Adult liver transplantation : UCL experience

J. Lerut, P.F. Laterre[1], F. Roggen, O. Ciccarelli, M. Donataccio[2], J. Martinez[3], J. de Ville de Goyet, R. Reding, M.A. Carlier[4], M. Dekock[4], P. Lavand'homme[4], L. Van Obbergh[4], F. Veyckemans[4], M. Janssen, E. Danse[5], P. Goffette[5], B. Van Beers[5], Ch. Sempoux[6], P. Wallemacq[2], A. Peeters[3], Cl. Guerrieri[7], J. Roeseler[1], D. Latinne[7], P. Goubau[8], Y. Horsmans[9], M. Van Hassel[10], J. Rahier[5], M. Reynaert[1], A. Geubel[9], P.J. Kestens, J.B. Otte,

Department of Digestive Surgery (Prof. R. Detry) ; (1) Intensive Care (Prof. M. Reynaert) ; (4) Anesthaesiology (Prof. Ph. Baele) ; (5) Radiology (Prof. B. Maldague) ; (6) Pathology (Prof. J. Rahier) ; (10) Medical Economy ; (2) Toxicology (Prof. P. Wallemacq) ; (3) Neurology (Prof. Ch. Sindic) ; (7) Immunohaematology (Prof. M. De Bruyère) ; (8) Virology (Prof. Burtonboy) ; (9) Hepato-Gastroenterology (Prof. A. Geubel). — Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, 1200 Bruxelles (B).
(2) Transplant Fellow Casa Sollievo della Sofferenza - IRCCS - San Giovanni Rotondo (Italy).
(3) Transplant Fellow Universidad Catolica de Chile - Santiago (Chile).

Abstract

Objective **: to evaluate the impact of standardized operative and peri-operative care on the outcome of liver transplantation in a single center series of 395 adult patients.**

Method and material **: between February 1984 and December 31, 1998, 451 orthotopic liver transplantations were performed in 395 adult patients (≥ 15 years) at the University Hospitals St-Luc in Brussels. Morbidity and mortality of the periods 1984-1990 (Gr I - 174 pat.) and 1991-1998 were compared (Gr II - 221 pat.). During the second period anti-infectious chemotherapy and perioperative care were standardized and surgical technique changed from classical orthotopic liver transplantation with recipients' vena cava resection (and use of veno-venous bypass) towards liver implantation with preservation of the vena cava (without use of bypass).**

Immunosuppression was cyclosporine based from 1984 up to 1996 and tacrolimus based during the years 1997 and 1998. Immunosuppression was alleviated during the second period due to change from quadruple to triple and even double therapy and due to the introduction of low steroid dosing and of steroid withdrawal, once stable graft function was obtained.

Indications for liver grafting were chronic liver disease (284 pat - 71,9%), hepatobiliary tumor (52 pat - 13,2%), acute liver failure (40 pat - 10,1%) and metabolic disease (19 pat - 4,8%). Regrafting was necessary because of graft dysfunction (21 pat), technical failure (12 pat), immunological failure (18 pat) and recurrent viral allograft disease (5 pat) ; three of these patients were regrafted at another institution. Follow-up was complete for all patients with a minimum of 9 months.

Results **: actuarial 1, 5 and 10 years survival rates for the whole group were 77,9%, 65,7% and 58,3%. These survival rates were respectively 77,3%, 69,7%, 62,5% and 73,2%, 59,6% 51,4% for benign chronic liver disease and acute liver failure ; those for malignant liver disease were 80,6%, 44,3% and 36,7%. Early (< 3 months) and late (> 3 months) posttransplant mortalities were 14,4% (57 pat) and 21.2% (84 pat). Early mortality lowered from 20% in Gr I to 9,4% in Gr II ($p < 0.02$) ; this was due to a significant reduction during the second period of bacterial (99/174 pat. - 56.9% vs 82/221 pat. - 37.1%), fungal (14 pat. - 8% vs 7 pat. - 3.2%) and viral (87 pat. - 50% vs 49 pat. - 22.2%) infections ($p < 0.05$) as well as of perioperative bleeding (92 pat. - 52.9% vs 39 pat. - 17.6% - $p < 0.001$). Late mortality remained almost identical throughout the two periods as lethal outcome was mainly caused by recurrent allograft diseases, cardiovascular and tumor problems. Morbidity in these series was important considering that almost, half of the patients had a technical complication, mostly related to bleeding (131 pat - 33,2%) and biliary problems (66 pat - 16.7%). Retransplantation index was 1.1 (54 pat. - 14%). Early retransplantation mortality was 24% ; it lowered, although not yet significantly, during the second period (8/25 pat. - 32% vs. 5/29 pat. - 17.2%).**

Conclusion **: Despite a marked improvement of results, liver transplantation remains a major medical and surgical undertaking. Standardization of operative and perioperative care, less haemorraghic surgery and less agressive immunosuppression are the keys for further improvement.** (Acta gastroenterol. belg., **1999**, 62, **306-318**).

Key words : liver transplantation, acute liver disease, chronic liver disease, hepatobiliary malignancy, surgical technique, complications, retransplantation, immunosuppression, economy.

Abbreviations

ALF	acute liver failure
Cy A	cyclosporine A
Gr	group
HBV	hepatitis B viral infection
HCV	hepatitis C viral infection
IBTL	ischaemic biliary tract lesions
IP	immunoprophylaxis
IS	immunosuppression
LDSt	low dose steroid therapy
MP	methylprednisolone
PB	piggyback allograft implantation
PB-CC	piggyback allograft implantation with cavo-caval anastomosis
PVT	portal vein thrombosis
R-IVC	recipient's inferior vena cava
(re)OLT	orthotopic liver (re)transplantation
StWD	steroid withdrawal
Tac	Tacrolimus
VVB	veno-venous bypass

Introduction

Since its first application in 1963 by Thomas Earl STARZL, liver transplantation (LT) has evolved to a therapeutic standard in the treatment of end-stage acute and chronic liver diseases as well as of selected cases of hepatobiliary malignancy and liver based metabolic diseases (1).

More experience with operative and perioperative management has led to extention of its use. Indications, morbidity and mortality of adult LT and retransplan-

Correspondance to : Prof. Jan P. Lerut M.D., Ph.D., Department of Digestive Surgery, Cliniques Universitaires St-Luc / 1400, Université Catholique de Louvain (UCL), Av. Hippocrate 10, 1200 Brussels - Belgium.

Table I. — **Indications for adult liver transplantation at St-Luc in 395 adult (≥ 15 years) patients (1984-1998)**

CHRONIC LIVER DISEASE				284 pat. - 71.9%
Hepatocellular	215 pat. (54.4%)			
• chronic viral induced				121
– C	69	BD	20	
– B	27	BC	4	
– paramyxo	1	BCD	2	
• cryptogenic				31
• alcoholic				45
• autoimmune				11°
Cholestatic	68 pat. (17.2%)			
• PBC	47			
• SBC	10			
• PSC	11			
Toxic				
• vitaminosis A	2 pat. (0.6%)			
Vascular				
• Budd-Chiari	1 pat. (0.3%)			
HEPATOBILIARY TUMOR				52 pat. - 13.2%
Malignant				
• Primary	44 pat. (11%)			
	– HCCa cirrhotic liver		30 (19•)	
	normal liver		4	
	– cholangiocellular Ca		4	
	– haemangioendothelioma		4	
	– angiosarcoma		1	
	– bile duct cancer		1	
• Secondary	5 pat. (1.3%)			
	– neuroendocrine		3	
	– colorectal		2	
Benign	3 pat. (0.8%)			
	– biliary papillomatosis		1	
	– polyadenomatosis		1	
	– Caroli's disease		1	
ACUTE LIVER FAILURE (on normal liver)				40 pat.□ - 13.2%
Fulminant hepatic failure (< 2 weeks)				
• Hepatitis		A	3	
		B	13	
		NANBNC	9	
		Herpes	1	
• Reye's syndrome			1	
• Toxic			1	
Subfulminant hepatic failure (> 2 to 8 weeks)				
• hepatitis		NANBNC	6	
		toxic	4	
• posthepatic resection			1	
Metabolic diseases				19 pat.■ - 4.8%
• Familial amyloidosis			6	
• Wilson's disease			5°°	
• Haemochromatosis			2	
• α-1-antitrypsin deficiency			3	
• Byler's disease			1	
• Oxalosis			1	
• Glycogenosis type I			1	

° = three patients transplanted because of ALF
• = tumor found in patients transplanted because of end-stage chronic liver disease
□ = one LT because of ALF due to haemorraghic allograft necrosis
■ = patients grafted for ALF due to Reye's syndrome (1), haemophilia A complicated by end-stage HCV and HBV-Delta cirrhosis (2 ×) and haemochromatosis complicated by stage IV HCCA (1 ×) are not included.

tation (re-LT) are discussed based on the results of a single center experience with 395 consecutive adult patients.

