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The Impact of *De novo* Tumors after Liver Transplantation on Long Term Survival

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Abstract

Background and aims: the purpose of this study is to describe *de novo* post-liver transplant (LT) malignancies and compare their frequency with incidence rates from Italian cancer registries.

Methods: three hundred and thirteen patients subjected to LT, from 1991 to 2006, surviving 12 months and without diagnosis of previous cancer (including hepatocellular carcinoma), were evaluated for development of *de novo* malignancies excluding non-melanoma skin cancers.

Results: during a total follow-up time of 1,753 person years (PYs), 40 (12.8%) *de novo* malignancies were diagnosed in 40 recipients. The most common cancers were non-Hodgkin lymphoma (NHL) (20%), cancer of the head and neck (17%), Kaposi sarcoma (KS) (17%) and esophageal tumors (12%). The 1, 3, 5 and 10 years estimated survival were 70%, 56%, 48% and 39%. Patients with *de novo* cancers had a lower 10 years survival (p=0.0047) than patients without (39% vs 75%). The risk of cancer after LT was 3-fold higher than that of the general population of the same age and sex (95% CI:2.0-4.3). *De novo* tumor sites or types with significantly elevated standardized incidence ratio (SIR) included KS (SIR=212), NHL (SIR=13.7), oesophagus (SIR=18.7), melanoma (SIR=10.1) and head and neck cancers (SIR=4.6).

Conclusion: tumors after LT are associated with lower long-term survival, confirming that cancer is a major cause of late mortality.

Keywords: *De novo* tumor; Immunosuppression; Liver transplantation; Tumor after transplantation

Introduction

Liver transplantation is the treatment of choice for end-stage liver diseases, as it is demonstrated by the excellent long term survival after this procedure [1]. However, due to the need for immunosuppression, a high price should be paid for the improvement of life expectancy of those patients in terms of many serious complications, such as increased risk and tendency of developing infection and post-transplant malignancies [2]. An increased incidence of *de novo* post-transplant malignancies in immunosuppressed organ transplant recipients was first predicted by Starzl in 1968 [3] and since then the Israel Penn Transplant Tumor Registry (formerly the Cincinnati Transplant Tumor Registry), a voluntaristic registry collecting all the information on transplant recipients with *de novo* post-transplant cancers, has received data from 7,796 malignancies occurring in 7,316 recipients of solid organ transplantation of whom 269 liver transplant recipients with *de novo* post-transplant cancer [4]. The incidence of *de novo* neoplasm excluding non-melanoma skin cancers after liver transplantation ranges from 3% to 16%, significantly higher than that observed in the general population [5], causing 25% of the deaths in patients who have survived more than 3 years after liver transplantation [6]. The aim of this study is to describe the incidence, epidemiology, characteristics and outcome of *de novo* post-liver transplant tumors, excluding non-melanoma skin cancers, occurring in two liver transplant centers located in the north east part of Italy and to compare it with incidence rates from Italian cancer registries.

Patients and Methods

A total of 313 patients who underwent deceased donor LT, from 1991 up to 2006, at two liver transplant centers located in the north east part of Italy (182 in Udine and 131 in Padova), surviving at least 12 months from the transplant procedure and without diagnosis of previous cancer (including hepatocellular carcinoma), were evaluated by retrospective charts review for the development of *de novo* post-transplant malignancies, including melanoma and excluding the other skin cancers. Records of these patients were reviewed, and data on age at the time of transplant, indication for transplantation, interval from transplantation to diagnosis of malignancy, factors predisposing to the development of malignancy, treatment of malignancy, immunosuppression regimen, area of birth and residency at the time of transplantation and survival from the time of diagnosis of the *de novo* malignancies were collected. The immunosuppression regimen consisted of calcineurin inhibitors (cyclosporine or tacrolimus) in combination with steroids with or without azathioprine or mycophenolate. Immunosuppressive dosages before the development of the *de novo* tumors were indicated to maintain desired blood levels (tacrolimus 5 to 15 ng/mL; cyclosporine 100 to 350 ng/mL)

