The pediatric liver transplant program at the Université Catholique de Louvain, Cliniques Saint-Luc, Brussels : Overall results in 444 children (1984-1997)

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Abstract

Between 1984 and 1997, a total of 444 children (< 15 years) received an orthotopic liver transplant (OLT) at Saint-Luc University Clinics. Biliary atresia constituted the indication for OLT in 304 cases (68%). Median age (range) at OLT was 2.1 years (0.3-14.5). 177 children (40%) received a whole liver graft, 184 (41%) a reduced-size graft, 26 (6%) a split liver graft, whereas a living-related donor graft was used in 57 children (13%). Most grafts were ABO-identical or -compatible, in 395 cases (89%) and 40 (9%), respectively. Overall actuarial patient survivals at one and five years were 85% and 81%. The overall retransplantation rate was 19%. The results of uni- and multivariate statistical analyses showed a significant impact of year of transplantation (learning curve effect), with a 15% improvement of patient survival between the 1984-7 and the 1995-7 periods ($p < 0.002$). Results differed according to the indications for OLT, the best survivals being recorded for familial cholestasis, the worst for liver tumor ($p = 0.004$). Five year patient survival was significantly better after elective OLT (82%), when compared to highly urgent OLT (63%) ($p < 0.001$). Patient survivals were comparable in the children receiving primary cyclosporin-A microemulsion or tacrolimus immunosuppression, which were significantly higher than in the historical group treated with cyclosporin-A. No impact of the age at OLT, type of graft and ischemic time could be reported. In conclusion, this series illustrates the progressive improvements introduced in our pediatric liver transplant program between 1984 and 1997, including the technical variants allowing pediatric OLT using adult donors as well as the introduction of new immunosuppressive strategies. (Acta gastroenterol. belg., **1999**, 62, **285-289**).

Key words : pediatrics, liver transplantation, survival analysis, risk factors.

Introduction

The first pediatric orthotopic liver transplantation (OLT) in continental Europe was performed at the University Hospital of Louvain in March 1971 (1). The indication of this 17-month-old child was biliary atresia, and he survived for 7 weeks before dying of hemorrhage related to a liver biopsy. The liver transplant program was reactivated at our center in 1984, considering the progress achieved in the early eighties in many disciplines involved in OLT, which brought it from the experimental field to standard clinical application. The complex care of children with preterminal liver failure challenged our pediatric, anesthetic, and surgical skills, and the OLT program in children was developed in a specific pediatric environment, which generated several innovations up to December 1997. This paper summarizes the overall results of the Pediatric Liver Transplant Program at Saint-Luc University Clinics during this interval, emphasizing particularly the impact of several risk factors specific to OLT in children.

Patients and methods

Between April 1984 and December 1997, a total of 444 children (< 15 years old) received 528 liver grafts at Saint-Luc University Clinics. The primary indications for OLT according to the age at transplantation are given in Figure 1. As detailed in Table I, the main indication was biliary atresia, in 304 children (68%), followed by the heterogeneous group of metabolic diseases in 41 children (9%), with a pathological liver (α-1-antitrypsin deficiency : n = 7 ; Wilson's disease : n = 8 ; tyrosinemia : n = 6 ; glycogenoses : n = 3 ; hemochromatosis : n = 1), or a normal liver except the specific metabolic defect (Crigler-Najar's disease : n = 7 ; hyperoxaluria : n = 6 ; miscellaneous : n = 3). The donor and the recipient were ABO-identical in 395 cases (89%), ABO-compatible in 40 cases (9%), and ABO-incompatible in 9 cases (2%). Regarding the type of liver graft, cadaveric liver were implanted in 387 cases, whereas 57 children received a living-related donor graft, this latter program being activated since July 1993 (fig. 2) (2-4). The first cadaveric donor graft was a whole-size liver in 177 cases, a reduced-size liver

Table I. — **Pretransplant diagnosis, age at transplantation and 5-year patient survival in 444 pediatric liver recipients grafted at Saint-Luc University Clinics between April 1984 and December 1997**

