Adult liver transplantation at UCL : update 2002

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Abstract

The authors present the results of a single centre study of 587 liver transplants performed in 522 adults during the period 1984-2002.

Results have improved significantly over time due to better pre-, peri- and post-transplant care. One, five, ten and fifteen year actuarial survivals for the whole patient group are 81.2 ; 69.8 ; 58.9 and 51.2%.

The high incidence of de novo tumors (12.3%), of cardiovascular diseases (7.5%) and of end-stage renal function (3.6%) should be further incentives to tailor the immunosuppression to the individual patient and to direct the attention of the transplant physician to the long-term quality of life of the liver recipient. (Acta gastroenterol. belg., **2004**, 67, **188-196**).

Key words : liver transplantation, immunosuppression, technique, complications, results, long-term follow-up, renal insufficiency, cardiovascular disease, tumor.

Abbreviations

CyA	cyclosporine A
HCCa	hepatocellular cancer
IS	immunosuppression
ITBL	ischemic type biliary lesion
IVC	inferior vena cava
(O)LT	(orthotopic) liver transplantation
TAC	tacrolimus
VVB	veno-venous bypass

Introduction

Without doubt, liver transplantation (LT) has become the standard therapy for many acute and chronic end-stage liver diseases, as well as for many selected cases of hepatobiliary malignancy and liver based metabolic diseases (1).

The immediate results of the procedure have improved greatly during the last decade. However the excellent results obtained nowadays after organ transplantation, have been overshadowed by the high incidence of extrahepatic complications, recurrent allograft disease and de novo tumor formation many years after a successful LT (2).

Review of the experience in a large single center study remains the best tool to judge short- term as well as long-term outcome after LT. Todays outlook and the future of LT are discussed based on this single center experience.

Patients and methods

Between February 1984 and June 2002, 1234 LT were performed in 1000 patients at Cliniques Universitaires Saint-Luc in Brussels. 587 LT were performed in 522 adult patients (age ≥ 15 years). Their mean age was 46.5 years (range : 15.3 to 73). Sixty-seven patients (12.8%) were aged over 60 years. 485 whole livers were implanted orthotopically, three heterotopically. In 9%, a technical variant was used : right split (27 ×), reduced size (11 ×), living related (9 ×) and domino (1 ×) LT. Combined kidney-LT was performed 10 times and combined pancreas-LT once. 87.1% (464 patients) were transplanted once ; fifty-two patients (11.9%) twice and five patients (0.8%) three times and one patient (0.2%) had four transplants. Re-LT index was 1.12. Ischemic type biliary lesions (ITBL) are the most frequent indication for re-LT. Four patients were retransplanted at another transplant center, three for HCV allograft reinfection and one for chronic rejection.

The indications for LT, classified according to the disease leading to the indication were chronic failure 69.7% (364 patients) ; benign (8 patients) or malignant (72 patients) hepatobiliary tumor (15.3%, 80 patients) ; acute liver failure in a non-cirrhotic liver (10.4%, 54 pat) and metabolic liver based disease (4.6%, 24 patients).

One third of the patients were transplanted because of chronic, viral induced hepatopathy ; post-viral C cirrhosis becoming the most frequent indication (Table I).

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Table I. — **Indications of LT at Cliniques Saint-Luc 1984-june 2003-11-27**

Chronic liver disease			364 - 69.7%
– hepatocellular	258	49.4%	
– cholestatic	99	19%	
– vascular	4	0.8%	
– toxic	3	0.6%	
Hepatobiliary tumor			81 - 15.5%
– malignant	72	14%	
– benign	8	1.5%	
Acute liver failure			54 - 10.4%
Metabolic disease			24 - 4.6%

Table II. — **Evolution of surgical technique in adult LT**

Implantation	1984-91	1992-02
Classical	231 (91.7 %)	22 (6.6 %)
Piggy-back	19	40 (11.9 %)
Cavo-caval	2	273 (81.5 %)
VVB-use	224 (88.9 %)	30 (8.8 %) (last 5 yrs : 5 !)

Sixty patients were transplanted because of hepatocellular cancer (HCCA), 18 of them had LT for end-stage liver disease in the presence of HCCa. HCCa was staged according to the UICC classification. Hemangioendothelioma (6 patients), neuroendocrine tumors (6 patients) and polycystic liver disease (6 patients) have become more frequent indications in latter years.

