Transplantation
Issue: Volume 66(9), 15 November 1998, pp 1193-1200

Publication Type: [Clinical Transplantation]
ISSN: 0041-1337
Accession: 00007890-199811150-00014

[Clinical Transplantation]

COMPARATIVE INCIDENCE OF DE NOVO NONLYMPHOID MALIGNANCIES AFTER LIVER TRANSPLANTATION UNDER TACROLIMUS USING SURVEILLANCE EPIDEMIOLOGIC END RESULT DATA[1]

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[1]This work was presented in part as a poster at the 15th annual meeting of the American Society of Transplant Physicians, May 26-30, 1996, Dallas, TX (P- 110, page 200).

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Received 28 May 1998.

Accepted 23 July 1998.

Abstract

Background. An increased incidence of de novo nonlymphoid malignancies has been shown in immunocompromised patients. However, the true risk over time compared to the general population has not been determined.

Methods. One thousand consecutive patients were carefully followed for an average of 77.8±11.1 (range, 56.3-96.3) months after primary liver transplantation at a single center. All de novo nonlymphoid malignancies were recorded. Each malignancy was compared with a standard Occupational Cohort Mortality Analysis Program population matched for age, sex, and length of follow-up using modified life table technique and surveillance epidemiology end result (SEER) data.

Results. Fifty-seven patients accounted for de novo malignancies and contributed 4795.3 total person years, a mean±SD of 36±21 (median, 36; range, 6-74) months after liver transplantation. Twenty-two of these malignancies were skin malignancies including two melanomas. Oropharyngeal cancers (n=7) were found to be 7.6 times higher ($P<0.05$) and respiratory malignancies (n=8) were 1.7 times higher ($P>0.05$) compared to the SEER incidence rate. Female reproductive system malignancies including breast cancer (n=3) were 1.9 times lower ($P>0.05$) and genitourinary malignancies were (n=5) 1.5 times lower ($P>0.05$) than their matched cohorts. No differences was observed in gastrointestinal malignancies (n=5). There was a significant difference in survival of the patients after

diagnosis of malignancy depending on the type of cancer. There were two Kaposi's sarcomas, two metastatic unknown primaries, one thyroid, one brain, and one opthalmic malignancies in the series. Mortality for Kaposi's and metastatic disease of unknown primary was 100% within 5 months, while the 1-year mortality for oropharyngeal cancer was 57.1% and that for lung cancers was 62.5%. Long-term survival for skin cancer was highest: 86.4% at 3 years (*P*=0.015 by log-rank test).

Conclusion. An increased incidence of de novo cancers in the chronically immunocompromised patient demands careful long-term screening protocols which will help to facilitate the diagnosis at an early stage of the disease. This is particularly true for oropharyngeal cancers where the risk is more than 7 times higher compared to SEER incidence data matched for age, sex, and length of follow-up.

An increased incidence of de novo malignancies in immunosuppressed organ transplant patients was first predicted by Dr. Thomas E. Starzl in 1968 (1) and confirmed shortly thereafter (2-4). Since then, the frequency of de novo malignancies in this population has been estimated to range from 4.1% to 16% (5). Predominant among these tumors are post-transplant lymphoproliferative disorder (PTLD*), squamous cell carcinoma of skin, and Kaposi's sarcoma. Previous studies have been based on renal transplant experience with azathioprine, prednisone, and/or cyclosporine immunosuppression. This report examines the frequency and types of nonlymphoid malignancies in patients undergoing primary liver transplant under tacrolimus immunosuppression. We compare the incidence of various malignancies with the expected frequency of the given type of malignancy in the general population matched for age, gender, and length of follow-up in this group of patients. Specific outcomes of the malignancies are also reported.

PATIENTS AND METHODS

Study population. The study population consisted of 1000 consecutive patients, who received primary orthotopic liver transplantation (LTX) between August 1989 and December 1992 at a single center. The demographic features of the patients have been described previously (6). There were 600 male and 400 female patients, with a mean±SD age of 42.6±20.2 years at the time of LTX. Patients were followed until death or until the end of the study (August 31, 1997). The mean length of follow-up was 77.8±11.1 months (range, 56.3-96.3 months).

The diagnosis of malignancy was established by histologic examination of biopsies and/or surgical specimens. The date of the biopsy or surgical procedure was designated as the date of diagnosis of cancer. The tumor node metastasis classification and staging was based on radiological, surgical, and pathologic findings. Cases of PTLD and premalignant or noninvasive lesions were excluded from consideration. The incidence of PTLD of 3.5% over a mean follow-up of 6.4 years has been reported separately for this population (7). In patients who had known cancers before LTX, recurrence of the same malignancy was excluded; however, all 1000 patients were considered at risk of development of de novo cancers and were retained in the study. The demographic characteristics of the patient population are described in Tables 1-4.

