De Novo Neoplasia After Liver Transplantation: An Analysis of Risk Factors and Influence on Survival

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Immunosuppression increases the risk of posttransplant malignancy and it may increase posttransplant mortality. The finding of factors related to the development of post-transplant malignancy may serve as a guide to avoid those risk factors and to develop strategies of posttransplant surveillance. The incidence and risk factors of malignancy were studied in 187 consecutive liver transplant recipients surviving more than 3 months. None of the 12 patients surviving less than 3 months had *de novo* neoplasia. The impact of malignancy on survival was studied in a case-control study. After a median follow-up of 65 months, 49 patients developed 63 malignancies: 25 patients had 35 cutaneous neoplasias and 27 patients had 28 noncutaneous malignancies. The 5- and 10-year actuarial rates of cutaneous neoplasia were 14 and 24% and the rates of noncutaneous neoplasia were 11 and 22%, respectively. Risk factors for the development of cutaneous malignancy were older age and Child-Turcotte-Pugh A status. Risk factors for the development of noncutaneous malignancy were older age, alcoholism, and smoking. Cutaneous neoplasia had no effect on survival, whereas patients with noncutaneous malignancy had a significant reduction of survival. The overall relative risk of cutaneous and noncutaneous neoplasia, as compared with the general population were 16.91 (95% confidence interval: 11.78-23.51) and 3.23 (95% confidence interval: 2.15-4.67), respectively. The relative risk of cancer-related mortality (after excluding recurrent malignancy) was 2.93 (95% confidence interval: 1.56-5.02). Multivariate analysis showed that noncutaneous malignancy was an independent risk factor for posttransplant mortality. In conclusion, liver transplant recipients have a higher risk of cancer-related mortality than the general population. This increased risk is due to the development of noncutaneous neoplasia. Older age, alcoholism, and smoking increase the risk of *de novo* noncutaneous neoplasia.

The loss of immunovigilance induced by immunosuppressive drugs increases the risk of *de novo* malignancy[1] and it may cause a greater risk of mortality.
In fact, *de novo* malignancy is 1 of the leading causes of late mortality in liver transplant recipients.[2] The risk of malignancy is not homogeneous in all liver transplant recipients. In previous studies, we found that older patients have a greater risk of malignancy[3] and a recent report from Valencia (Spain) suggested that alcohol, hepatitis C, and strong immunosuppression could increase the risk of malignancy.[4] The characterization of the predisposing factors for the development of neoplasia may increase the clinical suspicion in a given patient, may give a basis for the use of less potent immunosuppression in patients with greater risk of malignancy, and may help us to develop surveillance programs in selected patients. The main goals of this study were to assess which risk factors are associated to the occurrence of posttransplant malignancy and to investigate the effect of posttransplant malignancy on survival.

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PATIENTS AND METHODS

Patients

We retrospectively studied all the patients receiving their 1st liver transplantation between April 1990 and October 2001 at our institution. All the patients were followed until the beginning of 2003. Patients with a survival lower than 3 months were excluded from the study.

Immunosuppression

Induction immunosuppression protocols have been described previously.[5] Until 1996, immunosuppression was based in the combination of cyclosporine, azathioprine, and steroids. From 1997 to 2001, it was based on cyclosporine or tacrolimus, combined with steroids; most patients received also azathioprine.

Until 1996, maintenance immunosuppression was based on triple therapy, combining cyclosporine, azathioprine, and prednisone, with the exception of those patients with intolerance to azathioprine or with diabetes mellitus. Cyclosporine monotherapy was not attempted before the end of the 2nd posttransplant year. After 1997, steroid withdrawal was attempted between the 3rd and the 6th posttransplant month. After steroid withdrawal, azathioprine was withdrawn, thus monotherapy with cyclosporine or tacrolimus was usually attempted between the 3rd and the 9th month after transplantation.

Treatment of rejection consisted of the increase of cyclosporine or tacrolimus doses, or the administration of up to 3 1-gm boluses of methylprednisolone. Refractory rejection was treated with OKT3.

