

2016 Liver Transplantation: Global view

Incidence, risk factors and outcomes of *de novo* malignancies post liver transplantation

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Abstract

Liver transplantation (LT) is associated with a 2 to

7 fold higher, age and gender adjusted, risk of *de novo* malignancy. The overall incidence of *de novo* malignancy post LT ranges from 2.2% to 26%, and 5 and 10 years incidence rates are estimated at 10% to 14.6% and 20% to 32%, respectively. The main risk factors for *de novo* malignancy include immunosuppression with impaired immunosurveillance, and a number of patient factors which include; age, latent oncogenic viral infections, tobacco and alcohol use history, and underlying liver disease. The most common cancers after LT are non-melanoma skin cancers, accounting for approximately 37% of *de novo* malignancies, with a noted increase in the ratio of squamous to basal cell cancers. While these types of skin cancer do not impact patient survival, post-transplant lymphoproliferative disorders and solid organ cancer, accounting for 25% and 48% of malignancies, are associated with increased mortality. Patients developing these types of cancer are diagnosed at more advanced stages, and their cancers behave more aggressively compared with the general population. Patients undergoing LT for primary sclerosing cholangitis (particularly with inflammatory bowel disease) and alcoholic liver disease have high rates of malignancies compared with patients undergoing LT for other indications. These populations are at particular risk for gastrointestinal and aerodigestive cancers respectively. Counseling smoking cessation, skin protection from sun exposure and routine clinical follow-up are the current approach in practice. There are no standardized surveillance protocol, but available data suggests that regimented surveillance strategies are needed and capable of yielding cancer diagnosis at earlier stages with better resulting survival. Evidence-based strategies are needed to guide optimal surveillance and safe minimization of immunosuppression.

Key words: Liver transplant; Immunosuppression; Risk; Outcomes; Malignancy

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Core tip: The risk of new cancers is significantly increased after liver transplantation (LT), and is driven by patient factors, oncogenic viruses and lifelong immunosuppression. *De novo* malignancy is a major risk factor for mortality after LT, equaling the risk of cardiovascular disease or infectious diseases. The risk of *de novo* malignancies may be reduced by attention to patient risk factors and minimization of immunosuppression when possible. Ultimately rigorous surveillance is needed to allow for early diagnosis and attenuation of mortality risk.

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INTRODUCTION

Liver transplantation (LT) is the definitive therapy for decompensated end-stage liver disease regardless of etiology. During the past 2 decades, the outcomes of LT have steadily improved as a result of more widespread expertise, better surgical techniques and more effective and better tolerated immunosuppressive agents. The growing number of LT recipients and improving survival rates place particular importance on the factors that jeopardize long term survival. Inherent to this population is the need for lifelong immunosuppression, which is associated with some broad categories of risk for morbidity and mortality. These include infection, cardiovascular risks, renal injury and cancer. When studied in patients surviving the early post LT period, *de novo* malignancy emerges as the leading category of immunosuppression associated long term mortality risk, accounting for approximately 21% to 25% of deaths^[1,2]. This review summarizes current knowledge of *de novo* malignancy post LT including; epidemiology, pathogenesis, disease burden, clinical implications, preventive and surveillance considerations, while emphasizing risk factors and outcomes.

INCIDENCE

Multiple studies report widely varying incidence rates of *de novo* malignancy post LT, along with considerable variations in associated risks, cancer types and outcomes. The incidence of *de novo* malignancies in relatively large cohorts (subjectively defined as more than 150 patients) is summarized in Table 1, the last row of which contains the means of the respective variables. These include single center experiences^[3-7], registry based studies^[8-11], and the majority are retrospective with few exceptions^[12]. Variability in *de novo* malignancy

incidence rates reflect actual differences (based on differing cohort characteristics and risks) and artificial differences (based on differing methodologies and study design). The factors impacting actual differences in cancers types and their incidence may include age, gender, racial and geographical considerations, as well as the predominant underlying liver diseases and their associated comorbidities. Whereas artificial heterogeneity may be less apparent, yet could arise from variability in the: (1) definitions of *de novo* malignancy, *e.g.*, not all include non-melanoma skin cancers; (2) designated time threshold for of exclusion of cancers that are likely pre-existing before LT; (3) method of identification of malignancies, *e.g.*, in-center chart review vs utilization of cancer registries; (4) surveillance protocols and frequency of clinical follow up at study centers (critical for in-center reporting of cancer cases); (5) duration of follow up post LT since cancer incidence increases with time^[8,13]; and (6) in the case of standardized incidence ratio (SIR) calculations, the control population used and type of cancers captured by the respective registries. In this review, we have described incidence rates of cancers and as well as the SIR where possible, as it allows age and gender adjusted risk analysis. SIR is calculated as the ratio of observed incidence in a cohort to the expected incidence in the population (hence has no unit).

