Transplant Research and Risk Management

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REVIEW

Lung transplantation for chronic obstructive pulmonary disease

This article was published in the following Dove Press journal:
Transplant Research and Risk Management
3 July 2013
Number of times this article has been viewed

Theodore G Liou
Sanjeev M Raman
Barbara C Cahill

Division of Respiratory, Critical Care and Occupational Pulmonary Medicine, Department of Medicine, School of Medicine, University of Utah, Salt Lake City, Utah, USA

Abstract: Patients with end-stage chronic obstructive pulmonary disease (COPD) comprise the largest single lung disease group undergoing transplantation. Selection of appropriate candidates requires consideration of specific clinical characteristics, prognosis in the absence of transplantation, and likely outcome of transplantation. Increased availability of alternatives to transplantation for end-stage patients and the many efforts to increase the supply of donor organs have complicated decision making for selecting transplant candidates. Many years of technical and clinical refinements in lung transplantation methods have improved survival and quality of life outcomes. Further advances will probably come from improved selection methods for the procedure. Because no prospective trial has been performed, and because of confounding and informative censoring bias inherent in the transplant selection process in studies of the existing experience, the survival effect of lung transplant in COPD patients remains undefined. There is a lack of conclusive data on the impact of lung transplantation on quality of life. For some patients with end-stage COPD, lung transplantation remains the only option for further treatment with a hope of improved survival and quality of life. A prospective trial of lung transplantation is needed to provide better guidance concerning survival benefit, resource utilization, and quality of life effects for patients with COPD.

Keywords: outcomes, emphysema, COPD, alpha-1-antitrypsin deficiency, survival, single lung transplant, bilateral sequential single lung transplant, lung volume reduction, referral, guidelines, health related quality of life

Introduction

Lung transplantation is a treatment option for selected patients with advanced lung diseases who have failed conventional medical therapy. Between 1985 and 2010, the latest year of data available, the number of lung transplants performed worldwide increased from 5 to 3519 combined single lung transplants (SLT) and bilateral sequential single lung transplants (BSSLT).[1] The most common indication for lung transplantation is chronic obstructive pulmonary disease (COPD) exclusive of alpha-1-antitrypsin deficiency (AATD) related emphysema, accounting for 34% of all lung transplants performed between 1995 and 2010. AATD related lung transplantation accounts for an additional 6.1% of all lung transplants performed worldwide.[1] In this review article, we discuss the role of lung transplantation in advanced COPD, efforts to increase the availability of organs for transplantation, quality of life after transplant, and alternatives to lung transplantation.

COPD – natural history and classifications

COPD is a chronic respiratory disease characterized by some degree of irreversible expiratory airflow limitation. The primary cause of COPD in industrialized nations is

Correspondence: Theodore G Liou
26 North Mario Capecchi Drive,
Salt Lake City, Utah 84132, USA
Tel +1 801 581 7806
Fax +1 801 585 3355
Email ted.liou@utah.edu

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Dovepress
http://dx.doi.org/10.2147/TRRM.S10765

cigarette smoking. A minority of COPD patients have AATD that may lead to early onset of unexpectedly severe disease in the absence of smoking,[2,3] although survival may not be affected.[3] A different group of patients may develop COPD due to exposure to specific pulmonary toxins or chronic smoke exposure, for example, from cooking over a poorly ventilated wood burning stove.[4] While these latter patients may be the largest single group with COPD worldwide,[5] they originate primarily from parts of the world where lung transplantation is rare.

Airflow limitation or obstruction is diagnosed by pulmonary function testing. It is most often defined as a decreased ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) on spirometry, and it is quantified by the degree of reduction in the spirometric measurement of FEV_1.[6–8] There is discussion of the use of the lower limit of normal for FEV_1 as a more sensitive defining measurement for COPD, particularly for patients of advanced age;[9] however, the Global initiative for Obstructive Lung Disease (GOLD) favors use of the FEV_1/FVC ratio over lower limit of normal for FEV_1.[10] Potential lung transplant candidates are likely to be diagnosed as having COPD by both methods. In any case, the diagnosis of COPD requires constant presence of airway obstruction that is never completely responsive to bronchodilators.[6–10]

The GOLD has proposed a classification system for COPD based on spirometric lung measurements.[10] Using post-bronchodilator spirometric measurements, patients are defined as having COPD if the FEV_1/FVC ratio is less than 0.7. Stage I, mild disease is defined in patients with $FEV_1 \geq 80\%$ of predicted; Stage II, moderate disease patients have an $FEV_1 \geq 50\%$ and $FEV_1 < 80\%$ of predicted; Stage III, severe disease patients have an $FEV_1 \geq 30\%$ and $FEV_1 < 50\%$ of predicted; Stage IV, very severe patients have $FEV_1 < 30\%$ of predicted or have $FEV_1 < 50\%$ in the presence of chronic respiratory failure.[10] This classification is useful for identifying patients that may be candidates for lung transplantation, but it is not precise enough to provide specific or individual prognostic information or recommendations for transplantation without considering other patient characteristics.

The GOLD has proposed an additional grading system in the latest update to estimate risk of exacerbations based on both spirometric lung measurements and measurements of dyspnea.[10] In this new classification, patients are divided into low risk (Stage 1 or 2) or high risk (Stage 3 or 4) groups. Within these two risk groups, patients are divided again into two groups based on high or low severity of dyspnea using the modified British Medical Research Council or COPD Assessment Test.[11,12] The resulting four categories are: Patient Group A – low risk, less symptoms; Patient Group B – low risk, more symptoms; Patient Group C – high risk, less symptoms; and Patient Group D – high risk, more symptoms. These categories have prognostic implications. A recent study of 6628 Danish patients with COPD found an increasing likelihood of acute exacerbations, hospitalizations, and death for patients categorized from A to D.[13] This alternate grading system allows a care provider to consider dyspnea in addition to spirometry; however, this is not clearly advantageous compared to the original GOLD classification scheme for identifying candidates for lung transplantation.

The natural history of COPD is characterized by a progressive decline in FEV_1, often initiated and accelerated by continued cigarette smoking.[14] Declines in FEV_1 may continue despite cessation of smoking, although at a slower rate than for patients who continue to smoke.[14] A substantial proportion of COPD patients who continue to smoke develop hypoxemia, hypercapnia, and right heart failure.[15,16] Many continue on to death from chronic respiratory failure. Worldwide, COPD caused more than 3 million deaths in 2004 and is the fourth leading cause of death.[17] The incidence and prevalence of COPD are projected to rise with a consequent continuing rise in mortality attributable to COPD.[18]

AATD is an inherited disorder characterized by a deficiency of alpha-1-antitrypsin protein (AAT), the primary inhibitor of neutrophil elastase.[19,20] AATD accounts for a minority of patients with COPD, but 6% of lung transplantation recipients. There are a number of common AAT genotypes and accompanying phenotypes: M (normal), S, Z, and null.[2,3] The degree of AATD is associated with the severity of COPD. Local deficiency of AAT in the airway and airspaces leads to unopposed protease activity, particularly by neutrophil elastase. Subsequently, patients suffer permanent loss of elastin, tissue destruction, and compromised structural integrity of airways eventually leading to clinically severe lung disease. The threshold AAT level in serum associated with increased risk of COPD is 11 μM. All patients with homozygous Z, or Z and null, genotypes have serum AAT levels below the threshold whereas only a small portion of SZ and no M possessing heterozygotes cross this threshold.[21] Intravenous augmentation therapy with AAT concentrated from pooled human plasma is recommended for patients with serum AAT level below 11 μM. Patients with a lesser degree of deficiency may be considered for treatment, especially if the rate of decline in FEV_1 exceeds 120 mL/year. For patients that have already undergone lung transplantation

for AATD related COPD, it is unclear whether augmentation therapy should be continued.[22] AATD related COPD is under recognized but should be suspected in individuals with onset of emphysema before 45 years of age, or in the absence of a recognized risk factor for COPD such as smoking or occupational dust exposure.[2,3,19,20]

