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Liver retransplantation in children. A 21-year single-center experience*

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Summary

In this study, the epidemiology and outcome of graft loss following primary pediatric liver transplantation (LT) were analysed, with the hypothesis that early retransplantation (reLT) might be associated with lower immunologic risks when compared with late reLT. Between March 1984 and December 2005, 745 liver grafts were transplanted to 638 children at Saint-Luc University Hospital, Brussels. Among them, a total of 90 children (14%) underwent 107 reLT, and were categorized into two groups (early reLT, $n = 58$; late reLT, $n = 32$), according to the interval between either transplant procedures (< or >30 days). Ten-year patient survival rate was 85% in recipients with a single LT, vs. 61% in recipients requiring reLT ($P < 0.001$). Ten-year patient survival rates were 59% and 66% for early and late reLT, respectively ($P = 0.423$), the corresponding graft survival rates being 51% and 63% ($P = 0.231$). Along the successive eras, the rate of reLT decreased from 17% to 10%, whereas progressive improvement of outcome post-reLT was observed. No recurrence of chronic rejection (CR) was observed after reLT for CR (0 of 19). Two children developed a positive cross-match at reLT (two of 10, 20%), both retransplanted lately for CR secondary to immunosuppression withdrawal following a post-transplant lymphoproliferative disease. In summary, the results presented could not evidence better results for late reLT when compared with early reLT. The former did not seem to be associated with higher immunologic risk, except for children having withdrawal of immunosuppression following the first graft.

Introduction

In pediatric liver transplantation (LT), the past two decades were characterized by significant progresses in surgical techniques, intra- and postoperative management, as well as immunosuppressive regimens, with correspondingly improved outcomes and quality of life after LT [1–3]. Despite these achievements, graft failure is still encountered in a variety of situations, essentially technical or immunologic complications. In such instances, retransplantation (reLT) constitutes the only chance of survival, with reLT rates of published series having varied between 12% and 29% [3–7]. Following reLT, however, lower patient and graft survival rates are reported [7]. So far, most published pediatric series reporting on reLT particularly analysed the etiologies of primary graft losses as well as the prognostic value of pre-reLT parameters [1,8]. In this study, the reLT series at Saint-Luc University Hospital was reviewed with the specific aim to compare early reLT (<30 days after a first LT) and late reLT (>30 days), with respect to the hypothesis that the former might be associated with a reduced incidence of anti-human leukocyte antigen (HLA) immunization (related to a shorter exposure to histocompatibility antigens of the primary allograft). Accordingly, the epidemiology, immunologic parameters

and outcome of pediatric reLT were analysed in order to clarify this issue.

Patients and methods

Study population

Between March 1, 1984 and December 31, 2005, a total of 745 liver grafts were transplanted to 638 children (age <15 years) at the Saint-Luc University Hospital, Brussels, Belgium. Among them, 90 children (14%) underwent 107 reLT during this period: 76 children (84%) were retransplanted once, 11 children (12%) received two reLT, and three children (3%) received three reLT each. Only the 90 first reLTs (secondary LTs) were studied in this study, and were categorized into two groups: early reLTs or late reLTs, defined as reLTs performed before and after the first 30 days of the initial transplantation, respectively. Pediatric end-stage liver disease (PELD) score was calculated at pre-reLT assessment by computation of total bilirubin, albumin, international normalized ratio (INR), age and growth retardation [9]. The PELD score was available for only 31 children (16 early reLTs, 15 late reLTs) among the 90 retransplanted children of the study because of INR availability only after 1996 at our center, and the impossibility to reconstruct an INR value from prothrombin time data. All data were obtained by retrospective review of inpatient and outpatient records. This study was approved by the research ethics board of the institution.

