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ORIGINAL ARTICLE

# Head and neck and esophageal cancers after liver transplant: results from a multicenter cohort study. Italy, 1997–2010

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## Summary

This study quantified the risk of head and neck (HN) and esophageal cancers in 2770 Italian liver transplant (LT) recipients. A total of 186 post-transplant cancers were diagnosed—including 32 cases of HN cancers and nine cases of esophageal carcinoma. The 10-year cumulative risk for HN and esophageal carcinoma was 2.59%. Overall, HN cancers were nearly fivefold more frequent in LT recipients than expected (standardized incidence ratios - SIR=4.7, 95% CI: 3.2–6.6), while esophageal carcinoma was ninefold more frequent (SIR=9.1, 95% CI: 4.1–17.2). SIRs ranged from 11.8 in LT with alcoholic liver disease (ALD) to 1.8 for LT without ALD for HN cancers, and from 23.7 to 2.9, respectively, for esophageal carcinoma. Particularly elevated SIRs in LT with ALD were noted for carcinomas of tongue (23.0) or larynx (13.7). Our findings confirmed and quantified the large cancer excess risk in LT recipients with ALD. The risk magnitude and the prevalence of ALD herein documented stress the need of timely and specifically organized programs for the early diagnosis of cancer among LT recipients, particularly for high-risk recipients like those with ALD.

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**Conflicts of interest**
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## Introduction

Improved survival and increasing number of solid organ transplants performed in many developed countries [1] have greatly contributed to the growing number of patients treated with antirejection therapies. It has been well known for decades that acquired immune deficiency caused by the long-term use of these drugs is associated with elevated cancer risks [2–5] in recipients of solid organ transplants. Among liver transplant (LT) recipients, an overall twofold to fivefold increased risk was consistently documented in comparison with the age- and sex-matched general population. Particularly elevated risks were renowned for virus-related cancers, for example, post-transplant lymphoproliferative disorders (PTLD) associated to infection with the Epstein-Barr virus (EBV), Kaposi sarcoma (KS) related to infection with the KS human herpes virus (KSHV), or skin cancers related to infection with different types of human-papilloma virus (HPV). Furthermore, elevated relative risks have been also described for cancers related to life style habits, which are among the main causes of liver diseases such as heavy alcohol consumption [6,7].

The spectrum of *de novo* cancers (DNCs) following LT has been deeply investigated by several large scale studies in the United States [4], Canada [7], Japan [8], and Northern Europe [3,9]. In Southern Europe, some investigations, mostly clinical-based, were conducted in Spain [10] and in Italy by this group [11,12]. LT recipients face post-transplant cancer risks higher than in the corresponding general population, and these risks are particularly elevated for those who underwent LT because of alcoholic liver disease (ALD) [13]. Accordingly, in this article, we present results from an ongoing multicenter study carried out among recipients of solid organ transplants in Italy. The aim was to quantify, in LT recipients, the risk of cancers known to be associated with alcohol abuse in the immunocompetent population.

## Materials and methods

This cohort study used clinical and epidemiological information collected among LT recipients who, between 1990 and 2010, underwent transplant in nine centers from all over Italy. According to study protocol exclusion criteria, LT recipients were not included in the analysis due to the presence of one of the following conditions: a cancer diagnosis other than hepatocellular carcinoma (HCC) within 5 years preceding transplant; a previous transplant; a follow-up shorter than 30 days after LT; and age at LT transplant below 18 years.

In each of the nine participating centers, a trained study coordinator retrieved pertinent information from clinical charts and checked data quality for completeness and accuracy. Data were transposed in a standardized questionnaire, which included personal information (e.g., age at transplant, sex, area of origin, and residence), transplant information (e.g., date of LT, transplant center, underlying disease, infections, donor status, use of immunosuppressive therapy), and follow-up data. Thereafter, data were entered in an electronic database for the purposes of statistical analysis. For the aim of this analysis, the follow-up was updated to June 30, 2012.

The minimum abstinence period from alcohol consumption before inclusion in the transplant list is 6 months. Alcohol abstinence is thereafter checked at each pretransplant visit, and recidivism in alcohol consumption is a transplant exclusion criterion. Accordingly, information on such habit is routinely collected in Italian LT centers. LT recipients with a history of alcohol abuse were identified according to a standardized clinical and laboratory based protocol (i.e., alcohol abusers were defined as those whose alcohol consumption was deemed to be the cause of the liver disease that led to liver transplant—i.e., ALD). Conversely, cigarette smoking is not a liver transplant exclusion criterion, and data on smoking are not routinely recorded. Hence, only four of the nine transplant centers participating in this investigation actually collected data on smoking in at least 80% of LT recipients.