Advanced COPD: general referral guidelines and recipient selection

Patients with advanced lung disease and their caretakers should consider referral to a lung transplant center if clinical status continues to deteriorate despite good adherence to maximal medical therapy, and the likelihood of survival beyond 2 to 3 years falls below 50%.[23,24] Patients must meet general eligibility criteria for lung transplantation and may not have any of the absolute contraindications to transplantation such as active cancer or multisystem disease. There are additionally a number of relative contraindications such as a suggested maximum physiologic age (Table 1).[23,24]

Demonstrated high adherence to therapy improves posttransplantation survival.[25] Prediction of high posttransplantation adherence is uncertain; however, pretransplantation predicts posttransplantation substance abuse.[26] More than 20% of patients who smoke prior to lung transplant resume smoking after the procedure.[26] Smoking cessation is a critical element for both slowing COPD progression and improving posttransplantation outcomes.[14,25,27–29] Thus smoking addiction and use of nicotine containing products such as smokeless tobacco or nicotine replacement products are contraindications to lung transplantation.[23,24] Dependencies on alcohol or other substances of abuse affecting a different but partially overlapping group of patients are likewise prohibited.

Screening of transplant candidates should include biochemical testing for smoking byproducts. Self-reported smoking cessation failure is accurate, but self-reported success has both wide-ranging sensitivity and specificity.[30,31] Thus verification of actual smoking cessation is an important although imperfect[30] adjunct to the evaluation of candidates for lung transplantation. A number of biochemical markers can be measured to verify smoking cessation.[31,32] Nicotine measurements can be made from saliva, blood, or urine and are highly accurate; however, detection is limited by the short half-life of nicotine.[33] Nicotine detection cannot distinguish between smoking and nicotine replacement therapy;[32] however, this is something of an advantage for transplant evaluation because any use of nicotine is prohibited.[23,24] Cotinine, a metabolite of nicotine, has a longer half-life and may be detectable in plasma or saliva for up to a week after smoking.[32] Cotinine detection is the current

Table 1 General eligibility criteria and contraindications for lung transplantation (adapted)[23,24]

General eligibility criteria	Advanced lung disease failing maximal medical therapy
	FEV_1 irreversibly $<25\%$ of predicted
	$PaCO_2 \geq 55$ mmHg
	Elevated $PaCO_2$ with a need for oxygen supplementation
	Elevated pulmonary artery pressures with progressive deterioration
	Severe functional impairment or NYHA functional class III or IV
	Absence of significant extra pulmonary organ dysfunction
Contraindications	**Absolute**
	Active malignancy in last 5 years (except non melanoma skin cancer)
	Untreatable non pulmonary organ system dysfunction (eg, liver, kidney)
	CAD not amenable to PCI or CABG, associated with significant left ventricular dysfunction
	Incurable chronic extra pulmonary infection such as chronic active HBV, HCV, HIV
	Chest wall or spinal deformity
	Documented history of nonadherence
	Untreatable psychiatric or psychological condition that compromises ability to cooperate with treatments
	Active substance addiction/abuse (tobacco, alcohol, narcotics)
	Relative
	Physiological age $>$ 65 years
	Poor functional status with limited rehabilitation potential
	Colonization with highly resistant or virulent bacteria, fungi, or *Mycobacteria*
	Severe or symptomatic osteoporosis
	Mechanical ventilation
	Severe obesity (BMI $>$ 30 kg/m^2) or underweight (BMI $<$ 18 kg/m^2)

Abbreviations: BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; FEV_1, forced expiratory volume in 1 second; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; $PaCO_2$, arterial partial pressure of carbon dioxide.

preferred method of smoking cessation verification.[32] Carbon monoxide is commonly measurable from blood with arterial blood gas determinations,[34] and exhaled carbon monoxide gas determination has been successfully used to detect failure of smoking cessation,[35] but smokeless tobacco will not be detected.[32] However, there are environmental sources of carbon monoxide so low-level detections may not identify light smokers.[32] Measurements of anabasine and anatabine, tobacco alkaloids not derived from nicotine, are sensitive and specific for smoking,[36] but because they do not detect nicotine, they may not be suitable in transplantation evaluation. Thiocyanate measured from saliva or sputum has been frequently used to assess smoking activity,[30] but it is insufficiently sensitive and specific for detection of smoking, especially compared to cotinine measurements.[32]

In patients with advanced COPD, maximal therapy usually includes short- and long-acting β-adrenergic and anticholinergic bronchodilators, corticosteroids, as well as long-term oxygen therapy and pulmonary rehabilitation.[7,8] As reviewed, long-acting β-adrenergic and anticholinergic bronchodilators reduce acute exacerbations and reduce lung function loss. In the context of a transplantation waiting list, these therapies can reduce complications during sometimes multiyear waiting times.[7]

Long-term oxygen therapy has been demonstrated to improve survival for patients with COPD and severe hypoxemia.[37,38] However patients with milder hypoxemia do not have a clear survival benefit.[39,40] In such patients, a randomized trial demonstrated improvement in quality of life;[41] however, many patients with improved quality of life declined to use oxygen following the end of the trial suggesting that the cost in effort to use oxygen was greater than the benefit in quality of life.[41] In patients with COPD that have normal oxygen saturation at rest but desaturate with exertion, a randomized trial of supplemental oxygen found that patients had better responses to pulmonary rehabilitation when given oxygen.[42] Whether oxygen therapy has, or should have, an effect on timing of lung transplantation has not been explored; however, patients with resting severe hypoxemia should receive oxygen while awaiting transplant, and those undergoing pulmonary rehabilitation should receive oxygen during rehabilitation sessions to treat hypoxemia, even if oxygen saturation is normal at rest.

Pulmonary rehabilitation in COPD improves exercise capacity,[43] reduces hospitalization days,[44] reduces readmissions for acute exacerbation,[45] reduces dyspnea,[46] and improves health related quality of life.[44,46] Among patients referred for lung transplantation, a short-term pulmonary rehabilitation program utilizing Nordic walking improved dyspnea, 6 minute walk, and quality of life.[47]

Inflammation is a key underlying pathophysiologic feature of COPD;[48–53] however, anti-inflammatory treatments are limited primarily to inhaled and systemic steroids. Inhaled steroid therapy reduces rate of lung function decline, increases lung function in the short-term, reduces rate of exacerbations, and improves quality of life, but individual responses vary widely.[54–57] Thus, maximal therapy for some patients may include recurrent or chronic treatment with inhaled corticosteroids. Oral steroids are not recommended for chronic use; but used in the short-term, they can be useful for shortening duration and reducing severity of an acute exacerbation.[58,59]

Roflumilast, a novel anti-inflammatory phosphodiesterase 4 inhibitor was recently introduced for treatment of COPD. However, the effect of therapy is mild, and adverse events are relatively frequent and serious. Understanding of its clinical efficacy is incomplete.[60]

Despite maximal therapy, patients with severe disease remain at increased risk of death.[61,62] For selected patients, lung transplantation offers a possibility of improved survival. Timing of referral for transplantation may determine the size of any survival improvement. There are limited survivorship studies of patients with COPD,[61,62] and predicting survival for most patients with COPD is imprecise. Clinicians are left to make best estimates and discuss with patients the limitations of survival estimates and the risks and benefits of lung transplantation.

