Extension of the adult hepatic allograft pool using split liver transplantation

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Abstract

Background : **The ever increasing number of, especially, adults waiting for a liver transplantation necessitates to develop techniques allowing to extend the available donor liver pool.**

Materials and Methods : **Between November 1988 and December 2004, 37 (6.6%) of 559 adults underwent split liver transplantation at Saint-Luc Hospitals. There were 36 were right and one left split procedures ; 27 split grafts were obtained ex-situ and 10 in-situ. Results of these series are analysed and compared to literature data of split liver transplantation.**

Results : **Three and 12 months patient survival rates were 89.2% and 78.4% respectively. Five years actuarial patient survival was 75.7%. Early (< 3 months) and late (> 3 months) mortality rates were 10.8% (4 pat.) and 21.6% respectively. Early mortality was significantly higher in case of urgent split liver transplantation (3/5 patients vs. 2/32 elective patients – p 0.001).At present 25 patients are alive, with a mean Karnofsky score of 90%.**

Three and 12 months graft survival rates were 91.7% and 87.1% respectively. Three and one grafts were lost due to primary and early graft non-function.

In-situ split grafts had shorter mean warm, cold, total ischemia and operating times as well as less need for blood transfusion ; all these differences were however not statistically significant.

Surgical complications occurred in 19 (51%) patients. All but one complications occurred early (< 3 months). There were sixteen biliary complications in 13 (35.1%) patients : 9 anastomotic stenoses, 3 anastomotic and 4 transection margin leakages. Six vascular complications occurred in 6 (15.2%) patients : three arterial and 3 portal vein thromboses. Seven (18.9%) patients had a postoperative bleeding.

Conclusions : **Graft and patient survival rates of split liver transplantation can be compared to those of classic liver transplantation. However the care of these patients is demanding due to the high number of technical complications. Results of split liver transplantation must be further improved in order to foster it's more widespread use necessary to overcome the actual shortage of liver allografts.** (Acta gastroenterol. belg., **2005**, 68, **369-375**).

Key-words : liver transplantation, donor pool extension, split liver transplantation.

Abbreviations

BC	biliary complications
BDAL	bile duct anastomotic leakage
BDAS	bile duct anastomotic stenosis
BL	postoperative bleeding
CIT	cold ischemia time
HAT	hepatic artery thrombosis
LT	liver transplantation
OT	operating time
PNF	primary non-function
PRBC	packed red blood cells
PVT	portal vein thrombosis
SpLT	split liver transplantation
TIT	total ischemia time
TML	transection margin leakage
WIT	warm ischemia time

Introduction

The gap between available liver grafts and patients waiting for liver transplantation is constantly widening (1,2). For this reason, transplant surgeons are obliged to develop surgical techniques aimed at expansion of the organ pool. Excluding living donor liver transplantation, three methods have been developed to overcome this shortage : hepatic bipartition, better knows as split liver transplantation (SpLT), domino or sequential transplantation (DLT) and the exceptional re-use of liver allografts.

This paper reviews our experience with Split LT in adult recipients and compares the obtained results with those reported in the recent literature.

Materials and methods

Between November 1988 and December 2004, 37 (6.62%) of 559 adult patients underwent SpLT at Saint-Luc University Hospitals in Brussels. There were 22 males and 15 females, having a mean age of 50 years (range 29-67). Their diagnosis was acute liver failure (2 pat.), familial amyloid polyneuropathy (2 pat.), carcinoid hepatic metastases (1 pat.), primary (3 pat.) and secondary (1 pat.) biliary cirrhosis, cryptogenic cirrhosis (3 pat.), alcoholic cirrhosis (6 pat.), HBV (5 pat.) and HCV cirrhosis (13 pat.) and retransplantation for intrahepatic biliary tract problems (1 pat.). Eleven patients had also a hepatocellular cancer.

Thirty-two transplantations were performed electively and five urgently.

Thirty-six grafts were right lobe split livers (including segments 1 and 5 to 8) and one was a left lobe split (including segments 2 to 4). Twenty-seven procedures

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Table 1. — **Comparison of operative data of in-situ to ex-situ Split liver transplant procedures**

PROCEDURE	EX-SITU (27 pats – 73%)		IN-SITU (10 pats – 27%)		p
–	Mean	Range	Mean	Range	
WIT (min)	51	32-89	43	29-74	0.919
CIT (min)	826	400-2511	863	352-801	0.249
TIT (min)	1000	432-2600	617	380-875	0.255
OT (min)	540	300-690	480	400-690	0.265
PRBC (ml)	2725	0-10400	1413	0-5422	0.113

WIT, CIT, TIT, OT : warm, cold, total ischemia and operating times ; PRBC packed red blood cells.

