Review Article

Bilateral versus single lung transplantation: are two lungs better than one?

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Abstract: There is a long-standing debate over whether single or bilateral lung transplant provides better short and long-term clinical outcomes. We performed a detailed PubMed search on relevant clinical research publications on single (SLT) and bilateral lung transplantation (BLT). We included studies that were published before and after the implementation of the lung allocation score (LAS). We reviewed disease-specific short- and long-term outcomes associated with each transplantation technique. The majority of published studies are retrospective cohort studies that use institutional data or large patient registries. Outcomes associated with transplantation technique vary by disease specific indication, age, and patient severity. Over the past decade, the relative proportion of bilateral lung transplantation has increased. Increasing adoption of bilateral lung transplant likely reflects the general acceptance of several advantages associated with the technique. However, making a clear, evidence-based decision is difficult in light of the fact that there has never been and probably never will be a randomized trial. Our institutional preference is bilateral lung transplant. However, consideration for the technique should still be made on a case-by-case basis.

Keywords: Bilateral; single; lung transplantation; outcomes

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Introduction

Since the first successful isolated lung transplant performed by Dr. Joel Cooper at the University of Toronto in 1983, lung transplantation has been considered an optimal therapy for multiple causes of end stage pulmonary disease (1). The initial isolated transplant operations were single lung transplants performed on patients with severe idiopathic pulmonary fibrosis (IPF). Since then, lung transplantation has been more heavily utilized to treat patients with multiple conditions including interstitial lung disease (ILD), chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), pulmonary hypertension, and more (2). Over the past several decades, changes in donor selection, postoperative care, and immunosuppression therapy have broadened the use of lung transplant and improved outcomes for transplant recipients (3). While new guidelines have been created to help guide transplant candidate selection and management, there is still substantial debate surrounding the utilization of single versus bilateral lung transplantation in patients eligible for either strategy (2,4,5). To date, much of the decision-making regarding use of single versus bilateral lung transplant is based on individual institutional case series experience or retrospective reviews of large lung transplant registries. There is a lack of high quality, prospective data to provide clear criteria favoring single or bilateral lung transplantation when either strategy is possible. Furthermore, there is a lack of consensus on the philosophical dilemma: should a bilateral operation with better palliation be offered to fewer patients, or should a lesser unilateral operation be offered to more recipients? The purpose of this chapter is to review the existing

literature regarding single and bilateral lung transplantation. Specifically, this review will highlight the following subjects:

- Disease-specific indications for single (SLT) *vs.* bilateral lung transplantation (BLT), with a focus on emphysema and pulmonary fibrosis;
- Impact of procedure type on post-transplantation functional status;
- Impact of procedure type on post-transplantation quality of life (QOL);
- Chronic rejection after lung transplantation;
- Ethical challenges facing the choice between single and bilateral transplants;
- The novel strategy of "staged BLT (SBLT)".

Disease-specific indications for lung transplantation

There is a wide variety of indications for lung transplantation, including end-stage COPD, ILD, pulmonary hypertension, CF and bronchiectasis and others (2). Because patients with septic lung disease (including CF and bronchiectasis) almost always undergo BLT due to the infectious risk posed by the retained native lung, they will not be discussed further in this chapter (6). The International Society for Heart and Lung Transplantation (ISHLT) provides the most comprehensive data on long-term survival associated with BLT and SLT for all recipients (7). They collect data from 256 lung transplant and 180 heart-lung transplant centers, and represent an estimated 75% of international thoracic transplant activity. The registry is ideal for examining longitudinal trends, as the registry requires submission of follow-up data on a yearly basis. In the 2017 ISHLT report summarizing survival trends from 1990–2015, recipients of a lung transplantation operation had a median survival of 6.0 years. In unadjusted analysis, BLT recipients had better survival post-transplant compared to SLT recipients. This difference was first seen at 1 year post-op, but increased over a 14-year follow-up period. Survival for BLT and SLT groups were 90% and 88% at 3 months, 82% and 78% at 1 year, 69% and 61% at 3 years, 59% and 48% at 5 years, and 41% and 23% at 10 years, respectively. That high level comparison simply begins the discussion, but there are multiple issues of selection bias and confounding that cloud the comparison of single or bilateral transplantation outcomes. Additional literature has focused on short and long-term outcomes associated with transplantation type within subgroups of patients with specific diagnoses. Much of the existing literature examines the use of SLT and BLT in patients with either advanced COPD or IPF.

COPD

Emphysema (which encompasses COPD and alpha-1 antitrypsin deficiency) has been the most common indication for lung transplantation (2). The first successful experience with transplantation in the COPD population involved isolated SLT, initially described by Dr. Joel Cooper and his team (1). However, with the development of BLT and improvements in technique, BLT has received increased clinical adoption and use in patients with COPD (6,8). The prevailing physiologic reasoning supporting use of BLT is that the technique reduces the risk of early ventilation/perfusion mismatch and eliminates the issue of subsequent hyperinflation in the unresected emphysematous native lung that occurs after SLT (8). During the accumulation of the early experience, there was a tendency to offer BLT to younger patients with the notion that they might have greater physiologic reserve to be able to withstand the increased stress of a more prolonged surgery (1,4,6). That selection bias might have also burdened the SLT cohort with an older and frailer group of patients who would be at greater risk for premature death regardless of the differential contribution of SLT versus BLT.