Clinical characteristics sometimes facilitate further categorization of COPD patients into specific groups that can inform decision making concerning the usefulness of lung transplantation compared to alternative treatments. Early reports of lung volume reduction surgery in patients with severe emphysema, whether with isolated giant bullae or more diffuse disease, found potentially marked improvements in lung function, quality of life, and survival.[63–65] Small randomized trials involving 37 and 48 patients comparing lung volume reduction surgery to medical management seemed to confirm significant benefit in lung function and quality of life.[66,67] Patients that were candidates for these procedures were also potential candidates for lung transplantation, thus lung reduction surgery appeared to provide an alternative treatment. Unfortunately, a large randomized trial more recently showed that patients with COPD generally have no benefit from lung reduction surgery.[68] However, in subgroup analysis, patients with upper lobe predominant emphysematous disease and low baseline exercise capacity (despite rehabilitation) appeared

to have a survival benefit from lung volume reduction. This defined group of patients may benefit more from lung volume reduction surgery than lung transplantation, provided they meet criteria (Table 2).[68]

Much of the hesitation with lung volume reduction surgery stems from mortality risk related to the surgery itself. Recent efforts to achieve the potential benefits of lung volume reduction without surgical risks have highlighted the possibility of endobronchial lung volume reduction as a treatment. Endobronchial valves modestly improve expiratory flow rates, 6 minute walk times, and quality of life but at a cost of increased exacerbations, pneumothorax, and hemoptysis.[69] Bronchial blockade via in situ polymerizing "hydrogel,"[70] polymer airway sealant,[71,72] and thermal vapor ablation[73] have also been proposed and tested in preliminary studies with statistically significant but small improvements in lung function, 6 minute walk distances, and quality of life. Most recently, bronchoscopically placed coils to compress emphysematous lung were investigated in 16 volunteers with severe COPD. The prospective, nonrandomized trial demonstrated a statistically significant 15% improvement in FEV_1, reduction in residual volume, improvement in 6 minute walk time, and improvement in St George Questionnaire measurement of quality of life.[74] The mechanism of action remains unclear, but the improvements are similar to those achieved by endobronchial valves and thermal vapor ablation.[75] Final recommendations are lacking whether these are good alternative options for patients contemplating lung transplantation.

Progressive decline in FEV_1 and resulting chronic hypoxemic (Type I) or hypercapnic (Type II) respiratory failure identify COPD patients with especially elevated risk of near term mortality.[62] For patients with hypoxemic respiratory failure, long-term oxygen therapy can lengthen survival, improve quality of life, and improve exercise performance (see this section, paragraph on Long-term oxygen therapy).

Acute on chronic hypercapnic respiratory failure during an exacerbation is associated with 1- and 2-year mortality rates of 43% and 49%, respectively.[76] Acute exacerbations requiring admission to the intensive care unit (ICU) are associated with a 1-year mortality rate as high as 35%.[77] In contrast, the median survival after lung transplantation for COPD is 5.3 years.[1] Because of the markedly increased mortality risk among COPD patients with either hypercapnic or hypoxemic phenotypes, lung transplant is a reasonable therapeutic option. For these patients, lung transplantation offers a potential doubling of survival although it requires risking markedly decreased survival due to realization of acute surgical risks for a minority of patients.

Hypercapnic respiratory failure may be treated with noninvasive ventilation in an effort to reduce early mortality and improve survival to lung transplantation. In patients with acute exacerbations of COPD requiring admission to critical care settings, mechanical ventilation via noninvasive mask was a good substitute for endotracheal intubation reducing both the need for endotracheal intubation and mortality.[78–80] A number of randomized controlled trials have examined the effect of adding noninvasive ventilation to standard treatments for patients with severe acute exacerbations of COPD for whom mechanical ventilation was not immediately indicated. Studies (available in English with sufficient numbers of events and patients for meaningful analysis and excluding one duplicated study) found a reduction in the need for endotracheal intubation.[81–85] One found a decrease in hospital mortality.[82] Taking into account differing entry criteria, trial designs, and goals, a recent extensive review estimated that the use of noninvasive ventilation in COPD resulted in a relative risk of 0.39 for endotracheal intubation and a relative risk of 0.52 for hospital mortality.[86] These estimates were quite similar to those derived from a recent comparative efficacy report based on a similar set of studies from the US Agency for Healthcare Research and Quality.[87]

Patients with COPD that have respiratory failure requiring mechanical ventilation or extracorporeal life support are a distinct group that have no reasonable expectation of sustained survival without lung transplantation.[88] Expert opinion suggests that invasive ventilatory support is a relative contraindication for lung transplantation.[23,24] However, a number of authors have reported cases and series of patients with measurable prolongation of life following transplantation in the setting of ongoing mechanical ventilation or extracorporeal life support for patients with COPD[65,89–92] and other diseases.[88,89,93–96] In all cases, patients had varying lengths of survival following transplantation with the median times measured in months or years; one group specifically examined the outcome of mechanical ventilation for end-stage lung disease and found an enormous, statistically significant advantage of lung transplantation compared to conventional nonsurgical care (Figure 1).[88]

Discussion has focused on whether these patients are appropriate recipients for organs because of the possibility of reduced posttransplant survival and therefore reduced graft survival compared to patients transplanted from extremely ill states without mechanical ventilation or extracorporeal support.[97] Individual patients on invasive ventilation or extracorporeal support indisputably have a positive transplantation outcome compared to nontransplantation;[88]

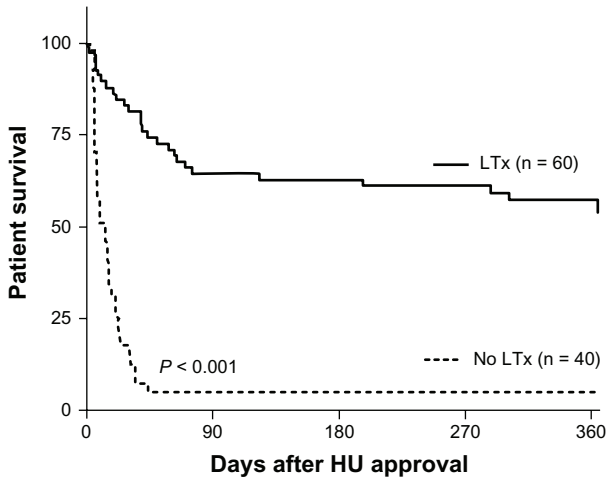

Figure 1 Kaplan–Meier curves for overall 1-year mortality of candidates on invasive respiratory support after first high urgency (HU) approval for the effect of lung transplantation versus non lung transplantation.
Notes: Survival was calculated from the time of HU approval to the time of death. Reprinted with permission Gottlieb J, Warnecke G, Hadem J, et al. Outcome of critically ill lung transplant candidates on invasive respiratory support. *Intensive Care Med*. 2012;38(6):968–975.[88] With kind permission from Springer Science and Business Media.
Abbreviation: LTx, lung transplantation.

however, posttransplantation survival is likely reduced in these patients when compared to that of transplant recipients that were spontaneously breathing prior to transplantation, regardless of pulmonary diagnosis.[97,98] Thus patients with the largest relative increase in survival may not be the same patients that have the longest posttransplantation survival, but they comprise a group with a high likelihood of death on the transplant wait list who derive great survival benefit from transplantation.