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during follow-up and were modified after the diagnosis of the *de novo* tumors with the same schedule in the two LT centers. The diagnosis of malignancy was always established by histological examination of biopsies or surgical specimens of the tumour. The date of the biopsy or of the surgical procedure were designated as the date of cancer diagnosed. Patients were examined, including liver function tests and routine blood tests, every 3 months for the first year, every 6 months from the second to the fourth year, and then annually after transplantation in both LT centers. Person-years (PYs) at risk for cancer were computed from 30 days after enrolment (i.e., the date of transplant) to the date of last follow-up visit, or to the date of cancer diagnosis, or to the date of death. Observed cancers were the incident cases diagnosed during the study period and cancer diagnoses recorded during the follow-up visits were histologically confirmed and coded according to the International Classification of Diseases and Related Health Problems, 10th revision (ICD-10). To avoid follow-up losses, information on cancer and on vital status was actively elicited either from clinical records, cancer registries (when available), or the census bureau of the town of residence. Multiple primary cancers were separately considered in the statistical analysis. Non-melanoma skin cancers *in-situ* and pre-neoplastic lesions were not included in the present analysis as i) information on basal cell carcinoma was not recorded, and ii) the report of squamous cell carcinoma might not have been complete. The number of observed incident cancer cases was compared to the expected number. This was computed from sex- and age-specific incidence rates from Italian cancer registries [7]. Standardized incidence ratios (SIRs) were computed dividing the number of observed cases by the number of expected ones. Ninety five percent confidence intervals (CIs) of SIRs were determined using the Poisson distribution [8]. Analysis of estimated survival was done with the Kaplan-Meier survival curves and log-rank test was done for comparison (SPSS 9.0.0 for Windows); a p-value less than 0.05 was considered significant.

Results

A total of 313 liver transplant recipients were analyzed for the development of *de novo* tumors covering a time period of 15 years (1991-2006). This cohort resulted from two liver transplant centers (Udine and Padova) located in the north east part of Italy; 182 patients were transplanted in Udine and 131 in Padova. The median age at transplantation of the 313 transplant recipients herein investigated (219 males and 94 females) was 51 years (range 44-57) with no differences between the two LT centers, while variations in their distribution according to calendar year at transplantation were due to differences in starting of liver transplant program in the two hospitals (Table 1).

Most of our study group was born (59.4%) or resided (70.6%) in northern Italy: during a total follow-up time of 1,753 PYs, 40 (12.8%) *de novo* malignancies were diagnosed in 40 recipients of LT; there were 10 females and 30 males with a median age at the diagnosis of *de novo* tumor of 58 years old (range 44-69); 15 (8.2%) were diagnosed in the cohort from Udine and 25 (19%) in the cohort from Padova, the median follow-up was respectively 4.3 years (1.3-6.6) and 8.2 years (4.2-10.6) in the centers of Udine and Padova. The median time from transplantation to diagnosis of all type of *de novo* cancer was 54 months (range 2-245 months) and was not different between solid organ tumors 52 months (range 2-245 months) versus post-transplant lymphoproliferative disease (PTLD) 66 months (range 12-106 months) (p=0.73), solid organ tumors vs Kaposi sarcoma 25 months (range

	Total		Padova		Udine	
Characteristics	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
Total	313	(100)	131	(100)	182	(100)
Gender						
Females	94	(30.0)	35	(26.7)	59	(32.4)
Males	219	(70.0)	96	(73.3)	123	(67.6)
Age at transplantation (years)						
Median (IQR)	51.3	(44.4-57.1)	47.3	(37.3-54.3)	53.3	(47.4-58.4)
<35	32	(10.2)	27	(20.6)	5	(2.8)
35-49	109	(34.8)	51	(38.9)	58	(31.9)
≥50	172	(55.0)	53	(40.5)	119	(65.4)
Calendar year at transplantation						
1991-1995	77	(24.6)	77	(58.8)		0
≥1996	236	(75.4)	54	(41.2)	182	(100.0)
Area of birth						
Northern Italy	186	(59.4)	68	(51.9)	118	(64.8)
Central Italy	21	(6.7)	13	(9.9)	8	(4.4)
Southern Italy	92	(29.4)	47	(35.9)	45	(24.7)
Abroad	14	(4.5)	3	(2.3)	11	(6.0)
Area of residence						
Northern Italy	221	(70.6)	75	(57.3)	146	(80.2)
Central Italy	18	(5.8)	13	(9.9)	5	(2.8)
Southern Italy	72	(23.0)	42	(32.1)	30	(16.5)
Abroad	2	(0.6)	1	(0.8)	1	(0.6)
Transplantation centre						
Padova	131	(41.9)				
Udine	182	(58.2)				
Follow-up time (years)						
Total		1,753		985		768
Median (IQR)	5.8	(1.8-8.5)	8.2	(4.2-10.6)	4.3	(1.3-6.6)