Surgical techniques

The technical details of the whole, reduced-size and split liver grafts retrieved from deceased donors, as well as of left hepatic lobe retrieved from living donors were previously reported [10,11]. In brief, in reduced-size grafts, the donor liver underwent a partial resection on a bench table, which discarded the right lobe and preserved either the left lateral segment (segments 2 and 3) or the full left lobe (segments 2, 3, and 4); split grafts were obtained by division of the liver parenchyma and of the vascular and biliary pedicles to obtain two grafts, the larger right lobe being transplanted into an adult recipient and the left lateral segment into a child. The liver grafts were allocated by EuroTransplant using an allocation system taking into account waiting times as well as medical urgency [12]. The operation in the living-related donor included an intraoperative cholangiogram to define the biliary duct anatomy of the donor and consisted in the procurement of either segments 2 and 3, or the entire left liver, according to the recipient size [11]. All retransplanted children received in each case a deceased donor liver graft. The liver graft hepatectomy included a total excision of the hepatic vein patch of the first donor, except in two cases where a caval cuff of the first graft was kept for implantation of the second transplant. No veno-venous bypass was used in the reLT cases.

Post-transplant management and immunosuppressive protocols

The general postoperative management has been previously described [13]. Regarding the immunosuppression practices at primary LTs, a triple-drug regimen including cyclosporine, steroids and azathioprine was used until mid 1997, after which a double immunosuppression regimen was administered, consisting of tacrolimus and steroids. More recently, from 2001 onwards, a steroid-free protocol has been used, combining tacrolimus and basiliximab [14]. Except that a steroid-free regimen was never used in reLTs, no specific immunosuppressive protocol was used, with the exception of chronic rejection (CR) where tacrolimus was used since mid 1991. The diagnostic criteria of CR were used as previously published (clinical and biochemical cholestasis, associated with a histologic picture of bile ducts loss in more than 50% of portal triads). No specific immunosuppressive protocol was used in case of presence of anti-HLA antibodies prior to reLT or in case of positive T-cell cross-match at reLT.

Statistical methods

Numeric variables were expressed as median and range, and were compared between groups by the Mann–Whitney test. Chi-squared tests were used for comparing categorical variables. The Kaplan–Meier method was used for assessing graft and patient survival rates, and the log-rank test was used to compare these rates between groups. A *P*-value below 0.05 was considered statistically significant. The analyses were performed with the SPSS 11.5 (SPSS Inc, Chicago, IL, USA) statistical software.

Results

Overall results

The patient survival rates at 5 and 10 years in recipients with a single LT were 86% and 85% respectively versus 66% and 61% respectively in recipients with multiple LTs ($P < 0.001$; Fig. 1). As shown in Table 1, the rate of reLT decreased from 17% to 10% according to transplant eras. In parallel, the survival of patients requiring reLT was improved along the transplant eras, as shown in Fig. 2. The patient survival rates at 5 years were 54%, 61%, 85%, and 83% for patients requiring reLTs 1984–1989, 1990–1994, 1995–1999, and 2000–2005, respectively. The rate of reLTs was significantly lower for children who received a living-related donor graft when compared with children

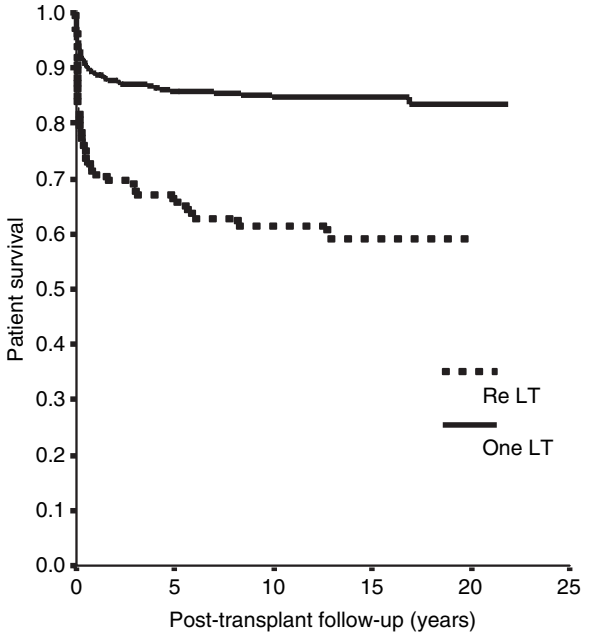

Figure 1 Patient survival in liver recipients with single versus multiple liver transplantations, in a series of 638 pediatric liver recipients, transplanted between March 1, 1984 and December 31, 2005. The actuarial patient survival rates at 5 and 10 years in recipients with a single transplant were 86% and 85%, vs. 66% and 61% in recipients requiring retransplantation (reLT) ($P < 0.001$).