The Lung Allocation Score in the United States

To make the best use of an extremely scarce resource – donated lungs – the Lung Allocation Subcommittee of the Organ Procurement and Transplantation Network (OPTN) Thoracic Organ Transplantation Committee performed statistical modeling of outcomes using historical waiting list death and posttransplantation survival as inputs. After prolonged deliberation with public input, the Lung Allocation Score (LAS), a model with balanced consideration of urgency and posttransplantation survival, was proposed and adopted in the US.[99]

One result of balancing of urgency and posttransplant survival is an increase in likelihood and number of transplants for patients on mechanical ventilation and extracorporeal support. Prior to the LAS, with a wait listing system based on accrued time on the list, patients with critical illness requiring invasive support rarely survived long enough to undergo transplantation. Probably, many such patients were never listed. Under the LAS, the equal weighting of urgency with postoperative survival facilitates listing and transplantation of these high risk patients. Such patients are less likely to be removed from the waiting list because they are considered too sick to be transplanted. Both these effects may be reflected in the trend towards rising LAS scores of transplanted patients.

The immediate and most dramatic effect of the introduction of the LAS in May 2005 was a sharp drop in the number of patients on the active waiting list.[100] The effect on waiting list mortality was less clear due to the enormous change in composition of patients on the waiting list. Unadjusted summary rates of death of patients on the waiting list, which had been decreasing prior to the advent of the LAS, have since been slowly rising.[100] At the same time, actual assigned LAS have been steadily rising.[100] The implication is that patients with more severe illness are being listed. However the potentially negative effect on waiting list deaths has been mitigated by the rising numbers of organ donors, which has increased from 3.2 per million population in 2000 to 5.6 per million in 2009.[100] A simple interpretation of these changes and an assessment of survival benefit or harm due to the LAS are not possible due to the complexity and changing mix of patients, diagnoses, and individual severities of disease.[101–103]

Because the algorithm attempts a balance between inherently noncomparable criteria, there is a system for appeals to allow special consideration of individual patient characteristics, especially those factors that imply higher mortality risk but are not considered in the calculation of the LAS.[104] For patients potentially in need of a multiple organ transplant, allocation strategies are complex. Specific OPTN policies do not address all cases and remain under development.[104]

Timing of referral for transplantation

The difficulty of optimizing selection of potential transplant recipients underscores the need for timely referral of patients for transplantation. Late referrals increase the risk that a patient may not survive long enough to receive a transplant while early referral may increase the chance that lung transplantation is performed when there may not be a survival advantage. A systematic, multidisciplinary evaluation of potential lung transplant candidates weighing risks and benefits should be performed as part of any transplant referral process.

In the US, the LAS has somewhat simplified timing considerations. Patients that are referred early will simply receive a low score that makes early transplantation unlikely. They are not forced off the list and are assessed no penalty for staying

on the waiting list for an extended period. Whether patients suffer adverse side effects from simply being on the waiting list is an unexplored but potentially important question. At the other end of severity, even patients on ventilatory support are not necessarily too sick for transplantation and, as discussed above, are given higher scores because of the urgency of needs. Other considerations such as hepatitis C infection, concurrent cardiac failure, or low or high weight, may be more important in affected patients for declining listing for transplantation.[105,106]

Predicting survival in COPD patients

Scoring systems that quantify survivorship in COPD are potentially of great use in timing transplant referral. The ability to predict time of likely death due to COPD might allow maximization of improvement in survival due to successful transplantation. Lung function predicts survival in COPD, particularly for patients with existing severe disease and reductions in FEV_1.[107,108] However, for the selection of lung transplantation candidates, a more precise predictor is required. The LAS was not designed for this task as it was developed and is applied only to patients already selected to enter the waiting list for transplantation.[99] While computation of a high LAS is perhaps a pragmatic way to identify patients likely to receive a transplant if listed, the score has unknown accuracy as a predictor of survival in unselected patients with COPD.

Recent work has produced three scoring systems for COPD with each appearing superior to using FEV_1 alone. An index based on body mass index, airflow obstruction measured by percent predicted FEV_1 (FEV_1%),[109] dyspnea measured by the modified Medical Research Council dyspnea scale,[110] and exercise capacity measured by 6 minute walk,[111] with the acronym BODE (Body mass index, Obstruction, Dyspnea, Exercise capacity), was developed from cohorts of patients with COPD from the US, Venezuela, and Spain.[112] The index was developed using 207 patients and validated with an additional 625 patients. It is superior to FEV_1 alone as a predictor of survival. The same group of investigators recently published a supplementary scoring system for comorbidities that they termed a COPD specific comorbidity test (COTE).[113] When used in conjunction with the BODE score, refined survival predictions result.[113]

A separate research group tested the BODE score in different cohorts of 232 patients from Switzerland and 342 from Spain.[114] They found that the score did not perform as well in predicting survival in either Swiss or Spanish cohorts compared to a new scoring system based on age, dyspnea,[115–117] and airflow obstruction expressed as FEV_1%, termed the ADO score.[114] However, following calibration for the new cohorts, the BODE score performed equally well as the ADO score, and Puhan et al[114] suggested that both models should be calibrated should they be used in new cohorts. Both scores were used to make 3-year mortality predictions, a specific prediction that the authors suggest would be useful for determining treatments.

Concerned with the difficulty of assessing exercise capacity for all patients with COPD and wishing to include smoking status and number of acute exacerbations in the assessment of patient severity, an international group of investigators developed a model (acronym DOSE) based on dyspnea using the Medical Research Council dyspnea scale, airflow obstruction using cutoff values for FEV_1% derived from GOLD classification,[10] cigarette smoking status, and number of COPD exacerbations in a year,[118] as a modifier of clinical outcomes.[119]

The BODE, ADO, DOSE, and COTE modified BODE scores each seek to identify COPD patients with high risk of death within a few years. This time frame roughly matches waiting times for transplantation making these models potentially useful for identifying COPD patients most at risk for death and thus potential lung transplant candidates. Models that make predictions on shorter time scales may be useful for management but may not be as useful for gauging the appropriateness of transplantation. Due to timing of publications, only the BODE score was highlighted in the 2006 update of International Society for Heart and Lung Transplantation (ISHLT) guidelines for selection of patients to consider for transplantation.[23] BODE scores of 7 to 10 were identified as potentially identifying patients apt to gain a survival advantage with lung transplantation. Equivalent scores are easily derived with the other scoring systems. None of these scores have been investigated prospectively for this purpose.

Lung transplantation for COPD: unilateral versus bilateral

The most appropriate choice of lung transplant procedure in patients with end-stage emphysema remains unsettled. During the early experience, en bloc double lung transplantation was considered the procedure of choice for emphysema, having evolved from the heart–lung transplant procedure. However, double lung transplantation patients suffered from high rates of tracheal anastomotic complications,[120] and the method is uncommonly performed today.