Follow-Up

After discharge, patients were seen in the outpatient clinic every week during the 1st postoperative month, twice a month until the end of the 3rd month, monthly between the 3rd and the 6th month, and every 2 months between the 6th and the 12th month. Thereafter, patients were seen every 3 months.

Preoperative assessment of neoplasia included chest and abdomen computed tomography scans, head magnetic resonance imaging, and upper gastrointestinal endoscopy. Total colonoscopy was performed in all patients who were older than 50 years of age.

Routine check-up for neoplasia included a dermatology visit, chest X-ray film, and abdominal ultrasonography every 6 months during the 1st year and yearly thereafter. Those patients actively smoking after transplantation were seen every year in the ear-nose-throat outpatient clinic. Colonoscopy was repeated 1 year after transplantation in those patients who had adenomatous polyps. Colonoscopy was repeated every 2 years in the case of finding new polyps. None of the patients in the present series had ulcerative colitis.

Evaluation of Risk Factors for the Development of Neoplasia

The following variables were recorded in every case: age and gender of donor and recipient, blood group, indication of liver transplantation, Child-Turcotte-Pugh status at transplantation, patient body mass index at transplantation, personal and family history of malignancy, past history of tobacco or alcohol consumption, donor and recipient serology status for Epstein-Barr virus and cytomegalovirus, immunosuppression, and history of acute rejection. Tobacco and alcohol consumption were considered as potential risk factors if they exceeded 10 pack-years or 80 grams per day for more than 10 years, respectively. For immunosuppression, use of cyclosporine or tacrolimus was considered. Azathioprine and steroids were considered as potential risk factors if they were administered for more than 6 months.

The potential influence of these variables in the development of neoplasia was studied. Separate analysis for the assessment of the potential influence of these variables in the development of cutaneous neoplasia (basal-cell and squamous-cell carcinoma) and the development of noncutaneous neoplasia were performed. For the assessment of the potential risk factors related to cutaneous neoplasia, region of residence (North [more cloudy] or Center-South [more sunny] of Spain) and work (outdoors or indoors) were analyzed.

Evaluation of the Influence of Malignancy on Survival

The possible influence of malignancy on survival was assessed in a case-control study. Two controls were chosen for every patient with neoplasia, i.e., those who had been transplanted immediately before and after the case patient and who were alive at the moment of diagnosis of neoplasia in the case. To assess if posttransplant neoplasia had an independent influence on survival, the possible influence on survival of the variables mentioned in the previous section was also assessed.

Similar case-control studies were performed to assess the influence of survival of patients with cutaneous and noncutaneous neoplasia.

Relative Risk of Neoplasia and of MalignancyRelated Death as Compared With General Population

For comparison with the general population, observed nonmelanoma cutaneous and noncutaneous neoplasia and cancer-related deaths in the study group were compared with those expected, based on age- and sex-specific incidences of neoplasia and cancer-related mortality rates, for Navarra, Spain, in 1993–1997.[6] The 95% confidence limits for the relative risk (ratio of observed to expected) was obtained after assuming a Poisson distribution for the development of malignancy and for malignancy-related death.

Statistical Analysis

Results are expressed as mean (standard deviation) for continuous variables and proportion for qualitative variables. Actuarial survival rates and risks of development of tumor were obtained with the Kaplan-Meier method and comparison between groups was performed with the log-rank test. The risk of development of neoplasia and the influence of the different factors on survival was considered in an univariate Cox proportional hazards model. All predictors with $P<.1$ in univariate analysis were entered in a multivariate Cox proportional hazard model; $P<.05$ was considered significant. All statistical analysis were performed with the software SPSS 11.0 (SPSS, Chicago, IL).

RESULTS

Characteristics of the Patients

In the period studied, 199 patients received their first liver transplantation in our center. A total of 12 patients were excluded because their survival was less than 3 months; none of them had any malignancy diagnosed before dying. The characteristics of the 187 patients included in this study are shown in Table 1. Median follow-up of the patients was 65 months. Patients were followed for a total of 1,121 patient-years.