Diagnosis	n (%)	Median age/OLT	5 year pat. surv.
Biliary atresia	304 (68%)	1.5 y	82%
Metabolic disease	41 (9%)	4.1 y	85%
Familial cholestasis	28 (6%)	4.1 y	96%
Fulminant hepatitis	24 (6%)	3.6 y	71%
Ductular paucity	19 (4%)	3.5 y	68%
Liver tumor	8 (2%)	8.3 y	33%
Other cirrhoses	20 (5%)	7.4 y	74%

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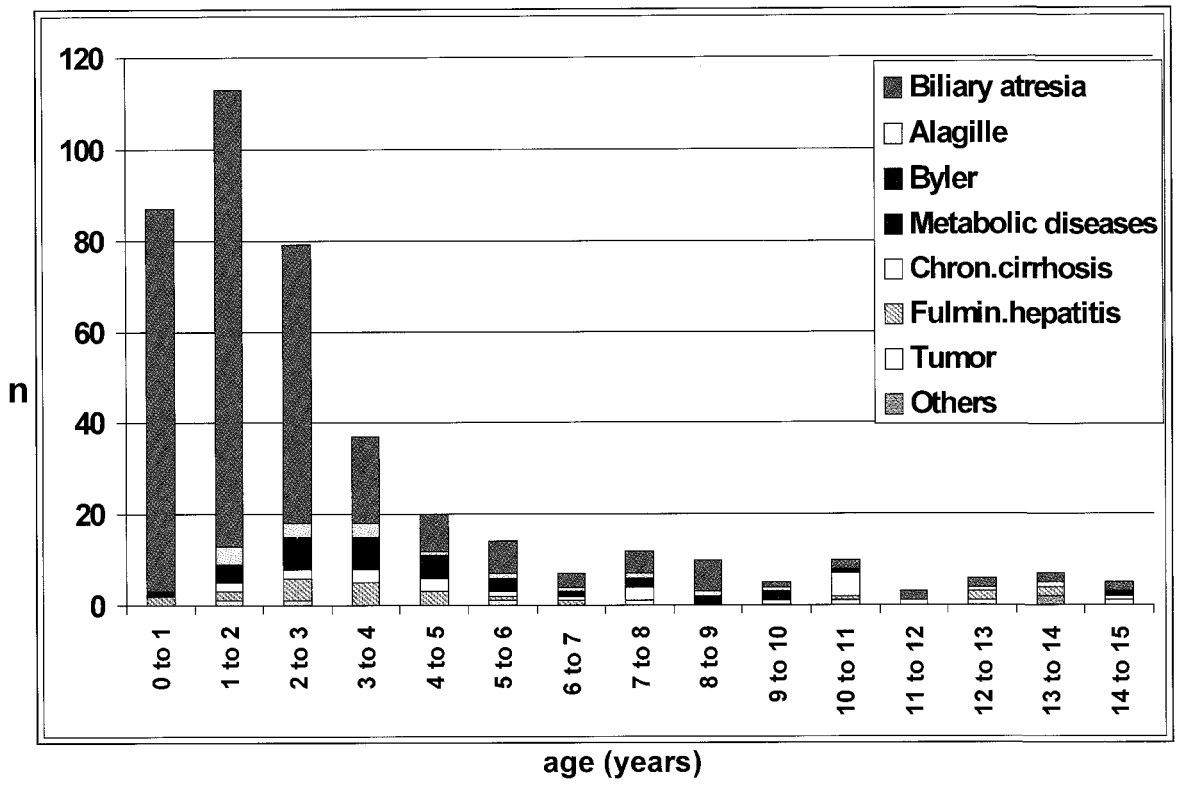

Fig. 1. — Pretransplant diagnosis according to the age at transplantation, in 444 pediatric liver recipients, grafted at Saint-Luc University Clinics between April 1984 and December 1987.