Cancer diagnoses were actively sought by means of a specific case research form through revision of the clinical charts updated at each follow-up visit. Cancer diagnoses were histologically confirmed and coded according to the International Classification of Diseases and Related Health

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Problems, 10th revision (ICD-10). The vital status was also actively checked, and for deceased individuals without a cancer diagnosis, the death certificate was eventually scrutinized for the presence of a neoplastic disease. This analysis focused on neoplastic sites known to be associated with alcohol abuse in the immunocompetent population with at least five cases observed in the follow-up of our cohort (i.e., carcinomas of tongue, oral cavity, larynx, and esophagus).

Person-years (PYs) at risk for cancer were computed from 30 days following LT to the date of death, the date of cancer diagnosis, the date of last follow-up, or the date of study closure (i.e., June 30, 2012), whichever came first. After a cancer diagnosis, patients did not further contribute follow-up time to the determination of person-years at risk for that cancer type. However, those patients did continue to contribute follow-up time for other cancer types.

Cancer incidence rates were calculated using the Kaplan–Meier product-limit method [14]. The number of observed incident cancer cases in LT recipients was compared to the one expected from sex-, age-, area of residence-, and period-specific incidence rates in the Italian general population. These rates derived from all Italian cancer registries, as published in Cancer Incidence in Five Continents, vol. VII (for the period up to 1992), vol. VIII (1993–1997), vol. IX (1998–2002) [15] or from ITACAN (from 2003 thereafter) [16]. Standardized incidence ratios (SIRs) were computed dividing the number of observed cases by the number of expected ones. SIRs and 95% confidence intervals (CIs) were determined using the Poisson distribution [14]. Incidence rate ratios (IRRs) and 95% CIs—adjusted for age, sex and time since transplantation—were computed to assess the association between these characteristics and cancer risk using the Poisson multivariate regression analysis [14]. For variables with zero observations, the median unbiased estimate of the incidence rate ratio was calculated using the exact Poisson regression. The probability of surviving 5 or 10 years after LT, or after cancer diagnosis, was calculated by means of the Kaplan–Meier method [14].

All statistical analyses were performed using commercially available software (SPSS version 21, SPSS Inc., Chicago, Illinois; and STATA version 13, StataCorp LP, College Station, TX, USA).

## Results

Among the 3042 LT recipients eligible for the study, 272 did not fit inclusion criteria and were therefore excluded, and the remaining 2770 LT recipients were included in this analysis. They were followed-up for a total of 16 350 PYs, with a median duration of follow-up of 4.6 years and a median age at transplant of 53.5 years (Table 1). The majority of LT recipients were men (74.7%), the transplanted liver was almost always from a deceased donor (96.1%), and about three-quarter of recipients in this cohort underwent LT in 2001 or later (Table 1). With regard to baseline liver diseases, the two most common causes of LT were cirrhosis (documented in 87.0% of LT recipients) and hepatocellular carcinoma (HCC) (documented in 34.4%). Infections with hepatitis B virus (HBV) and hepatitis C virus (HCV) were documented in, respectively, 42.1% and in 49.8% of recipients. Alcohol abuse leading to ALD was documented in 26.9% of study subjects. Nearly all patients (98.6%) underwent immunosuppressive therapy with calcineurin inhibitors, whereas very few (1.9%) were treated with mTOR inhibitors (Table 1) (AE, Q2).

During the 16 350 PYs of observation, 178 LT recipients were diagnosed with 186 cancers other than nonmelanoma skin cancers (median age at cancer diagnosis, 53.8 years). These 186 cancer diagnoses included 32 cases (17.2% of all cancers), of head and neck cancers (HN) - i.e., 16 cases of larynx carcinoma (9.5% of all cancers), six cases of tongue carcinomas (3.2% of all cancers), 10 cases of other cancers of the oral cavity (5.4% of all cancers) - and nine cases of esophageal carcinoma (4.8% of all cancers).

