World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v22.i1.427

World J Gastroenterol 2016 January 7; 22(1): 427-434
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

MINIREVIEWS

Solid, non-skin, post-liver transplant tumors: Key role of lifestyle and immunosuppression management

Christophe Carenco, Stéphanie Faure, José Ursic-Bedoya, Astrid Herrero, Georges Philippe Pageaux

Christophe Carenco, Stéphanie Faure, José Ursic-Bedoya, Astrid Herrero, Georges Philippe Pageaux, Liver Transplant Unit, CHRU Montpellier, 34090 Montpellier, France

Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Conflict-of-interest statement: No potential conflicts of interest. No financial support.

Correspondence to: Georges Philippe Pageaux, Professor, Liver Transplant Unit, CHRU Montpellier, 191 Avenue du Doyen Gaston Giraud, 34090 Montpellier, France. gp-pageaux@chu-montpellier.fr
Telephone: +33-4-67337061
Fax: +33-4-99632247

Received: September 1, 2015
Peer-review started: September 1, 2015
First decision: September 29, 2015
Revised: October 18, 2015
Accepted: November 13, 2015
Article in press: November 13, 2015
Published online: January 7, 2016

Abstract

Liver transplantation has been the treatment of choice for end-stage liver disease since 1983. Cancer has emerged as a major long-term cause of death for liver transplant recipients. Many retrospective studies that have explored standardized incidence ratio have reported increased rates of solid organ cancers post-liver transplantation; some have also studied risk factors. Liver transplantation results in a two to five-fold mean increase in the rate of solid organ cancers. Risk of head and neck, lung, esophageal, cervical cancers and Kaposi's sarcoma is high, but risk of colorectal cancer is not clearly demonstrated. There appears to be no excess risk of developing breast or prostate cancer. Environmental risk factors such as viral infection and tobacco consumption, and personal risk factors such as obesity play a key role, but recent data also implicate the role of calcineurin inhibitors, whose cumulative and dose-dependent effects on cell metabolism might play a direct role in oncogenesis. In this paper, we review the results of studies assessing the incidence of non-skin solid tumors in order to understand the mechanisms underlying solid cancers in post-liver transplant patients and, ultimately, discuss how to prevent these cancers. Immunosuppressive protocol changes, including a calcineurin inhibitor-free regimen, combined with dietary guidelines and smoking cessation, are theoretically the best preventive measures.

Key words: Liver transplantation; Tumors; Calcineurin inhibitors; Immunosuppression; Risk factors; Tacrolimus; Review; Incidence

Core tip: Liver transplantation results in two to five-fold mean increase in the rate of solid organ cancers. In this paper, we review the results of studies assessing the incidence of non-skin solid tumors in post-liver transplant patients to understand the mechanisms underlying solid cancers in these patients, and discuss how to prevent these cancers. Risk of smoking and viral-related malignancies is high, but recent data

also implicate the role of calcineurin inhibitors, whose cumulative and dose-dependent effects on cell metabolism might play a direct role in oncogenesis.

Carenco C, Faure S, Ursic-Bedoya J, Herrero A, Pageaux GP. Solid, non-skin, post-liver transplant tumors: Key role of lifestyle and immunosuppression management. *World J Gastroenterol* 2016; 22(1): 427-434 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i1/427.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i1.427

INTRODUCTION

Liver transplantation (LT) has been the treatment of choice for end-stage liver disease since 1983[1], and more than 5500 of these procedures are performed in Europe each year[2]. Infections and surgical complications are the primary causes of mortality during the early post-transplantation period. However, cancer has emerged as a major long-term cause of death in liver transplant recipients[2-5].

The rate of post-transplant lymphoproliferative disorders (PTLD) and skin cancers is 10 to 30-fold higher than for the general population[6-9]. The calcineurin inhibitors (CNIs), tacrolimus (TL) and cyclosporine, which are the cornerstones of all immunosuppressive treatments used following LT, are well-established risk factors for PTLD[10] and cutaneous cancers[11].

Recently, many studies have compared the incidence of *de novo* solid tumors in the general population to liver transplant recipients, and the risk factors involved. These studies have demonstrated that patients who receive a liver transplant often have well-established or suspected risk factors for solid cancers: (1) Tobacco and/or alcohol consumption before transplantation is extremely common in patients, especially those who undergo LT for alcoholic cirrhosis, which account for 36% of the LTs performed in Europe[2]. Continued smoking after LT is common, and resumption of alcohol consumption is not unusual; (2) CNI exposure occurs with all liver transplant patients. It promotes infection by viruses that have oncogenic potential such as human papilloma virus (HPV) and herpes human virus 8 (HHV8). CNIs may also have direct oncogenic effects; and (3) Metabolic syndromes, particularly obesity and diabetes, are common before the LT, and they are further exacerbated by exposure to CNIs after the LT.

In this review we specifically study the literature on the incidence and risk factors for non-skin solid cancers after LT.

LT RESULTS IN A TWO TO FIVE-FOLD MEAN INCREASE IN THE RATE OF SOLID ORGAN CANCERS

In an observational study using the United Kingdom transplant database[9], which contains 6771 liver transplant recipients, the standardized incidence ratio (SIR) was 2.2 for non-skin solid tumors following an LT. Similar results were found in smaller cohorts[6,8,11-17] in Italy (SIR = 2.6), the Netherlands (SIR = 4.4), Spain (SIR = 2.3), France (SIR = 3.7), and Canada (SIR = 2.5). These results are summarized in Table 1. In another Italian study[18], the incidence rate of non-skin solid tumors did not increase after LT; however, this study had the shortest median follow-up time.

