Lung Cancer and Lung Transplantation

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KEYWORDS

• Lung transplantation • Malignancy • Immunosuppression

KEY POINTS

- Lung transplantation remains a viable option for patients with endstage pulmonary disease.
- The issue of lung malignancy becomes an increasing concern.
- There have been concerns about the addition of immunosuppression increasing the risk of native lung malignancies in these patients. Despite removing the affected organ and replacing both lungs, the risk of lung malignancies still exists.
- Incidental evidence of malignancies may be identified in the explanted lungs of recipients.
- Regardless of the mode of entry, lung cancer affects the prognosis in these patients and diligence is required.

INTRODUCTION

Lung transplantation remains a viable option for patients with endstage pulmonary disease. According to the 2016 Annual Report of the International Society for Heart and Lung Transplantation (ISHLT), 55,795 adult lung transplants are entered into the ISHLT Registry. The median survival after primary lung transplantation for all indications is 5.7 years.[1] These patients have a substantial survival benefit and a dramatic improvement in their quality of life.

With improvements in selection criteria and perioperative management, these patients live longer. Because of this, as well as extended donor criteria, the issue of lung malignancy becomes an increasing concern. In the pretransplant population, these patients may have an increased risk of malignancy due to their smoking status or environmental exposure before being evaluated for transplant. This risk continues well into the posttransplant period, especially for individuals undergoing single lung transplant. The overall prevalence of malignancy is 5.1%, 18.2%, and 28.7% at 1, 5, and 10 years, respectively, after both single and double lung transplantation. Cause of death from all nonlymphoma malignancy is 0.1% (0–30 days), 3.0% (31 days to 1 year), 8.4% (>1–3 years), 11.8% (>3–years), 14.5% (>–years), and 13.7% (>10 years).[1]

There have been concerns about the addition of immunosuppression increasing the risk of native lung malignancies in these patients. In addition, despite removing the affected organ and replacing both lungs, the risk of lung malignancies still exists in these patients. Finally, incidental evidence of malignancies may be identified in the explanted lungs of recipients.

Regardless of the mode of entry, lung cancer affects the prognosis in these patients and diligence is required.

LUNG CANCER AS AN INDICATION FOR TRANSPLANT

Lung transplant for lung cancer was initially described in 1963 by Dr Hardy and colleagues[2]

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from the University of Mississippi. This patient lived 17 days and died from complications related to renal failure and malnutrition. Currently, it is well established that patients with a history of malignancy within the past 5 years are not candidates for lung transplant.

There is a variant of bronchogenic carcinoma that may benefit from double lung transplant. Patients who have a subtype of bronchogenic carcinoma may be candidates for lung transplant. Initially called bronchioloalveolar carcinoma (BAC), it is characterized by a high incidence of intrapulmonary dissemination, whereas lymph node and extrathoracic metastasis is rare. In this context, lung transplantation could be an option in the treatment. BAC is now classified as either advanced multifocal (diffuse or pneumonic) adenocarcinoma in situ or minimally invasive adenocarcinoma of the lung.[3]

Patients with advanced multifocal adenocarcinoma may have a pneumonic-type lung adenocarcinoma that exhibits a diffuse consolidative pattern without bronchial obstruction. There are areas of both ground-glass appearance and solid consolidation, demonstrating the heterogeneous nature of this form of adenocarcinoma. Histologically, in addition to a lepidic predominant growth pattern, there may be areas of invasive components along with desmoplastic stroma. Alveolar spaces may fill with mucin, which would portend a poorer prognosis.[3]

These patients typically do not have nodal or distant metastasis. There is significant diffuse pulmonary involvement that renders the patient unresectable by thoracic oncologic standards, such as sublobar resection, lobectomy, or pneumonectomy, due to the bilateral nature of the spread. In addition, the rate of progression of lepidic predominant adenocarcinoma is slow. Therefore, some patients benefit from double lung transplant. This was initially described in 1997 by Dr Etienne and colleagues[4] for what was formerly known as BAC.

Because there has been a shift to mutational analysis for adenocarcinoma, a striking feature of mucinous adenocarcinoma is the absence of EGFR mutation but presence of KRAS mutation. It would make using a tyrosine kinase inhibitor ineffective in these patients but there is a growing use of drugs with a KRAS mutation.[5] Despite these studies, the 1-year survival for this population remains poor.[6]

In the patients with this variant of adenocarcinoma who are transplanted, the recurrence rate still exists. Some studies have demonstrated equivalent disease-free survival of noncancerous lung transplant subjects. In a study that used a questionnaire sent to 150 programs associated with the ISHLT registry, of the total of 8000 lung transplantations performed, 69 patients were found to have a bronchogenic carcinoma in the explanted lung with an incidence of 0.9%.[7]

Of these subjects, 26 were known to have multifocal (at the time) BAC. Nine subjects underwent single lung transplant. Four of these subjects died postoperatively due to primary graft failure (2), right ventricular failure (1), or cardiogenic shock (1). Seventeen subjects underwent double lung transplant with no postoperative deaths. Of the 22 subjects who survived surgery, 13 (59%) developed recurrence between 5 and 49 months after transplant (median of 12 months). Of these subjects, 9 died between 11 and 82 months post-transplant. Eleven of these recurrences developed in the transplanted lung. Overall survival at 5 and 10 years was 39% and 31%, respectively. Five-year recurrence-free survival was 35%

Another study used the United Network for Organ Sharing database to evaluate subjects undergoing lung transplantation with primary diagnosis of BAC or bronchogenic carcinoma between 1987 and 2010. Not included were subjects with incidentally discovered bronchogenic carcinoma. Twenty-nine out of 21,533 were identified to have BAC (0.13%). Double lung transplant was performed in 79% of BAC subjects. All explants were noted to have multilobar tumor involvement. Fifty-two percent (14) had pure BAC histology. Forty-one percent (11) had a focus of invasive or other features consistent with adenocarcinoma on a predominant background of BAC. Seven percent (2) had predominant adenocarcinoma, mucin production was noted in 11 tumors (41%), and papillary and acinar features were noted in 15% and 19% of invasive tumors, respectively. Of the 20 subjects whose lymph node specimens were evaluated, metastatic carcinoma was identified in 18.5% hilar nodes and 14.8% in mediastinal lymph nodes. A complete resection (R0) was achieved in 93% of the evaluated specimens. Graft survival was not statistically different between BAC and non-small cell lung cancer (NSCLC) subjects and noncancer transplant subjects at 5 years (44% and 47%) and at 10 years (19% and 24%). It was also identified that the evidence of invasive tumor or lymph node metastasis did not preclude the possibility of long-term survival. Presence of invasive cancer on histologic examination was associated with a trend toward decreased survival. From this study, subjects with advanced diffuse tumor have a high mortality rate associated with their disease process and median survival is approximately 1 year without treatment. The investigators suggest that a future