Incidence, risk factors and outcome of *de novo* tumors in liver transplant recipients focusing on alcoholic cirrhosis

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Abstract

Orthotopic liver transplantation (OLT) is an established life-saving procedure for alcoholic cirrhotic (AC) patients, but the incidence of *de novo* tumors ranges between 2.6% and 15.7% and is significantly increased in comparison with patients who undergo OLT for other etiologies. Tobacco, a known carcinogen, has been reported to be between 52% and 83.3% in AC patients before OLT. Other risk factors that contribute to the development of malignancies are dose-dependent immunosuppression, advanced age, viral infections, sun exposure, and premalignant lesions (inflammatory bowel disease, Barrett's esophagus). A significantly more frequent incidence of upper aerodigestive (UAD) tract, lung, skin, and kidney-bladder tumors has been found in OLT recipients for AC in comparison with other etiologies. Liver transplant recipients who develop *de novo* non-skin tumors have a decreased long-term survival rate compared with controls. This significantly lower survival rate is more evident in AC recipients who develop UAD tract or lung tumors after OLT mainly because the diagnosis is usually performed at an advanced stage. All transplant candidates, especially AC patients, should be encouraged to cease smoking and alcohol consumption in the pre- and post-OLT periods, use skin protection, avoid sun exposure and over-immunosuppression, and have a yearly otopharyngolaryngeal exploration and chest computed tomography scan in order to prevent or reduce the incidence of *de novo* malignancies. Although still under investigation, substitution of calcineurin inhibitors for sirolimus or everolimus may reduce the incidence of *de novo* tumors after OLT.

Key words: *De novo* malignancies; *De novo* tumors tobacco consumption; Alcoholic cirrhosis; *De novo* cancer; Liver transplant

Core tip: Incidence of *de novo* tumors is significantly increased in patients who undergo liver transplantation for alcoholic cirrhosis. The association of alcohol and tobacco consumption and immunosuppression contribute to the development of *de novo* malignancies, mainly located in upper aerodigestive tract, lung and skin.

INTRODUCTION

The occurrence of *de novo* tumors is considered the second cause of late mortality after orthotopic liver transplantation (OLT)[1-3]. Initially, similar frequency of *de novo* tumors (carcinomas of the lung, prostate, breast, colon, and uterine cervix) was published among transplant recipients in comparison with the non-transplant population[4]. Subsequently, a higher incidence of posttransplant lymphoproliferative disease (PTLD) and skin cancer was established in OLT patients *vs* non-immunosuppressed population[2,5-7]. Moreover, the incidence of other tumors is controversial so that, depending on the series of OLT, an increased incidence of upper aerodigestive (UAD) tract[1,5,6,8-16], colon[5,6,17], and kidney tumors[5] can be found. It has been reiterated that the most important contributing factors for increased incidence of *de novo* tumors are the long period of follow-up of the recipients and the presence of risk factors, such as abuse of alcohol and tobacco, sun exposure, overimmunosuppression, advanced age, inflammatory bowel disease, hepatitis B virus (HBV) and hepatitis C virus infections, Epstein-Barr virus, herpes virus 8, and human papilloma virus[5,8,11,14,18-21]. Alcoholic cirrhosis (AC) constitutes the leading cause of end-stage liver disease in Western countries, and many of these patients may potentially benefit from OLT if they fulfill the usual criteria for this technique[22]. However, the OLT patients for AC show an increased incidence of *de novo* malignancies after transplant[9,11-16,23-32].

The objective of this review is to analyze the incidence, risk factors, location and characteristics of *de novo* tumors in AC patients who underwent OLT, and also to evaluate the prognosis and survival after diagnosis of malignancies.

RESEARCH

We performed MEDLINE search considering the most important series related with *de novo* tumors after OLT that were reported in English literature. We analysed the incidence of *de novo* malignancies in OLT recipients in comparison with the non-transplant population as control group, and also we will mainly focuss on the different series which studied the incidence, risk factors and predisposing conditions for developing *de novo* tumors, locations, survival after diagnosis, surveillance, and immunosuppression changes as prevention or therapeutics measures for control these tumors. In addition, we analysed the incidence of *de novo* tumors in comparative studies between alcoholic and non-alcoholic recipients of OLT.