Meyer and colleagues in 2001 performed one of the early index studies comparing BLT and SLT in the COPD population (4). Using the ISHLT/United Network for Organ Sharing (UNOS) registry, they performed a retrospective analysis of patients with COPD undergoing lung transplantation. They attempted to study the correlation between transplantation technique (SLT *vs.* BLT) and survival, stratified by age (41–50, 51–60, 61–70 years). They identified 2,260 lung transplant recipients (1,835 SLT, 425 SBLT) from 1991–1997 and performed risk-adjusted survival analysis using Cox regression, Kaplan-Meier analysis, and calculation of risk ratios for mortality. Among all transplant recipients, recipient age and procedure type (SLT *vs.* BLT) were found to be associated with increased risk for mortality, with advanced age, SLT, and their interaction demonstrating significant associations. On Kaplan-Meier analysis, the authors demonstrated that BLT was associated with higher survival in both the 41–50 and 51–60 years age categories across all time points, with a more pronounced survival benefit occurring further out from surgery. Survival rates among younger patients (<50 years) who underwent SLT

were 93.6%, 80.2% and 43.6% at 30 days, 1 year, and 5 years, respectively, compared to 94.9%, 84.7%, and 68.2% in the young BLT group (P=0.001). Among those aged 51–60 years, the differences in long-term survival were slightly less pronounced. Those who received SLT had 30-day, 1 year, and 5-year survival rates of 93.5%, 79.4%, and 39.8%, respectively, compared to 93.0%, 79.7%, and 60.5% for patients of similar age who received BLT (P=0.05). After age 60, however, the trend reversed. Survival associated with SLT was considerably higher (93.0%, 72.9%, and 36.4%) compared to BLT (77.8%, 66.0%, with 5-year mortality data unavailable) (P=0.2). When using risk ratios to calculate risk of mortality across all ages, the authors noted an increased probability of mortality for recipients of SLT between ages 40–57 (P=0.001 at each age). At approximately age 57, the trend reversed. Additionally, the authors focused on US transplant cases to examine 3-year morbidity associated with transplantation technique. They measured events of hospitalization for rejection, onset of bronchiolitis obliterans (BOS), bronchial airway complications, and hospitalization for infections. No significant differences were observed between BLT and SLT in any of these measures. However, the study did not measure variables associated with short-term morbidity, which may be more relevant in older patients. The study concluded that BLT was associated with greater short and long-term survival in patients less than 60 years of age.

Thabut and colleagues confirmed the positive long-term survival advantage that BLT offered to the younger COPD population (9). They completed a large retrospective analysis of the ISHLT registry between 1987 and 2006. Thabut performed a survival analysis of 9,883 patients with a diagnosis of COPD. Additionally, they documented important trends in the use of BLT for COPD. For example, the proportion of patients with COPD who underwent BLT more than doubled from the 1990s to more recently (21.6% in 1993 to 56.2% in 2006). Using modern propensity score matching (a technique lacking in previous papers on the subject) to control for possible treatment selection bias associated with each transplant method, Thabut determined that median survival time was significantly greater for those who received BLT (6.41 years, 6.02–6.88 years) compared to SLT (4.59 years, 4.41–4.76 years) (P<0.0001). However, the survival advantage associated with BLT did not hold for patients greater than 60 years of age. The practical suggestion was similar: to offer BLT to younger COPD patients but to accept the lack of a difference in older recipients and perhaps use other criteria to choose the transplantation strategy in this population.

The authors' institution (Washington University in St. Louis/Barnes Jewish Hospital) is a high-volume lung transplantation center, and BLT has been the preferred transplantation method. Cassivi performed a 13-year review of lung transplantation for COPD patients at Barnes-Jewish Hospital between 1988 and 2000 looking at in-hospital mortality and 5-year survival rates among patients with COPD and alpha-1-antitrypsin deficiency (10). More than 70% of emphysema patients received BLT, reflecting the strong institutional preference for the method. Cassivi acknowledged that the preference for BLT was due to a record of increased survival and ease of postoperative ventilator management. When examining long-term survival, COPD patients who received BLT had significantly higher 5-year survival at 66.7% compared to 44.9% for single lung replacement (P<0.001). Conversely, many other studies did not find the same survival benefit conferred by BLT.

Bennett and colleagues performed a retrospective single center review of COPD patients undergoing lung transplantation, with a special focus on patients older than 55 years of age (11). These authors noted that it was standard policy since the inception of their transplantation program to only perform SLT on emphysema patients older than 55 years of age. They attempted to identify specific patient subgroups that benefit from SLT. They examined 5-year survival rates between patients receiving SLT (206 patients) and BLT (30 patients) from 1992–2012. As expected, the SLT cohort tended to be older and had reduced pre-transplant pulmonary function and physical conditioning compared to the BLT cohort. Within this institution, 30-day, 1-year, and 5-year survival estimates between treatment cohorts were similar, with long-term survival trending slightly higher for BLT patients. Due to their small pool of BLT patients, they also compared their institutional data to the outcomes of SLT and BLT patients in the UNOS registry. When comparing institutional data to SLT and BLT patients in the UNOS registry, Bennett noted that their own institution's SLT patients had generally similar preoperative risk in terms of advanced age, comorbid condition, and pulmonary function. Their institution's SLT short and long-term survival rates were similar to those of the UNOS registry's BLT subset. This may reflect improved experience and perioperative care, given that SLT is their institutional preference. They concluded that while BLT may provide an individual survival benefit, SLT

had substantial utility and should be promoted as much as possible given the overall impact that it can have in increasing the number of patients receiving transplantation.