Cancer registry data used to calculate expected age and gender adjusted incidence rates for SIR estimation doesn't capture non-melanoma skin cancers (NMSCs). Therefore SIR analyses succinctly reflect the risk of more life-threatening types of cancer. Interestingly, purely registry based analyses yield higher SIR values for *de novo* malignancy post LT, ranging from 2.2 to 4.9^[10,14-16], than 1.4 to 3.1^[2,9,11,17,18] of single and multi-center studies. The reasons for this are unclear but could reflect differing approaches to immunosuppression given the reporting bias for higher transplant volume centers.

RISK FACTORS FOR *DE NOVO* MALIGNANCY

The risk factors for the development of *de novo* malignancy after LT are not fully understood, but it is likely that patient, transplant and environmental factors interact to shape that risk.

Immunosuppression related risk

Over the past few decades, a better understanding of the role of the immune system in preventing malignancy in immunocompetent individuals helped establish the concept of immunosurveillance^[19]. Transplant recipients receive lifelong immunosuppression with chronic impairment of immunosurveillance, which promotes proliferation and survival of malignant cellular clones. Though immunosuppressive drug dose intensity likely contributes to cancer risk, the evidence for this is

Table 1 Summary of study characteristics and reported incidence of de novo malignancy post liver transplantation in large series

Ref.	Year published	Country of study center	Study period	No. of liver transplant recipients	⁴ Duration of follow-up (yr)	⁴ Age at transplant in patients with de novo malignancy (yr)	Proportion of males with de novo malignancy	⁴ Interval to de novo malignancy (yr)	Overall incidence of de novo malignancy (number of patients)	5/10/15 and 20 yr incidence of de novo malignancy	Estimated overall risk relative to control population
Jonas <i>et al</i> ^[28]	1997	Germany	1988-1994	458	4.2	46 ± 14	48%	3.6	7.2% (33)	14.6%/-/-/-	-
Jain <i>et al</i> ^[6]	1998	United States	1996-2006	1000	6.5 ± 1	Approximately 56	77%	3	5.7% (57)	-	SIR calculated for specific cancer types
Kelly <i>et al</i> ^[25]	1998	United Kingdom	1988-1996	888	-	Approximately 52	46%	2 ± 1.5	² 4.4% (29)	-	-
Galve <i>et al</i> ^[16]	1999	Spain	1984-1997	1827	-	-	-	2.5 ± 1.8	3.8% (70)	-	-
Haagsma <i>et al</i> ^[8]	2001	The Netherlands	1979-1996	174	5.1	Approximately 49	29%	5.9	12% (21)	6%/20%/55%/-	RR = 4.3 (95%CI: 2.4-7.1)
Sanchez <i>et al</i> ^[5]	2002	United States	1985-1999	1421	5.5 ± 3.7	50 ± 12	55%	-	8.8% (125)	-	-
Saigal <i>et al</i> ^[4]	2003	United Kingdom	1988-1999	1140	-	51.5	70%	3.8 ± 2.8	2.6% (30)	-	-
Benloch <i>et al</i> ^[60]	2004	Spain	1991-2001	772	4.3	50	59%	3.5	5.3% (41) ¹	-	-
Oo <i>et al</i> ^[65]	2005	United Kingdom	1982-2004	1778	6.5	-	43%	-	7.9% (141)	-	SIR = 2.1 (95%CI: 1.7-2.2) RR = 2.9 (95%CI: 1.6-5.0)
Herrero <i>et al</i> ^[7]	2005	Spain	1990-2001	187	5.5	-	-	-	26% (49)	-	-
Yao <i>et al</i> ^[60]	2006	United States	1988-2000	1043	6.7	53.2	52%	-	4.8% (50)	-	-
Aberg <i>et al</i> ^[9]	2008	Finland	1982-2005	540	6.3	-	53%	5.1	6.7% (36) ³	5%/13%/-/16%	³ SIR = 2.6 (95%CI: 1.8-3.5)
Jiang <i>et al</i> ^[10]	2008	Canada	1983-1998	2034	-	-	53%	3.5 ± 2.8	5.5% (113) ¹	2%/8.6%/-/-	¹ SIR = 2.5 (95%CI: 2.1-3.0)
Watt <i>et al</i> ^[12]	2009	United States	1990-1994	798	10	-	60% ¹	-	21.4% (171)	12%/22%/-/-	-
Finkenstedt <i>et al</i> ^[8]	2009	Austria	1982-2007	779	4.1	-	-	4.4	12.3% (96)	10%/24%/32%/42%	¹ SIR = 1.9 (95%CI: 1.5-2.4)
Baccarani <i>et al</i> ^[27]	2010	Italy	1991-2005	417	6.7	-	74%	4.2	10.3% (43) ¹	-	¹ SIR = 2.6 (95%CI: 1.9-3.6)
Tjon <i>et al</i> ^[27]	2010	Denmark	198-2007	85	5	-	-	-	3% (50)	10%/19%/34%/-	SIR = 2.2 (95%CI: 1.6-2.8) ¹ RR = 7.7 for men and 7.3 for women
Park <i>et al</i> ^[67]	2012	South Korea	1998-2008	1952	3.5 ± 2.8	56	79%	3.4 ± 2.4	2.3% (44) ¹	-	-
Chatrath <i>et al</i> ^[2]	2013	United States	1997-2004	534	5.7 ± 3.2	53 ± 12	67%	4 ± 2.2	13.7% (73)	12%/25%/-/-	¹ SIR = 3.1 (95%CI: 2.9-3.2)
Wimmer <i>et al</i> ^[64]	2013	Germany	1985-2007	609	5.2	53 ± 10	73%	5.7	11.5% (70)	10%/26%/35%/-	-
Ettore <i>et al</i> ^[11]	2014	Italy	1990-2008	1675	5.2	-	-	3.2	5.9% (98) ¹	-	-
Yu <i>et al</i> ^[69]	2014	China	2005-2011	569	3.5 ± 2.2	-	76%	-	3.2% (17)	-	¹ SIR = 1.4 (95%CI: 1.2-1.7)
Antunucci <i>et al</i> ^[17]	2015	Argentina	2006-2014	168	-	67 ± 7	75%	1.3	7.5% (12)	-	-
Sanaei <i>et al</i> ^[68]	2015	Iran	1992-2012	1700	-	34 ± 10	63%	5.5	2.2% (38)	-	-
Overall means				940	5.5	52	61%	3.8	8.10%	11%/22%/39%/29%	3.0