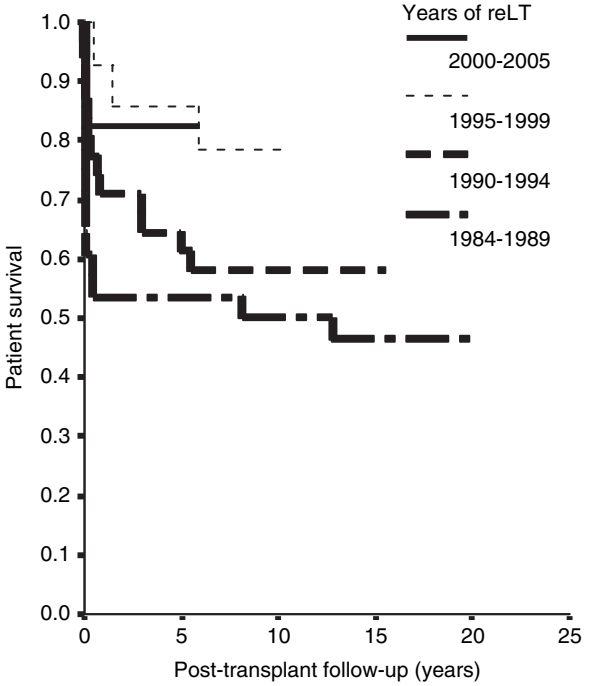

Figure 2 Patient survival following retransplantation according to transplant eras, in a series of 638 pediatric liver recipients, transplanted between March 1, 1984 and December 31, 2005. The rate of retransplantation decreased from 18% to 6% along the transplant eras ($P = 0.1218$).

Table 1. Rate of retransplantation according to transplant eras, in a series of 638 pediatric liver recipients, transplanted between March 1, 1984 and December 31, 2005 ($P = 0.03$).

Transplant eras	Primary LT (*n*)	reLT (*n*)	reLT rate (%)	Early reLT (*n*, %)	Late reLT (*n*, %)	Early reLT/late reLT
1984–1989	165	28	17	22 (13)	6 (4)	3.6
1990–1994	194	31	16	20 (10)	11 (6)	1.82
1995–1999	126	16	13	8 (6)	8 (6)	1
2000–2005	153	15	10	8 (5)	7 (5)	1.14

LT, liver transplantation; reLT, liver retransplantation.

Table 2. Rate of retransplantation according to the type of graft at first transplantation, in a series of 638 pediatric liver recipients, transplanted between March 1, 1984 and December 31, 2005 ($P = 0.01$).

Type of graft	Primary LT (*n*)	reLT (*n*)	reLT rate (%)
Whole	228	35	15
Reduced-size	213	44	20
Split	57	7	12
Living donor	140	4	3

LT, liver transplantation; reLT, liver retransplantation.

who received a whole, a reduced-size or a split liver as first transplantation ($P < 0.001$; Table 2).

Early versus late retransplantation

Among the retransplanted children, 58 (64%) required early reLT, and 32 (36%) late reLT. The ratio between early and late reLT varied according to transplant eras (Table 1). The median age at first LT for early and late reLT was 1.9 years (range 0.3–12.9) and 2.9 years (range 0.5–14.5), respectively. The median interval between first and second LT in groups with early and late reLT was 4 days (range 1–30) and 711 days (range 41–6529), respectively. The median age at second LT was 2.0 years (range 0.3–12.9) in the group with early reLT, and 6.4 years (range 1.6–2.2) in the group with late reLT. Diagnoses at first LT were biliary atresia (67% in the group with early reLT, and 66% in the group with late reLT), cholestatic diseases (9% and 16%), fulminant hepatic failure (9% for both groups), and miscellaneous indications (15% and 9%). As detailed in Table 3, the most common indications of reLT in the group with early reLT were primary nonfunction (40%), hepatic artery thrombosis (HAT, 33%), and portal vein thrombosis

Table 3. Indications for early and late retransplantation, in a series of 638 pediatric liver recipients, transplanted between March 1, 1984 and December 31, 2005.