Several studies of BLT *vs.* SLT were performed on institutional or national databases that captured data before the 2005 implementation of the lung allocation score (LAS). Schaffer compared SLT and BLT in the post-LAS era (12). Using the UNOS registry from 2005-2012, Schaffer compared graft survival between transplantation types. Graft survival represented a composite of post-transplantation mortality and graft failure rates. These patients were propensity matched to reduce the impact of treatment selection bias on the results of the study. Among 3,174 COPD patients, 1,299 underwent SLT and 1,875 underwent BLT. The median follow-up was carried over 2 years post-transplant, and there was no significant association found between type of transplant and median graft survival (67.7 months for BLT *vs.* 64.0 months for SLT; P=0.23). This distinction from previous study results may be explained by the novel way that patients were selected for transplantation using the LAS. Compared to the pre-LAS era, during which time on the waiting list gave priority for transplantation, patients with COPD in the LAS era must be comparatively more impaired to achieve a higher transplantable score (13). The use of the LAS to prioritize recipients for transplantation may have reduced the apparent benefit of BLT for patients with COPD.

ILD and interstitial pulmonary fibrosis (IPF)

ILD, which includes IPF, carries the worst overall prognosis among end stage pulmonary disease indications for lung transplantation (14). Median survival time for patients with IPF ranges from 2–3 years post diagnosis without lung transplantation, with 5-year post-transplant survival rates ranging from 30–50% (14,15). Non-surgical therapies are limited (14,16). Lung transplantation has thus far been the only restorative therapy to offer a proven survival benefit. The short natural history of IPF without transplantation gave that diagnosis a competitive edge when the LAS was rolled out in 2005. With the application of the LAS in the United States, the rate of lung transplantation in this IPF population has risen dramatically. Despite the rising number of lung transplants in patients with IPF, there is no definitive survival advantage consistently shown to be associated with either BLT or SLT. Overall, however, the use of BLT in patients with IPF is on the rise. In 2011, approximately 54% of lung transplant operations among IPF patients were bilateral (17). In a retrospective institutional case series performed at Cleveland Clinic, Mason and colleagues [2007] studied 82 patients who underwent lung transplantation for IPF (18). They compared overall 30-day, 1-year, and 5-year survival between patients with IPF and propensity-matched, non-IPF patients. Overall survival among IPF patients was significantly worse at all time points compared to their non-IPF matched counterparts. Additionally, they calculated that BLT conferred a survival advantage among IPF patients (81% *vs.* 67% and 55% *vs.* 34% at 1 and 5 years, respectively). However, they could only compare BLT versus SLT in 10 matched pairs due to the strong selection bias attributed to their institutional preference to perform BLT in younger patients. Interestingly, they failed to note advanced age as an independent risk factor for mortality in BLT.

Additional studies have also supported the use of BLT in IPF patients because of an apparent survival advantage. Weiss focused on transplantation in IPF patients after the institution of the LAS score (19). They examined all-cause mortality 1-year after transplant in 1,256 IPF patients listed in the UNOS registry between 2005 and 2007. Additionally, they further examined the effect of pre-transplant disease severity on mortality outcomes by stratifying patients into LAS quartiles. Quartiles 1–3 indicated lower risk IPF patients, while quartile 4 contained the highest risk IPF patients. They determined that IPF patients with higher LAS were more likely to receive BLT. They observed a trend towards greater usage of BLT in sicker patients, with 21% more patients receiving BLT in the highest LAS quartile compared to the lowest (59.5% *vs.* 38.4%, P<0.05). Within the highest quartile, SLT was associated with a 14.4% increased risk in cumulative mortality compared to BLT. However, in the lowest quartile, SLT was found to be an independent protective factor in terms of mortality. There was no demonstrated short-term survival benefit associated with either transplantation type. Their findings are counterintuitive to the notion that BLT should be reserved for younger patients with more physiologic reserve, and instead suggest a role for BLT specifically for those with potentially higher pre-operative risk.

Force conducted one of the largest retrospective reviews of lung transplantation among IPF patients (20). This report also demonstrated a survival advantage associated with BLT among IPF patients. The authors performed a retrospective review of the UNOS registry from 1987 to 2008 studying 3,860 patients (2,431 SLT and 1,429 BLT) using propensity score matching. Propensity-matched analysis failed to show

a substantial survival benefit for BLT (HR 0.90, 95% CI, 0.78–1.0, P=0.11). However, when a one-year conditional survival analysis was performed, the authors found that BLT had significantly better long-term survival (12.08 versus 6.8 years, P=0.0006). When analyzing for risk factors for death within the BLT group, they reported recipient age, donor age, and year of transplantation to be significant predictors of mortality. Specifically, they observed that patients over the age of 57 had higher 1-year post-transplant mortality risk. Based on the conditional survival analysis and the significant correlation between advanced age and mortality risk, the authors concluded that younger IPF patients would most likely benefit from BLT to enhance long-term survival.

Not all available studies found a survival advantage associated with BLT. Chauhan performed a review of the UNOS registry from 2001–2009, examining actuarial post-transplant graft survival (21). In a unique approach, they studied 1,001 lung transplant recipients with IPF who were concurrently listed for BLT and SLT. Four hundred thirty-four (43%) of these patients underwent SLT while the remaining 57% underwent BLT. The authors noted significant differences in baseline comorbidities, functional status, pulmonary function tests, and recipient disease severity. Despite these baseline differences, there were no observed differences in short or long-term graft survival. Based on these comparable outcomes, the authors advocated for more liberal use of SLT among IPF patients. However, they did note that a major limitation of their study was the assumption that organ assignment was random and based solely on the availability of one or two donor lungs. At the institutional level, or even the surgeon level, there may be great variability in willingness to accept any individual donor lung based on several donor and recipient characteristics. For example, a hospital may list a patient for either SLT or BLT, suggesting equipoise, but that same group may have a low threshold to decline a single lung donor. This effectively would make their original assumption about the equivalence of the transplanted lungs less valid.