INCIDENCE

Overall incidence of *de novo* tumors after OLT ranges between 2.6% and 33.6%[1,2,5-8,11,12,16,17,25,26,32-44] (Table 1). The disparity of *de novo* tumors incidence among these series is attributed to exclusion of some type of tumors, such PTLD in the study of Saigal *et al*[26] (incidence of 2.6%). The increased incidence of *de novo* tumors after OLT is mainly due to the intensive surveillance, and the life-long immunosuppressive therapy the transplant recipients receive[1,5]. In our series of 528 adult transplant recipients with a mean follow-up of 6.7 years, the cumulative risks for development of non-cutaneous malignancies at 5, 10, and 15 years post-OLT, were 9%, 18%, and 25%, respectively[45]. A recent series reports a 15-year cumulative incidence of *de novo* tumors of 34.7% as compared to 8.9% for the non-transplant population, and emphasizes the continuously increasing incidence of tumors over time following OLT[44]. The mean interval between OLT and tumor diagnosis was reported to be between 19.2 and 82.7 mo, and the mean age of recipients at the time of diagnosis was between 53 and 59.5 years[14,32,37,38,44]. A significantly higher incidence has been observed in patients who underwent OLT for AC in comparison with other non-AC diseases[9,11-13,15,23,24,26,28,29] (Table 2). In our series of 701 adult recipients of OLT, the incidence of *de novo* tumors in AC patients was significantly higher (25% in AC patients *vs* 9.4% in non-AC recipients; *P* < 0.001)[28].

RISK FACTORS AND PREDISPOSING CONDITIONS FOR *DE NOVO* TUMORS AFTER OLT FOR AC PATIENTS

Recipient age

Liver transplant series showed recipients older than 40 years[5], and older than 51 years old at the time of OLT[25] as having independent risk for *de novo* malignancies. In two recent studies it was also observed that older age and smoking were independently associated with a higher risk of malignancy[38,46], especially lung, head and neck, kidney and urinary tract[46].

Tobacco and alcohol consumption

Prevalence of tobacco use among the non-transplant population is between 20% and 30%, and as high as 40% in OLT recipients[47].

Smoking fewer cigarettes over a long period seems more damaging than smoking more cigarettes over a shorter period[47]. Tobacco discontinuation is usually required for heart and lung transplantation candidates, but in OLT candidates the requirement of smoking discontinuation is less clear and remains controversial. The association of alcohol and tobacco consumption

Table 1 Overall incidence of *de novo* tumors after liver transplantation n (%)

Ref.	No. OLT	Follow-up period	Time from OLT-DNT	Pts with DNT	DNT incidence	Overall SIR
Jonas et al[18]	458	50/22 mo	43 mo	33	34 (7.2)	-
Jain et al[1]	1000	78 mo	36 mo	57	58 (5.7)	7.6 (UAD)
Kelly et al[33]	888	29.3 ± 25.2 mo	24 ± 16.8 mo	39	43 (4.8)	-
Peyrègne et al[8]	251	50.5 mo	24.3 mo	11	12 (4.8)	-
Galve et al[34]	1827	20 ± 18 mo	30.7 ± 22 mo	70	70 (3.8)	-
Sheiner et al[2]	121	499 persons/yr	19.2 mo	18	19 (15.7)	3.9
Haagsma et al[5]	174	61 mo	-	21	23 (13.2)	-
Xiol et al[25]	137	69 mo	12-104 mo	22	30 (21.9)	-
Jiménez et al[35]	505	8-168 mo	47.8 mo	57	62 (12.2)	-
Saigal et al[26]	1140	69 mo	45 mo	30	30 (2.6)	-
Sanchez et al[6]	1421	67 mo	-	125	125 (8.8)	-
Benlloch et al[11]	772	51 mo	40 mo	41	41 (5.3)	-
Herrero et al[36]	187	65 mo	49.5 mo	49	63 (33.6)	-
Oo et al[12]	1778	-	57 mo	141	141 (7.9)	2.07
Aberg et al[7]	540	3222 persons/yr	61 mo	47	50 (9.2)	2.59
Jiang et al[17]	2034	-	42.2 ± 33.8 mo	113	113 (5.5)	2.5
Baccarani et al[37]	417	81.6 mo	51 mo	43	43 (10.3)	2.7
Chatrath et al[38]	534	68 ± 38.4 mo	48 ± 26.4 mo	73	80 (14.9)	3.1
Collett et al[39]	6846	-	-	-	-	2.2
Tjon et al[40]	385	> 4 mo	-	50	66 (17.1)	2.2
Engels et al[41]	6291	-	-	-	-	2.2
Krynitz et al[42]	1221	61.2 mo	-	150	150 (12.3)	3.4
Sampaio et al[43]	43216	-	31.2 mo	1923	1923 (4.4)	-
Ettorre et al[32]	1675	62.4 mo	38.4 mo	98	100 (5.9)	1.4
Schrem et al[16]	2000	-	82.7 mo	115	120 (6)	1.94
Wimmer et al[44]	609	57.3 mo	68.4 ± 44.4 mo	71	87 (14.3)	-

OLT: Orthotopic liver transplantation; DNT: *De novo* tumors; UAD: Upper aerodigestive tumor.

