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High Frequency of Bronchogenic Carcinoma After Single-lung Transplantation

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Abstract

Background—Lung transplantation is a commonly employed therapy in the treatment of patients with advanced lung diseases related to tobacco use. Little is known about the long-term incidence or risk factors for primary lung cancer after lung transplantation. To determine the frequency, clinical features and risk factors for primary bronchogenic malignancy after lung transplantation, we designed a matched cohort study of single and bilateral lung transplant recipients with extended follow-up.

Methods—We retrospectively reviewed the records of 262 lung transplant recipients who survived 90 days post-transplant and assessed for the development of primary lung cancer. One hundred thirty-one consecutive single-lung transplant (SLTx) recipients were matched to 131 consecutive bilateral lung transplant (BLTx) recipients by native disease. Risk factors for lung cancer development were derived using univariate and multivariate proportional hazards models.

Results—Of the SLTx recipients, 6.9% developed primary lung cancer after transplantation as compared with 0% of the BLTx recipients ($p = 0.002$), after a mean of 52 months. Histologically, non-small-cell cancers were present in the native lung, which led to death in 67% (6 of 9) of the patients despite treatment. Significant risk factors for the development of primary lung cancer were increasing age ($p = 0.004$), >60-pack-year smoking history ($p = 0.03$), and SLTx as compared with BLTx ($p < 0.001$).

Conclusions—Single-lung transplant confers a significantly elevated risk of developing primary post-transplant lung cancer as compared with BLTx in patients with comparable native disease, age and tobacco history.

Lung transplantation, either single or bilateral, is a commonly employed therapy in the treatment of patients with advanced lung diseases related to tobacco use. Despite the increased risk of lung malignancy due to tobacco use in non-transplant patients, little is known about the long-term incidence or risk factors for primary lung cancer after lung transplantation. Specifically, the relative risk for post-transplant bronchogenic lung cancer after single-lung transplantation (SLTx), with the presence of a remaining native lung, as compared with bilateral lung transplantation (BLTx), is unknown. Although one would expect SLTx recipients to be at elevated risk for developing lung cancer given their smoking history and immunosuppression, previous reports have suggested a relatively low post-transplant incidence of bronchogenic cancer in patients with SLTx, ranging from 0% to 2.5%.^{1–5} In contrast, rates of overall post-transplant malignancy have increased, and

projections based on the world's largest transplant tumor registry indicate that malignancy is an increasingly prominent late cause of mortality among all solid-organ transplant recipients.⁶ In addition, since the publication of some earlier reports, the mean age of lung transplant recipients has increased steadily along with a concurrent increase in chronic obstructive lung disease (COPD) as an indication for transplantation relative to other non-tobacco-related diagnoses⁷; thus, the risk of lung cancer in lung transplant recipients may be increasing secondarily to these trends in transplant demographics.

In this study we sought to determine the frequency, clinical features and risk factors for primary bronchogenic malignancy in a large cohort of lung transplant recipients with extended follow-up. We specifically hypothesized that patients receiving SLTx would have an elevated frequency of bronchogenic carcinoma as compared with BLTx recipients, after adjusting for native disease, age and tobacco exposure. To test this hypothesis we used a matched cohort design in a population of 262 lung transplant recipients.

METHODS

After appropriate institutional review board (IRB) approval was obtained, we reviewed the medical records of patients who received lung transplants at the Duke University Medical Center. Between January 1992 and October 2005, 149 SLTx were performed at our institution. Of these, 131 were performed on first-time recipients who survived for >90 days post-transplant; these patients constituted our study population. The indications for lung transplant in these patients included chronic obstructive pulmonary disease (COPD) in 98 (75%), idiopathic pulmonary fibrosis (IPF) in 16 (12%), α_1 -anti-trypsin deficiency (A1A) in 10 (8%), sarcoidosis in 5 (4%), primary pulmonary hypertension in 1 (1%) and eosinophilic granuloma in 1 (1%). A control population was generated from consecutive patients undergoing BLTx between October 1993 and March 2005, matched by underlying disease to the study population of SLTx recipients.

The medical records of all patients were reviewed retrospectively for evidence of malignancy. Data extracted from medical records for all patients included pre-transplant computerized tomography (CT) scans; pathologic inspection of the explanted lung(s); and all post-transplant radiographic, bronchoscopic, pathologic and clinical reports. Patient demographics were reported using means, medians and interquartile range (IQR), and results were analyzed using the chi-square test, Fisher's exact test, 2-tailed *t*-test, Cox proportional hazards model analysis or Kaplan-Meier (KM) survival analysis. No patients were lost to follow-up. Mean post-transplant follow-up was estimated using KM analysis.

