



Post-transplant malignancies in alcoholic liver disease

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Abstract: Post-transplant malignancy is emerging as an important cause of mortality in patients with cirrhosis undergoing liver transplant (LT). However, establishing the exact relationship between the two needs further evaluation. It has been observed that approximately 30% deaths after 10 years of hepatic transplantation occur due to *de novo* malignancies. Various known risk factors include immunosuppression, age of patient, alcoholic liver disease (ALD) or primary sclerosing cholangitis, smoking, and oncogenic viral infections. There is scanty literature on the post-transplant malignancy risk in patients with alcoholic cirrhosis. The current evidence suggests a particularly increased risk of oropharyngeal and lung cancers in patients transplanted for ALD. Abstinence from alcohol, smoking and other tobacco-containing products along with optimization of immunosuppression are paramount for decreasing the risk of post-transplant malignancies.

Keywords: Alcoholic cirrhosis; hepatic transplantation; cancer; *de novo* malignancy

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Introduction

Liver transplantation (LT) is the treatment of choice for patients with end-stage liver disease. Post-transplantation malignancy is becoming a major problem with the increased longevity of these patients. Professor Thomas Starzl and co-workers in 1968 envisioned increased incidence of *de novo* malignancies in immunocompromised patients which was later confirmed by others (1-3). The incidence of post-transplant *de novo* malignancies ranges from 3% to 26% (4-7). This variation may be due to the difference in the duration of follow-up, geographic variations and different ways of reporting. Various studies have reported a 2-times higher risk of solid organ tumors and a ≥ 30 -times higher risk of lymphoproliferative neoplasia as compared to general population (8-11). The mortality due to *de novo* malignancies account for 0.6% and 8.0% in this population (12,13). Various studies have demonstrated higher incidence of *de novo* malignancies in alcoholic as compared to non-alcoholic

LT recipients (4,14-18). Immunosuppression, hepatitis C virus (HCV) infection, smoking, alcoholic cirrhosis, and sun exposure have been shown to be important risk factors for the development of post-transplant *de novo* malignancies in a systematic review (19,20). However, there is paucity of literature regarding these factors. In the present review, we will discuss post-transplant malignancies, summarize the evidence behind increased risk of malignancies after transplantation for alcoholic liver disease (ALD) and outline suggested screening and preventive strategies.

Post-transplant malignancies

Neoplasms developing post-transplant are called *de novo* malignancies. About 1% patients develop solid organ malignancies annually, with an overall incidence of 3–15% after LT (14,19). Post-transplant lymphoproliferative disorders (PTLDs) occur in about 20% of cases (21). Incidences of various neoplasms in these patients have been

reported as follows: Kaposi's sarcoma (17%), head and neck cancer (17%), esophageal carcinoma (12%), lung cancer (10%), gastric adenocarcinoma (7%), melanoma (5%), colorectal cancer (5%), cervical cancer (5%), and breast cancer (2%) (21).

Several risk factors linked to the development of cancer in the general population also have relevance in the post-transplant setting. These include the consumption of alcohol, smoking, immunosuppression, recipient age and oncogenic viral infections like HCV and Epstein-Barr virus (EBV). The use of immunosuppressants like OKT3, anti-thymocyte globulin and calcineurin inhibitors like tacrolimus are important risk factors for the development of *de novo* malignancies post-transplant (22,23). However, mTOR inhibitors like sirolimus have been associated with a decreased risk of malignancies (24,25). Other risk factors identified by a recent systematic review include the use of tobacco and alcohol, older age and pre-malignant conditions as the important risk factors for the development of post-transplant malignancies (20).

Skin cancer

Squamous cell carcinoma is the most common dermatological cancer in the post-transplant setting in contrast to basal cell carcinoma which is more common in the general population. Various factors like higher age, increased intensity and prolonged use of immunosuppressive therapy, human papillomavirus infection, prolonged exposure to ultraviolet rays, history of actinic keratosis, CD4 lymphocytopenia, blue or hazel eyes have been implicated (26,27). Patients undergoing LT for primary sclerosing cholangitis and alcoholic cirrhosis are at a higher risk of developing skin cancer in comparison to patients of other etiologies (4,15,28,29).

PTLD

PTLD has been reported to be the second most common malignancy in LT recipients being 0.9% to 2.6% in comparison to 0.03% in general population (6,16). EBV and HCV have been implicated in the development of PTLD in various studies (22,30-33). The incidence of PTLD is not specifically higher in patients transplanted for ALD (17). However, the mortality after development of PTLD was higher in patients transplanted for ALD as compared to other etiologies (34-37).

