Published in final edited form as:

Ann Thorac Surg. 2015 November ; 100(5): 1826–1833. doi:10.1016/j.athoracsur.2015.05.008.

What is the Optimal Transplant for Older Patients with Idiopathic Pulmonary Fibrosis?

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Abstract

Background—There is controversy regarding the optimal type of lung transplant (single [SOLT] vs bilateral [BOLT]) for patients with idiopathic pulmonary fibrosis. We performed the following study to determine which type of transplant is more appropriate for older patients with this condition.

Methods—We conducted a review of the United Network for Organ Sharing database from 2005–2013 for patients ≥65 years of age with idiopathic pulmonary fibrosis. A 1:1 nearest-neighbor propensity match was utilized to determine differences in survival by transplant procedure type (SOLT vs BOLT). Logistic regression modeling taking into account interaction terms between pre-specified variables and the type of transplant was utilized to determine variables which altered the survival outcomes associated with SOLT vs BOLT.

Results—Of 1,564 patients who met study criteria, 521 (33.3%) received a BOLT. After propensity-matching 498 BOLT recipients to 498 SOLT recipients, BOLT was associated with a significantly improved 5-year survival (48.7% vs 35.2%, $p < 0.01$). However, the mortality hazard associated with BOLT varied from a non-significant reduction in survival within three-months following transplant (HR: 1.24, 95% CI: 0.80–1.93) to a significant survival benefit for patients who survived beyond one year (HR: 0.64, 95% CI: 0.47–0.86). Functional status was also found to be a significant predictor of the survival benefit associated with BOLT.

Conclusions—BOLT is associated with significantly improved survival over SOLT for older patients with idiopathic pulmonary fibrosis, driven by a late survival benefit from bilateral transplantation. However, patients with a reduced pre-operative functional status do not appear to derive a similar benefit from bilateral transplantation.

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Keywords

Transplantation; lung (incl related subjects); Interstitial Lung Disease; Outcomes (incl mortality, morbidity, survival, etc.)

Lung transplantation has provided clinicians with a method for treating a wide spectrum of end-stage lung diseases including chronic obstructive pulmonary disorder, cystic fibrosis, and idiopathic pulmonary fibrosis (IPF) [1-3]. For many diseases, bilateral orthotopic lung transplantation (BOLT) has been demonstrated to be associated with a significant survival benefit over single orthotopic lung transplantation (SOLT) [4, 5]. In theory, BOLT provides the recipient both the advantage of the removal of the native lungs, which decreases the risk of native lung complications, and offers substantially more allograft tissue and thus potentially higher pulmonary capacity [6, 7]. However, BOLT also requires a more extensive surgical procedure often leading to longer intensive care unit and total hospital lengths of stay, and a higher risk of immediate post-operative complications [8, 9].

IPF is a progressive lung disease often associated with poor outcomes [10]. Historically, SOLT was the standard type of transplant for IPF patients, as BOLT was not shown to be associated with a significant survival benefit in this population [11, 12]. However, recent studies have demonstrated that BOLT may be associated with significantly improved survival among certain subgroups of IPF patients, including patients with a high lung allocation score (LAS) [13]. Previous work by Thabut et al demonstrated that despite no significant difference in overall survival among IPF patients treated with BOLT or SOLT, there was an increased hazard of death in the initial post-operative period associated with BOLT as compared to SOLT, followed by a survival benefit associated with BOLT in the later period [14].

There are many etiologies that have been proposed and perhaps may be responsible for the reduced early survival among BOLT patients demonstrated in the Thabut et al study. Nevertheless, there is concern that certain groups of patients may be at an increased risk for peri-operative mortality associated with BOLT vs SOLT, such as older patients [15, 16]. We hypothesized that older patients with IPF are at an increased risk for peri-operative mortality associated with BOLT as compared to SOLT. This increase in peri-operative mortality may reduce the overall survival benefit associated with BOLT seen in previous studies. We therefore investigated the optimal type of transplant (BOLT vs SOLT) for older patients with IPF.

