic and technical improvements that will guide the expansion of LDLT in the years to come.

The confidence that permitted us to perform LDLT in urgent pediatric recipients was not rewarded in our efforts with critically ill adults [3, 4, 10–12]. In this study, 4 adults met the criteria for UNOS status 1 or 2A. Three of these patients received right lobes, and the fourth a left lobe. Of these 4 patients, 1 suffered delayed graft function from a bile leak and outflow obstruction, 1 exhibited SSS, and another developed aspergillosis, ultimately leading to 3 deaths and a 75% mortality, consistent with other observations [8]. In our study population, adults had worse preoperative synthetic liver function, characterized by elevated preoperative INR value, which was directly correlated with increased mortality. It appears that, for the time being, restriction of adult LDLT to elective cases is appropriate. This recommendation has been made by Marcos [21], though Broelsch has contested this conclusion [22]. The causes of the decreased survival in adults are probably multifactorial, though it may be that the small-for-size liver grafting inherent in adult LDLT is the crucial cofactor resulting in bad outcomes. It is evident that chronically ill adults are quite fragile and are often infected at the time of transplantation. Such patients would be expected to tolerate initial liver function and biliary leakage poorly. Another important variable that has not yet been addressed in the literature is the impact of hepatitis C virus on the outcomes of adult LDLT. Although hepatitis C has not had a large effect on survival in standard liver transplant patients, recipients may face greater hazards

with LDLT. First, the small graft must regenerate early, a factor that could theoretically enhance the early reinfection of the graft. Second, early recurrent hepatitis C complicates the differential diagnosis of postoperative liver dysfunction.

Another lesson assumed from our pediatric experience was that graft size did not matter. We have characterized both regeneration and graft diminution associated with apoptosis as children rapidly adapted to grafts that were either too large or too small [23]. Recent reports in the literature and the debate regarding the utility of left lobe grafts and the safety of right lobe grafts focus attention on another critical difference between adult and child recipients. We originally characterized a syndrome of functional insufficiency with a prolonged cholestatic phase in small liver grafts in 1996 [6]. Though only one graft was lost to primary nonfunction, delayed initial function contributed to a prolonged hospital course and led to death from sepsis in several other cases. Although all living-donor allografts are arguably small-for-size, there were 5 adult patients whose postoperative graft function exhibited SSS, in particular. These patients typically required at least 14 days for return of synthetic function and clearance of total bilirubin. Four of the 5 patients received left lobe allografts. SSS from left lobe allografts contributed to fatalities in 2 adult recipients. Kawasaki et al. reported survival of 11 of 13 patients up to 35 months after full left lobe LDLT [7]. In their review they advocated the use of left lobes over right lobes for safety in donors, without evidence of postoperative failure in recipients. Left lobe grafts, although they may be adequate for select recipients, will not add significantly to the donor pool.

The high rate of biliary complications after right lobe grafting gives testimony to the increased technical demands of the procedure, which requires understanding of the right-sided biliary anatomy, and presents the unique challenges of reconstructing tiny ducts. Biliary leaks, which plagued early results of standard orthotopic liver transplantation, have gradually disappeared, occurring in less than 2% of our whole liver grafts with primary duct anastomosis. This low rate led to our abandonment of T-tubes several years ago, because the frequency of tube-related problems exceeded the risk of the complication the tube was designed to prevent [24]. We chose to avoid stents in pediatric LDLT because of problems maintaining external tubes in babies, and a concern that the anastomotic stents might traumatize the tiny duct reconstructed in these procedures [25]. Although leak rates after cadaveric transplantation have traditionally been reported to be around 10% [26], the incidence of biliary leak in adult recipients in our study was 21.7%, compared with only 9.1% in children. In LDLT, a second variable is added which may increase the likelihood of biliary leakage, the divided liver surface or free-edge. The meticulous technique of parenchyma fractioning with clipping and ligation of free biliary radicals is critical. However, the construction of the end-to-end biliary anastomosis in 65% of adults may be a very potent contributor to leakage. Anastomotic edema with end-to-end biliary reconstruction may lead to increased biliary pressure and retrograde leak across the free edge. This situation might lead to the early presence of a biloma, which will resolve once anastomotic edema resolves, provided adequate external drainage of the collection is maintained. Some surgeons have turned to biliary stenting to reduce the incidence of biliary complications. Marcos observed a high rate of biliary leakage in his initial experience, and this complication was essentially eliminated in subsequent patients by systematic use of biliary stents [8, 27]. Three of the 5 adults with bile leaks in the current study ultimately died, and those deaths were related, directly or indirectly, to that leak. Four of the 5 leaks required operative repair or drainage, and the fifth was a resolved leak, found incidentally at the time of delayed abdominal closure. The increased incidence of leaks and delay of their diagnosis mandates early detection and treatment in this higher risk population. As a result, we have turned to T-tube biliary stenting to decrease resistance to flow and prevent stasis, for early detection of cholestasis, and obligatory biliary imaging on POD 7. Since the implementation of requisite T-tube drainage with duct-to-duct reconstructions, we have had no bile leaks.

