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TOPIC HIGHLIGHT

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Neoplastic disease after liver transplantation: Focus on *de novo* neoplasms

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Abstract

De novo neoplasms account for almost 30% of deaths 10 years after liver transplantation and are the most common cause of mortality in patients surviving at least 1 year after transplant. The risk of malignancy is two to four times higher in transplant recipients than in an age- and sex-matched population, and cancer is expected to surpass cardiovascular complications as the primary cause of death in transplanted patients within the next 2 decades. Since exposure to immunosuppression is associated with an increased frequency of developing neoplasm, long-term immunosuppression should be therefore minimized. Promising results in the prevention of hepatocellular carcinoma (HCC) recurrence have been reported with the use of mTOR inhibitors including everolimus and sirolimus and the ongoing open-label prospective randomized controlled SILVER. Study will provide more information on whether sirolimus-containing *vs* mTOR-inhibitor-free immunosuppression is more efficacious in reducing HCC recurrence.

Key words: Liver transplantation; *De novo* neoplasms; Immunosuppression; mTOR inhibitors; Hepatocellular carcinoma

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Core tip: With the notable increase in life expectancy after liver transplantation, together with the lengthy exposure to immunosuppression, transplant recipients are at risk of developing neoplastic disease, which accounts for almost 30% of deaths 10 years after liver transplantation. The risk of malignancy is two to four times higher in transplant recipients than in an age-

and sex-matched population, and cancer is expected to surpass cardiovascular complications as the primary cause of death in transplanted patients within the next 2 decades, making this an important topic for clinicians to consider.

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INTRODUCTION

With excellent long-term survival rates, the causes of morbidity and mortality of liver transplant (LT) recipients are primarily cardiovascular diseases, renal insufficiency, and *de novo* neoplasm, the latter of which account for almost 30% of deaths at 10 years post transplantation. Apart from hepatic causes, neoplasm has been reported as the most common cause of death in patients surviving at least 1 year after LT, and is responsible for approximately 40% of deaths[1,2]. Overall, it is estimated that in LT recipients the incidence of neoplasms is between 3.1% and 14.4%, and the cancer-related mortality rate is between 0.6% and 8.0%[3,4].

Although the risk of some neoplasms including breast cancer (1.9 times lower) and genitourinary cancer (1.5 times lower) in women seem to be reduced compared to those of the general population[5], in general terms, the status of transplant recipient is associated with an increased risk of developing *de novo* neoplasm. As shown in a study analyzing 1000 consecutive LT recipients in Pittsburgh and comparing this population's incidence of neoplasms compared to the general population, the former have a significantly elevated risk for developing neoplasm, which is 7.6 times higher for oropharyngeal cancer and 1.7 times higher for respiratory malignancies (Table 1).

Since a more prolonged exposure to immunosuppression is associated with an increased frequency of developing neoplasms, the cumulative risk of developing *de novo* malignancy rises from 20% at 10 years to 55% at 15 years after transplant[6]. In an Italian study analyzing 313 LT recipients who survived more than 12 mo after transplant, during a total follow-up time of 1753 person-years, *de novo* malignancies were diagnosed in 40 (12.8%) subjects, with a median time from transplantation to diagnosis of 54 mo (range, 2-159 mo)[7]. Other studies have reported a slightly lower mean interval between LT and diagnosis of non-lymphoid malignancies (36.2 mo, range, 5.8-74.1)[5].

Not only are malignant neoplasms more frequent in transplant recipients, but they also have a more aggressive behavior, present at an earlier age compared to the non-transplant population, and take a higher toll on survival[8]. Mortality after diagnosis of *de novo* malignant neoplasms is particularly elevated, with reported rates as high as 55% and a median survival of 54 mo after diagnosis[7]. Overall, estimated survival rates for all types of *de novo* malignancies are reportedly 70%, 56%, 48%, and 39% after 1, 3, 5, and 10 years, respectively. For certain types of cancer, mortality is particularly high, reaching 100% for lung cancer, 62.5% for esophageal and gastric cancers, 57% for head and neck cancer, 50% for post-transplant lymphoproliferative disorder (PTLD), and 50% for Kaposi Sarcoma (KS)[7].

Table 1 Estimated standardized incidence ratios for *de novo* malignancies after liver transplantation (data according to[7,9,15,46-48,61,72,174-182])

Cancer site/type	Estimated incidence (%)	SIR
All cancers	5-6	1.94-3
Kaposi's sarcoma	0.14-2.8	> 100
Skin (non melanoma)	0.9-3.2	> 30
PTLD	0.9-2.6	6-20
Gastrointestinal and oropharyngeal sites		
Lip/oropharyngeal/head and neck cancers	0.1-2.0	5-14
Esophagus[1]	0.5-1.19	12-18.7
Colorectal overall	0.0-0.65	1.41
Colorectal in IBD/PSC	0.7-7.9	3-5
Stomach	0.25	3
Vulva	0.25	8-23.8
Lung	0.6-1.2	2-8
Renal	0.35	2-2.65
Thyroid	0.20	4.60
Prostate	0.25-0.6	1 (risk not increased)
Breast	0.40	1 (risk not increased)
Colorectal in non-IBD/PSC	0.30	1 (risk not increased)

[1]Although there are no population-based SIR estimates showing an increased risk of esophageal cancer after LT, an Italian study reported an SIR of 23.4 on the basis of cases ascertained by medical record reviews[178]. This association may be related to prior alcohol exposure; 2 of 3 patients diagnosed with esophageal cancer in a US cohort underwent LT for ALD[1]. IBD: Inflammatory bowel disease; PSC: Primary sclerosing cholangitis; PTLD: Posttransplant lymphoproliferative disease; SIR: Standardized incidence ratio.

