Adult hepatic retransplantation. UCL experience

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Abstract

Introduction **: Retransplantation is a rescue operation in orthotopic liver transplantation. Its appropriateness has been questioned on medical, economical and also on ethical grounds.**

Material and methods **: During the period february 1984-december 1997, 54 (14.5%) of 372 adult patients were retransplanted ; three (0.8%) of them had two retransplantations. Indications were graft dysfunction [(primary non function (8×) and early dysfunction (14 × in 13 patients)], immunological failure [acute (9 × in 8 patients) and chronic (9×) rejection], technical failure [(hepatic artery thrombosis (5 × in four patients), allograft decapsulation (1×), ischaemic biliary tract lesions (6×)] and recurrent viral allograft disease [HBV (4×) and HCV (1×)].**

Results **: Five year actuarial patient survival after retransplantation was 70.8%, which was identical to this of non retransplanted patients (72%).**

Early (< 3 mo) mortality was significantly lower in elective procedures (9.1% - 2/22 pat. vs 34.4% - 11/32 pat. in urgent procedures - p < 0,05).

Mortality was highest in the graft dysfunction (23.8%, 5/21 pat.) and immunological failure (41%, 7/17 pat.) groups. Five of six patients retransplanted for rejection, whilst being on renal support, and two of three patients retransplanted urgently twice died of infectious complications.

All patients retransplanted because of recurrent allograft disease were long-term (> 3 mo) survivors. Both HBV-infected patients died of allograft reinfection 7 months later ; the two HBV-Delta infected patients were, free of infection, 44 and 6 months after retransplantation under HBV-immunoprophylaxis.

Length of hospitalisation after primary transplantation and retransplantation were identical (median of 16 days - range 11 to 40 vs 14 days (range 7 to 110). Economical study during the period 1990-1995 showed that costs of the first hospitalization of primary transplantation and of retransplantation could be equalized during the period 1994-1995 as a consequence of the more frequent use of elective retransplantation (median 1,3 million BF, range 720.988 to 8.887.145 vs 1.1 million BF, range 943.685 to 1.940.409).

Conclusions **: Hepatic retransplantation is a successful safety net for many liver transplant patients. Every effort should be made to do this intervention electively under minimal immunosuppression. In case of immunological graft failure and hepatic artery thrombosis retransplantation must be done early in order to avoid infectious complications ; the same holds for ischaemic biliary tract lesions which cannot be cured by interventional radiology. Retransplantation for recurrent benign disease should be restricted to those diseases which can be effectively treated by (neo- and) adjuvant antiviral therapy.** (Acta gastroenterol. belg., **1999**, 62, **261-266**).

Key words : liver transplantation, retransplantation, technical problems, graft dysfunction, rejection, recurrent allograft disease.

Abbreviations

- AR : acute rejection
- CR : chronic rejection
- HAT : hepatic artery thrombosis
- IBTL : ischaemic biliary tract lesions
- MOF : multiorgan failure
- PTLD : posttransplant lymphoproliferative disease
- (Re)LT : liver (Re) transplantation

Introduction

The results of liver transplantation (LT) improved during the last decade due to better surgical techniques, organ preservation, perioperative care, immunosuppressive therapy and finally introduction in routine practice of hepatic retransplantation (re-LT) (1). Re-LT allows to rescue many patients presenting with irreversible graft failure or technical problems. Its role is however still debated not only on medical and economical but also on ethical grounds, the latter mainly due to the organ shortage (2,3,4).

This study analyses a large single center experience of re-LT in an adult liver transplant program focusing on indication, results in function of different indications, and on economical impact.

Material and methods

During the period february 1984-december 1997, 54 (14.5%) of 372 adult patients (≥ 15 years) were retransplanted ; three of them (0.8%) had two re-LTs. The indications for re-LT are listed in Table I.