Instead, unilateral or bilateral SLT with anastomoses at the level of main stem bronchi are now generally favored.[121] Unilateral SLT is employed for most end-stage lung disease patients with COPD or interstitial disease, while BSSLT is generally reserved for patients with pulmonary vascular disease or purulent lung disease, primarily cystic fibrosis.[1,100] SLT carries the added advantage of allowing two individuals to be transplanted from a single donor. In contrast, BSSLT was theorized to confer a larger spirometric improvement in lung function and greater respiratory reserve over SLT in the event of development of chronic lung allograft rejection or bronchiolitis obliterans syndrome.[122]

Historically, SLT was considered to be too risky a procedure for patients with emphysema. Much of this early reticence stemmed from concerns about the potential for postoperative native lung hyperinflation compromising the transplanted organ.[123] Based on early experiments with dogs with emphysema, it was feared that differential elastic properties created by SLT would lead to increased hyperinflation of the native emphysematous lung shifting the mediastinum toward the allograft and causing respiratory compromise and hemodynamic instability.[124] There have been case reports and series of complications attributable to native lung hyperinflation that occurred at varying times following SLT that were corrected by bullectomy with volume reduction or even partial pneumonectomy leading to improvement in pulmonary function.[125–128] However, these patients are a minority, and although native lung hyperinflation was commonly seen radiographically after the introduction of SLT,[129] it proved clinically insignificant in the majority of SLT recipients.[130]

By the late 1990s, most reports showed that short-term outcomes for unilateral SLT and BSSLT were comparable.[131–133] One group found that BSSLT was significantly superior in their first report but found no clear advantage in their updated report published 3 years later.[134,135] More recent discussion has focused on whether intermediate and long-term survival benefits are equivalent between SLT and BSSLT. Several reports found weak but statistically significant advantage for BSSLT in the long-term.[132,134,136] However, the updated report[135] and three others found no statistically significant advantage of BSSLT over SLT.[133,137,138] Most publications evaluating survival benefits of SLT versus BSSLT are derived from retrospective studies performed at single institutions with small numbers of patients (Table 3). Changing institutional practices, unrelated secular effects, and evolving selection and wait listing criteria may have created bias that cannot easily be detected or corrected. A clear potential source of bias is seen in that unilateral SLT is generally used in older patients, while BSSLT is preferentially used in younger, fitter patients.

Despite a lack of convincingly better results (Table 3), the overall number of BSSLT performed for end-stage COPD has steadily increased compared to SLT.[1,100] In 2000, slightly more patients received SLT than BSSLT.[100] By 2010, four fifths of COPD patients received BSSLT outside of the US,[1] while 67% of US COPD transplant patients received BSSLT.[100] The latest ISHLT Registry report shows a small but statistically significant improvement in survival with BSSLT compared to SLT.[1] These results are conditioned on surviving the first posttransplant year; however, the interpretation of these promising results cannot be complete without knowing survival during the first year. Furthermore, the authors caution that these results should be interpreted with care due to the possibility of confounding variables related to patient selection and clinical status at the time of transplant, as well as the condition of donated lungs.[1] For example, poor condition in some donated lungs may preclude BSSLT; alternatively, extreme urgency in two patients simultaneously at one center may result in a decision to perform SLT in both rather than risk loss of one patient while waiting for a second donation to allow two BSSLT procedures.

Table 2 Indications and contraindications for lung volume reduction

Indications and prerequisites	Nonsmoker
	Heterogeneous emphysema with upper lobe predominance on high resolution CT scan. Exercise capacity less than sex specific 40th percentile after rehabilitation
Contraindications	Current smoker
	Presence of giant bullae $\geq$ one third volume of ipsilateral hemithorax
	Homogeneous/diffuse/non upper lobe predominant emphysema
	$FEV_1 \leq 20\%$ predicted or $D_LCO \leq 20\%$ predicted
	Previous sternotomy, lobectomy, or surgical LVR
	Post rehabilitation 6MWD $<$ 140 meters
	Other comorbidities such as congestive heart failure, coronary artery disease with history of myocardial infarction, malignancy

Abbreviations: CT, computed tomography; D_LCO, single breath diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; LVR, lung volume reduction; 6MWD, six minute walk distance.

Table 3 Published studies assessing outcomes of bilateral sequential single lung transplant versus unilateral single lung transplant

Study[a]	Study site	Transplants total number (BSSLT/SLT)	Pretransplant patient characteristics	Major outcome variables assessed	Results
Algar et al[137]	University Hospital, Cordoba, Spain	39 (24/15)		1-, 3-, and 7-yr survival	No statistically significant differences
Bando et al[131]	University of Pittsburgh, USA	48 (9/39)[b]	No differences	30-day and 1-yr mortality, improvement in pulmonary function	Significantly better 1-yr mortality in SLT group and pulmonary function in BSSLT group
Bavaria et al[134]	University of Pennsylvania, USA	76 (29/47)	BSSLT group was younger and SLT group had more females[c]	Incidence of PGD, 60-day, and 1- and 2-yr survival	Lower incidence of PGD ($P = 0.049$), better 60-day, 1-, and 2-yr survival in BSSLT group
Cassivi et al[136]	Washington University, St Louis, USA	306 (220/86)		5-yr survival, freedom from BOS	BSSLT had significantly better 5-yr survival ($P < 0.001$) and freedom from BOS ($P < 0.006$)
Christie et al[1]	Multicenter, ISHLT Registry	34,102 (20,831/13,271) COPD only: 11,587 (5539/6048)		Median survival conditioned on survival to 1 yr posttransplant	BSSLT median survival 9.4 yrs; SLT median survival 6.5 yrs
Delgado et al[133]	University Hospital A Coruña, Spain	62 (33/29)		Overall survival and freedom from BOS	No statistically significant differences
Pochettino et al[135]	University of Pennsylvania, USA	130 (46/84)	Patients in BSSLT group were younger and predominantly male	90-day mortality, 1-, 3-, and 5-yr actuarial survival	No statistically significant differences
Stavem et al[138]	Rikshospitalet University Hospital, Oslo, Norway	126 (56/70) COPD only: 86 (37/49)	Primarily COPD	Survival before transplant and before and after 90 days posttransplant	No transplant survival advantage for COPD. No difference in BSSLT versus SLT in COPD. Improved survival with BSSLT in non COPD patients
Sundaresan et al[132]	Washington University, St Louis, USA	119 (69/50)	SLT group was older and had more females	90-day and 1-, 3-, and 5-yr survival	No statistically significant differences
Thabut et al[139]	Multicenter, ISHLT Registry	9883 (6358/3525)	3024 BSSLT patients matched to 3024 SLT patients by propensity score	Posttransplant survival	BSSLT had a hazard ratio of 0.89 by propensity based matching

Notes: [a]All studies listed were single center, unless noted, and retrospective in nature; [b]includes 3 en bloc double lung transplants with BSSLT; [c]approximately 10% of included patients did not have emphysema but had either LAM or OB.

Abbreviations: BOS, bronchiolitis obliterans syndrome; BSSLT, bilateral sequential single lung transplantation; COPD, chronic obstructive pulmonary disease; ISHLT, International Society for Heart and Lung Transplantation; LAM, lymphangioleiomyomatosis; OB, obliterative bronchiolitis; PGD, primary graft dysfunction; SLT, unilateral single lung transplant.

To adjust for potential bias due to selection of patients for SLT or BSSLT, Thabut et al used ISHLT data and applied a propensity score for BSSLT to examine the survival effects relative to SLT for 9883 patients transplanted because of COPD between January 1987 and March 2007.[139] Proportional hazards modeling of survivorship found that across ages and nationalities, BSSLT was about 5% better than SLT 5 years after the procedure. Propensity scores seek to control variables that potentially influence, in this case, the choice of procedure. As the authors discuss, controlling potential or known bias by propensity scoring is not equivalent to controlling with randomization. Factors such as acuity of disease, the acuity of other patients that might benefit from immediate SLT, and availability of organs suitable for BSSLT may still introduce significantly biased estimates of effect. However, given a choice, this paper supports use of BSSLT over SLT.

Thabut et al[139] did not address the critical issue of whether any benefit of BSSLT is worth the wait over an immediate SLT. In a study of 1211 adult first lung transplant candidates listed for transplantation from July 1995 through July 2006, Wang et al[140] found that SLT was associated with a significant and large reduction in hazard ratio for death compared to waiting for BSSLT in pulmonary fibrosis patients.

