ABO-incompatible living kidney transplantation. Transplantation 1998; 65: 224.
3. Tanabe K, Takahashi K, Sonda K, et al. Clinicopathological analysis of rejection episodes in ABO-incompatible kidney transplantation. Transplant Proc 1996; 28: 1447.
4. Takahashi K, Yagisawa T, Sonda K, et al. ABO-incompatible kidney transplantation in a single-center trial. Transplant Proc 1993; 25: 271.
5. Toma H. ABO-incompatible renal transplantation. Urol Clin North Am 1994; 21: 299.
6. Spital A. Unrelated living donors. Transplantation 1994; 57: 1722.
7. Sumrani N, Delaney V, Ding Z, et al. Renal transplantation from elderly living donors. Transplantation 1991; 51: 305.
8. Alexandre PJ, Squifflet JP, DeBruyere M, et al. Present experience in a series of 26 ABO-incompatible living donor renal allografts. Transplant Proc 1987; 19: 4538.
9. Bannet AD, McAlack RF, Raja R, Baquero A, Morris M. Experiences with known ABO-mismatched renal transplants. Transplant Proc 1987; 19: 4543
10. Nelson PW, Helling TS, Shield CF, Beck M, Bryan CF. Current experience with renal transplantation across the ABO barrier. Am J Surg 1992; 67: 879.
11. Colvin RB. The renal allograft biopsy. Kidney Int 1996; 50: 1069.
12. Pirsch JD, Miller J, Deierhoi MH, et al. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression after cadaveric renal transplantation. Transplantation 1997; 63: 977.
13. Schleibner S, Krauss M, Wagner K, et al. FK506 versus cyclosporin in the prevention of renal allograft rejection: European pilot study- six-week results. Transplant Int 1995; 8: 86.
14. European Mycophenolate Mofetil Cooperative Study Group. Placebo-controlled study of Mycophenolate Mofetil combined with cyclosporin and corticosteroids for prevention acute rejection. Lancet 1995; 1: 1321.
15. Sollinger HW for the US Renal Transplant Mycophenolate Mofetil Study Group. Mycophenolate Mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. Transplantation 1995; 60: 225.

Received 28 September 1999.
Accepted 11 April 2000.

0041-1337/00/7009-1335/0
TRANSPLANTATION
Vol. 70, 1335–1342, No. 9, November 15, 2000
Printed in U.S.A.

LONG-TERM FOLLOW-UP AFTER LIVER TRANSPLANTATION FOR ALCOHOLIC LIVER DISEASE UNDER TACROLIMUS[1]

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Background. **Liver transplantation (LTx) for alcohol-related liver disease (ALD) is an accepted modality of treatment and is one of the most common indications for LTx in the United States. The present report examines the long-term patient survival, graft survival, rates of recidivism, and development of de novo cancers in this group, and compares these results with a contemporaneous group of patients who were transplanted for non-ALD indications.**

Methods. **Between August 1989 and December 1992, 185 adults received LTx for ALD (group I). During the same time interval, 649 adults received LTx for non-ALD (group II). The mean follow-up time was 94±10.7 months for group I vs. 92±11 months for group II. Kaplan-Meier survival estimates and the incidence of cancers using Surveillance Epidemiologic End Result data were compared in both groups.**

Results. **At 5 years after orthotopic LTx, the overall patient survival and graft survival for group I were 72.0% and 66.5% vs. 66.5% and 60.3% for group II, respectively. After 5 years, the patient survival and graft survival for the alcoholic group were significantly lower ($P=0.001$) compared to the non-alcoholic group. The rate of de novo oropharyngeal cancer and lung cancer was 25.5 times and 3.7 times higher, respectively, in ALD group compared with the general population matched for age, sex, and length of follow-up ($P=0.001$), whereas this was not higher in the non-ALD group. Prior pretransplant length of sobriety and alcohol rehabilitation was not associated with the rate of post-LTx rate of recidivism, which was 20%. Out of 79 deaths in group I, only 1 was attributed to recidivism and 3 to noncompliance with recidivism. The other deaths occurred from de novo cancer (n=13), posttransplant lymphoproliferative disorder (n=5), age-related complications (n=23), and other infection or miscellaneous causes (n=34).**

Conclusions. **Patient and graft survival past 5 years after orthotopic LTx is significantly lower for ALD for**

[1] Presented in part at the 49th Annual Meeting of the American Association for the Study of Liver Diseases, November 6, 1998, Chicago, IL, and the 18th Annual Meeting of the American Society of Transplantation, May 15, 1999.

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a variety of reasons (P=0.001). The rate of upper airway malignances was significantly higher in ALD patients than for non-ALD post-LTx patients and the general public. Graft loss/death related to recidivism or chronic rejection was extremely low. More attention is needed for early diagnosis of de novo cancer and prevention of cardiorespiratory and cerebrovascular complications.

Once recognized as a socially and ethically controversial indication for liver transplantation (LTx), alcoholic liver disease (ALD) is now not only widely accepted but is also one of the commonest indications for LTx in the United States. Although initial results of LTx under cyclosporine demonstrated comparable patient survival for ALD compared with non-ALD indications (*1, 2–9*), very little has been published on the long-term LTx outcome of alcoholics under tacrolimus immunosuppression (*10*). We report on the long-term outcome of alcoholic cirrhosis examining patient survival, graft survival, causes of repeat transplantation, and causes of death. In particular, we demonstrate the contrasting risks of developing de novo cancer in alcoholic and non-alcoholic liver transplant recipients and compare this rate to the general population.