No.	Age/sex (yr)	Etiology of ESLD	Malignancy	Months to onset	Site involved	Treatment	Survival (months after diagnosis)[b]
1	70/M	PNC-E	SCC	41.0	Ear	Surgery	47.1a
2	62.1/M	Cryptogenic	BCC	37.7	Scalp	Surgery	0.3d
3	38.1/F	NANB	SCC	40.6	Thigh	Surgery	51.3a
4	44.6/F	AFF	SCC	75.1	Nose	Surgery	20.5a
5	73.1/M	PNC-E	SCC	27.0	Cheek	Surgery	38.3a
6	62.7/M	HCC	SCC	37.9	Arm, back	Surgery	36.7a
7	64.4/M	PNC-E	SCC	68.4	Back, ear, neck	Surgery	6.4d
8	47.1/F	PBC	BCC	46.5	Back	Surgery	46.3a
9	56.2/M	PNC-E	BCC	8.2	Eyelid	Surgery	80.6a
10	72.9/M	PSC	BCC	19.7	Head, cheek	Surgery	47.1d
11	52.4/M	PNC-E	SCC	27.5	Face, multiple	Surgery	55.6a
12	58.9/F	PBC	SCC	16.5	Chest	Surgery	56.0a
13	58.5/M	PNC-E	SCC	48.5	Forehead	Surgery	43.7a
14	55.1/M	PNC-E	SCC	46.7	Neck	Surgery	19.6a
15	58.7/M	PNC-E	SCC	52.6	Face	Surgery	32.1a
16	65.4/M	PNC-E	BCC	59.4	Face	Surgery	32.8a
17	46.8/M	PNC-E	BCC	48.0	Neck	Surgery	40.2a
18	67.0/M	PNC-E	BCC	39.2	Face	Surgery	33.5a
19	59.0/M	Cryptogenic	BCC	10.6	Face	Surgery	52.8a
20	69.5/M	HAV	BCC	26.3	Face, chest	Surgery	39.6a
21	77.3/M	PSC	Melanoma*	14.4	Back	Surgery, Chemo, DxT	18.2d
22	64.9/M	Hemochromotosis	Melanoma**	9.7	Back	Surgery	55.3a
Mean	*60.2*			*36.4*			
SD	*10.0*			*18.8*			
Median	*37.7*			*38.5*			

[a] SCC, squamous cell carcinoma; BCC, basal cell carcinoma; *, Clark's level IV; **, Clark's level II. BCC and SCC were usually T1N0N0, stage 1; however, many were excised in local facilities and detailed pathology reports were not available in all cases. PNC, postnecrotic cirrhosis; E, ethanol; NANB, nonA nonB hepatitis; AFF, acute fulminant failure; HCC, hepatocellular carcinoma; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; HBV, hepatitis B virus; HCV, hepatitis C virus; HAV, hepatitis A virus; ESLD, end-stage liver disease.
[b] a, alive; d, dead.

Table 1. Skin malignancy including melanoma[a]

No.	A. Respiratory malignancy									Survival (months after diagnosis)
	Age/sex (yr)	Etiology of ESLD*	Organs involved	Months to onset	Histology	TNM	Stage	Presenting symptoms	Treatment	
1	67.2/M	PNC-E/HCC	Lung	36.9	Adeno CA	T1NxMx	I	Follow-up CT scan	Surgery	9.6d
2	67.4/M	PNC-E	Lung	11.2	Non-small cell CA	T2N1M0	II	Routine chest x-ray	Surgery	66.2a
3	73.6/M	HCV	Lung	28.8	Adeno CA	TXNXMX	ND	Pneumonia, Wt. loss	None	0.1d
4	57.5/M	PNC-E/HCC	Lung, brain, bone	51.6	Small cell CA	T4N2MX	IV	Headache, hypercalcimia	Chemo	17.5a
5	63.2/M	PNC-E	Lung, brain	64.3	Non-small cell CA	T2N0M1	IV	Left-sided weakness	DxT	3.1d
6	53.5/M	PNC-E	Lung	84	Small cell CA	T3NOM0	IIIA	Rib pain/shortness of breath	Surgery + DxT	9.3d
7	59.5/F	PBC/HCC	Lung	49.8	Adeno CA	T1N0M0	I	Follow-up CT scan	Surgery	18.0a
8	49.4/F	PNC-E/HCC	Lung	61.4	Oat cell CA	T3N1M1	IV	Chest pain	None	0.4d
Mean	*62.2*			*48.5*						
SD	*7.4*			*22.7*						
Median	*61.6*			*50.7*						

Table 2. Malignancy[a]

1	48.2/M	PNC-E	Larynx, Supraglottic, Lymphnodes	9.5	SCCA	T4N2cM0	IV	Sore throat, hoarseness	Surgery + DxT	9.7d
2	52.7/F	PNC-E	Larynx	11.1	SCCA	TXNXMX	I	Dysphagia	DxT + chemo	11 d
3	54.3/M	PNC-E	Floor of mouth	37.3	SCCA	T1NxMo	I	Swelling, pain	Surgery	32.7a
4	64.5/F	Hemochromotosis	Palate, lung mets	23.5	SCCA	TXN2M1	IV	Sore throat	DxT	8.6d
5	64.2/M	ANB/HCC	Pharynx	55.7	SCCA	T4N2M0	IV	Sore throat, dysphagia	Surgery	12.9d
6	60.0/M	PNC-E	Tonsil, lung	36.3	Squamous cell CA	T4NXM0	IIIB	Wt. loss, sore throat, cough	Palliative surgery	1.6d
7	52.1/M	PNC-E	Tongue, pharynx, epiglottis	68.9	SCCA	T4N1MX	IV	Ulcer tongue	DxT + Chemo	7.9a
Mean	*56.6*			*34.6*						
SD	*6.4*			*22.1*						
Median	*53.3*			*36.3*						

[a] For abbreviations, see Table 1. CA, carcinoma; DxT, radiotherapy; ND, not delineated; SCCA, squamous cell carcinoma.
[b] Case 2 in Table 3B, who subsequently developed laryngeal cancer, is also not included here.

