Lung Transplantation for Multifocal Lung Adenocarcinoma (Multifocal Lung Carcinoma)

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KEYWORDS

• Bronchioloalveolar • Transplant • Lung cancer • Adenocarcinoma • Multifocal

KEY POINTS

- Lung transplantation is a treatment option for some patients with lung-limited, multifocal adenocarcinoma.
- Preoperative tissue assessment to confirm the primary histology and mutation status and to evaluate mediastinal sites will help ensure proper patient selection.
- Multifocal, minimally invasive adenocarcinoma, even in the presence of lymph node metastases, does not necessarily preclude durable survival after double-lung transplantation in very carefully selected patients.

INTRODUCTION

Resection of early stage non–small cell lung cancer (NSCLC) provides the best opportunity for cure and remains the gold standard of treatment.[1] In patients who are medically fit with minimally invasive disease, lobar resection with mediastinal lymph node staging is the currently recommended therapeutic modality. However, there is a large subset of patients who are medically inoperable, either by virtue of poor pulmonary function or advanced disease. These patients will be relegated to wedge resection, radiation therapy, chemoradiotherapy, or palliative chemotherapy depending on the specifics of the presentation of cancer. However, there is a very small fraction of patients with a unique and rarely observed set of circumstances that are traditionally classified as medically inoperable, whose lung cancer and respiratory insufficiency can be effectively palliated through lung transplantation.[1,2]

Lung transplantation is most commonly used for the treatment of end-stage chronic obstructive pulmonary disease (COPD), cystic fibrosis, and idiopathic pulmonary fibrosis.[3] Over the course of the last decade, there has been increasing survival following lung transplantation, attributed to improvements in donor preservation strategies and postoperative critical care management.[3] New strategies for lung allocation have decreased the wait times and death rates for transplant candidates and improved efficiency within the system.[4] These strategies have allowed for an expanded recipient pool for lung transplantation, as prior absolute contraindications are being relaxed: (1) age greater than 65 years, (2) coronary artery disease, and (3) malignancy.[5,6] Although

The authors have nothing to disclose.

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Thorac Surg Clin 24 (2014) 485–491
http://dx.doi.org/10.1016/j.thorsurg.2014.07.011
1547-4127/14/$ – see front matter

there is still some controversy regarding these relaxed requirements, emerging data justify this practice, including some evidence to support transplantation in patients with lung cancer.[7–12]

The recommendation against transplantation in the setting of cancer stems from the chronic immunosuppression mandatory for the maintenance of the donor organ. Even in the absence of a history of cancer, chronic immunosuppression is known to increase the rates of de novo malignancy in transplant patients, with the risk of lung cancer being highest in lung transplant recipients.[13] Curiously, there are presentations of NSCLC, though occasionally widely disseminated within the pulmonary parenchyma, that have a limited invasive component and limited lymph node burden.[14] These patients can undergo a curative resection through bilateral lung transplantation and surprisingly may not possess excessive risk of cancer recurrence compared with the general population of lung transplant recipients.[11] It is paramount to appreciate the rarity of this unique presentation of NSCLC and understand when a pulmonary transplant is indicated in this setting.

PATIENT SELECTION

The selection of patients for this controversial area of lung transplantation is very stringent, as lung cancer therapy mandates the establishment of universally accepted regulations. The guidelines published in 2006 by the International Society for Heart and Lung Transplantation (ISHLT) specify absolute and relative contraindications to transplantation that could preclude a survival benefit from transplantation.[5] Most of these are common for all solid-organ transplants. Excluding history of cancer, absolute contraindications to lung transplantation include (1) a secondary untreatable advanced organ dysfunction, (2) non-curable chronic extrapulmonary infection, (3) significant chest wall or spinal deformity, (4) untreatable psychiatric condition that renders patients unable to comply with medical therapy, (5) absence of social support system, (6) substance addiction, and (7) documented noncompliance with treatment regimen.[5] Patients with untreatable advanced organ dysfunction, such as kidney or liver, lack the reserve necessary to tolerate the high-risk operation of lung transplantation. It should be noted that patients with heart dysfunction not amenable to coronary artery bypass grafting or percutaneous coronary intervention may be candidates for concurrent heart-lung transplantation.[5,6] Some chronic infections are incompatible with the required chronic immunosuppression needed to prevent graft rejection. Anatomic deformities increase the technical difficulty of an already high-risk operation. Finally, acceptable posttransplant outcomes are tightly linked with adherence to complex medication regimens and close follow-up. Any personal or mental issues precluding recipients from actively participating in their own care should be examined in depth before listing the patients for transplant.[15]

Several relative contraindications serve to increase the morbidity of transplantation. These include (1) age greater than 65 years, (2) pretransplant mechanical ventilation requirement, (3) poor functional status and muscle wasting, (4) obesity, (5) severe osteoporosis, and (6) colonization with highly resistant organisms.[5,6] Consequently, candidacy for lung transplantation is complex and confounded by multiple independent issues. Assuming these can be appropriately adjudicated, timing and referral for listing for lung transplantation ultimately depend on the severity of the disease and the expected pretransplant mortality as well as survival after transplant.

Lung transplant candidates can expect a median posttransplant survival of 5 years,[3] and this must exceed their predicted pretransplant survival by a significant margin. The severity of disease and, more importantly, the rate of functional deterioration must be appreciated. The Lung Allocation Score (LAS) has been developed to help clinicians rank candidates based on priority. Not surprisingly, patients with the most urgent need for transplant (eg, on mechanical ventilation from primary lung failure) receive the highest LAS but are also at the highest risk for poor outcomes after transplantation.[4,16] These guidelines serve as a starting point when considering lung cancer presentations, which might allow patients to be considered for lung transplantation.

Bronchioloalveolar Carcinoma and Current Classification

In 2011, a paradigm shift in the pathologic classification of lung cancer occurred with the collaborative publication of a new lung adeno carcinoma (ACA) classification sponsored by the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society.[17] The most notable change from the 2004 World Health Organization classification was the discontinuation of bronchioloalveolar carcinoma (BAC) terminology.[14,17] BAC referred to at least 5 disparate tumor histologies with varying clinical outcomes and molecular properties. The new classification provides for several new entities, including ACA in situ (AIS) or minimally invasive ACA (MIA),