Figure 1 illustrates the cumulative risk of HN cancers and esophageal carcinoma following LT. The cumulative risk was higher for HN cancers than for esophageal carcinoma, both after 5 years (1.39% and 0.31%, respectively), and after 10 years from diagnosis (1.84% and 0.75%, respectively).

As compared to the age- and sex-matched general population of Italy, the 2770 LT recipients herein studied were at a nearly fivefold higher risk for HN cancers (SIR=4.7, 95% CI: 3.2–6.6), with a particularly elevated risk recorded for tongue carcinoma (SIR=8.0, 95% CI: 3.0–17.5). Furthermore, esophageal cancer was diagnosed nine times more frequently than expected (SIR=9.1, 95% CI: 4.1–17.2) (Table 2). When this analysis was stratified by sex, SIRs appeared to be particularly elevated in women (SIR=12.3 for HN cancers, and SIR=31.1 for esophageal cancer) (data not shown in tables).

SIRs—stratified according to the presence of ALD—are listed in Fig. 2. As compared to the general population, among LT recipients transplanted because of ALD the SIR turned out to be more than 10-fold higher than expected. The SIR was 12 for HN cancers (95% CI: 7.5–18), 23 for tongue (95% CI: 7.5–54), and 13 for larynx (95% CI: 6.3–22). A 24-fold higher risk for esophageal carcinoma was also documented (95% CI: 9.6–49) (Fig. 2). In non-ALD recipients, the excess risks were of lower magnitude and none of them turned out to be statistically significant (Fig. 2).

A multivariate analysis of the associations between selected study variables and the presence of HN cancers and esophageal carcinoma combined—as compared to LT recipients without those neoplasms—is presented in

**Table 1.** Baseline characteristics of 2770 patients who underwent liver transplantation: Italy, 1990–2010.

| | All patients ($n$ = 2770) *N*. (%) | Patients with *de novo* cancers ($n$ = 178) *N*. (%) |
|---|---|---|
| Sex | | |
| Male | 2069 (74.7) | 140 (78.7) |
| Female | 701 (25.3) | 38 (21.3) |
| Age at transplant (years) | | |
| <45 | 610 (22.0) | 33 (18.5) |
| 45–54 | 931 (33.6) | 68 (38.2) |
| 55–59 | 619 (22.4) | 44 (24.7) |
| 60+ | 610 (22.0) | 33 (18.5) |
| Baseline disease/s* | | |
| Cirrhosis | 2411 (87.0) | 155 (87.1) |
| Liver cancer | 970 (35.0) | 62 (34.8) |
| Cholestatic liver disease | 128 (4.6) | 9 (5.1) |
| Acute liver failure | 114 (4.1) | 6 (3.4) |
| Metabolic liver disease | 70 (2.5) | 4 (2.2) |
| Miscellaneous | 11 (0.4) | 0 (0) |
| History of HBV infection | | |
| No | 1605 (57.9) | 99 (55.6) |
| Yes | 1165 (42.1) | 79 (44.4) |
| History of HCV infection | | |
| No | 1391 (50.2) | 102 (57.3) |
| Yes | 1379 (49.8) | 76 (42.7) |
| History of alcohol abuse† | | |
| No | 2024 (73.1) | 113 (63.5) |
| Yes | 746 (26.9) | 65 (36.5) |
| Ever smoker‡ | | |
| No | 502 (18.1) | 18 (10.1) |
| Yes | 796 (28.7) | 51 (28.7) |
| Unknown | 1472 (53.1) | 109 (61.2) |
| Calendar year at transplant | | |
| ≤2000 | 708 (25.6) | 80 (44.9) |
| 2001–2005 | 1020 (36.8) | 57 (32.0) |
| ≥2006 | 1042 (37.6) | 41 (23.0) |
| Area of origin | | |
| Northern Italy | 602 (21.7) | 45 (25.3) |
| Central Italy | 504 (18.2) | 36 (20.2) |
| Southern Italy | 1560 (56.3) | 96 (53.9) |
| Abroad | 104 (3.8) | 1 (0.6) |
| Status of the donor | | |
| Living | 107 (3.9) | 5 (2.8) |
| Deceased | 2663 (96.1) | 173 (97.2) |
| Use of CNI§ | | |
| No | 40 (1.4) | 0 (0) |
| Yes | 2730 (98.6) | 178 (100) |
| Use of mTORi§ | | |
| No | 2718 (98.1) | 178 (100) |
| Yes | 52 (1.9) | 0 (0) |
| Follow-up | | |
| Total person years (PYs) | 16 349.9 | – |
| Length of follow-up (years)¶ | 4.6 (2.3–8.9) | – |