Early reLT (*n* = 58)	Late reLT (*n* = 32)
PNF (*n* = 23, 40%)	CR (*n* = 19, 59%)
HAT (*n* = 19, 33%)	HAT (*n* = 5, 16%)
PVT (*n* = 9, 15%)	Biliary complication* (*n* = 4, 13%)
Budd Chiari (*n* = 3, 5%)	Immune cirrhosis (*n* = 2, 6%)
Biliary complication* (*n* = 2, 3%)	Hepatitis C cirrhosis (*n* = 1, 3%)
Fulminant hepatic failure (*n* = 1, 2%)	PTLD† (*n* = 1, 3%)
Viral infection (*n* = 1, 2%)	

Early and late retransplantations were defined according to the time interval between the first and secondary transplants (< or >30 days, respectively).
reLT, liver retransplantation; PNF, primary nonfunction; HAT, hepatic artery thrombosis; PVT, portal vein thrombosis; CR, chronic rejection; PTLD, post-transplant lymphoproliferative disease.
*Biliary complications were first treated by surgery or radiology, the decision to perform retransplantation was for secondary biliary cirrhosis caused by long-term failure of treatment.
†This child was retransplanted for an isolated localization of lymphoma into the graft.

Table 4. Indications for early retransplantation according to transplant eras, in a series of 638 pediatric liver recipients, transplanted between March 1, 1984 and December 31, 2005.

	Transplant eras			
	1984–1989 (*n* = 22, %)	1990–1994 (*n* = 20, %)	1995–1999 (*n* = 7, %)	2000–2005 (*n* = 9, %)
PNF	11 (50)	8 (40)	2 (29)	2 (22)
HAT	5 (23)	10 (50)	2 (29)	2 (22)
PVT	2 (9)	2 (10)	2 (29)	3 (33)
Budd Chiari	1 (4)	0	0	2 (22)
Biliary complication	1 (4)	0	1 (14)	0
Fulminant hepatic failure	1 (4)	0	0	0
Viral infection	1 (4)	0	0	0

Early retransplantation was defined according to the time interval between the first and secondary transplants (<30 days).
PNF, primary nonfunction; HAT, hepatic artery thrombosis; PVT, portal vein thrombosis.

(PVT, 15%). Indications of early reLT varied over time according to transplant eras, as shown in Table 4. The main indication of late reLT was CR, as observed in 59% of the cases (Table 3). The median PELD score at reLT was 20.5 for children with early reLT compared with 13.4 for children with late reLT. Patient survival rates at 5 and 10 years following early reLT were 63% and 59%, respectively, compared with 70% and 66% following late reLT ($P = 0.423$) (Fig. 3). Graft survival rates at 5 and 10 years following early reLT were 53% and 51%, respectively, when compared with 63% and 63% following late reLT ($P = 0.231$) (Fig. 3).

HLA immunization

T-cell cross-matches at both primary LT and reLT were available in 53 cases, 31 in the group with early reLT and 22 in the group with late reLT. Three of the 31 T-cell cross-matches available in the group with early reLT were positive at the first LT (three of 31, 10%); among the 28 negative cross-matches at the first LT, three showed a positivation at reLT (three of 28, 11%). One of the 22 T-cell cross-matches available in the group with late reLT was positive at the first LT (one of 22, 5%); among the 21 negative cross-matches at the first LT, three showed a positivation at reLT (three of 21, 14%). A CR occurred in 19 cases of the 638 primary transplants (19/638, 3%); among them, 15 were primary CR and four were CR secondary to immunosuppression withdrawal for post-transplant lymphoproliferative disease (PTLD). All reLT for CR were in the group with late reLT (Table 3). The 5, 10, 15, and 20 years actuarial survival rates free from graft loss caused by rejection were 96.78%, 96.48%, 95.56%, and 94,49%, respectively. No recurrence of CR on the secondary transplant was observed after reLT for CR on the first graft (0 of 19). Among the 19 children retransplanted for CR, T-cell cross-matches at both primary LT and reLT were available for 10 children, including three secondary CR. Two of them developed a positive T-cell cross-match at reLT (two of 10, 20%) both retransplanted for CR secondary to immunosuppression withdrawal in the context of PTLD (two of three, 67%). No positivation of the cross-match at reLT was observed for children retransplanted with primary CR under continued immunosuppression until reLT (0 of 7, 0%).