Patients and Methods

Patient Population

The United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research Files were queried for patients 65 years of age or older undergoing isolated lung transplant for a primary diagnosis of idiopathic pulmonary fibrosis (code 1604) during the years 2005 to 2013. Patients were excluded if they had a previous transplant or did not have a recorded LAS. We specifically excluded patients who were transplanted prior to the implementation of the LAS as patients with IPF transplanted before 2005 have been demonstrated to be

substantially different from those transplanted in the current era [8]. Patients were categorized on the basis of whether they underwent a SOLT or BOLT. The Duke University Institutional Review Board approved the study.

Statistical Analysis

Groups were compared for baseline characteristics, transplant characteristics, and outcomes. Standardized differences were determined for each of the baseline and transplant characteristics. For outcomes, continuous variables were compared using the Kruskal-Wallis rank sum test, while categorical variables were compared using Fisher's exact test or the chi-square test as appropriate. Kaplan-Meier analysis was utilized in order to determine the unadjusted association of the type of transplant (SOLT vs BOLT) and long-term survival. Patients were censored if they were lost to follow-up. Survival differences at specific follow-up time points of interest were compared using Kaplan-Meier estimates and standard errors.

A multivariable logistic regression model was created in order to determine factors associated with undergoing a BOLT as compared to a SOLT among this cohort. Variables incorporated in the model were determined a priori and included age, sex, race, body mass index (BMI), diabetes, hypertension, pre-transplant glomerular filtration rate (GFR), oxygen requirement prior to transplant, LAS, steroid treatment prior to transplant, functional status (all activities of daily living performed independently [Karnofsky performance scale 70-100%], assistance needed for activities of daily living [Karnofsky performance scale 50-60%], and disabled/hospitalized [Karnofsky performance scale 10-40%]), smoking status within the past six months, any history of malignancy, extracorporeal membrane oxygenation (ECMO) or ventilator support at the time of transplant, and center volume over the study period. Missing variables were assumed to be missing at random. Backwards stepwise variable selection was utilized in order to determine the final model. All variables were tested for linearity prior to inclusion in the model, and categorized or transformed as appropriate.

A 1:1 nearest neighbor algorithm propensity-matched analysis was then performed in order to adjust for non-random treatment selection among this cohort of older patients. Patients were matched on the basis of variables chosen a priori which included age, sex, race, BMI, pre-transplant GFR, oxygen requirement prior to transplant, LAS, steroid treatment prior to transplant, functional status, smoking status within the past six months, time on the waiting list, any history of malignancy, ECMO or a ventilator support at the time of transplant, transplant year, and center volume over the transplant period. Standardized differences and the overlap of propensity scores between groups were compared to evaluate the success of the match. Outcomes were again compared between groups, including long-term survival using Kaplan-Meier analysis. Univariable cox proportional hazards models were used to determine the associated hazard of BOLT vs SOLT both in the peri-operative period (within three months) as well as beyond one year.

Cause of death was compiled for patients who died in each of three time periods (within three months, between three months and one year, and beyond one year) from the overall (non-matched) cohort. Cause of death was defined as cardiovascular (cause of death codes

2200-2299), cerebrovascular (cause of death codes 2400-2499), graft/pulmonary failure (cause of death codes 2300-2399), hemorrhage (cause of death codes 2500-2599), infection (cause of death codes 2100-2199), malignancy (cause of death codes 2600-2699), multiple organ failure (cause of death code 2705), or other/unknown (cause of death codes 998 to 999 or missing). The Fisher Exact test was used to compare differences between groups.

A second multivariable logistic regression model was created among the initial cohort in order to determine if there were any subpopulations for which a BOLT was associated with significantly increased peri-operative mortality as compared to a SOLT among older patients with IPF. The outcome in this model was mortality at 90 days post-transplant. Age, sex, BMI, diabetes, pre-transplant GFR, oxygen requirement prior to transplant, LAS, steroid treatment, functional status, and the use of ECMO or ventilator support prior to transplant were initially included in the model, along with an interaction between each variable and the use of BOLT. Backwards stepwise variable selection was performed to determine the final model. All variables were tested for linearity prior to inclusion in the model, and categorized or transformed as appropriate. Kaplan-Meier analysis and univariable Cox models were used to investigate survival differences among subgroups found to have a significant interaction with the type of transplant (BOLT vs SOLT). All statistical analyses were performed using R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria). A p-value of 0.05 was used to determine statistical significance.