*The sum does not add to the total because of overlapping conditions.
†Clinically defined as a cause of the disease that led to liver transplant.
‡Data on smoking were collected in 4 of 9 transplant centers.
§Considered as initial immunosuppressive therapy (CNI: Calcineurin Inhibitors; mTORi: mTOR inhibitors).
¶The data are presented as medians and IQRs.

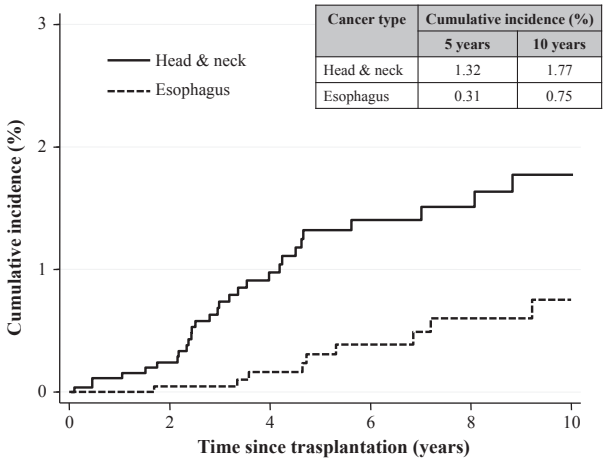


**Figure 1** Cumulative incidence of *de novo* malignancies after liver transplant, according to cancer type and time since transplant. Italy, 1990–2010.

Table 3. IRRs were significantly elevated for LT recipients aged 50 years or older at transplant (IRR=2.7), for those with a transplant period equal to or >2 years (IRR=2.2), and for those with ALD (IRR=7.4). Among 1298 LT recipients with smoking information (46.9% of the whole study group), the combination of cigarette smoking and ALD conferred a very high risk of HN and esophageal cancers (IRR=35.1, 95% CI: 11–107), as compared to recipients who were either nonsmokers, or smokers without ALD, or nonsmokers with ALD. All cases of HN or of esophageal cancer underwent CNI treatment, whereas none of them was treated with mTORi (Table 3).

Overall, the estimated median time of survival after LT was 24.3 years for recipients without a DNC, 8.6 years for those with HN cancer, and 6.2 years for those who developed an esophageal carcinoma. After 10 years from LT, the survival probability was 0.48 for recipients with HN and 0.44 for recipients with esophageal cancers (Fig. 3). The median time from transplant to cancer was 37.5 months for HN cancers and 57.7 months for esophageal carcinoma, while the 5-year survival probability after cancer diagnosis


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**Table 2.** Standardized incidence ratios (SIR) and 95% confidence intervals (CI) for alcohol-related malignancies with at least five observed cases following liver transplantation. Italy, 1990–2010.

| Cancer site | ICD-10 | No. of cancer cases | | SIR (95% CI) |
|---|---|---|---|---|
| | | Observed | Expected | |
| Head & Neck | C00-C14, C30-C32 | 32 | 6.83 | 4.69 (3.21–6.62) |
| Tongue | C01-C02 | 6 | 0.75 | 8.04 (2.95–17.49) |
| Oral cavity, others | C00, C03-C10 | 10 | 3.01 | 3.32 (1.59–6.11) |
| Larynx | C32 | 16 | 3.08 | 5.19 (2.97–8.43) |
| Esophagus | C15 | 9 | 0.99 | 9.07 (4.14–17.21) |