Table 1: Characteristics of 313 patients who underwent liver transplantation.

3-67 months) (p=0.13) and PTLD vs Kaposi (p=0.09). The type, characteristics and outcome of the 40 patients with *de novo* tumors are detailed in Table 2. The cumulative hazard of developing any type of *de novo* tumors included in this study is reported in Figure 1.

The most common type of *de novo* tumors diagnosed was PTLD (non-Hodgkin lymphoma) in 20% of cases, followed by cancer of the head and neck (17%), Kaposi sarcoma (17%), esophageal tumors (12%), lung cancer (10%), gastric adenocarcinoma (7%), colon, melanoma and cervix cancer (5% each) and breast tumor (2%). Eighty-seven percent of patients diagnosed with head & neck or upper gastrointestinal tumors have had the liver transplant for alcoholic liver disease; also 3 of 4 lung cancers had a history of smoking before LT continuing also after the transplant. Conversely, 6 out of 8 (75%) patients diagnosed with *de novo* PTLD were HCV positive and the remaining 2 were HBV positive; overall all the patients diagnosed with *de novo* PTLD were transplanted for viral cirrhosis.

Twenty-two out of 40 (55%) patients with *de novo* tumors died for causes related to their cancer; this mortality was higher for lung tumor (100%), followed by esophageal and gastric cancer (62.5%), tumor of the head and neck (57%), Kaposi sarcoma and lymphoproliferative disease (50% each). Mortality due to solid tumor and melanoma, was 58% (15 out of 26) and for Kaposi sarcoma and lymphoproliferative disease was 50% (7 out of 14). The 1, 3, 5 and 10 years estimated survival were respectively 70%, 56%, 48% and 39% for all types of *de novo* tumors, with a median survival of 54 months (Figure 2). The 1, 3 and 5 years estimated survival was not different between solid tumors and