Prevalence of *De Novo* Malignancy

A total of 49 patients developed 63 malignancies. The overall incidence was 26.2%. The

5- and 10-year actuarial risks of neoplasia were 25 ± 4% and 39 ± 5%, respectively. Cutaneous neoplasia was diagnosed in 25 patients (5- and 10-year actuarial risks were 14 ± 3% and 24 ± 5%, respectively); they had 35 tumors (22 squamous-cell and 13 basal-cell carcinomas). Most of these tumors were located in the head (20 / 22 squamous-cell and 12 / 13 basal-cell carcinomas); the other 3 tumors were located in the lower limbs. Median time between transplantation and the diagnosis of skin neoplasia was 49.5 (range: 4-156) months.

Other malignancies were diagnosed in 27 patients (Table 2). The 5- and 10-year actuarial risks of noncutaneous neoplasia were 11 ± 3% and 22 ± 4%, respectively. Histologically, the epidermoid tumors were the most frequent malignancies (10 cases), followed by lymphomas (7 cases), and adenocarcinomas (7 cases). A total of 3 patients had both cutaneous and noncutaneous neoplasia: 1 patient had cutaneous squamous-cell carcinoma and lymphoma, another had basal-cell carcinoma and lung cancer, and the 3rd one had 2 basalcell carcinomas, pancreas adenocarcinoma, and esophagus cancer. Median time until diagnosis of noncutaneous cancer was 44.5 (range: 5-102) months. Actuarial prevalences of *de novo* neoplasia, cutaneous neoplasia, and noncutaneous neoplasia are shown in Figure 1A–C.

Risk Factors for Malignancy

In univariate analysis, 9 variables were associated with the development of neoplasia (Table 3). In multivariate analysis, past history of alcohol consumption, older age, and Child-Turcotte-Pugh A status at transplantation were independently associated with the development of neoplasia. Cutaneous cancer was independently associated to a greater age and Child-Turcotte-Pugh A stage at transplantation (Table 4). Age and history of smoking and alcohol abuse were independently associated with the development of noncutaneous malignancy (Table 5).

Analysis of Survival

All the patients with cutaneous cancer or Kaposi sarcoma were free of disease at last follow-up. Four patients with cutaneous neoplasia died after the diagnosis of neoplasia; the causes of these deaths were noncutaneous neoplasia (2 cases), sudden death (1 case), and biliary cirrhosis after hepatic artery thrombosis (1 case). A total of 4 of 7 patients with lymphoma died because of the tumor or complications of antineoplastic therapy; 1 of them died of recurrent hepatocellular carcinoma after lymphoma complete remission, and 2 of them are currently alive (1 of them is free of disease and the 2nd one is still receiving chemotherapy). A total of 10 of the 18 patients with solid organ neoplasia died because of malignancy, 2 of them are alive with persisting disease, and 6 patients are alive and free of neoplasia.

Therefore, 15 of the 27 patients with noncutaneous neoplasia died (median after diagnosis of tumor: 5 months; range: 1-31) and 12 of them are alive (median after diagnosis of tumor 27.5 months; range: 2-128). Figure 2 shows the survival of patients after the diagnosis of cutaneous cancer and noncutaneous neoplasia.

Patients with tumor had a significantly lower survival than control patients without neoplasia (Fig. 3A). This was due to the marked and significant decrease in survival showed by patients with noncutaneous neoplasia, while cutaneous tumors had no impact on survival (Fig. 3C and B, respectively). Multivariate analysis showed that development of noncutaneous neoplasia and withdrawal of azathioprine before the 6th posttransplant month were independently associated to lower survival (Table 6).

Relative Risk of Malignancy and MalignancyRelated Death as Compared With the General Population

Table 7 shows observed and expected number of patients diagnosed of cutaneous and

noncutaneous neoplasia and deaths related to cancer. The overall relative risks were 18.91, 3.23, and 4.29, respectively. A total of 6 of the patients died of recurrent tumors (hepatocellular carcinoma in 1 case and rectum sarcoma in 1 case). After excluding these cases of mortality, the relative risk of cancer-related mortalitywas 2.93 (95% confidence interval: 1.56-5.02).