Routine follow-up of lung transplant recipients at our institution includes chest radiographs daily during post-transplant hospitalization, weekly for 1 month after discharge, and thereafter at 3-month intervals. Bronchoscopic inspection is routinely performed at 1, 3, 6 and 12 months after transplantation and yearly thereafter. Standard immunosuppression consists of cyclosporine before 2002 and tacrolimus after 2002, with azathioprine, corticosteroids and induction therapy with monoclonal IL-2 receptor antagonists since 1999. Details of surgical procedure, post-transplant management and follow-up have been described previously.^{8,9}

RESULTS

Patient Demographics

The demographic characteristics of our study population of 262 lung transplant recipients are shown in Table 1. The cohort of consecutive SLTx recipients was matched exactly by native disease to consecutive bilateral transplant recipients. COPD was the most common

indication for transplant, followed by IPF. There were no significant differences in age or gender at time of transplantation between the SLTx and BLTx groups. Mean smoking history was 48.2 pack-years (IQR 25 to 60) among all patients, and was almost identical among single vs bilateral recipients. Mean follow-up time was also similar between groups and extended over 5 years in each group.

Primary and Secondary Lung Malignancies

No patients had any evidence of malignancy in the explanted lungs at the time of transplant. Primary post-transplant lung cancer was significantly more common among SLTx recipients than BLTx recipients. As shown in Table 2, 6.9% of SLTx recipients developed primary lung cancer as compared with 0% of BLTx recipients ($p = 0.002$, Fisher's exact test). All primary bronchogenic cancers in the SLTx recipients developed in the native lung. Metastatic cancer occurred in 2 SLTx recipients (1 in the transplanted lung and 1 in the native lung, both from skin primaries) vs 1 BLTx recipient (renal primary). Thus, a total of 8.4% (11 of 131) of SLTx recipients developed primary or metastatic lung cancer as compared with <1% of bilateral transplant recipients (1 of 131) ($p = 0.005$, Fisher's exact test).

Clinical Features and Outcomes in Patients With Primary Native Lung Malignancies

Clinical characteristics of the patients who developed primary lung malignancies are shown in Table 3. All patients had a prior smoking history and 1 patient had evidence of smoking after transplantation. The mean interval between transplantation and diagnosis of malignancy was 52.3 months. Pathology was consistent with squamous-cell cancer in 6 of 9, adenocarcinoma in 2 of 9 and carcinosarcoma in 1 of 9 cases. A representative CT image from a patient who presented with Stage III disease is shown in Figure 1. Four patients presented with advanced stage disease and were not eligible for resection. Five other patients underwent resection after the diagnosis. Of the 5 patients undergoing initial surgical resection, 3 had recurrent malignancy at a mean of 44.3 months after initial surgery. Sixty-seven percent (6 of 9) of patients died during the period of follow-up, all related to progressive or meta-static lung cancer. Three patients with malignancy remained alive at the time of follow-up, but only 1 of whom had >4 months of follow-up post-diagnosis. Survival after the development of primary lung cancer was 50% at 1 year and 25% at 5 years from the time of diagnosis, as shown in Figure 2.

Risk Factors for Primary Lung Cancer After Transplant

To determine the risk factors for development of post-transplant primary bronchogenic lung cancer, we performed a series of univariate Cox proportional hazard models that considered the following factors upon the time to onset of post-transplant malignancy: age (as continuous variable); native disease; gender; prior pack-years smoking (as continuous variable); and type of transplant operation. In univariate analysis, SLTx and increasing age were significantly associated with the development of malignancy (Table 4). Although every patient who developed malignancy had a prior smoking history, the relatively small number of patients with no prior smoking history limited our ability to consider the actual risk incurred by smoking on bronchogenic cancer in this population. When prior smoking was dichotomized at 60 pack-years (selected because it defines the upper quartile of the population), however, smoking also showed significance in univariate analysis (Table 4). In the univariate analysis, the most significant risk for post-transplant bronchogenic cancer was conferred by SLTx (vs bilateral), with a relative risk of 4.31 (95% confidence interval [CI]: 3.30 to 5.63; $p < 0.001$). In the multivariate analysis, after adjusting for other co-variables, SLTx (relative to BLTx) remained the most significant risk factor for the development of primary lung cancer after transplantation (relative risk: 5.306; $p < 0.0001$; 95% CI: 4.012 to

7.019). Smoking history and age were not significant risk factors according to multivariate analysis.