Overall, the risk of developing a post-LT non-skin solid tumor is high, as confirmed by several studies comparing liver transplant recipients with the sex and age-matched general population, both in large-scale registry studies and single-center studies. Median time to develop post-LT non-skin solid tumor was 4.2 years in Baccarani[8] cohort and 5 years in Haagsma[4] and Aberg[6] cohorts. In our cohort of 465 patients[13], the median time to diagnosis of solid cancers after LT was 6.3 ± 4.3 years (6 years median). Indeed, sufficient follow-up time is necessary in order to highlight the elevated risk of solid tumors.

INCIDENCE AND RISK OF SITE-SPECIFIC CANCERS

Risk of smoking-related malignancies is high

Head and neck cancers have the highest increased risk in all of the European cohorts (SIR of 2.7-15.8, Table 1). A non-significant increased risk was also found in Canadian[14], Taiwanese[15], and Japanese[16] studies.

An elevated risk of lung cancer has been established, although it is not encountered in all studies. Indeed, in the United States the NKKD cohort[7] demonstrated a SIR of 1.9 for lung cancer in 37958 liver transplant recipients, and a SIR of 1.6 was found in the United Kingdom transplant registry of 6771 patients[9].

Three studies[8,13,16] found an increased risk of esophageal cancer (SIR of 10.5-23.4).

Finally, the risk of cancer of the urological tract was significantly higher in three studies[12,15,17] after LT (SIR of 2.9-6.2).

Risk of virus-related malignancies is well established

The relative risk of developing Kaposi's sarcoma was high in two Italian studies, with a SIR of 144 and 128 for the Baccarani *et al*[8] and Maggi *et al*[17] studies, respectively; however, this cancer is an exception and it mainly occurs in Mediterranean populations. It is related to HHV8 infection. The highest incidence is found in Saudi Arabia, and the lowest incidence is in Western nations, such as the United States[19].

In a study by Baccarani *et al*[8] an excessive risk of cervical malignancies was found, with a SIR of 30.7; this was probably related to HPV infection.

Risk of colorectal cancer is probably increased

The excess risk of colorectal cancer (CRC) remains

Table 1 Standardized incidence ratio (95%CI) of non-skin solid cancer after liver transplantation, *n* (range)

Ref.	LT patients (*n*)	Country	Median follow-up time (yr)	All non-skin solid tumors	Head and neck	Lung	Colorectal	Anal	Esophageal	Pancreatic	Kidney	Prostate	Urological tract	Kaposi's sarcoma	Breast	Cervical
Engels *et al*[7]	37958	United States				1.9 (1.7-2.2)					1.8 (1.4-2.3)					
Collett *et al*[9]	6771	United Kingdom		2.2 (2-2.4)	10 (5.9-16)	1.6 (1.2-2.2)	2.3 (1.7-3)	3.3 (0.4-12)			1.8 (0.8-3.6)			0	0.8 (0.5-1.1)	
Ettorre *et al*[18]	1675	Italy	5.2	0.9 (0.7-1.2)	4.5 (2.7-7.1)	1.1 (0.9-1.9)	1.2 (0.6-2.2)			1.1 (0.3-3.9)			0.8 (0.3-1.6)		0.7 (0.1-1.9)	
Aberg *et al*[6]	540	Finland	6.3		14.8 (0.4-82)	0	1.6 (0.2-5.7)			2.3 (0.1-13)	4.2 (0.5-15)	1.2 (0.2-4.5)			0.3 (0.1-1.4)	
Herrero *et al*[12]	297	Spain	6.5	2.34 (1.7-3.2)	4.1 (1.7-8.5)	2.4 (0.6-4)	2.5 (1.3-3.5)						2.9 (1.7-4.8)			
Baccarani *et al*[8]	417	Italy	6.8	2.6 (1.9-3.6)	7 (3-13.7)	1.6 (0.4-4.1)	1.4 (0.2-5.1)		23.4 (4.6-55)					144 (53-313)	0.6 (0-3.4)	30.7 (6.3-90)
Jiang *et al*[14]	2034	Canada		2.5 (2.1-3)	2.5 (0.5-7.3)	1.4 (0.7-2.6)	2.6 (1.4-4.4)			3.3 (0.7-9.6)	3.1 (0.8-7.9)	1 (0.3-2.4)			0.6 (0.2-1.4)	
Haagsma *et al*[4]	174	The Netherlands	5.1	4.4 (2.4-7.3)	2.7 (1.2-5.2)		12.5 (2.5-36)				30 (6.1-87)					
Hsiao *et al*[15]	444	Taiwan	4.2		0 (0-5.7)	1.9 (0.2-6.7)	0 (0-2.84)			6.2 (0.1-34)			10.2 (1.1-36)	0	2.3 (0.3-8.4)	
Kaneko *et al*[16]	360	Japan	7.5		3.7 (0.5-26)		3.5 (1.8-7)		16.9 (2.4-18)	6.4 (1.6-25)		2.2 (0.6-8.9)			0.9 (0.1-6.4)	
Maggi *et al*[17]	494	Italy	7.2	2 (1.4-2.9)	3.4 (0.9-8.8)	2.1 (0.8-4.6)	1.6 (0.3-4.6)					1.6 (0.4-4.1)	2.9 (1-6.9)	128 (51-263)	1 (0.2-2.9)	5.7 (0.1-32)
Carenco *et al*[13]	465	France	7.8	3.7 (2.8-4.9)	15.8 (9.4-27)	5.1 (2.9-9)	2.7 (1.3-5.6)		10.5 (3.9-28)					0		

SIR: Standardized incidence ratio.

unclear. An increased risk was found in four European studies[4,9,12,13], one Japanese study[17], and one Canadian study[14]. This risk was not observed in three Italian studies[8,17,18] and one Taiwanese study[15]. However, in a meta-analysis, Sint Nicolaas[20] found that the risk of developing CRC was 2.5 times higher (95%CI: 1.65-4.05) in liver transplant recipients.

