Single- Versus Double-Lung Transplantation in Pulmonary Fibrosis: Impact of Age and Pulmonary Hypertension

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Background. **Double-lung transplantation (DLT) has better long-term outcomes compared with single-lung transplantation (SLT) in pulmonary fibrosis. However, controversy persists about whether older patients or patients with high lung allocation scores would benefit from DLT. Moreover, the degree of pulmonary hypertension in which SLT should be avoided is unknown.**

Methods. **A retrospective analysis using the United Network for Organ Sharing database was performed in all recipients of lung transplants for pulmonary fibrosis. Kaplan-Meier survival for SLT versus DLT was compared and stratified by age, allocation score, and mean pulmonary artery pressure. Cox regression and propensity-matching analyses were performed.**

Results. **Between 1987 and 2015; 9,191 of 29,779 lung transplants were performed in pulmonary fibrosis. Ten-year survival rates were 55% for DLT and 32% for SLT ($p < 0.001$). When stratified by age, DLT recipients had improved survival at all age cutoffs, except age ≥70 years. In addition, DLT recipients had improved survival across all lung allocation scores (<45, ≥45, ≥60, ≥75) and all pulmonary artery pressure categories (<25, ≥25, ≥30, ≥40 mm Hg). Among DLT recipients, pulmonary artery pressure and allocation score did not affect survival. Among SLT recipients, a pressure ≥25 mm Hg did not influence survival. Conversely, patients with a pressure ≥30 mm Hg and an allocation score ≥45 had decreased survival. On Cox regression and on propensity matching, DLT had improved survival compared with SLT.**

Conclusions. **In pulmonary fibrosis, DLT has improved survival compared with SLT and should be considered the procedure of choice in patients younger than 70 years of age. SLT in patients with mean pulmonary artery pressure ≥30 mm Hg and an allocation score ≥45 should be discouraged.**

(Ann Thorac Surg 2018;■:■–■)

In 2007, the Registry of the International Society for Heart and Lung Transplantation (ISHLT) reported that double-lung transplantation (DLT) has superior 5-year survival compared with single-lung transplantation (SLT) in patients with interstitial pulmonary fibrosis (IPF) [1]. Subsequent ISHLT Registry reports confirmed these findings [2]; however, there is controversy about whether DLT should be recommended to all lung transplant candidates with IPF [3].

In the absence of a prospective randomized trial, the survival advantage found to be associated with DLT could be a consequence of selection bias. However, several studies have retrospectively demonstrated that DLT is superior to SLT by using propensity matching and multivariable regression analysis [3–5]. The survival advantage of DLT becomes evident after 1 year and continues at 5 and 10 years of follow-up. Nevertheless, subpopulations in which this superiority diminishes have not been determined.

DLT is a technically more challenging operation, especially in the IPF population. The restricted chest, in addition to a more complex dissection, often prolongs the ischemic time, and oversize mismatch can be more common. Furthermore, the disruption of the chest wall

Accepted for publication April 2, 2018.

Presented at the Sixty-fourth Annual Meeting of the Southern Thoracic Surgical Association, San Antonio, TX, Nov 8–11, 2017.

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The Appendix and Supplemental Figures can be viewed in the online version of this article [https://doi.org/10.1016/j.athoracsur.2018.04.060] on http://www.annalsthoracicsurgery.org.

0003-4975/$36.00
https://doi.org/10.1016/j.athoracsur.2018.04.060

Abbreviations and Acronyms

DLT = double-lung transplantation
IPF = interstitial pulmonary fibrosis
ISHLT = International Society for Heart and Lung Transplantation
LAS = lung allocation score
mPAP = mean pulmonary artery pressure
PGD = primary graft dysfunction
SLT = single-lung transplantation
UNOS = United Network for Organ Sharing

from a bilateral thoracotomy may lead to increased morbidity. Consequently, a clinician can encounter a difficult decision to recommend DLT to an older or frailer recipient. An age cutoff at which DLT should be avoided is currently unknown.

Evidence has been reported that DLT has improved outcomes compared with SLT in patients with IPF who have a high lung allocation score (LAS) [6, 7]. Intuitively, it is less attractive to offer a more complex operation to a sicker patient with a high LAS. However, the enhanced respiratory function provided by DLT can be beneficial for the critically ill recipient. Accordingly, contemporary results in patients with IPF that address these complex factors are needed.