22.2% (116 patients) were transplanted urgently (UNOS 1). 17.6% of patients presented with an abnormal portal vein at LT : in sixty-nine patients (13.2%) it was had a thrombosed and/or severely inflamed ; 23 patients (4.4%) had had previous portal hypertension surgery. At the time of LT, 76 patients (14.6%) had an active infection and 42 patients (8%) needed renal support (hemodialysis, ultrafiltration, continuous veno-venous hemodialysis).

Results were analysed according to two time periods : 1984-1991 (group I, n = 215) and 1992-2002 (group II, n = 307). Early and late events were determined following the practice of the European liver transplant registry (ELTR) as events occurring within or after the first three post-transplant months. Follow-up was complete for all patients with a minimum of one and a maximum of 19 years.

Technique

During the first period, 91.7% of LT were done using the classical implantation technique described by STAR-ZL, after removal of the recipient's inferior vena-cava (R-IVC) with the diseased liver. Veno-venous bypass (VVB) was used in 224 procedures (88.9%). From 1992 to 2002, 81.5% and 11.9% of LT were done using the cavo-caval and piggyback implantation techniques whilst preserving R-IVC ; VVB was used selectively in 30 patients (8.8%) (Table II) (3).

Technical adjustments were also made in relation to splanchnic vein thrombosis. During the second study period, eversion thrombectomy and superior mesenteric vein implantation were almost exclusively used to circumvent the problem of localised or extended venous thrombosis. In two patients with complete thrombosis of the splanchnic venous system successful cavo-portal hemitransposition was achieved.

Immunosuppression and anti-infectious chemotherapy (Table III)

Prophylactic immunosuppression (IS) was profoundly changed over time from aggressive, quadruple immunosuppression to steroid-free tacrolimus based monotherapy. From 2000, all patients were included in a prospective, randomised, blinded, placebo controlled study comparing tacrolimus-low dose, short-term (2 months), steroids and tacrolimus monotherapy.

Therapeutic IS was also profoundly changed. During the first study period, treatment of rejection consisted of high dose steroids followed, in the case of a non response, by administration of mono- or polyclonal anti-lymphocytic sera. During the second study period, treatment of rejection became more moderate. Initial treatment consisted only of three to five 200 mg boluses of methylprednisolone ; antilymphocytic sera were rarely given. From 1997, treatment of rejection was further refined. All liver biopsies were classified according to

Table III. — **Evolution of immunosuppression therapy in adult LT**

1984-1988	– **QUADRUPLE DRUG IS**		
	ALS-ATG polyclonal antibodies		
	OKT3 monoclonal		
1989-1990	– Prospective randomized study :		
	quadruple	:	OKT3 or anti-IL-2 receptor(Lo-Tact-1)
	vs triple IS	:	CyA - Aza - Steroid
1991	– Triple drug IS	:	CyA - Aza - Steroid
1992	– Triple drug IS	:	CyA – Aza - low dose Steroid (LD St)
1997-1999	– Prospective randomized study :		
	triple vs double IS	:	Anti-CD 2a antibody (Lo-CD-2a) - Tac – LD St
	vs		Tac-LDST
2000-2002	– Prospective randomized, placbo controlled study Minimisation immunosuppression		
	Double	:	Tac-LDSt vs
	MONODRUG IS	**:**	**TAC**