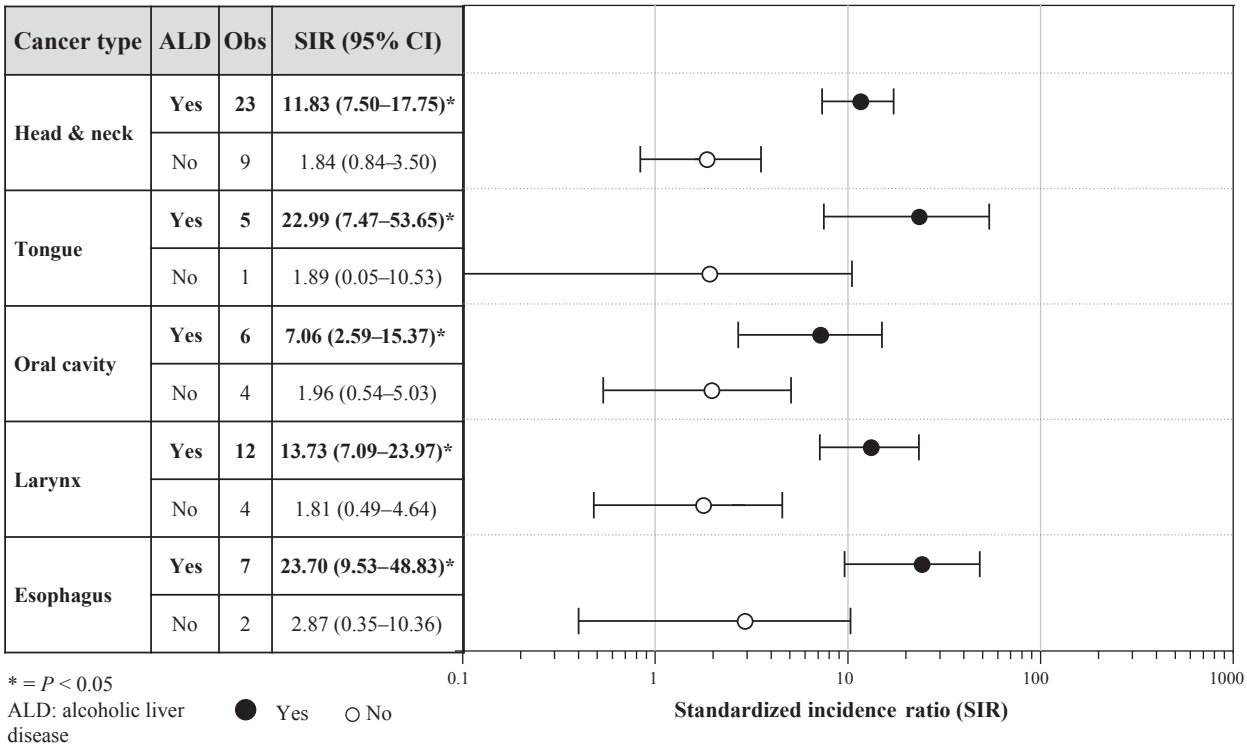



**Figure 2** SIRs for selected cancer sites according to history of Alcoholic Liver Disease. Italy, 1990–2010.

was 35.2% for HN patients, and 14.5% for patients diagnosed with esophageal carcinoma (data not shown in tables). Of the 30 ALD recipients of liver transplant who developed HN cancers or esophageal carcinoma, alcohol consumption after liver transplantation was documented in four (13.3%) (two cases of oral cavity and two cases of cancer of the esophagus). In these ALD LT recipients, the time between transplant and cancer diagnosis was similar (range: 21–104 months) to that of the remaining 26 ALD LT recipients (range: 14–133 months) (data not shown in tables).

Stage at cancer diagnosis was available for 20 of these 41 LT recipients with HN cancers or esophageal carcinoma: Eight cases (40.0%) were early stages (i.e., stage I-II), and 12 (60.0%) cases had advanced disease (i.e., stage III-IV). With regard to the treatment of these 41 neoplasms, chemotherapy was administered in 10 (24.4%), surgery in 18 (43.9%), and radiotherapy in 23 (56.1%). Combinations of these therapeutical approaches were documented in 20 LT recipients (48.8%) with these cancers (e.g., eight cases underwent both surgery and radiotherapy).