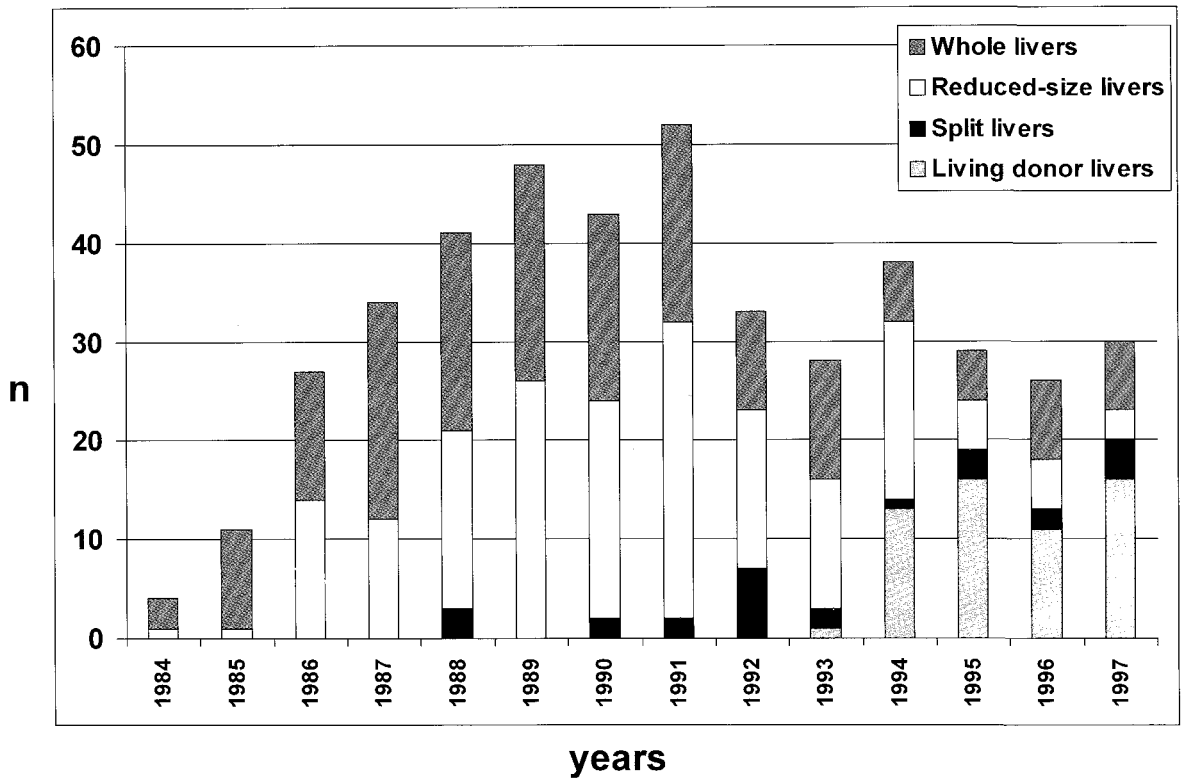

Fig. 2. — Liver transplant techniques according to the year of transplantation in 444 pediatric liver recipients, grafted at Saint-Luc University Clinics between April 1984 and December 1987.