Lung cancer

LT recipients have a higher risk of lung cancer (0% to 1.2%) than that of the general population (0.06%) (4,16). The mean time to diagnosis of lung cancer ranges from 42 to 50 months (38-41). The diagnosis of lung cancer is often made in advanced stages and carries a poor prognosis. Etiologically, patients with alcoholic cirrhosis undergoing LT have a 2 to 4 times higher risk of lung cancer (42). The risk is further compounded by the fact that many patients who drink alcohol are also smokers.

Head and neck cancers

Head and neck cancers occur more frequently (0.1–2%) after LT than in the general population (16,41). The mean time to diagnosis varies from 34.3 to 61.2 months (4,38,40,43,44). Patients with alcoholic cirrhosis undergoing LT are more prone to develop oropharyngeal cancer as compared to patients transplanted for other etiologies. In fact, in one single-center study, no case of oropharyngeal cancer was reported in the absence of history of alcohol intake or cigarette smoking (45).

Esophageal and gastric cancer

Gastric and esophageal cancers are infrequent in LT recipients but their incidence is higher than the general population (46). In a study of 313 LT recipients over a span of 15 years, 40 patients developed *de novo* malignancy of which 12% had esophageal cancer (21). In a German study of 1,926 LT recipients, 9 patients developed esophageal cancer and 1 developed cancer of the cardia (47). In this study, squamous cell carcinoma was seen in 7/10 and adenocarcinoma in 3/10 patients and 9 of these 10 patients had undergone LT for alcoholic cirrhosis (47). Increased risk of esophageal cancer in patients transplanted for ALD has also been in other studies (4,22,48).

Colorectal cancer

Colorectal cancer occurs more frequently in the post-transplant setting (0–0.6%) compared to the general population (0.05%) (6,39,40,49). A study from the Netherlands showed a 12 times higher risk of colorectal neoplasia after LT (19). This high incidence may be attributed to the presence of ulcerative colitis in patients with primary sclerosing cholangitis who underwent

Table 1 Incidence of *de novo* malignancies post-transplant in alcoholic vs. non-alcoholic groups

Malignancies	Incidence		Reference number
	Non-alcoholic	Alcoholic	
Skin cancer	Not increased	Increased	(4,15,28,29)
PTLDs	Not increased	Not increased	(17) [high mortality: (34-37)]
Lung cancer	Not increased	Increased	(42,53-56)
Head and neck cancer	Not increased	Increased	(17,22,43,45,53,54)
Esophageal and gastric	Not increased	Increased	(4,22,47,48,53)
Colorectal	Not increased	Not increased	(17)
Genitourinary		Insufficient data	
Gynecological		Insufficient data	

PTLD, post-transplant lymphoproliferative disorder.

transplant (50-52). However, the risk of colorectal cancer does not appear to be increased in transplant recipients of alcoholic cirrhosis (17).

Genitourinary cancer

In LT recipients, the incidence of prostate cancer is not increased and that of bladder and renal cancer is higher than that of the general population (4,22,38). The average time taken to diagnose these genitourinary neoplasms varies between 20 to 55.3 months (4,38). There is insufficient data to draw conclusions regarding alcoholic cirrhosis.

Gynecological cancer

The incidence of cervical and ovarian cancers is higher in LT recipients in comparison to the general population (4,39,40). On the other hand, the risk of breast cancer does not appear to be higher in LT recipients as compared to the general population (12). However, there is limited data to comment on the incidence of malignancies in the specific subgroup of patients transplanted for ALD.

ALD and post-transplant malignancy

There is limited data on the risk of post-transplant malignancies in alcoholic cirrhosis vis-à-vis patients transplanted for non-alcohol related etiologies (Table 1). In a multicentric, US study including almost 800 recipients, alcoholic cirrhosis was an independent risk factor for the development of post-transplant malignancy with a hazard ratio of 2.4 (14). The increased risk of *de novo* malignancies

in patients transplanted for ALD was confirmed in a recently published *French National* follow-up study of 11,226 recipients of whom 36% had been transplanted for ALD (53). This increased risk was present in both genders. A significantly increased risk of neoplasms of the larynx, esophagus, lip-mouth-pharynx, and lung was observed in patients who had been transplanted for ALD as compared to non-alcohol related etiologies (53).

The available data suggests that risk of lung cancers, upper respiratory tract and oropharynx is particularly increased after transplantation for ALD (17,22,43,53-56). In a Spanish study, upper respiratory tract and lung cancers were seen in 8% patients transplanted for alcoholic cirrhosis as compared to 0.8% of patients transplanted for non-alcohol related etiologies (55). In a study of 700 recipients, post-transplant lung cancer was detected in 17 (2%) patients of which 12 (1.7%) had been transplanted for alcoholic cirrhosis (56). Jiménez *et al.* also demonstrated higher rates of lung cancer in those who underwent LT for alcoholic cirrhosis than those transplanted for other etiologies (4.3% vs. 0.7%, $P < 0.001$). Almost 75% of the lung cancer patients in their study used to drink alcohol heavily and they were also intermediate or heavy smokers (54). There is some evidence regarding the use of annual chest X-rays or computed tomography (CT) scans as surveillance in these patients, particularly in smokers (57-59).