Nearly a decade ago we described the consequences of outflow obstruction in pediatric segmental transplantation and proposed a technical strategy, which has eliminated this complication in left lobe grafting [19]. The use of the right-sided graft reintroduces the challenge of outflow reconstruction in hepatic grafting. It seemed initially obvious that end-to-end suture of the right hepatic vein would provide excellent outflow for the right lobe graft. In fact, hepatic vein reconstruction of the right-sided graft can be affected by graft anatomy and position of the liver early, and the consequences of stenosis and regeneration later on. A long right hepatic vein as the solitary outflow for the graft can kink and cause early graft dysfunction. In addition, careful study of the anatomy of the right hepatic venous system indicated that the middle hepatic vein accounts for much of the outflow of the right lobe in one third of livers [28]. Though some authors have contested the importance of reconstructing the components of the middle hepatic drainage of the right lobe [13, 14], Kim has reported superb results with vein grafting to reconstruct the drainage of segments 5 and 8, an approach we have adopted selectively. Marcos has also addressed this technical challenge in his review of right lobe recipients [8, 21, 29]. Our incidence of hepatic vein complications was 17%. More discriminatory donor selection with preoperative magnetic resonance angiography will help identify graft venous complexity and subsequently reduce the incidence of hepatic venous complications. In addition, proper attention and aggressive reimplantation of multiple veins, respecting segmental drainage, in combination with short, triangulated surgical technique will decrease outflow complications. Finally, as the graft regenerates and its axis gradually rotates to the left, we anticipate relative narrowing of some hepatic reconstructions unless they are planned to adapt to those changes in position.

Donor outcomes from LDLT, although not the primary focus of this study, are an important consideration in assessing the utility and efficacy of the procedures. Our 2 donor groups for adults and children were significantly different in demographic background. Donors for children were almost exclusively relatives; moreover, they were mainly parents of the sick child. In contrast, almost 30% of donors for adults consisted of unrelated spouses or friends, and many, over 50%, were offspring of the recipient. Donor outcome, despite discordant demographics and extents of parenchymal resection for adult and child donors, did not differ significantly. The donors of adults did not experience a higher incidence of complications, even when comparing right lobe donors to left lateral segment donors. This is the only large series in which there were no bile leaks in donors, although we may be observing the consequences of our conservative technique in the more difficult reconstructions of the recipients. A detailed analysis of our donor outcomes has been reported elsewhere [30].

In conclusion, adult outcomes were significantly worse than pe-

diatric results in our series. These differences are inherent in the patients treated, as is the inevitable issues of small graft size in most of the recipients of adult-to-adult donations. Modifications in patient selection and surgical technique must be made to allow for these differences. Technical challenges to right lobe grafting include biliary and outflow considerations and the optimal approaches to these procedures remains a subject of active investigation worldwide. Three donor deaths have been reported in approximately 600 cases of adult-to-adult LDLT as of the end of 2000, for a rate of 0.5%. This reality must be balanced by the desperate need of the recipient population, providing new technical and biologic challenges for the next generation of liver transplant surgeons. Optimism is in order based on the ever-improving outcomes in this field.