Method and material

During the period february 1984 - december 1998, 451 LT's were performed in 395 adult patients (age ⩾ 15 years). Their mean age was 47.8 years (range 15 to 73.1). 448 livers were implanted orthotopically and 3 heterotopically. Thirty-three patients (8,6%) had a technical variant of LT (20 right split LT ; 11 reduced size LT and 2 living related donor LT).

Combined liver-kidney transplantation was performed in five patients and one patient had a combined liver-pancreas transplant. 344 patients were transplanted once (87,1%) ; 47 patients twice (11,9%) ; 3 patients (0,8%) three times and finally one patient (0,3%) four times. Three of them had reLT at another institution. Retransplantation index of these series was 1.1.

Several patients had more than one diagnosis, they were however classified in relation to the disease finally leading to the indication for LT (table I). 71,9% (284 pat) were transplanted because of chronic liver disease ; 13,2% (52 pat) because of hepatobiliary tumors ; 10,1% (40 pat) because of acute liver failure in a non-cirrhotic liver and finally 4,8% (19 pat) because of a metabolic liver based disease.

Fulminant liver failure was defined as the occurrence of severe encephalopathy within two weeks after onset of jaundice ; subfulminant failure was defined as occurrence of encephalopathy from the third to the eighth week after onset of jaundice (2). Two patients with Wilson's disease and one patient with autoimmune cirrhosis are classified in the chronic disease group although they were grafted because of acute liver failure (ALF).

Hepatocellular cancers were staged following UICC-classification (3). Stages I and II, correspond to solitary small, unilobar tumors without or with vascular invasion ; stage III to solitary, large (> 2 cm) tumor with vascular invasion or multiple, unilobar, large tumors with or without vascular invasion and stage IV to multiple, bilobar tumors presenting macrovascular invasion. Nineteen patients were grafted because of chronic end-stage liver disease whilst having a small hepatocellular cancer detected before or after LT.

The risk factors of the transplanted population are listed in table II.

Due to modifications in operative and perioperative care, results of these series were analyzed in function of two periods nl. 1984-1990 (Gr I - 171 pat.) and 1991-1998 (Gr II - 221 patients).

Early and late events were determined following the European Liver Transplant Registry, as events occurring within or after the first 3 post-LT months.

Follow-up was complete for all patients with a minimum of 9 months (median 7 years, range 3 to 180 mo.).

Table II. — **Risk factors of adult liver transplantation**

		Patients	%
- Child-Pugh C classification	:	187	47.3
- Urgent Transplantation (UNOS 1)	:	94	**23.8**
- Previous surgery : upper abdomen	:	85	21.5
portal hypertension	:	20	**5.1**
- Portal vein modification	:	50	**12.7**
- Pre-OLT infection	:	51	12.9
renal failure*	:	34	8.6
- Age > 60 years	:	37	9.4
- ABO incompatibility	:	9	2.2
- Previous organ transplantation	:	7	1.7
bone marrow transplant.	:	1	0.2

* pre-LT renal failure is defined a failure necessitating organ support.

Table III. — **Evolution of surgical technique in adult liver transplantation**

Implantation	1984-90	1991-98
Classical	199 (100%)	43 (17.1%)
Piggy-back*	/	50 (19.8%)
Cavo-caval	/	159 (63.1%)
VVB-use	181 (94.8%)	68 (27%) (last 5 yrs : 2 pat.)

* anastomosis between recipient's hepatic vein cuff and donor's inferior vena cava cuff.

Surgical technique (table III)

During the first study period, liver procurement and transplantation were performed following the methods described by Starzl (1). The recipient's inferior vena cava (R-IVC) was always removed and a veno-venous bypass (VVB) was almost universally used. Afterwards, the great majority of the patients had LT whilst preserving the R-IVC and VVB was only used selectively (4,5). During the last five years, cavo-caval piggy-back LT (PB-CC) was used in all but one patient (fig. 1) and VVB was only used twice (2/128 grafts - 1,5%). In case of splanchnic vein thrombosis there was a shift from blind thrombectomy during the first period to eversion thrombectomy and superior mesenteric vein implantation during the second period (6) (fig. 2).

Since 1994, biliary tract reconstruction was done without stenting.

Perioperative cytoprotective therapy, using prostaglandin E1 (Prostin® - Upjohn - Pharmacia - S) and ursodeoxycholic acid (Ursofalk® - Falk - G), was used since 1993 (7).

Immunosuppression (IS) (table IV)

Prophylactic

During the period 1984-1990, IS was cyclosporine A (CyA) (Sandimmun® - Novartis - CH) based. It consisted of quadruple IS, using methylprednisolone (MP) (Medrol® - Upjohn - S), azathioprine (Imuran® - Wellcome - UK) and either polyclonal (ALS or R-ATG® - Fresenius - G), monoclonal (OKT3-Orthoclone® - Cilag-Jansen - USA) or anti-IL-2-receptor (Lo-Tact®-1 - Biotransplant - USA) antibodies.

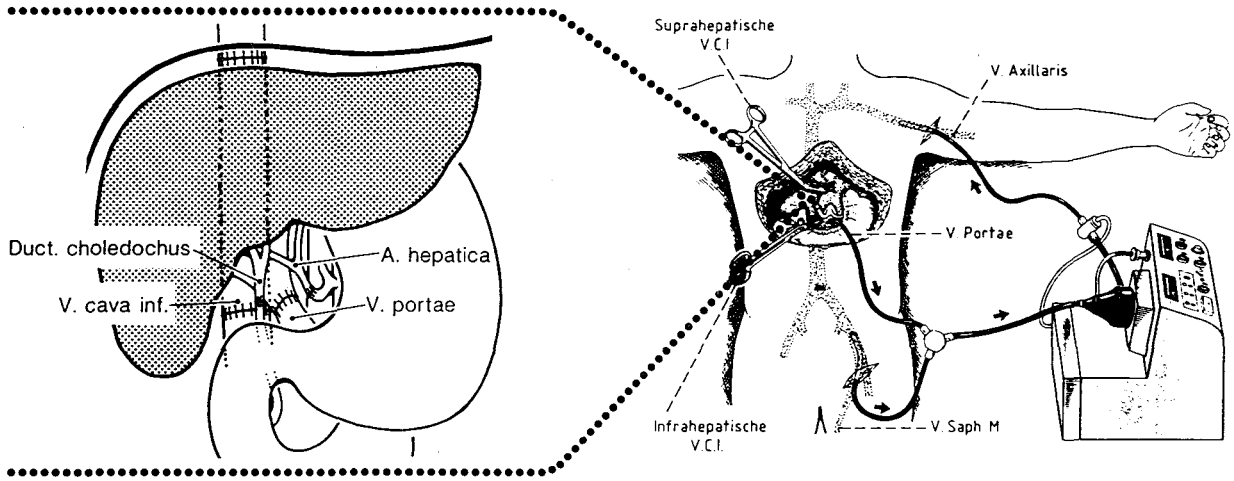

Fig. 1a

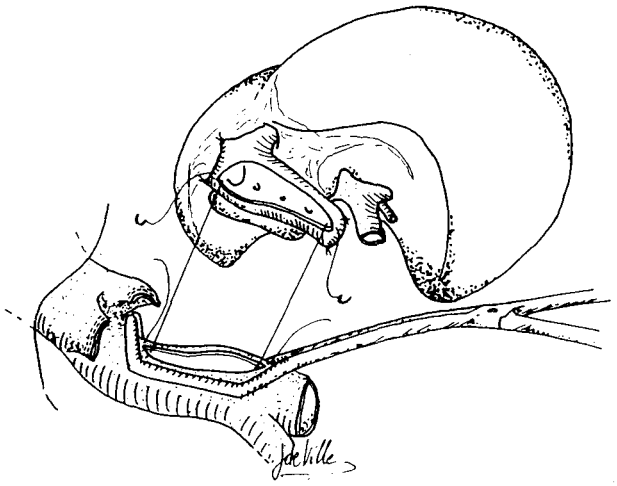

Fig. 1b

Fig. 1. — Evolution of surgical technique of LT from (a) classical allograft towards (b) cavo-caval implantation.