However, analysis of patients with COPD found no advantage or disadvantage of immediate SLT compared to waiting for BSSLT.[140] Thus, while there is evidence that BSSLT results in a survival advantage over SLT,[1,100,132,134,136,139] the survival cost of waiting additional time for BSSLT may not be worthwhile, on average, for patients with COPD, and the issue remains unresolved.

A randomized trial of SLT versus BSSLT observing survival from entry onto a waiting list has the best chance to resolve the question of which surgery to undertake. However, the estimates based on results from Thabut et al[139] suggest that 3000 patients with COPD randomized to either SLT or BSSLT followed for 5 years would be required. Such a study seems unlikely.

Increasing the supply of donor lungs

The use of SLT has a distinct advantage over BSSLT in terms of increasing the supply of organs. However, the increasing use of BSSLT and the increased number of patients with increased or extreme urgency undergoing lung transplantation has increased the need for a greater supply of good quality donor organs. Strategies that have been enacted or proposed include extended criteria donors, presumed consent, donation after cardiac death, living related donation, ex vivo lung perfusion, and xenotransplantation.[141–143]

Extended criteria donation

Extended criteria donors are those that fail to qualify for donation with usual screening criteria. For patients with high urgency, possibly with difficult matches in blood type or organ size, extended criteria for acceptance of marginal organs are already in use. In the Eurotransplant experience, extended criteria donors may have older age (greater than 55 years), a medical history complicated by malignancy, substance abuse including cigarette smoking, sepsis, meningitis, or positive virology for hepatitis B, or C, or Cytomegalovirus. Findings on screening exams may include airway purulence on bronchoscopy, areas of consolidation, or other abnormality on chest X-ray (CXR), or a low PaO_2 to FiO_2 ratio.[144] The initial experience with extended criteria addressed an observed 20%–30% mortality among patients waiting for heart or lung donations. By accepting organs with PaO_2 to FiO_2 ratio less than 350, airway secretions on bronchoscopy, or infiltrates on CXR, ten patients received organs sooner. Of the ten recipients, one died on day 5, and another died within 4 months. The investigators concluded that there was no significant impact on short-term survival;[145] however, the small numbers require further investigations.

A recent review found multiple studies of lung transplantation utilizing extended criteria or marginal donor lungs.[146] Many studies reported approximately 50 to 100 recipients of extended criteria lungs compared to approximately equal or larger numbers of recipients of standard lungs and found no significant differences in lung function, or short- or long-term survival up to 1 year following transplantation.[147–152] However, a number of similarly sized studies suggested caution in proceeding with transplantation using extended criteria donor lungs based on increased rates of early or late mortality,[153,154] increased primary graft dysfunction either in the postoperative period or after 1 or more years after transplant,[153,155] longer ICU courses, or prolonged hospital stays.[155] Interpretation of these studies is generally difficult because of the moderately small numbers of patients with widely varying characteristics and multiple paths to qualification as an extended criteria donor. The transplant programs involved in these studies did not treat different extended criteria with specific or constant relative weightings, and the degree of screening of extended criteria organs likely differed from any one organ and recipient potential pairing to the next, further complicating understanding.

Some larger studies of transplant recipients for COPD have examined the potential influence of single extended criteria such as age, smoking status, or low oxygenation. While easier to interpret, these studies vary in reported outcome and may not be directly comparable to one another.

Studying the effect of donor age, Moreno et al studied 255 transplant recipients and found increased graft failure but shortened hospital stay for the 57 recipients of organs from donors older than 40 years. There was no evidence of increased mortality 1, 3, 5, or 10 years after transplantation.[156] Novick et al reported that in multivariate logistic regression analysis of 5052 patients transplanted at 88 centers in the US and 48 in other countries, donor age less than 10 years or older than 50 years were both significantly and independently associated with increased 30-day and 1-year mortality.[157] Dahlman et al studied 212 patients divided into four groups based on donor and recipient ages < 55 or ≥ 55 years and found no group had better or worse ventilator dependence time, ICU length of stay, or 30-day or 1-year survival. Irrespective of donor age, younger recipients had better long-term survival during up to10 years of follow up.[158] Similarly, Pizanis et al studied donors and recipients younger or older than 55 years and found no age related significant differences in 186 posttransplant outcomes.[159] Pilcher et al found a statistically significant correlation between donor age and recipient posttransplantation PaO_2/FiO_2, but the model fit was poor ($R^2 = 0.04$), and there

was no impact on long-term survival.[160] None of these papers provided COPD specific results.[156–160]

The Toronto Lung Transplant Program studied the effects of extended donor organs on 467 transplant recipients (129 COPD) during a 12 year experience. Multivariate logistic regression revealed no association between receiving an organ from a donor 60 years of age or older and increased 30-day mortality. Ten-year mortality was decreased for the 60 extended donor recipients (15 with COPD), but the cause of death shifted from sepsis to bronchiolitis obliterans.[161] Using multiple linear regression, Thabut et al found no effect of 10 year intervals of donor age on postoperative oxygenation, or long-term survival.[162]

A study of the effects of smoking donor lungs found prolonged ICU length of stay and decreased 90-day survival in 454 patients, including 50 with COPD.[163] A larger analysis of 1295 lung transplantations in the UK found that 510 involved organs from donors with positive smoking histories.[164] Using a case–control design, investigators found that patients who received lungs from smoking donors had lower maximum FEV_1 in the 2 years following transplantation, and lower 30-day, 90-day, and 3-year survival. Median survival was reduced from 6.5 years to 4.9 years for recipients of smoking donor lungs. The hazard ratio associated with donor smoking was 1.46 (95% confidence limits 1.20–1.78) and was relatively unchanged after correction for five other risk factors. Lungs donated by smokers of more than 20 cigarettes per day were associated with further decreased posttransplant survival.

However, the authors of this careful analysis examined the survival cost of waiting for nonsmoking donor lungs. They found that the hazard ratio of accepting smoking donor lungs was 0.79 when compared to remaining on the waiting list. For patients with COPD, the risks of smoking donor lungs on posttransplant survival and the risk of remaining on the waiting list and refusing smoking donor lungs were similar to the overall results.[164]

Lungs from donors with suboptimal oxygenation prior to donation have been studied a number of times. Lardinois et al included 39 COPD patients in a study of extended criteria donation and found no effect of low oxygenation donors; however, the number of patients studied was small.[151] In a study of 362 heart–lung and lung transplants, Luckraz et al found that low donor oxygenation had no significant effect on 30-day mortality; COPD specific outcomes were not separately analyzed.[165] Thabut et al found that lower donor oxygenation reduced postoperative recipient PaO_2/FiO_2. In multivariate analysis, every increment of 100 in the PaO_2/FiO_2 ratio independently and significantly reduced the hazard ratio for death by 10% during up to 11 years of follow up. This study included 250 COPD patients but found that recipient diagnosis had no effect on posttransplant outcomes.[162]

No blanket statement of the advisability of using all the different extended criteria for lung donation can be made; however, specific criteria can be considered. Lungs from older and smoking donors are associated with poorer posttransplant outcomes; however, waiting for a more ideal organ is associated with poorer outcomes than the decision to undergo transplantation. Poor donor oxygenation is associated with poorer posttransplantation outcomes, but the cost in poorer outcomes of the transplant decision due to waiting for better organs has not been assessed. Where diagnosis specific data are available, the outcomes of COPD patients are not clearly distinguished from those of other patients. For transplant programs evaluating posttransplant outcomes, the use of extended criteria donor organs should be considered as an important correction factor. For patients, families, and their providers, additional information and more specific guidelines concerning extended criteria donors would be helpful, but the continuing challenge is balancing individual urgency of transplantation and the cost of waiting for more ideal lungs.