Excess risk of developing kidney, pancreatic, or brain cancer is not proven

The risk of developing kidney cancer after LT remains unclear. In the NKKD cohort[7] and a cohort in a study by Haagsma *et al*[4], the incidences of kidney cancer were significantly higher than expected compared with the general population. However, this was not the case for a cohort in the United Kingdom[9], and in two other studies[6,13].

Only one Japanese study[16] has found a significantly increased risk of pancreatic cancer after LT, but this result has not been confirmed by other studies.

To the best of our knowledge, there are no solid data regarding the development of brain cancer in liver transplant recipients. Engels[7] did not show excess risk in 175732 organ transplant recipients.

There is no excess risk of developing breast or prostate cancer

No study to date has shown an increased risk of prostate or breast cancer after LT, although these are among the most common malignancies in the general adult population. Indeed, in a meta-analysis of 31977 solid organ transplant recipients (97% were renal transplants)[21] there was no evidence for a significantly increased SIR for breast or prostate cancer.

Prospective cohort studies with large numbers of liver transplant recipients, a rigorous collection of *de novo* solid cancers after LT, risk factor data, and sufficient follow-up times are necessary to obtain accurate information about the risk of each site-specific cancer. Indeed, current data do not allow elucidation of the risk of kidney, brain, stomach, pancreatic, and anal cancer after LT.

Table 2 Risk factors for non-skin solid tumors after liver transplantation from multivariate analyses

	Ref.	Risk factor	Associated cancer	SIR, HR, RR, or OR (95%CI)
Viral infection	Baccarani *et al*[8]	HPV exposure	Cervical	SIR = 30.7 (6.3-90)
	Collett *et al*[9]		Anal	SIR = 3.3 (0.4-12)
	Baccarani *et al*[8]	HHV8 exposure	Kaposi's sarcoma	SIR = 144 (53-313)
	Maggi *et al*[17]			SIR = 128 (51-263)
Demographic data	Herrero *et al*[22]	Recipient's age	All non-skin tumors	HR = 1.90 (1.32-2.73)
	Watt *et al*[23]		All non-skin solid tumors	HR = 1.33 (1.05-1.66)
	Herrero *et al*[34]		Smoking-related tumors	HR = 1.09 (1.03-1.15)
Indication for LT	Watt *et al*[23]	Alcohol cirrhosis	All non-skin solid tumors	HR = 2.14 (1.22-3.73)
		Primary sclerosis cholangitis	All non-skin solid tumors	HR = 2.62 (1.50-4.56)
Lifestyle	Benlloch *et al*[53]	Alcohol consumption	All non-skin tumors	RR = 3 (1.5-5.8)
	Herrero *et al*[22]			HR = 2.87 (1.15-7.19)
	Herrero *et al*[22]	Tobacco consumption	All non-skin tumors	HR = 3.07 (1.32-7.16)
	Watt *et al*[23]		All non-skin solid tumors	HR = 1.72 (1.06-2.79)
	Carenco *et al*[13]			OR = 5.5 (2.5-12)
	Herrero *et al*[34]		Smoking-related tumors	HR = 19.17 (4.17-88.10)
	Carenco *et al*[13]			OR = 14.7 (1.8-119)
	Carenco *et al*[13]	Obesity	All non-skin solid tumors	OR = 2.2 (1.1-4.3)
Immunosuppression	Carenco *et al*[49]	Mean tacrolimus TC during first year post-LT	All non-skin solid tumors	OR = 2.01 (1.57-2.59)

SIR: Standardized incidence ratio; HPV: Human papilloma virus; HHV8: Herpes human virus 8; HR: Hazard ratio; RR: Relative risk; OR: Odds ratio; CI: Confidence interval; TC: Through concentration.

RISK FACTORS FOR NON-SKIN SOLID MALIGNANCIES

Environmental risk factors

Viral infection: In a meta-analysis involving 31977 solid organ transplant recipients (97% of whom were renal transplants) Grulich[21] demonstrated a high risk of HHV8-related cancer (Kaposi's sarcoma) and HPV-related cancer (cervical, anal, vulval, vaginal, and penile cancer, as well as head and neck cancer) in these immunocompromised patients. In this study, similar results were found for people with HIV/AIDS. This further supports the notion that the risk of infection with an oncovirus and, consequently, the risk of cancer, is increased in immunocompromised patients (Table 2).

Is this also the case for liver transplant recipients who require a lower level of immunosuppression than that received by kidney transplant recipients? Kaposi's sarcoma is rare in the general population; several studies have described an incidence of 0.5%-2.8% for this disease after LT[22-24]. As shown by the Italian studies[8,17], Kaposi's sarcoma occurs much more frequently in patients living in areas where HHV8 is endemic[25,26], compared to the general population, while none of the 6846 liver transplant recipients developed this cancer in the United Kingdom cohort[9].

