Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Long-term results after liver transplantation

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Keywords
complications, liver transplantation, long-term results, survival.

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Received: 14 December 2006
Revision requested: 9 January 2007
Accepted: 15 October 2007

doi:10.1111/j.1432-2277.2007.00596.x

Summary

Liver transplantation (OLT) has become a successful surgical therapy for terminal liver failure. We here report about long-term results of OLT in a single center over a period of 15 years. Between 1988 and 2002, 1365 adult OLTs were performed. Mean follow-up was 103 ± 56 months. Main indications for OLT were viral-induced cirrhosis (27.1%), alcoholic liver disease (21%), tumors (15.7%) and cholestatic liver disease (14.6%). Retransplantation was necessary in 120 (9.6%) patients because of initial nonfunction (26.9%), recurrence of underlying disease (20.2%), acute and chronic rejection (16.8%) or thrombosis of the hepatic artery (16.8%). 275 patients (22.1%) died. Causes of death included recurrence of disease (32.1%), infections (21.8%), *de novo* malignancies (13.5%) and cardiovascular disease (11.6%). Patient survival after OLT was 91.4%, 82.5%, 74.7% and 68.2% after 1, 5, 10 and 15 years, and graft survival was 85.8%, 75.3%, 67.3% and 61.7% after 1, 5, 10 and 15 years, respectively. Patient survival after retransplantation was 81.6%, 68.8% and 57.1% and 48.0% after 1, 5, 10 and 15 years. This analysis reveals excellent long-term results after OLT achieved in a single center.

Introduction

For more than two decades, liver transplantation (OLT) has become standard therapy for patients with terminal liver failure. Continuous improvements in immunosuppression [1], surgical technique, peri-operative and intensive care management [2,3] allow 1-year-survival rates of more than 90.0% and 10-year-survival rates of up to 70.0% in experienced transplant centers [4–9]. Because of these encouraging results, the spectrum of patients considered eligible for OLT has steadily increased and currently includes also patients with malignancies such as irresectable hepatocellular carcinoma [10–12].

Infections and acute rejections are still the major complications during the early postoperative period [3,13], whereas development of *de novo* malignancies, occurrence of cardiovascular diseases and recurrence of the primary disease are reasons for poor outcome in the long-term course [8,9,14–17].

Most reports focus on subgroups of patients, while there are only few reports analysing long-term results of all patients transplanted in a single center [8,9,14–17]. We here report about the outcome of more than 1300 OLTs performed in our center over a period of 15 years.

Patients and methods

Between 1988 and 2002 1365 cadaveric OLTs in 1245 adults (727 males, 518 females, mean age 47.2 ± 11.2 years) were performed. Indications for OLT and re-OLT are listed in Tables 1 and 2. Preoperative Child–Pugh score was documented in 1174 recipients [Child A $n = 201$ (17.1%); B $n = 641$ (54.6%); C $n = 332$ (28.3%)] and original MELD score could be calculated in 1230 patients at the time of OLT [MELD ≤ 10 $n = 219$ (17.8%); MELD 11–18 $n = 498$ (40.5%); MELD 19–24 $n = 168$ (13.7%); MELD ≥ 25 $n = 345$ (28.0%)]. One thousand one hundred and twenty-five patients received one, 109 patients a second and 11 patients a third graft. Twenty-five patients underwent split-liver transplantation using the right lobe in

Table 1. Indications for liver transplantation.

Indications	Patients (*n*)	(%)
Viral-induced cirrhosis	**337**	**27.1**
Hepatitis B virus (HBV)	158	12.7
Hepatitis C virus (HCV)	165	13.3
Hepatitis B + C	14	1.1
Alcoholic liver disease	**261**	**21.0**
Tumor	**195**	**15.7**
Hepatocellular carcinoma (HCC)	60	4.9
HCC associated with HBV cirrhosis	29	2.3
HCC associated with HCV cirrhosis	56	4.5
Cholangiocellular carcinoma	24	1.9
Cystic liver disease	19	1.5
Carcinoid metastases	6	0.5
Malignant hemangioendothelioma	1	0.1
Cholestatic liver disease	**182**	**14.6**
Primary biliary cirrhosis	96	7.7
Primary sclerosing cirrhosis	67	5.4
Secondary cholestasis	11	0.9
Congenital cholestasis	5	0.4
Caroli's syndrome	3	0.2
Cryptogenic cirrhosis	**80**	**6.4**
Acute liver failure	**70**	**5.6**
Cryptogenic	28	2.2
Hepatitis B infection	19	1.5
Budd–Chiari	8	0.6
Toxic agent	6	0.5
Hepatitis C infection	3	0.2
Wilson's disease	3	0.2
Hepatitis A infection	1	0.1
Autoimmune	1	0.1
Trauma	1	0.1
Metabolic liver disease	**48**	**3.9**
Wilson's disease	15	1.2
Hemochromatosis	12	1.0
Alpha1-anti-trypsine deficiency syndrome	8	0.6
Cystic fibrosis	4	0.3
Oxalosis	3	0.2
Porphyria	2	0.2
Medicamentous-toxic	2	0.2
Glykogenosis type 1	1	0.1
Amyloidosis	1	0.1
Autoimmune cirrhosis	**47**	**3.8**
Vascular liver disease	**25**	**2.0**
Budd–Chiari syndrome	20	1.6
Osler's disease	5	0.4
Total	**1245**	**100.0**

Table 2. Indications for retransplantation.