Table 2 Comparative studies between alcoholic cirrhotic and non-alcoholic cirrhotic patients who underwent orthotopic liver transplantation, incidence of *de novo* tumors n (%)

Ref.	No. OLT	Follow-up period	DNT overall incidence	DNT-AC	DNT-non-AC	P-value	DNT excluded
Duvoux et al[9]	90	45.2 ± 21.2 mo	11 (12.2)	8 (26.7)	3 (5)	0.01	-
Jain et al[23]	834	9 4 ± 11 mo	81 (9.7)	36 (19.4)	45 (6.9)	< 0.05 (UAD)	-
Bellamy et al[24]	513	81.7 mo	57 (11.3)	33 (26)	24 (6.1)	0.0001	PTLD
Saigal et al[26]	1140	69 mo	30 (2.6)	10 (7.5)	20 (1)	0.001	-
Benlloch et al[11]	772	40 mo	41 (5.3)	18 (9.4)	23 (3.9)	0.01	Skin DNT
Oo et al[12]	1778	-	141 (7.9)	15 (8.8)	126 (7.8)	0.001	-
Dumortier et al[13]	594	-	42 (7)	37 (12.1)	5 (1.7)	0.05	-
Jiménez et al[28]	701	9-206 mo	109 (15.5)	69 (25)	40 (9.4)	0.001	-
Biselli et al[29]	147	-	11 (7.5)	7 (14.3)	4 (4)	0.042	-
Zanus et al[15]	638	48 mo	43 (6.3)	16 (11)	27 (5)	0.02	-

AC: Alcoholic cirrhosis; OLT: Orthotopic liver transplantation; PTLD: Post-transplant lymphoproliferative disease; DNT: *De novo* tumors; UAD: Upper aerodigestive tumor.

has been published to be as high as 90% in alcoholic patients[48,49]. It has been documented that 52% of AC patients were active smokers before OLT and 44% after OLT[50]. In our series of OLT for AC, 83.3% of patients were smokers *vs* 43% of non-AC patients[28]. Smokers show an increased risk of cardiovascular disease, stroke and cancer[51]. Moreover, tobacco consumption has also been associated with squamous cell carcinoma (SCC) of the skin in the non-transplant population[52] and OLT recipients[20,27]. In addition, malignancies seem to develop much earlier after OLT in tobacco users[50]. In a comparative study among active smokers, ex-smokers, and non-smokers who underwent OLT, a significantly increased cardiovascular-specific mortality and sepsis

mortality but not malignancy-related mortality was demonstrated in the active smokers group[53]. On the other hand, other authors showed a significantly higher 10-year cumulative rate of *de novo* tumors in active smokers (12.7%) *vs* non-smokers (2.1%), but without an effect of smoking on skin cancer or cardiovascular disease[50]. Liver transplant recipients who ceased smoking had a lower incidence of such tumors in comparison with patients who continued to smoke[46].

A synergistic effect has been demonstrated when patients are exposed to combined alcohol and tobacco consumption, resulting in a more than 7-fold increased risk of tumors[54,55]. In the general population, tobacco and alcohol abuse are well-known risk factors for oral,

pharyngeal, laryngeal, esophageal, upper airway, bladder and cervix tumors[54,56-60]. In a more recent review of the non-transplant population, a causal association was established between alcohol intake and cancers of the oral cavity, pharynx, larynx, esophagus, liver, colon, rectum, and in women, breast[61,62]; an association is suspected for cancers of the pancreas and lung[61]. However, the carcinogenic effects of alcohol have not been fully defined and probably differ by target organ. Alcoholic drinks might act as a solvent for carcinogens (*e.g.,* tobacco-derived), facilitating penetration through the mucosa of the upper aerodigestive organs[63]. Heavy alcohol intake seems to affect folate metabolism which changes DNA methylation and the control of expression of genes with a potential role in carcinogenesis (colon, rectum and breast)[64]. For breast cancer, alcohol carcinogenicity is thought to be due to increased estrogen concentration[65]. Production of reactive oxygen species and nitrogen species is a possible mechanism of alcohol-related liver carcinogenesis[66].

