

Full-Right-Full-Left Split Liver Transplantation: The Retrospective Analysis of an Early Multicenter Experience Including Graft Sharing

M. Zambelli^a, E. Andorno^b, L. De Carlis^c,
G. Rossi^d, U. Cillo^e, T. De Feo^f, A. Carobbio^g,
A. Giacomoni^c, G. Bottino^b, and M. Colledan^{a,*}

^aDepartment of Surgery, Ospedali Riuniti, Bergamo, Italy

^bDepartment of Transplantation, San Martino University Hospital, Genova, Italy

^cDepartment of Transplantation, General Surgery II and Liver Transplantation Unit, Niguarda Ca'Granda Hospital, Milan, Italy

^dGeneral Surgery and Liver Transplantation Unit, Fondazione IRCCS Ca'Granda, Ospedale Maggiore Policlinico, Milan, Italy

^eHepatobiliary and Liver Transplantation Unit, University of Padua, Italy

^fOrgan and Tissue Transplantation Immunology, Regenerative Medicine Department, Fondazione IRCCS Ca'Granda, Ospedale Maggiore Policlinico, Milan, Italy

^gDepartment of Haematology, Biostatistics, Ospedali Riuniti, Bergamo, Italy

*Corresponding author: Michele Colledan,
mcolledan@ospedaliriuniti.bergamo.it

Full-right-full-left split liver transplantation divides a donor liver into two grafts to be transplanted in adult-size patients. Major technical and organizational difficulties have limited its application to few single center series. We retrospectively analyzed the long-term results of the first multicenter series of this procedure with graft sharing. Between November 1998 and January 2005, 43 transplants were performed by five centers from 23 full-right-full-left *in situ* split liver procedures; 65% of the grafts were shared. A total of 31 (72%) patients had complications above grade II; 3 (6.9%) were retransplanted. Hospital mortality was 23% with sepsis as the main cause. Six patients died in the long term, two of them for a road accident. A total of 27 patients are alive after a median follow-up of 3200 days (2035–4256). Actuarial survival at 1 and 10 years were 72.1%, 62.6% and 65.1%, 57.9%, respectively for patients and grafts. These figures are similar to those reported for adult living donor liver transplantation by the European Registry over a similar period. Multicenter collaboration in sharing of these grafts is feasible and can help facing the organizational limits, thus increasing diffusion of full-right-full-left split liver transplantation.

Key words: Adults, adult to adult, full-right-full-left graft, partial graft, Split liver, splitting technique, graft sharing

Abbreviations: FRFLSL, full-right–full-left split liver transplantation; SL, split liver transplantation; CSL, conventional SL; GRWR, graft to recipient weight ratio; MELD, model for end stage liver disease; FRG, full-right graft; FLG, full-left graft; UNOS, United Network for Organ Sharing; FRGR, full-right graft recipient; FLGR, full-left graft recipients; R, range; SD, standard deviation; PNF, primary nonfunction; SFS, small for size; HR, hazard ratio; LDLT, living donor liver transplantation.

Received 25 September 2011, revised 02 March 2012 and accepted for publication 03 March 2012

Introduction

Split liver transplantation (SL) enables an increase in the number of liver grafts available for transplantation. Conventional SL (CSL) (1–5), dividing the deceased donor liver into the left lateral segment and a right trisegment graft, has eliminated the organ shortage for small pediatric candidates (6,7) without detrimental effect for the adult population, patient survival rates being, equal to the best results achievable with other techniques (8–20). However, the size of the left lateral segment graft is suitable for safe transplantation in small children only (21,22). For adults, representing the largest number of candidates to liver transplantation, or for adult size adolescents, CSL provides no actual benefit.

Early attempts to transplant two adult sized patients with one liver were unsuccessful (23–25) until 1999, when two of us reported having performed the division of a deceased donor liver along its main fissure and the successful transplantation of the full-right graft (FRG) and full-left graft (FLG) into an adult and an adult-size adolescent (26). In 2001 Azoulay et al. at Paul Brousse Hospital reported the first large series of liver splitting for two adult recipients (27). Other series were subsequently reported with more than encouraging results (28–35).

Important technical improvements were introduced by the Hamburg group (36,37) that in 2005 published the largest series, with results identical to those obtained with whole size liver transplantation (38). In spite of the universal scarcity of grafts for adult liver transplantation, the full-right-full-left split liver technique (FRFLSL) has obtained minimal diffusion, clearly lower than its potential (39). In 1997 the centers belonging to the North Italy Transplant program started a collaborative program of CSL with that rapidly developed to what is probably the world largest multicenter experience (40). After the first successful FRFLSL, the environmental situation was that subsequently five centers in the area, all familiar with the techniques of splitting and willing to collaborate on a basis of reciprocal trust, started exploring together the potential of this new technique. The aim of this study is to retrospectively report the features and the early and long-term results achieved in the early phase of this experience.

Patients and Methods

The donor and recipient documents of all the FRFLSL procedures performed at our five institutions between November 1998 and January 2005 were retrospectively reviewed; enrollment was then stopped in order to achieve a long-term follow-up for all the surviving patients. Follow-up was closed at Sept 2010.

Donor selection and splitting policy

All the procedures were performed on optimal multiorgan brain-dead donors, allocated under a center based system. The donor selection criteria for FRFLSL included age below 50 years; inotropic support not superior to 5 mcg/Kg/min of Dopamine; normal macroscopic appearance of the liver and transaminases not superior to twice the normal values (41). However, these were only indicative, splitting was not mandatory and the center to which the liver was allocated was free to decide whether to transplant it as a whole or to perform a split procedure, even outside these criteria, as well as to choose the type of split: CSL or FRFLSL. In general the latter was considered as a second option, with pediatric activity being given priority. The policy was as liberal as possible, as the center was free to share or not one of the grafts. As an incentive to sharing, the favor of any split graft offered and shared was returned on the next available occasion of splitting, the center offering a share would therefore transplant two patients anyway.

Choice of the center with which to share was also initially allowed, whereas a rotation system was subsequently adopted. The splitting was performed by surgeons from both centers involved and independently on the donor hospital being or not familiar with major liver surgery.

Recipient selection

The recipients were selected by each center among the ABO compatible patients on their respective waiting lists. At the time when this experience started, the definition of size matching criteria and the concept of small for size liver transplantation were not yet well established (42,43). Donor to recipient size matching was therefore not accurate. Only later, as evidence in this field progressively appeared, efforts were made to keep the expected graft to recipient weight ratio (GRWR) above 1. Similarly the model for end-stage liver disease (MELD) was not established for the evaluation of transplant priority and risk at that time (44–47). Severity of the illness, UNOS status 1 or 2A or the presence of severe portal hypertension was not exclusion criteria. All the patients had given informed consent to receiving

a partial organ as alternative to a whole graft both at the time of inscription on the waiting list and before the transplantation.