Table-2B: Oropharyngeal Malignancy[b]

No.	Age/sex (yr)	Etiology of ESLD	Organs involved	Months to onset	TNM	Stage	Histology	Presenting symptom	Treatment	Survival (months after diagnosis)
A. Gastrointestinal malignancy										
1	60.0/M	PNC-E	Right colon	24.8	T3N0M0	II	AdenoCA	Anemia	Surgery	48.0a
2	59.3/M	PSC	Esophagus, Lower third	24.0	T3N1MO	III	AdenoCA	Dysphagia	Chemo DxT	17.1d
3	48.6/M	PSC	Rectum	11.6	T3N0M0	II	AdenoCA	Routine colonoscopy	Surgery	52.1a
4	60.3/M	PNC-E	Sig. Colon	53.7	T3N0M0	II	AdenoCA	Bleeding PR	Surgery	22.8d
5	62.5/M	PNC-E	Right Colon	75.0	T3N1MX	III	AdenoCA	Routine colonoscopy	Surgery	6.5d
Mean	*58.1*			*37.8*						
SD	*5.5*			*25.9*						
Median	*60.0*			*24.8*						
B. Genitourinary malignncy										
1	47.3/M	PNC-E	Prostate	5.8	T3N0M0	III	AdenoCA	Impotency	Surgery	72.4a
2[b]	65.5/M	PNC-E	Kidney, hip, larynx	55.3	T2-4NXM1	IV	Renal cell CA + SC CA	Pain hip	Surgery, DxT, Chemo	16.7d
3	71.3/M	Cryptogenic	Prostate	15.8	T2aN0M0	II	AdenoCA	Routine PSA	DxT	41.1a
4	60.7/M	HCC, PNC-E	Bladder	31.5	ND	ND	Trans. Cell CA	Dysurea	Surgery	15.1d
5	57.1/M	PNC-E	Prostate	18.4	T2N0M0	II	AdenoCA	Routine PSA	DxT + Harmone	55.9a
Mean	*60.4*			*25.4*						
SD	*9.0*			*19.1*						
Median	*60.7*			*18.4*						

[a] For abbreviations, see Table 1. CA, carcinoma; DxT, radiotherapy; ND, not determined; PSA, prostate-specific antigen; RP, per rectum; SC, squamous cell; Sig, sigmoid.
[b] Patient had bony metastatic disease from renal cell CA; he subsequently developed laryngeal CA.

Table 3. Malignancy[a]

No.	Age/sex (yr)	Diagnosis of ESLD	Malignancy	Organs involved	Months to onset	TNM	Presenting symptom	Treatment	Survival (months after diagnosis)
1	60.2/F	PBC	Duct CA	Breast	41.4	T1N0M0	Breast lump	Surgery	22.0a
2	50.3/F	PNC-E	Duct CA	Breast	90.53	T2N0M0	Breast lump	Surgery + Chemo	5.8a
3	41.4/F	Budd chiari	Duct CA	Breast	46.20	T1N0M0	Breast lump	Surgery + DxT	19.6a
4	40.2/M	HBV	Kaposi's	Skin, stomach, duodenum	7.5	NA	Fatigue	Alpha Interferone	4.6d
5	69.8/M	PNC-E	Kaposi's	Skin	10.8	NA	Skin lesion	Surgery	2.6d
6	60.9/M	PNC-E	Metastatic, adeno CA; unknown primary	Bone, brain, and lung	27.0	NA	Pain	None	0.4d
7	56.8/M	PSC	Metastatic, adeno CA; unknown primary	Liver hilum	29.2	TxN1M1	Weight loss	Surgery	4.1d
8	65.8/F	HCV	Glioblastoma	Brain	16.9	TxNxMx			7.5d
9	56.9/M	PSC	SC CA	Conjunctiva	35.3	T1N0M0	Eye lesion	Surgery	9.5d
10	44.3/F	Cryptogenic	Papillary CA	Thyroid	8.43	T2N0M0	Swelling front of the neck	Surgery	48.9a
Mean	*54.7*				*31.3*				
SD	*10.2*				*24.9*				
Median	*56.9*				*28.1*				

[a] For abbreviations, see Tables 1–3. NA, not applicable.

Table 4. Other malignancy[a]

Pretransplant screening studies included chest x-ray and computerized tomography scan of the abdomen in all patients, and upper and lower gastrointestinal endoscopy in adults (age >40 years) and whenever clinically indicated. Likewise, female patients (>35 years of age) were advised to have pretransplant mammograms and gynecological evaluations. Before transplantation, all patients were without signs or symptoms suggestive of the malignancy that subsequently developed in the posttransplant period. All patients received tacrolimus-based immunoprophylaxis with concomitant use of steroids from the time of transplant. Management of acute rejection episodes has been described previously (8).