Out of 417 post-LT patients, Baccarani[8] encountered three patients with cervical cancer (0.7%), which was 30 times more than expected. It has been shown that before solid organ transplant, 29% of patients were infected with a high-oncogenic potential HPV serotype[27]. Moreover, it is now established that HPV infection is a risk factor for epidermoid head and neck carcinomas[28], which could partly explain the high rate of these cancers after LT.

Long-term immunodeficiency places liver transplant recipients at risk of oncoviral infection, which is conducive to malignancy and necessitates efficient management of the immunosuppressive therapy.

Alcohol and tobacco consumption: For the general population, tobacco and alcohol consumption are known risk factors for oral, pharyngeal, laryngeal, esophageal, and upper airway tumors[29-32]. There is a synergistic effect when patients are exposed to both tobacco and alcohol; the risk of these tumors is more than seven times higher in heavy drinkers and smokers[30-33].

Using a multivariate analysis in a retrospective study of 722 liver transplant patients, previous alcohol abuse was associated with a three-fold risk of developing a *de novo* tumor following LT (P = 0.002, 95%CI: 1.5-5.8)[33]. In a smaller cohort, using a multivariate model, Herrero *et al*[22] found a hazard ratio of 2.87 (95%CI: 1.15-7.19) of developing a non-skin tumor after LT among patients who consumed large amounts of alcohol. In two other studies[17,23], patients who received a transplant for alcoholic cirrhosis had a higher risk of non-skin solid cancers after LT, but alcohol consumption was not an independent cancer risk factor, unlike tobacco use. We found similar results in a study with 465 patients[13]: using a univariate analysis, alcohol consumption was a risk factor for developing a solid cancer, but in multivariate analysis it was not an independent risk factor, unlike tobacco consumption and obesity before LT.

A history of smoking is common in patients who undergo LT for alcoholic liver disease, and tobacco consumption is now an independent risk factor for the development of a non-skin solid cancer after LT[13,22,23]. Herrero *et al*[34] specifically described the incidence and risk factors for "smoking-related malignancies" (SRM), defined as head and neck, esophageal, kidney, and urinary tract carcinomas, in 339 liver transplant recipients. Compared to a sex and age-matched general population, they observed a relative risk of 8.5 for the development of SRM in active smokers, and 4.4 in former smokers *vs* 0.36 in patients who never smoked. In a multivariate analysis, significant smoking was an independent risk factor, with a hazard ratio of 19.

Interestingly, in our cohort of 465 liver transplant recipients[13], 38 patients developed an SRM, and tobacco consumption before and after the LT were the only independent risk factors found when using a multivariate analysis. Therefore, it is paramount that all patients cease tobacco and alcohol consumption prior to and after LT.

Personal risk factors

Age and gender: Age is a well-established risk factor for solid cancer in the general population. Using a multivariate analysis, Herrero *et al*[22] and Watt *et al*[23] concluded that this is also the case for liver transplant recipients. In our series of 465 patients[13], we did not find this to be a risk factor, probably due to the low standard deviation of age within our patient cohort.

Numerous single-center studies have failed to find a statistically significant difference between male and female liver transplant recipients in terms of the development of *de novo* solid tumors using a multivariate analysis after LT[13,15,22,23]. This is probably because of the much greater weight of other risk factors.

Obesity: Liver transplant recipients often present with a metabolic syndrome before transplantation, or develop it after the procedure; these syndromes can be triggered and aggravated by anti-calcineurins and corticosteroids[35].

In our series of 465 patients[13], 27.4% of the 65 patients who developed a non-skin solid tumor after LT were obese, *vs* 15.8% of the rest of the cohort. Using a multivariate analysis, we found that obesity and tobacco consumption before LT were independent risk factors for non-skin solid tumors. Interestingly, in a subgroup analysis of 427 patients with 27 different cancers (eight colorectal, eight prostate, four breast, and seven other types of cancer), obesity was the only independent risk factor after excluding smoking-induced cancer (head and neck, lung, esophageal, and urinary tract cancer). To the best of our knowledge, there are no other studies that have investigated this risk factor after LT, although obesity and excess body weight are independent risk factors for breast, endometrial, esophageal, and colorectal cancers in the general population[36].

In addition to cardiovascular complications that can cause obesity, it seems that obesity could be responsible for non-skin solid cancers after LT. Regular physical activity and a balanced diet are essential for these patients.

Specific LT risk factors

Indications for LT: The incidence of CRC after LT differs depending on the series; it has been found to range from 0.03% to 3.1%[4-9,16,23,37]. This spread can be explained by the proportion of patients who received a transplant for primary sclerosing cholangitis (PSC) in association with chronic inflammatory bowel disease (IBD). Indeed, Watt *et al*[23] found 25 cases of CRC in 798 liver transplant recipients (3.1%); 127 (15.9%) of these patients received LT for PSC. This variable was the strongest risk factor for developing a solid cancer after LT, and reflects the high risk of CRC in patients with IBD.

In Europe, PSC represents 4% of LT indications[2], yet in a study of a large series the incidence of CRC was two to three times higher than that observed in the general population[9]. This was also observed in a single-center study in Japan[16], with one patient transplanted for PSC. In our series of 465 patients[13], only six patients received a transplant for PSC, and none of the patients developed CRC; however, in the entire study, we found an incidence of CRC that was 2.7 times higher than expected. Moreover, in a meta-analysis excluding patients transplanted for PSC, Sint Nicolaas[20] found a 1.8-fold higher risk of CRC after LT.