Indication	Patients (*n*)	(%)
Initial nonfunction	**32**	**26.7**
Recurrence of underlying disease	**28**	**23.3**
Hepatitis B virus	13	10.8
Hepatitis C virus	12	10.0
Budd–Chiari	2	1.7
Primary sclerosing cirrhosis	1	0.8
Vascular complications	**21**	**17.5**
Hepatic artery thrombosis	17	14.1
Portal vein thrombosis	2	1.7
Thrombosis/stenosis of the vena cava	2	1.7
Rejection	**19**	**15.8**
Chronic rejection	12	10.0
Acute rejection	7	5.8
Ischemic type biliary lesions	**18**	**15.0**
***De novo* hepatitis B**	**2**	**1.7**
Acute liver failure	1	0.8
Cirrhosis	1	0.8
Total	**120**	**100.0**

piggy-back technique. Forty-three OLTs were combined with renal transplantation and 18 with simultaneous partial pancreatoduodenectomy for bile duct carcinoma. Mean waiting time was 95 days (range: 0–818 days). One thousand and two hundred and ninety-six grafts were preserved with University-of-Wisconsin-solution and 69 with Histidine-Tryptophane-Ketoglutarate-solution. Mean cold ischemia-time was 9.8 ± 3.5 h. Mean donor age was 37.9 ± 15.7 years (range: 7–80 years). All OLTs, except split-transplantation, were performed with standard technique using veno-venous bypass. Following completion of all vascular anastomosis with end-to-end cavo-caval, end-to-end porto-portal and end-to-side arterio-arterial anastomosis, biliary anastomosis was performed as side-to-side (n = 1218; 89.2%) or end-to-end (n = 27, 2.0%) choledocho-choledochostomy with routine insertion of a t-drain. Hepaticojejunostomy or hepatico-duodenostomy was performed in 120 pts (8.8%), predominantly in patients with PSC. Mean operation time was 337 ± 93 min. (range: 160–840) for OLT and 347 ± 124 min. for re-OLT.

Immunosuppression

Immunosuppression consisted of either Cyclosporine (CsA) or Tacrolimus (Tac) based regimens. Five hundred and fifty-two patients (44.3%) received CsA and 693 patients (55.7%) Tac-based protocols. Until 1995, quadruple induction therapy with anti-thymocyte globulin or anti-interleukin-2 receptor antibody, azathioprine and steroids was performed. Thereafter, protocols consisted of Tac, basiliximab and low-dose steroids with or without mycophenolatemofetil. Target Tac whole blood trough levels for the first month after OLT were 10–12 ng/ml and 5–10 ng/ml for the first postoperative year, for CsA 150–250 ng/ml and 100–180 ng/ml, respectively. Thereafter, OLT target whole blood trough levels were 4–8 ng/ml

for Tac and 80–120 ng/ml for CsA. Steroids were intended to be withdrawn within 6 months. In patients with hepatitis C, steroids were tapered faster or patients were treated with steroid free regimens to reduce the rate of reinfection. Patients with autoimmune or cholestatic liver disease usually received low dose steroids (2.5–5 mg prednisolone/day) permanently to reduce increased rejection rates and recurrence of disease.

Postoperative treatment

Until 1998, all patients received peri-operative antibiotic prophylaxis (cephalosporine + metronidazole) for 3 days as well as oral selective bowel decontamination (polymyxin + tobramycine + amphotericin) for 3 weeks after OLT. After 1998, selective bowel decontamination was omitted. For prevention of pneumocystis-carinii- or herpes-simplex-infection, cotrimoxazole (3 × 480 mg/week) and aciclovir (3 × 200 mg/day) were administered for the first 6 weeks after OLT. Until 1996, cytomegalovirus (CMV) prophylaxis consisted of i.v. CMV-hyperimmunglobulin (50 IU/kg bw) on postoperative days (POD) 1 + 14. During later years, CMV-prophylaxis was abolished.

Prophylaxis against hepatitis B (HBV) reinfection was performed initially by anti-HBV-hyperimmunglobulin (blood level > 100 IU/l) alone; since 1993 famcyclovir (3 × 500 mg/day) or since 1996 lamivudine (1 × 100 mg/day) was added. In case of HBV recurrence with prophylaxis, patients received anti-viral therapy with tenofovir or entecavir only.

For prophylaxis against hepatitis C (HCV), patients received ribavirin (3 × 300 mg/day) combined with either interferon-alpha (3 × 3 million IU/week) since 1995, peginterferon-alpha-2a (1 × 180 mg/week) or -2b (1 × 1.5 mg/kg bw/week) since 2000 at the time of OLT. As consequence of unchanged reinfection rates for different prophylactic treatments, patients received anti-viral therapy only at the time of proven HCV-reinfection by increasing HCV-RNA.

Twenty percent of the patients received ribavirin and pegylated interferon as pre-emptive treatment for individual reasons.

Radiographic cholangiography was performed routinely via t-tube on POD 5 and before removal of the t-tube on POD 42.

All patients were continuously followed by our transplant clinic and routine check-up visits at the transplant center were scheduled 6 months and 1, 2, 3, 5, 7, 10, 13, and 15 years after OLT/re-OLT. Routine biopsies were performed at each check-up visit starting 1 year after OLT. Additional biopsies were performed, if rejection or recurrence of primary disease was suspected.

Statistical analysis

The software SPSS (version 11.0; Statistical Software, Chicago, IL, USA) was used for statistical analysis. All data were expressed as mean ± SE of the mean. Follow-up maturity of all data was considered with log-rank tests. Differences in mean and SD calculated from the patients characteristics were evaluated for statistical significance using the chi-squared tests for categorical comparisons. Differences between the indications were calculated by matched pairs regarding recipient age, gender, Child–Pugh score and immunosuppressant (Tac/CsA). Kaplan–Meier survival curves were generated and evaluated for significance using the log-rank test for patient and graft survival. Cox regression models were used to adjust survival comparisons for relevant covariates. For the abnormal distributed variables, the Wilcoxon-Ranking and Kruskal–Wallis test were used. Significance was reached at $P < 0.05$.

Results

Follow-up

Mean follow-up was 103.2 ± 56.3 months (range: 0–214 months).

Survival and causes of death

Overall patient survival was 91.4%, 82.5% and 74.7% at 1, 5 and 10 years after OLT (Fig. 1). Survival rates according to indication for OLT are depicted in Fig. 6. Split-OLT resulted in 1- and 5-year survival rates of 87.0% and 82.4%. Graft survival was 85.8%, 75.3% and 67.3% after 1, 5 and 10 years, respectively (Fig. 1). Patient survival after re-OLT was up to 20% lower than after primary OLT, whereas combined liver and kidney transplantation resulted in survival rates similar to solitary OLT (90.0%, 84.1%, 57.9 at 1, 5 and 10 years).

