Liver Transplantation-Associated Lung Cancer: Comparison of Clinical Parameters and Outcomes

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Abstract

We performed a retrospective comparison of patients with postliver transplantation lung cancer (PLTLC), patients with transplant-naive lung cancer, and patients with liver transplantation. The standardized incidence ratio for lung cancer in liver recipients was 4.4 in the women and 2.6 in the men. Post-transplant survival was reduced in the PLTLC group; the overall survival (OS) after the diagnosis of lung cancer was similar. OS after lung cancer does not seem to be reduced by liver transplantation. Considering the increased incidence, routine screening should be considered for liver transplantation patients with a history of smoking.

Background: The incidence of lung cancer (LC) is increased in patients with a history of liver transplantation (LT). The purpose of our study was to compare the clinical characteristics and outcomes of patients with postliver transplantation LC (PLTLC) with cohorts of patients with "transplant-naive" LC, and LT patients without LC. **Patients and Methods:** All the patients who had undergone LT or had been diagnosed with LC from 1987 to 2012 were included in the present analysis. The PLTLC cohort was compared with a LT cohort (n = 725) and the local LC registry (n = 2803). The standardized incidence ratios (SIRs) were computed in the classic manner after adjustment for sex, age, and year of follow-up. **Results:** Within the LT cohort, 22 patients (5 women) developed PLTLC (2.3%). The SIR for LC in LT recipients was 4.4 in the women and 2.6 in the men. The PLTLC cohort was older at LT (58.4 vs. 53.3 years; $P = .028$). Also, 90.5% of the PLTLC group had a history of smoking; 8 patients (42.1%) had had LC detected by annual routine lung cancer screening. The median post-LT survival was significantly inferior in the PLTLC cohort (117.1 vs. 182.6 months; $P = .041$). The median overall survival (OS), starting from the diagnosis of LC, was similar in the PLTLC and LC cohort (14.7 vs. 15.1 months; $P = .519$). **Conclusion:** The incidence of LC is significantly increased in the LT population. Therefore, LC screening might be an option for LT patients with a history of smoking. The prognosis of LC does not seem to be impaired by LT, suggesting a minor effect of LT on OS in patients with lung cancer.

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Introduction

Liver transplantation (LT) is the only curative treatment option for patients with end-stage liver disease. Within the past three decades the progress in immunosuppressive and anti-infective treatment options has significantly improved the long-term outcomes in LT patients. In Europe, the 1-year survival rate after LT has reached approximately 83%.[1] With the increase in long-term survival, cardiovascular diseases and cancer have become the leading causes of death in liver transplant recipients.[2] It is expected that malignancy-associated mortality will exceed cardiovascular mortality in these patients within the next 2 decades.[3]

Compared with the incidence of malignancies in the general population, the cancer incidence in LT recipients is increased, ranging from 3% to 26%, depending on the length of surveillance.[4-10] Life-long immunosuppression is considered to be one of the main causes of the increased cancer incidence. A correlation between the duration and extent of immunosuppressive therapy and the incidence of de novo malignancies has been reported in kidney graft

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recipients.[11] It has been postulated that the loss of immunosurveillance caused by immunosuppressive drugs contributes to a pro-oncogenic environment.

Additional risk factors for the development of de novo malignancies after solid organ transplantation include alcohol and tobacco use, age, and hepatitis C, JC, and Epstein-Barr virus.[4,10,12] Compared with the general population, the incidence of lung cancer (LC) is increased two- to threefold in patients who had undergone LT.[13-15] It has been estimated that smoking accounts for approximately 90% of all LCs in the general population[16] and also contributes to the development of LC after LT.[14] To date, only limited data are available incorporating the clinical characteristics and outcomes of patients who developed LC after LT.[15,17] To our knowledge, data comparing LT patients who developed LC and patients with LC without LT in the same geographic region are lacking.

The aim of the present retrospective analysis was to assess the incidence of LC in a cohort of patients who had undergone LT during a period of 25 years and to compare the overall survival (OS) and clinical and demographic characteristics of these patients with the characteristics of 2803 patients with LC and 725 LT patients from the local registries.

Patients and Methods

Study Design

This was a retrospective, single-center study conducted at the hepatology and oncology units of the Medical University of Innsbruck (Innsbruck, Austria). The clinical and demographic characteristics of the patients were collected from 2 databases (the TYROL study [Twenty Year Retrospective Of LC] and the Tyrolean LT registry)[14,18-20] by reviewing the patients' medical records. Both registries focus on the clinical parameters with regard to the underlying diseases. The local institutional review board and ethics committee approved the data acquisition and analysis for these projects.

Cohort Definition

The post-LT LC (PLTLC) cohort consisted of 22 patients. This cohort included all the patients who had undergone LT from 1987 to 2012 at the Medical University of Innsbruck and had developed LC.

The LT cohort consisted of 725 patients. The patients who had undergone LT from 1987 to 2008 were used as a reference group to compare the LT-related long-term survival and clinical and demographic characteristics.

The LC cohort (n = 2803) included the patients with LC diagnosed at our facility from 1987 to 2008.

Sex- and Age-Matched General Population

A data set of the Tyrolean cancer registry was used to determine whether the incidence of LC is increased in patients receiving LT compared with that in the general population. This registry incorporates the clinical data from the general population living in the delineated region of Tyrol.[21]

Parameters Assessed

The tumor-related parameters, including the demographic characteristics, smoking history, age at diagnosis, tumor stage (according to the Union for International Cancer Control, 6th edition), histologic subtype, and circumstances of the diagnosis (incidental finding, during post-LT screening, or symptoms), were assessed. Age at transplantation, the indications for LT, a history of graft rejection, and a history of alcohol abuse were included as LT-related parameters.

Survival Analysis

OS was defined as the interval from the diagnosis of LC (according to histologic verification) to the last follow-up visit or death. OS in the LT cohort was calculated as the interval from the date of LT to the last follow-up visit or death.

Statistical Analysis

The qualitative parameters included the number and percentage of the various modalities. Descriptive statistics included the standard deviation, 95% confidence intervals (CIs), mean, and median. Differences between variables were tested for significance using the χ^2 test or Student's t test. The median OS was estimated using the Kaplan-Meier method with the log-rank test for comparison of subgroups. Standardized incidence ratios (SIRs) were computed in the classic manner after adjustment for sex, age, and year of follow-up. The standard was given by the Tyrolean population.[21] $P < .05$ was considered statistically significant. All analyses were performed using SPSS software, version 20.0 (IBM Corp., Armonk, NY).

Results

Incidence of LC After LT

From 1987 to 2012, 967 patients underwent LT at our facility. Within this cohort, 22 patients developed histologically verified LC. This corresponds to an incidence of 2.3%. The SIR for LC in a sex- and age-matched general population of our geographic area was 4.38 (95% CI, 1.57-11.28) for women and 2.56 (95% CI, 1.49-4.10) for men.

Figure 1 Graph of Interval From Liver Transplantation (LT) to Diagnosis of Lung Cancer in the Post-LT Lung Cancer (PLTLC) Cohort. The Median Interval Was 78.6 Months (95% Confidence Interval, 46.8-110.3 Months)