Why do non-PSC liver transplant recipients appear to have an increased risk of CRC? John Cunningham virus (JCV) reactivation in adenomas could be a possible mechanism for this increased risk[38]. Another possibility could be the presence of precursor lesions for CRC before the LT. A case-control study found that 7.3% of the 82 liver transplant recipients developed advanced neoplasia, compared to 1.2% in the 82 control patients from the general population[39]. Another study retrospectively identified 92 liver transplant recipients who underwent a screening colonoscopy; the relative risk for advanced neoplasia was 8.9 compared to a large asymptomatic cohort[40].

CNI exposure: As well as their ability to promote infection by viruses with oncogenic potential, there is evidence from animal studies that suggests CNIs also have carcinogenic potential. This may be caused by activation of the Ras pathway[41], induction of tumor growth and metastatic potential from TGF-β1 activation[42,43], and disruption of angiogenesis and

apoptosis[44-46].

In a study of kidney transplant recipients by Dantal *et al*[47] the incidence of cancer (mainly skin malignancies) was higher in patients with elevated cyclosporine target levels (*e.g.*, 150-250 ng/mL *vs* 75-125 ng/mL). More recently, in liver transplant recipients, Vivarelli *et al*[48] found a higher risk of hepatocellular carcinoma recurrence in patients exposed to higher doses of anti-calcineurin, either cyclosporine or TC, during the first three months after LT.

We monitored the blood concentrations of TC in 247 patients treated with TC for at least one year after LT[49]. The mean TC concentration during the first year after LT was significantly higher in patients who developed non-skin solid tumors (10.3 and 7.9 ng/mL, respectively, $P < 0.0001$). The independent risk factors for developing solid cancer using a multivariate analysis were tobacco consumption before the LT, and the mean annual TC concentration during the first year after LT. Indeed, a model that takes into account smoking and mean TC concentration during the first year after LT strongly predicted the occurrence of a solid cancer in our sample population.

How can we change our immunosuppression strategies to prevent cancer? In liver transplant recipients, short-term complications are dominated by infections and post-operative complications; rejection is less problematic than in other organ transplantations. Acute cellular rejection is a rare event that may be easily controlled either with an increase in TC or a bolus of steroids.

Therefore, it might be interesting to rapidly decrease CNI concentrations to minimize the risk of solid cancer after LT. To avoid organ rejection, one could use drugs that block proliferative signaling, such as mTOR inhibitors. mTOR inhibitors have major immunosuppressive activity through their intracellular binding to FKBP12 and inhibition of mTORC1, which blocks cell cycle progression and IL-2 signaling in T cells. Indeed, these are already used in patients with CNI-related nephrotoxicity. As well as their immunosuppressive properties, these drugs have anti-oncogenic effects in preclinical models, and they are currently being investigated as anti-cancer agents in clinical trials[50]. For kidney transplantations, the CONVERT trial[51] has demonstrated lower cancer rates (mainly skin cancer) in renal allograft recipients who were switched to a sirolimus-based, CNI-free immunosuppressive treatment.

However, mTOR inhibitors have significant side effects, including rejection, delayed wound healing, mouth ulcers, and leg edema, and there is a 46% discontinuation rate among renal transplant recipients[52]. Therefore, data for liver transplant recipients from large cohorts are needed to accurately determine the risk/benefit balance of using mTOR inhibitors before they can become routine treatment for all patients.

CONCLUSION

In conclusion, *de novo* malignancy is currently the second-leading cause of death for liver transplant recipients after cardiovascular complications, and the risk of developing a non-skin solid tumor is high. This risk is higher than that observed in the general population, especially for smoking-induced cancers (head and neck, lung, and esophageal), CLC, and virus-induced cancers (cervical and Kaposi's sarcoma).

While the role of alcohol and tobacco consumption in this high rate of solid cancers is indisputable, recent data also implicate the role of CNIs, whose cumulative and dose-dependent effects on cell metabolism might play a direct role in oncogenesis. Therefore, it is paramount that LT patients cease alcohol and tobacco consumption before and after transplantation, and that the minimum dose of CNI is administered to reduce the risk of malignancy, while still preventing graft rejection.

In the future, we will evaluate the safety and efficacy of CNI-free regimens through prospective studies.

REFERENCES

1 National Institutes of Health Consensus Development Conference Statement: liver transplantation--June 20-23, 1983. *Hepatology* 1984; **4**: 107S-110S [PMID: 6363254]

2 **Adam R**, Karam V, Delvart V, O'Grady J, Mirza D, Klempnauer J, Castaing D, Neuhaus P, Jamieson N, Salizzoni M, Pollard S, Lerut J, Paul A, Garcia-Valdecasas JC, Rodríguez FS, Burroughs A. Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). *J Hepatol* 2012; **57**: 675-688 [PMID: 22609307 DOI: 10.1016/j.jhep.2012.04.015]

3 **Gelson W**, Hoare M, Dawwas MF, Vowler S, Gibbs P, Alexander G. The pattern of late mortality in liver transplant recipients in the United Kingdom. *Transplantation* 2011; **91**: 1240-1244 [PMID: 21516069 DOI: 10.1097/TP.0b013e31821841ba]

4 **Haagsma EB**, Hagens VE, Schaapveld M, van den Berg AP, de Vries EG, Klompmaker IJ, Slooff MJ, Jansen PL. Increased cancer risk after liver transplantation: a population-based study. *J Hepatol* 2001; **34**: 84-91 [PMID: 11211912 DOI: 10.1016/S0168-8278(00)00077-5]

5 **Watt KD**, Pedersen RA, Kremers WK, Heimbach JK, Charlton MR. Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. *Am J Transplant* 2010; **10**: 1420-1427 [PMID: 20486907 DOI: 10.1111/j.1600-6143.2010.03126.x]