Résumé. Pendant la dernière décennie, nous avons enregistré d'excellents résultants avec un taux de survie dépassant les 90% de la transplantation du foie pédiatrique en utilisant un foie de donneur vivant (LDLT). Les principes établis chez ces patients pédiatriques ont été étendus à l'adulte. Le but de cette étude a été de comparer l'évolution des donneurs et des receveurs entre les patients transplantés, adultes et pédiatriques, dans un seul centre. On a revu les dossiers de 45 LDLT réalisées entre jan 1998 et fév 2001. On a réalisé 23 LDLT chez des adultes (54 ± 6.5 ans) et 22 LDLT pédiatriques (33.7 ± 53.5 mois). La fonction hépatique préopératoire était plus détériorée chez l'adulte (International Normalized Ratio (INR) 1.5 ± 0.4 vs. INR 1.2 ± 0.5; $p = 0.032$). Quatre adultes (17%) étaient stades 1 ou 2A. Seul un enfant a eu besoin d'une transplantation en urgence. On a effectué des statistiques descriptives et une analyse selon Kaplan-Meier. La mortalité du donneur a été de 0% avec une (2.4%) ré-exploration. La médiane du séjour hospitalier a été de 6.0 jours (4–12). La morbidité chez les donneurs et la durée médiane de séjour n'ont pas été différentes en ce qui concernait le sexe, l'étendu de la résection hépatique ou entre les adultes et les enfants ($p = 0.49$). En revanche, les résultats chez les receveurs étaient bien inférieurs en ce qui concerne les adultes. La survie à un an a été de 65% (3 retransplantations (ReTx), 5 décès) chez les adultes vs. 91% pour les enfants (1 ReTx, 1 décès) $p = 0.02$. Les greffons perdus étaient en rapport avec un sepsis ($n = 3$), une incompatibilité de taille ($n = 2$), un suicide, et une thrombose de l'artère hépatique, alors que chez l'enfant, ils étaient en rapport avec une thrombose porte et une insuffisance hépatique secondaire à la nutrition parentérale totale (TPN). Les fuites biliares se sont produites chez 22% des adultes et chez 9% des enfants. Une thrombose de la veine hépatique s'est formée chez 17% des adultes et chez aucun des enfants. La médiane de séjour a été comparable (adulte, 16.5 jours (7–149); enfant, 17 jours (10–56), $p = 0.2$). La fonction du greffon (bilirubine totale (TBili) < 5mg/dl, INR < 1.2, transférases (AST) < 100 U/l) s'est normalisée au jour 4 chez l'enfant et au jour 14 chez l'adulte. Les adultes ont eu plus de mauvais résultats avec toute une gamme de problèmes qui n'ont pas été observés chez l'enfant, et en particulier, l'occlusion des veines hépatiques et le syndrome du petit foie. Les fuites biliaires ont été diagnostiqués plus tardivement chez l'adulte, nécessitant un drainage biliaire, et ont été fatales dans trois cas. Enfin, l'utilisation de la LDLT chez l'adulte décompensé s'est terminé par un décès chez trois patients sur quatre: cette technique devrait être sélective et limitée chez l'adulte.

