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Results after liver retransplantation in a group of 50 regrafted patients: two different concepts of elective versus emergency retransplantation

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Abstract. Liver retransplantation remains the only alternative therapy for irreversible graft failure. Previous studies have demonstrated lower survival rates for liver retransplantation than for primary grafts. After reviewing our clinical experience with 55 retransplantations out of 365 liver transplants, we found that the risk and results depend on the surrounding circumstances. Elective retransplantation was shown to be as safe as the first liver transplantation, while emergency retransplantation yielded significantly higher morbidity and mortality rates.

Key words: Liver transplantation, retransplantation – Retransplantation, liver

Recent advances in organ preservation and immunosuppression, together with technical refinements, have increased the probability of 1-year survival in liver transplant (LTx) patients to 70%–85% [5, 12]. However, in irreversible graft failure, the lack of artificial liver support methods makes retransplantation (retx) the only available alternative. In this setting, the clinical course is often complicated by multiorgan failure and lower survival rates, especially in adult patients [1, 6, 7, 10, 13]. We have retrospectively analyzed the outcome of 55 retx, the clinical course, and the causes of graft failures in order to determine the effect on patient survival. We have also attempted to identify factors that may influence the prognosis after retx. Our clinical experience with liver retx indicates that risks and results after the procedure depend on the surrounding circumstances.

Materials and methods

Between December 1984 and January 1990, 365 LTx were performed in 310 adult patients (age range 12–64 years) at Baylor University Medical Center (Dallas, Tex., USA). Fifty of these patients (16.1%) underwent retx, five of them twice.

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The first 166 livers were preserved in Euro-Collins solution and the rest in University of Wisconsin (UW) solution.

The recipient operation was performed according to the technique described by Starzl et al. [11]. Veno-venous bypass was established routinely with a Biomedicus pump for the anhepatic phase. Arterial reconstruction was done whenever possible by hepatic-to-hepatic artery anastomosis. In some cases an arterial anastomosis to the recipient aorta was necessary, using an interposed iliac graft. Biliary reconstruction was accomplished by duct-to-duct anastomosis or Roux-en-Y hepaticojejunostomy. Intravenous imipenem was used as an intraoperative prophylactic antibiotic, as well as during the first 5 postoperative days. Patients in the ICU or under lactulose therapy before LTx received 10–15 days of amphotericin (10 mg IV per day) for antifungal prophylaxis.

Doppler ultrasound studies were done 24 h after LTx to rule out vascular complications. T-tube cholangiogram was done 1 week after LTx. Abdominal ultrasonography, CT scan, HIDA scan, or conventional angiogram was performed when complications were suspected. Liver function tests were performed daily and liver biopsies were taken routinely 1–2 weeks after transplantation or if graft dysfunction was suspected.

Standard immunosuppression was achieved using cyclosporin A in combination with prednisolone. Cyclosporin levels were maintained between 250 and 400 ng/ml (RIA monoclonal test, 12-h though, whole blood). Azathioprine (1–3 mg/kg) was added if nephrotoxicity or renal failure necessitated reduction or discontinuance of cyclosporin therapy. Episodes of rejection were initially

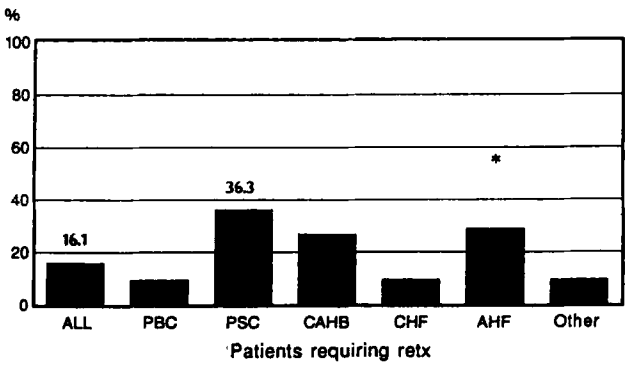

Fig. 1. Frequency of retx according to pretransplant disease. *PBC* Primary biliary cirrhosis; *PSC* primary sclerosing cholangitis; *CAHB* chronic active hepatitis B; *CHF* chronic hepatocellular failure; *AHF* acute hepatic failure. *P = 0.001 (PSC vs ALL)