6 **Aberg F**, Pukkala E, Höckerstedt K, Sankila R, Isoniemi H. Risk of malignant neoplasms after liver transplantation: a population-based study. *Liver Transpl* 2008; **14**: 1428-1436 [PMID: 18825704 DOI: 10.1002/lt.21475]

7 **Engels EA**, Pfeiffer RM, Fraumeni JF, Kasiske BL, Israni AK, Snyder JJ, Wolfe RA, Goodrich NP, Bayakly AR, Clarke CA, Copeland G, Finch JL, Fleissner ML, Goodman MT, Kahn A, Koch L, Lynch CF, Madeleine MM, Pawlish K, Rao C, Williams MA, Castenson D, Curry M, Parsons R, Fant G, Lin M. Spectrum of cancer risk among US solid organ transplant recipients. *JAMA* 2011; **306**: 1891-1901 [PMID: 22045767 DOI: 10.1001/jama.2011.1592]

8 **Baccarani U**, Piselli P, Serraino D, Adani GL, Lorenzin D, Gambato M, Buda A, Zanus G, Vitale A, De Paoli A, Cimaglia C, Bresadola V, Toniutto P, Risaliti A, Cillo U, Bresadola F, Burra P. Comparison

of de novo tumours after liver transplantation with incidence rates from Italian cancer registries. *Dig Liver Dis* 2010; **42**: 55-60 [PMID: 19497797 DOI: 10.1016/j.dld.2009.04.017]

9 **Collett D**, Mumford L, Banner NR, Neuberger J, Watson C. Comparison of the incidence of malignancy in recipients of different types of organ: a UK Registry audit. *Am J Transplant* 2010; **10**: 1889-1896 [PMID: 20659094 DOI: 10.1111/j.1600-6143.2010.03181.x]

10 **Bakker NA**, van Imhoff GW, Verschuuren EA, van Son WJ. Presentation and early detection of post-transplant lymphoproliferative disorder after solid organ transplantation. *Transpl Int* 2007; **20**: 207-218 [PMID: 17291214 DOI: 10.1111/j.1432-2277.2006.00416.x]

11 **Mithoefer AB**, Supran S, Freeman RB. Risk factors associated with the development of skin cancer after liver transplantation. *Liver Transpl* 2002; **8**: 939-944 [PMID: 12360438]

12 **Herrero JI**, Alegre F, Quiroga J, Pardo F, Iñarrairaegui M, Sangro B, Rotellar F, Montiel C, Prieto J. Usefulness of a program of neoplasia surveillance in liver transplantation. A preliminary report. *Clin Transplant* 2009; **23**: 532-536 [PMID: 19681977 DOI: 10.1111/j.1399-0012.2008.00927.x]

13 **Carenco C**, Faure S, Herrero A, Assenat E, Duny Y, Danan G, Bismuth M, Chanques G, Ursic-Bedoya J, Jaber S, Larrey D, Navarro F, Pageaux GP. Incidence of solid organ cancers after liver transplantation: comparison with regional cancer incidence rates and risk factors. *Liver Int* 2015; **35**: 1748-1755 [PMID: 25488375 DOI: 10.1111/liv.12758]

14 **Jiang Y**, Villeneuve PJ, Fenton SS, Schaubel DE, Lilly L, Mao Y. Liver transplantation and subsequent risk of cancer: findings from a Canadian cohort study. *Liver Transpl* 2008; **14**: 1588-1597 [PMID: 18975293 DOI: 10.1002/lt.21554]

15 **Hsiao CY**, Lee PH, Ho CM, Wu YM, Ho MC, Hu RH. Post-transplant malignancy in liver transplantation: a single center experience. *Medicine* (Baltimore) 2014; **93**: e310 [PMID: 25526480 DOI: 10.1097/MD.0000000000000310]

16 **Kaneko J**, Sugawara Y, Tamura S, Aoki T, Sakamoto Y, Hasegawa K, Yamashiki N, Kokudo N. De novo malignancies after adult-to-adult living-donor liver transplantation with a malignancy surveillance program: comparison with a Japanese population-based study. *Transplantation* 2013; **95**: 1142-1147 [PMID: 23572128 DOI: 10.1097/TP.0b013e318288ca83]

17 **Maggi U**, Consonni D, Manini MA, Gatti S, Cuccaro F, Donato F, Conte G, Bertazzi PA, Rossi G. Early and late de novo tumors after liver transplantation in adults: the late onset of bladder tumors in men. *PLoS One* 2013; **8**: e65238 [PMID: 23785414 DOI: 10.1371/journal.pone.0065238]

18 **Ettorre GM**, Piselli P, Galatioto L, Rendina M, Nudo F, Sforza D, Miglioresi L, Fantola G, Cimaglia C, Vennarecci G, Vizzini GB, Di Leo A, Rossi M, Tisone G, Zamboni F, Santoro R, Agresta A, Puro V, Serraino D. De novo malignancies following liver transplantation: results from a multicentric study in central and southern Italy, 1990-2008. *Transplant Proc* 2013; **45**: 2729-2732 [PMID: 24034034 DOI: 10.1016/j.transproceed.2013.07.050]

19 **Penn I**. Posttransplant malignancies. *Transplant Proc* 1999; **31**: 1260-1262 [PMID: 10083562]

20 **Sint Nicolaas J**, de Jonge V, Steyerberg EW, Kuipers EJ, van Leerdam ME, Veldhuyzen-van Zanten SJ. Risk of colorectal carcinoma in post-liver transplant patients: a systematic review and meta-analysis. *Am J Transplant* 2010; **10**: 868-876 [PMID: 20420641 DOI: 10.1111/j.1600-6143.2010.03049.x]