In 1989-1990, a prospective randomized study was done comparing quadruple IS, using OKT3® or Lo-Tact®, and triple IS (8).

Since 1991, IS was alleviated substantially and consisted till 1996 of a CyA-based triple regimen using Sandimmun or Neoral® (Novartis - CH), MP and azathioprine. Moreover, low dose steroid therapy (LDSt), representing administration during the first 10 post-LT days of 362 mg of MP, as well as systematic steroid withdrawal (STWD) from the third post-LT month onwards, in presence of stable graft function (except for the year 1994), were applied (table IV).

In 1997-1998, a prospective randomized study was done comparing triple IS, using LDSt, anti-CD-2a antibody (BTI 322 - Biotransplant - USA) and tacrolimus (Tac) (Prograft®-Fujisawa), to double IS, using Tac and LDSt.

Therapeutic

Treatment of rejection was based on clinical, biochemical and histological findings. In Gr I, treatment of rejection consisted of administration of several boli of MP (up to 6,5 gr). Corticoresistant rejection was treated with a 10 to 14 days course of OKT3® or R-ATG®. Since introduction of LDSt and STWD protocol (Gr II) rejection has been treated with 0.6 to 1 gr MP only ; "corticoresistance" has been treated by switching treatment from CyA to Tac. In case of resistance to this switch, a ten day course of OKT3 was given.

Table IV. — **Evolution of immunosuppression (is) in adult liver transplantation**

1984-1988	:	– quadruple immunosuppression : CyA - azathioprine - steroids and ALS-ATG polyclonal antibodies; OKT3 monoclonal
1989-1990	:	– randomized study : quadruple (OKT3 or anti-IL-2-receptor Lo-Tact-1) vs triple IS (CyA - azathioprine - steroids)
1991-1992	:	– prospective study : triple drug IS CyA - azathioprine - steroids vs CyA - azathioprine - Low Dose Steroids [LDSt]
1997-1998	:	– randomized study : triple (Tac - LDSt - anti-CD2a BTI 322) vs double IS (Tac - LDSt)

Fig. 2. — Eversion thrombectomy in case of extended portal vein thrombosis.

Anti-infectious chemotherapy

During the period 1984-1987, antibiotherapy was not standardized ; since 1988 a four day course antibiotherapy was according to the status of the patient. In case of elective (low risk) LT, antibiotherapy consisted of temocilline (Negaban® - Smith-Kline - Beecham - B) and oxacilline (Penstapho® - Bristol - Myers Squibb - I) ; in case of emergency and haemorraghic (high risk) LT, ceftazidime (Glazidim® - Glaxo-Wellcome - I) and vancomycine (Vancocin® - Eli Lilly - USA) were administered.

Since 1990, systemic anti-infectious chemotherapy was completed with selective bowel decontamination consisting of four daily intakes of a mixture of polymycine B, netilmicine (Netromycine - Shering - Plough - USA) and amfotericine B (Fungizone® - Bristol - Myers - Squibb - F) during the whole posttransplant hospital stay (8).

Gr II had viral prophylaxis consisting of high dose acyclovir (Zovirax® - Glaxo - Wellcome - UK) or sequential gancyclovir (Cymevene® - Roche - CH) and Zovirax® administration for 4 to 6 months (10). Fungal prophylaxis consisted of a 10 day course of low dose (10 mg) Fungizone and protozoal prophylaxis consisted of trimethoprim sulfametoxazole (Bactrim® - Roche - CH) three times a week until CyA or Tac monotherapy was reached (11).

Since september 1989, hepatitis B viral (HBV) infected recipients were treated, from the anhepatic phase onwards, with high doses of specific anti-HBS immunoglobulins (CAF - Red Cross - B) in order to obtain anti-HBS antibody levels above 200 mUI/ml (12) ; there was no prophylactic antiviral treatment in case of LT for hepatitis C viral (HCV) disease.

Cost-containment study

Costs of first transplant hospitalization during the years 1990-91, 1992-93, 1994-95 and 1996-97 were analyzed for elective and urgent primary LT and re-LT. The analysis took into account costs related to procurement and transplant procedures, diagnostic procedures, medication, medical care and hospitalization costs. The results were displayed in such a way that it was extremely difficult, or even impossible to adapt costs to the different time periods. There were indeed many different price adaptations over the years within cost-subgroups as e.g. hospitalization (+ 41%), medication, and medical acts (+ 20.4%). There is however no doubt that medical cost expenditure enhanced markedly over time ; during the study period 1990-1997 the index rose by 17%.

Results

One, five and ten year actuarial survival rates for the total transplant group of 395 patients were respectively of 77,9%, 65,7% and 58,3%.

At the end of follow-up, 254 (64.3%) patients are still alive ; fifty-seven patients (14,4%) died during the first three post-LT months, 84 patients (21.2%) died later on.

Posttransplant mortality

Early mortality was dominated by infectious and bleeding complications (table V). This mortality gradually and significantly decreased over the years (table VI) mainly due to significantly lower incidence of infectious and bleeding complications in Gr II (tables VII and VIII).

Table V. — **Early (< 3 mo) mortality after adult liver transplantation**

- Sepsis w/wo multiorgan failure		19
- Perioperative haemorrhage		19
- Multiorgan failure		7
- Recurrent	• viral disease	1
	• tumor	1
	• leucaemia	1
- Cerebral	• haematoma (ICP monitoring)*	1
	• oedema	2
- Graft vs host disease		1
- Lymphoproliferative disease		1
- Lyell syndrome		2
- Iatrogenic pulmonary bleed°		1
- Myocardial infarction°		1
- Haemodynamic failure		1
		57/395 pat. (14.4%)

* ICP : intracranial pressure monitoring.
° complications in context of severe early allograft dysfunction.

Table VI. — **Evolution of early motality after adult liver transplantation**

1984-87	11/45	24.4%	
88	10/48	20.1%	20%
99	10/45*	20%	
90	4/37**	10.8%	
1991	5/43**	11.6%	
92	2/28	7.1%	
93	3/34	8.8%	
94	3/27*	11.1%	9.4%
95	3/27*	11.1%	
96	3/25	12%	
97	2/24*	8.3%	
98	1/25	4%	
	57/395 pat.	14.4%	p < 0.02

* patients had LT and re-LT during different years.

Table VII. — **Evolution of infectious morbidity and mortality after adult liver transplantation**

Early infections	Gr I 1984-90 (174 pat.)	Gr II 1991-98 (221 pat.)
Bacterial	99 - 56.9%	82 - 37.1%
Fungal	14 - 8%	7 - 3.2%
Viral	87 - 50%	49 - 22.2%
CMV infection	63 - 36.4%	32 - 14.5%
tissue invasion	47 - 28%	22 - 9.9%
Mortality		
sepsis w/wo multiorgan failure	12 - 6.9%	7 - 3.2%*
of pre-LT infected pat.	12/33 - 39.4%	1/19 - 5.3%

* $p < 0.08$; all others $p < 0.05$.

Table VIII. — **Evolution of perioperative bleeding complications after adult LT**

	Gr I - 1984-90	Gr II - 1991-98	p
- Perioperative bleeding needing reintervention	92/174 - 52.9%	39/221 - 17.6%	< 0.001
- Mortality related to bleeding	18/92 - 19.6%	1/39 - 2.5%	< 0.05

Late mortality was dominated by recurrent allograft disease, infectious, tumoral and cardiovascular complications (table IX).

Seven (1.8%) patients died of liver failure due to chronic rejection ; four of them whilst waiting for re-LT.