Eight (8/54 pat. - 14.8%) patients were retransplanted because of primary non function (PNF), thirteen (13/54 pat. - 24.1%) because of early non function (ENF) ; all, but one, had urgent retransplantation (Table II). Diagnosis of PNF was based on current criteria used to define acute liver failure (5). Severe dysfunction responsible for encephalopathy, lowering of prothrombin time and/or factor V levels less than 20 to 30%, and rising blood lactate from the moment of revascularisation in the absence of triggering factors (as e.g. bleeding or infection) was attributed to PNF. Early non function was defined as a severe liver dysfunction presenting after initial stabilization or improvement of liver func-

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Table I. — **Indications of liver retransplantation in 54 adult patients**

Non function	early	13°	24.1%	21/54 - 38.9%
	primary	8	14.8%	
Rejection	acute	8°	14.8%	17/54 - 31.5%
	chronic	9	16.6%	
Ischaemic biliary tract lesions		6	11.1%	
Hepatic artery thrombosis		4°	7.4%	11/54 - 20.4%
Decapsulation		1	1.9%	
Recurrent viral disease		5	9.3%	5/54 - 9.3%

(° three patients were retransplanted twice)

tion tests or lowering of blood lactate levels. The worsening of the liver function was usually caused by extrahepatic factors such as surgical bleeding and infection. Absence of technical and immunological causes of graft failure were confirmed by surgery and histology.

PNF occurred three times after haemorrhagic surgery ; one patient had a split liver graft. Two patients presented cardiac arrest at allograft reperfusion related to severe graft steatosis. All eight PNF patients were ventilated artificially and four were haemodialyzed at moment of re-LT. Median delay between primary and re-LT was 3 days (range 2 to 14).

All, but one, ENF related to haemorrhagic transplant surgery. Two patients had a split liver graft : the first had a total graft ischemia of 26 hours ; the counterpart of the second patient, grafted at another center, also presented with irreversible ENF.

At re-LT all patients were ventilated, and six were on renal support. Median delay between primary and re-LT was 5 days (range 2 to 17).

Eight (8/54 pat. - 14.8%) patients were retransplanted because of acute allograft rejection (AR). Five had an unfavorable immunological constellation at primary LT related to ABO-incompatibility LT (4 ×) and to 100% T and B cell crossmatch positivity (1 ×). One patient was retransplanted twice for AR.

At re-LT all patients were ventilated and five were on renal support. Four patients received at least two courses of antilymphocytic antibodies. Median delay between primary and re-LT was 14 days (range 5 to 42). Seven patients had urgent re-LT.

Nine (9/54 pat. - 16.6%) patients were regrafted because of chronic rejection (CR) ; two patients were operated at another center.

Two patients were ventilated, one was also on renal support. Two patients had at least two courses of antilymhocytic antibodies. All patients were retransplanted electively. Four other patients died due to end-stage graft failure whilst waiting for re-LT. Median delay between primary and re-LT was 270 days (range 32 to 476).

Four (4/54 pat. - 7.4%) patients had five re-LT because of hepatic artery thrombosis (HAT). Two other patients died of HAT-related sepsis before re-LT could be performed ; one other graft could be saved by surgical thrombectomy and two other grafts were rearterialized by spontaneous collateralization. Median delay between primary and re-LT was 18 days (range 3 to 34). Three patients were retransplanted urgently.

One patient was regrafted urgently because of uncontrolable bleeding related to allograft decapsulation.

Six (6/54 pat. - 11.1%) patients were regrafted electively because of diffuse ischaemic biliary tract lesions (IBTL) in absence of angiographically proven HAT (fig. 1). Fifteen other patients had successful interventional radiology for this complication. None of the retransplanted patients was on life support. Median delay between primary and re-LT was 189 days (range 53 to 908). All patients were retransplanted electively.