Lymphomas

Lymphoma was diagnosed in 7 patients. All of them were of lymphocyte-B origin. A total of 3 of them were diagnosed in the 1st 6 months after transplantation. All of them were restricted to the liver hilum. A total of 2 of these 3 patients died as a consequence of lymphoma and the 3rd one died of recurrent hepatocellular carcinoma 23 months after lymphoma diagnosis.

The other 4 patients had systemic lymphoma (3 patients) and central nervous system lymphoma (1 case), diagnosed 17–97 months after transplantation Two of them died of lymphoma, 1 of them is alive and free of disease 81 months after the diagnosis of lymphoma, and the 4rth one is currently under therapy.

The only 2 factors associated with a higher risk of lymphoma (univariate analysis) were an older age of the transplant recipient and his / her Epstein-Barr virus– seronegativity before transplantation.

DISCUSSION

The improvement of immunosuppression and other refinements in the management ofpatients have led to a marked increase of survival after liver transplantation. Thus, long-term complications of liver transplantation have become more important in the last years. One of these complications is the development of malignancies. In this series, 1 of every 4 patients surviving more than 3 months developed *de novo* neoplasia.

Fortunately, the most frequent neoplasias found in our series were squamous-cell and basal-cell cutaneous carcinomas. A close surveillance allowed early diagnosis and it led to null mortality due to these tumors. On the other hand, the development of noncutaneous neoplasia has a poor prognosis and noncutaneous malignancy was independently related to mortality. In this series, the incidence of noncutaneous neoplasia (14.4%) was higher than in most series of neoplasia in liver transplant recipients previously published.[1,4,7–23] Only Bellamy et al.[17] had a higher incidence (17%). It may be related to a longer follow-up (although some series had lower incidences with comparable follow-ups) or with the routine use of azathioprine in our immunosuppressive protocol. Although this drug was related to the development of neoplasia in other series,[4] when we studied whether a longer treatment with azathioprine increased the risk of neoplasia, we did not find such an association. Our high incidence of neoplasia may also have been related to the high proportion of patients with alcoholic cirrhosis in our series. This was 1 of the predisposing factors for the development of neoplasia in our multivariate analysis. Unsurprisingly, the only series with an incidence of noncutaneous malignancy higher than the present series was a series of patients transplanted for alcoholic liver disease.[17]

The identification of the predisposing factors for the development of neoplasia may be important for 2 reasons: 1) it may help us to reinforce healthy habits (i.e., to avoid tobacco and alcohol use), and 2) the identification of those patients with a higher risk of neoplasia may lead us to use less potent immunosuppression or to develop surveillance programs for them. In our series, a greater age and alcohol and cigarette abuse were significantly related to the development of noncutaneous cancer. This is not surprising, as most of the solid organ cancers diagnosed were

related to tobacco and alcohol (e.g., lung, head and neck, and esophageal and pancreatic carcinomas) and age is a well-known risk factor for cancer. Other authors have previously suggested the role of previous alcoholism as a predisposing factor for malignancy after liver transplantation.4,22,24

Benlloch et al.[4] recently suggested that patients being transplanted for alcoholic cirrhosis should be strictly followed, with yearly screening for head and neck cancer, because of their high risk. We agree with this policy of neoplasia surveillance in liver transplant recipients, as they may be considered patients with high risk of malignancy.

It has been suggested that the risk of neoplasia is higher in recent years and tumors have a more aggressive behavior.[4] The reason for this finding could be the use of stronger immunosuppression. Our findings have been similar: patients receiving tacrolimus had a higher risk of neoplasia than those receiving cyclosporine. Patients receiving steroids for shorter periods of time had also a higher risk of neoplasia, but this finding may be related to tacrolimus use, because the proportion of patients receiving steroids for more than 6 months was higher in the cyclosporine group (84%) than in the tacrolimus group (9%). Anyway, these variables did not have influence in multivariate analysis. So, we cannot be sure that the relative strength of immunosuppression is a predisposing factor for the development of neoplasia. Another argument against an increased risk of neoplasia in patients receiving stronger immunosuppression is the absence of a relationship between rejection and malignancy. Another possible influencing factor for the increased risk of neoplasia in recent years is age, because the mean age of patients being transplanted is currently higher than the age of patients being transplanted a decade ago.