PATIENTS AND METHODS

The study population consisted of 834 consecutive adults (age, >18 years) who underwent primary LTx between August 1989 and December 1992. Initially, 188 patients were classified as having alcoholic cirrhosis; however, on detailed review of their records, 3 patients did not have a history of sufficient alcohol abuse. Thus, 185 ALD patients (group I) were compared with 649 non-ALD adult primary liver transplant patients (group II). The demographics of both groups are shown in Table 1. The mean age was 50.8±10 years (range, 26–75 years) in group I vs. 49.7±13 years (range, 18–76 years) in group II. All patients were followed until January 1999, with a mean follow-up of 94±10.7 months for group I and 92±11 months for group II. There were 24 patients in group I who also had hepatitis C virus (HCV) infection (tested either by ELISA or polymerase chain reaction), 2 patients who had hepatitis B virus (HBV) infection, and 8 patients who had incidental hepatocellular carcinoma.

TABLE 1. Patient demographics[a]

	Group I	Group II	*P*-value
Age			NS
Mean (yr)	50.8±10.4	49.7±13.03	
Range	25.9–75	18.1–76.2	
Gender			
M/F, n (%)	131/54 (70.8/29.4)	373/276 (57.4/42.6)	0.001
Status at LTx			NS
Home-bound, n (%)	24 (12.9)	96 (14.7)	
Hospital-bound, n (%)	67 (36.2)	254 (39.1)	
ICU-bound, n (%)	94 (50.8)	299 (46)	
Mean age (donor)	33.49±13.93	34.25±14.9	NS
Cold ischemia time	15.2±5.4	15.7±5.1	NS
Blood type			NS
A, n (%)	80 (43.2)	277 (42.6)	
B, n (%)	26 (14)	94 (14.4)	
AB, n (%)	9 (4.8)	32 (4.9)	
O, n (%)	70 (37.8)	246 (37.9)	
Mean follow-up (mo)	94.4±10.78	92.8±11.3	NS

[a] NS, not significant; ICU, intensive care unit.

Medical records of the patients were reviewed to identify the pretransplant length of sobriety, history of alcohol rehabilitation, and rate of recidivism. The clinical records were also examined to determine rate of repeat transplantation, cause of repeat transplantation, cause of death, and de novo malignancy. Recidivism was defined as any alcohol use endorsed by the patient or by positive blood ethanol levels. Post-LTx patients were followed closely by the transplant coordinators, who monitored patients' laboratory values, attendance at clinic appointments, and compliance with immunosuppressive and other medications. Patients were questioned about alcohol use, and random blood alcohol levels were checked if drinking was suspected or if hepatic enzymes were elevated. Prospective alcohol measurements were not used during this time interval.

The immunosuppressive protocol has been previously described (*11–16*). Briefly, patients who received transplants before February 1990 received tacrolimus at 0.15 mg/kg/day intravenously as a 2–4 hr infusion. From February 1990 onward, the dose was reduced to 0.1 mg/kg/day, and, after August 1991, it was further reduced to 0.05 mg/kg/day. The first 53 patients received 1 g of methylprednisolone with a total of 600 mg of methylprednisolone tapered over the next 5 days. The remaining of patients received 20 mg of methylprednisolone per day immediately after LTx.

Kaplan-Meier estimates were used to calculate survival curves. Differences in survival curves were compared using log-rank statistics. Cox proportional hazard models were also fit to test differences in survival. Differences in proportions were tested using a chi-square test (or Fisher's exact test). P-values less than 0.05 were considered statistically significant. Analyses were performed using SPSS 8.0 (Statistical Package for Social Sciences software for Windows; SPSS, Chicago, IL) and Stata (1999 Stata Statistical Software, release 6.0; Stata Corp., College Station, TX).

The incidence of de novo cancers in group I and group II was compared with the general population matched for age, gender, and length of follow-up using the modified life table technique of the Occupational Cohort Mortality Analysis Program (OCMAP-PLUS; adapted for cancer incidence data) (*17*). The "person-years at risk" contributed by each patient were jointly classified by age group, gender, and time period. The expected counts of malignancies were computed by multiplying the average annual gender-age-time-specific incidence rates by the corresponding gender-age-time-specific person-time. The incidence rates for malignancy for Caucasians were used exclusively, as 85% of the LTx patients were white and the remaining 15% represented a mix of nonwhite races for which standard incidence rates were unavailable. Standard incidence rates were obtained from the 1990–91 Surveillance Epidemiologic End Results (SEER) data (*18*). As a result of SEER reporting limitations, the expected number of malignancies for the time period of 1989–1999 were based on 1989–93 incidence rates.

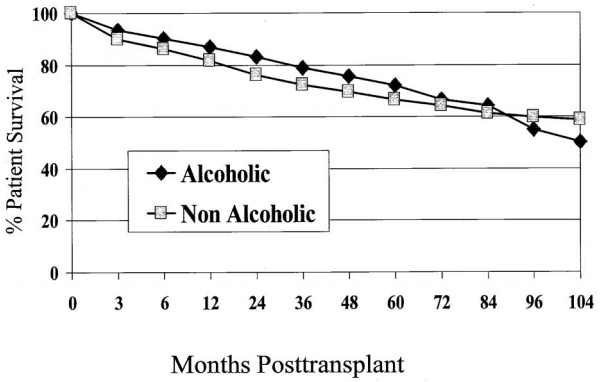

FIGURE 1. Kaplan-Meier overall post-LTx patient survival for alcohol-related liver disease and non-alcohol-related liver disease.

Comparative malignancy incidence was expressed as a standard incidence ratio (SIR), that is, the ratio of the observed number of malignancies to the expected number of malignancies. A SIR value greater than 1.0 indicates excess risk, whereas a value less than 1.0 is a decreased risk. Statistically significant deviations of the SIR above and below 1.0 were identified using Poisson probabilities (*19*). Because SEER data for malignancies of the eye, Kaposi's sarcoma, other epithelial skin cancers, and unspecified sites are not available, SIRs were not computed for these categories.