Splitting technique

The main technique for splitting was briefly described in 1999, and subsequently more extensively reported by others (26, 27). The division of the liver was performed *in situ*. The liver anatomy was studied by intra operative ultrasound and occasionally also by intraoperative cholangiography. The gallbladder was removed, the right branch of the hepatic artery and of the portal vein were encircled, as well as the left hepatic duct. Then the right lobe of the liver was freed from the inferior vena cava by ligature and section of the small accessory hepatic veins, preserving those exceeding 5 mm of diameter for future implantation on the recipient. The right hepatic vein was then encircled.

The parenchymal transection was conducted by Kelly fracture, or using devices that were locally available or carried by the donor team. The transection plane was kept 1 cm to the right of the Cantlie line after identification of the middle hepatic vein by intraoperative ultrasound and careful hemostasis was achieved. After aortic cross-clamping and organ flushing, the two split grafts were separately removed. The FRG included segments V–VIII, with the right branches of the hepatic artery and portal vein, the common bile duct and the right hepatic vein. The FLG included segment I (including the paracaval portion or segment IX (48,49) to IV, together with the vena cava, the arterial axis and the portal vein. After its description by the Hamburg group the split cava technique was applied in some circumstances (36).

Transplant surgical technique

The FRG was transplanted with a substantially identical technique to that of a right graft procured from a living donor. The FLG was transplanted with a technique similar to that of a whole liver transplantation either conventional or piggyback, according to center preferences. When splitting of the vena cava was performed, the inferior vena cava was preserved in both recipients.

Data collection and statistical analysis

All the data were collected in a database. Categorical and noncategorical variables were considered both for the donors and the recipients. Chi-square test and *t*-tests were used in order to compare groups or group's means. When sample size allowed it, a univariate analysis of potential prognostic factors was performed through the Kaplan–Mayer method. Thresholds leading to the lowest *p* values were chosen after serial trials. Multivariate analysis by Cox model was attempted but achieved no significant result due to the limited sample size. Statistical significance was assumed for *p* < 0.05. All statistical analysis were performed using SPSS software (SPSS Inc., Chicago, IL, 1988–1999).

Results

A total of 23 full-right-full-left split procedures were performed the characteristics of the donors are reported in Table 1.

The transplant centers were respectively Milano Niguarda (A) 16 transplants (37%) (9FRG, 7FLG), Genova (B) 13 (30%) (8FRG, 5FLG), Bergamo (C) 7 (16%) (7FLG), Padova (D) 4 (9.3%) (2FRG, 2FLG) and Milano Policlinico (E) 3 (6.9%) (2FRG, 1FLG). Three grafts from different donors were not transplanted. These were 2 FRG that were deemed unsuitable for safe transplantation by the

respective centers, one for a triple venous outflow misdiagnosed at intraoperative ultrasound, and the other for an intravenous drug abuse of the donor that was known only after the end of splitting, the respective FRG being anyway used for an urgent retransplantation. The third was a FLG whose selected recipient withdrew his consent. Of the 46 grafts generated 43 (93.5%) were therefore actually transplanted.

Thirteen couples or 26 grafts (60.5%) were actually shared among the five centers with different combinations (Table 2). A total of 17 grafts were not shared, these were the 3 grafts the contra laterals of which were not transplanted and 7 couples transplanted at 2 single institutions (5 at Center A and 2 at Center B). The transplants were performed simultaneously in five and sequentially in two of these latter couples.

Surgical technique of splitting

In one case the procedure could not be completed *in situ*, due to hemodynamic instability in the donor, and was necessarily completed *ex situ*.

Occasional modifications to the technique were reported in terms of distribution of the pedicles between the grafts. The vena cava was attributed to FLG on 17/23 procedures and the split cava technique performed on 4/23 procedures (17.4%). The portal vein and the arterial axis were kept on the FLG on 20/23 and 21/23 procedures respectively. The common bile duct was kept with the FRG in the majority of the procedures (17/23).

Grafts characteristics

The weight of the grafts was available for only 28 grafts (65.1%). The mean weight was 864 ± 212 g and 660 ± 185 g

Table 1: Donor characteristics (n = 23)

Sex (pts)	Male	20 (87%)
	Female	3 (13%)
Age (years)	30.6 (17 – 51.7) [#]	
Weight (kg)	80 (60 – 97) [#]	
Height (cm)	175 (155–190) [#]	
BMI	26 (21–30) [#]	
Cause of death (pts)	Trauma	16 (70%)
	Intracranial hemorrhage	6 (26%)
	Other	1 (4%)
Dopamine (pts)	No	2 (8.7%)
	<10 γ	17 (73.9%)
	= 10 γ	4 (17.4%)
Norepinephrine (pts)	Yes	8 (35%)
	No	15 (65%)
s-Na (mEq/l)	147 (138 – 160) [#]	
s-ALT (U/L)	31.5 (13 – 158) [#]	
ICU stay (days)	2 (1 – 10) [#]	
% of Steatosis (range)	0 – 10 [*]	

[#]Median, (range), (γ) = mcg/kg/min

^{*}Intraoperative biopsies were performed only on 7/23 patients, when surgical evaluation of the graft was not considered reliable enough.

Table 2: Graft sharing

Center	Donors = n	Graft = n (%)
Not shared grafts		
A	6	11 (55)
B	3	5 (25)
C	0	0
D	1	1 (5)
E	0	0
Overall	10/23	17/43 (39.5)
Shared grafts		
C-B	5	10 (23.2)
C-A	2	4 (9.3)
B-E	1	2 (4.6)
B-A	1	2 (4.6)
B-D	1	2 (4.6)
E-A	1	2 (4.6)
E-D	1	2 (4.6)
A-D	1	2 (4.6)
Overall	13/23	26/43 (60.5)

Transplant centers:

A Milano Niguarda

B Genova

C Bergamo

D Padova

E Milano Policlinico

for the RG and LG respectively. The mean total liver weight was 1520 ± 356 . The weight of the left graft represented in mean 43.1% (SD 6.26) of the total weight of the liver. Only in one case the FLG was larger than the FRG (600 vs. 550 g).

The expected graft weights were estimated by attributing respectively to the FRG and FLG 60% and 40% of the expected total liver volume, calculated with the Urata formula (50) from the anthropometric donor data available and were then compared with the actual weight of the grafts. The correlations between the expected and actual weights, reported separately in Figures 1 and 2, were poor, particularly for the LG.