Concerning risk factors for cutaneous neoplasia, age and Child-Turcotte-Pugh A at the moment of transplantation were the only predisposing factors. As cutaneous neoplasia is directly related to cumulative sun radiation,[25] the relationship to age is not surprising. Contrary to this fact, we did not find an association of cutaneous neoplasia with sun exposure (as roughly estimated by occupational or geographical reasons). These 2 data elements may be insufficient to determine the risk of cancer, because recreational exposure was not measured, and the sensitivity of every patient to sunlight was not taken in account. Patients transplanted in Child-Turcotte-Pugh A status also had an increased risk of cutaneous cancer. Most of them were transplanted for hepatocellular carcinoma. This finding is consistent with the association of hepatocellular carcinoma and cutaneous cancer found byXiol et al.[18] It is possible that these patients have an increased genetic susceptibility to cancer that makes them more prone to develop both hepatocellular carcinoma and cutaneous neoplasia.

In our experience, surveillance has offered mixed results. Despite an aggressive protocol of surveillance, only 3 out of 28 noncutaneous neoplasias were detected on surveillance studies. But, fortunately, these 3 tumors were diagnosed at early stages and these 3 patients are currently alive and free of neoplasia. The lack of efficacy of our surveillance protocol may be due to the poor adherence to it. For instance, only 1 of the 4 patients with head and neck cancer was diagnosed as the consequence of surveillance; another patient was diagnosed before the 1st yearly ear-nose-throat visit, and in the other 2 patients, the surveillance protocol was not followed because they had quit smoking.

Our findings stress the importance of 2 modifiable risk factors (i.e., alcohol and tobacco) in the development of posttransplant malignancy. So, the 1st step to avoid cancer-related mortality should be cessation of use of alcohol and tobacco. We believe a protocol surveillance may be useful for the early diagnosis of malignancy. According to our results, older patients and those transplanted for alcoholic liver disease and who smoke (even if they have quit smoking) should be followed more strictly, including chest X-ray and earnose-throat consultation and the examination of urinary sediment to rule out microhematuria. In patients with heavy smoking, pretransplant ear-nose-throat consultation could be ofvalue in order to detect early neoplasia or

premalignant lesions. We did not find any neoplasia as a consequence of yearly X-ray films. This is not surprising, as screening of lung cancer coupled with early intervention has failed to show any beneficial effect on mortality.[26] Whether more aggressive surveillance protocols, such as computed tomography scans,[27] could be a possible alternative, at least for heavy smokers, remains unknown.

Despite the limited statistical power of this singlecenter series, we conclude that neoplasia is a frequent complication following liver transplantation. Liver transplant recipients have an increased risk of cancerrelated mortality. Cutaneous cancer did not cause any mortality, but noncutaneous cancer has a significant impact on survival. A greater age and alcohol and tobacco use before transplantation increase the risk of noncutaneous neoplasia after transplantation. Whether those patients with a higher risk of neoplasia could benefit from a reduction of immunosuppression and / or a close surveillance protocol for the diagnosis of early tumors remains unknown.

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Table 1. General Characteristics of the Patients

Age (years)	55 (10)
Gender (male/female)	73 % / 27 %
Cause of liver disease	
Alcoholic cirrhosis	36%
Hepatitis C	35%
Hepatitis B	7 %
Chronic cholestasis	5 %
Metabolic diseases	7 %
Others	11%
Hepatocellular carcinoma	31%
Past history of neoplasia*	33%
Family history of neoplasia	18%
Child-Turcotte-Pugh stage (A/B/C)	15 % / 14 % / 41 %
Cytomegalovirus status (positive)	95%
Epstein-Barr virus status positive	90%
History of smoking	32%
History of alcoholism	45%
Induction immunosuppression	
Cyclosporine	64%
Tacrolimus	36%
Azathioprine > 6 months	51%
Prednisone > 6 months	57%
Rejection	32%

*Including hepatocellular carcinoma.