Alcoholic cirrhotic patients have a longer history of tobacco use than the general population[67] and also a higher tobacco consumption than patients undergoing OLT for other etiologies[9,35]. Multivariate analysis of a series from the Mayo Clinic showed an increased probability of developing any solid organ *de novo* malignancy with increased age, a history of smoking, and AC or primary sclerosing cholangitis as indications for OLT[14]. In our experience, there is a significantly higher incidence of *de novo* tumors (overall and partial incidence of skin, upper aerodigestive, and lung tumors) in AC patients compared with non-AC patients, a feature that is also related with a significant consumption of alcohol and tobacco in the AC group[27,28,35].

After 10 years of smoking, OLT recipients presented a significantly higher risk of non-skin tumors[51]. It has also suggested that alcohol abuse can produce genetic alterations that potentiate those induced by tobacco smoke[60], and tobacco can also alter the cellular immune system by decreasing the number of natural killer cells[68,69].

The association of immunosuppressive drugs and smoking may have adverse additive effects, mainly in liver transplant patients for AC with a long history of alcohol and tobacco abuse, where there has been a demonstrated higher incidence of UAD and lung *de novo* tumors[1,9-11,14,18,23-25,27,28,45,46,70,71] and even bladder[46] or skin tumors[23,27].

Infections
Kaposi's sarcoma (KS) is a tumor exclusively seen in the immunocompromised patients and is clearly related with type 8 human herpes virus[72]. Human papillomavirus increases the risk for anal, genitourinary, oropharyngeal, and skin tumors, and even for cervical cancer in kidney transplant recipients[73]. PTLDs are associated with Epstein-Barr virus-infected B-lymphocytes and have been reported to have an incidence between 1.7%

and 4% after OLT[21,74]. The incidence of PTLD is lower in OLT recipients in comparison with other solid organ transplants[74].

Immunosuppression
The influence of immunosuppression on the development of *de novo* tumors has been directly related to the intensity as well as the cumulative dose of immunosuppressive drugs[75].

Cyclosporine (CyA) and tacrolimus promote the spread of tumors in immunodeficient mice, probably by increasing the production of growth factors that enhance angiogenesis, tumor growth and metastasis[76]. The pathogenic process triggered by immunosuppressors consists of direct damage to the host DNA and impairment of the recipient's immunosurveillance, which reduce their antitumor and antiviral immunity[77,78]. A retrospective study suggested a dose-dependent immunosuppressive drug relationship with *de novo* tumor development[11]. By contrast, other authors did not find that immunosuppression is an independent risk factor for *de novo* malignancy[26]. Several studies found a higher *de novo* tumor risk for CyA-based[33,38,45] or tacrolimus-based[36,44], whereas others did not observe significant differences between CyA- and tacrolimus-based immunosuppressive therapy[18,38,79]. It was pointed out that CyA therapy increased malignancy risk when C_2 monitoring (blood concentration at 2 h post-dose) was performed and the patient consequently received a significantly higher CyA dose[40]. Azathioprine has also been described as an independent risk factor for higher incidence of *de novo* malignancy, mainly due to inhibition of DNA repair, and its metabolite 6-thioguanine has been shown to accumulate in skin cells *in vitro*[80]. A recent report revealed that standardized incidence ratio for *de novo* tumors were similar for patients who received tacrolimus- or CyA-based immunosuppressive protocols as long-term immunosuppression (mean = 7.4 years) with or without mycophenolate mofetil, azathioprine, or prednisolone as a co-medication[16]. As summary, there are no randomized control studies designed to evaluate the influence of different immunosuppression schedules over the development of post-OLT *de novo* malignancies.

Premalignant conditions
Barrett's esophagus is a premalignant condition with increased risk for development of esophageal tumor; a rapid progression to high-grade of dysplasia has been reported after OLT[81], as well as the development of esophageal carcinoma[82].

There has been suggested an increased incidence in colorectal *de novo* tumors in patients with ulcerative colitis or sclerosing cholangitis who underwent OLT[19,83].