Meyer performed a large-scale retrospective review of the early UNOS registry experience in 2001 that included a cohort of 821 lung transplant patients (636 SLT, 185 BLT) with pulmonary fibrosis (4). They produced an age-stratified comparison of survival by procedure type. On crude univariate analysis, they found that younger IPF patients (30–49 years) with SLT had better short and long-term survival post-transplant than similar patients after BLT (90.9% *vs.* 77.1% at 1 month; 63.8% *vs.* 46.2% at 3 years; P=0.02). The same trend favoring single lung replacement was observed in older patients. However, when a 1-month post-transplant conditional survival analysis was performed, there were no significant subsequent differences seen between procedure types at any age group. This suggests that there may be greater periprocedural mortality associated with BLT. Propensity score matching and multivariate regression analysis failed to show survival differences between procedure types. Nwakanma focused their analysis on bilateral versus single lung transplants in IPF patients older than 60 years of age (22). Performing a large-scale analysis of 1,656 IPF patients in the UNOS registry between 1998 and 2004, they concluded that SLT was favored in this age group, with 78% of the patients in that sample undergoing SLT. Propensity score analysis demonstrated similar short and median-term survival between BLT and SLT. Transplantation type was not associated with mortality. Thus, they could not advocate for the use of either procedure type in older IPF patients.

When examining diagnosis-specific survival outcomes for BLT versus SLT, the existing literature demonstrates mixed findings. Comparing bilateral and single lung transplant effects by indication is crucial as the underlying pathophysiology of each disease is very different, and could greatly affect outcomes. The use of bilateral transplant for both COPD and IPF is on the rise. Both techniques have been utilized in younger and older populations despite previous notions that older individuals may "lack the reserve" to tolerate the procedure (4,9,10,19,20). Some data have demonstrated a greater advantage for using bilateral transplant in younger COPD populations, but the evidence in that disease is still conflicting (4,9). The picture is even more mixed in analyses of IPF patients. The available literature is relatively lackluster because most studies are small, retrospective, single-center case reviews. These studies are often limited in sample size and may be affected by institutional comfort and experience with a preferred technique. Other studies have relied on large retrospective database analysis of the ISHLT and UNOS registries, and many are based on data obtained before the institution of the LAS prioritization scheme. With the implementation of the LAS, the patient characteristics of those undergoing transplant are different, with a priority given to those with higher severity of illness instead of longer time spent on the waitlist (12). A randomized control trial is neither practical nor feasible in this setting. High quality, prospectively collected data collected from a variety of institutions that

comprehensively take into account the effects of age and multiple comorbidities will be useful in further unmasking the effect of transplantation type for advanced COPD and IPF patients. Until that time, the data are diverse and conflicting enough to simply state that there is equipoise between the two strategies. Factors other than patient survival or graft survival must be considered as well.

Post-transplant functional status and procedure type

In addition to collecting data on short- and long-term survival, several authors have examined the influence of BLT versus SLT on post-transplantation functional status. Functional status is most commonly quantified by spirometry, which has been strongly correlated with QOL in lung transplant patients (23). However, other measures such as the 6-minute walk test (6MWT) and comprehensive surveys on each patient's ability to perform daily activities have also been used. Mason and colleagues performed a single institution study of the relative impact of lung transplantation on recipient pulmonary function, with a particular focus on measuring percent-predicted forced 1-second expiratory volume (FEV1%) (24). They had 9,471 postoperative FEV1 and forced vital capacity (FVC) values from 509 adult transplant recipients, and performed a longitudinal temporal evaluation of FEV1% values for each patient. Mason and colleagues found that for both BLT and SLT patients, FEV1% typically peaked at 1 year after transplant. Forced 1-second expiratory volume increased from 50% in the immediate postoperative period to 55% at 1 year post-operatively in SLT recipients, and then gradually declined to 47% by three years. BLT recipients exhibited a similar trend but had higher overall FEV1 values at every time point (60% immediately post-transplant, 75% 1-year post-transplant, and 65% 3 years post-transplant). The authors also noted an increased mortality risk associated with decline in post-transplant FEV1 values in all recipients. Although patients undergoing either SLT or BLT exhibited increased risk of death with declining FEV1, this association in BLT recipients was notably tempered. The authors suggested that BLT may confer a protective effect on FEV1—and thus survival—likely as a function of providing recipients with enhanced pulmonary reserve. They recommended consideration of functional status in identifying which age groups would obtain maximal benefit from lung transplantation.

Pêgo-Fernandes also demonstrated relative improved pulmonary function (as measured by spirometry) among patients who underwent BLT (23). They performed a small, single-institution review of FVC and FEV1 data among lung transplant recipients between 2003 and 2006. Twenty-nine patients underwent transplant and were alive after the first postoperative year, and were thus included in analysis. Of these, 11 patients underwent SLT and 18 patients underwent BLT. All patients underwent spirometry pre-transplantation, and at 1-, 3-, 6-, 9-month, and 1-year intervals post-transplantation. Baseline characteristics of each cohort showed that patients who underwent BLT were younger but had significantly worse pre-transplant pulmonary function (mean FEV1 23.68 in BLT patients versus 44.11 in SLT, $P<0.001$). Similar to the findings demonstrated by Mason and colleagues, FEV1 and FVC peaked at 1-year post-transplantation for all transplant recipients. The BLT group had proportionally higher 1-year post-transplantation FEV1 values. The authors hypothesized that worse spirometry results among SLT patients could be attributed to hyperinflation or progression of the underlying disease in the native lung. However, the extremely small sample size of each cohort should be noted.