Table 2. — **Early and late surgical complications after adult Split LT in 19 patients**

Complication			Early (< 3 mo)		Late (> 3 mo)	Type of split	
						ES	IS
BC	16 (43,2%)	BDAS	15 (40,5%)	8 (21,6%)	1 (2,7%)	6	3
		BDAL		3 (8,1%)	–	3	–
		TML		4 (10,8%)	–	3	1
HAT	3 (8,1%)		3 (8,1%)		–	2	1
PVT	3 (8,1%)		3 (8,1%)		–	2	1
POB	7 (18,9%)		7 (18,9%)		–	4	3

BC biliary complications, BDAS bile duct anastomotic stenosis, BDAL bile duct anastomotic leakeage, TML transection margin leakage, HAT hepatic artery thrombosis, PVT portal vein thrombosis, POB postoperative bleeding.

were performed ex-situ and ten in-situ. Early and late survival rates and complications were recorded following the ELTR practice : this means events occurring within three or after three months.

Results

Three and twelve months actual overall patient survival rates were 89,2% and 78,4%. Five years actuarial survival rate was 75,7%. Early (< 3 mo) and late (> 3 mo) death rates were 10,8% (4 pat.) and 21,6% (8 pat.) respectively.

Causes of death were PNF (1× at day 5), haemorrhage (1× at day 7), PVT and HAT (1× at day 27), myocardial infarction (1× at day 57), sepsis (1× at day 80), allograft disease recurrence (3x HCV infection at days 127, 176 and 275), chronic rejection due to non-compliance (1× at day 1080), trauma (1× at day 2813) and metastatic colorectal disease (2× at days 1962 and 2423). Three out of five urgently transplanted patients died early after SpLT, in contrast to only two (6.25%) deaths out of 32 electively transplanted patients (p 0.001).

Twenty-five patients are actually alive ; 19 (76%) patients have a Karnofsky score of 100%, 3 (12%) patients have a score of 90% and 3(12%) patients a score of 70%. Their mean score is 90% (range 70-100).

Three and twelve months actual graft survival rates were 91,7% and 87,1%. Three grafts were lost due to primary non function (PNF) and one graft due to late dysfunction. All four patients underwent reLT ; one patient died at day 5 of PNF and one died at 63 months of colorectal cancer.

Mean ischemia and operative times as well as the need for intraoperative blood product use for ex-situ and in-situ split grafts are displayed in table 3. Although all these data were in favour of the in-situ grafts, these differences were not statistically different (Table 1).

Twenty-nine surgical complications were recorded in 19 (51,3%) patients. All ,but one, surgical complications occurred early (< 3 months). Sixteen biliary complications (BC) occurred in 13 (35,1%) patients : 9 bile duct anastomotic stenoses (6 ES and 3 IS split), 3 bile duct anastomotic leakages (all ES split), 4 transection margin leakages (3 ES and 1 IS split). Six vascular complication occurred in 6 (16,2%) different patients : 3 hepatic artery (2 ES and 1 IS split) and 3 portal vein thromboses (2 ES and 1 IS split).

There were seven post-transplant bleedings (4 ES and 3 IS split), needing 6 relaparotomies. Three bleedings were associated with at least one of the other mentioned complications.

All these complications were similarly frequent in ex-situ and in-situ split techniques (Table 2).

The results of split liver transplantation obtained in our experience compare favourably with those obtained in case of liver transplantation using full size livers or using other technical variant grafts (Figs. 1-3).

Discussion

After the introduction of reduced size liver transplantation by Bismuth in 1984 (3), Pichlmayr reported in 1988 the first hepatic bipartition. Two liver parts obtained from the same organ were successfully implanted in an adult and a paediatric recipient (4).