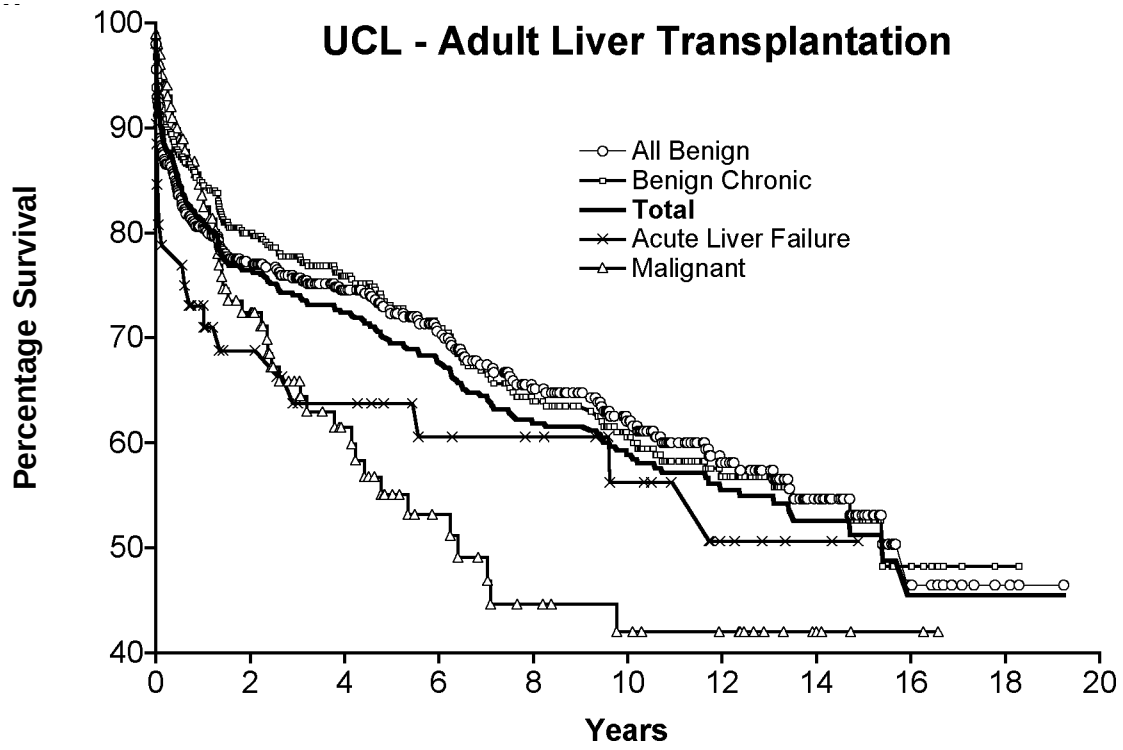


Fig. 1. — Long-term survival after adult Liver Transplantation

Table IV. — **Early mortality (< 3 mo) mortality after adult LT**

– Sepsis +/- multiorgan failure		21
– Perioperative haemorrhage		20
– Multiorgan failure		7
– Miscellaneous		14*
– Graft failure	. haemor. necrosis	2
	. small for size	1
	64/522 pat. (12.2%)	

the Banff classification ; rejection was considered moderate or severe if the Banff score was higher than 6 or 8 (5). Biochemical score was based on the evolution of rising bilirubin, relative and absolute (> 600) eosinophilia and lowering of platelets during the early post-LT period. Biochemical evolution was considered significant if more than 2 of these modifications were simultaneously present. Treatment of rejection was only considered if the Banff score was ≥ 6 and if Bio-score was > 2 simultaneously with a Bio-score > 2 (6).

Anti-viral, bacterial and fungal therapies were standardised from 1992 with short-term (4 days) antibiotic therapy, short-term (10 days) anti-fungal chemotherapy with amphotericine B, CMV-prophylaxis with gancyclovir (4 months), and pneumocystis pneumoniae prophylaxis with trimethoprim sulfamethaxozole until IS monotherapy was reached (7).

Results

One, five, ten and fifteen year actuarial survival rate for the total group of 522 patients are 81.2% ; 69.8% ; 58.9 and 51.2% respectively (Fig. 1).

64 patients (12.2%) died during the first three months and 126 patients (24.1%) died after 3 months. 332 patients (63.7%) are still alive.

Early transplant mortality was dominated by perioperative bleeding and multiorgan failure (Table IV). Due to progresses both technically and medically, especially immunosuppressive treatment, this mortality gradually and significantly decreased from 20% in group 1 to 6.3% in group 2 (Fig. 2). The influence of the implantation technique and of the modified approach to the splanchnic venous abnormalities on early posttransplant survival was very significant. Indeed, intraoperative blood product usage, the incidence of immediate extubation, and of severe perioperative bleeding or reintervention were significantly reduced during the second study period (Fig. 3).

Technical complications of the procedure remain a concern. Severe vascular complications are now rare but the number of biliary complications remains high. 115 patients presented with 128 major biliary complications ; almost one quarter of these complications were related to IBTL (Table V). Twelve of 37 patients needed reLT because of this complication, and all remaining patients needed repeated surgical and/or radiological interventions. Biliary problems, although not responsible