Donor age >50 years (Fig. 2), graft steatosis >50.0% and cold ischemia time >12 h resulted in significantly impaired graft survival. Additional predictors of poor survival were: recipient age ≥60 years, acute liver failure, renal insufficiency (creatinine >1.5 mg/dl and/or glomerular filtration rate (GFR) <60 ml/min). Furthermore, transfusion of packed red blood cells ($P < 0.001$) and fresh-frozen plasma ($P < 0.001$), arterial anastomosis with graft interposition ($P < 0.001$) and simultaneous pancreas resection ($P = 0.0001$) resulted in reduced patient survival. In contrast, neither Child-Pugh nor MELD score correlated with graft or patient outcome.

Overall, 275 of 1245 patients died (22.1%). Fifty-one patients (30 patients after OLT and 21 after re-OLT) died within the first 3 months, 107 within the first year. The

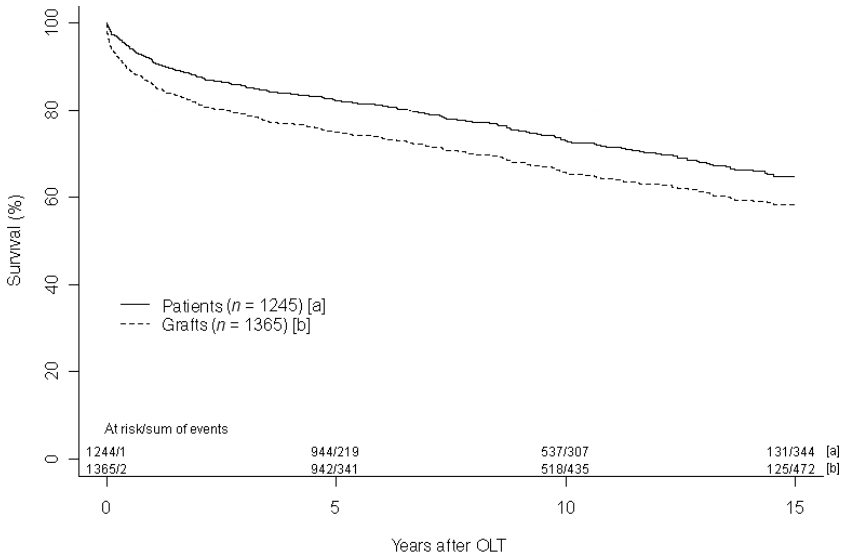

Figure 1 Patient survival in 1245 primary liver transplantation and 1365 grafts.

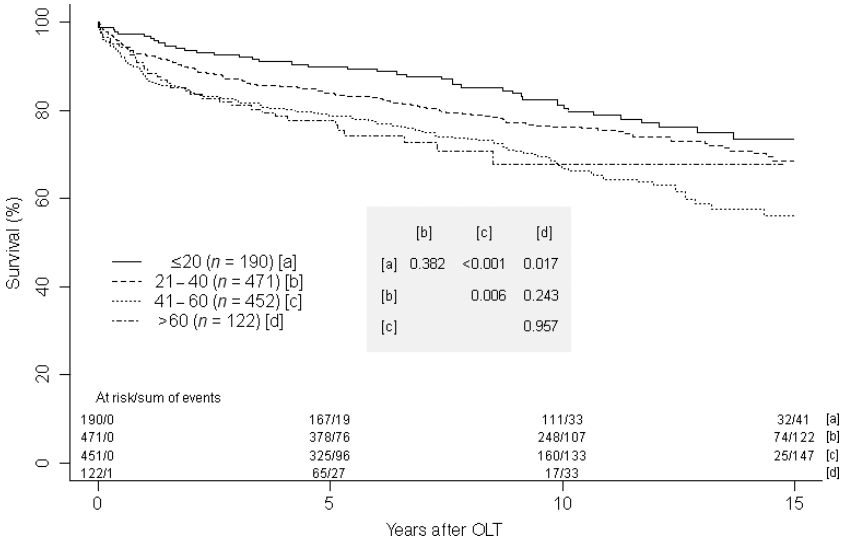

Figure 2 Patient survival depending on donor age ($a \leq 20$ years; b = 21–40 years; c = 41–60 years; $d \geq 60$ years).

main causes of death were: recurrence of disease (32.1%), infections (21.8%), *de novo* malignancies (13.5%) and cardiovascular diseases (11.6%). However, causes of death varied depending on the time interval after OLT. During the first 3 months after OLT or re-OLT, bacterial infections with sepsis and multiorgan failure or hemorrhage were predominant causes of death, whereas recurrence of the disease, *de novo* malignan cies and cardiovascular diseases were the leading causes of death thereafter.

Infections

1049 infections in 524 patients (42.1%; 43.3% women, 56.7% men) were documented. Eight hundred and eighty infections (83.9%) required treatment [cholangitis (20.2%), urinary tract infection (18.6%) and pneumonia (18.0%)]. The majority (n = 642, 73.0%) of symptomatic infections (345 mild; 243 moderate; 54 severe) were observed in 371 patients (57.8%) within the first 3 months after OLT. A total of 52.3% (n = 464) were bacterial infections. Viral infections (mainly CMV-infections) accounted for 16.8% (n = 108) and fungal infections (96.6% *Candida* or *Aspergillus* species), were responsible for 10.9% (n = 70) of symptomatic infections, 20% were asymptomatic. Treatment for symptomatic infections was necessary in 81.6% of fungal and 79.0% of viral infections.

Late postoperative infections (>3 months) were seen in 238 patients (27.0%). A total of 52.1% of these infections (n = 124) were classified as mild, 87 (36.6%) as moderate and 27 (11.3%) as severe. As observed for the early postoperative period, more than half of the infections

were bacterial infections ($n = 124$; 52.1%). However, fungal infections ($n = 45$; 18.9%) and viral infections ($n = 69$; 29.0%) were more frequent in the late postoperative period than during the early postoperative period. The distribution of infections was comparable between all indications for OLT.