Recipient characteristics, size matching and transplant procedure

The recipients characteristics are summarized in Table 3. Three FLGR were in pediatric age, the youngest being 10.7 years old, and all received a FLG. No patient was on renal replacement therapy.

There were 42 primary transplants and one second urgent retransplantation. Patient UNOS status were 1 (intubated), 2A (hospitalized under intensive treatment), 2B (frequently or persistently hospitalized), 3 (at home). The mean graft to recipient weight ratio (GRWR) was lower than 1 in two FRGR and one FLGR (0.94, 0.98 and 0.84 respectively, 10.7%).

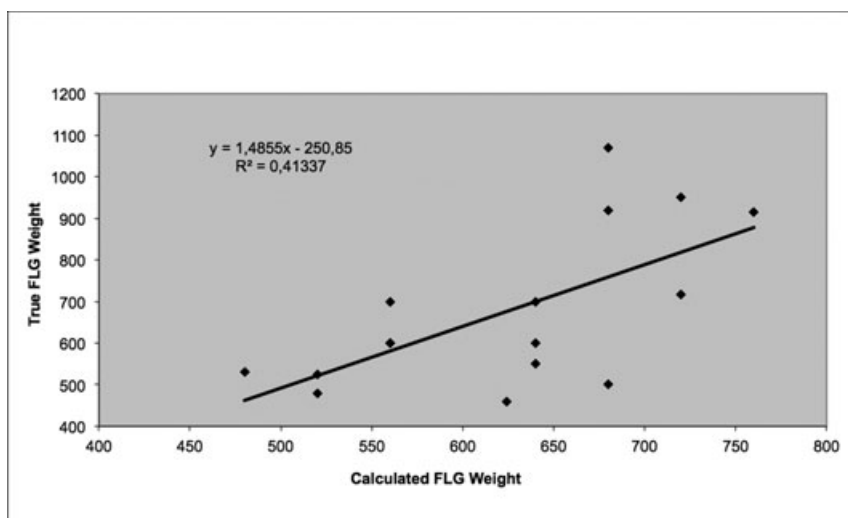


Figure 1: Correlation between FLG expected and actual weight (g).

Cold ischemia time, length of surgical procedure and amount of blood transfusion are reported in Table 4. Surgical time was significantly shorter in FLGR than in FRGR.

All FRGR had a bilio-biliary anastomosis (double anastomosis in two) whereas only 11 (50%) FLGR recipients did. A t-tube was placed in 27 (62.8%).

Postoperative management

An association of cyclosporine in 23 (53.5%) patients or tacrolimus in 20 (46.5%) and steroids was a common feature as immunosuppression. 16 (37.2%) patients also received mycophenolate mofetil. A total of 3 (7%) patients received an induction with Basiliximab.

The median postoperative intensive care unit and hospital stay (available for 28/43 patients) were 7.5 days ($r = 1-75$) and 36.5 days ($r = 7-76$) respectively. Differences between FRGR and FLGR were not significant.

Outcome

Morbidity

A total of 57 postoperative complications $\geq$ of grade III (51) were observed in 31 patients (72%), they are summarized in Table 5. No significant difference was observed between FRGR and FLGR. Two FLGR, from two different centers, had a thrombosis of the hepatic veins; they represented respectively the 4th and 14th cases of each center. One of them was successfully retransplanted and the other died. Two FRGR had a PNF, one of them died with sepsis and the other was successfully retransplanted, both after 7 days. Donor parameters were optimal for both except for dopamine infusion in one of them. Ischemia time was 536' and 840', operative time and intraoperative transfusions were particularly relevant: 960' and 720' and 35 and 18 blood units respectively. Both the respective FLGR had a good initial function one requiring however retransplantation for a thrombosis of the hepatic artery. The three

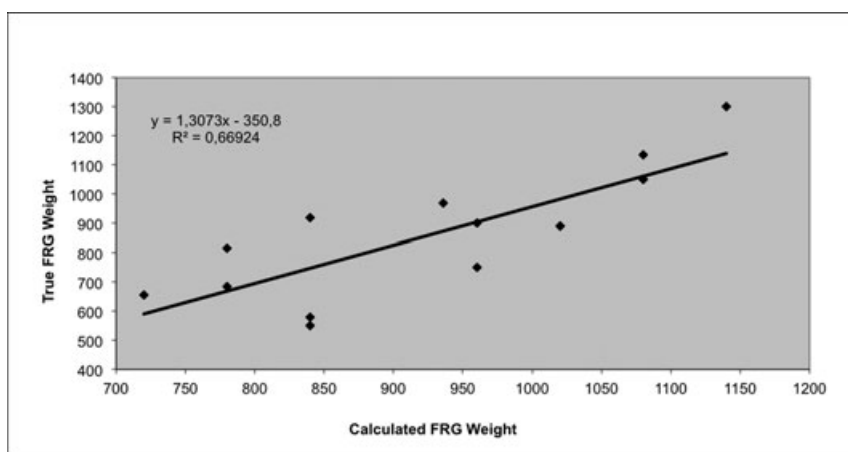


Figure 2: Correlation between FRG expected and actual weight (g).

Table 3: Recipient characteristics (n = 43 pts)

		FRGR	FLGR	Overall
Sex (pts)	M	8	7	15(35%)
	F	13	15	28(65%)
Age (years)		53 (25–60.8) [#]	54 (10.7–62.8) [#]	46.9(10.7–62.8) [#]
Weight (kg)		60 (55–76) [#]	54 (38–69) [#]	57(38–76) [#]
Height (cm)		162 (151–178) [#]	160(149–178) [#]	160(149–178) [#]
BMI		23 (20–29) [#]	20 (16–24) [#]	22(16–29) [#]
GRWR		1.45 ± .33 [§]	1.33 ± .31 [§]	1.38 ± .32 [§]
Indications to transplant (pts)	Viral hepatitis related cirrhosis	18	4	22(51%)
	Alcoholic cirrhosis	1	2	3(7%)
	HCC	1	2	3(7%)
	Biliary atresia	–	3	3(7%)
	Fulminant hepatitis	–	2	2(5%)
	Hepatoblastoma	–	1	1(2%)
	Other causes	1	8	9(21%)
UNOS status (pts)	1	0	2	2(5%)
	2A	6	0	6(14%)
	2B	13	14	27(62%)
	3	2	6	8(19%)
MELD*		17 (9–35) [#]	15 (6–23) [#]	16(6–35) [#]
Child-Pugh		9 (6–12) [#]	8 (5–12) [#]	8(5–12) [#]

[#]Median (range); [§] mean ± std.