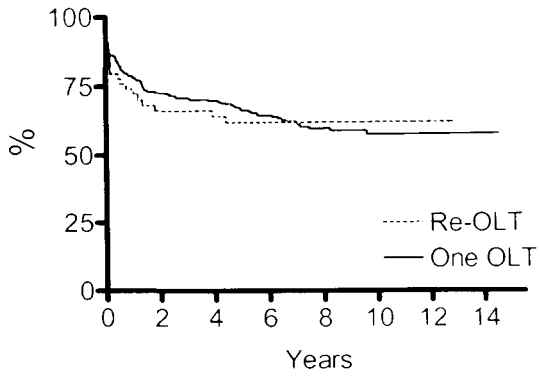

Fig. 1. — Similar results are obtained after primary LT and retransplantation in adults.

Five (5/54 pat. - 9.3%) patients were retransplanted because of viral allograft disease recurrence due to HBV (2 ×), HBV-Delta (2 ×) and HCV infection. The latter re-LT was performed urgently at another transplant center. The two HBV-Delta patients received pre- and post-re-LT antiviral therapy using anti-HBs immunoglobulins and lamuvidine (6).

Retransplantation was done using three different techniques : 39 × classical (with replacement of inferior vena cava), 6 × piggyback (with preservation of inferior vena cava and anastomosies of donor vena cava cuff to cuff of hepatic veins) (7) and 14 × cavo-caval piggyback implantation using a latero-lateral cavo-caval

anastomosis (8). The latter techniques were systematically performed since august 1991.

Allograft vascularization had to be adapted nine times (9/54 pat. - 16.7%) using 8 × free arterial graft (to the abdominal aorta) and once venous graft (to the superior mesenteric vein).

Early and late postoperative mortality and survival were defined as events occuring within or after the first three posttransplant months following the criteria of the European Liver Transplant Registry.

Survival analysis was performed by means of Kaplan-Meier method. P-value was statistically significant when < 0.05.

A study comparing length of hospitalisation and costs was done in patients transplanted at our institution during the period january 1990-december 1995. The analysis was restricted to this period because of standardization of surgical techniques, perioperative care, anti-infectious chemotherapy and availability of administrative data. All costs were calculated from the moment of transplantation onwards. In case of urgent retransplantation costs of the first and second transplant were considered together, both transplants being nearly always realized within some days ; in case of elective retransplants, the two transplant procedures were considered separately. This methodology was chosen because of the facts that costs related to pretransplant period, organ retrieval and transport were not considered neither in primary LT nor in re-LT. Pretransplant costs were not considered because of the impossibility to obtain the majority of the data from the authorities or insurance companies. Moreover, in our own experience, pretransplant costs of primary transplants are usually higher than those of retransplantation.

Results

Five year actuarial survival of retransplanted and non-retransplanted patients was almost identical (70.8% vs 72%).

Early mortality following re-LT was significantly lower in elective procedures (2/22 pat. - 9.1% vs 11/32 pat. - 34.4% in urgent procedures - $p < 0.05$) (Table II). In the total transplant series early mortality following elective LT was also significantly lower than this of urgent LT (37/286 pat - 12.9% vs 20/86 pat - 23.3%, $p < 0.01$). During the period 1983-1990, seven (30.4%) of 23 patients were regrafted once electively vs 15 (53.7%) of 28 patients during the period 1991-1997 (NS). Early mortality during the first period was 30.4% (7/23 pat.) vs 14% (4/28 pat.) during the second period (NS). Two of the three patients regrafted urgently twice, died because of infectious complications.

The incidence of PNF remained stable during the whole study period [1.5% - (3/201 grafts) during the period febr. 1984 - dec. 1990 vs 2.2% - 5/225 during the period jan. 1991 - dec. 1997]. Incidence of ENF dropped, during these periods, from 4.5% (9/201 grafts) to 1.8% (4/225 grafts), mainly as a result of less haemorrhagic surgery and routine use of prostaglandins E1 (Prostin VR® - Pharmacia - Upjohn, Belgium) during immediate post-LT period.