Statistical methods. The incidence of de novo nonlymphoid malignancies for 1000 LTX patients was examined during the time interval between August 15, 1989 and August 31, 1997. Using the modified life table technique of the Occupational Cohort Mortality Analysis Program (adapted to cancer incidence data), the person-years at risk contributed by each patient were jointly classified by gender, age, group, and time period (9). Expected counts of malignancies were computed by multiplying the average annual gender-age-time specific standard incidence rates by the corresponding person-years at risk. Incidence rates for whites were used exclusively, as 85% of the patients were white and the remaining 15% represent a mix of nonwhite races for which standard rates were unavailable. Standard incidence rates were obtained from the 1990-1991 Surveillance Epidemiologic End Results (SEER) data (10). As a result of SEER reporting limitations, the expected number of malignancies for the time period 1989-1997 were based on 1989-1993 incidence rates.

Comparative malignancy incidence was expressed as a standardized incidence ratio (SIR), that is, the ratio of the observed number of malignancy cases to the expected number of cases. A SIR value greater than 1.00 indicates

excess risk, whereas a value less than 1.00 is a decreased risk. Statistically significant deviations of the SIR above and below one were identified using Poisson probabilities (11). Because SEER incidence rates 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

Incidence. Fifty-seven patients, who accounted for 4795.3 total person-years, developed de novo nonlymphoid malignancies. The tumors were divided into six different groups according to the organ of origin (Tables 1-4). There were 44 men and 13 women, with a mean±SD age at the time of diagnosis of 59.1±9.4 (range, 38.1-77.3) years. The mean interval from LTX to cancer diagnosis was 36.2±21.0 (range, 5.8-74.1) months (Fig. 1).

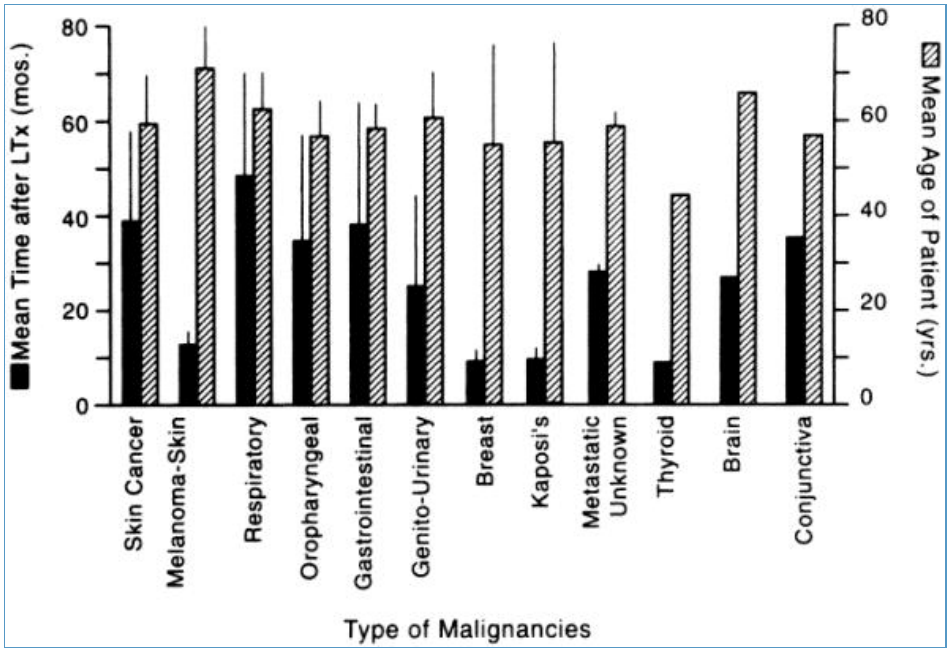

Figure 1. Mean age at the time of malignancies and mean interval to develop malignancies from LTX, for various malignancies. Pt., patient.

Skin cancer (Table 1). The most common type of malignancy was skin cancer, which was diagnosed in 22 (2.2% of the population and 33.3% of the cancers diagnosed) patients. These included 18 men and 4 women, with a mean age of 60.2±10 (range, 38.1-77.3; median, 60.6) years. The mean time to onset was 36.4±18.8 (range, 8.2-75.1; median, 38.5) months after LTX. The cases included 11 (50.0%) squamous cell carcinomas, 9 (40.9%) basal cell carcinomas, and 2 (9.1%) melanomas. The most common site of involvement was skin of the head, face, and neck (14 cases), followed by 4 lesions involving multiple sites, 3 lesions of the trunk, and 1 lesion on the leg. All skin lesions were surgically excised. Two patients with melanoma underwent wide excision, with one patient alive 53 months after diagnosis. Widespread metastases accounted for the death of the other melanoma patient 18 months after the diagnosis. In case 2, squamous cell carcinoma of the scalp was diagnosed 3 years after LTX and 10 days before death, which was caused by liver and renal failure. In case 7, multiple sites of squamous cell carcinoma were diagnosed, but death 6.4 months later was from sepsis related to intrahepatic bile duct stricture. Finally, case 10 died of myocardial infarction 47 months after basal cell carcinoma of head and cheek were removed.

Respiratory malignancies (Table 2A). Lung cancer was the second most common type of malignancy observed, occurring in eight patients (15.7%: six men and two women) with a mean age at the time of diagnosis of 62.5±7.9 years. The mean time of onset from LTX was 48.5±22.7 months, ranging from 11.2 to 64.3 months (median: 49.8). Two patients, cases 5 and 6, presented with brain metastases. Five patients died of lung cancer, while remaining three are alive after surgery with chemotherapy or radiotherapy.