21 **Grulich AE**, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet* 2007; **370**: 59-67 [PMID: 17617273 DOI: 10.1016/S0140-6736(07)61050-2]

22 **Herrero JI**, Lorenzo M, Quiroga J, Sangro B, Pardo F, Rotellar F, Alvarez-Cienfuegos J, Prieto J. De Novo neoplasia after liver transplantation: an analysis of risk factors and influence on survival. *Liver Transpl* 2005; **11**: 89-97 [PMID: 15690541 DOI: 10.1002/lt.20319]

23 **Watt KD**, Pedersen RA, Kremers WK, Heimbach JK, Sanchez W, Gores GJ. Long-term probability of and mortality from de novo malignancy after liver transplantation. *Gastroenterology* 2009; **137**: 2010-2017 [PMID: 19766646 DOI: 10.1053/j.gastro.2009.08.070]

24 **Farge D**. Kaposi's sarcoma in organ transplant recipients. The Collaborative Transplantation Research Group of Ile de France. *Eur J Med* 1993; **2**: 339-343 [PMID: 8252179]

25 **Bismuth H**, Samuel D, Venancie PY, Menouar G, Szekely AM. Development of Kaposi's sarcoma in liver transplant recipients: characteristics, management, and outcome. *Transplant Proc* 1991; **23**: 1438-1439 [PMID: 1989258]

26 **Jacobson LP**, Armenian HK. An integrated approach to the epidemiology of Kaposi's sarcoma. *Curr Opin Oncol* 1995; **7**: 450-455 [PMID: 8541391]

27 **Roka S**, Rasoul-Rockenschaub S, Roka J, Kirnbauer R, Mühlbacher F, Salat A. Prevalence of anal HPV infection in solid-organ transplant patients prior to immunosuppression. *Transpl Int* 2004; **17**: 366-369 [PMID: 15349721 DOI: 10.1111/j.1432-2277.2004.tb00456.x]

28 **Gillison ML**, D'Souza G, Westra W, Sugar E, Xiao W, Begum S, Viscidi R. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. *J Natl Cancer Inst* 2008; **100**: 407-420 [PMID: 18334711 DOI: 10.1093/jnci/djn025]

29 **Franceschi S**, Talamini R, Barra S, Barón AE, Negri E, Bidoli E, Serraino D, La Vecchia C. Smoking and drinking in relation to cancers of the oral cavity, pharynx, larynx, and esophagus in northern Italy. *Cancer Res* 1990; **50**: 6502-6507 [PMID: 2208109]

30 **Mashberg A**, Boffetta P, Winkelman R, Garfinkel L. Tobacco smoking, alcohol drinking, and cancer of the oral cavity and oropharynx among U.S. veterans. *Cancer* 1993; **72**: 1369-1375 [PMID: 8339227]

31 **Longnecker MP**. Alcohol consumption and risk of cancer in humans: an overview. *Alcohol* 1995; **12**: 87-96 [PMID: 7772271 DOI: 10.1016/0741-8329(94)00088-3]

32 **Castelli E**, Hrelia P, Maffei F, Fimognari C, Foschi FG, Caputo F, Cantelli-Forti G, Stefanini GF, Gasbarrini G. Indicators of genetic damage in alcoholics: reversibility after alcohol abstinence. *Hepatogastroenterology* 1999; **46**: 1664-1668 [PMID: 10430317]

33 **Kato I**, Nomura AM. Alcohol in the aetiology of upper aerodigestive tract cancer. *Eur J Cancer B Oral Oncol* 1994; **30B**: 75-81 [PMID: 8032304]

34 **Herrero JI**, Pardo F, D'Avola D, Alegre F, Rotellar F, Iñarrairaegui M, Martí P, Sangro B, Quiroga J. Risk factors of lung, head and neck, esophageal, and kidney and urinary tract carcinomas after liver transplantation: the effect of smoking withdrawal. *Liver Transpl* 2011; **17**: 402-408 [PMID: 21445923 DOI: 10.1002/lt.22247]

35 **Watt KD**. Metabolic syndrome: is immunosuppression to blame? *Liver Transpl* 2011; **17** Suppl 3: S38-S42 [PMID: 21761552 DOI: 10.1002/lt.22386]

36 **Calle EE**, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 2003; **348**: 1625-1638 [PMID: 12711737 DOI: 10.1056/NEJMoa021423]

37 **Chatrath H**, Berman K, Vuppalanchi R, Slaven J, Kwo P, Tector AJ, Chalasani N, Ghabril M. De novo malignancy post-liver transplantation: a single center, population controlled study. *Clin Transplant* 2013; **27**: 582-590 [PMID: 23808800 DOI: 10.1111/ctr.12171]

38 **Selgrad M**, Koornstra JJ, Fini L, Blom M, Huang R, Devol EB, Boersma-van Ek W, Dijkstra G, Verdonk RC, de Jong S, Goel A, Williams SL, Meyer RL, Haagsma EB, Ricciardiello L, Boland CR. JC virus infection in colorectal neoplasia that develops after liver transplantation. *Clin Cancer Res* 2008; **14**: 6717-6721 [PMID: 18927316 DOI: 10.1158/1078-0432.CCR-08-0961]

39 **Rudraraju M**, Osowo AT, Singh V, Carey EJ. Do patients need more frequent colonoscopic surveillance after liver transplantation? *Transplant Proc* 2008; **40**: 1522-1524 [PMID: 18589142 DOI: 10.1016/j.transproceed.2008.02.070]