Pochettino observed improved pulmonary function and exercise tolerance in COPD recipients of bilateral transplantation (25). Similar to previous studies, they performed a single center retrospective study of 130 patients with emphysema from 1991–1999. Eighty-four patients underwent SLT and 46 patients underwent BLT. In addition to survival, the authors measured secondary outcomes of spirometry and 6-minute walk distances pre-operatively and at 3- to 6-month intervals post-operatively. While the authors prefer BLT (especially in younger patients) given their own institutional experience, they had utilized SLT on a more frequent basis due to scarcity of available donors. BLT was rarely utilized for recipients >60 years of age. Baseline FEV1, FVC, and 6-minute walk scores were similar between cohorts. At all post-transplantation time points during a 4-year observation period, BLT recipients exhibited higher FEV1 and FVC values compared to SLT, despite having similar baseline pulmonary function. Additionally, BLT patients had a higher mean 6-minute walk distance at all follow-up time points compared to SLT patients, with the difference ranging from 100 to 400 feet. It should be noted that the comparisons of spirometry values and exercise tolerance in this study were not adjusted for confounding characteristics. For example, with the authors favoring the use of SLT in older recipients, the BLT recipients were measurably younger (51.1 versus

56.2 years, P<0.0001). In this sense, the SLT cohort was preferentially burdened by a group of patients with more advanced age, and presumably more comorbidities and frailty. Further assessment of comorbidity or pre-transplant disease severity was not performed. The authors concluded with their preference for BLT in younger recipients due to the superior functional results and quality-of-life payoff the bilateral approach affords. The degree to which their a priori programmatic adoption of a BLT strategy for younger recipients created this appearance of improved function is impossible to measure.

Gerbase performed a combined prospective analysis of post-transplantation functional status and QOL (26). Focusing on spirometry and 6-minute walk distance, they prospectively enrolled 44 patients prior to lung transplantation. Fourteen (32%) eventually received SLT, while the remainder received BLT. Spirometry measurements and exercise assessment were performed before the transplant, as well as 6 and 12 months post-transplantation. Patients included in the report were followed for at least 2 years post-transplantation, raising some concerns about "survivor bias" and challenging the degree to which the result apply to patients on the waiting list. Although transplantation provided higher FEV1% predicted compared to baseline in all patients, this effect was dramatically lower among SLT recipients. At each time point over four years post-transplantation, SLT patients consistently had spirometry values at least 20% lower than spirometry scores of BLT recipients. 6MWT distances were not significantly different between cohorts, however.

Instead of spirometry, Genao utilized a comprehensive performance score (Karnofsky performance score, KPS) to gauge functional status in older lung transplant recipients (27). Genao wanted to characterize the long-term (1–5 years post-transplantation) trajectory of physical function, and subsequently analyze trends in older (>65 years) recipients of single and bilateral lung transplants. The authors performed a retrospective review of 4,805 patients listed in the UNOS registry between 2005 and 2009. Of these, 774 patients were at least 65 years of age, and 63% of this older subset received SLT. They began their analysis at 11 months post-transplantation based on the assumption that all patients would naturally undergo a postoperative period of disability and functional recovery within the first year after transplantation. KPS were assessed for all patients. The KPS was initially developed in the 1940s, and was a clinician-rated measure that estimated the patient's ability to conduct his or her daily activities/self-care with none, some, or complete assistance. The score ranges from 0 to 100, and a score of 60 or less was traditionally associated with a higher risk for hospitalizations, the need for clinic visits, a serious functional decline, or mortality (28). The authors found that mean KPS scores at 1-year post-transplantation were higher than seen prior to transplantation for all recipients. One-year post-transplantation KPS was, on average, 2.6 points higher (on the scale of 100) for BLT than SLT recipients (P<0.0001). In subsequent years, there was an average 3.2 points decline for all patients, regardless of transplantation type. While BLT was associated with higher KPS post-transplantation, the authors noted that it was very rare for patients of either group to reach a level of disability predictive of poor outcomes (KPS ≤60) within the 5-year follow-up period. Thus, Genao and colleagues were unable to support the use of BLT in older recipients based on predicted KPS scores. There were important limitations to this study. The authors cautioned that conclusions regarding use of BLT *vs.* SLT based on their findings should be tempered, as they were unable to control for comorbidities or provider preference. Additionally, the study took into account the immediate perioperative functional decline associated with the recovery period of transplantation and included only patients were alive and had KPS scores after 11 months post-procedure. However, they did not discuss how they handled longitudinal measurement of KPS scores in patients who died after the 11-month cutoff. If QOL measurements were only taken from those who survived, there could be a survivor bias associated with the results. Additionally, the authors mention that the KPS is a clinician-based assessment, and is not a patient reported outcome instrument. Clinician assessment of a patient's QOL can vary from the individual patient's experience and the clinician might be biased when assigning such scores.

Post-transplantation QOL outcomes

For most patients with end-stage lung disease, lung transplantation cannot only provide a survival advantage, but can also influence dramatic changes in health-related QOL (HRQL). The most significant gains in HRQL are expected to be seen in physical health and functioning, and the greatest improvements are expected to occur early (within the first 6 months) after transplant (26). After 1 year, the risk of onset of BOS and the effect of other patient comorbidities can blunt the effect of transplantation on HRQL (29). Research into patient-centered outcomes

in the field of lung transplantation has received growing attention over recent years. However, the available literature on this topic is relatively lacking, and there are even fewer studies that attempt to examine the influence of transplantation type on QOL.

Certain cross-sectional studies have asserted a positive effect of BLT on HRQL measures. Anyanwu performed a European multicenter cross-sectional study of 255 lung transplant recipients (30). They administered the EuroQOL 5D (EQ5D) and visual analog scale (VAS) health-utility instruments to patients who received bilateral (n=79), single (n=106) and heart-lung (n=70) transplants. The EQ5D defines health quality in five dimensions: mobility, self-care, usual activities, pain and discomfort, and anxiety or depression (30,31). Survey takers can assign one of three labels to each dimension: no problem, moderate problem, or severe problem. Utility scores can then be assigned to each of these health states using regression analysis. The VAS allows participants to subjectively assess their own health on a scale of 0 to 100 (worst possible health to best possible health). In addition to stratifying results by transplant type, the authors repeated surveys at four different post-transplant time periods: 0–6, 7–18, 19–36, and >36 months. Problems in all five EQ5D domains in all time periods were more common among SLT patients than BLT patients. Those who received bilateral or combined heart-lung transplants had significantly higher EQ5D and VAS scores than their SLT counterparts in all time groups after 6 months (P=0.001). However, this study was limited by the lack of controlling for age and pre-transplant diagnosis.