TYPES OF *DE NOVO* NEOPLASMS

De novo malignancies are neoplasms that develop after transplantation, including solid tumors such as pancreatic cancer, lung cancer, colorectal cancer, gastric cancer, esophageal cancer, renal cell carcinoma, bladder cancer, thyroid cancer, oral cancer, brain tumors and laryngeal cancer, as well as non-solid tumors, primarily PTLD/non-Hodgkin Lymphoma (NHL) and leukemia. According to a large German study analyzing the frequency and distribution of *de novo* neoplasms after LT[9], 1 *de novo* malignancy is to be expected approximately every 120 person-years after LT (120 *de novo* malignancies/14490 person-years). It was also shown that cancer incidence rates for LT

recipients are almost twice as high as those for an age- and sex-matched general population. To quantify the risk that the status of transplant recipient conveys, cancer site-specific incidence rates in the transplant population are compared against the general population, with standardized incidence ratios (SIRs). Estimated SIRs for each malignancy, as well as the reported incidence are shown in Table 1. PTLD is the most frequent *de novo* malignancy after LT, accounting for approximately 20% of cases[7]. Other common types of *de novo* malignant tumors include KS (17%), head and neck cancer (17%), esophageal tumors (12%), lung cancer (10%), gastric adenocarcinoma (7%), melanoma (5%), colorectal cancer (5%), cervical cancer (5%), and breast cancer (2%), as shown in a study from Northern Italy[7].

Skin cancer

In a series of LT recipients with nonlymphoid *de novo* malignancies, skin cancer was reportedly the most common type of malignancy (22/57 patients with *de novo* cancer, representing 33.3%), including squamous cell carcinomas in 50%, basal cell carcinomas in 40.9%, and melanomas in 9.1%. Neoplasms were most frequent on the skin of the head, face, and neck (in 14 subjects), but there were also several cases of multiple site involvement, and the mean time to onset was 36.4 mo (range, 8.2-75.1 mo)[5]. Another study demonstrated that the prevalence of pre-malignant and neoplastic cutaneous lesions increased with time, with a frequency of premalignant lesions of 5% at 2-3 years, 12% at 3-5 years, 28% beyond 5 years, and frequency of malignant lesions of 0% at 2-3 years, 9% at 3-5 years, and 12% beyond 5 years of follow-up after transplantation. Furthermore, in that same study, the cumulative incidence of cutaneous lesions was significantly higher in patients treated with cyclosporine compared to recipients on tacrolimus[10]. One-year survival after diagnosis of skin cancer in LT recipients is reportedly 90.9%[5]. Several factors have been identified as being considered high risk for developing skin cancer, including increased age, increased intensity and longer duration of immunosuppressive therapy, infection with human papillomavirus, history of increased ultraviolet exposure, easily burned skin, history of actinic keratosis, CD4 lymphocytopenia, and blue or hazel eyes[11,12]. Primary sclerosing cholangitis[13] as well as alcohol-related liver disease as indications for LT are associated with a higher risk of skin malignancies compared to other etiologies of liver disease[14,15]. Other risk factors for the development of skin malignancy after LT include male sex, age over 55 years, Caucasian background, and monoclonal antibody induction therapy[11], while the use of polyclonal or interleukin (IL)-2 receptor antibody induction therapy, treatment for rejection, and non-cholestatic etiologies of liver disease as indications for LT, seem not to be associated with an increased risk.

PTLDs

PTLD encompasses a heterogeneous group of diseases characterized by excessive proliferation of lymphoid cells and it commonly results from *de novo* infection or reactivation of latent Epstein-Barr virus (EBV)[16,17], especially in the case of EBV seronegative recipients of organs from EBV seropositive donors. LT carries an intermediate risk of PTLD, in contrast with intestinal transplantation, which has the highest rates[18,19]. An increased intensity of immunosuppression[5,20-23] and the use of certain types of immunosuppressive agents, in particular T-cell depleting antibodies such as Muromonab-CD3 (OKT3) or anti-thymocyte globulin (ATG), cyclosporine, and belatacept (in renal transplant recipients) constitute additional risk factors for PTLD development[24-26]. In an Italian study, 15 cases of PTLD were described in 1011 solid organ transplant recipients; in 13/15 patients, induction immunosuppressive therapy with OKT3 was used, and EBV was detected in 10 of 13 patients in whom neoplastic tissue was available for analysis. Moreover, in 2 of the 3 patients who were negative for EBV, hepatitis C virus (HCV) was present, and positivity for HCV was significantly more frequent in patients who developed PTLD compared to those who did not, suggesting a possible role of HCV in the development of PTLD[19]. Other studies have also shown a correlation between the presence of HCV and the development of PTLD[27-29].