¹Excluding non-melanoma skin cancers; ²Excluding post-transplant lymphoproliferative disorder; ³Excluding basal cell skin cancer; ⁴Median or mean ± SD. SIR: Standardized incidence ratio.

indirect. Comparative studies indicate a lower SIR for de novo malignancies in LT (2.2) recipients compared with heart (2.5) or lung (3.6) recipients who typically require higher intensity of immunosuppression^[16,20]. A higher rate of hepatocellular carcinoma recurrence has been described with higher trough levels of the calcineurin inhibitors (CNI), tacrolimus and cyclosporine, particularly in the early post LT period^[21,22]. Calcineurin inhibitors inhibit T-lymphocyte cell mediated immunity, and may also increase the risk of malignancy by increasing synthesis of growth factors, e.g., transforming growth factor-β, interleukin-6 and vascular endothelial growth factor in tumor cells, and impair DNA repair, thereby enhancing tumor growth, metastasis and angiogenesis^[23]. The duration of immunosuppression also likely increases risk of malignancy, with increased incidence reported in recipients who were immunosuppressed before LT^[9].

The choice of immunosuppressive drug is a potentially modifiable cancer risk factor. Cyclosporine initially, and tacrolimus subsequently, have been and remain the mainstay of long term immunosuppression in LT over the last few decades. Even though some studies have shown higher carcinogenic risk with tacrolimus^[7,24], and others with cyclosporine based protocols^[2,25-27], there is no accepted cancer risk advantage for either agent^[3,28]. A more practical concern in choice of immunosuppressant relates to the class of mammalian target of rapamycin (mTOR) inhibitors, sirolimus and everolimus, though these agents are used mainly in renal sparing regimens. The putative

Table 2 A listing on known oncogenic viruses and the malignancies associated with them

Oncogenic virus	Associated malignancy
EBV	PTLD
Human papilloma virus	Cervical, skin, oropharynx, anal
Human T-cell lymphotropic virus type 1	Adult T cell leukemia
Kaposi's sarcoma-associated herpesvirus	KS, primary effusion lymphoma, castleman's disease
HBV	HCC
HCV	HCC, PTLD ¹

¹Role controversial. HCC: Hepatocellular carcinoma; EBV: Epstein-Barr virus; PTLD: Post transplant lymphoproliferative disorder; KS: Kaposi's sarcoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

anti-proliferative properties of mTOR inhibition include inhibition of cellular growth, proliferation, metabolism and angiogenesis^[29]. Though there is no prospective randomized controlled study data currently, a number of retrospective studies have described lower rates of hepatocellular carcinoma (HCC) recurrence^[30,31], and *de novo* malignancies^[32,33] with mTOR inhibitors post LT and renal transplantation^[34]. A meta-analysis of retrospective studies has shown that mTOR inhibitor, sirolimus, is of value in preventing recurrence and increasing survival in those transplanted for HCC^[35].