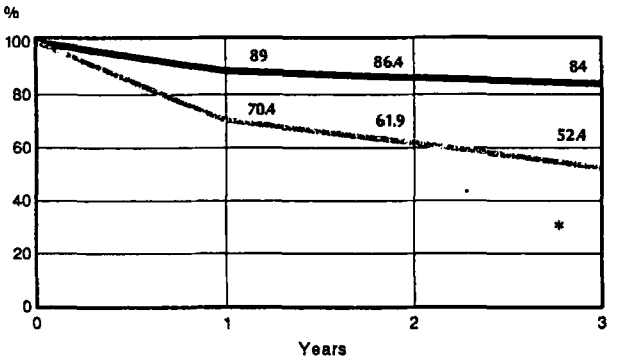

Fig. 2. Patient actuarial survival after liver transplantation. Single graft (■; n = 260) versus regrafted (■; n = 50) patients. *P = 0.0005

treated with methylprednisolone (1 g IV) and steroid recycling. Steroid-resistant rejection was treated with OKT3 therapy in most cases or with antilymphocyte globulin (ALG). Azathioprine (0.5–1 mg/kg) was added to cyclosporin and steroid therapy to maintain immunosuppression after the first rejection [3].

Pretransplant diagnosis categories included: primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), chronic active hepatitis B (CAHB), chronic hepatocellular failure (different than hepatitis B disease; CHF), acute hepatic failure (AHF), and other. Clinical status before the procedure was determined (according to United Network of Organ Sharing criteria) by the place where the patient was being maintained the day before LTx: home (HOME), hospital (HOSP), intensive care unit (ICU), or fulminant hepatic failure (FHF).

Cause of hepatic allograft failure was assigned to one of the following categories: primary nonfunction (PNF), hepatic artery thrombosis (HAT), technical failure (TECH), acute rejection (AR), chronic rejection (CR), and other (OTHER). PNF was defined as graft failure without any other cause (including rejection) within 6 weeks of LTx.

To evaluate the patient's status before the second graft and the timing of retx-influenced graft survival, we divided the patients into two more categories: "elective" retx, if performed during a readmission with the patient waiting at home or in the hospital (n = 23) and "emergency" retx, if performed during the primary transplant admission or during a readmission with the patient waiting in the ICU (n = 27).

For statistical analysis, values are expressed as mean ± standard deviation. Continuous variables were compared using a two-tailed Student's t-test for parametric distributed data, and the Mann-Whitney U-test for nonparametric data. Categorical variables were compared with a χ^2 or Fischer's exact test for sparse data. Actuarial patient and graft survival was calculated using the method of Kaplan-Meier. A P-value of < 0.05 was considered significant.

Results

Causes of hepatic allograft failure were: PNF (n = 10), HAT (n = 10), TECH (n = 3), AR (n = 6, including one case of hyperacute rejection), CR (n = 17), and OTHER (n = 9). This last group included: recurrent hepatitis B (n = 4, one associated with late HAT), "de novo" fulminant hepatitis B (n = 1), lymphoma of the graft (n = 1), graft infection (n = 2), and multiple biliary stricture subsequent to adjuvant radiotherapy after LTx in a patient with cholangiocarcinoma (n = 1).

The frequency of retx according to the previous disease is shown in Fig. 1. PSC patients comprised the highest rate of retx: 12 out of 33 (36.3%; P = 0.001) versus the retx rate of the whole population (16.1%). The rate of ABO identity in the PSC patients (94.1%) was similar to that in the entire group of transplant patients (92.8%). Therefore, the higher rate of graft loss must be explained by mechanisms other than that of ABO matching. Eight of these 12 PSC patients (66.6%) were retransplanted due to CR. This specific subgroup of patients represents 47% of all patients suffering from CR.

The incidence of graft loss according to the initial arterial reconstruction was hepatic-to-hepatic artery: 45 out of 234 LTx (19.2%) and arterial graft-to-aorta: 4 out of 32 LTx (12.5%). Primary hepaticojejunostomy revealed a higher rate of graft loss: 21 out of 74 LTx (28.3%) compared to duct-to-duct reconstruction: 28 out of 210 LTx (13.3%). Arterial reconstruction was achieved initially (in these 50 regrafted patients) by hepatic-to-hepatic artery anastomosis (n = 46) or by iliac graft-to-recipient aorta (n = 4). At retransplantation, 29 patients underwent hepatic-to-hepatic artery anastomosis, but 21 required an iliac graft anastomosed to the aorta. Thus, for the second transplant operation, 17 patients required a different arterial reconstruction than the first.