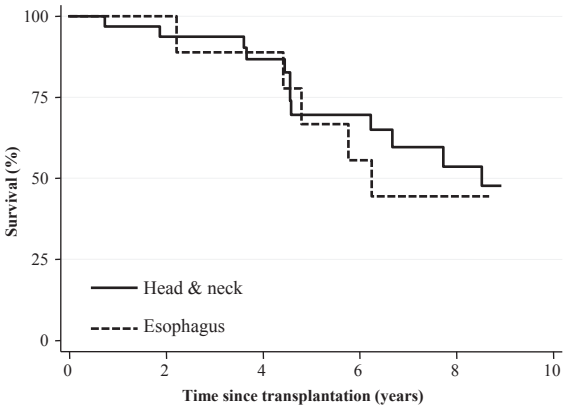
## Discussion

In this cohort of over 2700 Italian recipients of LT followed for up to 20 years, we quantified the strong impact of heavy

**Table 3.** Incidence rate ratios (IRR)* and 95% confidence intervals (CI) for cancers of the head and neck, and for cancer of the esophagus combined, by selected variables. Italy, 1990–2010.

| Variable | Head and neck and esophageal cancers (No. of cases) | IRR (95% CI) |
|---|---|---|
| Sex | | |
| Female | 7 | 1‡ |
| Male | 34 | 1.76 (0.77–3.99) |
| Age at transplant (years) | | |
| <50 | 9 | 1‡ |
| 50+ | 32 | 2.71 (1.29–5.69) |
| Time since transplantation (years) | | |
| <2 | 7 | 1‡ |
| 2+ | 34 | 2.21 (0.98–4.99) |
| History of ALD | | |
| No | 12 | 1‡ |
| Yes | 29 | 7.37 (3.64–14.92) |
| Ever smoker | | |
| No | 1 | 1‡ |
| Yes | 16 | 10.76 (1.46–79.14) |
| Unknown | 24 | 6.53 (0.91–47.03) |
| History of smoking and/or alcohol abuse† | | |
| None/smoking only/ALD only | 2 | 1‡ |
| Smoking and ALD | 15 | 35.08 (11.46–107.44) |
| Use of CNI§ | | |
| No | 0 | 1‡ |
| Yes | 41 | 0.70 (0.13–inf)# |
| Use of mTORi§ | | |
| No | 41 | 1‡ |
| Yes | 0 | 1.48 (0.00–8.25)¶ |

*IRR adjusted for sex age at transplantation and time since transplantation;
†The analysis was limited to patients with known smoking status;
‡Reference category;
§Considered as initial immunosuppressive therapy;
¶median unbiased estimates (MUE) due to missing values;
CNI: calcineurin Inhibitors; mTORi: mTOR inhibitors; ALD: alcoholic liver disease.




| Cancer type | Survival median (IQR) | Survival at 5 years percentage (95% CI) | Survival at 10 years percentage (95% CI) |
|---|---|---|---|
| None | 24.33 (8.19–NR) | 79.69 (77.98–81.29) | 71.83 (69.53–73.99) |
| Head & neck | 8.55 (4.59–19.38) | 69.62 (47.81–83.72) | 47.65 (25.28–67.06) |
| Esophagus | 6.24 (4.79–NR) | 66.67 (28.17–87.83) | 44.44 (13.59–71.93) |

**Figure 3** Probability of post-transplant survival according to cancer diagnosis for selected sites. Italy 1990–2010. DNCs: De novo cancers; NR: Not reached.

alcohol drinking on the risk of HN and esophageal cancers. More than 30% of men and 13% of women transplant recipients in this cohort underwent LT because of an ALD, and they had 10- to 20-fold excess risks of those cancers with a well-established association with alcohol abuse in the immunocompetent population. Moreover, LT recipients who developed alcohol-related cancers had a substantially reduced after transplant survival.

Although our results are not new and confirm previous epidemiological evidence on the risk of alcohol-related cancers in LT recipients [6,13,17], this investigation provides new estimates of very elevated cancer risks in a large group (i.e., 746 individuals) of LT recipients with ALD. More than 20-fold elevated risks for cancer of tongue or esophagus and up to more than 10-fold for oral cavity and larynx documented in these individuals have important clinical implications, particularly for early diagnosis of these cancers. They point to the importance, for transplant centers, to implement a multidisciplinary collaboration with oncologic institutions to provide post-transplant follow-up programs specifically targeted on early diagnosis of cancers of the upper aero-digestive tract. High-risk patients (e.g., smokers and those with a history of heavy alcohol consumption) deserve a particular attention, thus collection of smoking data should be reconsidered in all transplant centers. To this regard, a yearly clinical examination—eventually followed by instrumental exams—of LT recipients with ALD could play an essential role in preventing cancer progression and improving outcomes.