Table IX. — **Late (> 3 mo) mortality after adult liver transplantation**

- Recurrent allograft disease			41
tumor	primary	19	
	secondary	3	
hepatitis	C	10°	
	B	8	
metabolic		1	
- Infection			14•*
- Chronic rejection		7	
- Lymphoproliferative disease		5	
De novo cancer		5	
Medullary aplasia		1	
- Cerebral bleeding		4	
Cardiopulmonary failure		3	
Myocardial infarction		1	
- Intestinal volvulus		1	
- Suicide		2	
		84/395 pat. (21.2%)	

° two patients died of tuberculosis.
• two patients died of tuberculosis.
* including one sepsis each due to hepatic artery thrombosis and to ischaemic biliary tract lesions.

Technical complications

Most complications related to the biliary tree and to bleeding (table X). Ischaemic biliary tract lesions (IBTL) in the absence of, angiography proven, hepatic artery occlusion or stenosis accounted for one third of the biliary complications. In contrast to arterial and venous complications, not a single patient died during the early post-LT period as a consequence of biliary complications.

Changement of technique had a major influence on the incidence of perioperative bleeding and mortality related to bleeding (table VIII).

Intra-operative blood product use (less than one liter) lowered significantly ($p < 0.001$) and incidence of immediate extubation ($p < 0.01$) was enhanced significantly in Gr II (fig. 3).

Immunological complications (fig. 4)

With time the incidence of treated rejections lowered drastically from 96% during the first year of the study

Table X. — **Technical complications of adult liver transplantation**

Type	N	Patients N	Patients %	Grafts (%)	Early mortality
Biliary	73	66	16.7	16.7	0
Arterial	26	26	6.6	6.6	6 (23%)
• thrombosis	11				
• aneurysm	4				
• stenosis	6				
• splenic steel	5				
Venous	13	13	3.3	3.3	6 (46.2%)
• PV thrombosis	9				
torsion	1				
• Hepatic vein obstruction	3				
Haemorrhage	136	131	33.2	33.2	19 (14.5%)
VVB-complications	34	34/249	13.6	12	0

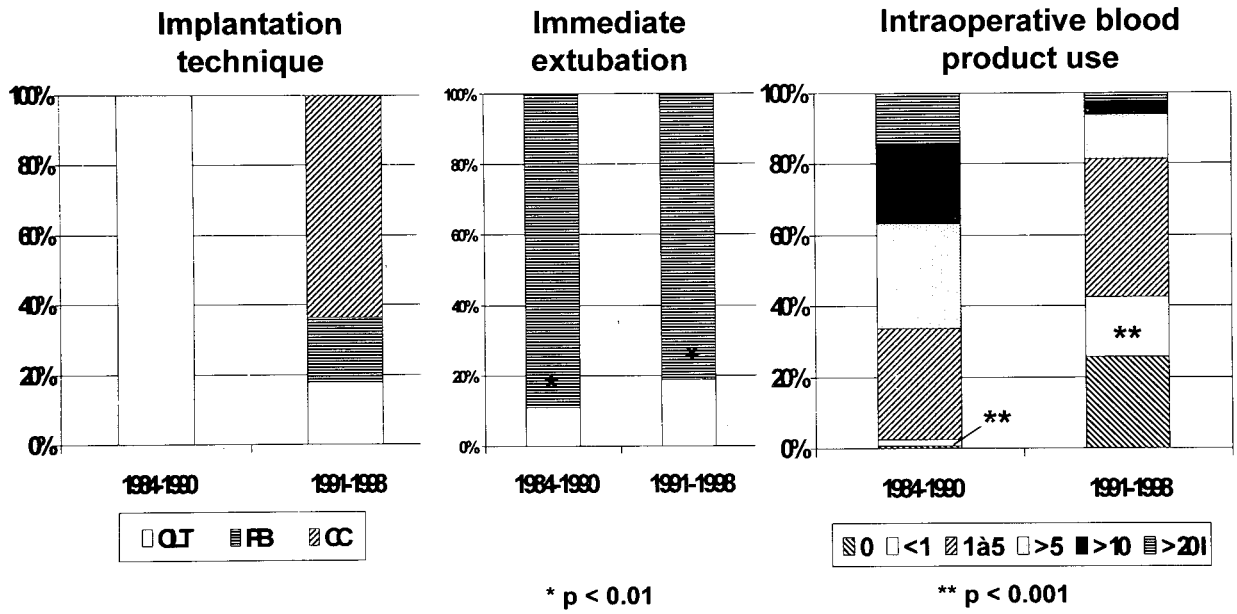

Fig. 3. — Influence of implantation technique on intraoperative blood product use and on duration of artificial ventilation.

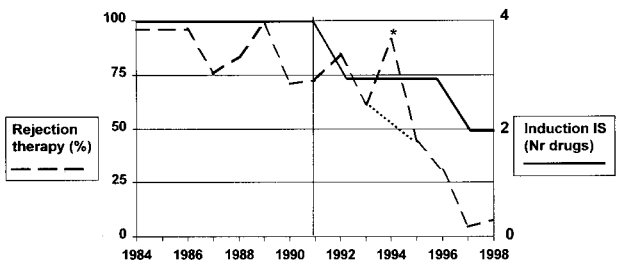

Fig. 4. — Evolution of immunosuppression strategy in adult liver transplantation (see text).

towards 7.7% at the end of the study, due to a better integration of biochemical, pathological and clinical data. The peak (91.7%) of treated rejection in 1994 related to a more rapid withdrawal of steroids leading many times to elevation of liver tests ; due to inexperience most of these patients were treated with 0,6 g of MP.

ABO incompatible grafting led to untreatable rejection in six of eight patients.

Liver transplantation for chronic benign liver diseases

284 patients (71.9%) were transplanted because of chronic benign liver diseases. One, five and ten years actuarial survival rates were respectively 77.3%, 66.1% and 58.7%.

The one, five and ten years survival rates of patients transplanted because of chronic hepatocellular diseases were 77.5, 74.9 and 55.7%. Best results were obtained in the cholestatic patient group with one, five and ten years survival rates of 79.4%, 73.4% and 68.1% (fig. 5).

The majority of LT in chronic benign liver diseases were done for chronic viral diseases (121/215 pat. - 54.4%).

One, five and ten years survival in patients transplanted because of postviral HCV liver cirrhosis were of 81.2%, 67.8% and 60.5%. 82.9% of patients presented

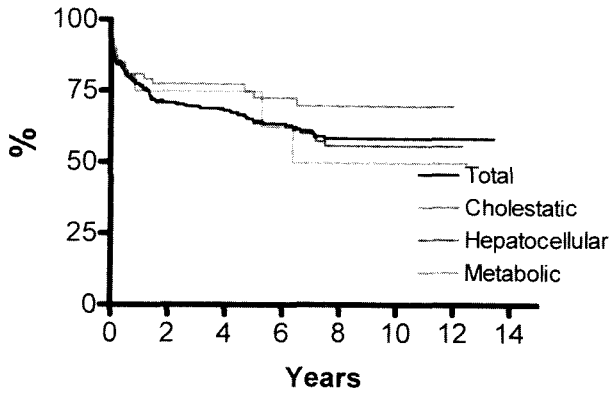

Fig. 5. — Actuarial survival following LT for bening chronic liver diseases.

allograft viral recurrent disease ; 15.8% of the 76 HCV long-term (> 3 mo.) survivors died due to recurrent viral allograft disease.

Patients transplanted for postviral B and B-delta cirrhosis had one, five and ten years actuarial survival rates of respectively 83.4%, 71.2% and 60.7%. The prognosis in this group was significantly influenced by adequate immunoprophylactic therapy (IP) using specific anti-HBs immunoglobulins (92.6% and 86.2% vs 69.2% and 50% one and five years survival in absence of IP - $p < 0.01$) as well by the presence of the co-infection with delta-virus (96.2% and 92.3% vs 75.2 and 54.9% one and five years survival in absence of B-delta co-infection - $p < 0.001$).

One and five years survival rates of non-replicating and replicating patients were not significantly different (85.9% and 78.1% vs 79% and 58.5%).

Liver transplantation for acute liver failure

Forty-four patients (11.1%) underwent LT for ALF ; their one, five and ten years actuarial survival rates were of 73.2%, 59.6% and 51.1%.