Resumen. Durante los últimos años hemos informado excelentes resultados con el trasplante hepático de donante vivo en pacientes (THDV) pediátricos, con una tasa de supervivencia del receptor superior a 90%. Los principios establecidos con tal experiencia han sido extendidos al THDV en adultos. El propósito del presente estudio fue comparar los resultados entre adultos y niños, tanto en los donantes como en quienes reciben el THDV, en un solo centro. Se revisaron las historias clínicas de 45 THDV entre 1/98 y 2/01, periodo durante el cual se efectuaron 23 THDV en adultos (54 ± 6.5 años) y 22 en pacientes pediátricos (33.7 ± 53.5 meses). El estado preoperatorio de la función hepática apareció peor en los adultos (*International Normalized Ratio* [*INR*] 1.5 ± 0.4 vs. *INR* 1.2 ± 0.5; $p = 0.032$). Cuatro (17%) adultos pudieron ser categorizados como status 1 ó 2A. Sólo un niño fue trasplantado de urgencia. El análisis incluyó las estadísticas descriptivas y el método de Kaplan-Meier. La tasa de mortalidad en el donante fue 0%, con 1 re-exploración (2.4%). La media del tiempo de hospitalización (TH) fue 6.0 días (4–12). No se encontró diferencia entre los adultos y los niños en cuanto a morbilidad en el donante o el TH según sexo o extensión de la hepatectomía ($p = 0.49$). Por el contrario, los resultados en el recipiente del trasplante fueron peores en el grupo de los adultos. La tasa de supervivencia a 1 año del transplante en los adultos fue 65% (3 retrasplantes, 5 muertes) vs. 91% en los niños (1 retrasplante, 1 muerte) $p = 0.02$. La pérdida del trasplante en los adultos se debió a sepsis ($n = 3$), tamaño muy pequeño ($n = 2$), suicidio y trombosis de la arteria hepática, en tanto que en los niños lo fue por trombosis portal y falla hepática por nutrición parenteral total. Se presentaron fugas biliares en 22% de los adultos y en 9% de los niños. Se registró obstrucción de la vena hepática en 17% de los adultos y en ninguno de los niños. La medida del TH fue comparable (adultos, 16.5 días [7–149]; niños, 17 días [10–56], $p = 0.2$). La función del trasplante a juzgar por bilirrubina total < 5 mg/dl, INR < 1.2, aspartato aminotransferasa < 100 U/l, se normalizó hacia el día 4 en los niños y hacia el día 14 en los adultos. La evolución clínica fue menos buena en los adultos, con una variedad de problemas que no se presentaron en los niños, particularmente la obstrucción de la vena hepática y el síndrome de "muy pequeño para el tamaño". Las fugas biliares fueron diagnosticadas tardíamente, requirieron drenaje biliar en los adultos, y resultaron mortales en 3 casos. Por último, el THDV en pacientes adultos descompensados resultó en la muerte de 3 de 4 pacientes, y debe ser restringido a uso electivo.

References

1. 2000 Annual Report of the U.S. Scientific Registry of Transplant Recipients and the Organ Procurement and Transplantation Network: Transplant Data 1989–1998. (2001, February 16). Rockville, MD and Richmond, VA: HHS/HRSA/OSP/DOT and UNOS. Retrieved April 27, 2002 from the World Wide Web: http://www.unos.org/frame_Default.asp?Category=anrpt
2. Fishbein TM, Gondolesi G, Marcos A, et al. The influence of adult living donor liver transplantation on transplant volume in UNOS region 9 (New York State). Am. J. Transplant. 2001;1(S1):921A
3. Broelsch CE, Whitington PF, Emond JC, et al. Liver transplantation in children from living related donors. Ann. Surg. 1991;214:428–439
4. Emond JC, Heffron TG, Kortz EO, et al. Improved results of living related liver transplantation with routine application in a pediatric program. Transplantation 1993;55:835–840
5. Heffron TG. Living-related pediatric liver transplantation. Semin. Pediatr. Surg. 1993;2(4):248–253
6. Emond JC, Renz JF, Ferrel LD, et al. Functional analysis of grafts from living donors: implications for the treatment of older recipients. Ann. Surg. 1996;225:544
7. Kawasaki S, Makuuchi M, Matsunami H, et al. Living related liver transplantation in adults. Ann. Surg. 1998;227:269–274
8. Marcos A, Ham JM, Fisher RA, et al. Single-center analysis of the first 40 adult-to-adult living donor liver transplants using the right lobe. Liver Transplant. 2000;6:296–301
9. Fan ST, Lo CM, Liu CL, et al. Safety of donors in live donor liver transplantation using right lobe grafts. Arch. Surg. 2000;135:336–340
10. Rogiers X, Broering DC, Mueller L, et al. Living-donor liver transplantation in children. Lang. Arch. Surg. 1999;384:528–535
11. Colombani PM, Lau H, Prabhakaran K, et al. Cumulative experience with pediatric living related liver transplantation. J. Pediatr. Surg. 2000; 35:9–12
12. Millis JM, Cronin DC, Brady LM, et al. Primary living-donor liver transplantation at the University of Chicago: technical aspects of the first 104 recipients. Ann. Surg. 2000;232:104–111
13. Tanaka K, Uemoto S, Tokunaga Y, et al. Surgical techniques and innovations in living related liver transplantation. Ann. Surg. 1993;217: 82–91
14. Wachs ME, Bak TE, Karrer FM, et al. Adult living donor liver transplantation using a right hepatic lobe. Transplantation 1998;66:1313–1316
15. Shiffman ML, Brown RS Jr, Olthoff KM, et al. Living donor liver transplantation: summary of a conference at The National Institutes of Health. Liver Transplant. 2002;8(2):174–188
16. Renz JF, Mudge CL, Heyman MB, et al. Donor selection limits use of living-related liver transplantation. Hepatology 1995;22:1122–1126
17. Emond JC. Clinical application of living-related liver transplantation. Gastroenterol. Clin. North Am. 1993;22:301–315

