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Prevalence and outcome of lung cancer in lung transplant recipients

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Summary
Background: Lung transplant is the only available therapy for patients with advanced lung disease. The goal of this study was to examine the prevalence, origin, management and outcome of lung cancer in recipients of lung transplant at our institution.
Methods: After institutional review board approval, we conducted a retrospective chart review of all lung transplantations in our institution from January 1990 until June 2012.
Results: The prevalence of lung cancer in the explanted lung was 6 (1.2%) of 462 and all cases were in subjects with lung fibrosis. All 4 subjects with lymph node involvement died of causes related to the malignancy.

Nine (1.9%) of 462 patients were found to have bronchogenic carcinoma after lung transplant. The most common location was in the native lung in recipients of a single lung transplant (6 out of 9 patients). In one case, the tumor originated in the allograft and was potentially donor related. The median time to diagnosis after lung transplant was 28 months with a range from 9 months to 10 years. Median survival was 8 months, with tumors involving lymph nodes or distant metastases associated with a markedly worse prognosis (median survival 7 months) than stage I disease (median survival 27 months).
Conclusions: The prevalence of lung cancer in lung transplant recipients is low. Using accepted donor screening criteria, donor derived malignancy is exceptionally rare. While stage I disease

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is associated with improved survival in this cohort, survival is still not comparable to that of the general population, likely influenced by the need for aggressive immune suppression.

Background

Lung transplantation provides a life-saving therapy for patients with end-stage pulmonary disease. Two of the three most common indications for lung transplantation include idiopathic pulmonary fibrosis (IPF) and chronic obstructive pulmonary disease (COPD). In the era of the Lung Allocation Score (LAS), transplantation for fibrotic lung disease is becoming more common. Lung transplant outcomes have greatly improved since the first lung transplant in 1983 [1], but significant morbidity still results from long-term immunosuppressive therapy needed to prevent graft rejection. Immunosuppression reduces the natural anti-tumor immune response, predisposing transplant recipients to an increased risk for malignancies [2]. In the last decade, there has been an increase in the development of lung cancer in lung transplant recipients [3]. This increase may be due to a longer survival time for transplant recipients [4] and an increased number of patients receiving transplants for COPD and IPF [3]. A review of the Scientific Registry of Transplant Recipients found an elevated standardized incidence ratio of 6.13 for the development of lung cancer in lung transplant recipients, higher than any other solid organ recipient cohort [5]. This may be partially explained by the fact that COPD and IPF, both conditions with a high prevalence of smokers are some of the most common indications for lung transplant. There is an increased risk of lung cancer in COPD, and whether obstructive lung disease itself is an independent risk factor for lung cancer is subject to debate [6]. Further, IPF has been linked to an increased risk for the development of lung cancer, 17% in one autopsy series [7]. This reflects a greater prevalence than in patients without IPF and seems to persist even when smoking habits are considered [8]. Finally and importantly, immunosuppressive regimens in lung transplant are substantially more aggressive than in other solid organ transplant, since the incidence of acute and chronic organ rejection is markedly higher, representing an important risk factor for development of malignancy post-transplant, through different mechanisms [9—13]. While the increased risk for cancer post-lung transplant has been documented, there are only a few studies presenting data detailing the discovery of bronchogenic carcinoma in the explanted lung at the time of surgery [14—16].

A better understanding of the prevalence of lung cancer and the definition of at-risk populations in patients undergoing lung transplantation could help to identify methods to improve transplant safety and the prognoses for patients who develop bronchogenic carcinoma. To this end, we conducted a retrospective study on both the discovery of lung cancer in explanted lungs and the development of *de novo* bronchogenic carcinoma post-transplant at Brigham and Women's Hospital.

Subjects & methods

We conducted a retrospective chart review of all patients who underwent a lung transplant at Brigham and Women's Hospital (BWH) between January 1990 and June 2012. The study was reviewed and approved by BWH institutional review board (Protocol Number 2011-P-002392/1).

In the study period a total of 457 subjects underwent lung transplant at BWH. Of these subjects, 5 received a re-transplant of an already transplanted lung, bringing the total number of lung transplant surgeries to 462. In these 5 cases, native lungs were counted as explants. Transplanted lungs were counted both as a transplant and explants. 4 patients were transplanted for chronic rejection and one patient was retransplanted for recurrent acute rejection.

Lung transplant recipients in whom cancer was identified in the explanted lung at the time of transplant, or in whom lung cancer was identified post-transplant either in the native lung or in the allograft, were identified from Brigham and Women's Hospital's computerized hospital records and lung transplant surgery database. Histology slides from all identified cases of malignancy were reviewed by a pulmonary pathologist (RP) to confirm the cancer diagnosis. Cases of post-transplant lymphoproliferative disorder were excluded from the post transplant lung cancer analysis.

During the study period, the policy at BWH required all patients listed for lung transplantation to keep computed tomography (CT) scans of the chest updated yearly prior to lung transplant. Suspicious findings on these scans were evaluated according to published guidelines [17], and any malignant findings seen on a biopsy, or a positive fludeoxyglucose positron emission tomography (FDG-PET) when biopsies are deemed unsafe because of the patient's respiratory compromise resulted in the removal of the subject from the lung transplant eligibility list. Of the patients who were found to have carcinoma in the explanted lung, only one was transplanted prior to the policy of yearly CT scans. The CT scan in this case was performed 21 months prior to transplant and had not shown any evidence of malignancy.

Donors with a greater than 20 pack year history of smoking were screened with chest CT scan prior to organ acceptance. Evidence of suspicious nodules on donor imaging or gross inspection at the time of procurement led to either biopsy with frozen section analysis and/or exclusion from lung donation.

Post-transplant, subjects received immunosuppression consisting of standard therapy at the time of transplant. In 2001 our program transitioned from cyclosporine A to tacrolimus (levels adjusted to 8—12 ng/ml in the first year post-transplant, and 6—8 ng/ml thereafter), and from azathioprine to mycophenolate (1 gm twice a day), as standard *de novo* immune suppression. In 2008, our