Results

Of the 1,564 patients who met criteria, 521 (33.3%) received a BOLT while 1,043 (66.7%) received a SOLT. Patients who received a BOLT had a higher median LAS (49.4 vs 44.6, Table 1). Upon analysis of unadjusted outcomes, patients undergoing a BOLT had significantly increased rates of airway dehiscence (3.9 vs 1.0%, $p<0.01$) and dialysis requirements (9.2% vs 2.7%, $p<0.01$, Table 2). Patients undergoing a BOLT also had significantly longer hospital lengths of stay (median 19 days vs 13 days, $p<0.01$). However, overall five-year survival was significantly improved for patients undergoing a BOLT as compared to a SOLT (48.3% vs 33.7%, $p<0.01$, Figure 1A).

Multivariable logistic regression was then performed in order to determine factors associated with undergoing a BOLT vs. SOLT. Age (adjusted odds ratio [AOR] per decade: 0.23, 95% confidence interval [CI]: 0.15, 0.35) and BMI 25-30 kg/m² as compared to less than 25 kg/m² (AOR: 0.75, 95% CI: 0.58, 0.98) were found to be significantly associated with receiving a SOLT as compared to a BOLT, while Black race as compared to White race (AOR: 2.28, 95% CI: 1.10, 4.75), an oxygen requirement greater than 5 L/min (AOR: 1.53, 95% CI: 1.14, 2.04), LAS (AOR per 10: 1.14, 95% CI: 1.05, 1.24), a history of malignancy (AOR: 1.47, 95% CI: 1.05, 2.05), and ECMO or ventilator support at time of transplant (AOR: 1.95, 95% CI: 1.14, 3.34) were all significantly associated with receiving a BOLT as compared to a SOLT (Figure 2, c-statistic: 0.67).

From the initial cohort, 498 patients who received a BOLT were matched to 498 patients who received a SOLT. Following propensity matching, there were no substantial baseline differences between the BOLT and SOLT groups. Patients who received a BOLT continued

to be significantly more likely to suffer from airway dehiscence (3.8% vs 0.8%, $p<0.01$) as well as require dialysis (8.7% vs 3.2%, $p<0.01$) following transplant. There also continued to be a significant difference in 5-year survival (48.7% vs 35.2% for BOLT and SOLT, respectively, $p<0.01$, Figure 3). When investigating specific time periods, BOLT was not associated with a significant reduction in survival within the early post-operative period (first three months post-transplant) as compared to SOLT (HR: 1.24, 95% CI: 0.80, 1.93). However, for patients who survived beyond 1 year, it became associated with a significant survival benefit (HR: 0.64, 95% CI: 0.47, 0.86).

When investigating the overall study cohort, patients who died within three months were more likely to die from cerebrovascular disease (11% vs 2% vs 3%, $p<0.01$) than patients who died between three and twelve months, and patients who died beyond twelve months, respectively (Table 3). Conversely, patients who died beyond one year were more likely to die from malignancy (19% vs 7% vs 2%, $p<0.01$) compared to patients who died between three and twelve months and patients who died within three months, respectively.

Multivariable logistic regression was then performed among the initial cohort in order to determine other variables which might place a patient at increased risk of peri-operative mortality secondary to BOLT vs SOLT. Of the variables included in the initial model, only functional status was found to have a significant interaction with the type of transplant. When examining the subgroup of patients with an independent functional status, BOLT was associated with a significant improvement in 5-year survival (54.7% vs 37.2%, $p=0.03$, Figure 4A) as compared with SOLT. Furthermore, there was no significant difference in the hazard for mortality by type of transplant within the first three months among this subgroup (HR: 0.84, 95% CI: 0.33, 2.14). However, among patients who required assistance with their activities of daily living, there was no significant difference in survival at 5-years (48.6% vs 35.8% for BOLTs and SOLTs, respectively, $p=0.07$, Figure 4B). Furthermore, in this cohort, there was a significantly increased mortality hazard for patients undergoing BOLTs as compared to SOLTs within the first three months (HR: 2.73, 95% CI: 1.42, 5.25).