In the pediatric population, PTLD is the most common tumor in solid organ recipients, with an overall incidence rate of 5% to 15% in different series or 298/100000 posttransplantation years of follow-up[30,31]. Reported mortality is unfortunately very high, of up to 60%, especially in infants who develop PTLD as a result of primary EBV transmission from EBV-positive allograft transplant[32-35].

The most important risk factors for PTLD development in the pediatric population include high levels of immunosuppression (especially associated with tacrolimus-based regimens[36]), young age, time from transplant (related to longer exposure time to immunosuppression), EBV seronegativity before transplant, and primary EBV transmission. Fukushima and collaborators, in a recently published study on 32 infants younger than 2 years who had undergone living-donor liver transplantation and were on tacrolimus-based immunosuppression, found that deteriorated tacrolimus metabolism (with elevated plasmatic levels) accompanied by an increase in Epstein-Barr viral load was more frequently associated with PTLD[36]. In a recently published paper by the Studies of Pediatric Transplantation Research Group[37] analyzing a large multicenter cohort of pediatric patients who underwent LT, transplants performed in the era 1995-2001 (*vs* those performed between 2002 and 2007), recipient EBV status, and frequent rejection episodes were associated with symptomatic EBV infection and

PTLD. The subgroup at a highest risk is constituted by younger infants with multiple rejection episodes. Importantly, the incidence of both symptomatic EBV infection and PTLD are seemingly decreasing in pediatric LT recipients, concomitantly with a reduction in immunosuppression[37].

In a recent study, Khedmat and Taheri[38] reviewed 250 cases of PTLD after liver transplantation published in the literature, of whom 212 were pediatric cases (18 years of age or less). PTLD was diagnosed at a mean age of 9.9 years and the mean ± SD interval between LT and diagnosis of PTLD was 28.7 mo (35.1 mo). Organs/areas involved included: orbit, skin, stomach, genitalia, central nervous system, spleen, kidneys, respiratory system, liver, bone marrow, small intestine, and colon; in comparison with their adult counterparts, histopathological features of PTLD were significantly of more benign types.

Analogous to management strategies in adults, a sequential approach is employed, starting with reduction or complete withdrawal of immunosuppression, initiation of inferferon-alpha, various chemotherapic regimens, surgery, and radiotherapy, escalating strategies if the previous alternative proves inefficacious[39]. Moreover, long-term withdrawal of immunosuppression has been shown to be feasible without graft rejection[40]. The use of the anti-B-cell monoclonal antibody rituximab has brought about improved results, and more recently, Gupta and collaborators reported on satisfactory outcomes employing a dual combination of rituximab and reduced dose chemotherapy, with two-year failure-free survival of 57% in liver transplant recipients[39].

Kaposi's sarcoma

KS is a multifocal angioproliferative mucocutaneous neoplasm driven by HHV-8 infection and represents approximately 4% of all post-transplant tumors. The risk of developing this neoplasm is increased 500-fold in solid organ transplant recipients compared with the general population[41,42]. In a large study on 2705 recipients of solid organs, amongst whom 159 LT recipients, KS was diagnosed in 1.44% of all transplant recipients, including 12.8% of LT recipients[43]. Contrary to most other neoplasms, the incidence of KS seems to decrease significantly with time after solid organ transplantation[44]. In the presence of infection with HHV-8, the most important risk factor for the development of this neoplasm is the intensity of immunosuppression, and its therapy is based on immunosuppression tapering, as well as the use of chemotherapeutic agents. Moreover, evidence is mounting on the usefulness of mTOR inhibitors in treating this tumor while at the same time providing effective immunosuppression[45].

Solid tumors

Lung cancer: The incidence of lung cancer among LT recipients is increased compared to the general population, and reportedly accounted for 15.7% of nonlymphoid neoplasms in a series of LT recipients, in whom it was diagnosed, on average, 48.5 mo (range, 11.2 to 64.3 mo) after LT, and a one-year survival of 37.5%[5]. In large case series of LT recipients, the mean time to diagnosis ranges from 42 to 50 mo[5,46-48]. Akin to the association between smoking observed in the general population, this carcinogen is correlated with an increased risk of lung cancer in transplant recipients[5,46]. Although probably representing an epidemiological association, as smokers are also frequently heavy drinkers, a study showed that patients with alcohol-related cirrhosis as an indication for LT had higher rates of lung cancer than those who underwent LT for other indications[49].

Head and neck cancers: Head and neck neoplasms are more frequent in the LT population than in the general population, and mean time to diagnosis is reportedly between 34.3 mo and 61.2 mo[5,15,47,50,51]. Oropharyngeal cancer is 25.5 times more frequent in patients transplanted for alcohol-related cirrhosis *vs* those transplanted for other indications[52]. Moreover, upper aerodigestive squamous carcinomas are more frequent in patients with alcohol-related cirrhosis as the main indication for LT[53]. Moreover, another study showed that whereas the incidence of oropharyngeal cancer was 16.7% in patients who underwent LT for alcohol-related liver disease, none of the patients who underwent LT for indications other than alcohol-related cirrhosis developed oropharyngeal malignant neoplasms (P = 0.001)[50]. Notably, there was not one case of oropharyngeal cancer in a small, single-center study involving patients without a history of smoking or alcohol use[54]. Likewise, tongue cancer and laryngeal cancer have been reported in smokers[5,46], and the carcinogenic effects of tobacco observed in the general population also applies for transplant recipients. It is difficult to establish the weight of alcohol compared to tobacco use as contributing risk factors for head and neck neoplasms, as alcohol is known to potentiate the carcinogenic effects of smoking[55], and also since patients who are heavy smokers also tend to be heavy drinkers[56].