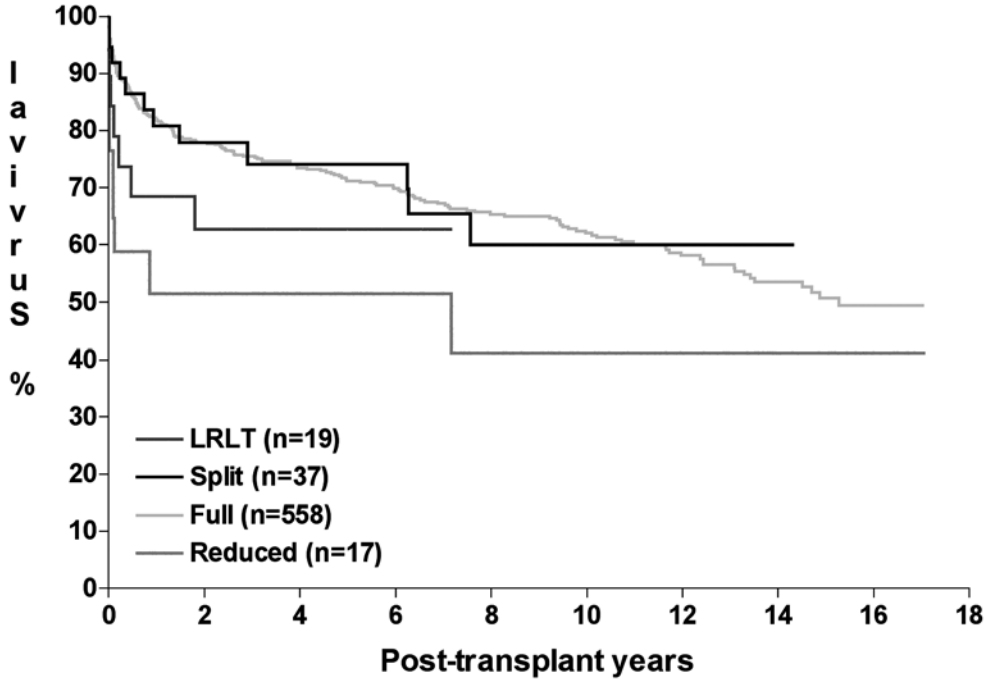

Fig. 1. — UCL-Adult liver transplantation : patient survival rates of all different technical variants

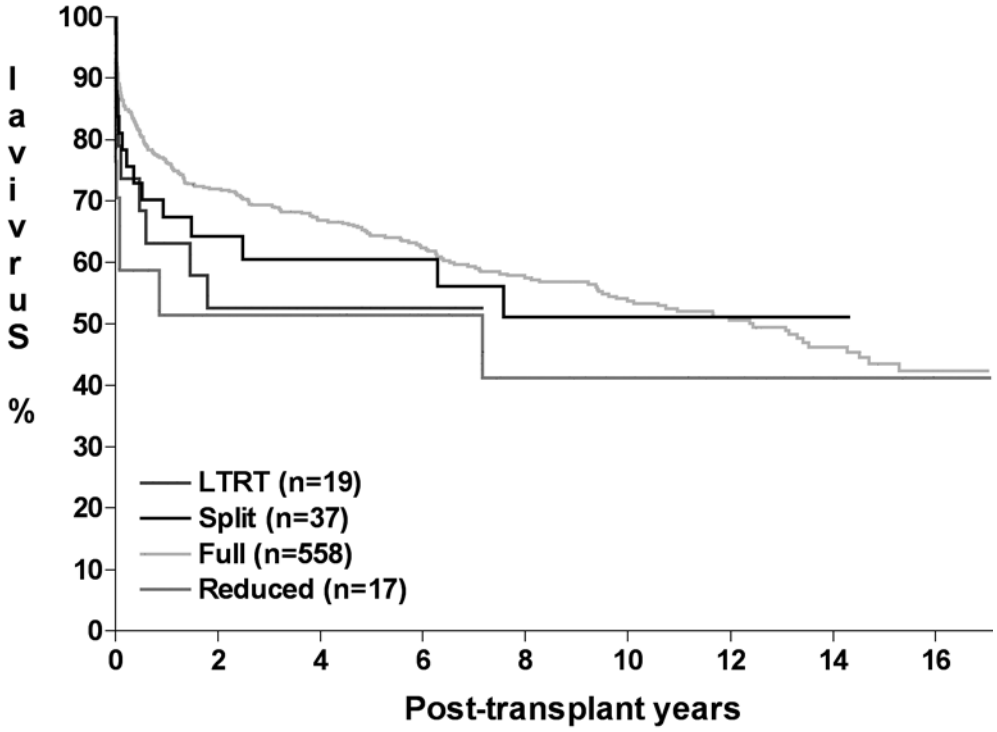

Fig. 2. — UCL-Adult liver transplantation : graft survival rates of all different technical variants