Screening for premalignant conditions should be performed in a pre-OLT evaluation, and patients with evidence of a premalignant state should be followed carefully after OLT for detection of malignancy[84]. Because of the increased incidence of *de novo* tumors

Table 3 Location and risk factors for the most frequent *de novo* tumors in patients who underwent orthotopic liver transplantation for alcoholic cirrhosis

Tumor location	Risk factors
UAD	Alcoholic cirrhosis[9-11,13-15,23,24,30]
	Tobacco consumption[9,14,38,46]
	Barrett's esophagus[82]
Lung	Alcoholic cirrhosis[14,28]
	Tobacco consumption[1,28,38,46]
Skin	Alcoholic cirrhosis[24,26,27]
	Tobacco consumption[20,27,51]
	Age > 40 yr[20] or age > 51 yr[25]
	Male, red hair, brown eyes[20]
	Sun exposure[20,36]
	Sclerosing cholangitis[20]
	CyA immunosuppression[20]
Kidney and genitourinary tract	Tobacco consumption[46]

CyA: Cycosporine A; UAD: Upper aerodigestive tumor.

in AC (frequently smokers), these candidates should be subjected to thorough evaluation to rule out tumor or premalignant condition before OLT[15]. Thus, these patients should be screened for oropharyngeal/laryngeal, esophageal, lung, bladder, and skin tumors as the most frequent tumors associated with alcohol and tobacco consumption.

LOCATION OF *DE NOVO* TUMORS IN OLT RECIPIENTS FOR AC

We analyzed the subset of *de novo* tumors that are usually developed in patients who undergo OLT because of AC. Thus, a significantly more frequent incidence has been published of UAD tract, lung, skin, and bladder tumors in liver transplant patients for AC. PTLD is the second most frequent *de novo* tumor after OLT, but it is not associated with AC. Other types of solid tumors, such as gastric, pancreatic, colorectal, prostate, breast, and uterine cervix tumors show a similar incidence after OLT for AC and non-AC recipients. Risk factors for most frequent *de novo* tumors after OLT for AC are shown in Table 3.

Upper aerodigestive tract tumors
In this group a subset of tumors located in the floor of the mouth, tonsil, tongue, pharynx, larynx and esophagus is included, which are significantly more frequent in male and smoker recipients who underwent OLT for AC[1,9,10,14-16,23,24,30,33,36]. In some series, the most common solid tumors were tumors of the UAD tract[32,38]. The incidence of UAD tumors in OLT recipients was published to be between 0.3% and 3.5% in several series[1,6,10,11,18,33]. The risk of the development of oropharyngeal/laryngeal malignancies was highest in AC patients, with 5- and 10-year risks of 3.2% and 4.6%, respectively, *vs* 0.16% and 0.32%, respectively, for non-AC patients[14]. In patients who underwent OLT for AC, the rate of UAD tumors was 25.5 times higher

than in patients with other etiologies[23]. The mean time from OLT to diagnosis of UAD tract tumors was reported to be between 24 and 62 mo after OLT[1,6,10,11,18,33]. In one series, UAD tract malignancies occurred exclusively in patients transplanted for AC[9]. In one of our studies, the incidence was also significantly higher in the AC group (8.1%) *vs* the non-AC group (0.8%), and among the patients who suffered UAD tract tumors 70% were heavy smokers and 75% had a history of heavy drinking[10]. In patients who underwent OLT for AC, immunosuppressors may enhance the effects of alcohol and tobacco, which are well-known risk factors for the development of UAD tract tumors[85,86].

The pathogenic mechanism of esophageal carcinoma remains unclear. However, experimental studies in animals suggest that oxidative damage from smoking and alcohol intake, or gastroesophageal reflux, which produces inflammation, esophagitis, and increased cell turnover, might initiate the carcinogenic process[87]. Esophageal *de novo* tumors have been diagnosed between 8 and 96 mo after transplant in patients who smoke and who underwent OLT for AC[8,88,89]. In a German series[89] of 10 *de novo* esophageal tumors, diagnosed at a mean time of 51 mo after OLT, all patients were males, 9 underwent OLT for AC and 1 for hepatocarcinoma, 3 were smokers, 9 were immunosuppressed with CyA, whereas 7 patients revealed SCC and 3 adenocarcinoma. Five of these patients were treated with chemo-radiotherapy and the other 5, who had a better general condition, underwent Ivor Lewis esophagectomy. In our published experience of 5 patients with *de novo* esophageal SCC, all were male and smokers, and underwent OLT for AC; diagnosis of SCC was performed at a mean time of 36 mo after OLT, and four patients were treated by transhiatal esophagectomy, showing a 3-year patient survival of 40%[90]. In spite of the elevated risk of OLT patients who suffer esophageal tumors, the mortality after surgical resection was reported as zero in both series[89,90]. To date, there is no experience of neoadjuvant chemo-radiotherapy associated with esophagectomy for the treatment of esophageal tumors after OLT, but the results for surgery are comparable with non-transplant patients who present with an esophageal cancer[89,90].