DISCUSSION

Our results demonstrate that primary bronchogenic carcinoma is a prominent long-term complication of SLTx. Furthermore, our analysis has demonstrated that, although disease was often considered resectable at presentation, the clinical course was frequently recurrent, aggressive and fatal, accounting for a significant number of deaths in the SLTx population. We identified increasing age, single-lung (vs bilateral) transplant and >60-pack-year history of tobacco use as significant risks for the development of primary bronchogenic cancer after lung transplantation.

This is the first study on this topic to have used a matched cohort design to specifically compare SLTx and BLTx as risk factors for the development of primary lung malignancy; this design allows for novel analysis of lung cancer risk, controlling for native disease, smoking history, type of transplant and demographic characteristics. Our results are in contrast to those of prior studies in lung transplantation, which have uniformly found a lower frequency of de novo bronchogenic carcinoma than we did. Prior studies have reported the frequency of post-transplant bronchogenic carcinoma to range from 0% to 2.5% in SLTx recipients and to be 0% in BLTx recipients.^{1–5} Our higher frequency of malignancy is likely explained in part by the longer-term follow-up in our study as compared with prior studies. In our cohort we included patients surviving >90 days post-transplant and who had a mean of >5 years post-transplant follow-up. The mean interval between transplantation and diagnosis of malignancy was 52.3 months in our patients, longer than the mean follow-up reported in any previous study. The higher incidence of malignancy in our study might also reflect improved survival in recent years after lung transplantation,⁷ such that more patients are now living long enough to develop lung cancer as a late cause of mortality.

Our increased incidence of malignancy as compared with prior studies might also in part reflect changes in the demographics of lung transplant recipients since the time periods of past studies. In the past 15 years, the mean age of lung transplantation recipients has risen concurrent with an increase in the frequency of COPD as an indication for transplantation relative to other non-tobacco-related diagnoses.⁷ The mean age of our study population (55.4 years) was older than that reported in prior studies (44 to 51 years; overall mean 46.9 years); similarly, the percentage of our patients who received transplantation for COPD (75%) far exceeded the range reported in past studies (32% to 56%).^{1–5} As our study demonstrated that increasing age and smoking history are risk factors for the development of primary post-transplant lung cancer, it is not surprising that these demographic trends would be accompanied by an increased frequency of lung cancer in this population.

Our matched cohort study design with similar demographics and smoking histories between our SLTx and BLTx groups enabled us to evaluate the added risk of cancer conferred on patients by SLTx. Increasing age and smoking history, both established risk factors for bronchogenic cancer,^{10–12} were confirmed by univariate analysis to be independent risk factors in our study. We suspect strongly that all 9 malignancies arose de novo after transplant, given the negative CT findings before transplantation. Thus, our results clearly demonstrate that SLTx confers a significantly greater risk for developing lung cancer than BLTx after adjusting for age, native disease and smoking history. One limitation of the analysis is that we did not formally control for effects of rejection episodes on the development of malignancy; however, all patients received a similar immunosuppressive regimen and there did not appear to be any increased incidence of rejection among the patients with lung malignancy.

Our results are consistent with studies of other types of solid-organ transplantation, which recognized malignancy as an increasing cause of late death.⁶ According to a validated lung cancer risk model,¹⁰ the 10-year risk of developing lung cancer in a non-transplant recipient of our population's mean age (55.5 years) and smoking history (49.5 pack-years) is no more than 2% with continued tobacco exposure. In our study, the frequency was 6.9% over a mean follow-up time <10 years (5.5 years in SLTx patients), implying a much higher than expected incidence of lung malignancy in the SLTx population. The increased frequency and refractoriness of cancer in this study's population likely reflects a synergistic interaction between native lung tobacco exposure, patient age and the carcinogenic effects of long-term immunosuppression. Proposed mechanisms for this latter etiology include the inhibition of immune-mediated tumor surveillance¹³ and direct immune-independent carcinogenic effects of cyclosporine and other immunosuppressants.¹⁴

Our results hold important implications for the current management of SLTx recipients. The increased frequency of lung cancer in this population, despite regular radiographic surveillance, underscores the importance of aggressive investigation of suspicious radiographic or clinical findings. The high recurrence rate (60%) in our patients who underwent resection suggests that aggressive surgical management may be preferred in patients with Stage I or II disease, and consideration should be given to adjunct chemotherapy even in milder stage disease. In general, an attempt was made to reduce immunosuppression after the diagnosis of lung malignancy.