RESULTS

Patient survival. Patient survival for ALD group was slightly better for the first 5 years after LTx when compared with the non-ALD group. After 5 years, the survival for ALD group was lower compared with non-ALD group (Fig. 1). Overall, actuarial survival for the entire follow-up period of 9 years was 50.2% for group I vs. 58.5% for group II and did not reach statistical significance ($P=0.82$). The overall follow-up period was divided into two separate groups: the first 5 years after LTx and beyond 5 years after LTx. At 5 years after LTx, 133 out of 185 (72%) patients were alive in group I and 432 out of 649 (65.5%) in group II ($P=0.14$). The Kaplan-Meier estimates of survival beyond 5 years after LTx were 69.9% and 88.4%, for group I and group II, respectively, normalizing survival at 5 years to 100%. This difference in survival for ALD group and non-ALD group was statistically significant (log rank; $P=0.0001$) (Fig. 2A). A Cox proportional hazard model showed that alcoholics were 2.3 times more likely to die than non-alcoholics after the 5-year mark. Adjustment for age at transplant had no effect.

The most common causes of death beyond the first year after LTx were de novo cancers and age-related problems of cardiac failure, respiratory failure, cerebrovascular accidents, and noncompliance. Recidivism accounted for only one death, a patient who died of recurrent alcoholic pancreatitis and liver failure 8 years after LTx. The causes of death at various times after liver transplantation are shown in Figure 3. There was no difference in survival between male and female patients with ALD (actuarial 9-year survival for male, 48.5% vs. female 56.5%; $P=0.85$). When comparing age at the time of transplant, actuarial 9-year survival for alcoholics >60 years (n=39) was lower (47.6%) when compared to age ≤60 years (51.3%; n=146), but this was not significant ($P=0.56$). Similarly, the 9-year actuarial survival for intensive care unit-bound (n=94) patients was worse (33.8%) compared to the 67 hospital-bound patients (64.6%) or 24 patients who came from home (53.3%) but did not reach statistical significance ($P=0.13$).

Graft survival. Graft loss was defined as loss of graft at the point of repeat transplantation or patient death. Overall, graft survival for ALD and non-ALD showed a trend similar to patient survival, given that "death with a functioning graft" was the major cause of graft loss after 6 months (Fig. 4). Actuarial overall 9-year graft survival for group I was 49.7% vs. 53.2% for group II (Fig. 4). Graft survival at 5 years was 66.5% for group I vs. 60.3% for group II. For those who survived beyond 5 years, graft survival was significantly poorer in the ALD group than the non-ALD group ($P=0.001$) (Fig. 2B). The causes of repeat transplantation in ALD group

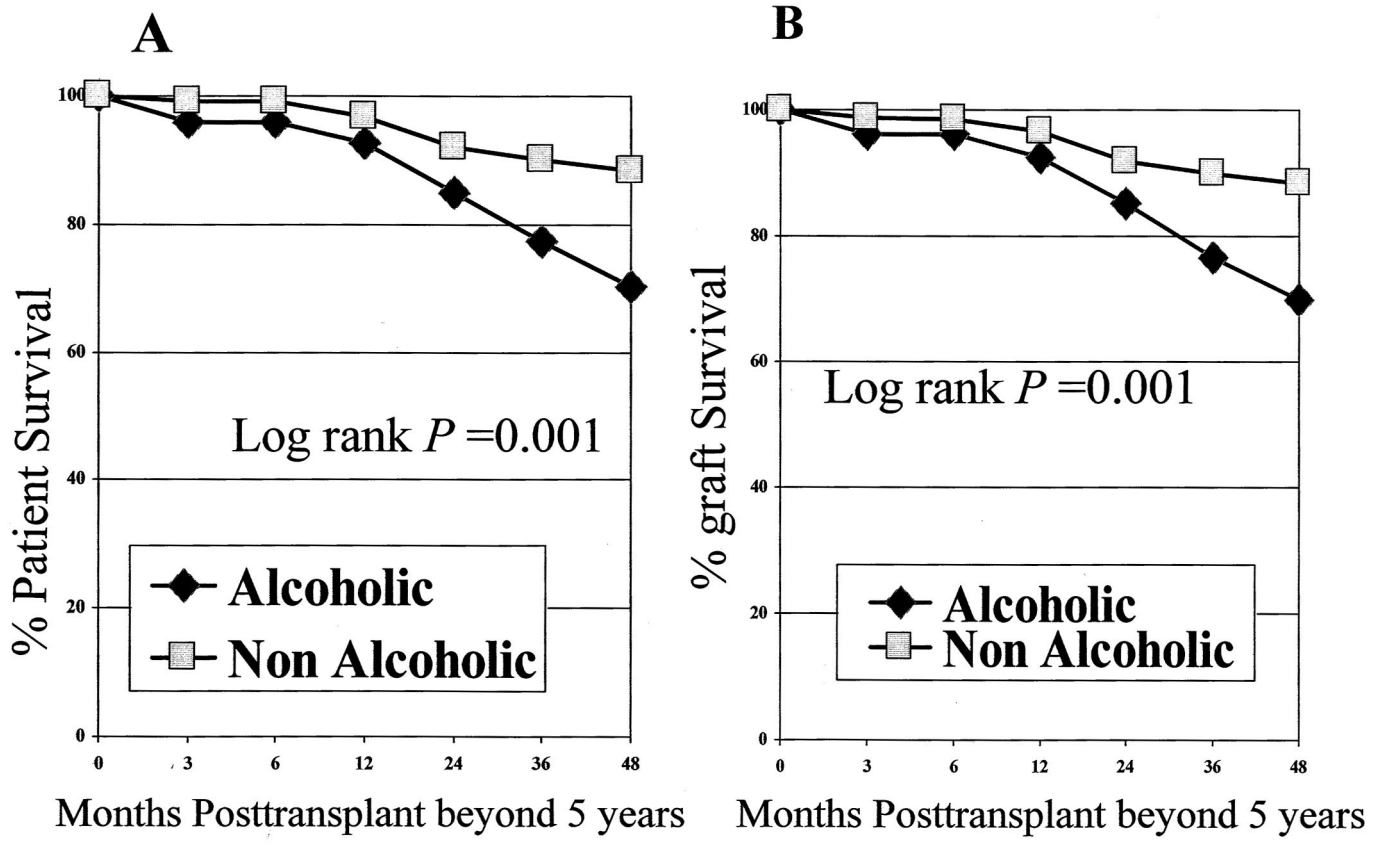

FIGURE 2. (A) Patient survival past 5 years after LTx for ALD and non-ALD group. (B) Graft survival past 5 years after LTx for ALD and non-ALD group.