Oropharyngeal cancer (Table 2B). Oropharyngeal cancer was the third most common malignancy in this series

and accounted for seven cases. There were five male and two female patients, with a mean age of 56.6±6.4 (range, 48.2-64.5) years at the time of diagnosis. The intervals from LTX to cancer diagnosis ranged from 9.5 to 68.9 months with a mean of 34.3±24.4 months. In addition to these seven patients, another patient was diagnosed with pharyngeal squamous cell carcinoma 2.5 months after renal cell carcinoma (case 2, Table 3B). This patient received multimodality treatment and died 16.7 months after the diagnosis of first cancer site. The patient with cancer of the floor of the mouth and another patient with cancer of the base of tongue and epiglottis have survived, after surgical excision, for 33 and 8 months, respectively. The other five patients died as a result of malignancy.

Gastrointestinal malignancies (Table 3A). Five male patients had gastrointestinal malignancies at a mean age of 58.1±5.5 (range, 48.6-62.5) years. The mean interval between LTX and diagnosis was 37.8±24.8 (range, 11.6-75) months. One patient with esophageal cancer received chemotherapy and radiotherapy, but died 17 months after diagnosis. Two patients with sigmoid lesion (case 4) and right-sided colonic lesion (case 5) died 22.8 and 6.5 months after surgery from systemic metastatic disease (case 4) and bacterial endocarditis with renal failure (case 5). The remaining two patients are currently alive, after colorectal surgery, for 48 and 52 months.

Genitourinary malignancies (Table 3B). Five male patients developed malignancies of the genitourinary tract. The mean age was 60.4±9.0 years (range, 47.3-71.3; median, 60.7) at the time of diagnosis. Three patients with prostate cancer had localized disease; one patient was treated surgically, one received radiation treatment, and the third received radiation and anti-androgen therapy. All three patients are still alive 41-72 months after diagnosis. The patient with cancer (case 4) underwent surgical resection but died 15.1 months later from end-stage liver and renal failure. Management of the case of metastatic renal cell carcinoma (case 2) was complicated by a concurrent pharyngeal cancer. This patient was treated with nephrectomy, radiation therapy to the head and neck, plus chemotherapy but eventually died 16.7 months after diagnosis as described above.

Miscellaneous de novo malignancies. Ten other patients accounted for a variety of other malignancies (Table 4). Three women aged 60, 50, and 46 years developed breast cancer at 41, 91, and 46 months after LTX. They underwent surgery followed with chemotherapy in one and radiotherapy in other. All three are still alive 6-22 months after diagnosis. Two male Saudi Arabian patients developed Kaposi's sarcoma after LTX; both died 2.6 and 4.6 months, respectively, after diagnoses. However, the patient with Kaposi's sarcoma of the skin (Table 4, case 5) died of end-stage liver failure from recurrence of hepatitis C viral infection, and renal failure. Two patients presented with widespread metastasis from a primary cancer of unknown origin. Glioblastoma of the brain was diagnosed in a female patient. One patient had squamous cell carcinoma of the conjunctiva, which was treated surgically at an apparently localized stage, but rapidly recurred in the orbit with metastases to the neck. These last six patients have died as a result of their malignancy. One 43-year-old woman developed papillary carcinoma of thyroid 8 months after LTX. She underwent total thyroidectomy and node resection along with radioactive iodine ablation, and she remains disease-free 49 months after diagnosis.

SIRs. Table 5 shows the observed and expected counts of cancer incidence and the ratio of observed to expected counts for selected sites. Figure 2 shows graphically observed and expected counts of cancer incidence for these combined cancer sites. As shown in Table 5, oropharyngeal cancer, respiratory malignancy, thyroid cancer, brain cancer, and melanoma all had elevated ratios (SIR>1.0) in this patient population. (Thyroid cancer and brain cancer SIRs are based on one case each.) There was a statistically significant increase in the incidence of oropharyngeal malignancies (SIR=7.6; 95% confidence interval: 2.4-15.73; $P<0.01$). Female gynecological malignancies (breast, ovary, uterus, and cervical) and genitourinary malignancies had reduced incidence ratios (SIR<1.0). No difference was observed in gastrointestinal cancers (SIR=1.06). Because incidence rates were not available for epithelial skin malignancies, Kaposi's sarcoma, and metastatic disease with unknown site, the expected cancer incidence could not be computed. However, observed counts of malignancy are shown in Table 5. For Kaposi's sarcoma, only the overall incidence for males in all areas of the United States, not specific for age, was available from SEER data, which was 5.8 for year 1993 per 100,000 people.

Malignant site groupings	Observed	Expected	Ratio observed/ expected	95% Confidence interval (*P*- value)
Skin				
Melanomas	2	1.03	1.94	0.23–6.7
Other skin cancer[a]	20			(*P*>0.05)
Respiratory				0.72–3.27
Lung and bronchogenic cancers	8	4.83	1.66	(*P*>0.05)
Oropharyngeal				2.7–15.73
Oral cavity, pharynx, and laryngeal cancer	7(+1)	0.92	7.61	(*P*<0.05)
Gastrointestinal				0.34–2.88
colon, rectum, stomach, pancreas, liver, and esophagus cancer	5	4.72	1.06	(*P*>0.05)
Genitourinary[b]				0.22–1.84
prostate, kidney and urinary bladder	5	7.4	0.68	(*P*>0.05)
Female gynecological malignancies[c]				
Breast	3	4.05	0.74	0.15–2.16
				(*P*>0.05)
Ovarian, uterine, and cervical cancers	0	1.64		0.0–2.5
				(*P*>0.05)
Other miscellaneous de novo malignancies				
Kaposi's sarcoma[d]	2	0.058		
Metastatic unknown primary[a]	2			
Thyroid[a]	1	0.31	3.26	0.08–18.17
Brain cancer[a]	1	0.46	2.19	0.06–12.22
Eye cancer[a]	1			

[a] Cannot compute expected counts because incidence rates are not available.
[b] Part of expected counts are based on male-only incidence rates for prostate cancer.
[c] Expected counts are based on female-only incidence rates.
[d] Incidence per year for males only, for all areas of US in year 1993.