The positive impact of BLT on HRQL was not demonstrated by all studies. Gerbase administered the St. George's Respiratory Questionnaire (SGRQ) and the VAS to 34 patients who had undergone SLT (n=14) or BLT (n=30) (26). The SGRQ primarily addresses three areas: respiratory symptoms, accomplishment of routine activities and disease impact on daily life (32). These patients were followed for at least 2 years (when the authors believed average onset of BOS occurs) and all data were collected prospectively. The authors noted that SGRQ and VAS scores were significantly improved after transplant compared to pre-transplant in both SLT and BLT groups. However, post-transplant, there was no significant differences in QOL scores between SLT and BLT groups. Scores were also independent of the underlying disease that led to transplantation. As described in the previous section, the authors also collected spirometric and 6MWT data and found that the post-transplantation improvement in FEV1% predicted scores were significantly less in SLT versus BLT recipients. 6MWTs were comparable between cohorts. The authors suggested that pulmonary function had limited influence on objective and subjective parameters of patient health-related QOL.

Copeland prospectively studied QOL measures in patients who were 1-year post-transplantation (33). They utilized a pre-existing study cohort of 131 lung transplant patients who were already prospectively enrolled in a cytomegalovirus (CMV) prevention trial. To obtain data on physical and mental health QOL measures, they surveyed these patients immediately pre-transplant, as well as 3, 6, 9, and 12 months after transplant using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36). As a part of the SF-36, scores are assigned to develop the Physical Component Survey and Mental Component Survey (34). These scores were followed longitudinally over the first post-transplant year. The authors used linear mixed modeling for repeated measures of QOL scores, which relied on any data collected at any time point to longitudinally estimate scores. This approach was used because the authors anticipated missing data from loss to follow-up or death. Over this time period, Physical Component Survey scores rose by an average of 10.9 points from baseline (P<0.0001), reaching a level close to the average US population score. Mental Component Survey scores did not exhibit a significantly dramatic rise. When stratified by transplant type, bilateral operations did not confer a significant advantage in gains in physical component scores over single lung transplant. Given that the functional outcome benefit conferred by bilateral procedures has been shown to be greater in the long term (>1 year), it would be interesting to see if there would be a clinically important difference in QOL scores if they were longitudinally followed over a longer period of time.

Associations between procedure type and chronic rejection

BOS syndrome after lung transplantation represents chronic allograft rejection and dysfunction (35). BOS syndrome is defined as a progressive airflow obstruction with deterioration of graft function, and affects up to 60% of lung transplant recipients who survive 5 years post-transplantation (36). The mean time between transplant and diagnosis is approximately 16–20 months (35). It has been characterized by a continuous deterioration in

FEV1% predicted, and can be pathologically confirmed by the presence of intraluminal fibromyxoid granulation tissue and extensive eosinophilic infiltrates on transbronchial biopsy (37).

BOS has been linked to many poor outcomes in transplant recipients, with increased mortality risk and an association with decreased functional and HRQL outcomes (35). While the exact physiologic mechanism behind the development of BOS is unknown, multiple studies have reported SLT as a risk factor for development of BOS (26,38,39). Neurohr and colleagues performed an institutional review of their lung transplant database and compared 46 SLT and 30 BLT recipients with a diagnosis of IPF (38). SLT was found to be a predictor for occurrence of BOS ≥ stage 1. Another small institutional study performed by Gerbase, who noted that risk of BOS development at 24 months post-transplant was more than two times higher in SLT recipients (RR 2.86; 95% CI, 1.22–6.67) (26). Hadjiliadis found SLT to be independently associated with BOS occurrence after transplantation (39). In their single center retrospective study of 225 transplant recipients, they found an overall incidence of BOS to be 41.3% at a median time of 4.2 years since transplant. After controlling for other patient comorbidities and characteristics, SLT was found to be significantly associated with BOS onset in multivariable regression analysis. Other variables including transplant center, recipient age, and end-stage lung disease diagnosis were not associated with risk of BOS development. As diagnosis of BOS depends on the decline in FEV1%, it makes sense that SLT patients are at increased risk of BOS development. Unlike BLT patients, SLT patients still have a diseased native lung, and its deterioration over time contributes to their overall FEV1%. Thus, in a hypothetical situation where the recipient risk factors and donor lungs are equal, an SLT patient may have a higher baseline risk for meeting the threshold of a BOS diagnosis compared to a BLT patient simply due to native lung dysfunction.

Transplant center, recipient age, re-sapient diagnosis, gender, acute rejection score and number of bronchoscopies in the first 6 months had no effect on the risk of BOS development.

Not all studies have demonstrated the same association between transplantation type and onset of BOS. In a much larger UNOS database analysis of 2,260 lung transplant recipients with primary diagnosis of COPD, Meyer and colleagues did not observe a difference in BOS incidence between SLT and BLT cohorts over the three-year follow-up period (4). Given the enormous morbidity and mortality burden that BOS imposes on lung transplant recipients, further research is warranted to investigate the physiologic mechanism of BOS and any possible link there may be to transplantation type.