Early mortality in the dysfunction group was 23.8% (5/21 pat.). Three of ten patients, being both on respiratory and renal support at moment of re-LT, died early after re-LT. Two (25%) of eight PNF-patients died because of cerebral bleeding and myocardial infarction. Three (23.1%) of thirteen ENF patients died as a consequence of invasive aspergillosis, posttransplant

Table II. — **Adult liver retransplantation - Influence of diagnosis and timing on early (< 3 mo) mortality**

	Elective	Mortality	Cause	Urgent	Mortality	Cause
Non function primary				8	2	- cerebral bleeding - myocardial infarction
early	1			11 (+ 1°)	3	- aspergillosis - PTLD - MOF
Acute rejection	1			6 (+ 1°)	4 (+ 1°)	- sepsis 2 (+ 1°) - MOF 2
Chronic rejection	9	2	- iatrogenic medullary aplasia - HAT and sepsis			
Ischemic biliary tract. lesions	6					
Hepatic artery thrombosis	1			2 (+ 1°)	(+ 1°)	- hepatic artery aneurysm and aspergillosis°
Decapsulation				1		
Recurrent benign disease	4			1		
	22	2 [9.1%]*		29 (+ 3°)	9 (+ 2°)	[31%]
				32	11*	[34.4%]* * $p < 0.05$

(° three patients were retransplanted twice)