*Data available for 38/ 43 patients.

FRGR= right graft recipient; FLGR= left graft recipient.

above-mentioned retransplantation (ReTx), all performed early, were the only ones in the series (6.9%). Two FLGR had a small for size syndrome with, with progressive cholestasis, ascites and impaired liver synthesis, their GRWR was 0.84 and 1.03 respectively. Interestingly, the two other recipients with GRWR lower than 1 had a good function of the graft.

Mortality

Overall, 16 patients (37%) died, a median of 45.5 days (r = 7–1701 days) after the transplant. Nine of 16 were RG recipients (56%) and 7/16 LG recipients (44%) (ns); the causes of death are listed in Table 6. Ten (62.5%) died during their first hospitalization, a median of 32 days (r = 7–101) after the transplant, for a surgical hospital mortality rate of 23%. Interestingly, a patient died of an unexplained massive hemorrhagic necrosis of his FLG, received as a second retransplantation for hepatic artery thrombosis after a transplant for acute hepatic failure and an a first retransplantation for primary nonfunction, both with whole size grafts. Two more patients (12.5%) died after the first

discharge but still during the first year: on day 135 and 108 respectively, for sepsis and associated multiorgan failure.

Four patients (25%) died in the long term, at 523, 1481, 1701 and 1659 days. The first of them died 25 days after a retransplantation, for severe acute rejection due to a noncompliance to the immunosuppressive therapy. Two others died as a consequence of a road trauma totally unrelated with the procedure; one of them had previously received a retransplantation for PNF and the other represented the only death among the three pediatric recipients.

Overall, sepsis was the main cause of death in 10/16 patients (62.5%).

Patients and graft survival

A total of 27 patients (63%) are alive, with a median follow-up of 3200 days (r = 2035–4256), 25 of them (93%) with their original split graft. They all have normal graft function.

Overall patients survival was 72.1%, 69.8%, 62.6% and 62.6% respectively at 1, 3, 5 and 10 years, overall graft

Table 4: Recipient operation

	FRGR (21 pts)	FLGR (22 pts)	p Value	Overall
Cold ischemia time ¹ (min)	435(124–840) ²	405(110–780) ²	0.1	420(110–840) ²
Surgical time (min)	540(360–960) ²	465(290–660) ²	0.018	480(290–960) ²
Blood units	9.5(4–35) ²	11(0–25) ²	0.7	10(0–35) ²

¹Ischemia time difference tested also for shared versus not shared graft was not significant (p = 0.3)

²Median; (range)

FRGR = right graft recipient; FLGR = left graft recipient.

Table 5: Morbidity

Class of complication	Events n (%)	FRGR n (%)	FLGR n (%)	p-Value	Detail of complication	Outcome/Treatment
Vascular	9/43(20.9)	5/43(11.6)	4/43(9.3)	0.65 = ns	Hat 3/43 (6.9%) Hvt 2/43 (4.6%)	2 death, 1 ReTx
Biliary	11/43(25.9)	5/43(11.6)	6/43(13.9)	0.79 = ns	Impaired venous outflow (2) H. artery pseudoaneurysm (1) Collections (9) -leaks (7) -dehiscence (2)	1 death, 1 ReTx 1 death 1 re-operation 2 re-operations
Infection	19/43(44.1)	9/43(20.9)	10/43(23.2)	0.86 = ns	Anastomotic stricture (2) Systemic infections (13) Pneumonia (1) Cholangitis (2) Deep abdominal infection (3)	1 stent + 1 percutaneous dilatation
Other	14/43(32)	6/43(13.9)	8/43(18.6)	0.58 = ns	Abdominal bleedings (6)	
Primary nonfunction	2/43(4.6)	2/43(4.6)	0	0.14 = ns		1death (pod 7) 1ReTx (pod 7) + death (pod 1659)
Small for size	2/43(4.6)	0	2/43(4.6)	0.14 = ns		2 deaths

FRGR = right graft recipient; FLGR = left graft recipient.

Hvt = hepatic vein thrombosis; Hat = hepatic artery thrombosis.

survival was 65.1%, 62.8% and 57.9% respectively at 1, 3, 5 and 10 years.

As shown in Figures 3 and 4, neither patient nor graft actuarial survival were significantly different between FRGR and FLGR in spite of a trend to better patient survival for the latter. The limited sample size did not allow stratification of the results between centers; however the survival of the patients transplanted both at the center contributing to this series with the largest number of transplants (center A) and at the center with the cumulated largest experience of split liver transplantation (center C) were not significantly different from the overall patient survival rate. No difference could be observed in survival in consecutive periods of this series.

Univariate analysis

All variables collected in the database were considered in the univariate analysis in order to identify possible prognostic factors influencing 1- and 3-year patient survival. Due to the limited sample size, only recipient male sex, post-operative sepsis and donor age above 46 years resulted as significant negative prognostic factors. It is however noteworthy that overall mortality was 62.5% (5/8) for patients in UNOS status 1 or 2A and 25.7% (9/35) for those in status 2B and 3.

Results of this analysis are reported in Table 7.

Discussion

FRFLSL is a very complex procedure, requiring extreme effort, that may potentially impact on waiting list mortality and improve the intention to treat survival rate. Its diffusion remains so far limited to very few centers performing

it only on rare occasions. Technical and organizational difficulties are probably the most relevant reasons for this lack of diffusion. Many of these are common to other technical options aiming at the same goals, such as living donor liver transplantation (LDLT). The latter, however, has achieved a diffusion that, albeit limited, is significantly larger, and is currently far more established. In fact, in spite of the advantage of not putting at risk the life of a healthy donor, FRFLSL has intrinsic elements of increased complexity. Among them are the fact of being an urgent procedure, with less extensive evaluation of the donor, donor operation often performed at night, in any donor hospital, and the fact of dealing with two recipients, therefore involving three rather than two difficult operations in rapid sequence or in part simultaneously. Very few centers indeed have enough skills and resources to reasonably face such a tremendous task, but in particularly favorable circumstances.

Sharing grafts can significantly reduce the organizational impact of the procedure by distributing the load over a larger base. This implies widespread familiarity with the techniques and mutual trust among centers, as well as willingness by the organ procurement organization.

To the best of our knowledge this is the largest series of FRFLSL transplantation ever published. It is also the first multicenter series of this procedure involving extensive sharing of the grafts: more than 60% of the grafts were actually shared. Also, in spite of being multicentric, it still maintains a good level of homogeneity. The base principles were well standardized, with only occasional modifications, mostly due to the progressive development of specific knowledge.