The risk of oropharyngeal cancers is also increased in patients transplanted for ALD in comparison to other etiologies. Duvoux *et al.* reported a higher incidence in patients transplanted for alcoholic etiology than non-alcoholic one (16.7% vs. 0%; $P = 0.001$) (43). The risk of post-transplant oropharyngeal cancer was reported to

Table 2 Suggested screening and preventive strategies for post-transplant malignancies in patients transplanted for alcoholic cirrhosis

Cancer type	Suggested screening and preventive strategy
Skin cancer	Annual dermatological examination beginning 5-year post-transplant Reduced sun-exposure (caps, long sleeve clothing and trousers) Sun-screens
Lung cancer	Annual chest X-rays or low-dose CT chest (particularly in smokers with cumulative pack years of >10) Stop smoking and tobacco products
Oropharyngeal and laryngeal cancers	Annual otolaryngology evaluation Stop smoking and tobacco products
PTLDs	EBV status prior to transplant No recommendations regarding post-transplant surveillance or screening
Colon cancer	Colonoscopy with surveillance biopsies as per local guidelines for general population
Breast cancer (in females)	Annual mammography at age 40 years or as per local guidelines for general population
Cervical cancer (in females)	Cervical cytology as per local guidelines for general population
Prostate cancer (in males)	Annual prostate specific antigen beginning at 50 years of age or as per local guidelines for general population

CT, computed tomography; PTLT, post-transplant lymphoproliferative disorder; EBV, Epstein-Barr virus.

be 25 times higher in alcoholic cirrhosis than in other etiologies by Jain *et al.* (17). In another Spanish study, alcoholic cirrhosis emerged as an independent risk factor for *de novo* malignancies post-transplant with a relative risk of 2 (22). Forty-four percent of those who developed *de novo* malignancies had alcoholic cirrhosis. The incidence of *de novo* malignancies post-transplant was 9% in alcoholic cirrhosis as compared to 3% in non-alcohol related etiologies. Majority of the neoplasms detected were classified oropharyngeal tumors and based on this the authors recommended annual screening for oropharyngeal malignancies in patients transplanted for ALD irrespective of abstinence (22).

Prevention

As post-LT patients are at a higher risk of developing malignancies, there is a need of intensive screening protocols. Finkenstedt *et al.* compared an “intensified” surveillance protocol comprising of yearly thoracic and abdominal CT scan, pap smear, mammography, urological and dermatologic evaluation along with colonoscopy every 5-year with a “historical” protocol of annual chest X-rays and ultrasonography (USG) of the abdomen (57). The

“intensified” protocol resulted in fewer malignancies being diagnosed at an advanced stage (46% *vs.* 75%) and an increased survival in non-dermatologic malignancies (3.3 years *vs.* 75%) as compared to the “historical” protocol (57). Herrero *et al.* also reported improved survival after cancer diagnosis using a multipronged surveillance protocol consisting of urine examination, chest X-ray, and abdominal-USG every 6 months in the 1st year and annually thereafter; mammography every 2 years and colonoscopy every 7–10 years. Additionally, annual otolaryngologic examinations and low-dose CT thorax were also performed in smokers (59). There have been concerns about the risk of radiation in these patients who have probably undergone multiple CT scans in the pre-transplant period. Low-dose CT protocols can help attenuate the radiation risk entailed and screening with yearly low-dose chest CT scans in smokers (cumulative pack years >10) helped diagnose post-transplant lung cancer in early stages in 12% patients (58). A suggested screening schedule is given in *Table 2*. The risk of colorectal and breast cancer does not seem to be significantly greater than that in the general population. Thus, screening for these conditions as per local guidelines for the general population should suffice (60). Smoking cessation and strict avoidance of tobacco-containing products is the

most important preventive measure as emphasized in the AASLD guidelines (61). Immunosuppression should be optimized and calcineurin inhibitors in particular should be minimized.

Conclusions

In conclusion, there is a high risk of post-transplant malignancies in LT recipients. The major factor appears to be immunosuppression. The incidence of certain malignancies including oropharyngeal and lung cancers are particularly increased in patients undergoing transplant for alcoholic cirrhosis. There is a need for cost-effective protocols for prevention of neoplasms in these patients.

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Footnote

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