Lung Transplantation: A Viable Option for End Stage Lung Disease

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Over the past 20 years lung transplantation has become a viable option for those patients with end stage lung diseases. The first attempt at lung transplantation in humans was in 1963, but long term clinical success was not achieved until 1981 when the Stanford group reported on their experience with heart lung transplantation. [1] In 1983, the first successful isolated single lung transplant was performed by Joel Cooper, [2] who essentially revolutionized lung transplantation. The introduction of the calcineurin inhibitors in the 1980's allowed lung transplantation to develop. Although the surgical techniques have not been significantly modified in the last 15 years, the improved survival that is now being reported is the result of more experienced surgeons and better post operative care. [3, 4]

This overview of lung transplantation, globally and on this campus, discusses the indications for lung transplantation, the outcomes, the complications anticipated, and the new lung allocation system.

Transplant Centers and Numbers

The number of centers reporting lung transplantation, approximately 110 throughout the world, has remained the same since 1997. The number of lung transplants performed per year increased almost 3 fold from 1990 to 2000 but since then has remained stable at 1700 over the past 3 years despite liberalizing the criteria of an appropriate donor.[5] The number of transplants performed is limited to organ availability since the number of donors has remained stable. The number of patients on the waiting list has grown, and the length of time on the waiting list is now 18-24 months. This will be further discussed in the section on lung allocation.

Most centers perform very few lung transplants. (Figure 1) Approximately 57% of the centers perform <10 transplants/year, but these centers only account for 13% of the transplants performed in the last 6 years. Only 31 centers performed more than 20 transplants/year but account for 60% of the transplants done in the world.[5]

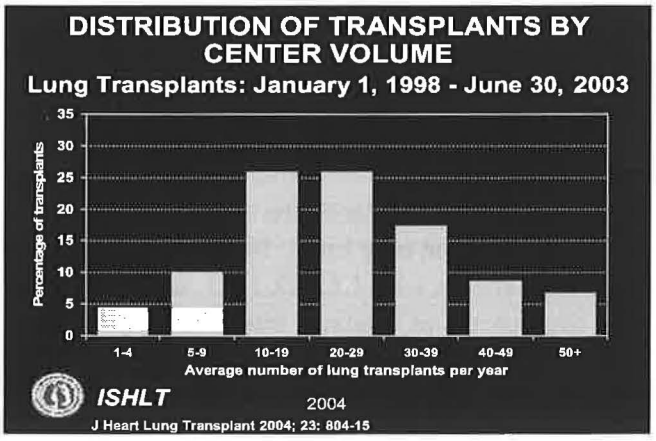

FIGURE 1

The UT Southwestern-St Paul Program performed its first transplant in 1990 and now has performed 139 lung transplants in 137 patients and 3 heart lung transplants. From 1990 to 1997,

we performed only 19 transplants whereas we have performed 17 transplants in the first 8 months of this year. Our program has averaged approximately 14 lung transplants per year over the last 4.5 years. Our volumes have been limited by the number of programs in our local organ resource and, prior to UT Southwestern's purchase of St. Paul, the number of contracts with major insurance providers.

Indications for Lung Transplantation

The major indications for transplantation have included COPD (including alpha-1-antitrypsin deficiency) 46.6%, pulmonary fibrosis including LAM and sarcoidosis 22.1%, cystic fibrosis and bronchiectasis 19.7%, and pulmonary hypertension 4%.[5] Because of our involvement with the Cystic Fibrosis Clinic, the UT Southwestern-St. Paul program has a higher percentage of cystic fibrosis patients. Our indications have included COPD 35%, Pulmonary Fibrosis 21%, cystic fibrosis 39%, and pulmonary hypertension 4%. Thus our percentage of COPD patients is less; and the percentage of CF/ bronchiectasis patients is more than most programs, whereas the number of pulmonary fibrosis and pulmonary hypertension patients are similar to the national statistics. As will be discussed later, the new lung allocation system may significantly alter the distribution of transplants with a lower number of COPD patients and a higher number of pulmonary fibrosis and cystic fibrosis patients being transplanted. The new system has an emphasis on survival benefit and not on how long patients remain on the waiting list.