Early mortality was 21.4%. Gr II patients had a marked, although not yet significantly reduced mortality (table XI).

Standardized anti-infectious chemotherapy and perioperative care shifted the causes of death from infectious problems in Gr I (6/19 - 31.6%) towards cerebral failure in Gr II (3/25 - 12%). One of the latter patients died because of cerebral bleeding caused by the intracranial pressure monitoring device.

Table XI. — **Early mortality after adult liver transplantation for acute hepatic failure**

	Gr I - 1984-90	Gr II - 1991-98	Total series
Fulminant	5/14 (35.7%)	3/19 (15.8%)	8/33 (24.2%)
Subfulminant	1/5	0/6	1/11 (9.1%)
	6/19 (31.6%)*	3/25 (12%)*	9/44 (20.4%)

* $p < 0.1$.

Liver transplantation for hepatobiliary tumors

One, five and ten years actuarial survival rates of patients transplanted because of malignant tumors were respectively 80.6%, 44.3% and 36.7%. Long-term survival was clearly influenced by the stadification of the tumor disease (fig. 6).

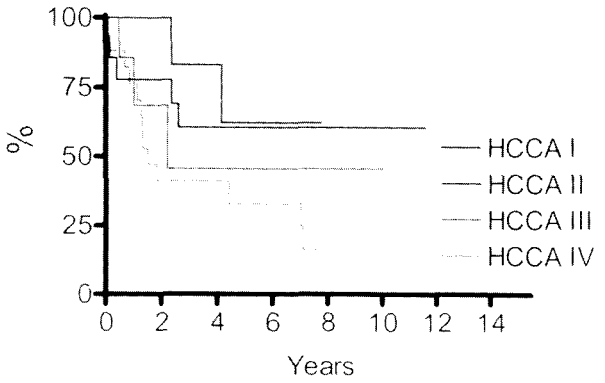

Fig. 6. — Actuarial survival following LT for hepatocellular cancer and cirrhosis.

Disease-free survival was significantly better for UICC stage I, II and III than for stage IV tumors (26/28 pat. - 92% vs 4/16 pat. - 25% - $p < 0.001$) (table XII).

Three long-term survivors transplanted because of cholangiocellular carcinoma died of tumor recurrence at 12, 36, 63 months ; one patient transplanted because of bile duct cancer died of tumor recurrence 12 months post-LT.

Table XII. — **Hepatocellular cancer in cirrhosis and adult liver transplantation : influence of tumor stadification**

UICC-stage			Disease free survival	
I	16	(12*)		
II	9	(7*)	26/28	(92.9%)°
III	7			
IV	17		4/16	(25%)°
	49	(12.4%)	30/44	(68.2%)

° $p < 0.001$.

* patients transplanted because of end-stage liver disease whilst presenting HCCa.

Four patients transplanted because of epithelioïd haemangioendothelioma were alive at 130, 130, 48 and 4 months ; one experienced allograft recurrence 10 years after LT.

Two patients, transplanted because of colorectal liver metastases, died of recurrent disease at 17 and 65 months post-LT.

Retransplantation

Fifty-four (13.6%) patients were retransplanted ; three of them at another institution. One, five and ten years

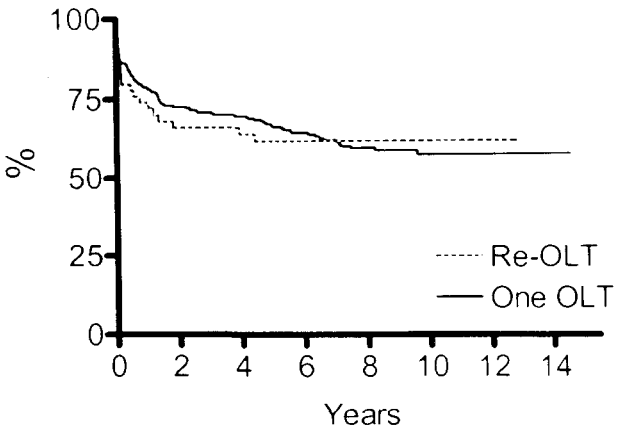

Fig. 7. — Actuarial survival following primary LT and retransplantation.

actuarial survival rates of retransplanted patients (74.1%, 61.8% and 61.8%) were similar to those of the non re-LT patients (fig. 7).

Early mortality was highest in the patient group retransplanted because of graft dysfunction (5/21 pat. - 23.8%) and because of acute or chronic graft rejection (7/18 pat. - 38.9%) (table XIII).

Only one (8.3%) of the 12 patients retransplanted because a technical failure died after re-LT.

Early mortality after elective re-LT was, although not significantly, different than that after urgent re-LT (2/22 pat. - 9.1% vs 11/32 pat. - 34.4% - $p < 0.06$).

Similarly, early mortality after re-LT in Gr II was, although not yet significantly, improved (4/28 pat. - 14% vs 7/23 Gr I patients - 30.4%).

Liver transplantation in the presence of splanchnic vein modifications

Sixty-six (16.7%) patients were transplanted whilst having major modifications of the splanchnic venous system (table XIV).

Early mortality of this group was 21.2% (14/66 patients). Due to modification of techniques, mortality could be significantly lowered in Gr II patients (3/40 pat. - 7.5% vs 11/25 pat. - 42.3% - $p < 0.05$).

Table XIV. — **Early posttransplant mortality in case of splanchnic venous abnormalities**

	1984-90		1991-98	
Incidence	26/174	(14.9%)	40/221	(18.1%)
PVT	2/11	(18.2%)	2/29	(6.9%)
PVT-itis	4/4	(100%)	1/5	(20%)*
PH Surgery	5/11	(45.5%)	0/6	(0%)
	11/26	(42.3%)*	3/40	(7.5%)*

* $p < 0.05$.

Cost-containment of LT and re-LT (table XV)

Costs of elective primary transplants lowered over time. This cannot be said about costs of emergency procedures, which enhanced especially due to the fact that several of these patients, who had been waiting for quite a while, were grafted in extremely advanced stages.

Costs of elective re-LT were almost equal to those of elective primary LT. Costs of urgent re-LT were highest but these figures mostly represented costs related to two successive transplant procedures done during one same hospitalization.

Discussion

After a 20 year long period, between 1963-1983, liver transplantation finally broke through due to amelioration of results mainly related to the introduction of cyclosporine in clinical solid organ transplantation. Improvement of results lead to rapid widening of its indications for different acute and chronic liver diseases (1). A critical review of a larger single centre adult series is a good means to define progress, possibilities and limitations of the procedure (1,13,14).

Our results reflect the learning curves in relation to indications and (peri)operative management. Standar-

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

		Patients	Grafts	Mortality	
			Early	Late	
Graft dysfunction	primary	8	8	2	2
	early	13□•°	14	3	2
Technical failure	art. thrombosis	4□	5	1	—
	decapsulation	1	1	—	—
	IBTL	7•	7	—	—
Immunological rejection	acute	8□	9	5	—
	chronic	10°	10	2	1
Recurrent disease	HBV	4	4	—	2
	HCV	1	1	—	
		54 **14%**	59	13 **24%**	7

•° same patients □ two re-LT for same indication.

Table XV. — **Adult liver (re)transplantation and total costs of first hospitalisation**

	Liver Transplantation		Liver Retransplantation	
Time period	Elective	Urgent	Elective	Urgent°
1990-91	1.390.633* (0.9 to 4.4)	2.223.590 (1 to 5.2)	1.259.417 (0.9 to 1.6)	1.939.361 (1.6 to 6.2)
1992-93	1.407.898 (0.8 to 4.2)	1.773.558 (1.4 to 2.9)	/	2.284.829 (1.7 to 5.1)
1994-95	1.228.914 (0.9 to 3.9)	2.009.759 (1.2 to 8.5)	1.257.984 (0.9 to 1.9)	1.970.439 (1.7 to 2)
1996-97	1.098.367 (0.8 to 2.9)	2.563.572 (1.5 to 8.6)	/	4.229.477 (3.2 to 5.2)

* median values in BF.
° includes costs of primary and urgent re-LT.

dization of operative and perioperative care significantly reduced early morbidity and mortality, merely related to bleeding and infectious complications. Modification of recipient hepatectomy, preserving the R-IVC, as well as modification of the allograft implantation technique, using PB-CC anastomosis, contributed to reduction of need for blood product use (5). PB-CC allows moreover to do allograft implantation without VVB-use, which is responsible for quite a number of specific complications (15). Adapted procedures in case of splanchnic vein thrombosis, nl venous eversion thrombectomy and venous iliac graft interposition between donor portal vein and recipient's mesenteric vein, should be decided early during intervention in order to minimize hazardous perihilar or retropancreatic dissection ; patients having inflammatory changes of splanchnic veins remain the most difficult group to manage (6,16,17).