A parallel pattern was observed with regard to the biliary reconstruction. For the first graft, duct-to-duct anastomosis was performed in 28 patients and Roux-en-Y hepaticojejunostomy in 22. For the second graft, only 18 patients underwent duct-to-duct anastomosis, but 32 Roux-en-Y, so that 10 patients were converted to a different biliary reconstruction during retransplantation.

The Kaplan-Meier analysis of 1- and 2-year actuarial survival demonstrated that more patients receiving a single graft survived (89% and 86.4%) than those who received a regraft (70.4% and 61.9%, P = 0.0005; Fig. 2).

Several intra- and postoperative factors of first graft versus regraft procedures were also compared (Table 1). Length of stay in the ICU was significantly lower for first LTx than for retx (6 ± 12 days vs 12 ± 19 days, P = 0.014). Intraoperative use of blood products and number of reoperations were not different in the two groups. The incidence of rejection was significantly lower for regrafts (39.1%) than for first grafts (59.8%, P = 0.01).

In order to determine what factors impact the decreased survival rate of regrafted patients, the 1- and 2-year graft survival of the second transplant was studied in different ways. The retx graft survival was not influenced by most of the initial pretransplant diagnosis categories:

Table 1. Intraoperative and postoperative aspects of first grafts versus regrafts. PRBC, Packed red blood cells (units); FFP, fresh frozen plasma (units); PLT, platelets (units)

	First graft Mean ± SD	Regraft Mean ± SD	P-value
Intraoperative:			
PRBC	7.9 ±8.3	7.9 ±4.9	NS
FFP	9.9 ±10.9	8.4 ±6.7	NS
PLT	9.4 ±12.1	9.2 ±13.2	NS
Days in ICU	6 ±12	12 ±19	0.014
Reoperations/LTx	0.35 ± 1.19	0.52 ± 1.27	NS
Rejection	59.8%	39.1%	0.01

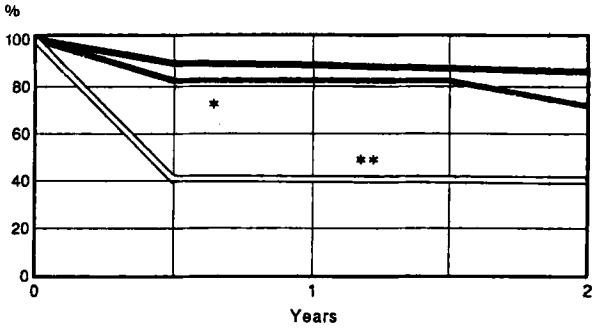

Fig. 3. Graft actuarial survival after liver transplantation. ■ Single graft versus ▩ elective retx versus □ emergency retx. *P = 0.14; **P = 0.005

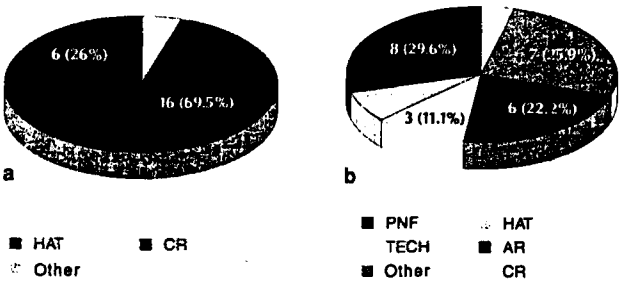

Fig. 4. Causes of retransplantation in **a** elective versus **b** emergency retx. *PNF* Primary nonfunction; *HAT* hepatic artery thrombosis; *TECH* technical failure; *AR* acute rejection; *CR* chronic rejection

PBC (60% and 40%), PSC (66% and 44%), CHF (50% and 50%), AHF (83% and 83%), OTHER (87% and 87%). Nevertheless, patients with previous CAHB showed lower graft survival (30% and 30%) after retx than the rest of the regrafted patients (69% and 57%, P = 0.044, Wilcoxon test).

Clinical status before the first graft did not have any influence on 1- and 2-year regraft survival: HOME: (62% and 54%); HOSP/ICU/FHF: (58% and 44%, NS). Patient status before retx HOSP/ICU/FHF had lower 1- and 2-year survival rates than HOME: (50% and 43% vs 81% and 60%, respectively; P = 0.052). Causes for retransplantation were analyzed, each one being compared to the rest. None except HAT showed statistically significant differences on 1st year graft survival: PNF (50%), HAT (100%, P = 0.025), TECH (33%), AR (33%), CR (81%), and OTHER (22%). Twenty-four patients were retransplanted early (within 90 days of the initial LTx) and 21 were retransplanted late (3–18 months after the first graft placement). Early retx also had a lower 1-year survival rate than late retx (54% vs 68%), but the difference was not statistically significant.