Patient No	De novo tumor	Liver disease	Sex	IMS	Time from OLT to malignancy (months)	Treatment	Outcome	Post-Tumor Follow-Up (months)
1	Esophagus	ALD	F	CyA	57	surgery	alive nf	122
2	Esophagus	ALD	M	CyA	49	rt+ cht + palliation	died nr	13
3	Esophagus	ALD	M	CyA	84	surgery + rt + cht	alive nf	83
4	Esophagus	ALD	M	FK	66	palliation	died nr	5
5	Esophagus	ALD	M	CyA	45	palliation	died nr	15
6	Neck	ALD	M	CyA	146	surgery	alive nf	18
7	Larynx	ALD	F	CyA	6	surgery + rt	died nr	139
8	Salivary gland	ALD	M	CyA	2	surgery + rt	alive nf	132
9	Larynx	HCV/HBV	M	CyA	98	palliation	died nr	7
10	Tongue	ALD	M	CyA	19	surgery	died nr	5
11	Tongue	ALD	M	FK	13	surgery + rt	alive nf	99
12	Pharyngeal	ALD	F	CyA	131	palliation	died nr	1
13	Stomach	ALD	M	CyA	49	surgery	died nr	4
14	Stomach	HBV	M	FK	77	surgery + rt + cht	alive nf	39
15	Stomach	ALD	M	FK	53	surgery	died nr	1
16	Lung	HCV/HBV	M	CyA	133	surgery	died nr	3
17	Lung	PLD	M	FK	13	rt+cht	died nr	2
18	Lung	PSC	M	FK	34	cht	died nr	29
19	Lung	ALD	M	FK	21	cht	died nr	10
20	Colon	HBV	M	CyA	159	surgery	died nr	10
21	Colon	PSC-HCV	M	CyA	133	surgery + cht	alive nf	30
22	Melanoma	ALD	M	CyA	97	surgery	alive nf	20
23	Melanoma	HCV/HBV	F	FK	15	surgery + ifn	alive nf	71
24	Cervix	ALD	F	CyA	84	surgery+rt	alive nf	84
25	Cervix	HCV	F	CyA	11	surgery	died nr	16
26	Breast	PBC	F	FK	13	surgery	alive nf	94
27	Kaposi	HBV-HDV	M	CyA	13	surgery	died nr	54
28	Kaposi	HBV	M	FK	36	surgery	died nr	93
29	Kaposi	HBV	M	FK	133	surgery	alive nf	7
30	Kaposi	SSC	M	CyA	56	surgery	died nr	40
31	Kaposi	ALD	M	CyA	5	reduction IMS	alive wn	108
32	Kaposi	HCV	F	FK	3	surgery	alive nf	94
33	PTLD	HBV	M	CyA	72	surgery cht	died nr	64
34	PTLD	PSC-HCV	F	CyA	66	surgery cht	died nr	13
35	PTLD	HCV	M	FK	36	cht	alive nf	32
36	PTLD	HCV-HBV	M	FK	58	cht+rt	alive nf	44
37	PTLD	HCV	M	FK	101	cht	died nr	3
38	PTLD	HBV	M	CyA	12	cht+rituximab	alive nf	24
39	PTLD	HCV	F	FK	106	cht	alive nf	16
40	PTLD	HCV	M	FK	80	palliation	died nr	0

ALD: Alcoholic Liver Disease; PSC: Primary Sclerosing Cholangitis; PBC: Primary Biliary Cirrhosis; PLD: Polycystic Liver Disease; SSC: Secondary Sclerosing Cholangitis; nf: neoplsia free; nr: neoplasia related; wn: with neoplasia; cht: chemotherapy; rt: radiotherapy; IMS: Immunosuppression; PTLD: Post-Transplant Lymphoproliferative Disease

Table 2: Clinical characteristics of the 40 patients with *de novo* tumor.

PTLD being 62%, 45% and 45% versus 75%, 62% and 62% respectively (p=0.97) (Figure 2). The 10-years patient survival was significantly lower (39% versus 75%, p=0.0047) in patients who developed a *de novo* tumor compared to patients without *de novo* tumors as reported in Figure 3.

Incidences rates (IR/100.000) and SIR with 95% CI according to cancer site/type and transplant group are shown in Table 3. Overall, the risk of cancer, excluding non-melanoma skin cancer, of these transplant recipients was 3-fold significantly higher than that of the general population of the same age and sex (95% CI: 2.0-4.3). Cancer sites or types with significantly elevated SIR included KS (SIR=212), NHL (SIR=13.7), oesophagus (SIR=18.7), melanoma (SIR=10.1) and head and neck cancers (SIR=4.6) (Table 3). These findings were substantially homogeneous with regard the two groups (i.e., Padova and Udine), though the small numbers which resulted from the stratified analysis decreased the statistical power.

Discussion

As most of the problems associated with the perioperative period have been overcome, attention has focused on factors affecting long-term survival of liver transplant recipients. Causes of premature patient and graft loss include recurrent disease and complications of immunosuppression, including cardiovascular disease, renal failure and malignancy. The incidence of *de novo* malignancies after liver transplantation ranges from 4.5% to 12.5% [9], however, the cumulative risk for *de novo* malignancy has been reported to accelerate the longer the allograft recipient survives, from 20% at 10 years to 55% at 15 years [10].