Causes of Death	Months Post Transplant											
	0 to 3	3 to 6	6 to 12	12 to 24	24 to 36	36 to 48	48 to 60	60 to 72	72 to 84	84 to 96	96 to 108	Total
Fungal	1	4	1								1	7
PTLD			1		1			1				3
Cardiac	2			1				1	4	1		9
CNS	1		1		2	1	1		2		1	9
Denovo Malignancy				1	3	1	2	5		1		13
Respiratory			1		1		1			2		5
Pancreatitis	2			1								3
sepsis	4							1				5
PNF	2		1									3
HAT		1		1		2		1	1			6
Noncompliance							1	1		1		3
MVA							1		1			2
Bile leak		1										1
Rec HCV				1								1
Denovo Hep B							1					1
Pneumocystis				1								1
Renal Failure						1						1
AAA Rupture						1						1
CMV									1			1
Recidivism										1		1
suicide				1								1
Splenic Infarct			1									1
unknown				1								1
Total	12	6	6	8	7	6	7	10	9	6	2	79

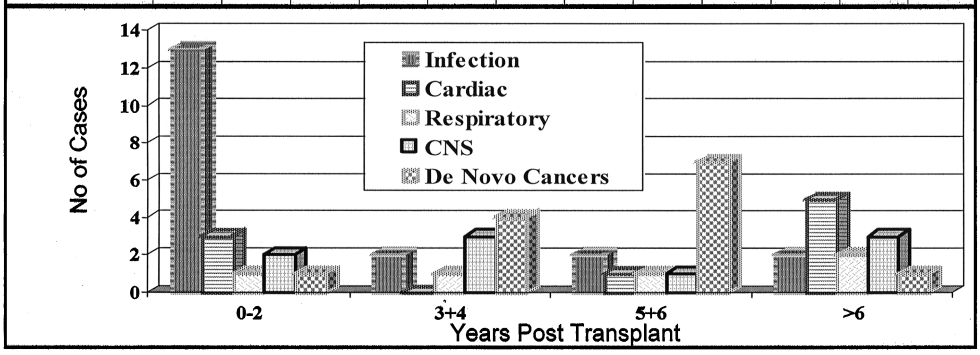

FIGURE 3. (Top) An account of number of deaths from various causes at specific time interval post-LTx. (Bottom) Pictorial representation of deaths from infection, cardiac, respiratory, cerebrovascular (CNS) or de novo cancers in first 2 years, 3rd and 4th years, 5th and 6th years, and more than 6 years post-LTx. (*, some patients had more than one cause of death. The significant primary event, which led to death, was used as the cause of death.) PNF, primary nonfunction; HAT, hepatic artery thrombosis; MVA, motor vehicle accident; Rec HCV, recurrent hepatitis C virus; Hep B, hepatitis B; AAA, abdominal aortic aneurysm; CMV, cytomegalovirus.

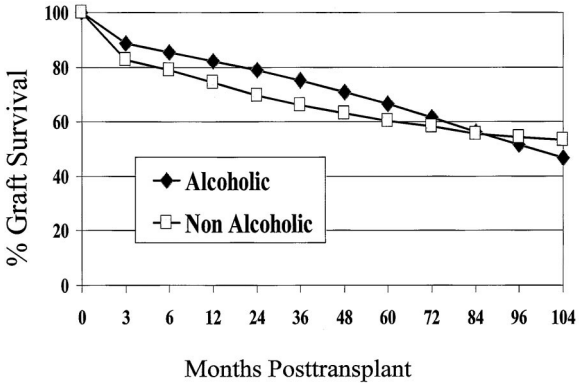

FIGURE 4. Overall liver transplant graft survival for ALD and non-ALD groups.

consisted of hepatic artery thrombosis (n=11), primary nonfunction (n=8), portal vein stenosis (n=1), intrahepatic stricture (n=1), and recurrent hepatitis C (n=1). The rate of repeat transplantation was 11.8% (n=22) in group I compared to 15.8% (n=103) in group II. In addition, three patients (1.6%) in group I received third transplant compared to 18 (2.7%) patients who received a third and fourth transplant (0.6%) in group II.

De novo cancers. A total of 36 patients (19.5%) developed de novo cancers in group I compared to 45 (6.9%) in group II. Non-melanoma skin cancer (squamous cell or basal cell cancers) accounted for 15 (8.1%) in group I vs. 16 (2.5%) in group II. Follow-up of group I and group II provided 978 and 3471 person-years from transplant to death or to January 1999, respectively. This was compared to SEER data for incidence of cancers matched for age, gender, and length of follow-up. Standard incidence ratios of observed to expected cancers in group I and group II for selected sites are shown in Table 2. The survival for patients who developed non-melanoma skin cancer was 86.2% at 6 years compared to 42.7% for other cancers in group I, which was statistically significant ($P=0.007$).

Post transplant lymphoproliferative disorder (PTLD). Six patients (five men and one woman) in group I developed PTLD in the following primary sites: lymph node (n=2), colon (n=2), and liver (n=2), at a mean of 37.8±39.0 months after LTx. Five of these patients died within 12 months after PTLD, and one patient with PTLD in an axillary lymph node is alive 48.9 months after PTLD and 87.9 months after LTx. In group II, 17 patients (2.6%) developed PTLD. Fourteen (82.5%) of these are alive currently. Thus, mortality after PTLD for the alcoholic group was significantly higher than for the non-alcoholic group and reported for all adult LTx population ($P=0.002$) (*20–23*).