The post LT cancer risk related to anti-metabolites has been described for azathioprine in one study, with an odds ratio (OR = 3.8, 95%CI: 1.7-8.6, $P = 0.004$)^[36]. Whereas mycophenolate mofetil has been shown to have anti-tumor properties in animal studies^[37], and was associated with a trend towards lower risk of non-skin *de novo* malignancies post renal transplant in a large United States, and European/Canadian registry based study^[38]. In a recent study of solid organ transplant, mycophenolate mofetil use was associated with lower risk of proximal colon cancer^[39].

Immunosuppression induction with anti-lymphocyte antibodies or anti-thymocyte globulin was associated with increased of skin cancer in one study^[9], however that risk was not seen in larger series using anti-thymocyte globulin induction^[2,28]. Rejection episodes also did not alter the risk of malignancy in LT recipients^[5,6,12,40]. These data suggest that higher levels of immunosuppression in the short term do not increase the long term risk of cancer.

Immunosuppression also increases the cancer risk related to latent oncogenic virus infections (Table 2)^[41]. Oncogenic virus associated tumors may be more immunogenic than those related to other factors, and may regress once immunosuppression is stopped or minimized^[42]. This provides the rationale for a decrease in immunosuppression as the first line intervention for some virus related cancers, such post-transplant lymphoproliferative disorder (PTLD), particularly when associated with Epstein-barr virus (EBV) viremia^[43].

Recipient related factors

The association of specific patient factors with cancer risk are organized and elaborated on below.

Age: Advanced age is a well described risk factor for *de novo* malignancy^[2,7,8,12,44,45], although this is not a universal finding^[25,28]. This suggests that other factors may supersede age in cancer risk, though some caveats are notable with the extremes of age. For example the SIR for early PTLD was high (18.1) in pediatric LT recipients in one study^[9], with a similar observation in another study^[10]. In another study, LT recipients older than 60 had > 2 fold higher 5-year incidence of new cancers (> 40%) compared to younger LT recipients (< 20%), largely due to non-skin cancers, with significantly higher cancer related mortality^[46].

Gender and race: There is conflicting data on the relative risk of *de novo* malignancy according to gender, with slightly higher SIR of cancers in females in one registry study^[14], and in males in another^[45], limiting any meaningful conclusion. Although skin cancer risk would be expected to differ according to race, there is limited data of cancer risk in relation to race. Non-Caucasian race was associated with a higher hazard ratio (HR = 2.5, 95%CI: 1.3-4.3) for non-skin cancers in one study, but the small size of that subgroup was limiting^[2].

Indication for LT: Patients who receive LT for certain indications are more prone to some malignancies. Patients with primary sclerosing cholangitis (PSC) in a United States multicenter prospective observational study had the highest cumulative incidence of non-skin cancer of 5.5%, 10.4%, and 21.9% at 1, 5, and 10 years, respectively^[12]. Patients with PSC and inflammatory bowel disease (IBD) and an intact colon at the time of LT were at increased risk of gastrointestinal (colon) malignancy (HR = 2.34, 95%CI: 1.02-5.38)^[12], which may not be surprising given the association of PSC and IBD with colon cancer risk. However, patients with PSC also exhibited an increased risk for PTLD, skin malignancies and solid organ malignancies^[12]. A high cancer risk for LT recipients with PSC was also observed in an Italian study, though cancer types were not specified^[47]. The reasons for generalized cancer risk are unclear, but may reflect immunosuppression before LT, and possibly vitamin D deficiency which may promote malignancy^[48].