40 **Koornstra JJ**, Wesseling J, de Jong AE, Vasen HF, Kleibeuker JH, Haagsma EB. Increased risk of colorectal neoplasia in asymptomatic liver-transplant recipients. *Gut* 2007; **56**: 892-893 [PMID: 17519499]

41 **Datta D**, Contreras AG, Basu A, Dormond O, Flynn E, Briscoe DM, Pal S. Calcineurin inhibitors activate the proto-oncogene Ras and promote protumorigenic signals in renal cancer cells. *Cancer Res* 2009; **69**: 8902-8909 [PMID: 19903851 DOI: 10.1158/0008-5472.CAN-09-1404]

42 **Hojo M**, Morimoto T, Maluccio M, Asano T, Morimoto K, Lagman M, Shimbo T, Suthanthiran M. Cyclosporine induces cancer progression by a cell-autonomous mechanism. *Nature* 1999; **397**: 530-534 [PMID: 10028970 DOI: 10.1038/17401]

43 **Maluccio M**, Sharma V, Lagman M, Vyas S, Yang H, Li B, Suthanthiran M. Tacrolimus enhances transforming growth factor-beta1 expression and promotes tumor progression. *Transplantation* 2003; **76**: 597-602 [PMID: 12923450]

44 **Yarosh DB**, Pena AV, Nay SL, Canning MT, Brown DA. Calcineurin inhibitors decrease DNA repair and apoptosis in human keratinocytes following ultraviolet B irradiation. *J Invest Dermatol* 2005; **125**: 1020-1025 [PMID: 16297204 DOI: 10.1111/j.0022-202X.2005.23858.x]

45 **Guba M**, von Breitenbuch P, Steinbauer M, Koehl G, Flegel S, Hornung M, Bruns CJ, Zuelke C, Farkas S, Anthuber M, Jauch KW, Geissler EK. Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. *Nat Med* 2002; **8**: 128-135 [PMID: 11821896 DOI: 10.1038/nm0202-128]

46 **Koehl GE**, Andrassy J, Guba M, Richter S, Kroemer A, Scherer MN, Steinbauer M, Graeb C, Schlitt HJ, Jauch KW, Geissler EK. Rapamycin protects allografts from rejection while simultaneously attacking tumors in immunosuppressed mice. *Transplantation* 2004; **77**: 1319-1326 [PMID: 15167584]

47 **Dantal J**, Hourmant M, Cantarovich D, Giral M, Blancho G, Dreno B, Soulillou JP. Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: randomised comparison of two cyclosporin regimens. *Lancet* 1998; **351**: 623-628 [PMID: 9500317 DOI: 10.1016/S0140-6736(97)08496-1]

48 **Vivarelli M**, Cucchetti A, La Barba G, Ravaioli M, Del Gaudio M, Lauro A, Grazi GL, Pinna AD. Liver transplantation for hepatocellular carcinoma under calcineurin inhibitors: reassessment of risk factors for tumor recurrence. *Ann Surg* 2008; **248**: 857-862 [PMID: 18948815]

49 **Carenco C**, Assenat E, Faure S, Duny Y, Danan G, Bismuth M, Herrero A, Jung B, Ursic-Bedoya J, Jaber S, Larrey D, Navarro F, Pageaux GP. Tacrolimus and the risk of solid cancers after liver transplant: a dose effect relationship. *Am J Transplant* 2015; **15**: 678-686 [PMID: 25648361 DOI: 10.1111/ajt.13018]

50 **Campistol JM**, Cuervas-Mons V, Manito N, Almenar L, Arias M, Casafont F, Del Castillo D, Crespo-Leiro MG, Delgado JF, Herrero JI, Jara P, Morales JM, Navarro M, Oppenheimer F, Prieto M, Pulpón LA, Rimola A, Román A, Serón D, Ussetti P. New concepts and best practices for management of pre- and post-transplantation cancer. *Transplant Rev* (Orlando) 2012; **26**: 261-279 [PMID: 22902168 DOI: 10.1016/j.trre.2012.07.001]

51 **Alberú J**, Pascoe MD, Campistol JM, Schena FP, Rial Mdel C, Polinsky M, Neylan JF, Korth-Bradley J, Goldberg-Alberts R, Maller ES. Lower malignancy rates in renal allograft recipients converted to sirolimus-based, calcineurin inhibitor-free immunotherapy: 24-month results from the CONVERT trial. *Transplantation* 2011; **92**: 303-310 [PMID: 21792049 DOI: 10.1097/TP.0b013e3182247ae2]

52 **Campbell SB**, Walker R, Tai SS, Jiang Q, Russ GR. Randomized controlled trial of sirolimus for renal transplant recipients at high risk for nonmelanoma skin cancer. *Am J Transplant* 2012; **12**: 1146-1156 [PMID: 22420843 DOI: 10.1111/j.1600-6143.2012.04004.x]

53 **Benlloch S**, Berenguer M, Prieto M, Moreno R, San Juan F, Rayón M, Mir J, Segura A, Berenguer J. De novo internal neoplasms after liver transplantation: increased risk and aggressive behavior in recent years? *Am J Transplant* 2004; **4**: 596-604 [PMID: 15023152 DOI: 10.1111/j.1600-6143.2004.00380.x]

P- Reviewer: Jang JW, Karatapanis S, Yankol Y **S- Editor**: Ma YJ
L- Editor: A **E- Editor**: Wang CH

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327