In the present series we report a cumulative incidence of *de novo* malignancies after LT, excluding non-melanoma skin cancers, of 12.8% in two LT centers, being 8.2% in the cohort from Udine and 19% in the cohort from Padova; this difference probably reflect the longer follow-up in Padova where LT started in 1991 while in Udine the LT program began in 1996.

Most published reports have shown increased incidence of *de novo* cancers such as malignant lymphomas and cutaneous neoplasms [11,12] but a decreased incidence of breast cancer [13]. We have found increased risk of non-Hodgkin lymphoma (SIR=13.7), cancer of the oesophagus (SIR=18.7), melanoma (SIR=10.1) and head and neck neoplasm (SIR=4.6) but no increased risk of colon, lung and breast cancers. Overall, the risk of cancer (non-melanoma skin cancer excluded) of these transplant recipients was 3-fold significantly higher than that of the general population of the same age and sex (95% CI:2.0-4.3).

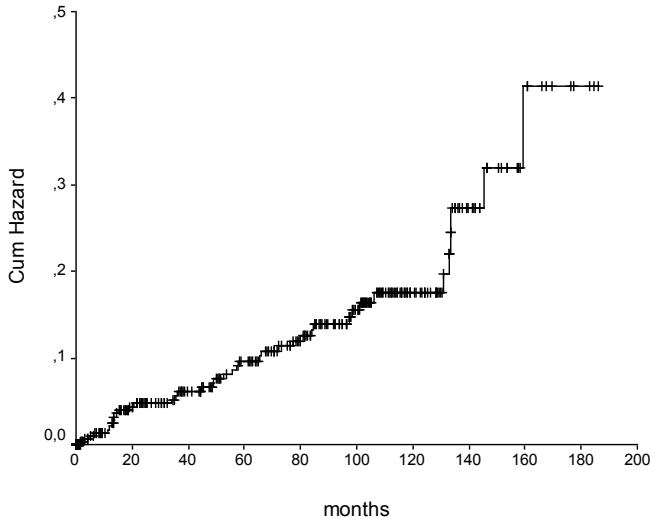

Figure 1: Risk of developing any type of *de novo* tumors (excluding non-melanoma skin cancers) after liver transplantation.

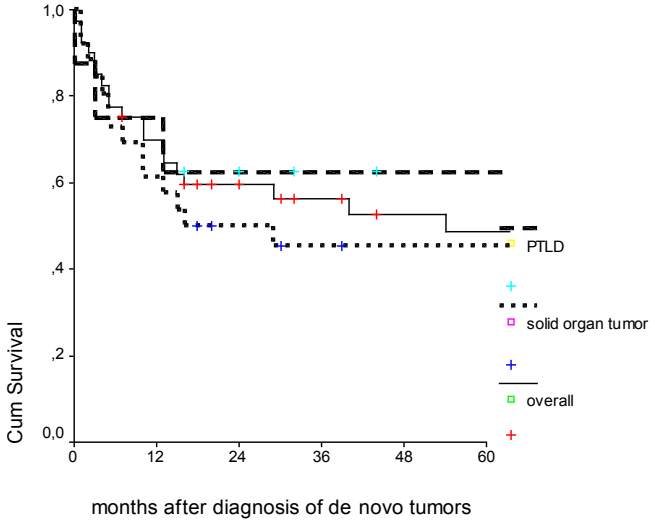

Figure 2: Overall survival of patients with diagnosis of *de novo* tumors, stratified then in solid organ tumors and PTLD.