Ethical considerations

Much of the debate surrounding use of BLT or SLT stems from the ethical challenge of how best to make use of a limited resource: donor lungs. The persistent ethical dilemma surrounding lung transplantation is whether the possible broader societal benefits of splitting a pair of donor lungs and thus reducing wait list time and wait list mortality outweighs the cost to the individual recipient to forego BLT. Several institutions, including our own, routinely use BLT for most lung transplant recipients (10). This brings to head the ethical dilemma posed by BLT, and challenges the reader to decide whether increased individual benefit is worth the societal cost of fewer patients transplanted.

Several groups have found innovative methods to determine the opportunity cost of providing bilateral operations. Anyanwu examined lung donors reported to the United Kingdom Cardiothoracic Transplant Audit between 1995 and 1998 for whom both lungs were utilized (40). They examined survival, rejection, and infection of donor recipients of these lungs to make comparisons between single lung and bilateral lung recipients. One-year graft survival for single lung and bilateral lung blocks were similar (65% *vs.* 71%). Of donor blocks that went to SLT recipients, both grafts were functioning in 44% of donor blocks, both grafts failed in 14% of donor blocks, and one of the two lungs failed in 42% of donor blocks. The authors estimated that splitting a lung block for SLT produced 1.8 survivors per donor block at 1-year post-transplant. One of the weaknesses in their study is that they did not stratify by clinical diagnosis, and they even included a large number of patients with CF and those undergoing re-transplantation in their analysis. In another study, Anyanwu and colleagues examined cost-effectiveness of transplantation versus medical therapy, and included additional comparisons of SLT and BLT (41). They determined that over a theoretical 15-year period, transplantation (compared to remaining on the waitlist with medical therapy) provided 2.1 and 3.3 quality-adjusted life-years (QALY) for SLT and BLT, respectively. The average cost of medical therapy for those not receiving a transplant during this period of time was $73,564. The costs of SLT and BLT were $176,640 and $180,528, respectively. Costs per each QALY gained were

$48,241 for SLT and $32,803 for BLT. Based on the cost per QALY gained, the authors concluded that SLT was the least cost-effective form of therapy for patients with end stage lung disease. However, they noted that they were unable to quantify the additional societal gain that would come from the SLT's ability to treat more patients. Also, it may be possible that the cost to society would be more accurately measured in total cost and not cost per QALY. A plan of more single lung transplant operations will lead to more operations in general and more patients on the very expensive post-transplant medications. The broad use of single rather than bilateral operations could greatly increase the total cost of lung transplantation programs to a society or a payer.

Wang took into account not only the ethical challenges in offering one versus two lungs, but the effect of remaining on the transplant waiting list longer with the hopes to undergo bilateral transplantation (42). Utilizing data obtained from national UK transplant database, they performed a sequentially stratified proportional hazards model on 1,211 adult lung transplant patients to address the following question: "should I accept SLT if offered or should I remain on the waiting list in the hope that I will be offered BLT in the future." They found that in patients with pulmonary fibrosis, SLT was associated with a significant reduction in mortality hazard relative to waiting for BLT (HR 0.81, 95% CI, 0.68–0.97, P=0.021). They concluded that for pulmonary fibrosis patients, accepting SLT outweighed remaining on the transplant list for a BLT by minimizing the high pre-transplant risk of death. There was no such benefit demonstrated in accepting SLT for patients with COPD, however. Munson and colleagues reached a different conclusion (43). They created a simulation of a lung transplant waitlist using actual post LAS implementation UNOS registry data to define waitlist size, donor frequency, waitlist mortality risk, and disease- and procedure-specific post-transplantation survival. They aimed to determine post-transplant survival associated with BLT versus SLT in the COPD population. They determined that SLT always increased the number of patients transplanted, without significant reductions in total post-transplant survival. A theoretical policy of uniform use of SLT in their model resulted in an absolute reduction in the risk of waitlist mortality of 4.2% among all listed patients. However, they noted that this pattern may not be reproducible once geographic donor variations are accounted for and could not be compared to other transplant disease indications.

While the common ethical argument suggests that SLT may provide greater societal benefit by maximizing utilization of the existing donor pool, this may not be an accurate depiction. One study used the UNOS registry to study lung block utilization in all SLTs performed between 1987 and 2011. There were 7,232 unique SLT donors identified. Of these donors, only 3,129 (43%) had both lungs used for SLT. The authors reported that more than 200 potential donor lungs went unused annually since 2005. Donor factors associated with the harvest and use of only one lung included type B/AB blood group, lower BSA, lower pO_2, pulmonary infection, extended criteria donor status, and traumatic brain injury or anoxia as cause of death. This study challenged one of the long-standing utilitarian arguments in favor of SLT (44).

At our own institution, there is a greater preference to perform BLT in part due to the prevailing notion that two lungs provide patients with greater physiologic reserve (10). Given this assumption, we often use what might be considered "marginal" donor lungs for BLT for patients—donor organs that would otherwise might be wasted if considered individually in single lung blocks and thus declined. Similarly, in geographic situations in which donor lungs are not considered by a large number of programs, the ability to use two lungs might allow a physically small donor to provide lung transplantation for a much larger recipient. Therefore, it is possible that there is an occasional situation in which the use of donor lungs is "both or none". In this sense, BLT may expand donor lung utilization. Further research into the use of marginal donors/extended donor criteria and subsequent impact on lung resource allocation will be necessary to clarify the nuances in the BLT *vs.* SLT.

The ethical considerations of BLT *vs.* SLT encourage surgeons and institutions to determine priorities: optimizing total number of potential recipients who get transplanted or enhancing post-transplant survival. It is likely that these two goals might be at odds with each other. While adopting SLT will definitely increase the number transplanted, this may come at the expense of post-transplant long-term survival. Implementation of the LAS on transplant lung allocation practices aims to reduce transplant waitlist mortality. However, much of the ethics surrounding the debate will be expressed by institutional preference and practice.