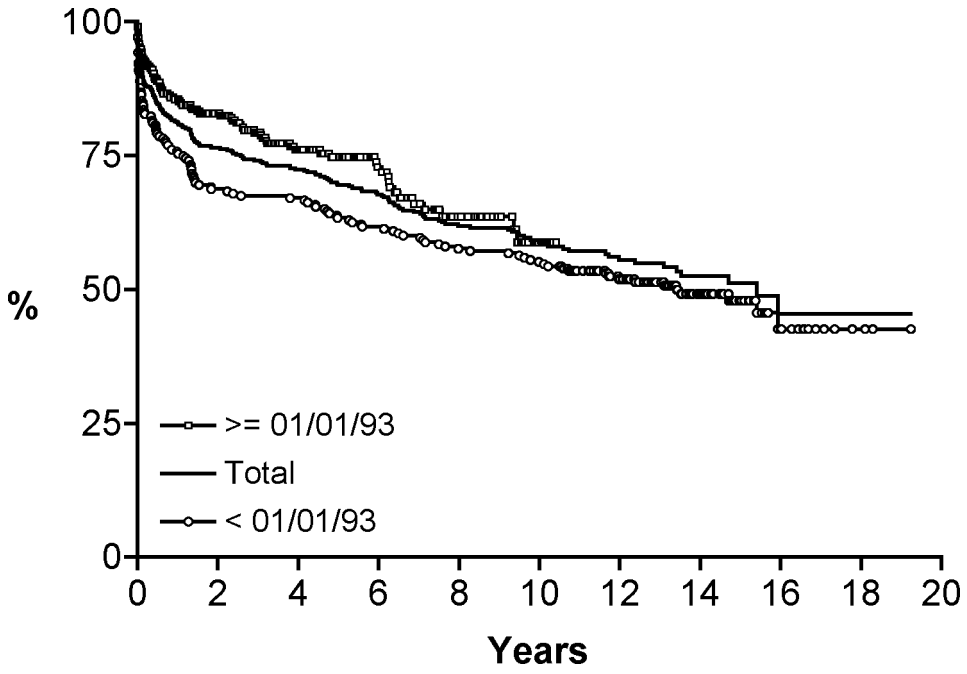


Fig. 2. — Evolution of [early (< 3 mo)] mortality after adult LT

Table V. — **Surgical complications after adult LT**

Type	Patients	Complications
* ARTERIAL	30	31
– thrombosis		15
– mycotic aneurysm		3
* VENOUS		
– portal	22	22
– hepatic	7	7
– IVC	3	3
* BILIARY	115	128
– ITBL		37
– fistula Kehr drain		13
anastomosis		9
– stenosis anastomosis		36

Table VI. — **Late (> 3 mo) mortality after adult LT**

– Recurrent Disease		57
Tumor primary/secondary	21/5	
Hepatitis C/B	20/9	
– Infection		21
– De novo tumor		18
– Cerebrovascular disease		11
– Chronic rejection		9
– Psychological		5
– Miscellaneous		5
	126/522 pat. (24.1%)	

for early mortality, heavily compromise the patient's quality of life.

Late mortality is dominated by the high incidence of recurrent allograft disease, de novo malignancies and cerebrovascular diseases (table VI). This is of concern as about a quarter of all long-term survivors are faced with problems of de novo tumors, cardiovascular diseases and renal insufficiency (table VII). It is notable that these late complications are much more frequent in recipients transplanted for postviral C and alcoholic cirrhosis.

Liver transplantation for chronic benign liver disease

One, five, ten and fifteen year actuarial survival rates in chronic benign liver diseases are 80.6% ; 72.3% ; 62.1% and 53.1% respectively (Fig. 4). Results are similar between the different disease groups.

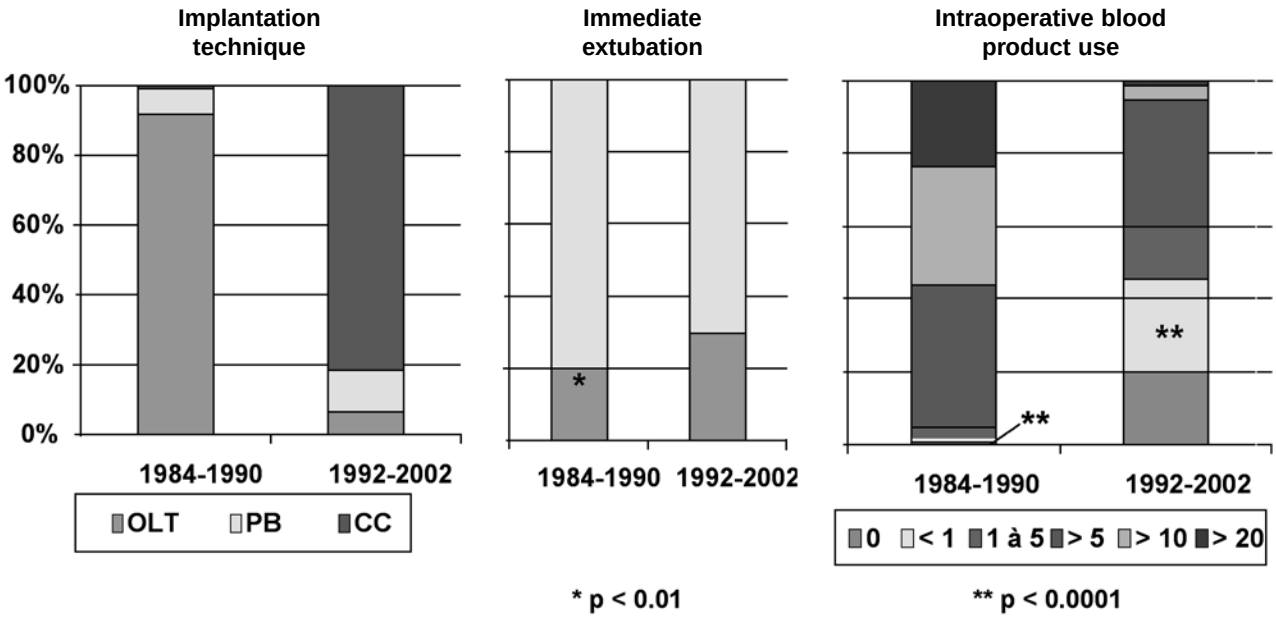
The results obtained after LT for postviral C cirrhosis worse with time and seem to be linked to less powerful IS (table VIII). It is supposed that lower IS might lead e.g. to up-regulation of viral activity.