Esophageal and gastric cancer: Although their incidence is increased with respect to the general population[57], gastric and esophageal cancers are reported infrequently in most series of LT recipients[58]. As well as for several other types of cancer, notably those of the oropharynx/larynx, alcohol is a well-established risk factor for esophageal malignant neoplasms[59], and this neoplasm occurs at a higher rate after LT in patients with alcohol-related liver disease[15,27,60]. In an Italian study on 313 LT recipients followed during a 15-year period, of 40 patients with *de novo* malignancy, esophageal cancer was diagnosed

in 12%, with a mortality (combined for esophageal and gastric cancer of 62.5%) being second only to that of lung cancer[7]. A German study analyzing 1,926 LT recipients found that 9 patients (0.5%) developed a *de novo* esophageal cancer and 1 patient developed cancer of the cardia (0.05%), diagnosed on average 51 mo after LT. The histological type of tumor was squamous cell carcinoma in 7/10 and adenocarcinoma in 3/10. Of note, 9/10 patients had undergone LT due to alcohol-related cirrhosis[61]. A predisposing lesion, Barrett's esophagus, has been demonstrated to rapidly evolve into adenocarcinoma after LT, which is why surveillance endoscopy with aggressive endoscopic treatment of Barrett's mucosa is paramount in these patients to prevent death from cancer[62-66]. In a Korean study of 6491 patients who underwent solid organ transplantation, 30 patients (0.46%) with 31 lesions were diagnosed with gastric cancer[67]. In another series, 36 cases of gastric cancer were identified among 7000 transplant-related malignant neoplasms, and 3 of the 34 were observed in LT recipients[68]. Moreover, another study reported 3 cases of gastric cancer amongst 329 cases of malignant neoplasms in LT recipients[69].

Genitourinary cancer: Although the incidence of prostate cancer does not seem to be increased in LT recipients, all other genitourinary cancers (including bladder and renal cancer) seem to be higher than that of the general population[5,15,27,46,47]. Mean time to diagnosis of non-prostate genitourinary cancer ranges from 20 to 55.3 mo, while in cases of prostate cancer the diagnosis is often performed between 5.8 and 18.4 mo after LT[5,15,47,48]. In LT recipients, prostate cancer is more often diagnosed at earlier stages and has a good prognosis, whereas renal and bladder cancers have a poor prognosis[5].

Gynecological cancer: Although it seems that breast cancer is no more frequent in LT compared to the general population[3], non-breast gynecological cancers (cervical and ovarian) are more frequent in LT recipients than in the general population[15,46,47]. It has been hypothesized that rigorous screening before LT has contributed to a tendency, albeit not statistically significant, for a lower incidence of breast cancer in LT recipients[5]. However, other studies have documented that breast cancer incidence is in fact elevated in the transplant population, with the advantage, however, that early detection is more common, and this has also resulted in decreased mortality compared to that of the general population upon similar diagnoses[46].

Colorectal cancer: The incidence of colorectal cancer seems to be higher in the LT recipient population *vs* the general population[46,47], although most of this difference in incidence, if not all, can be accounted for by the increased risk of colorectal cancer associated with LT for primary sclerosing cholangitis, probably due to the association with ulcerative colitis[70-72]. More frequently diagnosed between 16 and 50 mo after transplant, colorectal cancer in transplant recipients tends to be detected at an earlier age and has been associated with a worse prognosis compared to the general population[73,74].

***De novo* hepatocellular carcinoma:** A search performed by Trevisani *et al*[75] identified 14 cases of *de novo* hepatocellular carcinoma (HCC) which have been reported in the literature. Although until now a relatively rare occurrence, truly *de novo* HCC, that is, neoplasms arising from the liver graft and not recurrences of recipient HCC, might be seen more often in the future, due to the increased use of extended criteria grafts, especially those from older donors, donors carrying HCV or HBV infection, or alcoholic liver disease[76,77]. One of the principal risk factors for *de novo* HCC is recurrence of liver disease in the allograft, and especially the development of cirrhosis[75], and reported cases have been diagnosed on average 2 years after LT. As for non-transplant recipients, post transplant exposure to hepatocarcinogens like aflatoxin B1, nitrosamine, aromatic amines, vinyl chloride, azo-dyes, pesticides, arsenic, organic solvents, and cigarette smoking, can theoretically trigger the development of HCC, although no case has yet been reported in association with any of these factors. Immunosuppression regimens used in the 14 reported cases include OKT3, azathioprine, cyclosporine, corticosteroids, mycophenolate mofetil, basiliximab, and tacrolimus[78-82].