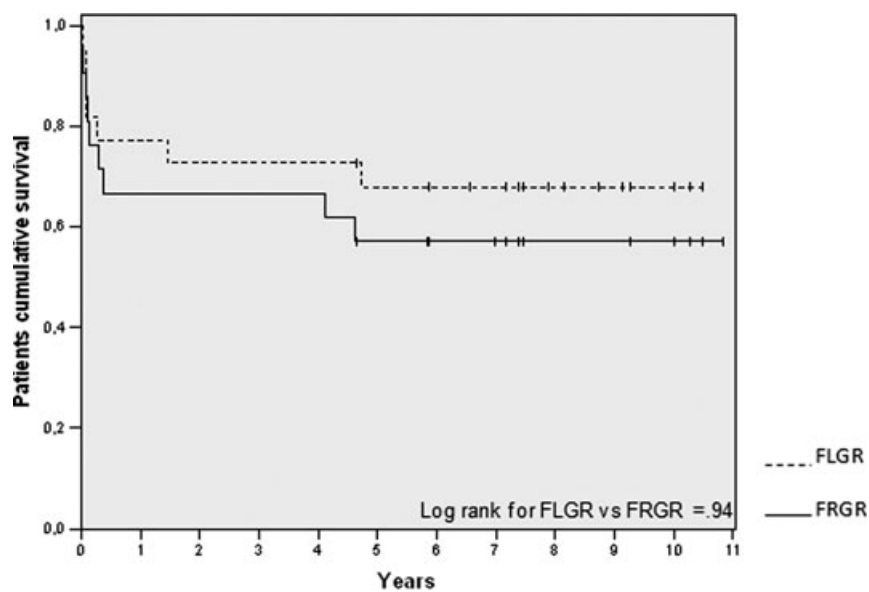
Table 6: Mortality

(Days) (Days)	(years) (years)	Child	UNOS	MELD	Indication	BMI	GRWR	Graft	Ischemia (min)	Cause of death	Associated complication
7 ¹	52	C10	2A	–	Viral	26	1.48	FRG	536	Hepatic failure (PNF)	Infection +vascular
9	19	–	1	–	Hat	20	1.20	FLG	416	Massive liver hemorrhagic necrosis	2 nd ReTx (see text)
11 ¹	60	B8	2B	–	Viral	23	1.62	FRG	417	Systemic fungal infection+ sepsis	
29 ¹	62	B9	2A	17	Viral	22	1.03	FLG	143	Hepatic failure primary dysfunction (> 7 days)	Infection
32 ¹	57	A5	3	11	Viral+Hcc	19	0.84	FLG	225	Small for size syndrome+ MOF	Infection
32 ¹	61	B8	2B	20	Viral	–	–	FLG	360	Sepsis+ MOF	Vascular (Hvt)
33 ¹	43	C12	2A	35	Viral	–	–	FRG	760	Sepsis +MOF	
42 ¹	60	B9	2B	10	Viral	27	1.75	FRG	294	Systemic fungal infection+ sepsis	
49 ¹	47	C11	2A	26	Viral	21	1.91	FRG	720	Bacterial pneumonia+ sepsis	
101 ¹	52	B9	2B	21	PBC	–	–	FLG	420	MOF	Infection
108	45	C12	2A	23	Viral	–	–	FRG	285	Sepsis + MOF	Biliary+ vascular (Hat)
135	57	B7	3	15	Viral	22	1.75	FRG	390	Sepsis +MOF	Infection +vascular
523	42	B7	2B	14	Alcohol	22	1.33	FLG	600	Fungal infection + severe rejection for not compliance to immunosuppression	Infection
1481	58	B8	2B	15	Viral	29	–	FRG	450	Sepsis + bacterial infection	Vascular (hat)
1659	56	A6	3	9	Viral	23	1.43	FRG	840	Road trauma	
1701	13	B8	2B	12	AIH	20	1.00	FLG	300	Sepsis + MOF after road trauma	

PNF = primary nonfunction; PBC = primitive biliary cholangitis; MOF = multiorgan failure; AIH = autoimmune hepatitis.

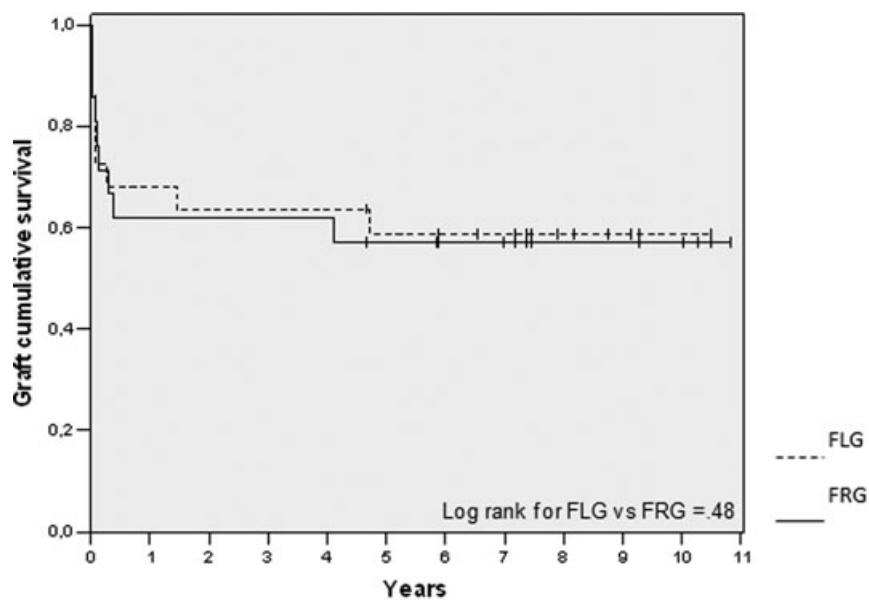
Hvt = hepatic vein thrombosis; Hat = hepatic artery thrombosis.

¹Death occurred at first hospitalization for n = 10/16 patients (62.5%).



Years	FRGR Survival (%)	FLGR Survival (%)	FRGR vs FLGR at risk (n)
1	66.7	77.3	14 vs 17
3	61.9	72.7	14 vs 16
5	57.1	67.9	11 vs 14
10	57.1	67.9	-

Figure 3: Patient survival (Kaplan-Meier).



Years	FRG Survival (%)	FLG Survival (%)	FRG vs FLG at risk (n)
1	61.9	68.2	13 vs 15
3	57.1	63.6	13 vs 14
5	57.1	58.7	11 vs 12
10	57.1	58.1	-

Figure 4: Graft survival (Kaplan-Meier).