Comment

Substantial disagreement exists regarding the optimal type of transplant for IPF. Although there are data demonstrating an overall benefit to BOLT as compared to SOLT, especially among certain subgroups of patients, the majority of data demonstrates similar long-term survival in patients treated with either a SOLT or BOLT [5, 11, 13]. Further investigation by Thabut et al demonstrated that while there was no significant difference in overall survival by treatment type, BOLT was associated with substantially increased early hazard for mortality [4]. It is likely that this non-proportional hazard for mortality is responsible for the variability seen among studies and by sub-groups.

In this study, despite our initial hypothesis to the contrary, we found that among patients 65 years of age or older, BOLT was associated with a significantly improved overall survival as compared to SOLT, even after adjustment for baseline patient characteristics. Similar to the findings by Thabut et al, we further demonstrated that there is a change in the mortality hazard over time, with a non-significant trend towards increased mortality hazard in the

immediate post-operative period, but significantly reduced mortality hazard in the later period. Our study also differs from previous studies as we focused on patients transplanted after the implementation of the LAS. Previous literature has demonstrated that the population of IPF patients who are being transplanted has changed dramatically since the inception of the LAS in 2005 [8].

The increased early mortality associated with a BOLT for IPF may be related to the mechanics of the disease and operation. Theoretically, the use of a clamshell incision in bilateral transplantation in combination with the restrictive nature of IPF may lead to issues with adequate ventilation post-transplant, thereby increasing the risk for pneumonia, ventilator dependency, and other respiratory disorders. Force et al reported that a BOLT provided significantly improved survival for younger patients with IPF; however, this was likely because younger patients have reduced early mortality risk as compared to older patients and overall better functional status. Thus an overall survival benefit could be seen, but this would still be driven by the improvement in late mortality conferred by the BOLT [5, 14].

This improvement in survival among patients receiving a BOLT must be weighed against societal concerns about resource utilization. In theory, one BOLT allograft could have been used for two separate recipients. In an era in which lung transplantation is somewhat limited by donor supply, the survival of two patients, albeit for a shorter duration, may be more important than an additional 13% improvement in five-year survival seen for one patient receiving a BOLT. It is for this reason that the authors favor a selective process of performing a BOLT for IPF patients likely to gain the most benefit, like those with higher functional status and lower perioperative risk. Unfortunately, there are many other factors that need to be taken into account in order to perform a detailed decision analysis on societal utilization, such as the high rate of contralateral lungs that go unused when a donor is used to supply a single lung [17].

We have also demonstrated that there are subpopulations which may preferentially benefit from a BOLT, while others may be at an increased risk of harm from the peri-operative mortality associated with a BOLT. Importantly, functional status as defined by the Karnofsky performance scale had a significant interaction with the type of transplant when investigating long-term survival. The Karnofsky performance scale is a validated tool used extensively to describe patient functional status especially among cancer patients [18, 19]. When analyzing patients with an independent functional status, we found that BOLT was associated with a significant survival advantage as compared to SOLT, likely due to a reduction in early post-operative mortality as seen in the overall older cohort. Conversely, patients with a dependent functional status had significantly increased peri-operative mortality, which reduced the overall benefit conferred from the BOLT. These findings provide evidence that selective utilization of BOLTs by patient functional status would optimize the utilization of lungs among older IPF patients.

We also investigated the cause of death at different time points following transplant. We demonstrated that deaths occurring in the earlier period were more likely to be those associated with peri-operative mortality, such as stroke, myocardial infarctions,

hemorrhages, and infections. Deaths beyond one year, on the other hand, were more likely to be related to respiratory or graft failure. This supports our hypothesis that patients at increased risk for peri-operative mortality due to specific risk factors (such as increased frailty) should be directed towards single lung transplantation, while patients who survive the peri-operative period benefit more from bilateral transplantation in order to prevent respiratory failure.