Prognosis seems dismal according to reported cases, despite tapering of immunosuppression, transarterial chemoembolization, radiofrequency ablation, hepatic resection, or retransplantation. Strategies for preventing this neoplasm include avoidance of recurrent graft damage as well as a judicious immunosuppression after LT[75]. While HCC recurrence is considered a contraindication for retransplantation, this therapeutic option could be contemplated in the setting of *de novo* HCC and has been reported in a case with development of this *de novo* malignancy 14 years after primary LT[82].

RISK FACTORS FOR THE DEVELOPMENT OF *DE NOVO* MALIGNANCIES

In a study analyzing risk factors for the development of solid neoplasms after LT, multivariate analyisis demonstrated that primary sclerosing cholangitis (HR = 2.62, 95%CI: 1.50-4.56), alcohol-related cirrhosis (HR = 2.14, 95%CI: 1.22-3.73), smoking (HR = 1.72, 95%CI: 1.06-2.79), and increasing age in decades (HR = 1.33, 95%CI: 1.05-1.66) were all significantly associated with *de novo* neoplasms[1]. A summary of the most important risk factors is provided in Table 2.

Table 2 Risk factors for the development of *de novo* malignancies according to tumor location/type (data according to[5,14-17,20-22,25,26,46,48,50,53,54,61,62,64,75,130,181,183,184])

Tumor location/type	Risk factor
Skin	Age > 40 yr
	Male gender
	Skin type
	Sun exposure
	Smoking
	Alcoholic cirrhosis
	Primary sclerosing cholangitis as indication for LT
	Cyclosporine-based immunosuppression
KS	Increased intensity of immunosuppression
	Infection with HHV-8
PTLD	Age > 50 yr
	Infection with EBV (especially seronegative recipients of organs from EBV seropositive donors)
	Increased intensity of immunosuppression
	OKT3 or anti-thymocyte globulin
	Cyclosporine-based immunosuppression
	Hepatitis C virus
Lung cancer	Cigarette smoking
	LT for alcohol-related liver disease
Head and neck cancers	Cigarette smoking
	LT for alcohol-related liver disease
Esophageal and gastric cancers	LT for alcohol-related liver disease
	Barrett's Esophagus
Colorectal cancer	Primary sclerosing cholangitis
	Inflammatory bowel disease
De novo HCC	Recurrence of liver disease in the allograft
Gynecologic cancers	Insufficient evidence
Genitourinary cancers	Insufficient evidence

EBV: Epstein-Barr virus; HCC: Hepatocellular carcinoma; HHV-8: Human herpesvirus 8; KS: Kaposi's sarcoma; LT: Liver transplantation; PTLD: Post-transplant lymphoproliferative disorder.

DONOR-TRANSMITTED MALIGNANCIES

The role of immunosuppression in reactivating dormant neoplasms is supported by the fact that transplant recipients who have received organs from donors with previously cured neoplasms may develop the donor's malignancy[83,84]. Reportedly, 0.5% to 3% of donors have a history of malignancy, and transmission from these donors to the recipients has been demonstrated in 0.02%-6% of cases[85-89], the risk being higher in LT recipients as compared to recipients of other organs[90,91]. According to the time elapsed from clinical remission of the neoplasm in the donor to the moment of donation, tumor site, and risk of transmission, recommendations for specific tumor types have been issued by the Malignancy Subcommittee of the Disease Transmission Advisory Committee of the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS). Organ shortage, a low risk of transmission of malignancy to the recipient, and the need for a life-saving transplant in cases of urgent LT may drive the decision of using organs from extended criteria donors, including donors with a neoplasm. It is important, however, to quantify the risk, based on the type of neoplasm. Thus, an organ from a donor with basal cell carcinoma is considered to be associated with a minimal risk (< 0.01%) of transmission and may be used as a graft, whereas at the other end of the spectrum, the history or presence of melanoma, lung cancer, or active breast cancer > stage 0 are considered at high risk of transmission (> 10%) and their use is discouraged[92]. Allegedly, organs from donors with central nervous system malignancies may be safely transplanted; in a study analyzing 62 recipients of organs from donors with a history of or active central nervous system neoplasm, 8 transmissions were identified, occurring 2-15 mo after transplant, with seven patients dying as the result of metastatic disease. The presence of one or more risk factors, identified as: high-grade tumors, ventriculoperitoneal or ventriculoatrial shungs, prior craniotomy and systemic chemiotherapy, entailed a risk of 53% of tumor transmission, whereas the rate was significantly lower (7%, $P < 0.01$) if no risk factor was present[93]. However, a more recent and larger study performed in the United Kingdom concluded that organs from donors who died as a consequence of primary intracranial malignancy, including those with high-grade tumors, should be considered for transplantation due to the small risk of tumor transmission. Identification of 448 recipients of 495 organs from 177 donors with primary intracranial malignancy, including 33 with high-grade malignancy (9 medulloblastomas and 24 grade Ⅳ gliomas amongst 179 donors) demonstrated not one single case of tumor transmission[94]. As in all medical interventions, a risk-benefit evaluation must be performed, the patient should be informed of the possibility of receiving one such organ, and this must be weighed against the risk of dying on the waiting list, which is much higher.