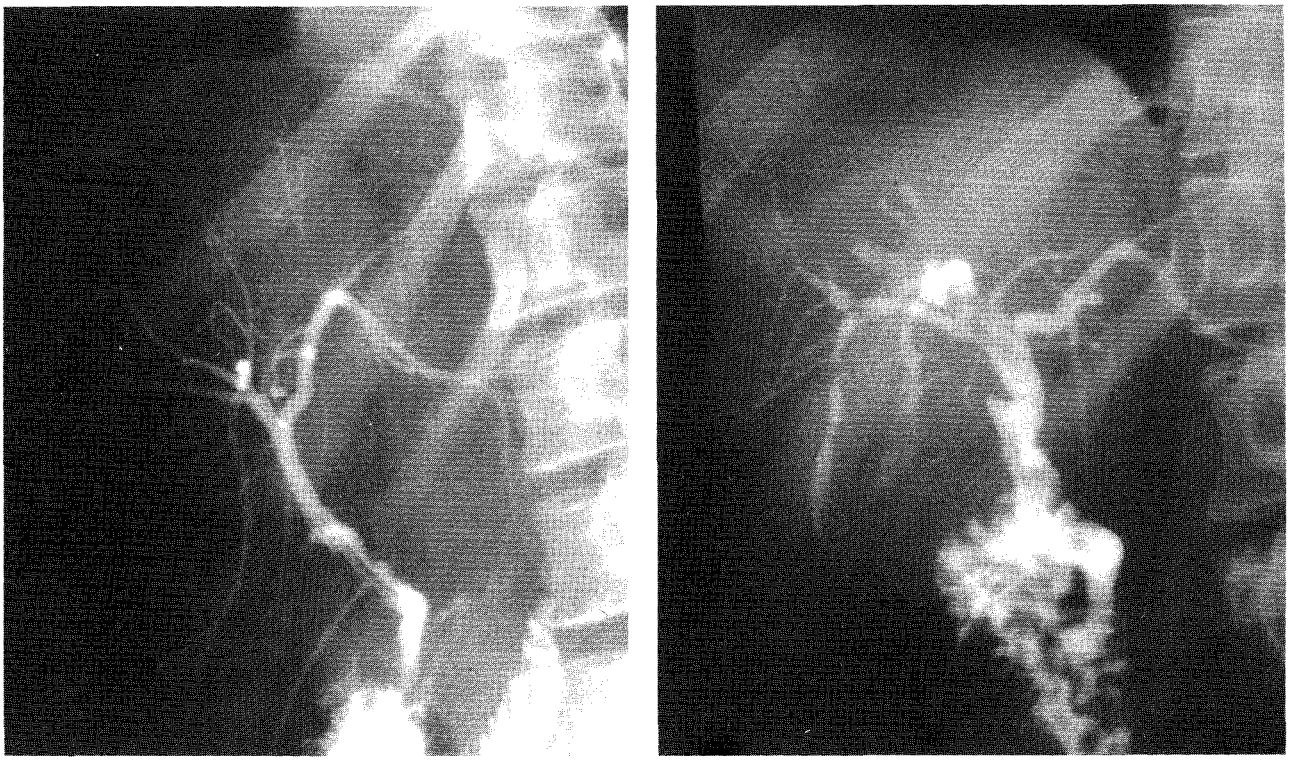

Fig. 2. — (a) Posttransplant percutaneous cholangiography showing a normal extra- and intrahepatic biliary tree. (b) Cholangiography, 3 months later, showing diffuse lesions of the biliary tree necessitating retransplantation.

lymphoproliferative disease (PTLD) and multiorgan failure (MOF).

Early mortality in the rejection group was 41% (7/17 pat.). Five (62.5%) of eight AR-patients died due to sepsis and MOF. Two (22.2%) of nine CR-patients died due to iatrogenic medullary aplasia and sepsis caused by HAT of the second graft.

Three of six patients, receiving multiple courses of antilymphocytic antibodies died due to infectious complications as did five of six patients being both on respiratory and renal support at moment of re-LT. The sixth, surviving, patient was retransplanted successfully without any rejection treatment ; he developed, 42 days after an uneventful LT, haemorrhagic allograft necrosis leading to coma, renal and respiratory failure.

One of four HAT-patients was regrafted twice, he died of fungemia due to a mycotic hepatic artery aneurysm.

All patients retransplanted because of decapsulation and IBTL survived re-LT ; they were all done under minimal or no immunosuppression. Two patients redeveloped IBTL in their second graft ; both were successfully treated by interventional radiology.

Both HBV patients retransplanted without adequate immunoprophylaxis died 7 mo. later due to fibrosing cholestatic allograft hepatitis. The two HBV-delta patients retransplanted using pre- and post-retransplant antiviral therapy with specific anti-HBs immunoglobulins and lamuvidine did well, free of HBV infection, 44 and 6 months after re-LT.

One patient, retransplanted urgently at another center, because of cholestatic HCV- recurrence, is doing moderately well 3 months after re-LT following a stormy postoperative course.

Evolution of costs of primary LT and re-LT, done since january 1990 are listed in table III. As a consequence of more frequent elective re-LT, costs of re-LT and LT became identical during the period jan. 1994-dec. 1995. Median hospital stays of primary and re-LT during this latter period were also similar [14 days, range 7 to 110, vs 16 days, range 11 to 40].

Discussion

Results of LT have been improved dramatically during the last decade (1). Re-LT was one of the factors contributing to this progress.

As re-LT still has an inferior outcome to primary transplantation, reaching even more than 20% (9-16), different studies were undertaken to look at preoperative data predicting outcome after re-LT. Recipient age, mechanical ventilation, serum creatinin and bilirubin elevation, presence of multiorgan failure, UNOS-status, renal failure, interval to re-LT and allograft ischaemia time were all said to negatively influence results of re-LT (16-19).

The present study underlines that re-LT can be done with equal success to primary LT and that results of re-LT must be judged in function of its indications and timing. Results are indeed better if re-LT is performed

Table III. — **Evolution of costs* of liver (re) transplantation during the period january 1990-december 1995**

Period	Primary transplant	Retransplant•	Urgent/Elective re-LT
1990-1991	1.466.042 (910.934 - 5.198.260)°	2.933.706 (1.568.841 - 6.140.771)°	8/1
1992-1993	1.878.274 (611.172 - 5.357.544)	3.191.913 (1.678.872 - 9.111.342)	5/1
1994-1995	1.323.125 (720.988 - 8.887.145)	1.100.677 (943.695 - 1.940.409)	1/7

* costs related to pretransplant work-up, organ retrieval and transport not included.
° median costs in belgian francs of the first hospitalization period.
• patients retransplanted twice were excluded from this analysis.

electively (17,19). The mortality of re-LT was higher in case of acute rejection, graft dysfunction and chronic rejection.