Alcohol use history and smoking: Many studies have described the carcinogenic properties of alcohol and smoking in immunocompetent individuals^[49,50]. Alcoholic liver disease (ALD) is associated with increased cancer risk post LT^[7,12,36,45,51-54]. Synergy between the carcinogenic effects of alcohol and smoking is well described^[55,56]. Smokers were more likely to have alcoholic liver disease than non-smokers (35% vs 13%,

Table 3 A summary of ranges of reported overall incidence rates and standardized incidence ratios of a number of cancer types following liver transplantation^[2-5,7-12,14-16,28,36,47,66,110,118-120]

	Incidence (%)	SIR
Skin cancers		
Represent 24%-54% of all cancers, average 37%		
Overall (non-melanoma)	0.9-11.6	2.1-70, average 24
Squamous cell cancer	0.6-15.3	Not reported
Basal cell cancer	0.6-10.6	Not reported
KS	0.2-1.4	128-144
Melanoma	0.2-3.9	4.4
Post-transplant lymphoproliferative disorders		
Represent 4%-57% of all cancers, average 25%		
Overall	0.5-2.9	3.9-21, average 12
Hodgkin's lymphoma	0.001-0.4	8.2-8.9
Non-Hodgkin's lymphoma	0.8-3.7	3.5-37.3
Solid organ cancers		
Represent 24%-75% of all cancers, average 48%		
Overall	1.4-7.5	1.4-3.1, average 2.3
Lip	1.8	14-24.8
Oropharyngeal	1.7-1.9	7-10
Lung	0.6-2.4	1.4-2.0
Stomach	0.2-0.7	0.5-3.7
Colorectal	0.5-1.1	1.4-4.9
Breast (in females)	0.2-0.6	0.6-1.6 ¹
Cervix (in females)	0.7-1.4	1.3-5.7
Prostate (in males)	0.2-1.8	0.6-1.6 ¹

¹The SIR was not found to be significantly higher for transplant recipients compared with the reference population. Of note, studies often reported either incidence rate or SIR, but rarely both values. SIR: Standardized incidence ratio; KS: Kaposi's sarcoma.

$P = 0.008$) in one study^[56], and patients transplanted for ALD were more likely to be smokers (82% vs 45%, $P = 0.001$) and smoked more cigarettes per day (27 ± 15 vs 16 ± 11 , $P = 0.001$) in another^[54]. A United Kingdom registry study reported a higher SIR (3.16) of *de novo* malignancy for ALD compared to all other LT indications (1.99)^[45]. In the immunocompetent population, there is evidence that the increased risk of cancer due to alcohol abuse could be reversed by abstinence^[57]. However, this effect may be delayed by a more than a decade^[58], with cancer risk carried through post LT.

History of cancer prior to LT: A history of cancer prior to LT was not associated with its recurrence after LT^[8,25]. However, LT for HCC has been associated with an increased risk of *de novo* malignancy^[7,44]. An increased incidence of non-skin cancers in patients with a history of non-liver cancer prior to LT (30.8% vs 8.3%, $P = 0.001$) has also been described, where it was additionally an independent predictor of non-skin *de novo* malignancies (HR = 2.5, 95%CI: 1.3-4.9, $P = 0.005$)^[2]. This association is supported by data from renal transplantation studies^[34,59,60]. Therefore, a prior history of cancer may reflect a patient's composite (genetic and epigenetic) risk of malignancy.

SITE SPECIFIC *DE NOVO* MALIGNANCIES

The risk of *de novo* malignancy is variable across a range of tumor types, as reported by cancer registry

studies. These cancers are commonly grouped according to three broad categories including; skin cancers, PTLD and solid organ cancers. The risks of specific tumors post LT are summarized in Table 3.

Skin cancers

Skin malignancy, typically NMSC, is the most common malignancy after LT^[2,7,9,12,40,61]. These include squamous cell cancer (SCC), basal cell cancer (BCC) and Kaposi's sarcoma (KS). Ultraviolet radiation is an important risk factor in the pathogenesis of skin malignancies, and exerts a field cancerization mutagenic effect in exposed areas of the skin^[62-65]. In a prospective study of LT recipients with comprehensive dermatology follow-up, only total pre transplant sun burden and skin characteristics were found to be the risk factors for NMSC^[66]. The relative risk of cutaneous malignancies in this cohort was found to be 20 fold higher than the general population. Conversely studies from Iran, South Korea and China described no to very low incidence rates of skin cancer, likely due to the prevalent skin types^[67-69]. In organ transplant recipients, SCC is more common than BCC, in contrast to the general population^[44,70]. Additionally, while SCC and BCC are easily surveyed and resected, SCC can behave more aggressively in LT recipients^[70,71]. In general though, LT recipients with SCC and BCC have similar survival to patients not developing *de novo* malignancies post LT^[2,40].