Hepatic bipartition into two adult recipients was reported by Bismuth, 1989 (4). The first split series were reported in 1990 by Broelsch (5). The initial poor results explain the hesitant development of this technique. In 1995, the outcome of 100 partial grafts performed in nine European centres during the period 1988-1993, was reported by de Ville de Goyet (6). The most important message of this paper was that success of SpLT strongly relates to recipient selection. Indeed in high-risk patients (intensive care unit and prolonged hospital stay), 6-months patient and graft survival was 30% inferior compared to survival rates of elective patients (61% for

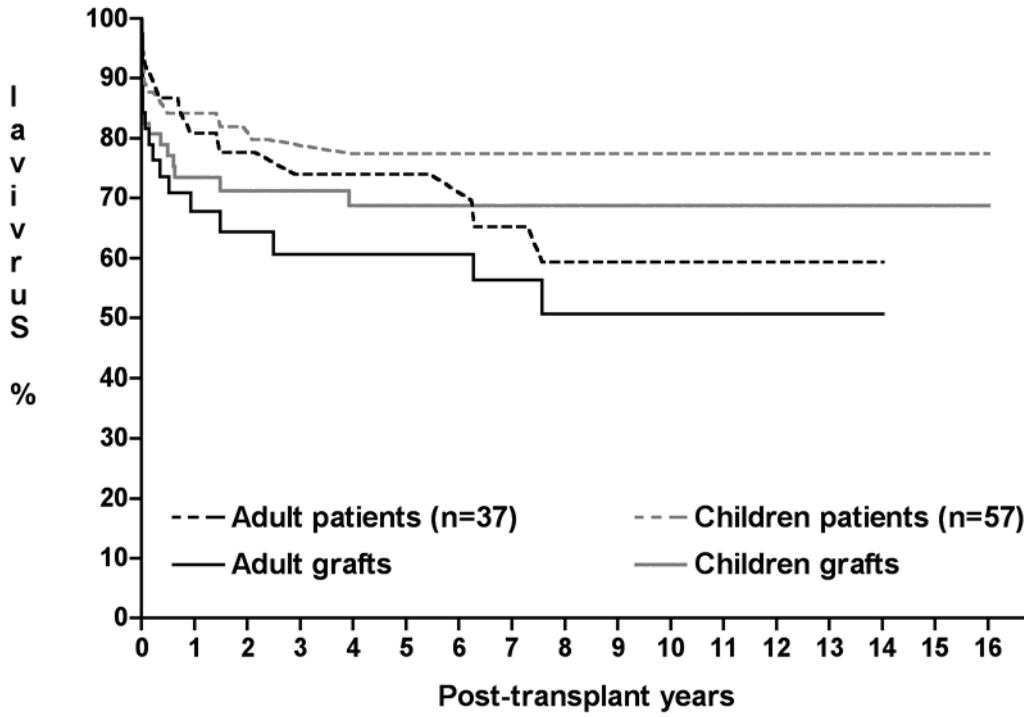

Fig. 3. — UCL-Experience of split liver transplantation : patient and graft survival rates in children (< 15 years) and adults

children and 55% for adults respectively, versus 80% and 72% respectively). Arterial, venous and biliary complication rates were 11.5%, 4% and 18.7% respectively. The second message was that good results related to transplant experience and, more specifically, to SpLT experience.

Problems of SpLT were related to inclusion of high-risk patients, poor know-how and suboptimal logistics. Efforts have been developed since then by many centres to ameliorate these aspects, leading nowadays to results comparable to those obtained in classical, whole-liver, transplantation (8-23).

The groups of Hamburg, Pittsburgh, Los Angeles and Bergamo developed the in-situ splitting technique, aiming to reduce haemorrhagic and biliary post-transplant complications (20,23-31).

Graft selection

The experience shows that it is not only necessary to better select the recipient, but also to better choose of the available graft. The ideal 'split donor ' to perform a successful hepatic is a 10 to (45-) 60 years, haemodynamically stable, heart-beating multi-organ donor having low-doses of vasoactive substances, staying less than 5 days in the ICU stay and having hepatic enzymes lower than 3× normal values and serum sodium less than 160 mmol/L, in the absence of major steatosis (microsteatosis < 50% and macrosteatosis < 20-30%) (19,21,25-27). A weight more than 50 kg preferable.

If full left (segments I-IV) and full right split (segments V-VIII) liver transplantation are envisioned, these criteria must be strictly respected because of the higher risk of graft dysfunction ("Small for Size Syndrome"), especially for the left graft.