Choice of Procedure

Over the past 10 years, the number of single lung transplants has decreased, and the number bilateral transplants have increased. Heart Lung Transplants are now reserved for those patients with congenital heart disease and patients with Eisenmenger physiology.[5] In the Heart Lung Transplant, the trachea is usually the site of anastomosis for the airway. Bilateral lung transplants are also performed with the anastomosis in the trachea. The most common bilateral lung transplant is a bilateral sequential transplant (BSL) in which the anastomoses are made in both main bronchi. This has resulted in less anastomotic complications with fewer instances of strictures and dehiscence and better healing.[4] In this protocol, bilateral transplants and bilateral sequential transplants will be considered synonymous and the terms used interchangeably.

In septic lung diseases (CF and bronchiectasis), bilateral lung transplants are uniformly performed to prevent infected secretions from contaminating the new lung. In the past, single lung transplants were the most common procedures for patients with COPD, ILD, and even pulmonary hypertension. Between 1993 and 2003, the percent of bilateral transplants more than doubled in both COPD (16% to 38%) and IPF (17 to 30%) patients.[5] The UTSW-St. Paul program has continued to utilize single lung transplants as reflected in our own values. (COPD-18% bilateral sequential transplants; Pulmonary Fibrosis-41% bilateral sequential transplants). We have reserved BSL transplants for those patients with septic lung disease, those with pulmonary hypertension, and those younger than 50. Otherwise, patients receive a single lung.

However, our program is re-evaluating our choice of single versus bilateral lung transplantation. In the past, the recommendation for a single lung transplant was based on the following: 1) an improvement in overall survival of all patients since 2 persons were receiving a lung instead of just one person receiving two lungs; 2) presumed lack of difference in functional status; 3) presumed lack of significant survival differences, and 4) preference based on the ease of the surgery and surgeons. More recent data have addressed the survival difference between the single and double lung transplant. The survival rates, according to the most recent ISHLT data, for single and bilateral transplant recipients were similar throughout the first year, but then begin to diverge.[5] (Figure 3). Both the half life and conditional half life of a bilateral transplant are significantly longer than seen in single lung transplantation. On the other hand, the other variables important in determining survival such as the patient's age, the indications for transplantation, and the condition of the patients at the time of transplant may have differed in these two patient groups.[5]

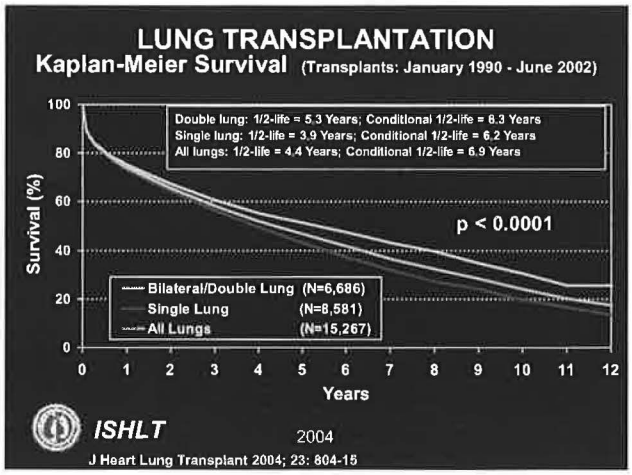

FIGURE 3

Thus these differences in survival may not be related to the use of 1 or 2 lungs but to other factors. Dan Meyer analyzed the ISHLT database between 1991 and 1997. In patients with COPD he found significantly better long term survival in patients younger than 60 who underwent bilateral transplants in comparison to single lung transplants.[6] However, this survival difference was not seen in patients older than 60. Unfortunately this was a retrospective study involving different programs and protocols. Dr. Meyer performed a similar review of pulmonary fibrosis patients but could not find a significant difference in survival between BSL and SL transplants if they at least survived 3 months. Otherwise, SL had a better survival which probably reflects the impact of surgical mortality.[7]

The long term survival is limited principally by the development of bronchiolitis obliterans, a form of chronic rejection which will be discussed later.

Both BSL and SL transplant recipients with COPD and PF show improvement in lung function post transplant. The improvement on lung function usually maximizes after 3-6 months. Patients who undergo a bilateral transplant usually achieve normal lung volumes, even when the recipients are significantly taller than their donors; however, in patients undergoing a single lung

transplant, the lung volumes usually are 50-60% of predicted value. [8, 9] In patients with primary pulmonary hypertension, there is no significant long term change in pulmonary function but a significant improvement in exercise tolerance.