Presumed consent

The default option determined by law in the US and other countries assumes non-consent for organ donation. In contrast, a number of countries with active organ transplant programs have presumed consent as the default for all potential donors. In those countries, the nominal donor consent rate is markedly increased, and there is a significant, though smaller, increase in actual organ donations compared to countries with a non-consent default.[166] Survey respondents in different countries generally favor presumed consent; however, minorities persist that are opposed to organ donation, and conflicts of interest between caring for severely ill patients and potential transplant recipients persist. Varying cultural and religious views within every country on organ transplantation may not be fully considered by national presumed consent policies and laws.[167] Even within similar populations that support presumed consent, there may be striking differences in underlying views of the altruism of organ donation.[168] The impact of these perceptions on actual organ donations is unknown.

Donation after cardiac death

Donation following brain death is the usual circumstance leading to organ donation for transplantation. In an effort

to expand available supplies, donation after cardiac rather than brain death has been explored for multiple organs including lungs. An initial case series reported 17 recipients of lung donation after cardiac death in uncontrolled settings. Organs were harvested from donors younger than 55 years that suffered sudden death at a known time with cardiopulmonary resuscitation starting within 15 minutes of cardiac arrest.[169] An update of this case series reported the results of 29 lung transplants after donation after cardiac death.[170] These papers reported the impression of increased primary graft dysfunction and decreased long-term survival, and there were significant univariate associations between mortality and ischemic times and between mortality and primary graft dysfunction. COPD patients constituted 41% of recipients. The authors cautioned that the success of donation after uncontrolled cardiac death was dependent on careful selection criteria of donated organs, but they concluded that such organs can be a valuable source of donated organs.

In the US, through 2007, there were 36 lung transplants using organs donated after controlled cardiac death recorded by the OPTN and the Scientific Registry of Transplant Recipients (SRTR).[171] By 2010, an additional 70 transplants using lungs donated after cardiac death were reported.[172] After withdrawal of care from donors without brain death, organs were harvested after cessation of heart beat. Survival following donation after cardiac death was comparable to survival after standard organ procurement. However, two patients required extracorporeal membranous oxygenation support posttransplant, suggesting an increased incidence of primary graft dysfunction. Anastomotic complication rates were comparable to rates for conventional procedures. The number of patients followed was too small to perform meaningful statistical analysis for any difference in bronchiolitis obliterans.

Transplantation using organs from donation after cardiac death appears to be a growing practice to address the increasing numbers of patients waiting for organs with increasing urgency of need. Results are superior for donation after withdrawal of care compared to donation after sudden death and cardiopulmonary resuscitation. However, comparisons of long-term outcomes with donation after brain death, while favorable, are not robust due to small numbers of patients and may be influenced by potential bias due to nonrandomized selection of donor organs and recipients. It remains unsettled whether potential recipients should be informed of an organ donated after cardiac death, particularly because of the uncertainty in long-term posttransplantation outcomes.

Living related lung donation

Classic articles describe living related donation and outcomes of lung transplantation, primarily for children and young adults with cystic fibrosis.[173–176] Living donors have been an important, although decreasing, source of organs for patients requiring kidney, pancreas after kidney, and liver transplants.[100] However, the latest US OPTN/SRTR report records only nine living donor lung transplants in the US since the implementation of the LAS and only two since 2008 through 2012. The changes in wait listing priorities have greatly improved the chances of receiving a cadaveric organ for patients with urgent illnesses thereby decreasing the potential utility of living donation.[100] The latest ISHLT report includes no mention of living donation for lung transplantation. The majority of the few remaining living related lung donation procedures are being done in Japan due to their continuing and severe shortage of organs, and none are being done for COPD.[177–179]

Ex vivo lung perfusion

Approximately 60% of donated lungs were not used for transplant in 2011.[100] Some of these may have been usable with careful screening through extended criteria donation programs. Some additional donated organs were marginal but beyond extended criteria. Ex vivo lung perfusion has been evaluated as a method to test if such suboptimal organs might still be implantable without negative consequences.[142]

Ex vivo lung perfusion involves explantation of a marginal organ and its treatment as an isolated perfused lung. If specific but still evolving criteria are met, the organ may be usable for human transplantation. Cypel et al[180] examined outcomes of transplantation in 136 patients who were serially recruited and who underwent transplantation with usual or ex vivo perfused high risk organs. Patients were not randomized, and blinding was not feasible. High risk organs had one of several criteria: PaO_2/FiO_2 below 300 mmHg, bilateral interstitial infiltrates in the absence of infection, poor inflation or deflation on visual examination, more than 10 units of blood transfusion, or donation after cardiac death. (More precise details can be found in the Methods section of that report.)[180]

The authors found a trend toward increased grade 2 or 3 primary graft dysfunction at 72 hours, the primary endpoint. There was a doubling of the rate of mortality at 30 days posttransplant, but this was due to only one additional death among the high risk organ recipients and was not statistically significant. The study was too small to exclude subtle problems with ex vivo perfused lungs. Further, the possibility of

bias arising from the nonrandomized, unblinded study design could not be excluded.[180] There was no statistically significant difference in 1 year survival. Survival during post-procedure follow up times of as long as 828 days were similar between the two groups, but statistical testing was not presented.

Extensive efforts by multiple groups are under way to explore the optimal conditions for ex vivo lung perfusion.[142] The number of centers currently performing this procedure remains small, and the total number of cases performed are insufficient to perform an extensive comparison of these outcomes, particularly long-term, with outcomes from the use of standard organs.

Xenotransplantation

No xenotransplants have been performed to directly treat human lung disease. It is proposed that lungs harvested from genetically modified pigs may one day provide a source of numerous, rapidly available organs. Unfortunately, enormous barriers exist due to vigorous human immune responses involving innate and acquired immunity, as well as the likelihood of coagulation dysfunction and pro-inflammatory responses by multiple cell types with multiple messenger molecules.[143] The nature of the barriers makes it clear that xenotransplants remain theoretical and will not be performed in human recipients in the near future.

Lung transplantation in COPD and life extension

Whether lung transplantation confers a survival benefit in the sense of extending life beyond that expected for a nontransplanted patient with COPD is unknown. Lack of randomized prospective studies eliminates direct methods of estimating any potential benefit. Imprecision in prediction of nontransplanted survivorship makes assessment of life extension based on retrospective data difficult if not impossible. Survival data exclusively derived from retrospective observational studies may be confounded and biased by the same concerns, for example, that make comparison of SLT and BSSLT survival difficult to interpret with confidence.