Table 7: Analysis of potential prognostic factors impacting survival

Recipient variables	Test	HR (95% CI)	p-Value
Graft	Right versus left	1.44(0.49–4.10)	0.520
UNOS status	1-2a versus 2b-3	2.73(0.90–8.22)	0.075 ⁺
Sex	M versus F	0.10(0.01 – 0.68)	0.020 ⁺
Indications to transplant	viral versus not viral	3.27(0.91–11.80)	0.070 ⁺
	HCV versus not HCV	2.54(0.87–7.42)	0.089 ⁺
	neoplasm versus not neoplasm	2.53(0.54–11.81)	0.237
Complications	Biliary	0.38(0.09–1.72)	0.210
	Vascular	1.47(0.46–4.72)	0.513
	Infection	11.67(2.58–52.77)	0.001 ⁺
	Other	1.28(0.43–3.82)	0.440
Re-Transplant	Yes versus No	0.62(0.08–4.85)	0.649
Age (years)	>50 versus ≤ 50	2.76(0.92–8.26)	0.070 ⁺
Hospital stay (days)	>30 versus ≤ 30	0.94(0.32–2.83)	0.923
ICU stay (days)	≥ 5 versus < 5	3.77(0.45–31.62)	0.221
Ischemia time (min)	>420 versus ≤420	0.67(0.22–2.02)	0.480
Surgical time (min)	>480 versus ≤480	0.56(0.18–1.68)	0.298
Donor variables			
Sex	M versus F	0.57(0.16–2.07)	0.397
Steatosis	= 10% versus <10%	0.98(0.55–1.17)	0.277
GRWR	< 1 versus ≥ 1	1.02(0.13–8.18)	0.984
Dopamine (γ)	≥ 10 γ versus < 10 γ	0.72(0.16–3.26)	0.672
Norepinephrine	Yes versus No	0.56(0.15–2.01)	0.376
Age (years)	≥ 46 versus < 46	6.12(1.68–22.27)	0.006 ⁺
s-Sodium (mEq/L)	>150 versus ≤150	1.09(0.32–3.70)	0.887
GPT (U/L)	>50 versus ≤ 50	3.14(0.61–16.23)	0.171
ICU stay (days)	>3 versus ≤ 3	0.80(0.18–3.63)	0.779

(+) Factors showing higher inverse correlation to the patients survival.

(γ) mcg/kg/min.

(CI) Interval of confidence.

The main limits of this study is its retrospective nature with consequent lack of completeness of data, and the still limited sample size; however some lessons were learned and some considerations can be drawn.

In two patients a small for size graft syndrome was reported. It is important to remember that these transplants were performed at the very beginning of the experience and at that time scientific knowledge in this field was extremely limited (42,43). Some mistakes were therefore made that were avoided later in the series as knowledge increased in the form of the scientific community learning curve rather than just being specific to this experience. The risk of transplanting an excessively small graft is well known today. In living donation the size of the graft can be accurately measured by imaging before the operation, allowing an appropriate size match with the recipient (52–54). This is not the case with FRFLSL, since performing a CT scan on the donor is often nonrealistic. Generally, the volume of the grafts can only be estimated before the procedure by a sequence of approximations. A precise matching cannot therefore be done preoperatively and a safety margin should be kept by reserving the procedure to larger donors and selecting smaller recipients. Sharing grafts among different centers increases the overall recipient pool and may help in finding the most appropriate candidates. It is therefore advisable that each center pre-

viously identifies smaller patients on the waiting list who are more likely to benefit from these grafts. The surgeon's evaluation of the liver volumes at the beginning of the donor procedure may also be crucial, at a time when an alternative recipient can still be selected.

Donor age above 46 years was significantly correlated with a poor outcome, this may more generally indicate that the procedure should be reserved, even more than in CSL, to extremely selected donors. Mortality in status 1 and 2A patients was particularly high and lack of selectivity may be the main reason for the results of this series being slightly worse than those achieved in most American and European single center series as shown in Table 8. Whether or not this can be acceptable in terms of transplant benefit (55) is beyond the scope of this paper. Surely a strict selection of the recipients is advisable in order to achieve better results. We currently avoid FRFLSL grafts in patients with urgent status, high MELD, severe portal hypertension or in retransplantations.

The splitting procedure can be performed either in or *ex situ*, on the back table after procurement of the whole organ. Although no evidence exists in favor of either option, we prefer the *in situ* technique with ischemia starting after the division of the liver at a time when both grafts can be directly shipped to the recipient hospitals (56), thus

Table 8: FRFLSL previous series

Series	FRFLSL n	Ex situ/in situ	Graft survival	Pts survival	PNF	Biliary complications	Vascular complications
Azoulay, Ann Surg 2001; 233:565	17 Full right 17 Full left	30 <i>ex situ</i> 4 <i>in situ</i>	Full right: 1 year 74% Full left: 1 year 75%	Full right: 1 year 74% Full left: 1 year 88%	Full right: 0% Full left: 18%	Full right: 18% Full left: 24%	Full right: 12% Full left: 12%
Yersiz, Liver Transpl 2001;7:1077–1080	4 Full right 4 Full left	<i>In situ</i>	–	Full right: 75% Full left: 100%	12%	37%	25%
Zamir, Transpl 2002, 12:1757–1761	3 Full right 3 Full left	<i>In situ</i>	Full right: 100 Full left: 33%	Full right: 100 Full left: 33%	0	33%	0
Broering, Ann Surg 2005; 242:802	16 Full right 19 Full left	24 <i>ex situ</i> 14 <i>in situ</i>	Full right: 75% Full left: 84%	Full right: 89% Full left: 90%	Full right: 0% Full left: 11%	Full right: 38% Full left: 21%	0
Adham, Liver Transpl 2007; 13:829	15 Full right	<i>Ex situ</i>	93%	1 year 94%	0	20%	27%
Humar, Transplantation 2008; 85:1420–1424	31 (full right/full left not available)	<i>In situ</i>	3 years 74%	3 years 74%	3%	3%	3%
Viganò, HPB 2010; 12:195–203	7 Full right	<i>Ex situ</i>	1 year 43%	1 year 71%	29%	29%	29%
Present Series	21 Full right 22 Full left	<i>In situ</i>	Full right: 1 year 62% Full left: 1 year 68%	Full right: 1 year 67% Full left: 1 year 77%	Full right: 4.6% Full left: 0%	Full right: 11.6% Full left: 13.9%	Full right: 11.6% Full left: 9.3%

limiting ischemia time. The median time in this series was shorter than 8 h. An advantage of splitting *ex situ* may be the possible application of the elegant technique of splitting the middle hepatic vein (37), not yet described at the time of this series, allowing optimal outflow for both grafts.