Table 5. Observed and expected cancer incidence for selected subgroups of cancer sites

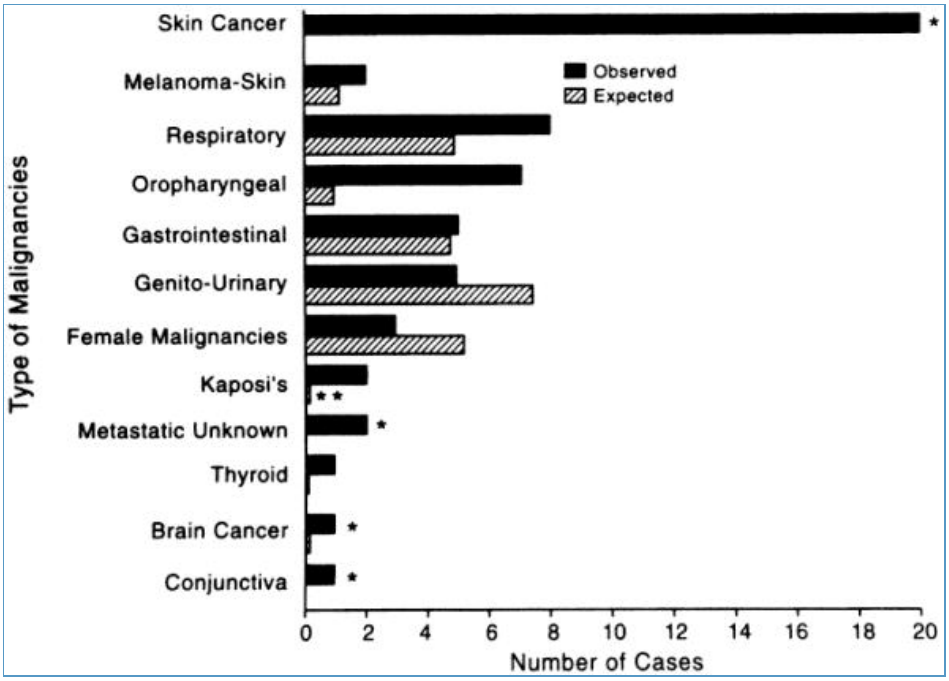

Figure 2. Frequency of distribution of various malignancies in LTX patients, compared to general population. Data are matched for age, sex, and length of follow-up per SEER (10). *Expected value not available in SEER (10); **expected rate not available; hence, the overall incidence for males in all areas of the United States is shown as per SEER (10).

Survival statistics. Overall, 25 (43.9%) patients died after diagnosis of malignancy. Three patients with skin cancer (Table 1, cases 2, 7, and 10) died of causes unrelated to de novo malignancy as described above. In addition, two patients, one with bladder cancer (Table 3B, case 4) and another with Kaposi's sarcoma of the skin (Table 4, case 5), died of combined liver and renal failure. Both were not considered for repeat transplantation. The remaining 20 deaths were directly attributed to development of de novo malignancies. Kaplan-Meier survival rates were significantly different for the type of cancer. One-year survival for skin cancer, oropharyngeal cancer, and lung cancer was 90.9%, 42.9%, and 37.5%, respectively. One-year survival for genitourinary and gastrointestinal malignancies was 100% and 80%, respectively; however, at 2 years, survival was only 60% and 40%, respectively (Fig. 3). All patients with metastatic disease with unknown primary, Kaposi's sarcoma, brain tumor, and cancer of conjunctiva died within 1 year from time of the diagnosis (*P*=0.015, log-rank).

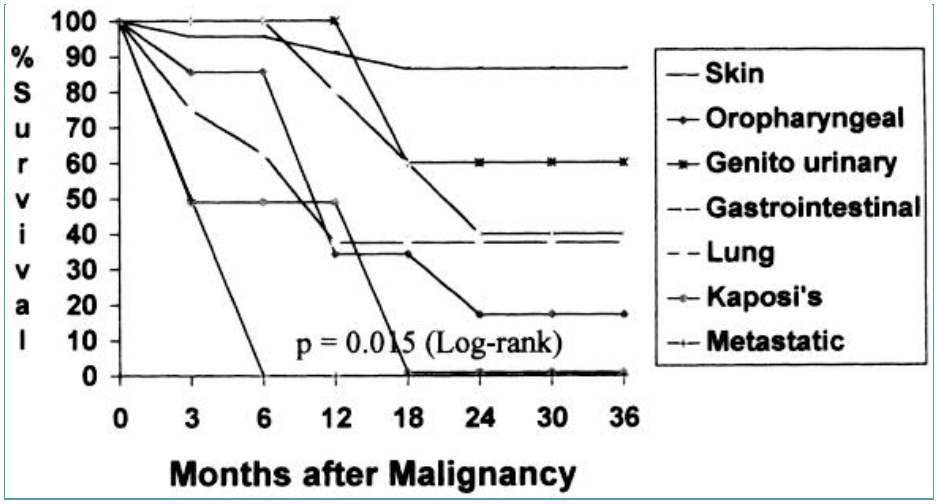

Figure 3. Kaplan-Meier survival after de novo malignancies for different types of cancers.