The very high mortality in the AR-group reflects the attitude of agressive immunosuppressive therapy in order to save at any price the allograft. This mortality, mainly due to infectious complications, is reinforced in the presence of renal failure needing life support, a condition known to be accompanied by further impairment of immune defenses (20). Because of the seriousness of this condition, every constellation known to favorize uncontrolable AR, such as ABO-incompatible LT, should be banned from clinical practice (1).

Results of re-LT for chronic rejection are more favorable (18,19). This condition leads to a slow progressing cholestatic disease, allowing to reduce immunosuppression and to perform elective re-LT.

Mortality of re-LT in case of severe early allograft dysfunction equals this of primary LT done in case of (sub)acute liver failure (5), the outcome being also related to infection, multiorgan failure, cerebral bleeding and haemodynamic instability.

The dramatic event of early allograft dysfunction can be substantially reduced by better selection of the donor liver and by adhering to non haemorrhagic surgery (7,21). Steatosic livers presenting more than 50% macrovesicular steatosis should be discarded for LT. Cytoprotection of the liver with prostaglandins and introduction of bioartificial liver may be other potential ways to overcome early, and maybe, primary non function of the graft (22,23).

The decision for regrafting in case of severe dysfunction should moreover not been taken within the first 48 posttransplant hours in order to allow repetitive evaluation of graft function. By doing so only one out of the last 130 full size grafts had to be retransplanted because of PNF.

Success of re-LT was high in case of technical allograft problems. In case of HAT, surgical thrombectomy should first be attempted ; if unsuccessful, patient must be relisted immediately in order to avoid infectious and/or biliary problems (24).

Ischaemic biliary tract lesions in the absence of HAT are more frequent since introduction of UW-preservation solution (25). Interventional radiology plays an important role in the treatment of this complication ; however if unsuccessful or if lesions are diffuse regrafting is usually necessary in order to avoid biliary sepsis ; the progression to cholestatic disease also allows to reduce or even withdraw immunosuppression in view of re-LT.

As the number of long-term survivors of LT is growing steadily, many re-LT's will be done in future for benign recurrent allograft diseases (27). Effective pre- and posttransplant antiviral therapies, using e.g. specific immunoglobulins and nucleoside analogs, allow to retransplant successfully well selected patients presenting HBV and HBV-Delta allograft recurrence (6,27). The debate is controversial in case of HCV-allograft recurrence (28,29,30) ; the introduction of interferon-ribavirin (neo)adjuvant treatment in clinical practice will probably allow to make progress in this field (31).

Retransplantation can be done on an economical justified base. When adhering to early relisting and maximal reduction of immunosuppression, costs and hospital stay can be equal to those of primary LT. Under these conditions repeated re-LT may be justified (32). When immunosuppression is drastically lowered, or stopped, in view of elective re-LT, these patients should however disserve priority on the waiting list. This concept is nowadays compromised by long waiting times due to the organ shortage ; indeed four of our patients died on the waiting list because of end-stage graft failure due to chronic rejection, developed following complete immunosuppression withdrawal in preparation of re-LT.

Conclusion

Hepatic retransplantation should keep its role as a safety net. Results of re-LT can be as good as those of primary LT on the condition that this reintervention is done electively and under minimal (or no) immunosuppression. If the patient is well prepared, re-LT can be cost-effective.

In order to define the exact role of re-LT, results must be judged in function of its different indications ; moreover each decision for re-LT should be taken on an individual basis. Due to the prohibitive early mortality, its indication must be especially questioned in case of rejection accompanied by necessity of renal support and in case of repeated re-LT. The role of re-LT in recurrent benign, especially viral, allograft diseases needs to be further evaluated in relation to availability of effective antiviral treatment.

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