Lung tumors
The incidence of *de novo* lung tumors after OLT is increased, and ranges between 0.1% and 2.4%[1,11,18,25,28,36,38,91,92]. Our incidence of these malignancies is 40-fold higher than that of the non-transplant population in Spain[28]. The main risk factors for post-OLT lung tumors are the longer time elapsed since transplant[3], AC as indication for OLT[1,11,24,28,32,46], and a long period of tobacco consumption[1,14,28,36,38,91,92]. The risk of developing a lung cancer was highest in AC patients, with 5- and 10-year risks of 2.0% and 4.8%, respectively, compared to non-AC patients with 0.15% and 1.3%, respectively[14].

In several small series[91-93] all patients with *de novo*

lung malignancies had indicated the antecedent of heavy smoking, and this addiction was also present in 62.5% of patients in Pittsburgh series[1] and in 83.3% in our series[28]. According to our experience, the continuation of smoking after OLT represents an additional risk factor for lung cancer[28]. The mean time from OLT to tumor diagnosis was reported to be between 42 and 83 mo[1,6,18,28,92]. The mean age of our patients at the time of lung tumor diagnosis was significantly lower than a Spanish non-transplant population[94].

Patients with lung tumors after OLT show similar symptoms to non-transplant patients[1,28,93]. These lung tumors are usually diagnosed at advanced stages[1,18,28,36,95] in almost two-thirds of cases[28,93]. To obtain early diagnosis of a potentially curable stage of lung cancer, the goal is to perform screening with a computed tomography (CT) scan every year of recipients at increased risk, especially in the subset of older recipients, over-immunosuppressed patients and smokers of more than 20-30 pack-year who have undergone OLT for AC[28,46,93,95-98].

According to OLT series[1,18,28,33,91], lung tumor resection can only be performed at early stages (I or II) and when the patients are in good general condition. In several reported series[1,28,33,36,91-93], there is little information about surgical resection of *de novo* lung tumors after OLT, but among 58 collected cases of these series there were only 13 resected cases (20.6%). In unresectable patients, palliative chemo and/or radiotherapy is an alternative option[1,8,18,28,93].

Skin tumors

Nonmelanoma skin cancer is the most common tumor in the post-OLT population, with an up to 70 times higher incidence in comparison with non-transplant patients[5,10,25,99-101]. Tobacco constitutes a risk factor for skin malignancies in non-transplant patients[53]. The overall incidence in most OLT series ranges from 1% to 6.9%[1,5,11,18,27,33]. Skin tumors represent between 16% and 55% of all tumors and can develop at any time after OLT[20,27,36,40]. The cumulative incidence of nonmelanoma skin malignancies 5, 10, and 15 years after OLT has been reported to be 5.1%, 10.2% and 19.7%, respectively[40].

A long history of sun exposure, personal or family history of actinic keratosis or skin cancer, human papillomavirus, male sex, patient age, red hair, brown eyes, primary sclerosing cholangitis, hepatocarcinoma[14,20,25,36,102], AC and smoking[1,24,27] are described as risk factors for the development of skin tumors. The most frequent sites for *de novo* skin tumors were the face, lips, head, neck, and ears[1,20,27]. As in the non-transplant population, in some series the most common histologic tumor type was basal cell carcinoma[27,103], in contrast to other experiences where SCC was the most frequent[1,20]. Immunosuppressors increase the risk of skin cancer, but whether CyA shows a higher risk in comparison with tacrolimus is unclear. Thus, in one series CyA-treated patients have been associated with a higher incidence and earlier development of skin tumors[20], but another

series failed to find significant differences between CyA and tacrolimus[18]. Nonmelanoma skin cancer does not affect mortality[40].

The incidence of KS ranges from 0.14% to 2.8% after OLT[99]. Viral infections, such as HBV, cytomegalovirus, and Epstein-Barr virus infections have been reported as risk factors for KS, but the main risk factor is human herpes virus 8[104,105]. Kaposi's sarcoma has been related with the degree of immunosuppression, and the lesions disappeared after immunosuppressive drugs were discontinued[106]. Almost all reported cases of KS are located on the skin, but some visceral cases with bad prognosis have also been described[72]. Full-skin examination may detect every kind of skin malignancy, such as melanoma, nonmelanoma cancer, KS or cutaneous lymphoma[107].