The Geneva group explored the potential of graft availability offered by SpLT. A "perfect donor", having all above mentioned criteria, allows to expand the donor pool by 16% in case of adult-paediatric SpLT, and by 9% only in case of adult-adult SpLT. Including only one unfavourable factor allows to increase the donor pool by 42% and 24%, respectively (32).

The final choice to perform hepatic bipartition depends on the combination of donor preoperative and perioperative data, as well as on the macroscopic aspect of the liver, the presence of anomalies (trauma, unknown lesions) and the haemodynamic stability of the donor during the procurement procedure. This explains why at the end 20 to 40% of livers are not used for split, leading to a realistic increase in the number of allografts using the split technique by 10 to 20%.

Split techniques

The key for successful split LT is the equal repartition of vascular and biliary structures between the two grafts. Evaluation of biliary and vascular anatomy can be performed by direct inspection, probing, and radiological examination of these different elements.

Split liver technique for adult-pediatric grafting (right lobe and left lobe) (Table 3)

This technique allows to obtain a left lobe (segments II and III also known as left lateral segment) and a right

Table 3. — **Published experience of Ex-situ and In-situ Split LT for children and adults (left lobe – right lobe splitting)**

EX-SITU				Survival rate (%)						
Author	Ref	Year	N	Patient	Graft	BC (%)	VC (%)	High risk pat (%)	PNF %	N° of Compl
Emond ([1])	6	1990	18	67	50	27	11,1	28	5.5	88
Broelsch ([1])	4	1990	30	60	52	19	22	40	8	> 35
Shaw	38	1990	10	50	50	40	10	70		
Houssin	7	1993	16	75	69	25	25	75	0	50
Slooff	8	1995	15	73	67	NR	NR	NR	NR	NR
Otte	9	1995	29	71	67	17,2	10,3	27	7	
de Ville 9 European Centers	5	1995	95	Elective 85 Emergency 63	76 57	11	19	33	4	
Azoulay	10	1996	27	79,4	78,5	22	15	7	4	48
Kaloyoglu	11	1996	12	91,6	75	16,6	8,3	8	0	35
Rogiers ([2])	22	1996	29	62	55,2	20,6	6,9		10,3	
Mirza	12	1998	24	78	68	12,5	8,3	58	4,2	50
Rela	13	1998	41	90	88	14,6	2,2	12		41
Fawcett	14	1998	36	77,7 Elective 96	75 96	11,1	8,3	30,5	0	22
Sindhy (UNOS)	15	1999	89	82	60,3					
Chardot	16	1999	16	66,7	62,5	25	43,7			
Reyes	18	2000	25	74	61	8	16	48	12	14
Deshpande	20	2002	80	96,2	93,7	8,7	7,5	20	0	
Broering*	29	2002	171	85,6	78,4					
Noujaim	19	2003	98 60 29	1998-2001 85 1992-1997 72	78 59	20 27,6	3.3 14	0	1,6 10,3	
UCL		2004	37 adults 57 children	77,9 79,1	63,7 71,4	43,2 –	16,2 –	15,4 –	8,1 –	29 –
IN-SITU				Survival rate (%)						
Author	Ref	Year	N	Patient	Graft	BC (%)	VC (%)	High risk patient (%)	PNF	Compl
Rogiers	22 17	1996 2000	14 83	92,8 83	85,7 75,9	0 /	0 /	21,4 /	0 /	
Goss	25	1997	28	92,3	86	0	0	38,5	10,7	
Bussutil @	23	1999	72	90.7	80.5	2.8	4.2	41.5	8,3	
Reyes	18	2000	29	96	81	3,4	7	27,5	6,8	
Ghobrial ([3])	24	2000	110	79	78	/	/	49	6,8	
Spada	27	2000	42	85	76	26,2	16,6	10	2,4	
Yersiz ([3])	26	2003	163	Le 78 Ri 78	68 69	9 10	15.6 7	38 48	8.6 10	52 24

(1, 2, 3) same center.

lobe (segment IV to VIII and I). This division, suited for one paediatric and one adult recipient, has the advantage that the adult pool is not compromised. The right lobe may be indeed used for any adult recipient without increased risks (33). The hepatic parenchyma is divided close to falciform ligament. The left hepatic vein is separated from the inferior vena cava and the left portal branch is sectioned close to main portal bifurcation. Arterial structures are divided in accordance to the recipient's need. In a way to promote this technique, certain groups routinely leave the principal arterial vascular axis with the right lobe. In that case the procedure is identical to the left lobe living donor procedure.