These patients' exercise capacity may not return to normal, but 80% of the patients report no limitation in activity. [5] We, in fact, have individuals competing in triathlons and one has actually run in a marathon. The 6 min. walk tests post transplant usually show a slightly longer distance in BSL vs SL patients, but other variables may explain these differences. [8, 9]

The typical response to exercise suggests a peripheral limitation to exercise that may be related to abnormal oxygen utilization by skeletal muscles. This has been attributed to the effect of cyclosporine on mitochondrial respiration. Overall, the exercise response after transplant reveals a maximum oxygen consumption of only 60% predicted, a normal but low anaerobic threshold, an adequate heart rate reserve, a normal breathing reserve, and normal gas exchange. [10-14] Nevertheless, most patients with an adequate functioning graft should be able to and, in fact, do perform their activities of daily living.

Disease Specific Guidelines

The goals for lung transplantation are a prolonged survival and an improvement in the quality of life. The new lung allocation system addresses the balancing of likelihood of death on the waiting list versus the likelihood of survival after a transplant. Most lung transplant programs utilized the guidelines set forth by the ISHLT, American Society of Transplant Physicians, American Thoracic Society, and European Respiratory Society as indications for transplantation, but over the last few years have liberalized these and taken marginal donors.[14]

Table 1: Guidelines for timing referral

Chronic obstructive pulmonary disease and α1-antitrypsin deficiency emphysema

Postbronchodilator FEV1<25% predicted

Resting hypoxia: PaO2 <55-60 mmHg

Hypercapnia

Secondary pulmonary hypertension

Clinical course: rapid rate of decline of FEV1, or life-threatening exacerbations

Cystic fibrosis

Postbronchodilator FEV1<30% predicted

Resting hypoxia: PaO2<55mmHg

Hypercapnia

Clinical course: increasing frequency and severity of exacerbations

Idiopathic pulmonary fibrosis

VC, TLC<60-65% predicted

Resting hypoxemia

Secondary pulmonary hypertension

Clinical, radiographic or physiologic progression on medical therapy

Primary Pulmonary hypertension

NYHA functional class III or IV

Mean right atrial pressure >10 mmHg

Mean pulmonary arterial pressure >50 mmHg

Cardiac index <2.5 L/min/m2

VC, vital capacity; TLC, total lung capacity.

The UT Southwestern-St. Paul Program has also incorporated these considerations in their evaluation of patients for transplantation.

COPD

The survival benefit of transplantation for patients with COPD has been questioned. This may in part be secondary to our inability to predict survival in patients with COPD. The Forced Expiratory Volume in 1 second (FEV_1) has been the standard utilized in determining the degree of airway obstruction. Mortality has been assumed to correlate with the degree of obstruction and has resulted in the premature listing of patients. Two major trials performed in the 70's evaluated the impact of the administration of oxygen on survival. The British Medical Research Council evaluated the impact of O2 therapy on hypoxemic men less than 70 years of age. The 5 year survival in those individuals without O2 was approximately 25%; whereas in those receiving O2, it was 41%.[15] In the nocturnal oxygen therapy trial performed in the U.S., those patients only using oxygen at night had an annual mortality of 20% vs 11% for the continuous oxygen users. The mean FEV_1 in these patients was approximately 0.75 L confirming the significant airway obstruction.[16] The NIH sponsored a trial on the value of IPPB in 985 patients with COPD who had baseline hypoxemia and followed them for 3 years. Age and FEV_1 were the best predictors of mortality, but the three year mortality rate in patients less than 65 years of age with an FEV_1 <30% predicted was only 31%.[17] Thus while FEV_1 may be a useful measurement of airway obstruction, it may not be the best predictor for survival or the need for transplantation. The mortality data does correlate with other factors including degree of dyspnea, weight change, exercise tolerance, need for hospitalization, and lung morphology.

More recently, Celli et al have concluded that 4 factors (body mass index, degree of airflow obstruction, dyspnea, and exercise tolerance as measured by a 6 minute walk) predict survival. Using these indicators, they developed a scale (BODE index) which has become a better predictor of mortality than FEV_1 alone. Those patients with a high index score had an 80% mortality at 52 months. Since all of the patients with an FEV_1 <35% were given the same score for obstruction, this index incorporates the other factors into predicting survival. [18] Thus, these other clinical factors are important adjustments in predicting survival in patients with COPD. Transplant programs should not rely solely on the degree of airway obstruction to list patients for lung transplantation.