Arterial and venous technical complications are rather unfrequent in adult LT (17,18), biliary tract complications, in contrary, remain a reason of concern (1,19).

The spectrum of biliary tract lesions has changed drastically since the prolongation of ischaemia times due to introduction in clinical practice of "better" preservation solutions as e.g. University of Wisconsin solution (19,20).

Biliary tract reconstruction complications, once the Achilles heel of LT, have been replaced by intra- or extra-hepatic IBTL (1,20,21). Ischaemic damage of the biliary mucosa, in the absence of hepatic artery allograft thrombosis, is responsoble for diffuse modifications necessitating interventional radiological procedures and even re-LT. In case of biliary infections, re-LT should done timely. Its incidence can be reduced by shortening ischaemia times, as well as by adequate lavage of the biliary system at organ procurement (19,22). Because differential diagnosis between IBTL and rejection can be very difficult or even impossible, agressive investigation of the biliary tree using different kinds of cholangiography must be realized if cholestatic enzymes remain elevated (1,20).

Improvement of results is also related to the use of a standardized systemic and topical, antimicrobial chemoprophylaxis and of a less aggressive IS guided by closer correlation between clinical, biochemical and histological findings. Standardized prophylactic, systemic and topical, antimicrobial therapy reduces the incidence of infection (8,11). Prophylactic antiviral, antimycotic and antiprotozoal treatments allow an efficient control of most of the infectious problems encountered after LT (9,10,11). Using such prophylactic regimen, successful LT is now possible even in the presence of localized infections.

Late post-LT morbidity and mortality are essentially dominated by viral and tumoral recurrent allograft diseases and by several long-term consequences of IS (1).

Allograft recurrence of hepatitis B viral infection can be almost completely prevented by a life-long, adequate, use of immunoprophylaxis against the B virus using specific anti-HBs immunoglobulins with or without antiviral nucleoside analogues (11,23). Under this condition, LT is even successful in replicating cases (24,25).

Selection of HCV patients for LT should be done cautiously as allograft HCV-recurrence is common after LT. Recurrence can even have a rapid lethal outcome. Due to insufficient serological markers and to its aspecific histologic criteria the "natural" evolution of this viral allograft disease is not yet fully understood. Effective prophylactic or therapeutic treatments are not yet available (26). Encouraging results have been published recently in relation to the combined pre- and post-LT use of interferon and ribavirine (27).

Progress in the peri-LT care had a major impact on outcome of LT for patients presenting acute liver failure. The decision for LT should be made before infectious and/or renal complications occur (28). Indication for LT can be made based on the combination of evolution of encephalopathy and of coagulation factors (2). Invasive intraarterial pressure monitoring should be used selectively as intracerebral bleeding may occur (28).

In view of the actual donor organ shortage, indication of LT for cholangiocarcinoma and for primary hepatocellular cancer in cirrhotic patients must be res-

tricted (3,29,30). Results of LT are excellent if restricted to solitary lesions (up to 3-5 cm diameter) and up to 3 nodules smaller than 3 cm without macrovascular invasion (12,31), findings usually corresponding to UICC stage I, II and III tumors. Results of stage IV tumors, representing mostly bilobar lesions with macrovascular invasion, are poor ; tumor recurrence within 2 to 3 years after LT is the rule (32).

All investigations should therefore be done in order to determine as precisely as possible the extention of the tumor. The final decision for LT must be taken at surgery. Value of pre- and post-LT intraarterial and/or systemic chemotherapy as well as the influence of the different kinds of IS on results of LT for cancer patients need to be examined by controlled clinical trials (32,33,34).

Nocive effects of prolonged and/or inadequate IS are well demonstrated by the development of lymphoproliferative disorders and by the late mortality due to de novo cancers, infectious and cardiovascular complications (1,35). The benefits of the lowest IS as possible, of the steroid withdrawal regimen and the refrained treatment of rejection have been well demonstrated (36,37,38). Steroid withdrawal moreover markedly improves quality of life by reducing the inherent side-effects of IS (38,39,40).

Re-LT can be the only outcome for graft dysfunction, immunological and technical failure as well as recurrent allograft disease. Early graft dysfunction becomes rather unusual due to the introduction of better preservation solutions and to better transplant surgery (5,14,19,21, 41). Its incidence can be reduced by shortening of ischaemia times, by avoiding implantation of severely steatotic grafts (1,19) and possibly, by introduction during immediate post-LT period of protecting prostaglandines E1 (7). As already stated re-LT for technical failure has moved from arterial and venous problems towards diffuse IBTL. Re-LT for graft dysfunction and immunological failure has a high early morbidity and mortality reflecting respectively the urgent degree of the procedure and the realisation of the procedure in an overimmunosuppressed patient. ABO incompatible grafts should anyway be avoided as the constellation is mostly responsible for uncontrolable rejection (1).

Re-LT, a major rescue operation, can be done with equal success to primary LT when aiming at elective surgery ; this means early relisting under maximal reduction or even withdrawal of IS (43).

The review of this larger adult single center liver transplant series confirms that LT can be performed with success in chronic as well as in acute liver diseases.

Major improvements are necessary in (neo)adjuvant treatment of hepatocellular malignancies (33,34) and of viral, especially HCV, diseases (26).

All progresses are in favour of the development of a procedure which becomes, not only medically, but also economically justified (43). The cost analysis survey of LT done at our institution shows that transplantation and re-LT can be done at an acceptable price.

Morbidity and mortality have significantly decreased by developing simpler technical procedures and by standardization of anti-infectious and anti-rejection chemotherapy (1,5,6,12,13,41,44). Results can be further improved by introducing the concept of operational tolerance making aggressive IS unnecessary (45,46). Better interpretation and correlation of clinical, biochemical and histological criteria of acute cellular rejection made it clear that, even severe, histological rejection doesn't always deserve aggressive IS treatment (47,48). Immunological attack of the graft may even be beneficial in the long-term ; indeed, interplay of donor and recipient immunological systems can lead to a state of tolerance based on the concept of microchimerism (45).

The major problem of the future remains the organ shortage. This must oblige transplant surgeons to develop as much as possible all available alternative techniques of allograft implantation such as split liver (49,50,51,52), domino procedures (53) and adult living related LT (54,55). Lessons learned out of larger experiences must contribute to improve the results of LT thereby consolidating its value in modern hepatology. Indeed, too many patients are still referred (too late) to the transplant centre in the end-stage of their acute and chronic liver diseases.

Acknowledgements

This study was supported by a grant from Euroliver Foundation - Belgium.

The authors want to thank all transplant coordinators and all nursing teams of Cliniques Universitaires St-Luc but especially F. Roggen, clinical transplant coordinator, M. Vanaise and F. Verheye, head nurses and the nurses of Digestive Surgery (Unit 53) and of Intensive Care (Unit C) involved in the care of the transplant patients ; the obtained results reflect their continuous and relentless support and enthousiasm.