Table 2. General Characteristics of 28 Noncutaneous Malignancies in 27 Liver Transplant Recipients

Neoplasia	Year of	Age at LT (years)	Gender	Stage	Time after LT (months)	Current Status / after Diagnosis (months)	Diagnosed
Non-Hodgkin	1991	54	Female	I	5	Died NR/1	No
Colon (adenocarcinoma)	1991	56	Female	III	127	Alive FON / 13	No
Kaposi sarcoma	1991	31	Male	NA	16	Alive FON / 128	No
Non-Hodgkin	1992	58	Male	IV	97	Died NR / 31	No
Non-Hodgkin	1993	61	Male	III	47	Alive FON / 81	No
Colon (adenocarcinoma)	1993	54	Male	0	70	Alive FON / 49	Yes
Lung (non-small cell)	1993	47	Male	IV	102	Alive with neoplasia /11	No
Lung (non-small cell)	1993	57	Male	IIIB	89	Died NR / 14	No
Head and neck	1994	60	Male	IV	75	Died NR / 1	No
Lung (non-small cell)	1994	72	Male	IV	69	Died NR / 5	No
Esophagus	1994	67	Male	IIA	69	Died OC / 15	No
Pancreas	1994	67	Male	III	69	Died NR / 15	No
Glioblastoma	1995	49	Male	NA	40	Died NR / 4	No
Kaposi sarcoma	1995	58	Male	NA	30	Alive FON / 61	No
Non-Hodgkin	1995	67	Male	IV	6	Died NR/3	No
Head and neck	1996	62	Male	IV	43	Died NR / 9	No
Esophagus (epidermoid)	1996	63	Male	IIA	50	Alive FON / 29	No
Uterus	1996	52	Female	IV	77	Alive with neoplasia / 2	No
Meningioma	1996	59	Male	NA	46	Alive FON / 17	No
Kidney	1997	63	Male	IV	28	Died NR / 2	No
Head and neck	1998	65	Male	I	29	Alive FON / 27	Yes
Non-Hodgkin	1998	69	Male	IV	51	Alive with neoplasia / 5	No
Non-Hodgkin	1999	67	Male	I	6	Died OC/23	No
Head and neck	1999	67	Male	IV	11	Died NR / 11	No
Kidney	1999	48	Male	I	36	Alive FON / 3	Yes
Stomach	2000	63	Female	IV	16	Died NR / 1	No
Non-Hodgkin	2000	63	Male	IV	17	Died NR / 1	No
Lung (non-small cell)	2000	55	Male	IA	16	Alive FON / 10	No

Abbreviations: LT, liver transplantation; NA, not applicable; NR, neoplasia-related; FON, free of neoplasia;
*Both tumors were diagnosed in the same patient.

Table 3. Risk Factors for the Development of Malignancy After Liver Transplantation in 187 Patients

Variable	Univariate Analysis		Multivariate Analysis	
	HR (CI 95%)	*P*	HR (CI 95%)	*P*
Age (decades)	1.86 (1.32–2.60)	<	1.90 (1.32–2.73)	.001
Gender (male)	2.36 (1.10–5.05)	.03		
HCC	1.69 (.94–3.04)	.08		
Child-Turcotte-Pugh (A)	2.47 (1.31–4.67)	.005	3.26 (1.64– .47)	.001
Donor age (years)	1.01 (.99–1.03)	.09		
Smoking	2.00 (1.13–3.51)	.02		
Alcoholism	2.07 (1.17–3.68)	.01	2.98 (1.59–5.57)	.001
Tacrolimus	2.17 (1.08–4.34)	.03		
Prednisone (<6 months)	2.10 (1.10–4.02)	.02		

Abbreviations: HR, hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma.

Table 4. Risk Factors for the Development of Cutaneous Malignancy After Liver Transplantation in 187 Patients

Variable	Univariate Analysis		Multivariate Analysis	
	HR (CI 95%)	*P*	HR (CI 95%)	*P*
Age(decades)		.013	1.81 (1.13–2.87)	.013
HCC		.051		
Child-Turcotte-Pugh (A)		.013	3.91 (1.25–2.67)	.013

Abbreviations: HR, hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma.