Furthermore, lung volume reduction surgery is also used as a mode of therapy. However, this procedure should be reserved for those patients with upper lobe emphysema whose FEV_1 >20% of predicted, whose diffusing capacity is >20%, and who have no CO2 retention.

Idiopathic Pulmonary Fibrosis

Pulmonary Fibrosis is a generic term for many diseases that result in a restrictive ventilatory defect and interstitial changes on chest x-rays. More recently further clarification of this diagnosis has allowed a better estimation of survival time. Idiopathic Pulmonary Fibrosis and Usual Interstitial Pneumonia (UIP) are essentially the same disease entity, whereas the other interstitial lung diseases (non-specific interstitial pneumonia, cryptogenic organizing pneumonia, acute interstitial pneumonia, respiratory bronchiolitis – interstitial lung disease, desquamative interstitial pneumonia, and lymphoid interstitial pneumonia) have varied responses to therapy and different estimates of length of survival. [19]

The median survival time for UIP is approximately 3 years from the time of diagnosis. In the past, the FVC and DLCO have been utilized as the best parameters that dictated the need for transplant consideration and presumably correlated with mortality. More recently, high resolution CT scans in addition to these physiologic variables have been utilized to predict survival. Nevertheless, our ability to predict survival remains poor. Serial deterioration in lung function is associated with a poor prognosis, but stability in lung function does not necessarily insure a good prognosis. In an analysis of the recent interferon gamma trial for interstitial pulmonary fibrosis, the control group of 168 patients manifested little change in the physiological variables followed over a median period of 76 weeks, but 21% of the patients died. Approximately half of the patients who died acutely deteriorated which would not have been predicted based on their previous pulmonary function data. [20, 21] Thus, in patients with idiopathic pulmonary fibrosis, the worse the lung disease the worse the prognosis, but stability of lung function does not imply lack of progression of the lung disease or freedom from death.

The therapeutic options for idiopathic pulmonary fibrosis remain scarce and essentially are of limited benefit. Thus early referral for transplantation remains a recommendation for patients with interstitial lung disease.

Cystic Fibrosis

The survival of the patients with Cystic Fibrosis has significantly increased over the past 20 years. The median survival in 2004 was approximately 32 years. The most likely cause of death remains respiratory failure. In 1992, the University of Toronto Cystic Fibrosis Center correlated survival with lung function. In their clinic, the 2 year mortality rate approached 50% when the FEV_1 was <30%. Women had a worse prognosis than men. [22] The University of Minnesota in a later study correlated survival not just with an absolute number but with the rate of decline in FEV_1. In their patient population, the median survival in patients with an FEV_1 <30% was 3.9 years; but in the patients who died, the rate of decline in FEV_1 per year was 1.80% of predicted FEV_1 in contrast to 0.73% of predicted FEV_1 in those who lived. [59]

"Old time" CF physicians had noted that clinical parameters such as nutrition, number of exacerbations per year, and the number of hospitalizations, correlated with the clinical outcome of their patients. The University of Utah Clinic utilized the CF Foundation patient registry to develop a multivariable logistic regression survival model for CF. The variables included age, sex, weight for height, type of infection, number of hospitalizations, and lung function. They divided the patients into 5 groups according to their predicted 5 year survival: Group I <30% predicted 5 year survival; Group II, 30 to <50% predicted 5 year survival; Group III, 50 to <70% predicted 5 year survival; Group IV 70% to <90% predicted 5 year survival; and Group V, 90% to 100% predicted 5 year survival. They concluded that FEV_1 alone did not predict 5 year survival. 27 of 292 (9.2%) patients in Group I had an FEV_1 >30% and would not have been considered at high risk of dying according to the FEV_1 alone. Furthermore, 381 out of 2086 (18%) Group IV patients had FEV_1 <30% and would have been considered for transplantation even though their 5 year survival was predicted to be between 70-90%.[23, 24] Consequently, lung function alone should not be the sole criteria in predicting survival in patients with CF.