The recommendations for screening in the donor so as to reduce the risk of undiagnosed neoplasm and subsequent transmission to the recipient include execution of complete medical history specifically inquiring on previous diagnosis of malignancy, radiological imaging, complete physical examination to rule out possible skin cancer, laboratory analysis for the detection of tumor markers, pathology examination of extracted organs, and in cases of unexplained intracranial hemorrhage and in women with menstrual disorders, underlying neoplasms must be excluded[95,96].

IMMUNOSUPPRESSION

Immunosuppression plays a fundamental role in the development of neoplasms, acting through several different mechanisms including decreased immune surveillance, increased susceptibility to infections, induction of insulin resistance, and a direct carcinogenic effect which has been described in the case of some immunosuppressive agents. The association between

alterations in the immune system and the development of neoplasms is also reflected in the elevated incidence of cancer in most medical conditions associated with immunosuppression[97,98] and the fact that the length of exposure and intensity of immunosuppression correlate with the incidence of malignant neoplasms[99,100]. Whereas in immunocompetent subjects there is continuous ongoing surveillance that acts as tumor suppressor, keeping in check possible accumulated cell damage resulting in neoplasms, immunosuppression in organ transplant recipients results in a lower threshold for immunosurveillance, allowing neoplastic cells to proliferate.

Moreover, chronic immunosuppression renders transplant recipients more vulnerable to viral infections, some of which have oncogenic potential. Although not all neoplasms are the result of viral triggers, the ones that are tend to be those that show the greatest rise in frequency amongst transplant recipients including B-cell lymphoma and PTLD (EBV), squamous cell skin carcinoma (HPV), Kaposi's sarcoma (HHV8), anogenital cancers (HPV), Merkel skin cancer (polyomavirus), and HCC (HBV, HCV)[97]. The viral oncogenic potential may be enhanced by the action of some immunosuppressants. Calcineurin inhibitors in particular, can favor the expression of EBV growth and virus-inducing factors including IL-1, IL-6, and transforming growth factor (TGF-β), can promote EBV replication, and can augment immunoresistance by favoring the expression of anti-apoptotic genes[101].

Aside from these indirect effects, several immunosuppressive drugs seem to have direct oncogenic effects, either by provoking damage to DNA or through other mechanisms not linked to immunosuppression. Azathioprine, for instance, induces chromosomal aberrations and increases skin cell sensitivity to photodamage[97].

Calcineurin inhibitors: There is evidence of direct pro-oncogenic activity in the case of calcineurin inhibitors, which induce tumorigenesis and tumor growth by inducing cancer cell invasiveness[102], hampering DNA repair mechanisms[103,104] and apoptosis[103], inducing tumor angiogenesis *via* the stimulation of vascular endothelial growth factor (VEGF)[105], and promoting the transcription and functional expression of the TGF-β1 gene which results in tumor cell invasion and metastatic potential[106]. In LT recipients, it has been shown than exposure to elevated concentrations of tacrolimus (> 20 ng/mL) in the weeks immediately after transplantation increases long-term mortality due to infections, cardiovascular events and development of neoplasms[107-110].

Furthermore, both calcineurin inhibitors and steroids exert a diabetogenic effect, causing impaired insulin secretion and inducing pancreatic beta cell apoptosis[111-113]. As many as 5%-27% of LT recipients develop neo-onset diabetes mellitus, and it is associated with a negative impact on patient and graft survival[114-116], diabetes being a recognized risk factor for neoplasms, playing an important role especially in HCC[117]. Calcineurin inhibitors, especially tacrolimus, have in fact been shown to increase the risk of developing new-onset diabetes mellitus after transplantation.

Other immunosuppressant agents: The use of other immunosuppressant agents, including OKT3 and ATG, has also been associated with an increased risk for the development of neoplasms after solid organ transplantation. Early PTLD has been shown to occur shortly after administration of OKT3, with an average of 7 mo from transplantation and/or administration to diagnosis of PTLD[118]. In other series, high total doses of OKT3, especially in individuals in whom a second course of therapy was administered, were associated with a higher frequency of lymphomas[119,120]. In contrast, a single-center study reporting on 1570 LT of whom 125 patients developed *de novo* tumors, did not show any relationship between OKT3 and the development of *de novo* neoplasms; the authors note that this is consistent with the concept that chronic maintenance immunosuppression is more important than short albeit intense periods of immunosuppression (treated with OKT3)[47]. A recently published Cochrane Database Systematic Review evaluated the benefits and harms of immunosuppressive T-cell specific antibody induction compared with placebo, no induction, or another type of T-cell specific antibody induction for prevention of acute rejection in LT recipients, and included studies using T-cell specific antibodies polyclonal antibodies [rabbit of horse antithymocyte globulin (ATG), or antilymphocyte globulin (ALG)], monoclonal antibodies (OKT3, anti-CD2, or alemtuzumab), and IL-2 receptor antagonists (daclizumab, basiliximab, BT563, or Lo-Tact-1). The authors concluded that there were no statistically significant differences in terms of malignancy[121].