Table 2. Intraoperative and postoperative aspects of "elective" versus "emergency" retransplantation

	Elective Mean ± SD	Emergency Mean ± SD	*P*-value
Intraoperative:			
PRBC	6.6 ± 4.5	9.1 ± 5.1	NS
FFP	5.7 ± 4.9	10.8 ± 7.3	0.026
PLT	1.7 ± 5.7	16.2 ± 14.3	0.0001
Days in ICU	2 ± 4	21 ± 23	0.0001
Reoperations	17.3% (4/23 pt)	28% (7/25 pt)	NS
Mortality (3 months)	8.7% (2/23)	51.8% (14/27)	0.001

Actuarial survival of the "elective" and "emergency" retx pairs was compared with single-graft survival. Elective retx 1- and 2-year graft survival was similar to single graft replacement: 82% and 72% vs 89% and 86%. Yet, emergency graft survival was significantly lower (40%, P = 0.0001 vs single graft, P = 0.005 vs elective; Fig. 3). Morbidity and mortality within 3 months of LTx were also higher for emergency than for elective retx (Table 2).

Looking into the causes of retx in these two different categories, we found that the main causes for elective retx were CR (n = 16; 69.5%) and late complications of HAT, such as biliary stricturing with hepatic abscess formation (n = 6; 26%). Causes of emergency retx were primarily PNF (n = 9; 33.3%), early HAT producing acute graft failure (n = 4; 14.8%), AR (n = 6; 22.2%), and OTHER (n = 7; 25.9%), including four cases of recurrent hepatitis B disease (Fig. 4).

Discussion

Several authors have reported on the different ascpects, indications, and survival rates of liver retx [1, 6, 13]. These previous reports indicate that retx is usually a simpler technical procedure because the dissection required in the recipients is considerably less and because portal hypertension is practically absent in all cases. We found this to be true, especially when the retx was performed shortly after the first LTx had been done. Yet, the scarring found during late retx was not an important technical obstacle. The percentages of retx survival described initially [7, 10] were significantly lower (30%–50%) than those corresponding to the first LTx. Shaw and Wood [9] recently described a 1-year success rate of 71% in a group of retx patients that included both pediatric and adult LTx, but even in that study, the survival rate for adult retx was only 53%. To our knowledge, no previous studies have attempted to determine the specific causes of a higher mortality for liver retx than for single grafts.

Our study confirms that liver retx has a higher morbidity and mortality rate than a first graft has. To our surprise, we found that the rejection rate was significantly lower for second grafts than for first LTx. This finding has not been described before and may be attributable to the pre-retx immunosuppression.

The specific studies on the group of retransplanted patients yielded some interesting conclusions, primarily that "elective" and "emergency" liver retx may be considered two completely different concepts. Elective retx behavior is similar to that of first LTx in terms of graft survival, intraoperative use of blood products, length of stay in the ICU, and number of reoperations. Emergency retx demonstrates lower actuarial survival and higher use of intraoperative blood products (fresh frozen plasma and platelets). Length of stay in the ICU and 3-month

mortality rate are also significantly higher. This increase is probably related to the fulminant liver failure in these patients, who have a significantly deranged coagulation system. Therefore, the higher morbidity and mortality of the whole liver regrafting group may be directly attributed to the number of emergency retx. In other words, an efficient way to improve the outcome after retx must be the treatment or modification of the underlying cause of graft failure that transforms an emergency retx into a later elective one.

A good example of this is our approach and management of HAT, a serious complication that often produces acute graft failure. Early aggressive management of HAT (if Doppler ultrasound is done routinely, as in our series) can dramatically change the prognosis of that complication. In fact, of eight patients who had early HAT with thrombectomy and subsequent revascularization, only three required retx due to late complications of HAT, such as bile duct strictures and hepatic abscesses [8]. This policy permitted the second graft operation on an elective basis rather than in an "emergency" situation due to acute graft failure. A similar observation has recently been reported by the Omaha group [4].

PNF is probably the single most common cause of early retx. Whether UW solution will reduce the incidence of this complication remains to be seen. Methods that predict viability of the graft (as plasma levels of MEGX, a lidocaine metabolite produced by the liver [2]) may also contribute to reducing the number of PNF and, subsequently, the number of emergency retx.

We conclude that an elective retx may be as safe as a first LTx. The higher morbidity and mortality rate incurred by emergency retx may be reduced by early diagnosis and treatment of complications such as HAT or AR.

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