18. Broelsch CE, Whitington PF, Emond JC, et al. Liver transplantation in children from living related donors: surgical techniques and results. Ann. Surg. 1991;214:428–437
19. Emond JC, Heffron TG, Whitington PF, et al. Reconstruction of the hepatic vein in reduced size hepatic transplantation. Surg. Gynecol. Obstet. 1993;176(1):11–17
20. Renz JF, Rosenthal P, Roberts JP, et al. Planned exploration of pediatric liver transplant recipients reduces posttransplant morbidity and lowers length of hospitalization. Arch. Surg. 1997;132(9):950–955; discussion 955–956.
21. Marcos A. Right lobe living donor liver transplantation: a review. Liver Transplant. 2000;6(1):3–20
22. Testa G, Malago M, Nadalin S, et al. Living related liver transplantation for decompensated end-stage liver disease. Am. J. Transplant. 2001;1(S1):501A
23. Bhagat G, Cataldegirmen G, Lefkowitch J, et al. Proliferation and apoptosis in living related liver allografts: correlation with graft size and rejection activity index. Hepatology 1999;30(4 part 2):304A
24. Randall HB, Wachs ME, Somberg KA, et al. The use of the T-tube following orthotopic liver transplantation. Transplantation 1996;61(2): 258–261
25. Kuang AA, Renz JF, Rosenthal P, et al. Decreased mortality from technical failure leads to improved results of pediatric liver transplantation. Arch. Surg. 1996;131:887–893
26. Everson GT, Kam I. Immediate postoperative care. In Maddrey WC, Michael F Sorrell, editors, Transplantation of the Liver. Philadelphia, Lippincott, Williams & Wilkins, 2001;144.
27. Marcos A, Ham JM, Fisher RA, et al. Surgical management of anatomical variations of the right lobe in living donor liver transplantation. Ann. Surg. 2000;231:824–831
28. Salamé E, Schmutz G, Emond JC, et al. Clinico-anatomical and radiological study of the drainage territory of the middle hepatic vein: application on living liver transplantation. Hepatology 2000;32(4 pt.2):360A
29. Marcos A, Fisher RA, Ham JM, et al. Right lobe living donor liver transplantation. Transplantation 1999;68(6):798–803
30. Salamé E, Goldstein MJ, Saouaf R, et al. Impact of the extent of the hepatectomy on liver function and clinical recovery in living donors for liver transplant. Am. J. Transplant. 2002;2:780–788