The native lung: potential complications and risk of cancer

One special consideration for the use of SLT is the risk

of potential complications in the native lung. Native lungs already have diminished lung function secondary to underlying disease process, and the use of SLT can potentially impose the additional complications. Venuta and colleagues described their experience in native lung complications in an institutional review (45). From 1991–1997, they reviewed 35 patients who received SLT, of which 11 patients experienced an early (<6 weeks) native lung complication. These complications included overinflation, pneumothorax, hemothorax, pneumonia, invasive aspergillosis, and active tuberculosis (which was present at time of initial transplant). These patients underwent a mix of medical and surgical therapy, with 3 patients receiving an operation. Mortality was still high, with 6 of these patients dying within 6 months. King and colleagues also described their institutional experience with SLT, and also studied outcomes of pneumonectomy for native lungs that experienced complications (46). In 180 single lung transplants performed from 1998–2008, 25 patients (14%) experienced significant native lung complications. Of these, 11 patients went on to receive a pneumonectomy for non-small cell lung cancer (NSCLC), aspergilloma, bronchopleural fistula, and recurrent infection. Complication rates after receiving pneumonectomy were high (36.4%), but there was no in-hospital mortality. Additionally, when comparing patients who received a pneumonectomy for a complication to those who did not experience a complication, there was no statistically significant difference in median survival (4.3 *vs.* 5.1 years). Thus, King concluded that while native lung complications impose serious morbidity and mortality, pneumonectomy could provide an acceptable solution.

While these studies highlight the potentially serious morbidity and mortality of native lung complications, certain points should be noted. First, the data presented in these studies are of limited sample size and are relatively outdated. The perioperative management of transplant patients has undergone substantial improvement over the years, calling into question whether high volume SLT centers today would experience the high rate of native lung complications. While early recognition and management of native lung complications is important, the possibility of developing a native lung complication does not necessarily preclude the use of SLT.

One additional concern regarding SLT is the risk of cancer development in the native lung. Citing increased risk associated with long-term chronic lung disease, possible recipient smoking history, increased age, and potential adverse effects of immunotherapy, one review documented a 9% prevalence of primary lung cancer found in native lungs after SLT (47). Olland and colleagues acknowledged that surgical resection for early stage NSCLC of the native lung should be pursued when possible, but the effects of chronic lung disease and immunosuppression may make surgery more challenging than when compared to a non-transplanted patient (47). Nevertheless, the benefits of a SLT may still outweigh the risks of a BLT in a patient with high LAS. Appropriate resource utilization should be geared towards thorough and aggressive surveillance for malignancy in high-risk SLT patients.

Future directions: SBLT?

As a possible compromise between SLT and BLT, Hartwig and colleagues have proposed SBLT for high-risk patients with ILD (48). To mitigate perioperative morbidity and mortality risk and to preserve the observed long-term benefit of BLT, these authors proposed utilization of SLT in some recipients and then relisting them for a subsequent contralateral SLT at a future date. Typically, an institution using this strategy will list individuals deemed to have higher perioperative risk (by age or comorbidity) to undergo SLT. After transplantation, these patients are reviewed for re-listing and all individuals who were noted to have acceptably low perioperative complications and reasonable functional status were considered. Re-listing for contralateral transplant was performed as soon as was clinically appropriate (as determined by adequate functional recovery and no presence of infection or rejection). The authors performed a matched cohort analysis with a primary outcome of survival. Twelve patients underwent SBLT, and matches were selected in a 1:2:2 ratio from SLT and BLT recipients with ILD and similar LAS score. When comparing characteristics between the first and second stages of the SBLT procedure, there were no significant differences between donor characteristics. LASs were significantly higher in the first stage compared to the second stage (48.6 *vs.* 24.5, P<0.01). When comparing between matched cases, the authors found no significant differences in survival. The authors thus proposed SBLT as an alternative to SLT and BLT. The concept of SBLT is intriguing, but the strategy itself is fraught with potential complications and ethical challenges. The authors noted that the staged bilateral option exposes patients to two operations, and there may be a pool of individuals who sustain the risks of a second procedure when they could

have done reasonably well with just the initial single lung transplant. Additionally, the existing knowledge on the immunologic consequences of receiving a second lung from a separate donor is relatively limited. It is unclear whether these patients will be at greater or reduced risk for developing lung allograft dysfunction long-term. From an ethical perspective, it is unclear whether SBLT truly results in a better redistribution of a limited resource. While more lungs would be available for use if individuals underwent a unilateral first stage operation instead of a BLT, many would ultimately reappear on the waitlist. It is unclear whether the second donor lung would achieve more benefit as a second implant for a staged procedure recipient or being utilized for a new patient who has never undergone transplantation. Although several important questions regarding use of SBLT exist, it still remains a controversial option and further investigation into the subject may be warranted.

Conclusions

BLT has grown in utilization among transplant centers nationally, and presents a useful option for patients with a variety of end-stage lung disease diagnoses. The increased adoption of BLT is likely reflective of increased comfort in practice among transplant surgeons and recognition of benefits measured by long-term survival and improvements in functional and QOL outcomes. However, much of the literature that examines the use of BLT versus SLT is conflicting, and the clinical picture is further nuanced by disease indication, age of recipient, donor lung quality and patient disease severity. Although it is our institutional preference to utilize BLT in our patient population when possible, we cannot recommend one procedure type over another given the lack of high quality evidence. Transplantation type will continue to be determined on an individual basis. The current clinical picture of transplantation in the post-LAS era is certainly different than before, but much of the existing data available is not yet reflective of this change. There will likely never be a randomized trial to clarify the respective roles of BLT and SLT. However, further large database analyses and prospective observational studies will be instrumental to bring clarity to this debate.

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Footnote

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