Discussion

Despite advances in surgical techniques, immunosuppressive regimens, and postoperative care, graft loss after pediatric LT remains a significant problem. In this study, during a 21-year experience a reLT rate of 14% was observed, a rate comparable with other reports of pediatic LT series [4–6]. As observed in this study (Fig. 1), patient and graft survival rates after secondary LT are indeed inferior to those after single grafting. Accordingly, in the context of organ shortage, reLT inevitably denies organs to recipients of primary grafts. However, despite its inferior results, reLT should be considered as a useful rescue measure which cannot be denied solely on the basis of

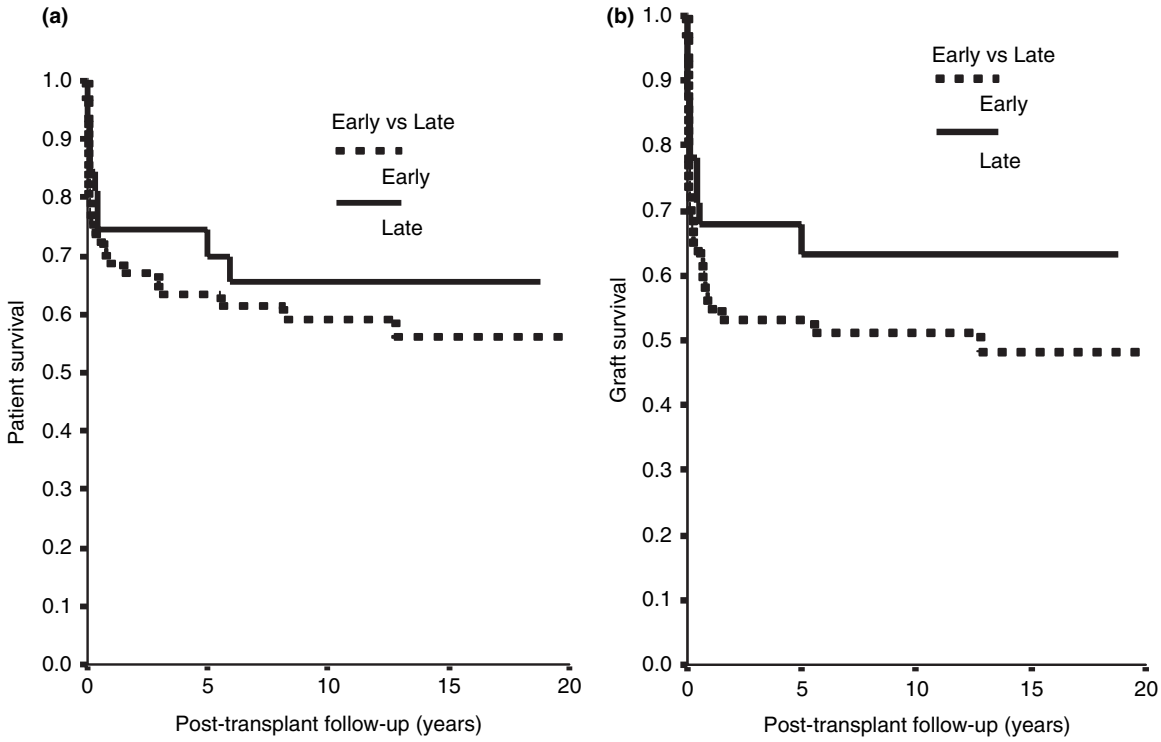

Figure 3 (a) Patient survival following early (<30 days after first transplant) versus late (>30 days) retransplantation, in a series of 638 pediatric liver recipients, transplanted between March 1, 1984 and December 31, 2005. The actuarial patient survival rates at 5 and 10 years were 63% and 59% after early retransplantation, vs. 70% and 66% after late retransplantation ($P = 0.423$). (b) Graft survival following early versus late retransplantation, in a series of 638 pediatric liver recipients, transplanted between March 1, 1984 and December 31, 2005. The actuarial graft survival rates at 5 and 10 years were 53% and 51% after early retransplantation vs. 63% and 63% after late retransplantation ($P = 0.231$).