A higher mean pulmonary artery pressure (mPAP) has been associated with primary graft dysfunction (PGD) in IPF [8]. The cardiac output can overflow an SLT graft or one lung during off-bypass DLT in the pulmonary hypertension recipient, thus leading to a higher degree of PGD. In this regard, the effect of pulmonary hypertension in a recipient undergoing SLT versus DLT has not been studied, and a clinical cutoff in which SLT should be avoided remains undetermined.

Finally, performing DLT in a single patient could have less gain from the societal perspective than performing SLT in 2 patients, and lingering for DLT may result in increased waitlist mortality [9]. To maximize the benefit, more information is necessary to develop a tailored approach. Consequently, we sought to determine the risks and benefits of DLT versus SLT in clinically relevant cutoffs for age, mPAP, and LAS and to compare the survival of listing for DLT versus SLT.

Patients and Methods

Study Population

The study protocol was approved by the Institutional Review Board of the Massachusetts General Hospital, Boston, Massachusetts. The United Network for Organ Sharing (UNOS) database was queried for all patients with IPF who underwent SLT versus DLT between 1987 and 2015. Diagnosis codes 1604 (idiopathic pulmonary fibrosis), 1521 (nonspecific interstitial pneumonia), 1519 (secondary pulmonary fibrosis), and 1613 (pulmonary fibrosis other specific cause) were included. Patients less than 18 years of age were excluded.

Recipients' age was analyzed with the following age cut points: <60, ≥60, ≥65, and ≥70 years. The effects of LAS and mPAP were considered for the following cutoffs: LAS <45, ≥45, ≥60, and ≥65 and mPAP <25, ≥25, ≥30, and ≥40 mm Hg. The lung transplant era was studied separately with a cutoff in May 2005 (UNOS LAS implementation). Posttransplant survival was determined by combined Social Security and Organ Procurement and Transplantation Network data.

DLT versus SLT waiting time was compared. Overall survival of activation or listing on or after 2015 for DLT or no SLT was compared with SLT listing. All deaths on the waiting list were included as events. Transplantations or removals with no deaths were considered censored.

Statistical Analysis

All data are presented as n (%) or mean ± standard deviation. Between-group differences in baseline characteristics were analyzed using a χ^2 or Fisher's exact test for categorical variables and a two-sided Student's t test for normally distributed continuous variables or a Mann-White rank sum test for nonnormally distributed continuous variables. Posttransplant survival was analyzed using the Kaplan-Meier method with a log-rank test for between-group differences. SLT versus DLT survival was compared using age, LAS, mPAP as categorical variables.

A multivariable Cox proportional hazards regression for survival was performed for these and a total of 28 characteristics. Age, LAS, mPAP, and transplant year were analyzed as continuous and categorical variables. Covariates were entered into the model with a stepwise probability of 0.05 for entry and 0.10 for removal. Hazard ratios and their 95% confidence intervals are reported. A p-value of ≤0.05 was considered statistically significant. IBM SPSS 25 for Windows statistical software was used (IBM, Armonk, NY).

A propensity-matching analysis on the basis of 19 recipient and donor characteristics was performed after May 2005 (Appendix 1). The match tolerance was 0.01.

Results

During the study period, 9,191 of 29,779 lung transplantations were performed in patients with IPF. Rates of DLT in IPF started increasing in 2004, and these operations were performed more often than SLT starting in 2008. Notably, in 2014, a fair number of SLTs were still performed (Fig 1). DLT was performed in 4,443 cases and SLT in 4,724. Demographics are summarized in Table 1. The mean follow-up was 3.3 years, with a maximum follow-up of 23 years, and a total of 30,041 patient-years. Unadjusted 10-year survival in DLT was 55% ± 1.5%, compared with 32% ± 1.2% in SLT ($p < 0.001$) (Fig 2). Mean overall survival was 9.7 ± 0.2 years. DLT mean survival was 11.4 ± 0.3 years compared with 8.2 ± 0.2 years for SLT. Survival was similar at 1 year of follow-up (3% better in DLT); however, it diverged progressively at 10 years of follow-up (22% superior for DLT).