Parenchymal transection is carried out by progressive ligation or clipping of all vascular and biliary elements. The section may be performed by kellyclasia or bipolar electrocoagulation. The hilar plate, containing segment II and III biliary tracts is transected sharply.

In the majority of cases, the right lobe contains the vena cava, including middle and right hepatic veins, right hepatic artery and common and right bile ducts.

Table 4. — **Published experience of full right - full left Split LT**

	Ref	Year	N	Patient survival (%)	Graft survival (%)	Complications (%)
Colledan	32	2000	6	83,3	66,6	75
Sommacale	33	2000	2	(100)	(100)	(50)
Kilic	34	2001	2	(100)	(100)	(50)
Humar (in situ)	35	2001	12	83,3	83,3	58
Azoulay (right/left) 30 ex-situ and 4 in-situ (24 grafts shared segm. IV)	36	2001	34	81 74 Right 88 Left	75 74 Right 75 Left BC 21% / VC 12% / PNF 9%	24
Andorno (abstract)	38	2001	10	100	80	NR
Broering (7 right / 9 left)	29	2004	16	86	80	NR

Table 5. — **Advantages and disadvantages of ex-situ and in-situ Split LT**

	EX-SITU	IN-SITU
Cold ischemia	Prolonged	Short for both grafts
Graft – Haemostasis	Incomplete	Better
– Bilistasis	Incomplete	Better
Bench surgery – Manipulation	More	Less
– Rewarming	More	Short or avoided
– Anatomical verification	Cholangio-/angiography and/or methylene blue injection and/or probing easier	Difficult and time consuming
Donor surgery – Duration	Shorter	Prolonged (1.5 to 2.5 hrs)
– Influence other organs	Better adapted to external environment	Possible adverse effect on thoracic organs
Graft Sharing	More complex logistics to share grafts	Easier sharing

The sites where the left hepatic and portal veins have been disconnected are sutured transversally.

Split liver technique for adult-adult graft (full right and full left split)

The limiting factor in the classical SpLT is the number of paediatric recipients waiting for a left lobe representing maximally 10% of total waiting list. The real expansion of the allograft pool is therefore achieved only if two grafts for two adult recipients are obtained.

Although the first report on such technique was reported in 1989, only few groups accepted the challenge to go on with this technique due to the poorer results achieved in full size left and right lobe LT.

This method allows to obtain a left liver (segments 2-4) for a small-sized adult and a right liver (segments 5-8) for a normal-sized adult.

The technical challenges are bigger due to the need to obtain optimal biliary and vascular drainage for all graft segments. Sometimes it may therefore be necessary to switch to a split for one adult and one child. Comparable to left lobe living donor graft, the venous drainage may represent a major problem. An optimised venous drainage must be obtained for both grafts. For this reason the vena cava bipartition concept has been introduced (split caval technique) (34). Cholangio- and angiography are crucial to choose the optimal vascular and biliary repartition of both grafts.

In comparison with adult-paediatric split liver series, few and limited studies have been published concerning adult-adult SpLT (Table 4).

The largest experience, obtained by the Paris group in 34 patients, shows the importance of obtaining enough mass for the two grafts, particularly the left graft is at risk of poor function. A good choice of the left liver recipient is thus utmost important to avoid the treat of a “small for size” syndrome. It is obvious that the adult to adult split liver technique has to be applied in elective transplantation for two adults, one of them being small-sized (35-39).

In-situ versus ex-situ split liver transplantation technique

In-situ split technique represents theoretically the method of choice for splitting. The procedure is the same as applied for the living donor graft retrieval. It allows to eliminate the back-table work, to reduce cold ischemia times and to obtain ideal haemo- and biliostasis. The drawback of the technique relates to the important extension of the length of the donor procedure (1.5 to 2.5 hours). Negative effects on intrathoracic organs could fortunately not be shown (24,25,27) (Table 5).

Different groups showed that both techniques have similar patient and graft survival rates, if performed by experienced transplant team. Results of SpLT in critically ill patients remain however inferior to those obtained in elective patients (19,25-29,31,40-42).

Conclusions

Our data and the review of recent literature allow to conclude that adult-paediatric split liver transplantation has become a standardised procedure giving excellent graft and patient survival rates. The procedure remains technically challenging as witnessed by it's higher incidence of technical complications. Even if this technique is more risky, results strongly relate to the evaluation and choice of donor and recipient.

The real expansion of the liver pool can be obtained only by splitting a liver for two adults (full right and full left split liver). The development of split LT for two adults must become the priority of the liver transplant community in order to cope with the ever growing problem of increasing waiting lists.

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