Hepatitis C virus (HCV) and hepatitis B virus infection in ALD patients. Twenty-four ALD patients (12.9%) were known to have associated HCV infection, and 2 (1.8%) pa-

TABLE 2. Observed and expected incidence of *de novo* cancers in alcoholic and non-alcoholic LTx patients[a]

Organ/System	Alcoholic LTx patients (group I) (n=185)				Non-alcoholic LTx patients (group II) (n=649)			
	Observed	Expected	SIR	95% Confidence Interval	Observed	Expected	SIR	95% Confidence Interval
Gastrointestinal (esophagus, stomach, colon, and rectum)	1	1.3	0.77	0.02–4.29	7	4.33	1.62	0.65–3.34
Genitourinary (kidney, ureter, prostate, bladder)	5	2.23	2.24	0.72–5.22	6	6.46	0.93	0.34–2.03
Oropharyngeal (oral cavity, pharynx, and larynx)	7	0.28	25.45*	10.23–52.43	1	0.79	1.25	0.03–7.01
Pulmonary (lung and bronchus)	5	1.34	3.72**	1.21–8.68	4	4.35	0.92	0.25–2.34
Female gynecological (breast, ovarian, uterine, and cervical)	1	1.08	0.92	0.02–5.02	3	5.8	0.52	0.11–1.52
Other								
Unknown primary[b]	1				1			
Melanoma[b]	1				1			
Skin cancer (squamous cell and basal cell)[b]	(15)				(16)			
Miscellaneous[b]					8			
Total	20+(15[c])				31+(16[c])			

[a] *, $P<0.01$; **, $P<0.05$.
[b] SEER rates not available.
[c] Nonmelanotic skin cancer.

tients had associated HBV infection at the time of LTx. Ten (41.6%) patients with HCV infection are alive, and 14 have (58.3%) died. The 9-year actuarial survival of patients with ALD and HCV infection was lower (44.1%) than ALD without HCV infection (56.5%) but did not reach statistical significance ($P=0.34$). Three patients with HCV underwent repeat transplant for hepatic artery thrombosis. One patient with HBV died from lung cancer (92 months post-LTx), and another patient died of recurrent HBV infection after four years.

Hepatocellular carcinoma (HCC). Eleven patients had incidental hepatocellular carcinoma (stage T1 to T3, N0, M0) at the time of liver transplantation. Six patients (54.5%) are alive and recurrence-free. Five patients died, one each from cardiac arrest, candidiasis, cryptoccocosis, cerebrovascular accident, and motor vehicular accident at 0.03, 2, 5, 78, and 75 months, respectively, after transplantation. The 9-year actuarial survival was 51% comparable to those without hepatocellular carcinoma (50.6%) for group I. In control group II, 127 patients had HCC and 76 patients died with the 9-year actuarial survival estimate 39.5%.

Post LTx alcohol-related morbidity and mortality. The details of pretransplant sobriety and alcohol rehabilitation were available for 170 (91.9%) patients from medical records, whereas, for 15 patients, this information was not documented. Eleven patients (5.9%) had sobriety intervals of ≤1 month, 46 patients (24.9%) between >1 month and ≤6 months, and 128 patients (65.4%) had >6 months before LTx. Sixty-five patients (35.1%) went to rehabilitation before transplant, of whom 59 (90.8%) completed successfully and six (9.2%) failed rehabilitation. Those who failed rehabilitation were required to resume alcoholism treatment and demonstrate sustained sobriety before transplantation.

Thirty-seven patients (20.0%) had documented history of recidivism after LTx of which one patient (2.7%) had sobriety intervals of ≤1 month, 15 patients (40.5%) had sobriety intervals of >1 month but ≤6 months, and 21 patients (56.8%) had sobriety intervals >6 months before LTx (Table 3). Of these 37 relapses, 18 (46.6%) went to rehabilitation before LTx, 16 (43.2%) did not go to rehabilitation and 2 (5.4%) had attended more than one rehabilitation; in 1 (2.7%) patient, the rehabilitation history was not known (Table 4). Neither pretransplant length of sobriety ($P=0.17$) nor pretransplant alcohol rehabilitation ($P=0.08$) were associated with posttransplant alcohol recidivism. Alcohol rehabilitation is not commonly thought to be useful for patients who have more than a 2-year history of sobriety. In our cohort, we had 50 such patients who were not referred for rehabilitation before

TABLE 3. Overall rate of recidivism and in relation to period of pretransplant sobriety

	Overall rate of Recidivism			
	Total	Yes n (%)	No n (%)	Unknown n (%)
	185	37 (20.0)	133 (71.9)	15 (8.1)
Sobriety period	Recidivism rate according to pretransplant sobriety			
	n (%)	Recidivism rate		
		Yes n (%)	No n (%)	Unknown n (%)
≤1 mo	11 (5.9)	1 (2.7)	10 (7.5)	
>1 to ≤6 mo	46 (24.9)	15 (40.5)	28 (21.0)	3 (20.0)
>6 to ≤12 mo	32 (17.3)	9 (24.3)	20 (15.0)	3 (20.0)
>12 to ≤24 mo	39 (21.1)	4 (10.8)	32 (24.1)	3 (20.0)
>24 mo	50 (27.0)	8 (21.6)	39 (27.6)	3 (20.0)
Unknown	7 (3.8)		4 (3.0)	3 (20.0)

TABLE 4. Rate of recidivism in relation to pre-LTx rehabilitation

Rehabilitation	No. of patients n (%)	Drinking after transplant		
		Yes	No	Unknown
Yes	59 (31.9)	18 (9.7)	35 (18.9)	6 (3.2)
No	91 (49.2)	16 (8.6)	69 (37.3)	5 (2.7)
Unknown	29 (15.7)	1 (0.5)	24 (13)	4 (2.1)
Relapse before LTx	6 (3.2)	2 (1.1)	4 (2.1)	0
Total	185	37 (20.0)	134 (72.4)	14 (7.6)

LTx. However, eight patients relapsed after transplantation (Table 4). Alcohol consumption was believed to be directly related to deaths of four patients. In one patient, persistent alcohol consumption for 8 years caused recurrent alcoholic pancreatitis and cirrhosis. In three others, alcoholism with simultaneous noncompliance with immunosuppressive medications, clinic appointments, and laboratory testing resulted in liver failure and death, 5–8 years after LTx (Fig. 3). None of these patients were considered for repeat transplantation as all patients failed repeated attempts at alcohol rehabilitation.