utilitarian considerations. This study showed that reLT rate has been decreasing along the successive transplant eras, probably as a result of adequate donor selection, and also attributable to progressive refinements of the surgical techniques, and to optimization of the immunosuppressive regimen. As shown in this study, the patient survival after reLT was also improved along the transplant eras (Fig. 2), the slightly lower results in modern eras observed in this study could be related to the use of donation after cardiac death.

The stratification of the indications of early reLT varied over time according to transplant eras (Table 4), it should be mentioned that in some case the indication was held on the basis of a combination of complications rather than an isolated one. Nevertheless, this study identified that the major indications of early reLT were technical complications (Table 3). The prevention of early reLT essentially has implied, in a technical sense, prevention of both vascular complications, such as HAT and PVT, and biliary complications. The prevention of HAT has benefited from the introduction of semi-microsurgical technique and intraoperative Doppler assessment of vascular patency [11]. Portal thrombosis caused by portal vein hypoplasia can be prevented by using venoplasty or jump grafts [11]. Prevention of biliary complications such as intrahepatic biliary duct strictures can also be achieved by reducing both total ischemic time and HAT incidence. Graft disease, and particularly CR, constituted the main indication for late reLT in 59% (Table 3). It was previously published that CR can be prevented in pediatric recipients of a primary liver transplant who are maintained on tacrolimus-based immunosuppression [15,16]. Such immunosuppressive protocol, by reducing CR incidence, could also contribute in the prevention of late reLT. The ratio between early and late reLT varied according to transplant eras, the number of early reLT was reduced in the last two eras according to progressive refinements of the surgical techniques, and to optimization of the immunosuppressive regimen. Following the results presented in this study, early reLT patient and graft survival were poorer than late reLT survivals although this difference did not reach the statistical significance. A recently published multicenter study showed significantly better survival for patient who underwent late reLT when compared with early reLT [17].

Moreover, the hypothesis that late reLT might represent an additional immunologic risk because of the longer exposure of the recipient to graft allogenic antigens could

not be confirmed in this study, which showed that the risk of anti-HLA immunization between first and reLT did not seem to be significantly higher after late reLT. Similarly, the results presented do not suggest that reLT for CR is associated with significant risk of CR recurrence. The only situation associated with an apparently increased risk of anti-HLA immunization (T-cell cross-match positivation) seems to be CR occurring in the context of PTLD and immunosupression withdrawal. Among the 10 children retransplanted for CR with T-cell cross-match available, two (20%) developed anti-HLA immunization, both retransplanted for CR secondary to immunosuppression withdrawal in the context of PTLD (two of three, 66.7%). This observation suggests that anti-HLA immunization may be maximal when immunosuppressive coverage is not maintained, allowing the recipient to mount an immune response against donor antigens. It could be also useful to continue and even to resume some immunosuppressive therapy in pre-reLT period in order to prevent anti-HLA immunization. In renal transplantation, post-transplant detectable anti-HLA, and particularly class II-reactive alloantibodies, are risk factor for CR [18]. In contrast, the adverse effect of an anti-HLA immunization in LT is not clearly supported by the literature. Nevertheless, a previous multivariate analysis from our group on a large population size showed that a positive T-cell cross-match independently impacts on acute rejection free graft survival [19].

In conclusion, this study showed that the need for reLT has been decreasing over the years, with progressive improvement of reLT outcomes. However, reLT results remain poor when compared with outcomes of children receiving a single transplantation. Even if patient and graft survivals of patient retransplanted late seems better than those retransplanted early, the results presented could not evidence statistically significant differences. It was also shown that late reLT do not confer higher immunologic risk, except in case of immunosuppression withdrawal in the context of PTLD.

Authorship

CB and AB performed study, collected data and analysed data. MJ and CdM contributed to data collection. JBO and ES contributed to clinical following of the patients. RR designed study. CB and RR also helped in preparing the manuscript.

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