References

1. STARZL T.E. and DEMETRIS A.J. Liver transplantation. Year Book Med. Publ. Chicago, 1994.
2. PAUWELS A., MOSTEFA-KARA N., FLORENT C., LEVY V.G. Emergency liver transplantation for acute liver failure. Evaluation of London and Clichy criteria. *Jrl. of Hepatology*, 1993, **17** : 124-127.
3. RINGE B., WITTEKIND C., BECHSTEIN W.O., BUNZENDAHL H., PICHLMAYR R. The role of liver transplantation in hepatobiliary malignancy. A retrospective analysis of 95 patients with particular regard to tumor stage and recurrence. *Ann. Surg.*, 1989, **209** : 88-98.
4. BELGHITI J., PANIS Y., SAUVANET A., GAYET B., FEKETE F. A new technique of side to side caval anastomosis during orthotopic hepatic transplantation without inferior vena caval occlusion. *SGO*, 1992, **75** : 271-272.
5. LERUT J., MOLLE G., DONATACCIO M., DE KOCK M., CICCARELLI O., LATERRE P.F., VAN LEEUW V., BOURLIER P., de VILLE

de GOYET J., REDING R., GIBBS P., OTTE J.B. Cavocaval liver transplantation without venovenous bypass and without temporary portocaval shunting : the ideal technique for adult liver grafting ? *Transpl. Int.*, 1997, **10** : 171-179.
6. LERUT J., MAZZA D., VAN LEEUW V., LATERRE P.F., DONATACCIO M., de VILLE de GOYET J., VAN BEERS B., BOURLIER P., GOFFETTE P., PUTTEMANS Th., OTTE J.B. Adult liver transplantation and abnormalities of splanchnic veins : experience in 53 patients. *Transpl. Int.*, 1997, **10** : 125-132.
7. HENLEY K.S., LUCEY M.R., NORMOLLE D.P., MERION R.M., McLAREN I.D., CRIDER B.A., MACKIE D.S., SHIECK V.L., NOSTRANT T.T., BROWN K.A., CAMPBELL D.A., HAM J.M., APPELMAN H.D., TURCOTTE J.G. A double-blind randomized, placebo-controlled trial of Prostaglandin E1 in liver transplantation. *Hepatology*, 1995, **21** : 366-372.
8. REDING R., FEYAERTS A., VRAUX H., LATINNE D., DE LA PARRA B., CORNET A., CORMONT Fr., JAMART J., SOKAL E., de VILLE de GOYET J., LERUT J., BAZIN H., OTTE J.B. Prophylactic immunosuppreesion with anti-interleukin-2 receptor monoclonal antibody Lo-Tact-1 versus OKT3 in liver allografting. A two-year follow-up study. *Transplantation*, 1996, **61** : 1406-1409.
9. WIESNER R.H., HERMANS P.E., RAKELA J., WASHINGTON J.A., PERKINS J.D., DICECCO S., KROM R. Selective bowel decontamination to decrease gram-negative aerobic bacterial and candida colonization and prevention infection after orthotopic liver transplantation. *Transplantation*, 1988, **45** : 570-574.
10. BADLEY A.D., SEABERG E.C., PORAYKO M.K., WIESNER R.H., KEATING M.R., WILHELM M.P., WALKER R.C., PATEL R., MARSHALL W.F., DEBERNARDI M., ZETTERMAN R., STEERS J.L., PAYA C.V. Prophylaxis of cytomegalovirus infection in liver transplantation. *Transplantation*,1997, **64** : 66-73.
11. CASTALDO P., STRATTA R.J., WOOD R.P., MARKIN R.S., PATIL K.D., SHAEFER M.S., LANGNAS A.N., REED E.C., LI S., PILLEN T.J., SHAW B.W.,-Clinical spectrum of fungal infections after orthotopic liver transplantation. *Arch. Surg.*, 1991, **126** : 149-156.
12. SAMUEL D., MULLER R., ALEXANDER G., FASSATI L., DUCOT B., BENHAMOU J.P., BISMUTH H., and the Investigators of the European Concerted Action on Viral Hepatitis Study. Liver transplantation in European patients with the hepatitis B surface antigen. New Engl. J. Med., 1993, **329** : 1842-1847.
13. BISMUTH H., FARGES O., CASTAING D., SAMUEL D., ADAM R., JOHANN M., AZOULAY D., FERAY C., ASTARCIOGLU I., SALIBA F. Evaluation des résultats de la transplantation hépatique : expérience sur une série de 1052 transplantations. *Presse Med.*, 1995, **24** : 1106-14.
14. BUSUTTIL R.W., SHAKED A., MILLIS J.M., JURIM O., COLQUHOUN S.D., SHACKLETON C.R., NUESSE B.J., CSETE M., GOLDSTEIN L.I., McDIARMID S.V. One thousand liver transplants. The lessons learned. *Ann. Surg.*, 1994, **219** : 490-499.
15. CHARI R.S., GAN T.J., ROBERTSON K.M., BASS K., CAMARGO C.A., GREIG P.D., CLAVIEN P.A. Venovenous bypass in adult orthotopic liver transplantation : routine or selective use ? *J. Am. Coll. Surg.*, 1998, **186** : 683-690.
16. SEU P., SHACKLETON C.R., SHAKED A., IMAGAWA D.K., OLTHOFF K.M., RUDICH S.R., KINKHABWALA M., BUSUTTIL R.W. Improved results of liver transplantation in patients with portal vein thrombosis. *Arch. Surg.*, 1996, **131** : 840-845.
17. LERUT J., TZAKIS A.G., BRON K., GORDON R.D., IWATSUKI S., ESQUIVEL C.O., MAKOWKA L., TODO S., STARZL T.E. Complications of venous reconstruction in human orthotopic liver transplantation. *Ann. Surg.*,, 1987, **205** : 404-414.
18. TZAKIS A., GORDON R.D., SHAW B.W., IWATSUKI S., STARZL T.E. Clinical presentation of hepatic artery thrombosis after liver transplantation in the cyclosporine era. *Transplantation*, 1985, **40** : 667-671.
19. STRASBERG S.M., HOWARD T.K., MOLMENTI E.P., HERTL M. Selecting the donor liver : risk factors for poor function after orthotopic liver transplantation.
Hepatology, 1994, **20** : 829-838.
20. SANCHEZ-URDAZPAL L., GORES G.J., WARD E.M., MAUS T.P., WAHLSTROM H.E., MOORE S.B., WIESNER R.H., KROM R.A. Ischemic-type biliary complications after orthotopic liver transplantation. *Hepatology*, 1992, **16** : 49-53.
21. LERUT J., GORDON R.D., IWATSUKI S., ESQUIVEL C.O., TODO S., TZAKIS A., STARZL T.E. Biliary tract complications in human orthotopic liver transplantation. *Transplantation*, 1987, **43** : 47-51.
22. LERUT J, de VILLE de GOYET J. Technique of multiorgan procurement. *Current opinion in organ transplantation*, 1997, **2** : 157-163.
23. NERY J.R., WEPPLER D., RODRIGUEZ M., RUIZ M., RUIZ P., SCHIFF E.R., TZAKIS A.G. Efficacy of Lamivudine in controlling hepatitis B virus recurrence after liver transplantation. *Transplantation*, 1998, **65** : 1615-1621.
24. KONIG V., HOPF U., NEUHAUS P., BAUDITZ J., SCHMIDT C.A., BLUMHARDT G., BECHSTEIN W.O., NEUHAUS R., LOBECK H. Long-term follow-up of hepatitis B virus-infected recipients after orthotopic liver transplantation. *Transplantation*, 1994, **58** : 553-559.
25. LERUT J.P., DONATACCIO M., CICCARELLI O., ROGGEN Fr., JAMART J., LATERRE P.F., CORNU Ch., MAZZA D., HANIQUE G., RAHIER J., GEUBEL A.P., OTTE J.B. Liver transplantation and HBsAG-positive postnecrotic cirrhosis : adequate immunoprophylaxis and delta virus co-infection as the significant determinants of long-term prognosis. *Jrl. Hepatology,*, 1999, in press.
26. ARAYA V., RAKELA J., WRIGHT T. Hepatitis C after orthotopic liver transplantation. *Gastroenterology*, 1997, **112** : 575-582.
27. CATTRAL M.S., KRAJDEN M., WANLESS I.R., REZIG M., CAMERON R., GREIG P.D., CHUNG S.W., LEVY G.A. A pilot study of Ribavirin therapy for recurrent hepatitis C virus infection after liver transplantation. *Transplantation*, 1996, **61** : 1483-1488.
28. HOOFNAGLE J.H., CARITHERS R.L., SHAPIRO C., ASHER N. Fulminant hepatic failure : summary of a workshop. *Hepatology*, 1995, **21** : 240-252.
29. FARMER D.G., ROSOVE M.H., SHAKED A., BUSUTTIL R.W. Current treatment modalities for hepatocellular carcinoma. *Ann. Surg.*, 1994, **219** : 236-247.
30. MADARIAGA J.R., IWATSUKI S., TODO S., LEE R.G., IRISH W., STARZL T.E. Liver resection for hilar and peripheral cholangiocarcinomas : a study of 62 cases. *Ann. Surg.*, 1998, **227** : 70-79.
31. MAZZAFERRO V., REGALIA E., DOCI R., ANDREOLA S., PULVIRENTI A., BOZZETTI F., MONTALTO F., AMMATUNA M., MORABITO A., GENNARI L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N. Engl. J. Med.*, 1996, **334** : 693-699.
32. CARR B.I., SALLY R., MADARIAGA J., IWATSUKI S., STARZL T.E. Prolonged survival after liver transplantation for advanced hepatocellular carcinoma.
Transplant Proc., 1993, **25** : 1128-1129
33. LIVRAGHI T., GIORGIO A., MARIN G., SALMI A., de SIO I., BOLONDI L., PIMPILI M., BRUNELLO F., LAZZARONI S., TORZILLI G., ZUCCHI A. Hepatocellular carcinoma and cirrhosis in 746 patients : long-term results of percutaneous ethanol injection. *Radiology*, 1995, **197** : 101-108.
34. RYU M., SHIMAMURA Y., KINOSHITA T., KONISHI M., KAWANO N., IWASAKI M., FURUSE J., YOSHINO M., MORIYAMA N., SUGITA M. Therapeutic results of resection, transcatheter arterial embolization and percutaneous transhepatic ethanol injection in 3225 patients with hepatocellular carcinoma : a retrospective multicenter study. *Am. J. Clin. Oncol.*, 1995, **27** : 251-257.
35. STARZL T.E., PORTER K.A., IWATSUKI S., ROSENTHAL J.T., SHAW B.W., ATCHISON R.W., NALESNIK M.A., HO M., GRIFFITH B.P., HAKALA T.R., HARDESTY R.L., JAFFE R., BAHNSON H.T. Reversibility of lymphomas and lymphoproliferative lesions developing under cyclosporin-steroid therapy. *Lancet*, 1984, **17** : 584-587.
36. STEGALL M.D. EVERSON G.T., SCHROTER G., BILIR B., KARRER F., KAM I. Metabolic complications after liver transplantation. *Transplantation*, 1995, **60** : 1057-1060.
37. PADBURY R.T.A., GUNSON B.K., DOUSSET B., HUBSCHER S.G., BUCKELS J.A.C., NEUBERGER J.M., ELIAS E., McMASTER P. Steroid withdrawal from long-term immunosuppression in liver allograft recipients. *Transplantation*, 1993, **55** : 789-794.
38. PADBURY R., TOOGOOD G., McMASTER P. Withdrawal of immunosuppression in liver allograft recipients. *Liver Transplantation and Surg.*, 1998, **4** : 242-248.
39. STEGALL M.D., EVERSON G.T., SCHROTER G., KARRER F.K., BILIR B., STEINBERG T., SHRESTHA R., WACHS M., KAM I. Prednisone withdrawal late after adult liver transplantation reduces diabetes. Hypertension, and hypercholesterolemia without causing graft loss. *Hepatology*, 1997, **25** : 173-177.
40. BELLI L., DECARLIS L., RONDINARA G., ALBERTI A., BELLATI G., DEGASPERI A., FORTI D., IDEO G. Early cyclosporine monotherapy in liver transplantation : a 5 year follow-up of a prospective randomized trial. *Hepatology*, 1998, **27** : 1524-1529.
41. DESCHENES M., VILLENEUVE J.P., DAGENAIS M., FENYVES D., LAPOINTE R., POMIER-LAYROIGUES , RAY A., WILLEMS B., MARLEAU D. Lack of relationship between preoperative measures of the severity of cirrhosis and short-term survival after liver transplantation. Liver *Transplantation and Surg.*, 1997, **3** : 532-537.
42. MARKMANN J.F., MARKOWITZ J.S., YERSIZ H., MORRISEY M., FARMER D.G., FARMER D.A., GOSS J., GHOBRIAL R., McDI-