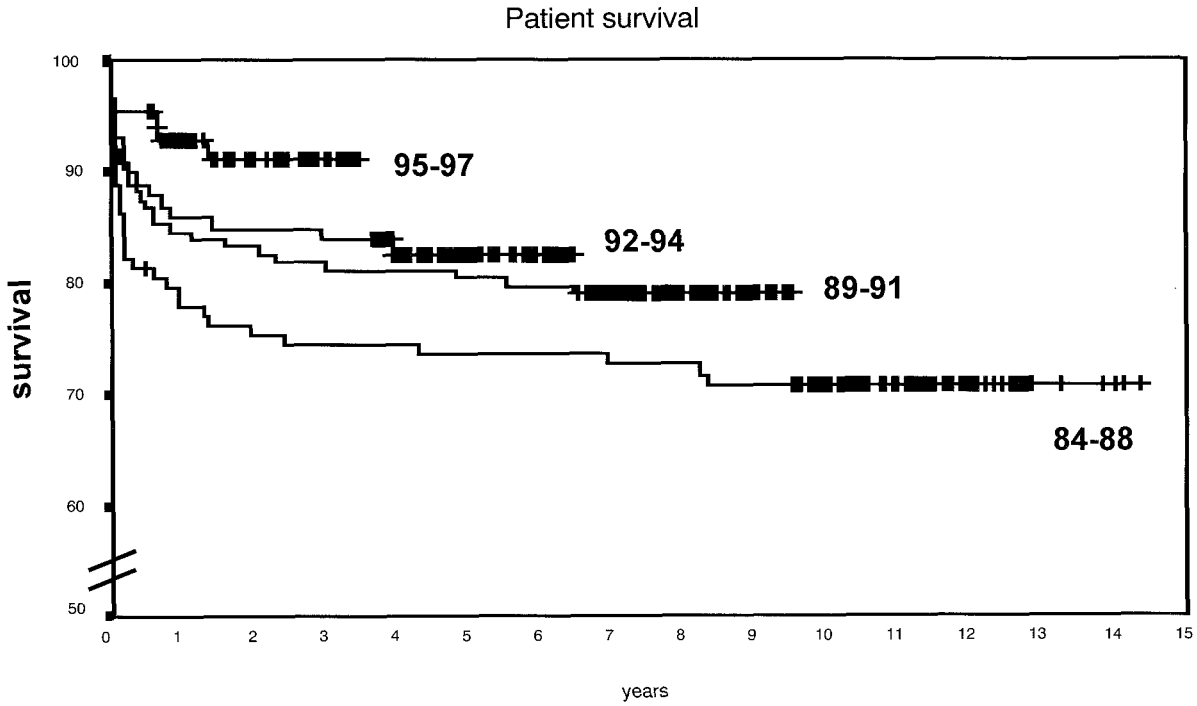

Fig. 3. — Actuarial patient survival curves according to era of transplantation in 444 pediatric liver recipients, grafted at Saint-Luc University Clinics between April 1984 and December 1987.