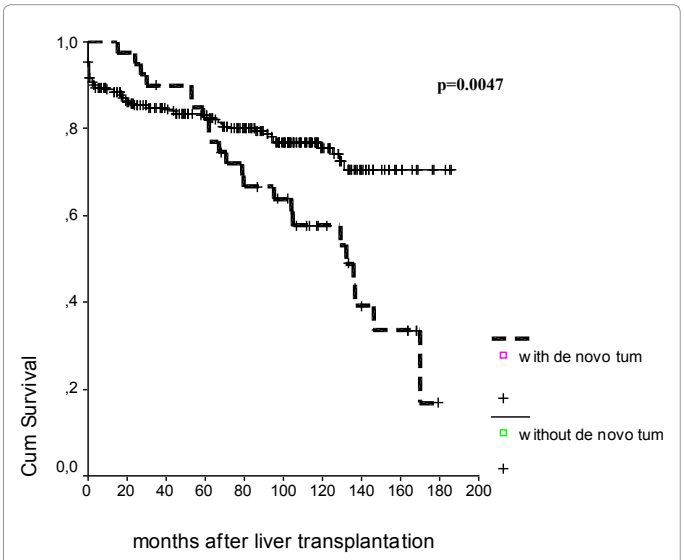

Figure 3: Survival after liver transplantation in patients with and without *de novo* tumors.

The most common *de novo* tumor in our study group, as reported by others [12,14,15], was PTLD accounting for 20% of all the cancers arising in our cohort, followed by tumors of the head and neck (17%) and Kaposi sarcoma (17%). PTLD is a significant cause of mortality in allograft recipients. Benlloch and colleagues [16] suggested that hematological appeared earlier than solid tumors, were more prevalent in those transplanted after 1995 than before and associated with a lower survival than solid organ tumors. We found that survival of lymphoid tumor was not different from that of solid organ tumors in our cohort.

			TOTAL		Padova group	Udine group
Cancer site/type (ICD-10)	**Obs. Tot. (PD/UD)**	**IR *100.000**	**SIR**	**95% CI**	**SIR (95% CI)**	**SIR (95% CI)**
Head and neck (C00-14 and 30, 32)	**7(4/3)**	**231.4**	**4.6**	1.3-11.9	**4.4** (0.5-16.1)	**4.8** (0.6-17.5)
Esophagus (C15)	**5 (3/2)**	**171.8**	**18.7**	3.9-54.7	**12.1** (0.3-67.6)	**25.7** (3.1-92.9)
Stomach (C16)	**3(2/1)**	**171.3**	**4.3**	0.9-12.6	**5.6** (0.7-20.4)	**2.9** (0.1-16.4)
Colon (C18)	**2(2/0)**	**114.9**	**2.5**	0.3-9.2	**5.2** (0.6-18.8)	**NC**
Lung (C34)	**4 (2/2)**	**114.2**	**0.9**	0.1-3.2	**0.9** (0.0-4.8)	**0.9** (0.0-5.2)
Melanoma of skin (C43)	**2 (1/1)**	**114.4**	**10.1**	1.2-36.3	**9.5** (0.2-53.2)	**10.6** (0.3-59.2)
Kaposi's sarcoma (C46)	**6 (6/0)**	**291.5**	**211.6**	68.7-493.8	**370.2** (120.2-863.9)	**NC**
Breast, female (C50)	**1(0/1)**	**193.3**	**1.2**	0.0-6.7	**NC**	**2.1** (0.1-12.0)
Cervix uteri (C53)	**2 (2/0)**	**192.8**	**12.8**	0.3-71.4	**28.1** (0.7-156.5)	**NC**
Non Hodgkin's Lymphoma (C82-85,C96)	**8 (3/5)**	**286.7**	**13.7**	4.5-32.0	**10.7** (1.3-38.7)	**16.9** (3.5-49.3)
All cancers but skin	**40 (25/15)**	**1822.1**	**3.0**	2.0-4.3	**4.0** (2.4-6.2)	**2.1** (1.1-3.8)

NC: the SIR was not computed because no cancer cases were observed

Table 3: incidences rates (IR) (*100.000) and standardized incidence ratios (SIR) with 95% confidence intervals (CI) according to cancer site/type and transplant.

The incidence of breast cancer after transplantation does not appear to be increased as already reported in the literature [13].