Immunosuppression with CNIs and azathioprine is a significant risk factor for NMSC^[72-76], but it is likely

the degree of immunosuppression that represents the main risk rather than the choice of agent^[62,77,78]. However, there is mounting evidence that mTOR inhibitors have protective effect against NMSC due to their aforementioned anti-proliferative properties^[72,77], especially in renal transplant recipients. In a randomized trial, converting renal transplant recipients with NMSC from CNi to sirolimus based immunosuppression was associated with a reduced risk of subsequent NMSC (relative risk 0.56, 95%CI: 0.32-0.98) and longer recurrence free interval (15 mo vs 7 mo, $P = 0.02$)^[79]. However, similar evidence in LT recipients is currently lacking.

Kaposi's sarcoma is related to human herpes virus-8 (HHV-8) and occurs only in immunocompromised individuals. The incidence of KS after LT reflects the prevalence of HHV-8 (also known as Kaposi's sarcoma-associated herpes virus), with high rates reported in the Mediterranean region^[80,81]. Not surprisingly the highest rates and SIR (commonly > 100) for KS post LT are reported in Italian transplant series^[11,17,47].

Post-transplant lymphoproliferative disorders

The term PTLTD encompasses a broad spectrum of lymphoproliferative disorders observed in the immunocompromised solid organ transplant recipients. It is the second most common malignancy in LT recipients, and is notable in its wide age distribution, extending to the very young^[14]. The rate of PTLTD is lower in the liver compared to other solid organ recipients^[82], likely due to lower immunosuppression levels needed to prevent liver allograft rejection, and possibly a smaller number of donor lymphocytes in the graft^[83]. The other factor driving PTLTD risk is EBV infection, with associated PTLTD generally occurring earlier, in the first 12 to 18 mo, after LT and involving younger patients^[82,84]. Infection with EBV and immunosuppression appear to play crucial roles in the pathogenesis of PTLTD. EBV mismatch between donor and recipient of LT increases the risk of PTLTD by 70 fold^[85,86]. Primary infection with EBV after LT also increases the risk significantly^[87]. Primary EBV or latent (of virus within B cells) infection can stimulate B cell proliferation and transformation^[88]. EBV associated PTLTD occurs three times more frequently in pediatric patients^[87,89]. This is likely a reflection of the EBV negative status of pediatric recipient, whereas EBV infects 90% of the adults worldwide^[90].

Another important phenotype of PTLTD develops later post LT in the absence of EBV infection involves older recipients and carries a worse prognosis^[82]. The pathogenesis of EBV negative PTLTD is uncertain^[91], but some risk factors were described in a study of 480 adult LT recipient PTLTD in France, where 16 developed PTLTD^[92]. These were age above 50, LT for hepatitis C virus (HCV) or alcoholic cirrhosis, and the use of anti-lymphocyte antibodies such as muromonab, the latter reported by others^[82,87]. The use of anti-thymocyte globulins in LT for HCV cirrhosis augmented PTLTD risk in another study (27% for HCV vs 6.4% for non-HCV

cases, $P = 0.08$)^[93]. When compared to lymphomas in the immunocompetent population, PTLTD are more likely to exhibit extra-nodal involvement, high-grade and poor outcomes^[94]. Factors which confer a poor prognosis with PTLTD are; high grade or stage at diagnosis^[43], T cell disease^[95], central nervous system and bone marrow involvement^[96,97], poor performance status^[98], higher number of extra-nodal sites^[98], and EBV negative disease^[43,85,99].

Solid organ cancers

Like PTLTD, this category of *de novo* malignancy carries significant risk of mortality post LT, but is a term loosely used to group a wide range of tumor types and organ involved. Some characteristics of risk are evident in relation to subgroups of solid organ cancers, including aerodigestive, gastrointestinal, genitourinary and gynecologic systems.

Aerodigestive cancers

Aerodigestive cancers are associated with smoking and alcohol use, and arise from the tissues of the aerodigestive tract, which include the respiratory tract and the upper part of the digestive tract (including the lips, mouth, tongue, nose, throat, vocal cords, and part of the esophagus and windpipe). These are largely reported as head and neck cancers and lung cancer post LT.

A meta-analysis of studies examining head and neck cancer after LT found an overall SIR of 3.8 (95%CI: 2.7-4.9)^[100]. They develop at mean post LT intervals that range from 34 to 61 mo^[3-5,92,101]. Liver transplant recipients with a history of tobacco use and ALD are at high risk for developing head and neck cancers^[7,12,102], and in some studies only developed in patients with a history of ALD^[6,103].