Liver transplantation for acute liver failure

One, five, ten and fifteen year actuarial survivals in acute liver failure are 59.5% ; 55.3% ; 50.6% and 42.2% (Fig. 1).

Early mortality after LT for acute hepatic failure is 15%. All patients who died early after LT during the second study period, did so because of cerebral and graft dysfunction. One patient died of worsening pre-LT cerebral oedema and one patient died because of cerebral bleeding caused by intracranial pressure monitoring device. These events translate the widening of the indication for LT to extremely (too ?) sick patients. One patient died because of a late hemorrhagic graft necrosis in the presence of a 100% positive cross match and one patient died of liver failure due to small for size liver grafting.

Eight patients were successfully bridged to LT using bio-artificial liver device (5 ×) or a molecular absorbent recycling system (MARS) (3 ×).



OLT classical LT ; PB piggyback LT ; CC cavo-caval LT.
Blood product use expressed in liters.

Fig. 3. — Influence of surgical technique on artificial ventilation and intraoperative blood product use

Table VII. — **Incidence of tumor, cardiovascular disease and renal insufficiency after adult LT**

De novo tumors	68	64 pat.	12.3%	
* > 5 yrs	32 pat.			
* postviral C and alcoholic cirrhosis		24 /15 pat.	(38.1 / 24%)	
* mortality	**20 pat.**	31%	7.5%	
Cardiovascular diseases	40	39 pat.		**Incidence :**
* mortality	**15 pat.**	38%		**23.4%**
Renal insufficiency		19 pat.	3.6%	
* hemodialysis / kidney transplant		14/5 pat.		
* postviral C and alcoholic cirrhosis		9/2 pat.	(47 / 10.5%)	
* mortality	**4 pat.**	21%		
Total Mortality	**39 pat/122**	**32%**		

Liver transplantation for hepatobiliary tumors

One, five, ten and fifteen year actuarial survival rates of 66 patients transplanted because of HCCa and cirrhosis were 83.1% ; 57.9% ; 44.6% and 44.6% respectively. Excellent long-term results could be obtained for 46 long-term UICC, stage I, II and III patients ; their disease-free survival of 95.7% is statistically significantly different from the 37% survival obtained in 19 UICC stage IV patients (fig. 5).

Cholangiocellular carcinoma and bile duct cancer are disappointing indications for LT ; none of the five transplanted patients survived more than five years (range : 12 to 63 months).

Results of LT because of epithelioid hemangio-endothelioma are excellent ; all six patients have long-term disease-free survival (ranging from 2 to 11 years).

Retransplantation

One, five, ten and fifteen year actuarial survival rates of 63 retransplant patients are 75.3% ; 66% ; 60% and 47.7. These results are similar to those obtained after primary LT.

Early mortality was highest in cases of re-LT for graft dysfunction and for immunological dysfunction, reflecting the severely compromised health status and the higher vulnerability due to heavier IS. In contrast, early mortality after reLT for technical failure or recurrent disease was rare (table IX).