Table 5. Risk Factors for the Development of Noncutaneous Malignancy After Liver Transplantation in 187 Patients

Variable	Univariate Analysis		Multivariate Analysis	
	HR (CI 95%)	*P*	HR (CI 95%)	*P*
Age (decades)	1.93 (1.21–3.08)	.006	2.42 (1.46–4.02)	.001
Gender (male)		.07		
Smoking	2.00 (1.13–3.51)	.0005	3.07 (1.32–7.16)	.009
Alcoholism		.002	2.87 (1.15–7.19)	.02
Tacrolimus		.02		
Prednisone (~6 months)		.01		

Abbreviations: HR, hazard ratio; CI, confidence interval.

Table 6. Risk Factors for Mortality After Noncutaneous Malignancy (Case-Control Study, Including 27 Cases and 54 Controls)

Variable	HR (CI 95%)	*P*	HR (CI 95%)	*P*
Age (decades)		.006		
Body-mass index		.03		
Smoking		.03		
Prednisone <6 months		.07		
Azathioprine <6 months		.001	7.18 (2.22–23.22)	.001
Noncutaneous cancer		.001	6.98 (2.45–19.91)	<.001

Abbreviations: HR, hazard ratio; CI, confidence interval.

Table 7. Relative Risk of Cutaneous and Noncutaneous Malignancy and of Malignancy-Related Mortality After Liver Transplantation

Event	Observed Cases	Expected Cases	RR (95% CI)*	Absolute Excess Risk†
Cutaneous malignancy	35	2.07	16.91 (11.78–23.51)	293.62
Noncutaneous malignancy	29	8.66	3.23 (2.15–4.67)	172.45
Malignancy-related deaths	19	4.35	4.37 (2.63–6.82)	130.63
Malignancy-related deaths after excluding recurrences‡	13	4.35	2.99 (1.59–5.11)	77.13

*Relative risk (95% confidence interval).
†Absolute excess risk, expressed per 10,000 patients-years, was calculated by substracting the expected number of cases from the absolute number of cases and dividing by person-years at risk.
‡After excluding 5 patients who died of recurrent hepatocellular carcinoma and 1 patient who died of recurrent rectum sarcoma.

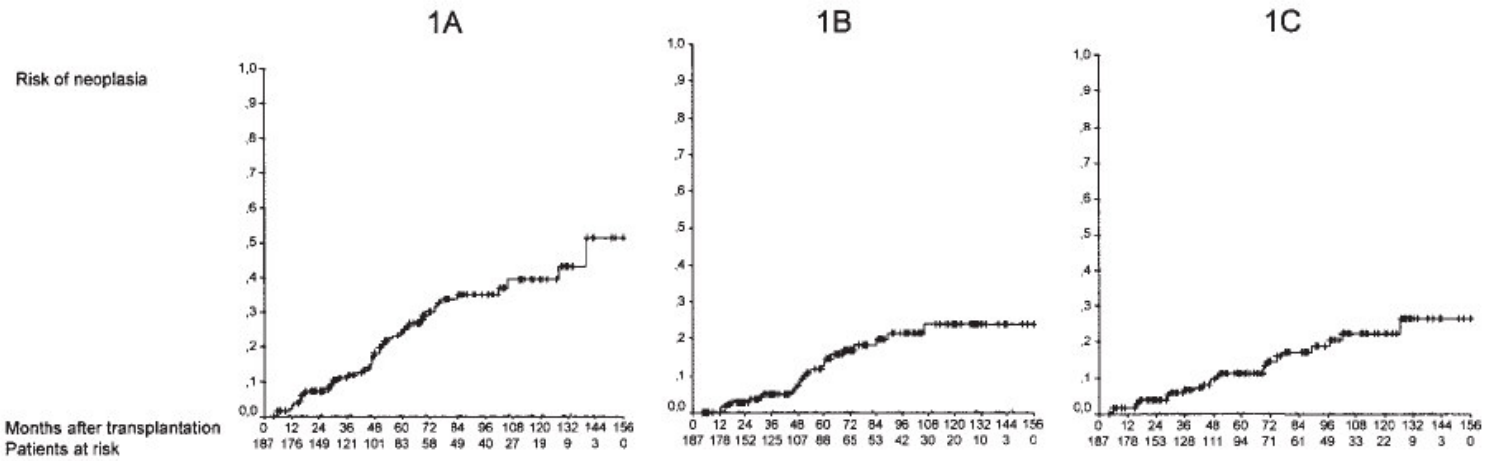

Figure 1. Actuarial prevalences of *de aovo* neoplasia (A), cutaneous neoplasia (B), and noncutaneous neoplasia (C) after liver transplantation in 187 patients.