Mammalian target of rapamycin inhibitors: Mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase downstream of the phophoinositide-3-kinase-related kinase family, which plays a fundamental role as regulator of various oncogenic processes including cell growth, proliferation, metabolism, and angiogenesis[122]. The combination of anti-tumoral as well as immunosuppressive properties render this family of drugs very attractive in the post-transplantation setting. There is growing evidence that the incidence of neoplastic disease is inferior in patients with gradual reduction of CNI with the introduction of mTOR inhibitors, *vs* those subjects treated with standard-dose CNI[123]. An anti-neoplastic activity has been demonstrated for everolimus with regard to various solid tumors, and a potential role in HCC and cholangiocarcinoma are being increasingly reported[105,124-127].

Table 3 Intensive screening protocols for tumor surveillance in liver transplant recipients (data according to[128-130])

Traditional screening	Intensive screening
Annual chest X-ray	Annual chest and abdominal CT
Annual abdominal ultrasound	Annual abdominal ultrasound
Chest and abdominal CT	Annual urologic screening with PSA determination
Mammography and urologic screening (with timing according to standard of care)	Annual Pap smear and mammography (every 1-2 yr)
	Annual skin examination
	Colonoscopy 1 year after LT in patients with adenoma on pre-LT colonoscopy, and repeated every 2-4 yr if more adenomas are found. Colonoscopy repetition every 10 yr in patients > 50-yr-old
	Ears, nose and throat clinic visit in patients with > 20 pack year smoking

CT: Computed tomography; PSA: Prostatic specific antigen; LT: Liver transplant.

PREVENTION

As most neoplasms are favored by immunosuppression, the long-term use of the lowest effective dose of immunosuppression to avoid rejection are recommended, as well as the avoidance of excessive sun exposure, treatment of premalignant lesions including warts and actinic keratoses, and avoidance of exposure to confirmed carcinogenic substances including those present in tobacco smoke.

Screening protocols are recommended in order to detect malignancies in early states, increasing the probability of opportune treatment and improving prognosis[128,129]. Some recommended strategies include monthly skin autoexam, annual dermatological visit, annual Pap smear, mammography every 2 years, annual digital rectal exam and prostate-specific antigen determination, annual fecal occult blood test, colonoscopy every 10 years, annual chest X-ray, abdominal ultrasound, chest and abdominal CT scan[130-135]. A summary of preventive measures is provided in Table 3.

Management of neoplastic disease in LT recipients: In general terms, management of malignant neoplasms in LT recipients is similar to that of the immunocompetent patient in terms of surgery, chemotherapy and radiotherapy, but, in contrast, one of the main pillars of the approach to a neoplasm in transplant recipients is represented by modification of immunosuppression, especially in tumors which are highly susceptible to immunosuppression, such as KS and PTLD.

Owing to their strong anti-angiogenic effects which result in inhibition of tumor growth, as well as their direct action on cancer cells by the inhibition of their dependence on the mTOR pathway for cell growth and survival, mTOR inhibitors are increasingly being used in the management of neoplasms in transplant recipients[105,136,137]. Since cyclosporine favors an invasive and aggressive tumor cell behavior, the combination with mTORi was hypothesized to be beneficial, adequately avoiding rejection while also providing malignancy control. This has been proven to be true, with significantly better survival times with mTORi plus cyclosporine treatment *vs* cyclosporine-only treatment in mice injected with tumor cells[138]. In fact, mTORi alone or mTORi plus cyclosporine impairs immunity and promotes allograft survival in experimental models, and the combination of sirolimus and everolimus with cyclosporine is effective in clinical transplantation, being approved by the Food and Drug Administration (FDA) for use in transplant recipients[139]. Specifically, everolimus is indicated for immunosuppression kidney heart and liver transplantation, while sirolimus has been approved for kidney transplantation. Malignancy rates post-conversion to sirolimus-based, CNI-free, immunosuppression regimen were significantly lower with respect to the CNI-based immunosuppression protocol in the RMR study and the CONVERT trials[140,141]. Moreover, experience in renal transplant recipients has demonstrated that the risk of *de novo* malignancies is significantly lower in patients treated with mTOR inhibitors (with or without CNIs) compared to patients on CNI-based regimens[142]. Thus, one of the recommended strategies in the management of post-transplant neoplasms is the conversion from CNIs to mTOR inhibitors or inclusion of mTOR inhibitors in a CNI-based immunosuppressive regimen[143-145]. Furthermore, in another study reporting on 10 LT recipients who had developed *de novo* neoplasms after LT, everolimus treatment significantly increased the probability of survival from 14% (in a similar historical cohort of patients not treated with everolimus) to 72% at 20 mo[146]. Moreover, in a recently published retrospective study analyzing prognostic factors for patients transplanted for alcohol-related cirrhosis who developed non-cutaneous *de novo* solid organ neoplasms, conversion to everolimus improved prognosis, with one- and five-year survival rates of 77.4% and 35.2% in patients converted to everolimus *vs* 47.2% and 19.4% in patients not treated with everolimus, respectively ($P = 0.003$)[147].