Despite the importance of these findings, our study has several limitations. First, as a retrospective study, there is always the possibility of confounding by unobserved variables. However, the mortality models built using the variables present in the UNOS database have been demonstrated to have good predictive ability in previous studies [20, 21]. Second, due to smaller samples sizes present among subgroups, we could not perform an adjusted analysis among patients grouped by functional status to determine how the type of transplant is associated with survival. Lastly, we analyzed follow-up from the time of transplant and not from the time of listing, and therefore our results may differ from that performed from an intention to treat standpoint starting at the time of listing.

In conclusion, among older patients with IPF, BOLT is associated with a significant overall survival benefit as compared to SOLT. Furthermore, this appears to be driven by a late survival benefit despite increased peri-operative mortality associated with bilateral transplantation. Lastly, we have demonstrated that patient functional status is an important determinant of whether bilateral lung transplantation optimizes survival among older IPF patients. Further research is necessary to determine how other patient factors influence the survival benefit associated with bilateral transplantation.

Acknowledgments

The data reported here have been supplied by the United Network for Organ Sharing as the contractor for the Organ Procurement and Transplantation Network. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the OPTN or the U.S. Government. This work was supported by the National Institute of Health funded Cardiothoracic Surgery Trials Network (BCG, JMM, and MGH), 5U01HL088953-05.

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Figure 1.

Association between bilateral (BOLT) vs single (SOLT) lung transplantation and survival among patients 65 years of age or older with idiopathic pulmonary fibrosis before propensity matching. BOLT – bilateral orthotopic lung transplantation. SOLT – single orthotopic lung transplantation.

Figure 2.

Patient variables associated with undergoing a bilateral (BOLT) lung transplant vs a single (SOLT) lung transplant among patients 65 years of age or older.

Figure 3.

Association between bilateral (BOLT) vs single (SOLT) lung transplantation and survival among patients 65 years of age or older with idiopathic pulmonary fibrosis after propensity matching. BOLT – bilateral orthotopic lung transplantation. SOLT – single orthotopic lung transplantation.

Figure 4. Association between bilateral (BOLT) vs single (SOLT) lung transplantation and survival among patients 65 years of age or older with idiopathic pulmonary fibrosis and who have an independent functional status (A) as well as require assistance with the activities of daily

living (ADLs, B). BOLT – bilateral orthotopic lung transplantation. SOLT – single orthotopic lung transplantation.

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Table 1
Baseline characteristics both before and after propensity matching