Rejections

537 patients (43.1%) experienced 576 episodes of acute (96.5%) or 21 chronic (3.5%) rejection. A total of 70.7% of these patients had one, 18.7% two, and 6.9% had more than two acute rejections. A total of 16.3% of all acute rejections were steroid-resistant. Rejection episodes occurred significantly more frequently among patients with autoimmune cirrhosis, cholestatic liver disease or acute liver failure. Rejection rate was 51.6% in patients treated with CsA and 35.4% in Tac treated patients ($P > 0.05$). Patients with Tac based immunosuppression experienced significantly less frequently chronic rejections than patients with CsA based immunosuppression.

Recurrence of disease

A total of 26.0% ($n = 324$) of all patients showed recurrence of their underlying disease [89.1% HCV ($n = 133$); 50.0% HBV ($n = 86$); 18.4% alcoholic liver disease ($n = 48$); 20.7% HCC ($n = 30$); 70.8% cholangiocellular carcinoma (=CCC; $n = 17$); 100% recurrent carcinoid metastases ($n = 6$); 1.5% PSC ($n = 2$); 1.0% PBC ($n = 1$); 5% Budd–Chiari ($n = 1$)].

Eighty-eight patients (27.1%) died of recurrence of their disease (100% HCC; 100% CCC; 16.3% HBV; 9.0% HCV; 20.8% ALD; 50% carcinoid metastases; 50% PSC; 100% PBC).

Recurrence of viral hepatitis was diagnosed by increasing blood levels of HBV-DNA or HCV-RNA and elevated transaminases.

Prophylaxis against HBV reinfection by treatment with anti-HBV-hyperimmunglobulin led to a recurrence rate of 45%. Since 1996, combination with lamivudine was introduced, which resulted in reduced recurrence rates of less than 10%.

Despite different treatments with ribavirin and pegylated interferon, HCV reinfection rate occurred in nearly 90% of the patients. Mean time point of recurrence was 10.1 ± 18.0 months after OLT.

Recurrence of alcohol abuse (19%) was determined according to reports from patient's relatives and friends as well as from comments by the primary care physician and/or from blood tests. Abusive drinking was assumed, if patients were admitted to the hospital for the treatment of alcohol-related complications.

Recurrence of malignant tumors was diagnosed by ultrasound, CT-scan or MRI. If necessary, biopsies for histological confirmation were performed.

Diagnosis of recurrent PSC or PBC relied on the combination of endoscopic and histological findings.

Vascular complications

Vascular complications were observed in 203 patients (14.9%) (Table 3). Most of the vascular complications (76.8%) involved the hepatic artery, while venous complications accounted for 23.3% of vascular complications. Patients with hepatic artery thrombosis had a significantly impaired graft survival ($P < 0.001$) (Fig. 3). However, venous complications had no statistical influence on patient or organ survival.

Complications of the biliary system

Three hundred and thirty-two (24.3%) complications of the biliary tract were diagnosed in 250 patients. Time point of occurrence varied tremendously and ranged from several days to several years after OLT. The most serious complication was ischemic type biliary lesion (ITBL), which was observed in 72 grafts (5.3%). The etiology of ITBL remains obscure; however, perfusion of the graft seems to play an important role as incidence of ITBL was lower in organs, which were harvested after pressure perfusion than in organs harvested after gravity perfusion ($P < 0.0001$) (52). Majority of patients with ITBL could be managed by repeated endoscopic interventions. However, in 25%, retransplantation became necessary eventually (Table 4). Although ITBL significantly impaired graft survival, it remained without influence on patient survival (Fig. 4).

Papillary dysfunction was observed in 5.4% ($n = 75$) of the 1245 patients who underwent either side-side- or end-end choledocho-choledochostomy. In 25% of these patients, papillary dysfunction was diagnosed within the first 6 weeks after OLT, whereas the majority of patients presented with papillary dysfunction between 1 and 5 years after OLT. Routine cholangiography on POD 5 had been uneventful in most of these patients. All patients were treated by endoscopic papillotomy.

Diabetes mellitus

Prior to transplantation 190 patients (15.3%) presented with diabetes, 26.8% ($n = 51$) of them required insulin, whereas 73.2% were noninsulin-dependent. During the first 3 months after OLT, increased blood glucose levels were observed in up to 49% of the patients. Steroids could be identified as a risk factor for the development of

Table 3. Incidence and treatment of vascular complications after 1365 liver transplantation (OLT).

Type of complication	(*n*)	(%)	Treatment (*n*)
Arterial complications	**156**	**11.4**	
Hepatic artery thrombosis	36	2.6	Re-OLT (17), biliary abscess drainage (7), hepatico-jejunostomy (4), thrombectomy (4), lysis (2), dissection of the arcuate ligament and banding of the splenic artery (2)
Type of anastomosis			
Gastroduodenal artery (*n* = 881)	13	1.5	
Celiac trunk (*n* = 299)	9	8.4	
Interpos. to the aorta (*n* = 166)	16	9.6	
Others (*n* = 19)	0	0	
Hepatic artery stenosis	39	2.9	Percutaneous transluminal angioplasty (9), embolization of the splenic artery (9), dissection of arcuate ligament (2), No therapy (19)
Type of anastomosis			
Gastroduodenal artery (*n* = 881)	24	2.7	
Celiac trunk (*n* = 299)	11	3.7	
Interpos. to the aorta (*n* = 166)	2	1.2	
Others (*n* = 19)	2	10.5	
Hepatic artery aneurysm	8	0.6	Resection of the aneurysm (8)
Arterial-steal syndrome	73	5.3	Coil-embolization (31), splenectomy (20), banding of the splenic artery (9), re-OLT (3), no therapy (10)
Venous complications	**47**	**3.4**	
Portal vein thrombosis	16	1.2	Conservative treatment (4), re-OLT (2), transjugular intrahepatic porto-systemic shunt (2), lysis (1), mesenterico-caval shunt (1), no therapy (6)
Portal vein stenosis	14	1.0	Conservative treatment (4), no treatment (10)
Vena cava thrombosis	6	0.4	Revision of anastomosis (3), re-OLT (2) percutaneous transluminal angioplasty (1)
vena cava stenosis	11	0.8	Conservative treatment (5), revision of anastomosis (3), re-OLT (2), percutaneous transluminal angioplasty with stent (1)
Total	**203**	**14.9**	