Immunological results

The reduction of the number of drugs used for induction IS was paralleled by a reduced incidence of treated

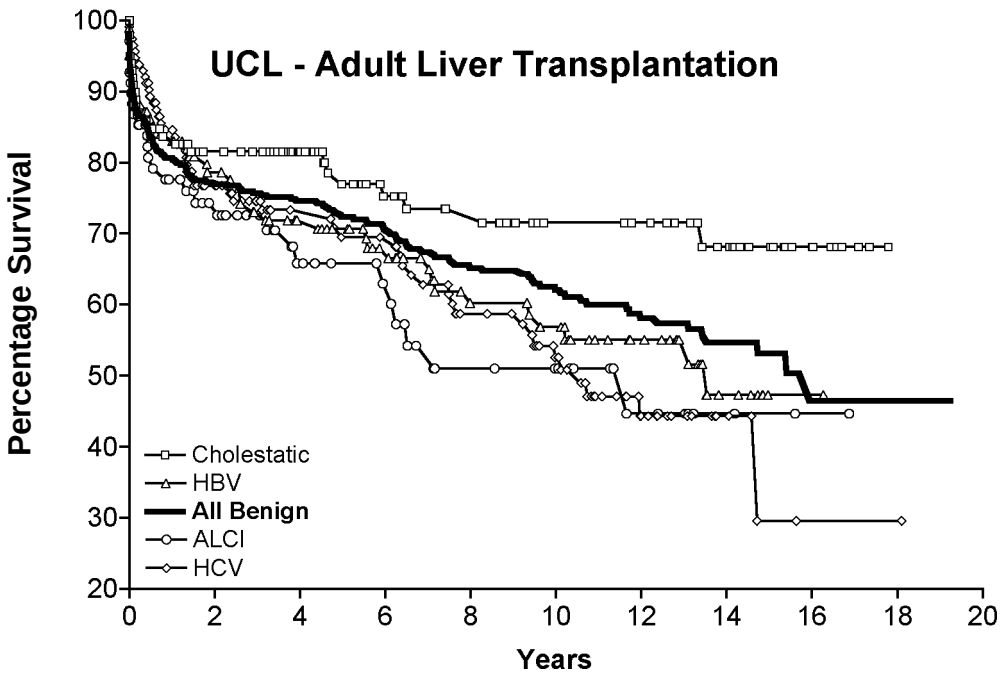


Fig. 4. — Long-term survival after liver transplantation for benign chronic liver diseases

Table VIII. — **Influence of Immunosuppression on results of LT for HCV related cirrhosis**

Immunosuppression	High	Low dose steroid	Minimal
Follow-up (yrs)	8.2	5.5	3
Steroid dose	high	low	low
Dose first week(mg)	> 1650	330	330
> 6 gr at 3 mo	80%	0%	0%
free at 12 mo	0%	90%	90%
Antilymphocytic antibody use	90.3%	57.1%	8%
Induction * (%)	74	4	8
Rejection° (%)	38.7	57.1	0
Treated rejection	72%	89%	4%
HCV-allograft cirrhosis	9.6%	9.5%	16.7%
HCV-related mortality	9.7%	14.3%	29.2%

* Induction therapy using ATG or monoclonal antibodies to Lo-CD2a.
° Rejection therapy using OKT3.

rejection (fig. 6). Immunological results obtained during the last five years are of particular interest. Indeed, all patients of this period were included in two prospective randomized studies comparing tacrolimus – low-dose, short-term (2 months), steroid IS vs double immunosuppression plus anti-CD2a monoclonal antibody or tacrolimus - low-dose, short-term (2 months) steroids versus tacrolimus monotherapy. Both investigator driven, studies were conducted on very strict application of the rejection score combining concordant early biochemical and histological Banff scoring. Both studies showed that LT can be done successfully using less aggressive IS. LT under the cover of tacrolimus monotherapy (even at apparently infratherapeutic doses), seems to be a very valuable approach that leads to a improved quality of life (Table X).

Discussion

The critical review of a large single center adult series remains a very good means to look at actual status, improvement and future outlook of a complex therapeutical option such as LT. Indications, implantation techniques and peri-operative care of LT have been standardized leading to a significant reduction of early post-LT morbidity and mortality. The high incidence of biliary complications, many of them occurring (or detected) late after the procedure remains of major concern. Routine (percutaneous transhepatic) cholangiography is necessary in order to document the exact incidence and extension of such complications (8). If diagnosed, a rapid therapeutic radiological or surgical decision should be made ; retransplantation should be scheduled