DISCUSSION

There are a number of reports showing comparable patient and graft survival in alcoholic cirrhotic and non-alcoholic cirrhotic patients undergoing LTx (*3–5*, *7–10*, *20–24*). The overall survival in this report was also comparable for ALD and non-ALD group; however, when the analysis was divided into before and beyond 5 years after LTx, there were notable survival trends. Although the early survival (from 0 to 5 years after LTx) was better in the ALD group compared to the non-ALD group, we also found that the survival in the ALD group was significantly less than that of non-alcoholic cirrhosis after 5 years. The survival for ALD group was better in the first 5 years compared to non-ALD group, partly because the ALD group was relatively free from recurrence of primary malignancy, recurrence of viral hepatitis (HCV and HBV) and recurrence of auto-immune processes. Everson and co-workers (*10*) gave an account of 68 alcoholic cirrhotic patients and observed decreasing long-term survival. They felt that patient death was partly related to consumption of alcohol. Initially, we also believed that recidivism would be an important factor in delayed patient death. However, in this report, only one death was attributed to recidivism, and three deaths occurred from the combination of noncompliance with immunosuppression medications, follow-up blood testing, and recidivism. Thus, the major causes of patient loss after this period would be nonpsychosocial causes and nonimmunological causes. It has been suggested that ALD recipients appear to have lower immunologic reactivity as expressed by lower incidence of both acute and chronic rejection (*20*, *25*). Indeed, Berlakovich and co-workers (*26*) reported favorable survival in 58 ALD patients after LTx and did not find any evidence of chronic rejection, which our present report appears to support.

Thus, the major cause of patient and graft loss appears to be nonimmunologic in nature. The majority of delayed deaths were related to de novo cancer, cardiorespiratory, and cerebrovascular events. The risk of death was 2.3 times higher for the alcoholic group of patients beyond 5 years after LTx adjusted for age. Patients with HCV infection in ALD group had lower survival, but this did not reach statistical significance in this series, presumably because of the small number of patients in this cohort. Bell and co-workers (*8*), analyzing the UNOS database containing more than 3000 patients, found HCV infection with ALD had slightly lower survival at 3 years, although not different in the first year. However, Weisner and co-workers (*27*)reported no difference in patients with ALD and HCV infection after LTx.

There was a significantly higher risk of oral, esophageal, pharyngeal, laryngeal, and hepatic cancers in nonimmunosuppressed middle-aged and elderly American individuals with moderate to large amount of alcohol consumption (*28*). Increased morbidity has also been reported from Europe (*29*). We have previously reported an increased incidence of certain de novo cancers in post-LTx patients under tacrolimus (*30*). For these comparative studies, we used the SEER data (*18*) and found the rate of oropharyngeal cancer in the ALD group was almost 25 times higher than the general population matched for age and sex. The risk did not appear higher for the non-ALD control group when similar comparisons were made. In addition, lung cancer was 3.7 times higher in the ALD group compared to nontransplanted population, and this risk was not higher in the control non-ALD LTx group under tacrolimus. Kelly and co-workers (*31*) also found an increasing incidence of de novo cancers in alcoholic cirrhotic but not higher in other LTx patients. However, other reports have suggested an increased risk of developing de novo cancer in post-LTx patients (*32–35*). This may be the result of failure to acknowledge different risks based on organ system. Genitourinary cancers were also 2.2 times higher in the alcoholic population but not in the non-alcoholic group; however, this did not reach statistical significance. Standardized incidence ratios for gastrointestinal cancer and female gynecological cancers were 0.77 and 0.92, respectively.

Although the rate of PTLD in the ALD group (3.2%) and the non-ALD group (2.6%) was similar, surprisingly, the mortality in ALD group with PTLD was significantly higher (83%) as compared to (17.6%) in non-ALD group ($P=0.002$). Although there are many reports on PTLD in LTx population, there is no report of increased mortality as a result of PTLD in LTx patients for ALD (*36–40*). This will need verification from other centers.

The rate of recidivism was 20% in this group of ALD transplant population, and this did not appear to correlate with the length of sobriety or rehabilitation before LTx. However, this is not to suggest that all alcoholic cirrhosis patients should receive transplants without any intervention, such as evaluation or rehabilitation. We believe that the key to providing LTx to ALD patients is with a dedicated team of psychiatrists, nurses, and social workers, who develop a follow-up plan with the patient and his/her family, monitor clinic attendance, and evaluate compliance with medical advise. This may be more important in determining abstinence than previously assumed factors such as length of sobriety and rehabilitation. In fact, the inability of various parameters to predict abstinence (*41*) supports this concept. Williams and co-workers and Foster et al. (*22*, *41*) have made similar observations and felt initial period of sobriety was not important in post-LTx drinking.

In summary, patient and graft survival for ALD through

the first 5 post-LTx years was better than that of non-alcoholic cirrhotic controls; however, after 5 years, it was significantly inferior. In our group of selected ALD patients who underwent LTx, the rate of recidivism was 20% and showed no correlation to length of sobriety or rehabilitation before LTx. The contribution of recidivism and noncompliance to mortality was minimal. The rate of de novo oropharyngeal cancers and pulmonary cancer for the alcoholic group was 25 times and 4 times higher when compared to the general population. This was not higher for the non-alcoholic control group after LTx, suggesting that immunosuppression per se, is not a factor in initiating malignant changes. Other factors, such as concurrent alcohol use and smoking, are likely synergistic factors in potentiating the development of de novo cancers in the ALD group. Thus, the challenge for these patients will be in detecting the development of such malignancies and intervening conditions such as cardiovascular disease, in order to improve long-term survival.