In a large study encompassing all solid organ transplants in the United States, the SIR for lung cancer after LT was found to be 1.95 (95%CI: 1.74-2.19)^[14]. Lung cancer develops at mean post LT intervals ranging from 42 to 50 mo^[3,5,28,61,101]. The main risk factors for lung cancer, similar to the general population, in LT recipients was smoking^[2,7,12,54]. Those transplanted for ALD also had increased risk of lung cancer compared to those transplanted for other causes (4.3% vs 0.7%, $P < 0.001$), though tobacco use which prevalent in this population may confound these observations^[7,12,54]. Post LT lung cancer is commonly diagnosed in advanced stages^[3,5,54], suggesting the need for diligent surveillance programs in the high risk population (smokers and those transplanted for ALD). It remains unclear how long tobacco and alcohol related cancer risk persist following cessation.

Gastrointestinal cancers

The most common gastrointestinal cancer seen in solid organ transplant recipients is colon cancer^[14]. The SIR for colon cancer in LT recipients ranges from 1.4 to as high 27.3 in subsets of high risk patients with PSC^[16,17,45].

Patients receiving LT for PSC are at particularly high risk for colon cancer, due to the association with IBD^[12,45,104-106]. In the study by Watt *et al.*^[12] PSC alone (HR = 1.9, $P = 0.12$) was not a risk factor for gastrointestinal malignancy, whereas patients with PSC, IBD and intact colons had a significant cancer risk (HR = 3.51, 95%CI: 1.48-8.36, $P = 0.005$). Colon cancer was more common in LT recipients with ulcerative colitis (SIR = 27.3 vs 3.5), than those without it, particularly in patients older than 40 (SIR = 4.8 vs 1 in younger patients)^[45]. Longer duration of IBD and more extensive colonic involvement increase the risk for colorectal cancer in LT recipients with PSC^[104-106]. Colorectal cancer develops at a younger age in LT recipients compared with the general population, and has a worse prognosis^[107,108]. A relatively high incidence of colon and stomach cancer have been reported in a South Korean study^[67], with otherwise relatively low (2.2%-2.3%) *de novo* malignancy incidence rates reported in East Asian studies^[67,69].

Genitourinary and gynecologic cancers

Registry studies indicate an increased SIR of some (cervical, vulvar, bladder and kidney) but not all genitourinary or gender-specific (breast, prostate, uterine, ovarian) cancers following solid organ transplant^[10,14-17,45]. In the largest of these, there was a slightly lower SIR for breast and prostate cancer in transplant recipients^[14]. Cervical cancer risk was significantly elevated in one series (SIR = 30.7)^[17], and other human papilloma virus related cancers (vulvar, vaginal, anal, penile) all appear to have higher SIR (range 2.4-7.6) relative to the general population^[14]. Bladder cancer risk is increased in a number of studies, with a range of SIR value from 1.5 to 2.4^[14-16], and were noted to develop late (10 years) post LT in one cohort^[47].

SURVIVAL AFTER *DE NOVO* NON-SKIN CANCERS

In a comparison of patients from a solid organ transplant cancer registry with a general population from the Surveillance, Epidemiology, and End Results database, transplant patients were more likely to be diagnosed with American Joint Commission on Cancer stage > 2 cancers, and worse cancer-specific survival^[109]. The relative risk of cancer-related mortality compared to the general population was 2.9 (95%CI: 1.59-5.11)^[7]. In a large single center study *de novo* malignancy, excluding NMSC, was a leading category of mortality risk (14.2%), along with infections (15%), disease recurrence (13%) and cardiovascular (9%) complications^[2]. Patient survival rates at 1.3 and 5 years after diagnosis of *de novo* malignancy were 55%, 36%, and 27% compared with 100%, 100% and 67% for patients with only NMSC, $P = 0.001$, respectively^[2]. Similarly, *de novo* malignancy excluding NMSC was associated with an increased risk of mortality [HR = 4.9 (95%CI: 1.67-14.2), $P = 0.003$] in another large series^[40], and probability of death after

diagnosis was 40% at 1 year, and 55% at 5 years, respectively^[12].

There is considerable variability in reported survival after PTLD, with median survival as low as 2 mo (95%CI: 0.3-3.5 mo) in one study^[36], likely as a result of heterogeneity in risk characteristics of PTLD^[95]. Longer median survival intervals (27 mo to 35 mo) are noted in other LT series^[12,14], with reported 1 and 5 year survival rates of 56% and 46%, respectively^[82]. Pediatric LT recipients with PTLD appear to have better outcomes, with median survival of 8.2 years and reported 10 years survival rates of 59%^[85,96], and no reported mortality in some series^[94]. Advanced stage, Burkitt or Burkitt-like PTLD, and c-myc translocations indicated poor prognosis and short survival in pediatric PTLD^[96].