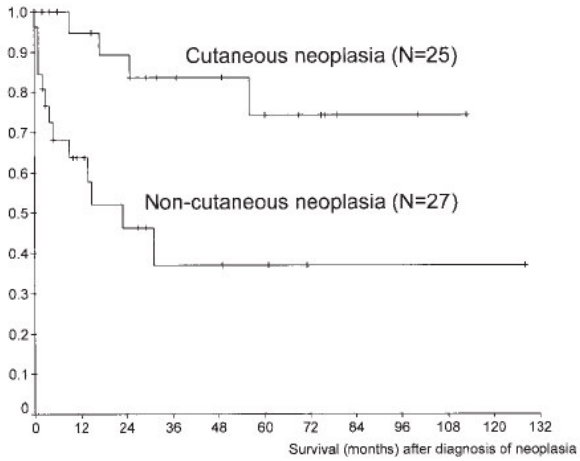

Figure 2. Actuarial survival after the development of cutaneous and noncutaneous neoplasia.

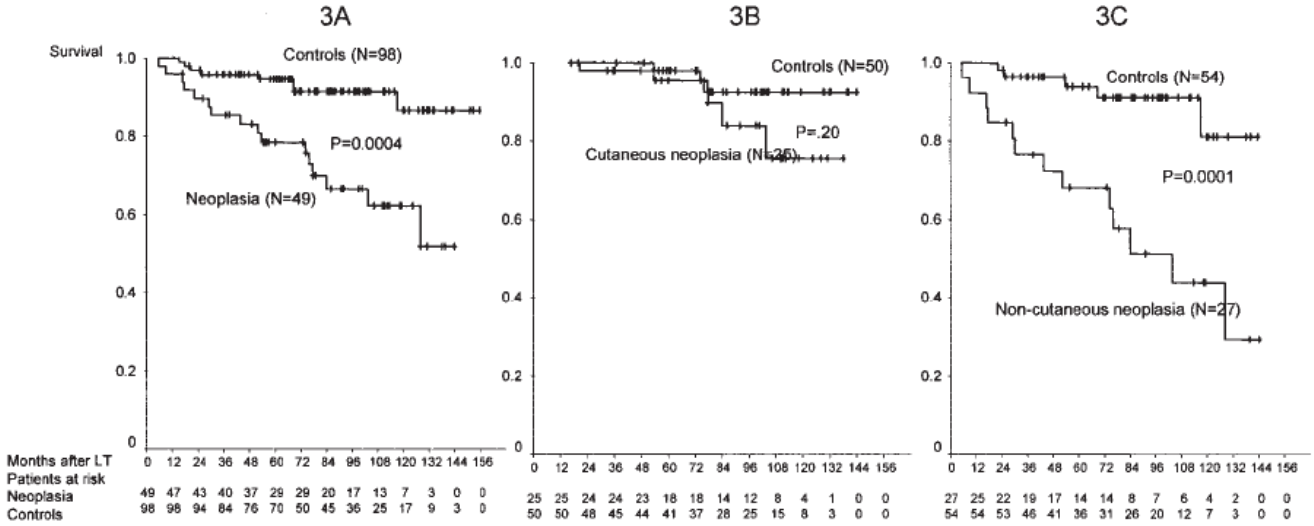

Figure 3. Actuarial survival after liver transplantation in patients developing neoplasia after liver transplantation vs. controls (A), patients developing cutaneous neoplasia vs. controls (B), and patients developing noncutaneous neoplasia vs. controls (C).