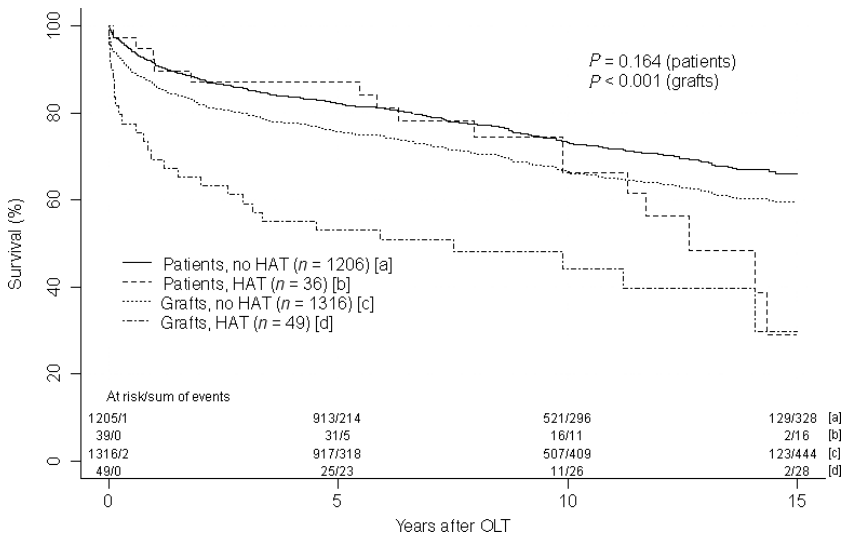

Figure 3 Patient and organ survival in patients with hepatic artery thrombosis (HAT).

diabetes during the first 6 months after OLT, but was without influence on the development of diabetes thereafter. Overall 301 patients (24.2%) presented with diabetes in the long-term course, half of them had been diagnosed with diabetes prior to OLT. *De novo* diabetes was associated with impaired survival. Interestingly, 4.3% of the patients with preoperative diabetes displayed normalization of glucose metabolism after OLT. The highest incidence of diabetes was observed in patients with ALD (30.2%), metabolic liver disease (30.6%), cryptogenic cirrhosis (26.3%) and in patients with viral-induced cirrhosis (overall 26.2%; 42.9% HCV).

Table 4. Incidence and treatment of biliary complications after 1365 liver transplantation (OLT).

Type of complication	(*n*)	(%)	Treatment (*n*)
Biliary leakage, insufficiency of anastomosis	**39**	**2.9**	Endoscopic stenting (16) Repeat bile duct anastomosis (12) Hepatico-jejunostomy (11)
Bile duct stenosis, stenosis of anastomosis	**77**	**5.6**	Endoscopic dilatation and stenting (43) Repeat bile duct anastomosis (17) Hepatico-jejunostomy (15) Choledocho-duodenostomy (2)
Bile duct anastomosis			
Side-to-side (*n* = 1218)	43 (3.5%)		
End-to-end (*n* = 27)	10 (37.0%)		
Hepatico-jejuno-/duodenostomy (*n* = 120)	24 (20.0%)		
T-drain complications (leakage, dislocation)	**45**	**3.3**	T-drain removal w/wo endoscopic stenting (35), surgical revision (10)
Stenosis of the papilla vateri/papillary dysfunction	**75**	**5.4**	Endoscopic papillotomy (75)
Choledocholithiasis	**24**	**1.8**	Endoscopic papillotomy/stone extraction (23) Hepatico-jejunostomy (1)
Ischemic type biliary lesion	**72**	**5.3**	Endoscopic dilatation and stenting (51) Re-OLT (18) Hepatico-jejunostomy (3)
Total	**358**	**26.2**	

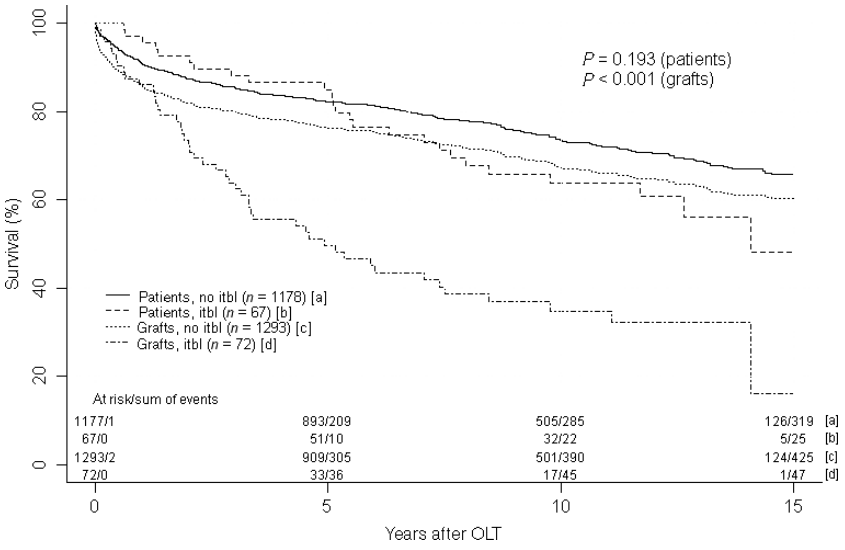

Figure 4 Patient and graft survival in patients with ischemic type biliary lesions (ITBL).

Arterial hypertension

Arterial hypertension (systolic pressure >140 mmHg, diastolic >90 mmHg) was observed in 7.5% of the patients prior to transplantation. During the first 4 months after OLT, increased blood pressure was recorded in 71.4% of the patients. In 67.6% of them, hypertension was mild or moderate (diastolic pressure 90–110 mmHg) and in 32.4% severe (diastolic pressure >110 mmHg). Most patients (70.6%) developed arterial hypertension within the first year. Immunosuppression with CsA could be identified in the univariate analysis as a risk factor for the development of hypertension.