The incidence of *de novo* cancers such as head and neck and upper gastrointestinal tumors (esophageal and gastric cancer) in which the abuse of alcohol is universally recognized as a risk factor was increased in our population of liver transplant recipients; 13 out of 15 patients (87%) diagnosed with one the those cancers have been transplanted for alcoholic liver disease. In the non-immunosuppressed population, alcohol abuse is associated with an increased risk for several malignancies, including liver and alimentary tract [17,18]. It has been shown that alcohol suppresses natural killer (NK) cell activity in murine models [19]. and NK cells have an antitumor effect [20,21], and consequently the suppressive effect of alcohol on NK cells could promote tumorigenesis. However, although the Cincinnati Transplant Tumor Registry confirms no increased tumor incidence, it suggests that these common tumors tend to occur at an earlier age (mean, 41 years) in transplant recipients compared with the general population [22]. However, the mean age at tumor diagnosis in the present series was not reduced (58 years), primarily because of the older mean age (51 years) at time of liver transplantation. A 3-fold increased risk of esophageal cancer after organ transplantation has been described [23]. Patients with esophageal cancer face an additional risk due to the habit of regular alcohol consumption. The occurrence may be related to a chronic exposure of alcohol and tobacco prior to transplantation, and was shown to play a more important role. Presser et al. [24] reported on 9 patients (0.5%) diagnosed with a *de novo* esophageal cancer and 1 patient with cancer of the cardia (0.05%) out of 1,926 subjected to liver transplantation from 1988 to 2006; all those 9 patients had a pre-transplant history of alcohol abuse. The incidence of *de novo* esophageal cancer after LT seems to be increased in patients with alcoholic cirrhosis, but not in patients with different underlying disease. Any factor that causes chronic irritation and inflammation of the esophageal mucosa appears to increase the incidence of esophageal and gastric cancer. Immunosuppression may enhance the oncogenic effects of pre-transplantation alcohol and tobacco consumption, as well established risk factors [25]. Strategies to facilitate the early detection of *de novo* malignancies and to reduce the risk for those malignancies, such as cessation of smoking and alcohol consumption, are of paramount importance to reduce the impact after transplantation.

KS was rare in the United States before the advent of AIDS and is always related to HHV-8 infection in immunocompromised patients. KS has been described primarily in kidney transplant recipients of Mediterranean descent, but some cases have been reported in liver transplant recipients receiving cyclosporine or tacrolimus [26]. All our cases of KS were HHV-8 positive at time of the diagnosis; the high prevalence of KS in our population (SIR=291.5) might be related to the geographical area of our patients with 46% of transplanted patients living in the Mediterranean area.

Hepatitis C virus (HCV) infection has been linked to increased risk of lymphoma among immunocompetent individuals [27]. Buda et al. [28] reported a higher proportion of HCV-positive patients developed PTLD than the HCV-negative cases (8% vs 2%, p = 0.017) in recipients of cardiac transplantation. Morton and colleagues [29] in a retrospective cohort study of all individuals in the United States who received their first solid organ transplant from 1994 to 2005 using Scientific Registry of Transplant Recipients data reported that 1,630 patients were diagnosed with PTLD and HCV prevalence at transplantation was 11.3%; they concluded that HCV infection did not increase PTLD risk in the total cohort. McLaughlin et al. [30] reported an increased risk for PTLD in HCV liver transplants recipients (7%) versus HCV negative recipients (0.8%, p=0.02). In our experience all patients diagnosed with *de novo* post-transplant lymphoproliferative disease were HCV or HBV positive confirming a role of viral infection in PTLD development.

In conclusion based on the analysis of this cohort of 313 liver transplant recipients during a total follow-up time of 1,753 PYs we have shown that the risk of cancer of those transplant recipients was 3-fold significantly higher than that of the general population of the same age and sex. KS (SIR=212), NHL (SIR=13.7), oesophagus (SIR=18.7), melanoma (SIR=10.1) and head and neck cancers (SIR=4.6) were the *de novo* malignancies more frequently encountered in this transplant cohort in comparison with the general population, while the incidences of such commonly occurring tumors as carcinomas of lung, breast, colon, and prostate are not uniformly increased across liver transplant recipients. The development of *de novo* post-LT malignancies in this cohort of patients is associated with lower long-term survival when compared to transplanted patients who were not diagnosed with tumors after liver transplantation, confirming that cancer is a major cause of mortality in the long term and that continuous tumor-surveillance is warranted in this immunocompromised population.

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