Idiopathic Pulmonary Arterial Hypertension (IPAH)

Over the past 15 years, there have been significant advancements in the medical management of patients with IPAH. Prostocyclin, endothelian receptor antagonists, and phosphodiesterase inhibitors have been utilized with improvement in exercise tolerance and ostensibly in survival. Furthermore, the combination of these drugs may even be more effective. The median survival of IPAH was reported to be 2.8 years but this was before the introduction of these newer therapies. [25] Thus response to therapy becomes an important factor in predicting survival or in consideration for transplantation. Those patients who remained at NYHA class III despite epoprostenol had a 2 year survival of 46% whereas those who improved to NYHA class I or II had a 2 year survival of
93%.[26, 27]

Consequently, very few of these patients now require transplantation. This explains the few number of IPAH patients in our transplant population despite the large size of the Pulmonary Hypertension Clinic.

Survival Outcomes of Lung Transplantation

The preceding discussion focused on the likelihood of death from the various lung diseases. Prior to recommending transplantation, both the expected survival following the transplant and the impact on the quality of life indicators should be considered. The Kaplan-Meier survival for all lung transplant recipients from January 1994 through June 2003 was 76% at one year, 60% at 3 years, and 49% at 5 years. Overall, these statistics appear dismal when compared to other organ transplants but are significantly better, in most cases, than what would have been expected with medical therapy alone. Since 1988, the survival rates have significantly improved as illustrated in Figure 4.

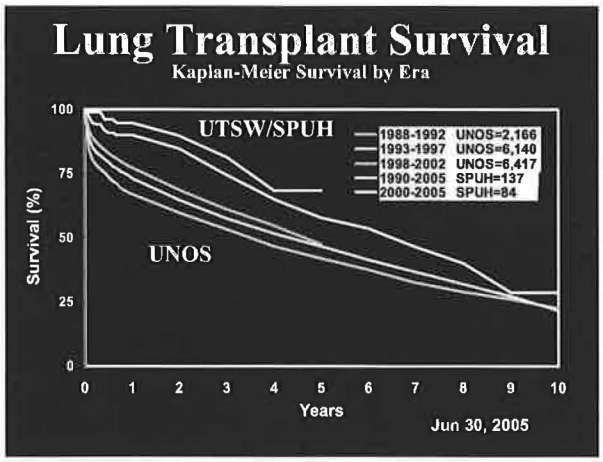

FIGURE 4

This improvement, in my mind is related to the first 3 months after the surgical procedure which reflects better preservation solutions, improved surgical skills and experience, and better handling of early post transplant complications. However, the downward slope in survival for the time period from 1988-1994, 1995-1999, and 2000-2003 remains the same. This progressive downward slope represents chronic rejection and reflects our ineffective efforts to reverse it. Both the age of the recipient and the type of disease process which prompted transplantation also impact the estimated survival. As can be seen in Figure 5, the survival in the patients between the ages of 18 to 49 was significantly better than in the patients older than 50, although this data did not adjust for other comorbidities. Viewed in another way, the relative risk of mortality begins to increase incrementally after age 50 as illustrated in Figure 6.[5]