The transplant operations in the recipients were technically complex, as demonstrated by the total surgical time and amount of blood transfusions which did not improve over time. Morbidity in the recipient was also relevant, particularly in terms of biliary and vascular complications, as is reported in most series of liver transplantation with partial grafts.

The overall survival rate at 3 and 10 years in this series was and 69.8% and 62.6% for the patients and 62.8% and 57.9% for the grafts. It is noteworthy that two of the late deaths were caused by road accidents and completely unrelated with the transplant procedure. These figures represent the result of the early learning curve of a multicenter experience with an extremely innovative technique of liver transplantation with segmental grafts. An evaluation on equal basis should, in our opinion, compare this with a similarly early multicenter series of living donor liver transplantation in adults. No such series are published in medical literature; however the European Liver Transplant Registry has produced a report of the early European experience of living donor liver transplantations performed between October 1991 and December 2005 showing a very similar graft survival of 64% at 3 years (57) in 1134 adults. Similar results were also reported for whole-size liver transplantation in European and American registries (58,59).

Indeed current single-center results of whole size liver transplantation are better. Hong and coworkers, at UCLA, comparing the results of different types of graft, reported a 71% 10-year patient survival for adult recipients of whole liver grafts (60), about 10 points higher than the present series. In terms of impact on the intention to treat survival, however, this is largely compensated by the fact that from 23 multiorgan donors 43 liver transplants were performed, with a net gain of 86%. This is the most relevant aspect to be considered in a context where mortality on—or dropout from—the waiting list for liver transplantation is still a relevant phenomenon.

In our opinion FRFLSL is largely justified and deserves further exploration and application. We have showed here that a collaborative program of sharing these grafts in a macro-system is feasible and may bring significant advantages by distributing the technical and organizational load and potentially allowing better donor to recipient selection and matching. We believe that collaborative activities of this kind should be encouraged by adequate allocation policies and incentives.

Acknowledgments

The authors wish to acknowledge: Giuseppe Remuzzi, MD, for his support and suggestion on revision of the manuscript. M. Lucchesini, Nurse, Transplant Coordinator at Liver Transplant Center, Genova, Italy A. Lucianetti, MD, D. Pinelli, MD, M. Guizzetti, MD, V. Corno, MD, Department of Surgery, Riuniti, Bergamo, Italy A.O. Slim, MD, A. Lauterio, MD, I. Mangoni, MD, P. Aseni, MD, Department of Transplantation, General Surgery II and Liver Transplantation Unit, Niguarda Ca' Granda Hospital, Milan, Italy for their clinical and logistic support to this work. Mr. Jonathan Hankins, for linguistic revision of the manuscript.

Funding Source

None

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

References

1. Pichlmayr R, Ringe B, Gubernatis G. Transplantation of a donor liver to 2 recipients (splitting transplantation)—a new method in the further development of segmental liver transplantation. *Langenbecks archiv Chir* 1988; 373: 127.
2. Broelsch CE, Emond JC, Thistlewaite JR, et al. Liver transplantation with reduced-size donor organs. *Transplantation* 1988; 45: 519.
3. Emond JC, Whittington PF, Thistlewaite JR, et al. Transplantation of two patients with one liver—analysis of a preliminary experience with “split liver grafting”. *Ann Surg* 1990; 212: 14.
4. Rogiers X, Malagò M, Habib N, et al. In situ splitting of the liver in the heart beating cadaveric organ donor for transplantation. *Transplantation* 1995; 59: 1081.
5. Otte JB, de Ville de Goyet J, Alberti D, et al. The concept and technique of the split liver in clinical transplantation. *Surgery* 1990; 107: 605.
6. Gridelli B, Spada M, Petz W, et al. Split-liver transplantation eliminates the need for living-donor liver transplantation in children with end-stage cholestatic liver disease. *Transplantation* 2003; 27: 1197.
7. Broering DC, Mueller L, Ganshow R, et al. Is there still a need for living-related liver transplantation in children? *Ann Surg* 2001; 234: 713.
8. De Ville de Goyet J. Split liver transplantation in Europe. 1988–93. *Transplantation* 59: 1371–1376.
9. Rogiers X, Malagò M, Gawad K, et al. One year experience with extended application and modified techniques of split liver transplantation. *Transplantation* 1996; 61: 1059.
10. Azoulay D, Astarcioglu I, Bismuth H, et al. Split-liver transplantation. The Paul Brousse Policy *An Surg* 1996; 224: 737.
11. Busuttil RW, Goss JA. Split Liver transplantation. *Ann Surg* 1999; 229: 313.
12. Rela M, Vougas V, Muiesan P, et al. Split liver transplantation. King's college hospital experience. *Ann Surg* 1998; 227: 282.