Genitourinary and gynecological tumors

Regular and current cigarette smokers in the non-transplant population have a higher risk of bladder cancer than those who never smoked, and there is a statistically significant dose-response relationship in bladder cancer risk between smoking duration, intensity and pack-year consumption[48]. People who discontinued smoking for 20 years or more remain at a higher risk of bladder cancer than people who never smoked, suggesting an early-stage irreversible effect of cigarette smoke[108,109].

Considering the frequent consumption of tobacco among AC patients, the incidence of bladder tumors after OLT must be increased in this group of patients. However, there is little information about the increased incidence of bladder tumors in smokers, except for a recent report where smoking and older age were associated with a higher risk of urinary tract and kidney tumors[46]. An earlier series of OLT reported a 30-fold increase in *de novo* kidney tumors[5].

It appears that the rate of non-prostate genitourinary tumors is increased in OLT patients, but the rate of prostate cancer may be comparable to that in the non-transplant population[31]. The incidence of non-prostate genitourinary cancer in OLT patients ranges between 0% and 0.4%[11,91]. Other authors did not find an increased incidence of breast, cervix or bladder tumors in OLT compared with the non-transplant population[12,32].

SURVIVAL AFTER DIAGNOSIS OF *DE NOVO* TUMORS

The increased mortality associated with *de novo* tumors is thought to be the consequence of aggressive immunosuppression that may give rise to increased proliferation and spread of the tumor, which in turn results in more advanced stages of disease at presentation, precluding surgical or chemo-radiotherapy options[14].

Patients with *de novo* non-skin cancer after OLT have diminished long-term survival in comparison with controls[23,37,40,110]. Aerodigestive tract malignancies

after OLT are greater causes of morbidity and mortality than recurrent alcohol liver disease[10,13]. *De novo* cancer-related death accounted for 21% of all deaths in patients surviving more than six months after OLT, and post-OLT survival was significantly lower in patients who developed *de novo* malignancy in comparison with patients without cancer (70% *vs* 82% at five years)[38]. In a series of 21 UAD and lung tumors diagnosed in 20 OLT recipients, 1-, 2-, and 3-year survival rates were 47.6%, 37.0% and 19.7%, respectively[10]. Moreover, in our series of 15 *de novo* lung tumors all patients died, and mean survival after tumor diagnosis was only 5.4 mo[28]. A recent study considering smoking-related malignancies (lung, head and neck, esophageal, kidney and urinary tract tumors) reports a significantly higher mortality in OLT recipients *vs* the non-transplant patients[46].

Once the tumor was diagnosed, and according to the specific site of the *de novo* tumors, the probability of death at 1 and 5 years was 33% and 48%, respectively, for gastrointestinal tumors; 59% and 84%, respectively, for lung tumors; 22% and 44%, respectively, for oropharyngeal/laryngeal tumors; and 21% and 29%, respectively, for genitourinary tumors[14].

SURVEILLANCE OF TRANSPLANT PATIENTS FOR AC

While smoking and alcohol use, age and existence of premalignant conditions generate suspicion for *de novo* tumor development, prevention and screening after OLT is of paramount importance[14,30,31]. Thus, pre-OLT screening is advised for candidates with Barrett's esophagus[111]. Moreover, all transplant patients who undergo OLT for AC and have a long history of smoking must be carefully reviewed for malignancy in the post-OLT setting, particularly in the oropharyngeal, laryngeal, lung[14,28,30,32,46], esophageal[46], skin[27], and kidney-bladder locations[46].

Periodic patient controls in outpatient clinic and patient education on the importance of preventive screenings are of vital importance. Thus, all OLT candidates should be encouraged to cease smoking and alcohol intake (for a minimum period of 6 mo to be included on the transplant waiting list). After OLT for AC, the recipients should continue with complete alcohol abstinence, avoidance of tobacco consumption, using sun protection with sunscreen and limiting sun exposure, undergo regular skin assessments, and routinely adhere to cancer screening tests[112,113]. Annual oto-pharyngo-laryngeal evaluation is advised in order to obtain early tumor detection[113]. Smokers of more than 20 pack-years who are actively smoking or have ceased tobacco abuse less than 10 years before OLT should be subjected every year to otolaryngeal evaluation and low-radiation CT scan[114]. Other authors only recommend annual chest X-rays for lung tumor screening[113].