From an etiological viewpoint, the study findings are in accordance with evidence showing the carcinogenicity of alcoholic beverages for HN and esophageal cancers [18,19]. It is difficult, in our population of LT with ALD, to quantify the proportion of the very high excess risk for alcohol-related cancers attributable to iatrogenic immune depression "*per se*". Adult recipients undergoing LT because of ALD have already been noted to have an almost twofold higher risk of nonskin cancers in comparison with recipients undergoing LT for other hepatic conditions, with the exception of primary sclerosing cholangitis [20]. However, the purported mechanisms of alcohol-mediated oncogenesis are poorly understood, and these mechanisms are likely to involve the carcinogenic properties of acetaldehyde and/or the inhibition of DNA methylation via the alteration of retinoid processing

[6,18]. In immunocompetent individuals with a history of heavy alcohol consumption, a higher frequency of chromosomal aberrations, sister chromatid exchange and micronuclei in the peripheral lymphocytes, and other cell types has been recognized, as well different types of DNA damage in tissues [18]. However, the relationship between oxidative stress-induced DNA lesions and alcoholic beverage consumption has not been well established. Moreover, despite molecular and epidemiological evidence for its role in cancer development, there are no data to disentangle the role of immune deficiency. In the setting of HIV infection and AIDS, immune restoration due to the use of highly active antiretroviral therapies (HAART) did not seem to influence the risk of head and neck cancers [5,21]. According to studies conducted in Italy, the risk for head and neck cancers in people with AIDS [21] in the HAART era was about 1.8-fold higher, a magnitude comparable to the one found in the 2024 recipients of LT without an ALD herein studied. Our findings on HN cancers seem thus to indicate that the high prevalence—in the pretransplant period—of heavy alcohol consumption represents the main explanation for the very high-risk patterns for alcohol-related cancers. On the other hand, although nonstatistical significant, the nearly twofold increased risk for HN cancers in non-ALD LT recipients points to the role of mother risk factors in immunosuppressed individuals, like EBV-infection [22] and/or cigarette smoking [6].

The probability of survival for an LT recipient after a diagnosis of *de novo* malignancy is dependent on the specific diagnosis, but it is generally worse than the probability for a nontransplant patient with the same cancer [20]. These study findings confirmed that recipients with a posttransplant alcohol-related cancer have a reduced life expectancy, a further observation that stresses the negative clinical implications of cancers that occur after LT,—and as already stressed—pointing to the need of specific programs for cancer surveillance and early diagnosis in the follow-up of LT recipients. In this study, 60% of ALD LT recipients with staged HN or esophageal cancers had advanced disease (R2, Q8), a further observation that indicates that LT recipients with ALD should be the target of specific secondary prevention programs to support early diagnosis and improving survival.

This was a clinical-based study, with lack of completeness in cancer diagnoses following LT representing a potential methodological limitation. Although we could not perform a linkage with population-based cancer registries for all LT recipients, the strict clinical follow-up of these patients is likely to ensure the completeness of the DNC reporting. Smoking history was available in less than 50% of study subjects because such information is not routinely collected in Italian LT transplant centers, a study drawback that has limited a thorough etiologic investigation of HN and esophageal cancers. However, the important role of smoking in the etiology of these cancers—and its large attributable fraction—are well known [23], and this drawback did not influence our aim of quantifying the risk of HN and esophageal cancers in LT recipients, particularly of those with ALD.

In conclusion, our study findings measured, in Italy, the increased risks of HN cancers and esophageal carcinoma on a large number of LT recipients followed for up to 20 years. Clinicians are already aware that LT recipients, those with ALD in particular, are a population group at high risk for cancers. However, in Italy organized programs for early cancer diagnosis in these patients are lacking, and these findings are thus supposed to offer new quantitative insights for the implementation of such programs for early diagnosis and for improving the cancer outcomes in the setting of solid organ transplantation.

## Authorship

PP: designed, organized the study, contributed to data analysis and interpretation, and wrote the manuscript. DSe: designed, organized and coordinated the study, contributed to data analysis and interpretation of data, and wrote the manuscript. DV, CC, and SV: contributed to data managing, analysis and interpretation of data. PB, AL, UB, GME, GBV, MR, MR, GT, FZ, IB, ADP, AR, and ADL: contributed to analyzing and interpretation of data, and writing the manuscript. LG, GF, DSf, GV, and FN: contributed to data collection.

Other members of the Italian Transplant and Cancer Cohort Study* contributed to data collection.

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