Variable	Before Propensity Matching			After Propensity Matching		
	SOLT	BOLT	Std Diff (%)	SOLT	BOLT	Std Diff (%)
N	1043 (67%)	521 (33%)		498 (50%)	498 (50%)	
Age (years)	68 (66, 70)	67 (66, 69)	35.1	67 (66, 69)	67 (66, 69)	-3.1
Female sex	230 (22.1%)	130 (25.0%)	-6.8	119 (23.9%)	124 (24.9%)	-2.3
Race/Ethnicity						
White	930 (89.2%)	450 (86.4%)	8.5	436 (87.6%)	429 (86.1%)	4.2
Black	17 (1.6%)	18 (3.5%)	-11.6	13 (2.6%)	18 (3.6%)	-5.8
Hispanic	65 (6.2%)	39 (7.5%)	-5.0	38 (7.6%)	38 (7.6%)	0.0
Other	31 (3.0%)	14 (2.7%)	1.7	11 (2.2%)	13 (2.6%)	-2.6
Hypertension	33 (3.2%)	9 (1.7%)	9.3	14 (2.8%)	9 (1.8%)	6.7
Diabetes	201 (19.4%)	108 (20.8%)	-3.5	111 (22.3%)	101 (20.4%)	4.8
Body Mass Index (kg/m ²)	27.1 (24.5, 29.4)	26.8 (23.8, 29.5)	4.9	27.1 (24.1, 29.4)	26.8 (23.8, 29.5)	3.8
Steroid Treatment	488 (47.7%)	239 (46.7%)	2.0	227 (45.6%)	230 (46.2%)	-1.2
Smoking History	675 (64.7%)	362 (69.5%)	-10.2	340 (68.3%)	346 (69.5%)	-2.6
GFR Pre-Transplant	85 (69.6, 91.8)	88.7 (70.9, 94.3)	-15.7	87.9 (71.5, 93.1)	88.7 (72.1, 94.3)	-6.7
Mean PRA	0 (0, 4)	0 (0, 4.9)	-11.0	0 (0, 5.9)	0 (0, 4.9)	9.0
Days on Waiting List	30 (11, 103)	30 (9, 103)	2.7	31.5 (11.2, 107)	31 (11, 106)	1.9
Functional Status at Transplant						
ADL With No Assistance	312 (30.2%)	145 (28.0%)	4.7	151 (30.3%)	141 (28.3%)	4.4
ADL With Assistance	424 (41.0%)	178 (34.4%)	13.7	175 (35.1%)	175 (35.1%)	0.0
Disabled/Hospitalized	297 (28.8%)	194 (37.5%)	-18.7	172 (34.5%)	182 (36.5%)	-4.2
LAS at Match	44.6 (39.2, 54.5)	49.4 (42.3, 66)	-35.6	47.7 (40.4, 62.1)	48.8 (42.1, 63.5)	-6.0
O2 Requirement at Rest (L/min)	3 (2, 5)	4 (2, 6)	-32.6	4 (2, 6)	4 (2, 6)	-8.4
History of Malignancy	123 (11.8%)	77 (14.8%)	-8.9	67 (13.5%)	74 (14.9%)	-4.0
On ECMO or Ventilator prior to Transplant	35 (3.4%)	45 (8.6%)	-22.4	22 (4.4%)	34 (6.8%)	-10.5
Center Volume over Study Period	42 (26, 58)	43 (28, 54)	-10.8	41 (25, 58)	43 (28, 54)	-6.0

ADL – Activities of Daily Living; ECMO – Extracorporeal Membrane Oxygenation; GFR – Glomerular Filtration Rate; LAS – Lung Allocation Score; PRA – Panel Reactive Antibody. Continuous variables presented as median (interquartile range). Categorical variables presented as frequency (percentage).

Table 2**Outcomes both before and after propensity matching**

Variable	Before Propensity Matching			After Propensity Matching		
	SOLT	BOLT	P-value	SOLT	BOLT	P-value
N	1043 (67%)	521 (33%)		498 (50%)	498 (50%)	
Airway Dehiscence	10 (1.0%)	20 (3.9%)	< 0.01	4 (0.8%)	19 (3.8%)	< 0.01
Dialysis	28 (2.7%)	48 (9.2%)	< 0.01	16 (3.2%)	43 (8.7%)	< 0.01
Infection (requiring antibiotics)	39 (40.6%)	13 (46.4%)	0.74	17 (38.6%)	12 (44.4%)	0.81
Stroke	21 (2.0%)	12 (2.3%)	0.84	12 (2.4%)	11 (2.2%)	0.99
Length of Stay (days)	13 (9, 21)	19 (12, 32)	< 0.01	13 (9, 21)	18 (12, 30)	< 0.01

Continuous variables presented as median (interquartile range). Categorical variables presented as frequency (percentage).

Table 3

Cause of death by time from transplant to death.

Cause of Death	Within 3 Months	3-12 Months	Greater than 12 Months	p-value
N	114 (19%)	167 (28%)	319 (53%)	
Cardiovascular	15 (13%)	11 (7%)	20 (6%)	0.07
Cerebrovascular	13 (11%)	3 (2%)	9 (3%)	<0.01
Graft/Pulmonary Failure	27 (24%)	45 (27%)	106 (33%)	0.11
Hemorrhage	6 (5%)	7 (4%)	1 (1%)	<0.01
Infection	31 (27%)	46 (28%)	59 (18%)	0.03
Malignancy	2 (2%)	12 (7%)	62 (19%)	<0.01
Multiple Organ Failure	9 (8%)	14 (8%)	6 (2%)	<0.01
Other/Unknown	11 (10%)	29 (17%)	56 (18%)	0.11