Our results contribute to ongoing debate regarding the appropriate type of transplant operation in patients with tobacco-related disease. In patients with emphysema, either single or bilateral lung transplant can be safely pursued. SLTx allows maximization of the limited donor pool by potentially allowing two recipients to benefit from a single donor. However, the benefits to society of SLTx must be weighed against the long-term outcome for each individual recipient. ISHLT registry data demonstrated improved long-term survival after BLTx compared with SLTx.⁷ Although the reasons for this improved long-term survival in recipients of BLTx are not entirely clear, our study has demonstrated that SLTx recipients with a history of tobacco-related lung disease are at increased risk of developing bronchogenic cancer in the years after transplantation, suggesting at least one reason for the worse overall survival of SLTx recipients as compared with BLTx recipients.

In summary, we have reported the development of de novo primary lung cancer in the native lung of 6.9% of recipients of single-lung transplantation in a large cohort of lung transplant recipients. In this population, native lung cancer was characterized by an aggressive and frequently fatal course. This frequency of primary lung cancer was shown to be higher than that reported in previous studies and significantly higher than in a control population of matched BLTx recipients. Thus, as improved medical and surgical management leads to improved longer-term outcomes after lung transplantation, primary lung cancer is likely to be an increasingly recognized complication in the native lung of SLTx recipients. Our results suggest that increased attention should focus on careful surveillance of the native lung in all SLTx recipients. Future studies should evaluate the frequency of lung cancer in STLx recipients over an even longer follow-up period, along with investigating additional potential risk factors and the relative effectiveness of different methods of surgical and medical management.

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Figure 1. Chest CT of a lung transplant recipient. The patient was a 67-year-old SLTx recipient (right lung). CT was performed 114 months after transplant. The spiculated mass in the medial aspect of the left upper lobe (arrow) was later demonstrated histologically to be non-small-cell carcinoma.

Figure 2.
Kaplan–Meier survival of STLx recipients with bronchogenic carcinoma, from the time of diagnosis.

Table 1

Patient Demographics

	SLTx	BLTx
Total	131	131
Disease		
Emphysema	98 (75%)	98 (75%)
Idiopathic pulmonary fibrosis	16 (12%)	16 (12%)
α_1 -anti-trypsin deficiency	10 (10%)	10 (10%)
Sarcoidosis	5 (5%)	5 (5%)
Eosinophilic granuloma	1 (1%)	1 (1%)
Primary pulmonary hypertension	1 (1%)	1 (1%)
Mean age at transplant, years (SD)	55.5 (7.64)	55.2 (8.5)
Male gender	65 (50%)	75 (57%)
Mean pack-years (pre-transplant)	49.5	47.0
Mean post-transplant follow-up (years)	5.5	6.4

Table 2

Frequency of Primary and Metastatic Cancers Among SLTx and BLTx Recipients

	SLTx		BLTx
	Native lung	Transplant lung	
Primary lung cancer	9 (6.9%)	0	0
Lung metastases from other primary cancer	1 (0.7%)	1 (0.7%)	1 (0.7%)
Total lung cancers		11	1

Table 3

Clinical Features of Patients With Primary Bronchogenic Cancer

Patient	Pre-transplant diagnosis	Age at transplant (years)	Pathology	Stage at diagnosis	Months until diagnosis after transplant	Treatment	Months survival after cancer diagnosis
1	Emphysema	52	Adenocarcinoma	Stage IA T1N0M0	61.5	Resection (lobectomy)	41.7 (alive)
2	Emphysema	56	Adenocarcinoma	Stage IA T1N0M0	37.2	Resection (twice—wedge resection, lobectomy)	69.3
3	Emphysema	60	Carcinosarcoma	Stage IA T1N0M0	69.4	Resection (wedge resection)	61.4
4	Emphysema	62	Squamous-cell carcinoma	Stage III	19.1	No treatment	1.4
5	Idiopathic pulmonary fibrosis	57	Squamous-cell carcinoma	Stage IV	9.2	Palliative radiation	1.5
6	Emphysema	55	Squamous-cell carcinoma	Stage IA T1N0M0	18.5	Resection (lobectomy)	19.6
7	Emphysema	58	Squamous-cell carcinoma	Stage IIB T3N0M0	82.5	Chemotherapy and radiation	3.5 (alive)
8	Emphysema	58	Squamous-cell carcinoma	Stage IIIA T3N1MX	119.2	Resection (lobectomy)	0.6
9	Emphysema	57	Squamous-cell carcinoma	Stage IA T1N0MX	53.9	Chemotherapy and radiation	2.4 (alive)

Table 4

Significant Risk Factors for Primary Post-transplant Bronchogenic Cancer in Univariate Analysis

Risk factor	Hazard ratio	95% CI	p-value
Increasing age (continuous)	1.03	1.01–1.04	0.004
Smoking (>60 pack-years)	1.38	1.03–1.85	0.03
Single-lung transplant	4.31	3.30–5.63	<0.001