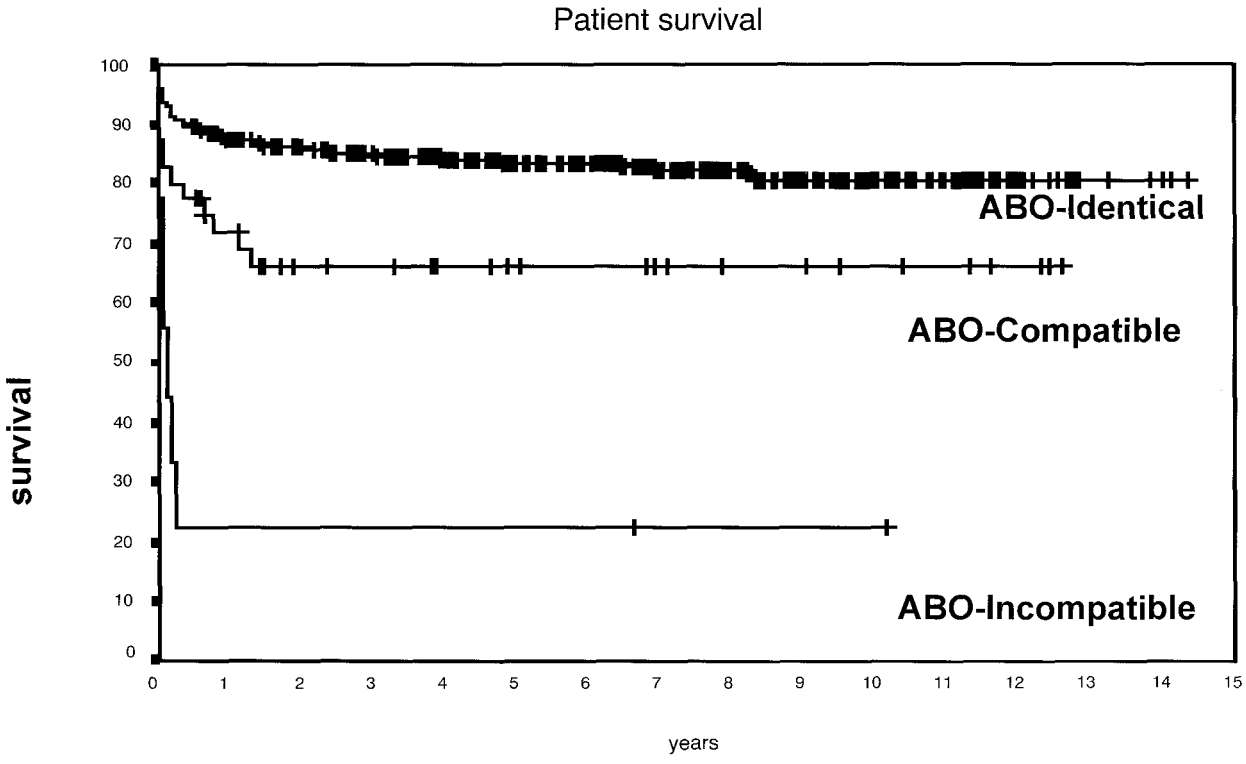

Fig. 4. — Actuarial patient survival curves according to donor-recipient ABO matching in 444 pediatric liver recipients, grafted at Saint-Luc University Clinics between April 1984 and December 1987.

in 184 cases, and a split liver in 26 cases. Primary immunosuppression consisted of cyclosporin-A (n = 344), cyclosporin-A microemulsion (n = 44), and tacrolimus (n = 54) ; it also included azathioprine and/or poly/monoclonal anti-T cell antibodies in 360 and 68 children, respectively (5,6). The median (range) follow-up period of survivors on June 30, 1998 reached 6.9 years (0.5-14.3).

Uni- and multivariate analyses were carried out to identify which of the following risk factors were independently correlated with patient survival : pre-transplant diagnosis, age at OLT, elective/urgent status, donor-recipient ABO group matching, sex matching, total graft ischemic time, type of graft (surgical technique), primary immunosuppression, and era of transplantation.

Results

Overall patient and first graft survival rates were 85% and 76% at one year, 81% and 70% at five years, and 78% and 69% at ten years post-OLT, respectively. The retransplantation, chronic rejection and lymphoproliferative disease rates were 16%, 3%, and 8%, respectively. The results of univariate statistical analyses showed : (1) a progressive improvement of patient survival along the years, with a one year survival at 78% in the 84-88 interval versus 93% in the 95-97 interval ($p = 0.003$) (fig. 3) ; (2) better patient survival rates to be expected for familial cholestasis, metabolic diseases, and biliary atresia, with five year patient survivals above 80% for all three pretransplant diagnoses ($p = 0.004$) (table I) ; (3) the lack of significant impact of total ischemic time and donor-recipient sex matching on patient survival ; (4) the negative impact of non-ABO identity between donor and recipient ($p < 0.001$) (fig. 4), as well as of OLT in highly urgent recipients ($p < 0.001$) ; (5) patient survivals comparable in the children receiving primary cyclosporin-A microemulsion or tacrolimus immunosuppression, which were significantly higher than in the historical group treated with cyclosporin-A ($p = 0.001$) ; in contrast, no advantage in terms of patient survival was associated with the use of azathioprine, or of poly/monoclonal anti-T cell antibodies. The multivariate analysis identified the following covariates as independently correlated with patient survival : pretransplant diagnosis, emergency status at OLT ($p = 0.003$), donor-recipent ABO-matching ($p = 0.001$), and era of transplantation ($p = 0.020$) ; all other risk factors were not independently correlated with patient survival, including the patient age at OLT, the type of liver graft, and the type of primary immunosuppression.

Discussion

The first pediatric OLT of the cyclosporin A era at Saint-Luc University Clinics was performed in April 1984 and, since then, one year patient survival significantly increased from 78% for OLT done in the 84-87 interval, to 93% for the 95-97 interval (fig. 3). This learning curve effect reflects the general improvement of the pre-, intra- and post-operative management of the transplanted children, as in all centers with a significant activity ; it includes the recruitment of a pediatric hepatologist and a clinical and donor transplant coordinator dedicated to the pediatric program, the availability of a pediatric liver unit from 1990, as well as several improvements regarding the operative technique (Argon beam coagulator, intra-operative arterial and portal flowmetry and echodoppler), and introduction of new immunosuppressants (tacrolimus, cyclosporin-A microemulsion, mycophenolate mofetil).