RECURRENCE OF NON-HEPATIC NEOPLASMS

With the broadening of eligibility criteria for LT, older patients are now being transplanted, increasing the probability of patients with past medical history of malignancy to be evaluated for LT, waitlisted, and transplanted. The risk of neoplastic recurrence upon commencement and maintenance of immunosuppression and its derived mortality must be weighed against the probability of survival without a transplant. Recurrence of a preexistent neoplasm can occur after

LT, and according to the risk of recurrence, neoplasms can be classified as low recurrence risk (0%-10%) as in the case of cervical carcinoma, endometrial carcinoma, myeloproliferative disorders, and lymphomas; intermediate recurrence rate (11%-25%) as in the case of colorectal cancer, non-melanoma skin cancer, and thyroid carcinoma; and neoplasms with a high recurrence rate (> 26%) as in the case of oral squamous carcinoma and breast cancer[148]. There is consensus that the tumor type and stage of the disease must be carefully evaluated, and according to this, recommendations have been made regarding the waiting time between achieving clinical "cure" or disease control and LT[149-151]. According to American[151] and European[95] guidelines, proposed malignancy-free delay periods before transplantation vary from no delay in cases of basal-cell skin cancers and incidental renal cell carcinoma, to less than 2 years in cases of small single focal neoplasms, low-grade bladder cancer, excised squamous cell carcinoma, 2 years in cases off testicular and thyroid neoplasms, to 2-5 years or more for malignant melanomas, breast cancer, invasive cervical cancer, and colorectal cancer. Nevertheless, since many patients being evaluated for LT are too sick to endure a long waiting period, provided that the neoplasm is adequately controlled and the stage of the neoplasm itself is not associated with a poor prognosis, LT may be considered before completion of the waiting period with informed consent of the candidate[152].

HCC RECURRENCE IN LT RECIPIENTS

In spite of the 5-year 60%-80% disease-free survival rate after LT for HCC in cases with unresectable early stages of the neoplasm, recurrence does occur in 3.5%-21% of cases, and is associated with a poor prognosis[153]. Tumor-related established risk factors for HCC recurrence after LT include high levels of alpha-fetoprotein[154,155], tumor grading[156,157], tumor stage[154,156-158], and vascular invasion[154,157,158], while immunosuppression-related risk factors for HCC recurrence are primarily the level of immunosuppression[156], mTOR- *vs* mTOR inhibitor-free immunosuppression regimen[154,159]. Clinical studies have shown a CNIs dose-dependent increase in the risk of developing HCC recurrence[102]. Elevated exposure to CNIs (mean trough concentrations of tacrolimus > 10 ng/mL or cyclosporine > 300 ng/mL) during the first postoperative period has in fact been associated with an increased risk of HCC recurrence[160]. Moreover, it has been observed that high doses of cyclosporine are associated with a lower recurrence-free survival in patients transplanted for HCC. In fact, a study on 219 patients transplanted for HCC undertaken in Milan revealed that elevated doses of cyclosporine or tacrolimus during the first 30 d after LT almost tripled the risk of HCC recurrence[127].

In contrast, mTOR inhibitors possess anti-angiogenic and anti-proliferative properties acting though the reduction of several growth factors and enhancing microvascular thrombosis, which correlates with lower metastatic potential[122,161]. The antineoplastic effect of mTOR inhibitors has also been shown in several clinical studies[162]. There is growing evidence that mTOR deregulation plays a significant role in hepatocellular carcinogenesis, and pre-clinical data indicate that deregulated expression of mTOR pathway effectors is present in 40%-50% of HCCs, and activation of the mTOR pathway is associated with less differentiated neoplasms, earlier tumor recurrence, and worse survival outcomes[163,164]. A recent meta-analysis comparing CNIs against sirolimus demonstrated a protective effect of the latter in terms of achieving a lower incidence of HCC recurrence after LT[165]. This protective effect was confirmed in a more recent meta-analysis[166], which demonstrated that sirolimus, compared with CNIs, was associated with lower HCC recurrence (OR = 0.30, 95%CI: 0.16-0.55, $P < 0.001$), lower HCC recurrence-related mortality (OR = 0.29, 95%CI: 0.12-0.70, $P = 0.005$), and lower overall mortality (OR = 0.35, 95%CI: 0.20-0.61, $P < 0.001$). In addition, a recent systematic review showed that patients on CNIs developed HCC recurrence significantly more frequently compared with patients on mTORi. In addition,patients on everolimus had significantly lower HCC recurrence rates compared with those on sirolimus or CNIs, although patients treated with mTOR inhibitors tended to have less advanced stages of HCC[167,168].

CONCLUSION

Overall, the risk of malignancy is two to four times higher in transplant recipients than in an age- and sex-matched population, and cancer is expected to surpass cardiovascular complications as the primary cause of death in transplanted patients within the next 2 decades[4,169]. *De novo* malignancy is a very significant cause of mortality, particularly for long-term survivors, and minimization of long-term immunosuppression should be aimed at reducing the incidence of *de novo* neoplasms[1,170]. Promising results in prevention of HCC recurrence have been reported with the use of mTOR inhibitors including everolimus and sirolimus[154,159,171] and the ongoing open-label prospective randomized controlled SILVER Study[172] will provide more information on whether sirolimus-containing *vs* mTOR-inhibitor-free immunosuppression is more efficacious in reducing HCC recurrence. The combined use of sorafenib, a multikinase antiangiogenic inhibitor, and an mTOR inhibitor has yielded positive results in treating patients with HCC recurrence after LT, despite notable associated toxity[173].

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