ARMID S.V., STRIBLING R., MARTIN P., MARTIN P., GOLDSTEIN L.I., SEU P., SHACKLETON C., BUSUTTIL R.W. Long-term survival after retransplantation of the liver. *Ann. Surg.,*, 1997, **226** : 408-420.
43. EVANS R.W., MANNINEN D.L., DONG F.B. An economic analysis of liver transplantation. *Gastroenterology Clin. N. Am.*, 1993, **22** : 451-472.
44. CACCIARELLI T.V., KEEFFE E.B., MOORE D.H., BURNS W., CHULJIAN P., BUSQUE S., CONCEPCION W., SO S.K.S., ESQUIVEL C.O. Primary liver transplantation without transfusion of red blood cells. *Surgery*, 1996, **120** : 698-705.
45. STARZL T.E., DEMETRIS A.J., TRUCCO M., MURASE N., RICORDI C., ILDSTAD S., RAMOS H., TODO S., TZAKIS A., FUNG J.J., NALESNIK M., ZEEVI A., RUDERT W.A., KOCOVA M. Cell migration and chimerism after whole-organ transplantation : the basis of graft acceptance. *Hepatology*, 1993, **17** : 1127-1152.
46. MAZARIEGOS G.V., REYES J., MARINO I., DEMETRIS A., FLYNN B., IRISH W., McMICHAEL J., FUNG J., STARZL T.E. Weaning of immunosuppression in liver transplant recipients. *Transplantation*, 1997, **63** : 243-249.
47. McVICAR J.P., KOWDLEY K.V., BACCHI C.E., BARR D., MARSH C.L., PERKINS J.D., CARITHERS R.L. The natural history of untreated focal allograft rejection in liver transplant recipients. *Liver Transplantation and Surg.*, 1996, **2** : 154-160.
48. NEUBERGER J., ADAMS D.H. What is the significance of acute liver allograft rejection? *Jrl Hepatology*, 1998, **29** : 143-150.
49. PICHLMAYR R., RINGE B., GUBERNATIS G., HAUSS J., BUNZENDAHL H. Transplantation einer Spenderleber auf zwei Empfänger (Splitting-Transplantation) - Eine neue Methode in der Weiterentwicklung der Lebersegmenttransplantation. *Langenb Arch. Chir.*, 1988, **373** : 127-130.
50. BROELSCH C.E., EMOND J.C., WHITINGTON P.F., THISTLETHWAITE J.R., BAKER A.L., LICHTOR J.L. Application of reduced-size liver transpantation : split grafts, auxiliary orthotopic grafts and living related segmental transplants. *Ann. Surg.*, 1990, **212** : 368-377.
51. OTTE J.B., de VILLE de GOYET J., ALBERTI D., BALLADUR P., de HEMPTINNE B. The concept and technique of the split liver in clinical transplantation. *Surgery*, 1990, **107** : 605-612.
52. GOSS J.A., YERSIZ H., SHACKLETON C.R., SEU P., SMITH C.V., MARKOWITZ J.S., FARMER D.G., GHOBRIAL R.M., MARKMANN J.F., ARNAOUT W.S., IMAGAWA D.K., COLQUHOUN S.D., FRAIMAN M.H., McDIARMID S.V., BUSUTTIL R.W. In situ splitting of the cadaveric liver for transplantation. *Transplantation*, 1997, **64** : 871-877.
53. FURTADO A., TOME L, OLIVEIRA F.J., FURTADO E., VIANA J., PERDIGOTO R. Sequential liver transplantation. *Transplantation Proceedings*, 1997, **29** : 467-468.
54. TANAKA K., INOMATA Y. Present status and prospects of living-related liver transplantation. *J. Hep. Bil. Pancr. Surg.*, 1997, **4** : 51-70.
55. KAWASAKI S., MAKUUCHI M., MATSUNAMI H., HASHIKURA Y., IKEGAMI T., NAKAZAWA Y., CHISUWA H., TERADA M., MIYAGAWA S.I. Living related liver transplantation in adults. *Ann. Surg.*, 1998, **227** : 269-274.