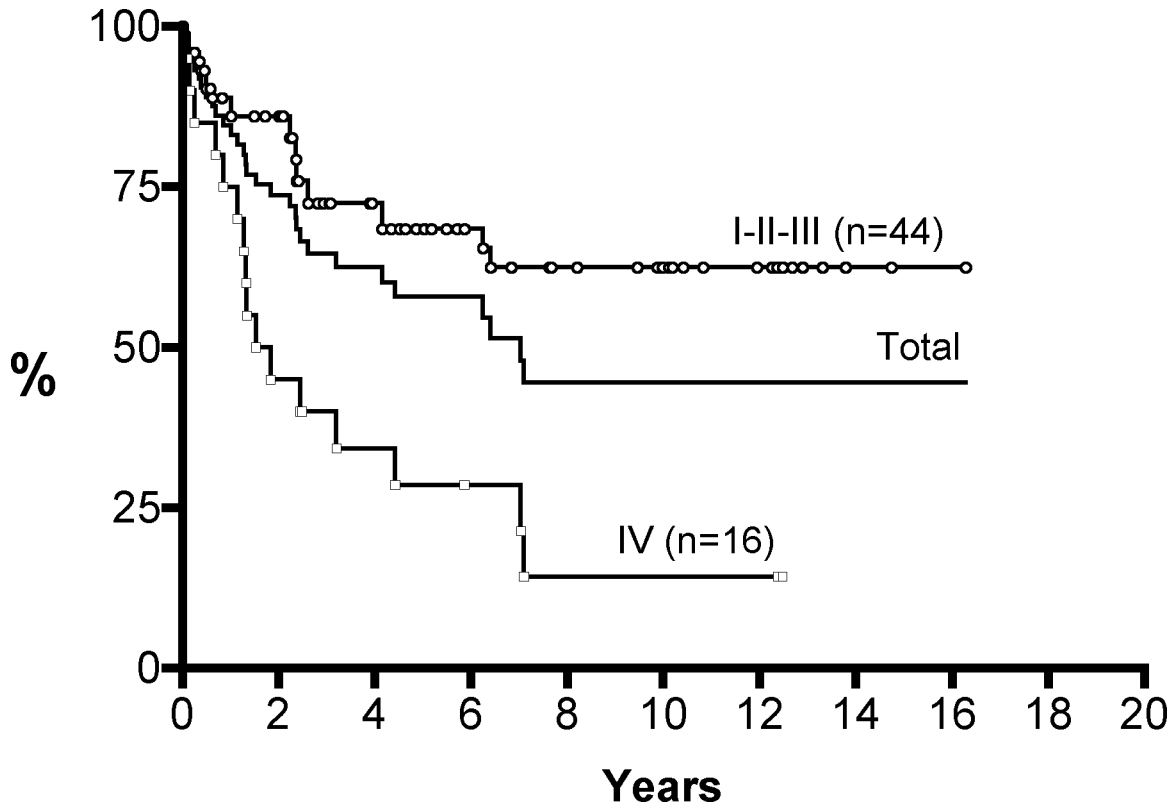


Fig. 5. — Survival after LT for hepatocellular cancer in relation to UICC stadification

Table IX. — **Results of retransplantation in function of indication**

Indication		N	Mortality (< 3 mo)	
* Non function	. primary	8	2	26%
	. early	15	4	
* Hepatic artery thrombosis		5	1	5%
* Graft rupture		1	/	
* ITBL		14	/	
* Recurrent disease	. HBV	4	/	0%
	. [HCV	4*	/ [1+]	
* Rejection	. acute	9	5	33.3%
	. chronic	9[+1]*	2	
		65[+5]	14[+1]	20%

***** Re-LT done at another transplant centre.

in time before the occurrence of uncontrollable septic complications. There is an urgent need to adapt liver procurement techniques to avoid these disastrous complications. Shortening of cold ischemia time, use of less viscous perfusion fluid (9) and of pressurised arterial perfusion are interesting approaches to solve this problem (10).

Recurrent allograft disease is the second important problem especially in post-viral C cirrhosis. Better pre- and posttransplant antiviral therapy must become available in order to prevent aggressive graft recurrence. It has now become clear that older donor age, long ischemia time, use of more powerful induction immunosuppression, powerful antirejection treatment and pretransplant viral load are main determinants in the outcome of LT for HCV-disease. Recipient and donor selection as well as tailored immunosuppression become important in order to control better viral allograft disease (11). Rapid decision to reLT remains an option but its value should be seen in view of the shortage of available organs.

Major progresses have been made in the field of hepatocellular cancer. Pretransplant therapies have been proven to be valid and progresses have been made in relation to better tumor staging (13). Combining both elements will allow to improve results. This is of utmost importance as more and more HCCa are detected using systematic screening of the high-risk patient groups (13).