Immunosuppression. All 1000 patients were treated with tacrolimus-based immunosuppression. The regimen has been described previously (8). All 57 patients who developed de novo cancers remained on tacrolimus-based immunosuppression; cyclosporine or Neoral was not used. Out of 57 patients, 11 patients received azathioprine (25-100 mg/day) in order to control tacrolimus-related nephrotoxicity. Forty-eight episodes of rejections were documented among the 57 patients during the study period. These were treated with methylprednisone, and six patients required OKT3.

DISCUSSION

This report is based on data drawn from the first 1000 consecutive primary LTX patients. The appearance of both new epithelial and mesenchymal malignancies iatrogenically immunosuppressed transplant patients has been reported (1-4,12,13). Previous studies addressing the development of de novo cancers in nonrenal organ transplant patients have emphasized an increase in the proportion of patients with PTLD, attributed in part to the more intensive immunosuppressive regimens required in these patients (2,14). An increase incidence in malignancies of other types can also be expected and there have been observed in frequencies ranging from 4% to 16% (5).

A worldwide registry of de novo malignancies in organ transplant patients was initially maintained at the University of Colorado, Denver and then at the Cincinnati Transplant Tumor Registry as the official database for these patients. However, as a result of the lack of information on the number of patients at risk at various times after transplantation, the true incidence of the different types of de novo malignancies cannot be assessed. The combined Australian and New Zealand Registry reported only a 2% de novo malignancy in LTX patients, although the follow-up was only 2 years after transplant, and no demographic information regarding the LTX population was provided (15). In our population of 1000 LTX patients under tacrolimus immunosuppression (median, 6.5-year follow-up), we report an overall frequency of de novo nonlymphoid cancers of 5.7%. With continued follow-up, additional cases can be anticipated.

The most striking finding is an increased frequency of oral cavity and pharyngeal cancer. Although not shown here, this statistically significant excess is seen in both males and females for all ages examined separately. This statistically significant excess of oral cavity and pharyngeal cancer constitute the largest observed excess of all cancer sites considered. Additionally, mortality for this population was significant for five out of seven patients (71.4%), who died within 13 months.

Some of our patients were at risk for the development of cancer irrespective of immunosuppression and organ transplantation. Colon cancer was identified in a man with a 24-year history of ulcerative colitis, whose prior colonoscopies and biopsies were remarkable for only inflammatory changes. In the seven patients who developed laryngeal cancer, four had a significant history of tobacco use. In the eight patients who developed lung cancer, at least five had documented a long-standing history of cigarette smoking; in the remaining three patients' medical

records, history of smoking was not documented.

The two cases of Kaposi's sarcoma involved were men of Mediterranean descent, who are known high-risk patients in the setting of immunosuppression. Although instances of regression of even visceral disease have been reported with cessation or reduction in immunosuppressive drugs (16,17), both patients failed to respond to a decrease in tacrolimus and corticosteroids. The reported incidence of Kaposi's sarcoma in transplant population ranges from 0.18% to 6%, with a latency of 20-24 months (18-20). The SEER age adjusted incidence rate (adjusted to the 1970 United States population) for 1993, for males of all races was 5.8 per 100,000 per year.

Seven out of 35 nonskin malignancies were discovered on routine screening (lung, 3; colon, 2; prostate, 2; none were screened for oropharyngeal cancer after LTX). Eleven of the deaths occurred with advanced disease at the time of diagnosis, and one adenocarcinoma of the lung was possibly underestimated as stage I by the thoracoscopic wedge resection. Rapid dissemination of the cancer in a setting of reduced immune surveillance could account for presentation at an advanced stage as well as accelerated malignant progression. A tendency towards aggressive behavior has been noted in malignancies in renal transplant patients (21). Although instances of tumor regression with cessation or reduction of the immunosuppressant regimen have been noted (22), most de novo cancers follow a virulent course unchecked by a return to normal immune surveillance.

Transplantation of malignant and metastatic cells from occult or unidentified donor malignancies can also occur, as exemplified by the early transplant experience with cancer victims as donors (23,24). Inadvertent cancer transmission via organ transplantation has been documented by correlation of donor autopsy findings or medical history with the subsequent development of a recipient malignancy. Although excluded as a de novo cancer case, one patient in this liver transplant population apparently developed carcinosarcoma in the liver as a result of donor transmission. The autopsy finding of carcinosarcoma in the donor's lung was only available after liver allograft reimplantation. Malignancies causing cerebral hemorrhage can also be difficult to identify, and special attention must be given to donors with intracranial bleeding (25). The donor for case 8 in Table 4 was a 38-year-old woman with a subarachnoid hemorrhage of unknown etiology; thus, one could speculate that the glioblastoma was possibly donor-transmitted. However, computerized tomography scan of abdomen and DNA or HLA studies on the glioblastoma or autopsy were not performed on this patient to confirm this.