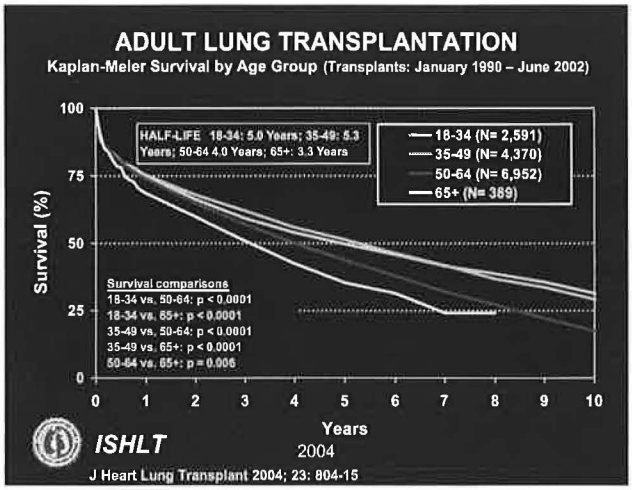

FIGURE 5

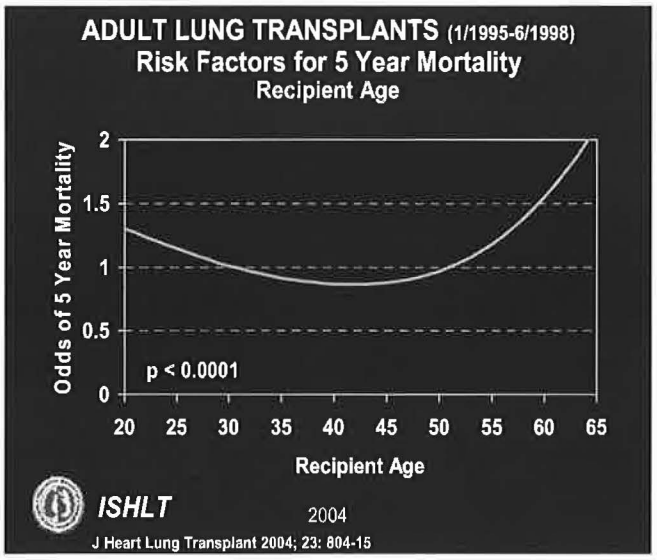

FIGURE 6

The type of disease also impacts survival both early (1 year) and late (5 years) which is illustrated in Figure 7. The difference in survival at one month in the PPH and IPF patients from the COPD patients undoubtedly reflects the increased surgical difficulty in these patients. Thus the survival data early on reflect the complexities of the surgical procedure, whereas the later survival data reflect the complications associated with the medications, chronic rejection, or the inherent medical problems associated with older patients. Patients with CF, PPH, and alpha-1-antitrypsin deficiency usually are young and thus have significantly better long term survival. [5]

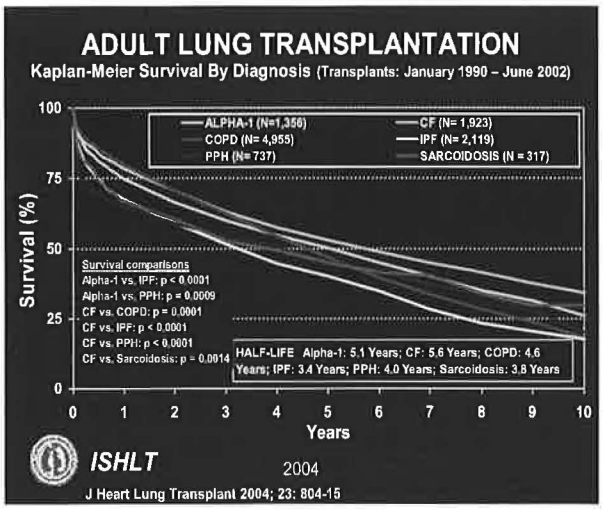

FIGURE 7

Patients undergoing lung transplantation unlike other solid organ transplants have no "back-up" should the organ fail and prior to April 2005 had no preference on the waiting based on the severity of their illness. Thus the one year adjusted graft survival for lung transplant patients is similar to the one year adjusted patient survival, in contrast to what is observed in kidney and liver patients. The one year survival for patients undergo solid organ transplants from deceased donors in the U.S. in 2002 was: lung 81.9%, SE 1.2; heart 87.3%, SE 0.7; liver 88%, SE 0.5; and kidney 96.5%, SE 0.2. The one year graft survival in these patients was lung 80.4%, SE 1.2; heart 86.3%, SE 0.3; liver 82.4%, SE 0.6; and kidney 89%, SE 0.3.[28]

The UT Southwestern-St. Paul program has had excellent survival rates. Since the inception of our program, Kaplan-Meier survival rates are 90% at 1 year, 74% at 3 years, and 59% at 5 years. Since 2000, we have performed transplants in 86 patients. Our survival statistics for these patients are 1 year 94%, 3 year 82%, and 5 year 70%. However, even though our program has a larger percentage of CF patients and thus younger patients, our expected death rates are significantly less than the U.S. Tables 2-5 compare our results with the other active Texas program, with the reputed dominant programs in the U.S., and with the programs in the U.S. ranked according to their survival rates.