Nevertheless, some estimates have been made. A nonproportional hazards model developed to analyze the effects of renal transplantation[181] was used to evaluate post lung transplantation survival relative to waiting list survival for 1208 Eurotransplant COPD patients.[182] Patients that died prior to 260 days posttransplant were estimated to have had a negative impact of transplantation while those that survived 260 days or more may have had a benefit in survival.[182] Similar results using similar models were noted for 163 patients with emphysema transplanted at the Papworth Hospital in the UK between 1984 and 1999.[183] Using proportional hazards regression with lung transplantation as a time dependent covariate,[184–186] investigators found an improvement in survival associated with lung transplantation in a cohort of 157 patients of whom 72 (46%) had emphysema and 76 were transplanted.[187,188]

In contrast, using a larger cohort of 1279 COPD patients derived from the accumulated US experience during the same era, Hosenpud et al used nonproportional hazards modeling and found no survival benefit of lung transplantation.[189] More recently, an analysis was performed on the entire Norwegian lung transplant experience from 1990 through 2003. The analysis included 132 patients listed with emphysema of whom 86 underwent SLT or BSSLT. The study utilized proportional hazards modeling with two time dependent covariates, one for lung transplantation and a second marking survival to 90 days to account for the possibility of nonproportional hazards of death during the immediate posttransplantation period.[138] Similar to Hosenpud et al, these authors found no evidence of survival benefit due to lung transplantation, even for the post 90 day period, in sharp contrast to the more positive reports discussed above.[182,183]

All of these papers are similar in evaluating COPD patients by comparing posttransplantation to waiting list survival and generating hazard estimates, with or without an assumption of proportionality. However, the papers observe different populations within national systems that vary dramatically in patient selection and pre- and posttransplantation management. These differences may have introduced different types of bias, and all the papers required study of patients over extended periods introducing the possibility of secular bias due to evolving patterns of care.

New analyses to estimate survival benefit remain highly desirable especially as the mix of patients appears to be changing as demonstrated by rising LAS scores in the US[100] and increasing frequency of transplantation of critically ill patients.[88,90–93,96,97,190,191] Unfortunately, a more contemporary analysis of United Network for Organ Sharing (UNOS) data cannot easily be done. By incorporating an equal weighting of urgency with posttransplantation survival in order to minimize waiting list deaths,[99] the LAS distributes scarce donated organs to those most acutely in need. However, this creates a confounding bias for evaluating the survival effect of transplantation itself. This bias may be insurmountable for assessing the survival impact of transplant. Additional survival data derived from COPD patients that have not undergone wait listing or transplantation and that are truly

comparable with patients that undergo waiting list placement is desperately needed. With rising costs, particularly for the critically-ill, and limited transplant resources, a prospective trial of lung transplantation must be done. A trial design that entails forgoing transplantation altogether for some patients is unlikely to be acceptable to either patients or practitioners, but a trial where patients randomly exchange LAS, perhaps similar to what we have previously proposed for patients with cystic fibrosis,[192] may derive sufficient data to better evaluate survival benefit without gross disruption of current practice.

Quality of life

The efforts embodied in performing lung transplantation seek to extend survival; however, patients and families view the quality of the life lived during that extension with equal or greater importance than merely surviving.[193–195] Incorporation of patient wishes and views of health related quality of life (HRQoL) into medical decision making may well appropriately alter the actual nature of delivered care,[195] including whether to proceed with lung transplantation. Survival and HRQoL are entities that by nature are incomparable and require measurement on more than one scale. We have suggested that predictions of survival of patients with severe lung disease are potentially correlated with HRQoL.[196,197] In COPD, various comparisons of HRQoL found both strong and weak correlations with measurements of walking ability and lung function.[198–200] Thus correlations between HRQoL and other types of outcome measurements are imperfect. Implicitly understanding this, patients may consider trading away survival time in exchange for better HRQoL under some circumstances,[193] were such bargains possible.

Assessments of HRQoL in lung transplantation, primarily among adult patients, have generally been favorable. Patients report that HRQoL is improved immediately after transplantation, and they further report that gains are sustained.[201–209] However, these findings may be influenced by a transplantation specific bias: there may be personal, familial, peer, and provider pressures for the patient to be convinced that the risks and costs undertaken to undergo this irreversible procedure were worthwhile. Due to the incomparable nature of HRQoL and survival, adjustments for patients with early mortality, a stubbornly persistent 10%–15% of all recipients within 6 months of transplantation[1,100] and more than 20% in selected groups,[1] cannot be done.

Application of positive findings in the papers reviewed[201–209] is limited in the context of modern lung transplantation for COPD. The studies were performed over several decades; studied patients and earlier surgical methods may or may not be comparable to current patients contemplating or awaiting lung transplantation and contemporary techniques, respectively. Methods for evaluation of HRQoL in the studies reviewed varied widely, and most studies involved patients with a variety of lung diseases and procedures. The instruments utilized were not specific for COPD, and few studies used the same instruments so comparisons are difficult.

Two types of measures have been used and studied for assessing patients with COPD: general and respiratory disease specific measures of well-being. A comprehensive review of 13 COPD specific and ten general instruments intended to measure HRQoL was recently published.[210] Studies were evaluated for reliability, validity, and responsiveness according to published consensus.[211] All measures had some substantial degree of validity in measuring patient specific impact of lung disease on well-being. Several were recommended as reliable in reporting the same scores over time for stable patients and responsive to changes in patient status, particularly due to treatments.[210] None of the instruments studied have been evaluated for applicability in lung transplantation, although some have been used.

The St George Respiratory Questionnaire (SGRQ) has good to excellent validity, reliability, and responsiveness.[210] Using the SGRQ, investigators found improving HRQoL with pulmonary rehabilitation despite a falling BODE score among COPD patients followed for 7 years without lung transplantation.[212] Measurements of SGRQ before and after lung transplantation for COPD demonstrated a marked improvement in HRQoL that was independent of pretransplantation BODE score.[213]

Two other disease specific instruments to measure HRQoL have been used in COPD patients with severe disease and were recommended,[210] but have not been used in lung transplantation. The Chronic Respiratory Questionnaire (CRQ) is valid, reliable, responsive both as an interviewer administered and self-administered questionnaire in multiple languages, and compares well with other HRQoL instruments.[114,115,198,210,214] CRQ results have been correlated to improvements in daytime $PaCO_2$, minute ventilation, and step counts in patients with chronic respiratory failure treated with nocturnal noninvasive positive pressure ventilation.[215] The COPD Assessment Test (CAT) was recently developed using data from 1503 patients from Germany, Spain, France, the US, the Netherlands, and Belgium.[12] The CAT utilizes only eight items, has high reproducibility, and is responsive to acute exacerbations of COPD.[12,210] It has been successfully used in assessing the impact of pulmonary rehabilitation on

patients with severe COPD.[216] Both the CRQ and CAT are of potentially high value for studying the HRQoL of lung transplantation.

The Short Form-36 (SF-36) is a general measure of HRQoL that has utility in COPD,[217,218] although other instruments are more sensitive to COPD health status[219] and are more responsive.[214] It is an unexplored question whether a COPD specific HRQoL assessment tool is the most appropriate for use after lung transplantation when patients qualitatively have a different illness. Thus a general measurement tool like the SF-36 may be a good choice of instrument because of the lack of focus on COPD. The SF-36 has been used to demonstrate that there are positive changes in HRQoL associated with lung transplantation for COPD.[208,209,213]

Conclusion

Patients with end-stage lung disease due to COPD currently comprise the largest single group of lung transplant candidates and recipients.[1,100] Over 25 years have passed since the first successful SLT for COPD was performed. Despite extensive experience with the procedure, however, the exact role of transplantation in the care of end-stage COPD patients remains unclear. Patient selection criteria to maximize survival benefit and simultaneously address urgency and improve HRQoL continue to evolve. The increasing number of patients requiring advanced supportive measures such as extracorporeal membranous oxygenation prior to transplantation reflects the increased emphasis on addressing urgency, but this increasingly common practice consumes greater amounts of resources. A prospective trial that incorporates a novel design that does not grossly upset current practice to study survival, resource utilization, and HRQoL effects of lung transplantation is needed now, more than ever before.

Disclosure

The authors have no conflicts of interest in this work. Dr Liou has recently completed service as a member of the Thoracic Board of the United Network for Organ Sharing.

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