13. Spada M, Gridelli B, Colledan M, et al. Extensive use of split liver for pediatric liver transplantation: A single centre experience. *Liver Transplantation* 2000; 6: 415.
14. Yersiz H, Renz JF, Farmer D G, et al. One hundred split liver transplantations: A single centre experience. *Ann Surg* 2003; 238: 496.
15. Renz JF, Emond JC, Yersiz H, et al. Split liver transplantation in the United States. Outcomes of a national survey. *Ann Surg* 2004; 239: 172.
16. Adam R, Cailliez V, Majno P, et al. Normalized intrinsic mortality risk in liver transplantation: European Liver Transplant Registry study. *Lancet* 2000; 356: 621.
17. Cardillo M, De Fazio N, Pedotti P, et al. Split and whole liver transplantation outcomes: A comparative cohort study. *Liver Transpl* 2006; 12: 402–410.
18. Broering DC, Topp S, Schaefer U, et al. Split liver transplantation and risk to the adult recipient: Analysis using matched pairs. *J Am Coll Surg* 2002; 195: 648.
19. Adam R, Mc Master P, O'Grady JG, et al. Evolution of liver transplant in Europe: Report of the European Liver Transplant Registry. *Liver Transplant* 2003; 9: 1231.
20. Abecassis M, Superina R, Axelrod D. Split liver sharing in the United States. *Am J Transpl* 2005; 5: 1583.
21. Schlitt HJ. Which liver is splittable? In Rogiers X, Bismuth H, Busuttil RW, Broering DC, Azoulay D (eds.). *Split Liver Transplantation. Theoretical and Practical Aspects*. Darmstadt: Steinkopff; 2002; 63.
22. Spada M, Petz W, Aluffi A, et al. Impact of graft size mismatch on outcome in pediatric liver transplantation. Abstracts of the 11th Congress of the European Society for Organ Transplantation, Venice. September 20–24 2003; 64.
23. Bismuth H, Morino M, Castaing D, et al. Emergency orthotopic liver transplantation in two patients using one liver. *Br J Surg* 1989; 76: 722.
24. Strasberg SM, Lowell JA, Howard TK. Reducing the shortage of donor livers: What would it take to reliably split livers for transplantation into two adult recipients? *Liver Transpl Surg* 1999; 5: 437.
25. Rogiers X, Broering DC, Topp S, et al. Technical and physiological limits of split liver transplantation into two adults. *Acta Chir. Belg* 2000; 100: 272.
26. Colledan M, Andorno E, Valente U, et al. A new splitting technique for liver grafts. *Lancet* 1999; 353: 1763.
27. Azoulay D, Castaing D, Adam R, et al. Split-liver transplantation for two adult recipients: feasibility and long-term outcomes. *Ann Surg* 2001; 233: 565.
28. Sommacale D, Farges O, Ettorre GM, et al. In situ split liver transplantation for two adult recipients. *Transplantation* 2000; 15: 1005.
29. Humar A, Ramcharan T, Sielaff TD, et al. Split liver transplantation for two adult recipients: An initial experience. *Am J Transpl* 2001; 1: 366.
30. Zamir G, Olthoff KM, Desai N, et al. Toward further expansion of the organ pool for adult liver recipients: Splitting the cadaveric liver into right and left lobes. *Transplantation* 2002; 74: 1757.
31. Giacomoni A, Lauterio A, Sammartino C, et al. Equal size split liver: preliminary experience at Niguarda Hospital. Abstracts of the 11th Congress of the European Society for Organ Transplantation, Venice. September 20–24 2003; 136.
32. Hwang S, Lee SG, Park KM, et al. A case report of split liver transplantation for two adult recipients in Korea. *Transpl Proc* 2004; 36: 2736.
33. Boillot O, Adam M, Le Derf Y, et al. Split liver transplantation for two adults with full-left and right lobes. Abstracts of the XXth International Congress of the Transplantation Society, Vienna. September 5–10 2004; 10.
34. Colledan M, Segalin A, Andorno E, et al. Modified splitting technique for liver transplantation in adult-sized recipients. Technique and preliminary results. *Acta Chir Belg* 2000; 100: 289–291.
35. Giacomoni A, Lauterio A, Donadon M, et al. Should we still offer split-liver transplantation for two adult recipients? A retrospective study of our experience. *Liver Transpl* 2008; 14: 999–1006.
36. Gundlach M, Broering D, Topp S, et al. Split-cava technique: Liver splitting for two adult recipients. *Liver Transplant* 2000; 6: 703.
37. Broering DC, Bok P, Mueller L, et al. Splitting of the middle hepatic vein in full right-full left splitting of the liver. *Liver Transplant* 2005; 11: 350.
38. Broering DC, Wilms C, Lenk C, et al. Technical refinements and results in full-right full-left splitting of the deceased donor liver. *Ann Surg* 2005 Dec; 242: 802–812, Discussion 812–3.
39. Toso C, Ris F, Mentha G, Oberholzer J, Morel P, Majno P. Potential impact of in situ liver splitting on the number of available grafts. *Transplantation* 2002 Jul 27; 74: 222–226.
40. Split and whole liver transplantation outcome: A comparative cohort study. Cardillo M et al; NITp Liver Transplantation Working Group. *Liver Transplant* 2006; 12: 402–410.
41. Porta E, Cardillo M, Pizzi C, et al. Split liver is an effective tool to transplant paediatric patients. *Transpl Int* 2000; 13: S144–S146.
42. Dahm F, Georgiev P, Clavien PA. Small-for-size syndrome after partial liver transplantation: Definition, mechanisms of disease and clinical implications. *Am J Transpl* 2005 Nov; 5: 2605–3610.
43. Heaton N. Small-for-size liver syndrome after auxiliary and split liver transplantation: Donor selection. *Liver Transpl* 2003 Sep; 9: S26–S28.
44. Malinchoc M, Kamath PS, Gordon FD, et al. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology* 2000 Apr; 31: 864–871.
45. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end stage liver disease. *Hepatology* 2001; 33: 464–470.
46. Wiesner RH, Mc Diarmid SV, Kamath PS, et al. MELD and PELD: Application of survival models to liver allocation. *Liver Transplant* 2001; 7: 567–580.
47. Wiesner RH, Edwards E, Freeman R, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003 Jan; 124: 91–96.
48. Couinaud C. The paracaval segments of the liver. *J Hep Bil Pancr Surg* 1994; 2: 45–51.
49. Murakami G, Hata F. Human liver caudate lobe and liver segment. *Anat Sci Int* 2002 Dec; 77: 211–224.
50. Urata K, Kawasaki S, Matsunami H, et al. Calculation of child and adult standard liver volume for liver transplantation. *Hepatology* 1995 May; 21: 1317–1321.
51. Dindo D, Demartines N, Clavien PA. Classification of surgical complication: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; 240: 205–213.
52. Trotter JF, Wachs M, Everson GT, Kam I. Adult-to-adult transplantation of the right hepatic lobe from a living donor. *N Engl J Med* 2002 Apr 4; 346: 1074–1082.
53. Florman S, Miller CM. Live donor liver transplantation. *Liver Transpl* 2006 Apr; 12: 499–510.
54. Trotter JF, Campsen J, Bak T, et al. Outcomes of donor evaluations for adult-to-adult right hepatic lobe living donor liver transplantation. *Am J Transplant* 2006 Aug; 6: 1882–1889.
55. Amin MG, Wolf MP, TenBrook JA, et al. Expanded criteria donor grafts for deceased donor liver transplant under the

- MELD system a decision analysis. *Liver Transplant* 2004; 10: 1468–1475.
56. Rogiers X, Bismuth H, Busuttil RW, Broering DC. *Split Liver Transplantation: Theoretical and Practical Aspects*. Darmstadt: Steinkopff Verlag; 2002.
57. Adam R. 1942 Living related LT 10/1991–12/2005 [*ELTR* web site]. Available at: <http://www.eltr.org>. Accessed September 2006
58. Adam R, McMaster P, O'Grady JG, et al. Evolution of liver transplantation in Europe: Report of the European Liver Transplant Registry. *Liver Transpl* 2003; 9: 1231–1243.
59. Qiu J, Ozawa M, Terasaky PI. Liver transplantation in the United States. *Clin Transpl* 2005; 17–28.
60. Hong JC, Yersiz H, Farmer DG, et al. Long term results for whole and segmental liver grafts in adult and pediatric recipients: A 10 year comparative analysis of 2988 cases. *Am J Transpl* 2009; 208: 682–689.