Cardiovascular complications

Cardiovascular and cerebrovascular [coronary artery disease (CAD) or myocardial infarction (MI) (*n* = 38), stroke (*n* = 5)] diseases were documented in 43 patients (3.5%) preoperatively. Postoperatively, 98 patients (7.9%) developed CAD and 11 patients experienced myocardial infarction. A total of 0.2% suffered from pulmonary embolism. All patients with cardiovascular disease (68% male, 32% female) presented with arterial hypertension and one third of them suffered from insulin-dependent diabetes mellitus.

Hypercholesterinemia, a risk factor for cardiovascular disease was observed in 74.0% of the patients with CsA

based immunosuppression ($P = 0.02$), and in 52.0% of the patients with Tac based immunosuppression ($P > 0.5$).

Overall, 48 patients (=3.9%) died of cardiovascular ($n = 32$; 24 after OLT; 8 after re-OLT) or cerebro-vascular disease ($n = 16$; 12 after OLT; 4 after re-OLT). Fourteen patients (=29.2%; 9 OLT; 5 re-OLT) died within the first 3 months. Because of inconsistent documentation of potential risk factors, statistical analysis was disclaimed.

Renal insufficiency

Renal insufficiency (RI) was defined as creatinine >1.5 mg/dl and GFR (calculated with the Cockcroft formula) <60 ml/min. A total of 30.3% of all patients presented with RI at the time of OLT. Postoperatively, 76.5% of all patients (68.9% after primary OLT, 79.2% after re-OLT) met the criteria for RI at least temporarily. The incidence of RI decreased to 51.6% after 3 months, and to 40.0% after 1 year. A total of 75.5% of the patients with RI displayed creatinine levels between 1.5 between 3.0 mg/dl and 24.5% displayed creatinine levels >3.0 mg/dl (GFR<30 ml/min). Overall, 19.9% of the patients required, at least temporarily, hemodialysis, 16.1% after OLT and 39.2% after re-OLT. This decreased to 14.1% and 35.0% after 3 months post-transplantation. Eventually 1.0% of all patients ($n = 13$) remained on hemodialysis for terminal RI, 1.1% ($n = 14$) underwent renal transplantation. Three patients (0.2.%) received a renal transplant during re-OLT.

The univariate analysis identified male gender ($P = 0.006$), viral-induced, cryptogenic cirrhosis and acute liver failure as risk factors for renal insufficiency. Patients with RI had a significantly increased risk for infections ($P = 0.001$), and for acute ($P = 0.008$) and steroid-resistant ($P = 0.009$) rejections. Because of the missing follow-up maturity of Tac and CsA trough levels as risk factors of RI, the statistical analysis was disclaimed.

Neurological disorders

We observed 734 neurological disorders, predominantly side effects of calcineurin inhibitors, in 530 patients (42.6%). A total of 83.3% of these disorders were mild (headache, tremor, paresthesia, vertigo) and 16.7% were severe (aphasia, dysarthria, paresis, seizures, psychoses or reduced consciousness). Nine percent of all patients displayed permanent neurological disorders more than 1 year after OLT. Female gender ($P = 0.016$), renal insufficiency ($P = 0.028$), re-OLT ($P = 0.0012$) and immunosuppression with Tac ($P = 0.0014$) could be identified as potential risk factors for neurological complications. Treatment consisted of tapering of calcineurin inhibitors and symptomatic physiotherapy. In some patients, replacement of Tac by CsA or vice versa was successful.

Osteoporosis

Overall, 34% of all patients suffered from osteoporosis and/or temporarily osseous pain after OLT. Seventy-six percent of these patients were female. Twenty-one percent of all patients required permanent medical treatment for osteoporosis and more than half ($n = 21$, 51.2%) of all 41 fractures observed were caused by osteoporosis.

De novo malignancies

De novo malignancies were observed in 70 patients (5.6%; 23 women; 47 men) (Table 5). Lymphoma, skin tumors and lung tumors were the most frequent malignancies

Table 5. *De novo* malignancies after liver transplantation (OLT).

Malignancy	(*n*)	(%)	Time point of diagnosis after OLT (months)	Patient age at diagnosis (years)	Mortality (*n*)
Skin	16	21.9	43 (4–112)	50 (25–67)	6
Lymphoma	11	15.1	31 (2–112)	50 (26–62)	5
Lung	10	13.7	56 (10–132)	52 (44–63)	10
Hypopharynx/oral cavity	7	9.6	56 (12–93)	52 (41–58)	4
Esophagus	5	6.8	23 (11–58)	57 (51–61)	4
Breast	5	6.8	39 (3–93)	56 (43–67)	1
Colon	4	5.5	34 (12–57)	45 (37–58)	2
Hepatocellular carcinoma	3	4.1	56 (27–108)	46 (41–54)	1
Bladder	3	4.1	62 (49–87)	54 (51–58)	1
Cervix	3	4.1	38 (13–75)	28 (20–35)	1
Gastric	2	2.7	72 (57–86)	55 (43–67)	1
Testicles	1	1.4	46	38	–
Kidney	1	1.4	60	58	1
Vagina	1	1.4	99	41	–
Thyroid	1	1.4	35	25	–
Total	73	100	50 (2–132)	47 (20–67)	37

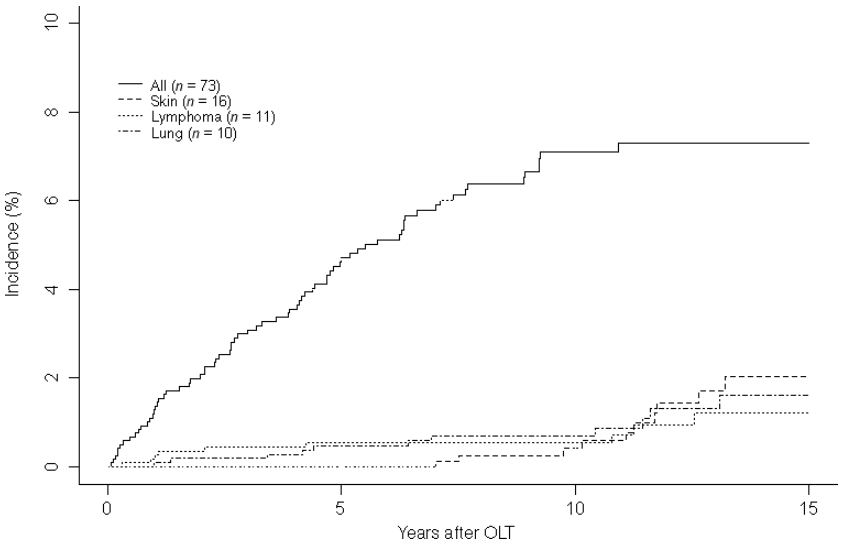

Figure 5 Incidences of *de novo* malignancies after liver transplantation.