The reported site-specific cancer survival rates for the aforementioned solid organ cancer categories are: Oropharyngeal cancer 1 and 5 year survival of 43% to 78% and 56% respectively, lung cancer 1 and 5 year survival of 41% to 43% and 16% respectively, gastrointestinal cancers 1 and 5 year survival of 67% to 80% and 52% respectively, and genitourinary cancers 1 and 5 year survival of 79%-100% and 71% respectively^[3,12].

SURVEILLANCE

The increased risk and mortality associated with *de novo* malignancies underlines the need for surveillance strategies to detect tumors at earlier stages, allow more effective treatments, and improve survival. However, there are no standardized surveillance protocols for LT recipients at present. Routine follow up visits alone were only capable of detecting 12% of the non-skin cancers in one series, and annual visits resulted in identifying half of all malignancies in another^[8,9]. Poor compliance with surveillance protocols was also cited as a limitation in a study where active surveillance identified only 3 of 28 non-skin cancers^[7]. These data further highlight the need for regimented surveillance strategies in this regard.

In a compelling study, the incidence and outcome of *de novo* malignancy were compared before and after institution of an intensified surveillance protocol which included: Annual chest and abdominal computerized tomography (CT), urological, gynecological (pap smear and mammography) and dermatological examination, and colonoscopies every 5 years^[18]. With a historical surveillance program consisting of annual chest radiographs and abdominal ultrasounds serving as the reference comparator, the detection rate for *de novo* malignancies increased from 4.9% to 13% with intensified surveillance ($P = 0.001$), fewer tumors were diagnosed at stage III or IV (46% vs 75%), and median survival following a diagnosis of non-skin cancer increased from 1.2 to 3.3 years ($P = 0.001$)^[18].

At another center, a similarly multifaceted surveillance protocol that included: (1) urinalysis, chest radiographs and abdominal ultrasounds performed every

6 mo in the first year post LT and annually thereafter; (2) mammography every two years; (3) colonoscopy every 7-10 years if no adenomas were detected; and (4) in patients with smoking history, an annual otolaryngological evaluation and low dose CT of the chest after 2006^[110]. Patients that were diagnosed with *de novo* malignancy through active surveillance had better survival (all were alive after 25 mo of follow up) compared with patients diagnosed with symptomatic disease or incidentally (median survival of 13.5 mo) ($P = 0.002$)^[110]. The use of annual low dose chest CT in LT recipients with more than 10 pack years of cumulative smoking history led to a diagnosis of early stage lung cancer in 12% of patients^[111].

Additionally, special populations amongst LT recipient and the specialized surveillance strategies that are or may be warranted for them include those with: (1) underlying PSC and IBD, or IBD alone of more than 8-10 years duration with annual surveillance colonoscopy; (2) a history of human papilloma virus infection with annual pap smear in females, and annual genital and anal pap/scraping in both genders; and (3) patients from the Mediterranean region with testing of HHV-8 titers due to increased prevalence and association with risk of KS^[112].

PREVENTATIVE MEASURES

Smoking is a major risk factor for cancer, especially nasopharyngeal cancers and lung cancer, as well cardiovascular disease related mortality^[56], and smoking cessation should be counseled as early as possible. Regular application of broad spectrum sunscreen (SPF > 50, with high-UVA absorption) over sun-exposed areas in solid organ transplant recipients, in conjunction with counseling of excessive sun exposure avoidance, reduced the risk of actinic keratosis, invasive SCC and BCC from developing in a prospective case control study in solid organ transplant recipients^[113]. Protective clothing has also been shown to protect against UV radiation^[114]. The minimization of immunosuppression without risking graft rejection is limited by the lack of accurate markers of over or under immunosuppression, but would likely to attenuate the risk of *de novo* malignancy in LT recipient. There is also insufficient evidence to guide the routine use of mTOR inhibitors in at risk patients, but those studies are ongoing^[115-120].

CONCLUSION

Liver transplant recipients are at increased risk of cancer when compared to the general population, and the most commonly encountered cancers are NMSC, PTLT, and aerodigestive. They are due mainly due to the effects of immunosuppression and latent oncogenic viruses prevalent in the population. Important risk factors for development of *de novo* malignancy include age, degree of immunosuppression, history of smoking and alcohol abuse and transplantation for PSC and ALD. *De novo* malignancies, excluding NMSC, represent a major risk

category for post LT mortality. There are no standardized surveillance protocols for *de novo* malignancy post LT, but available evidence supports adoption of some consistent surveillance strategies. Minimization of immunosuppression and attention and counseling related to other risk factors in LT recipients may reduce an individual's risk of developing cancers post LT, but more evidence is needed to optimize care.

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