IMMUNOSUPPRESSION CHANGES AS PREVENTION OR TREATMENT OF *DE NOVO* TUMORS

In long-term follow-up the maintenance drugs (CyA and tacrolimus) are associated with side effects such as cardiovascular complications, nephrotoxicity, neurotoxicity, diabetes, hepatocarcinoma recurrence, and the development of *de novo* malignancies[1,115,116]. The main objective is to get effective immunosuppression, while no promoting cancer development[117].

Higher degrees of immunosuppression increase the risk of tumor after transplant in a dose-dependent manner[118]. Recently, two immunosuppressive drugs, mycophenolate mofetil[119,120], and the inhibitors of mammalian target of rapamycin (mTORi: sirolimus and everolimus)[121-123] have shown protective effects against the development of cancer. However, there are no published controlled trials evaluating the effect of mTORi in preventing *de novo* tumors or recurrence of hepatocarcinoma after OLT[117,124].

Although much additional research is needed, several studies indicate that m-TORi may be effective in the prevention of malignancies, since a significantly reduced incidence of *de novo* malignancies was demonstrated when rapamycin was used alone or in combination with a reduced dose of CyA or tacrolimus[125], or combined with steroids only[126]. In addition, there is clinical evidence of the ability of sirolimus to suppress cancer progression in humans, as has been demonstrated in several kidney transplant series, 2 cases of complete remission of cutaneous Kaposi's sarcoma[127], and 12 cases of remission of *de novo* lymphoma[128]. A multicenter prospective clinical trial assessing the effectiveness of mTORi in avoiding the development of malignancies after OLT is currently under way in patients transplanted for hepatocarcinoma[129].

Nevertheless, the remarkable reduction of all *de novo* posttransplant malignancies and the excellent regression/control of the most common tumors in the early stages with mTORi immunosuppression is a strong reason to expand the role of mTORi in maintenance immunosuppressive therapy[130]. Immunosuppression protocols using sirolimus or everolimus monotherapy to replace calcineurin inhibitors (CNI) in patients who underwent OLT for hepatocarcinoma or who developed *de novo* tumors have been recommended because of their antitumor properties, absence of nephrotoxicity, well tolerated adverse events, and potent immunosuppressive effect, which prevents rejection, especially in recipients with long-term follow-up who have developed some tolerance[123,131-134]. In our preliminary experience using sirolimus monotherapy in 16 patients who developed post-OLT malignancies we did not see any case of acute rejection during a mean follow-up of 15.7 mo. The mean period elapsed from OLT to sirolimus monotherapy was 86 mo, and the mean

trough level of sirolimus was 8.9 ng/mL[131]. Recently, we published our experience of 57 patients using everolimus monotherapy (24 patients) or everolimus combined with low doses of CNI (33 patients) mainly in patients who underwent OLT for hepatocarcinoma (monotherapy, 9 patients; combined, 21 patients), or who developed *de novo* malignancies after OLT (monotherapy, 13 patients; combined, 6 patients); we observed only one case of acute rejection, improved renal function, and good tolerance of adverse effects[123]. In summary, independently of their antineoplastic efficacy, sirolimus and everolimus, in combination with low doses of CNI or as monotherapy at least one year after OLT, are safe and effective immunosuppresive drugs, which may be especially indicated in patients who underwent OLT for hepatocarcinoma or who are at high risk for development of *de novo* tumors (premalignant lesions, smokers or patients transplanted for AC).

CONCLUSION

Liver transplant recipients for AC are at higher risk than recipients with other etiologies for the development of post-OLT tumors, mainly due to frequent association of alcohol and tobacco consumption among these patients. *De novo* tumors related to AC patients are mainly located in the UAD tract, lung, skin and bladder-kidney. With the exception of skin tumors, these malignancies have very poor prognosis. Thus, strict surveillance (otolaryngeal exploration and yearly chest CT scan), and avoidance of alcohol and tobacco consumption should be advised to AC recipients in order to prevent the development of *de novo* malignancies or to obtain an early tumor diagnosis. Although the clinical antineoplastic efficacy of mTORi is not yet unambiguously demonstrated, a decreased CNI dose or substitution with mTORi after a minimun period of one year after OLT has been proposed in order to avoid hepatocarcinoma recurrence or the development of *de novo* tumors.

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