REFERENCES

1. Scharschmidt BF. Human liver transplantation: analysis of data on 540 patients from four centers. Hepatology 1984; 4(Suppl 1): 95S.
2. Van Thiel DH, Schade RR, Gavaler JS, Shaw BW Jr, Iwatsuki S, Starzl TE. Medical aspects of liver transplantation. Hepatology 1984; 4(Suppl 1): 79S.
3. Starzl TE, Van Thiel D, Tzakis AG, et al. Orthotopic liver transplantation for alcoholic cirrhosis. JAMA 1988; 260(17): 2542.
4. Bird GL, O'Grady JG, Harvey FA, Calne RY, Williams R. Liver transplantation in patients with alcoholic cirrhosis: selection criteria and rates of survival and relapse. Br Med J 1990; 301(6742): 15.
5. McCurry KR, Baliga P, Merion RM, et al. Resource utilization and outcome of liver transplantation for alcoholic cirrhosis: a case-control study. Arch Surg 1992; 127(7): 772.
6. Lucey MR, Merion RM, Henley KS, et al. Selection for and outcome of liver transplantation in alcoholic liver disease. Gastroenterology 1992; 102(5): 1736.
7. Gish RG, Lee AH, Keeffe EB, Rome H, Concepcion W, Esquivel CO. Liver transplantation for patients with alcoholism and end-stage liver disease. Am J Gastroenterol 1993; 88(9): 1337.
8. Belle SH, Beringer KC, Murphy JB, Detre KM. The Pitt-UNOS Liver Transplant Registry. Clin Transplant 1992; 17.
9. Snyder SL, Drooker M, Strain JJ. A survey estimate of academic liver transplant teams' selection practices for alcohol-dependent applicants. Psychosomatics 1996; 37(5): 432.
10. Everson G, Bharadhwaj G, House R, et al. Long-term follow-up of patients with alcoholic liver disease who underwent hepatic transplantation. Liver Transplant Surg 1997; 3(3): 263.
11. Jain AB, Kashyap R, Rakela J, Starzl TE, Fung JJ. Primary adult liver transplantation under tacrolimus: more than 90 months actual follow-up survival and adverse events. Liver Transplant Surg 1999; 5(2): 144.
12. Jain AB, Todo S, Fung JJ, et al. Correlation of rejection episodes with FK 506 dosage, FK 506 level, and steroids following primary orthotopic liver transplant. Transplant Proc 1991; 23(6): 3023.
13. Jain AB, Fung JJ, Todo S, et al. Incidence and treatment of rejection episodes in primary orthotopic liver transplantation under FK 506. Transplant Proc 1991; 23(1 Pt 2): 928.
14. Jain AB, Fung JJ, Todo S, et al. One thousand consecutive primary orthotopic liver transplants under FK 506: survival and adverse events. Transplant Proc 1995; 27(1): 1099.
15. Fung JJ, Eliasziw M, Todo S, et al. The Pittsburgh randomized trial of tacrolimus compared to cyclosporine for hepatic transplantation. J Am Coll Surg 1996; 183(2): 117.
16. Starzl TE, Donner A, Eliasziw M, et al. Randomised trialomania? The multicentre liver transplant trials of tacrolimus. Lancet 1995; 346(8986): 1346.
17. Marsh GM, Youk AO, Stone RA, Sefcik S, Alcorn C. OCMAP-PLUS: a program for the comprehensive analysis of occupational cohort data. J Occup Environ Med 1998; 40(4): 351.
18. Ries Lag K, Cl, Hankey, BF Harras, A Miller BA, Edwards BK. SEER cancer statistics review; 1973–1993: tables and graph. Bethesda, MD: National Cancer Institute, 1996.
19. Bailer JEF. Significance factors for the ratio of a Poisson variable to its expectation. Biometrics 1964; 20(1): 639.
20. Van Thiel DH, Bonet H, Gavaler J, Wright HI. Effect of alcohol use on allograft rejection rates after liver transplantation for alcoholic liver disease. Alcohol Clin Exp Res 1995; 19(5): 1151.
21. Lucey MR. Liver transplantation for the alcoholic patient. Gastroenterol Clin North Am 1993; 22(2): 243.
22. Pereira PW. Liver transplantation for alcoholic liver disease at King's College Hospital: survival and quality of life. Liver Transplant Surg 1997; 3(3): 245.
23. Pageaux GP, Michel J, Coste V, et al. Alcoholic cirrhosis is a good indication for liver transplantation, even for cases of recidivism. Gut 1999; 45(3): 421.
24. Lucey MR, Carr K, Beresford TP, et al. Alcohol use after liver transplantation in alcoholics: a clinical cohort follow-up study. Hepatology 1997; 25(5): 1223.
25. Berlakovich GA, Imhof M, Karner-Hanusch J, et al. The importance of the effect of underlying disease on rejection outcomes following orthotopic liver transplantation. Transplantation 1996; 61(4): 554.
26. Berlakovich GA, Steininger R, Herbst F, Barlan M, Mittlbock M, Muhlbacher F. Efficacy of liver transplantation for alcoholic cirrhosis with respect to recidivism and compliance. Transplantation 1994; 58(5): 560.
27. Wiesner R LM, Lake J, Everhart J, Detre, K. Liver transplantation for end stage alcoholic liver disease: an assessment of outcomes. Liver Transplant Surg 1997; 3(3): 231.
28. Thun MJ, Peto R, Lopez AD, et al. Alcohol consumption and mortality among middle-aged and elderly U.S. adults [see comments]. N Engl J Med 1997; 337(24): 1705.
29. Sales J, Duffy J, Plant M, Peck D. Alcohol consumption, cigarette sales and mortality in the United Kingdom: an analysis of the period 1970–1985. Drug Alcohol Depend 1989: 24(2): 155.
30. Jain AB, Yee LD, Nalesnik MA, et al. Comparative incidence of de novo nonlymphoid malignancies after liver transplantation under tacrolimus using Surveillance Epidemiologic End Result data. Transplantation 1998; 66(9): 1193.
31. Kelly DM, Emre S, Guy SR, Miller CM, Schwartz ME, Sheiner PA. Liver transplant recipients are not at increased risk for nonlymphoid solid organ tumors. Cancer 1998; 83(6): 1237.
32. Levy M, Backman L, Husberg B, et al. De novo malignancy following liver transplantation: a single-center study. Transplant Proc 1993; 25(1 Pt 2): 1397.
33. Penn I, Starzl TE. Malignant tumors arising de novo in immunosuppressed organ transplant recipients. Transplantation 1972; 14(4): 407.
34. Penn I. Neoplastic complications of transplantation. Semin Respir Infect 1993; 8(3): 233.
35. Penn I. The problem of cancer in organ transplant recipients: an overview. Transplant Sci 1994; 4(1): 23.
36. Jain AF, J Kashyap, R Rohal, S Nalesnik, M. Comparative study of posttransplant lymphoproliferative disorder and de novo cancer after liver transplantation under tacrolimus. Hepatology 1999; 30(2): A50.
37. Jain AB, Mazariegos G, Cacciarelli T, Kashyap R, Nalesnik M, Rohal S, Fung J. Incidence of post transplant lymphoprolifera-