The negative effects of a prolonged and/or inadequate IS have been well underlined by the high incidences of de novo renal insufficiency, tumor formation and cardiovascular disease (2,14,15). The lowest possible, prophylactic as well as therapeutic, IS is a necessity. Critical analysis of clinical, histological and biochemical behaviour of the patient is important in order to define the real incidence of immune activation or deregulation and thus the need for rejection treatment. The incidence of rejection has been reduced substantially and it has been confirmed that steroids can be safely withdrawn and even avoided in adult LT, as shown by the results obtained in our recent prospective randomised placebo-controlled

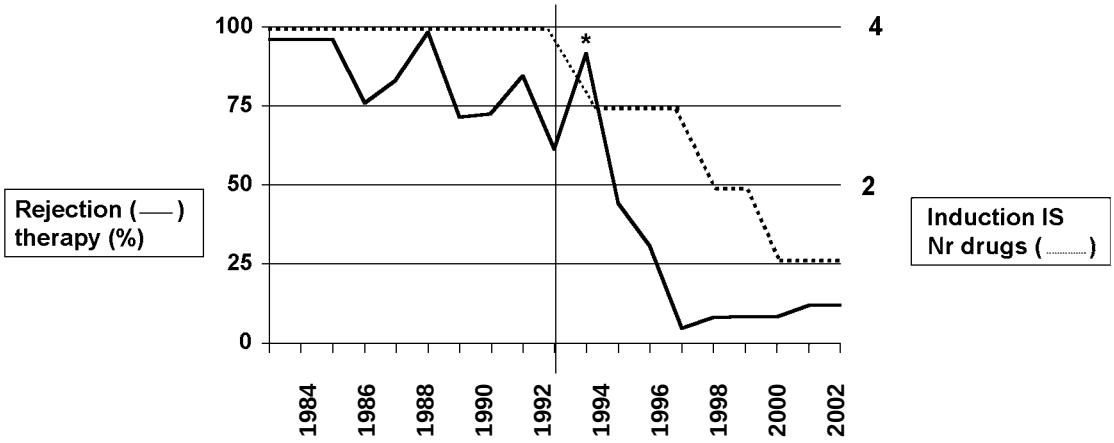


Fig. 6. — Reduction of immunosuppression over time

Table X. — **Results of tacrolimus monotherapy in adult (re)LT**

Rejection 0-90 days	TAC-PLACEBO	TAC-STEROID	
at day 7	0 (0%)	1 (2.5%)	
Treatment			
corticosensitive	4 (10%) [d23*,41,42°48]	5 (12.5%)	[d 14,15♦,26°,28,51]
corticoresistant	2 (5%) [d12 haemorraghic necrosis] [d31 OKT3]	1 (2.5%)	[d 9 OKT3]

*hepatic artery and portal venous thrombosis in context of small for size syndrome
° Is stop due to posttransplant lymphoma
♦ rejection at d 130, non compliance and refusal of therapy
° very low TAC-dose due to cerebrovascular accident

De Novo side effects	TAC-PLACEBO	TAC-STEROID	
Renal insufficiency (creat. > 1.5 mg/dl)	8.8%	5.5%	
IDDiabetes	2.9%	2.7%	
Hyperuricemia (> 9 mg/dl)	5.9%	0%	
Hypercholesterolemia (> 220 mg/dl - fasting)	17.6%	8.3%	(p 0.06)
Arterial hypertension	8.8%	5.5%	
Karnofsky score > 80%	97%	94.2%	

blinded study (4,16). The strategy of infratherapeutic monotherapy appears to be slowly becoming the door to IS withdrawal in LT (17).

The excellent short term results obtained nowadays after LT must direct the attention of the transplant physicians to long-term outcome of the recipient. Improved quality of life can only be obtained if a technically successful liver transplant procedure is followed by a progressive reduction or even withdrawal of IS. Such immunological strategy allows a better interplay between donor and recipient immunological systems, which may finally lead to the desired state of tolerance (18,19).

The strategies for the future of LT are clear : improvement of liver preservation aiming at a reduction in the incidence of biliary tract complications, modification of IS based on an individualized approach and finally progressive withdrawal of immunosuppression aiming at a reduction of extrahepatic complications, which can severely compromise the quality of life of the "successfully" transplanted patient.

Careful long-term multidisciplinary follow-up of liver recipients in high volume centers will remain the best instrument to judge if progress will be attended within a reasonable time span.

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