(Fig. 5). In patients transplanted for ALD, an accumulation of *de novo* tumors known to be associated with alcohol abuse (lung, esophagus, hypopharynx, oral cavity) was observed irrespective of recurrent alcohol abuse. In contrast, the distribution of de novo-malignancies was comparable between all other indications.

Discussion

Few studies report about the long-term outcome of more than 1000 OLTs of a single center [8,9,14–17]. The intention of this retrospective analysis was to determine long-term results, and the incidence of specific complications and after OLT over 15 years in a single center. During the last two decades, improvements in the therapeutic regimens of patients after OLT could particularly be observed in intensive care management [2,3,18–22], in immunosuppressive therapy [1,15] and in the treatment of specific complications [13,23–38]. These improvements have contributed to continuous excellent patient and graft survival, despite decreasing organ quality (i.e. increasing donor age) (Fig. 6).

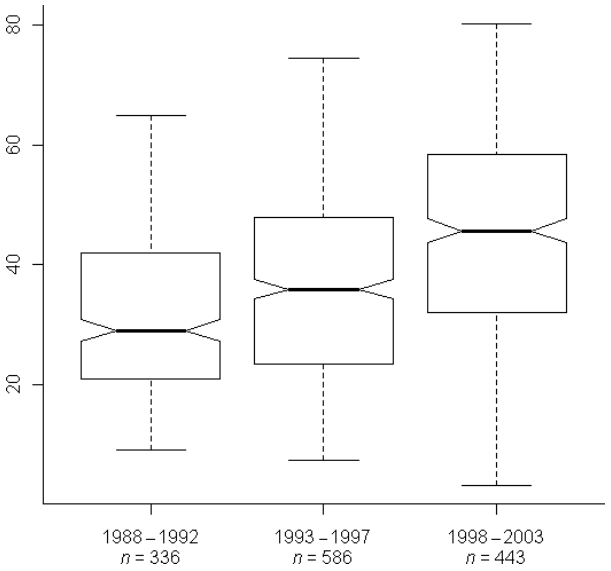

Figure 6 Development of donor age within 15 years in three periods.

This retrospective analysis revealed the highest survival rates in patients with cholestatic or cryptogenic liver disease, whereas patients with ALF or malignant tumors achieved the lowest survival rates (Fig. 7). Excellent long-term results were also observed in patients transplanted for alcoholic liver disease (Fig. 7). However, this was true only for abstinent patients, emphasizing the necessity of abstinence after OLT [39].

Important factors for patient survival in the univariate analysis were: recipient age >50 years, renal insufficiency, the number of intra-operatively transfused blood products, arterial anastomosis with interposition of an iliac artery graft to the aorta and simultaneous pancreas resection (see also Table 6). In accordance with previously published results, patients with CCC [40] or HCC, beyond the 'Milan criteria', are no longer considered for OLT because of disappointing results [12]. Prognostic factors for graft survival in the univariate analysis were donor age >50 years, graft steatosis (>50.0% fat) and cold-ischemia-time >12 h.

As reported by other groups, main causes of death in our patient population were recurrence of the underlying disease [8,9,36–38], infections [2,18,23], cardiovascular disease [36–38,41] and *de novo* malignancies [36,37, 42–46].

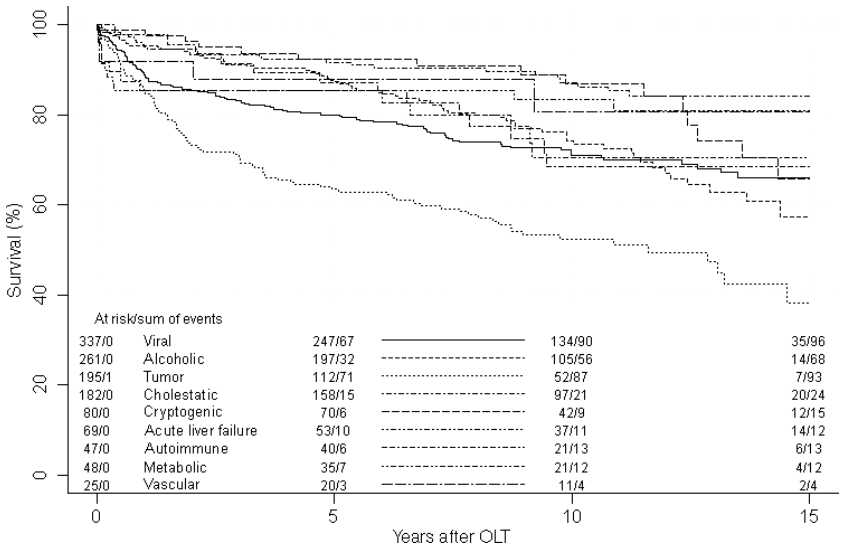

Figure 7 Patient survival for different indications for liver transplantation.

Table 6. Multivariate logistic regression analysis of independent prognostic factors for patient survival.