The progression to invasive and metastatic cancer is multifactorial. The immunosuppressed state provides a permissive environment for malignant growth, possibly precipitating an accelerated course of cancer progression in those already genetically or environmentally predisposed. The correlation of cancer with chronic immunosuppression, (irrespective of organ transplantation) is supported by the higher incidence of malignancies in patients with primary immunodeficiency disorders, autoimmune diseases treated with cyclosporine or azathioprine, and acquired immunodeficiency disease syndrome (26-29). Oncogenic virus activation, chronic antigenic immune stimulation, and impaired immune surveillance may represent the means by which immunosuppression in organ transplant patients contributes to neoplastic growth (30-32).

Recently, a large study on 1.2 million U.S. adults with alcohol consumption, showed a significantly higher risk of mouth, esophagus, pharynx, larynx, and liver cancers in middle aged and elderly men and women (33). In our series, 22.5% of the adult patient population received liver transplant for alcoholic liver disease. Interestingly, 70% of the patients who developed oropharyngeal, lung, and gastrointestinal cancers had an alcoholic history before transplant. Most of these patients were fully rehabilitated and were free from alcohol consumption before liver transplant and are thought to remain sober after the transplant. Whether this risk factor continues after discontinuation of alcohol or is purely the events of immunosuppression or the combination of both factors needs further evaluation. Additionally, 18 males out of 600 (3%) and 4 females out of 400 (1%) developed skin cancers. For other cancers, the rate was 4.0% for male and 2.3% for female. This male preponderance of developing de novo cancer may partially be related to higher rate of male transplanted for alcohol-related disease (70% male vs. 30% female), where incidence of oropharyngeal, lung, and esophageal cancer is higher. However, there may be other factors involved.

In conclusion, skin cancers were the most common (2.2%), type of de novo nonlymphoid malignancy observed in the study with best long-term survival. In liver transplant recipients compared to the general population matched for age, gender, and length of follow-up, the relative risk of developing oropharyngeal cancer was 7.6 times higher and lung cancer was 1.7 times higher. Rates of female gynecological (breast, ovary, uterus, and

cervix) cancer was actually 1.9 times lower (SIR=0.53), and may reflect a diligent policy of pre- and post-LTX mammography and gynecologic evaluation. The rate of genitourinary malignancy was 1.5 times lower (SIR=0.68), whereas the rate for gastrointestinal malignancy was unchanged (SIR=1.06). Rapid progression of de novo malignancies in chronically immunocompromised recipients warrants careful attention to the association of the de novo malignancies particularly in older population (age>50 years). Although cancer can develop in immunosuppressed patients at all ages, based on our data, we strongly recommend screening in all the patients above age 40 years with additional testing of indirect laryngoscopy, chest x-ray, prostate specific antigen in males, mammography plus continuation of cervical smears in female and colonoscopy in high-risk patients at regular intervals, during long-term follow-up. This screening procedures may facilitate diagnosis of these cancers at an early and (hopefully) curable stage of the disease.

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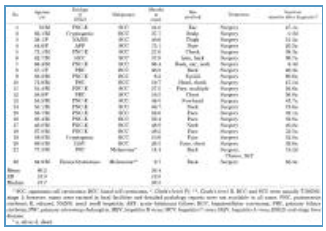

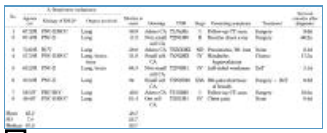

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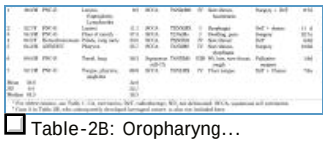

Table-2B: Oropharyng...

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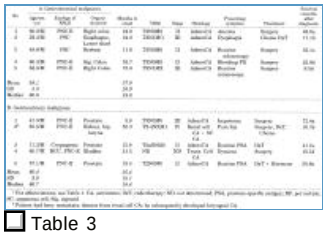

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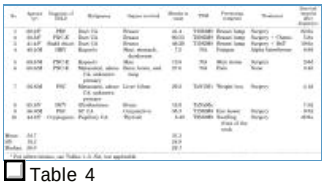

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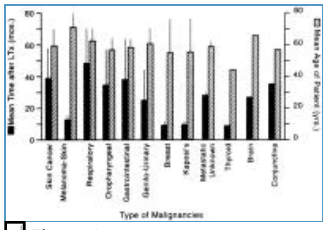

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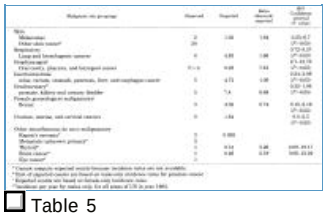

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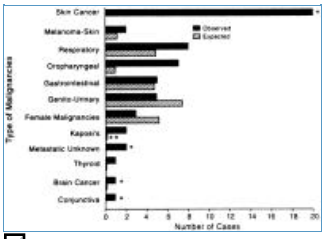

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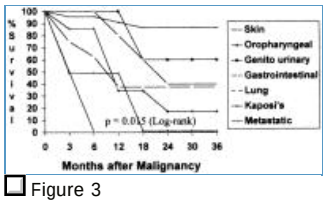

Figure 3

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