The relatively large number of pediatric OLT studied in this work allowed us to carry out uni- and multivariate analyses in order to identify the impact of several risk factors on patient survival. These analyses clearly demonstrated that the pediatric liver recipient should be transplanted early enough in a still preserved clinical condition (even below one year and using a technical variant), than wait until a size-matched whole graft is available, with the risk of clinical deterioration and mortality on the waiting list, and of poor post-transplant outcome. The current context of worsening cadaveric organ shortage lead us to initiate and develop a program of living related donor transplantation which constitutes for the pediatric recipients a unique opportunity to escape the uncertainty of the waiting time on the cadaveric list. The data recently collected at our center confirmed a higher pretransplant mortality rate for children registered on the cadaveric waiting list, when compared with that in the living donor program (7). Such program should be developed according to a precise ethical protocol, particularly regarding donor and recipient selection, informed consent, and regular audit of the clinical results (3). Within such a framework, the living donor liver transplant program can represent a stimulating "driving force" with a positive impact on the pediatric liver transplant activity of a given center.

References

1. OTTE J.B., DE VILLE DE GOYET J., REDING R., VAN OBBERGH L., VEYCKEMANS F., CARLIER M.A., DE KOCK M., CLEMENT DE CLETY S., CLAPUYT P., SOKAL E., LERUT J., DELBEKE I., DIERICK V., JANSSEN M., ROSATI R., LIBERT F. Pediatric liver transplantation : From the full-size liver graft to reduced, split, and living related liver transplantation. *Pediatr. Surg. Int.*, 1998, **13** : 308-318.
2. OTTE J.B., DE VILLE DE GOYET J., REDING R., SOKAL E., LERUT J., VANORMELINGEN P., JANSSEN M. Living related donor liver transplantation in children : The Brussels experience. *Transplant. Proc.*, 1996, **28** : 2378-2379.
3. REDING R.Transplantation hépatique pédiatrique à partir d'un donneur vivant parental : La question éthique. *Louvain Med.*, 1999, **118** : 1-12.
4. REDING R., WALLEMACQ P., MOULIN D., MANICOURT D., LAMBOTTE L., JAMART J., SOKAL E., DE VILLE DE GOYET J., OTTE J.B. Early hepatocyte, endothelial and bile duct cell injury after pediatric liver transplantation from cadaveric or living-related donors. *Transplantation*, 1998, **65** : 681-685.
5. REDING R., VRAUX H., DE VILLE DE GOYET J., SOKAL E., DE

HEMPTINNE B., LATINNE D., RAHIER J., JAMART J., VINCENZOTTO C., CORMONT F., DE LA PARRA B., DE BRUYÈRE M., SOKAL G., BAZIN H., OTTE J.B. Monoclonal antibodies in prophylactic immunosuppression after liver transplantation. A randomized controlled trial comparing OKT3 and anti-IL2 receptor LO-Tact-1. *Transplantation*, 1993, **55** : 534-541.

6. REDING R., FEYAERTS A., VRAUX H., LATINNE D., DE LA PARRA B., CORNET A., CORMONT F., JAMART J., SOKAL E., DE VILLE DE GOYET J., LERUT J., BAZIN H., OTTE J.B. Prophylactic immunosuppression with anti-IL-2 receptor monoclonal antibody LO-Tact-1 versus OKT3 in liver allografting. A two year follow-up study. *Transplantation*, 1996, **61** : 1406-1409.
7. REDING R., DE VILLE DE GOYET J., DELBEKE I., SOKAL E., JAMART J., JANSSEN M., OTTE J.B. Pediatric liver transplantation with cadaveric or living related donors : Comparative results in 90 elective recipients of primary grafts. *J. Pediatr.*, 1999, **134** : 280-286.