Factor	Coefficient	*P*-value	Risk ratio	95% CI
Indication for liver transplantation				
Tumor	0.615	0.000	1.849	1.328–2.574
Cholestatic liver disease	−1.236	0.000	0.291	0.169–0.500
Cryptogenic cirrhosis	−0.773	0.029	0.462	0.231–0.924
Recipient age	0.036	0.000	1.037	1.023–1.051
Donor age	0.013	0.002	1.013	1.005–1.021
Intra-operative transfusion of packed red blood cells	0.031	0.000	1.031	1.015–1.048
Postoperative development of renal insufficiency	0.353	0.020	1.423	1.056–1.917
Infection <3 months	0.220	0.000	1.246	1.105–1.405
Chronic rejection	0.854	0.031	2.348	1.083–5.092
Arterial hypertension	0.988	0.000	0.372	0.287–0.482
Bile duct anastomosis (end-end/side-side)	0.655	0.002	1.926	1.269–2.923

While the overall incidence of *de novo* malignancies in our patient population was similar to results reported in the literature [42–47], we observed a significantly increased incidence of malignancies in patients who were transplanted for alcoholic liver disease. In these patients, malignant tumors, known to be associated with alcohol abuse were the most frequent. As the development of these tumors was independent of recurrent alcohol abuse, one could speculate that drinking prior to OLT leads to irreversible toxic damage favoring the development of tumors under immunosuppression. As a consequence, these patients should be followed up meticulously after OLT irrespective of their drinking behavior [39].

The incidence of transplant specific complications, such as rejections, infections, vascular and biliary complications decreased over time. Rejection episodes were observed less frequently after Tac was used as preferential calcineurin inhibitor for immunosuppression instead of CsA. However, a significant superiority of Tac to CsA could only be shown in the frequency of chronic rejection and graft loss [4–6].

The frequency of infections was independent from the underlying disease, with minor but not statistically significant accumulation in patients with acute liver failure and Child–Pugh score C. As observed by other groups [2, 18–23], infections within the first 3 months were caused predominantly by bacteria, whereas later on, viral infections increased [2,18–23]. Fungal infections were rare and were distributed evenly among all patient groups [23].

One of the greatest improvements achieved during the last years was in the treatment of patients with HBV-induced cirrhosis [48,49]. Combination of anti-HBV-hyperimmunglobulin with lamivudine [49] reduced reinfection rates to less than 10.0% presently. Furthermore, in some patients, permanent immunity against HBV could be achieved by active immunization

post-OLT [50]. In contrast, treatment of patients with HCV remained troublesome. Reinfection rates ranged between 80 and 100% within the first year [51], and recurrent cirrhosis was observed in up to 30.0% despite anti-viral treatment with ribavirin and peginterferon.

Vascular complications were observed in 14.9% of all patients with hepatic artery thrombosis (HAT) being the most serious [28–31]. HAT occurred in more than 50% within the first 3 months after OLT and as 47.2% of the patients had to undergo retransplantation, a significant influence on graft but not patient survival was noted. HAT was observed, in particular, in patients with interposition of an iliac artery graft to the aorta ($P = 0.001$). Although the exact reason for the association of this type of anastomosis with HAT remains obscure, graft interposition to the aorta was avoided whenever possible.

Splenic artery steal syndrome occurred in 5.3% of all patients, but failed to be detected preoperatively in a number of patients. These patients were, therefore, treated by coil-embolization of the splenic artery. In three of these patients, steal syndrome had led already to irreversible biliary tree damage and retransplantation became mandatory. Splenectomy for the treatment of steal syndrome was avoided after it was realized that it was associated with considerable morbidity. Since 2001, arterial steal syndrome was suspected in all patients with enlarged ($>1.5 \times$ diameter of hepatic artery) splenic artery. Intraoperative ultrasound had been performed in a number of these patients, but without consistent results. Therefore, prophylactic banding of the splenic artery had been performed in all patients considered at risk for the development of arterial steal syndrome. Since then, the incidence of post-transplant steal syndrome had been reduced dramatically.

Venous complications [32] were rare, but showed serious consequences, especially, if the vena cava was involved. In 5 out of 6 patients, surgical revision of the anastomosis or re-OLT was necessary (Table 3). In contrast, complications of the portal vein could be managed conservatively in 62% of the patients.

We observed 24.3% biliary complications, a percentage, which is well within the reported range of 2.3–50.0% [33–36]. Stenosis or leakage of the anastomosis, papillary dysfunction and ITBL accounted for almost 75% of biliary complications. Endoscopic interventional therapy was the treatment of choice and was successful in 70% of the patients. To reduce the development of ITBL, the most serious biliary complication, pressure perfusion of the graft instead of gravity perfusion during organ harvesting was introduced in 1993 [52]. Standard technique for biliary anastomosis was a long side-to-side anastomosis between donor and recipient common bile duct. This type of anastomosis was associated with significantly less complications such as anastomotic stenosis than end-to-end choledocho-choledochostomy [53].

The incidences of diabetes [47,54–58], hypertension [47,59,60], cardiovascular diseases [41,61], neurological disorders [62,63] and osteoporosis [64] in our patients were comparable to the results published by other groups. Notable was the improvement in glucose metabolism in 4.3% of the patients with pre-existing diabetes. The observation of impaired survival rates of diabetics may in part be because of the increased risk of the development of cardiovascular disease in diabetic and hypertensive patients [56,57,60,61]. Therefore, attention should be paid to strict adjustment of glucose metabolism and arterial blood pressure after OLT.

Osteoporosis was observed in every third patient, irrespective of the age of the patient. To reduce the incidence of osteoporosis, preventive medical treatment should be initiated early after transplantation [64].

Renal insufficiency is an important complication after OLT and almost 20% of all patients required hemodialysis at least temporarily [65,66]. More important than the percentage of patients involved, was the fact that RI significantly influenced patient survival. After it was realized, that postoperative renal insufficiency may have been induced or at least worsened by calcineurin inhibitors, reduction of CsA and Tac and introduction of mycophenolatemofetil for immunosuppression became the cornerstone of treatment [2,25,26,65,66]. Furthermore, mycophenolatemofetil became a regular part of primary immunosuppression in our clinic [66].

In summary, OLT has developed into a safe and successful treatment for end-stage liver disease with excellent long-term results.

Authorship

RP & RN collected the data. RP & MH analyzed the data. RP & NN wrote and revised the paper.

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