tive disorder in adults and children: consecutive 1000 primary liver transplant recipients under tacrolimus. Transplantation 1999; 67(7): S246.
38. Jain AB, Fung JJ. Post transplant lymphoproliferative disorder following adult liver transplantation: retrospective study of 4000 patients over 15 years from Single center. Transplantation 1999; 67(9): S587.
39. Nalesnik MJR, Starzl TE. Experience with post transplant lymphoproliferative disorders in solid organ transplant recipients. Clin Transplant 1988; 6: 249.
40. Starzl TE, Nalesnik MA, Porter KA, et al. Reversibility of lymphomas and lymphoproliferative lesions developing under cyclosporin-steroid therapy. Lancet 1984; 1(8377): 583.
41. Foster PF, Fabrega F, Karademir S, Sankary HN, Mital D, Williams JW. Prediction of abstinence from ethanol in alcoholic recipients following liver transplantation. Hepatology 1997; 25(6): 1469.

Received 6 January 2000.
Accepted 24 April 2000.

0041-1337/00/7009-1342/0
TRANSPLANTATION

Vol. 70, 1342–1347, No. 9, November 15, 2000
Printed in U.S.A.

RENAL RESPONSE TO A PROTEIN LOAD PERSISTS DURING LONG-TERM FOLLOW-UP OF CHILDREN AFTER RENAL TRANSPLANTATION[1,2]

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Background. **Kidney donors and transplant recipients may be at risk of complications from glomerular hyperfiltration of the single kidney. It has been assumed that tests of the existence of renal functional reserve [Δglomerular filtration rate (ΔGFR), Δ effective renal plasma flow (ΔERPF)] can be used to demonstrate hyperfiltration. It would therefore be of interest to evaluate the response of the kidney graft to a protein load. i.e., testing the renal reserve and to find out whether a reduction in baseline GFR is preceded by a loss of ΔGFR.**

Methods. **We repeatedly studied the change in GFR and renal plasma flow (ERPF) after an oral protein load in 30 children after renal transplantation (Tx). Follow-up time was 1.0–8.0 years. Renal function was evaluated with the clearances of inulin and para-aminohippuric acid (PAH). Seven recipient/donor pairs were examined twice (median 0.3 and 4 years, after Tx).**

Results. **The baseline GFR and ERPF remained stable throughout the follow-up and the increase after stimulation (ΔGFR and ΔERPF) did not change in the whole group of Tx children over the years. However, a reduction in the baseline GFR from the first to the last investigation occurred in 23 of 30 children. In the 23 patients whose baseline GFR decreased, ΔGFR was still preserved. In the recipient/donor pairs, the baseline GFR and ERPF were the same, but on the second investigation, donors showed higher ΔGFR.**

Conclusion. **Despite fairly low baseline GFR and ERPF values in the Tx children, no change occurs in the capacity to increase GFR and ERPF after a protein load during follow-up, which suggests that they are not maximally hyperfiltrating.**

Renal functional reserve (RFR), i.e., the capacity of the kidney to increase its function with certain demands, such as a protein load, has been evaluated in healthy humans (*1–5*) and in various renal disorders including patients with single kidneys (*6–15*) and after renal transplantation (*16–21*). Most studies have been performed in adults, a few in children (*10*, *12–15*, *22*, *23*) and hardly any in pediatric renal recipients (*17*, *24*), especially not repeated studies of individual children.

In experimental studies, a reduction in renal mass leads to hyperfiltration in remnant nephrons and causes glomerulosclerosis and deterioration in renal function (*25*, *26*). Brenner et al. (*27*) suggested that the course in humans with reduced renal mass may be similar. When renal mass is lost, RFR is thought to be continuously utilized, although baseline GFR remains constant, until 50% of the nephron mass remains. Thereafter, baseline GFR gradually declines parallel to further nephron loss (*6*). Bosch et al. (*1*) found a reduced renal reserve in patients with renal disease, in proportion to the severity of the disease. They concluded that absence of renal reserve could be clinical evidence of hyperfiltration and might herald the fall in baseline GFR (*6*, *7*). The reduced renal mass in subjects with a single kidney suggests that it may be hyperfiltrating. From this point of view children who have undergone renal transplantation may be of interest for studies of renal reserve. In such patients, the single kidney is exposed to cyclosporine, which might also affect RFR (*28*, *29*).

[1] Presented in part at the European Society for Paediatric Nephrology meeting in Lausanne, 1996 (Abstract).

[2] Supported by the Samariten Foundation, Mayflower Foundation, Karolinska Institutet and the Swedish Medical Research Council, no. 6864.

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