Texas Lung Transplant Programs
One Year Survival
July 1, 2001 – December 31, 2003

Center	N	Surv-%	O/E	p Value
UTSW-St. Paul	37	100%	0.00	<0.01
UT San Antonio	51	84.31%	0.74	0.49
Baylor College of Medicine	46	63.04%	1.83	0.03
UT Galveston	15	53.3%	1.02	0.99
Baylor Dallas	31	80%	1.29	0.06
US Programs	2516	82	1.00	

UNOS/SRTR Center Specific Data
ustransplant.org July 2005

TABLE 2

Texas Lung Transplant Programs
Three Year Survival
July 1, 1999 – December 31, 2001

Center	N	Surv-%	O/E	p Value
UTSW-St. Paul	31	77.42%	0.52	0.09
UT San Antonio	24	58.33%	1.15	0.75
Baylor College of Medicine	30	43.3%	1.56	0.104
UT Galveston	5	20%	1.47	0.53
Baylor Dallas	34	50%	1.44	0.18
US Programs	2270	61.67	1.00	

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TABLE 3

UNOS US Lung Transplant Data
1 Yr Survival, Jan '01-Jun '03

Center	N	Surv-1	O/E	WL Mort
St Paul Univ Hospital	44	97.7%*	0.12	16%
Univ Florida, Shands Hosp	54	88.9%*	0.42	19%
UCLA Med Ctr	50	92.0%	0.42	10%
Univ Wisconsin, Madison	64	89.1%	0.57	14%
Univ Washington, Seattle	84	89.3%	0.65	34%
Duke Univ Med Ctr	127	85.0%	0.69	16%
Loyola Univ, Maywood, IL	66	85.4%	0.75	22%
Clarian/Methodist, Indiana	82	85.4%	0.75	16%
Inova Fairfax, VA	54	83.3%	0.75	33%
All U.S. Ctrs (N=69)	2486	80.9%	1.00	14%

UNOS/SRTR Center Specific Data
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TABLE 4

UNOS US Lung Transplant Data
3 Yr Survival, Jan '99-Jun '01

Center	N	Surv-1	O/E	WL Mort
Univ. California, San Diego	45	75.6%	0.60	12%
St Paul Univ Hospital	31	74.2%	0.61	16%
Clarian/Methodist, Indiana	61	75.4%	0.68	16%
Duke Univ Med Ctr	126	69.1%*	0.70	16%
Barnes-Jewish, St Louis	126	73.8%	0.72	9%*
Univ Minnesota, Fairview	78	70.5%	0.73	10%
Univ Alabama, Birmingham	84	71.4%	0.76	22%
Univ Colorado, Denver	66	71.2%	0.78	7% *
Univ Wisconsin, Madison	69	71.0%	0.79	14%
All U.S. Ctrs (N=70)	2213	61.4%	1.00	14%

UNOS/SRTR Center Specific Data
ustransplant.org, Jan 2005

TABLE 5

Causes of Death

The survival curves clearly demonstrate a steady decline in the slope which has not significantly changed in the past 14 years despite the introduction of new therapies and agents. Analyzing the deaths in the ISHLT database from 1992 to 2004, several aspects became evident. Very few patients die from acute vascular rejection, and infection accounts for approximately 1/5 to 1/3 of the deaths post transplant. Table 6 compares the causes of death in our program with the ISHLT registry data.[5]

Causes of Death in Lung Transplant Population 2005

	ISHLT	%	UTSW	%
Bronchiolitis	921	15.5%	20	40%
Acute rejection	132	2.2%	0	0
Graft failure	1146	19%	4	8%
Malignancy	371	6.2%	6	12%
Infection	1622	27%	10	20%
Other	1728	30%	10	20%
TOTAL	5920	100%	50	100%

TABLE 6

The definition of graft failure occurring after 1 year is unclear. Our program classifies graft failure occurring after one year not caused by acute rejection as bronchiolitis obliterans or bronchiolitis obliterans syndrome. In our program, infection accounts for approximately ¼ to 1/5 of the deaths, malignancy for 6-12% despite the careful pre op screening, and bronchiolitis for 40% of the deaths. Our program has had 50 patients die; and infection, bronchiolitis, and malignancy account for 74% of the deaths. Death occurred at the following times post transplant: bronchiolitis 1263 $\pm$ 706 days, infection 466 $\pm$ 432 days, and malignancy 1993 $\pm$ 695 days.

Malignancy and bronchiolitis will be discussed more extensively even though infection plays an important role.

Bronchiolitis Obliterans

The long term survival after lung transplantation is limited by the development of bronchiolitis obliterans which is a form of chronic rejection. It occurs in 50-60% of the patients who are alive at 5 years and accounts for approximately 15-35% of the deaths in the U.S. and 40% of the deaths in our program. [5]

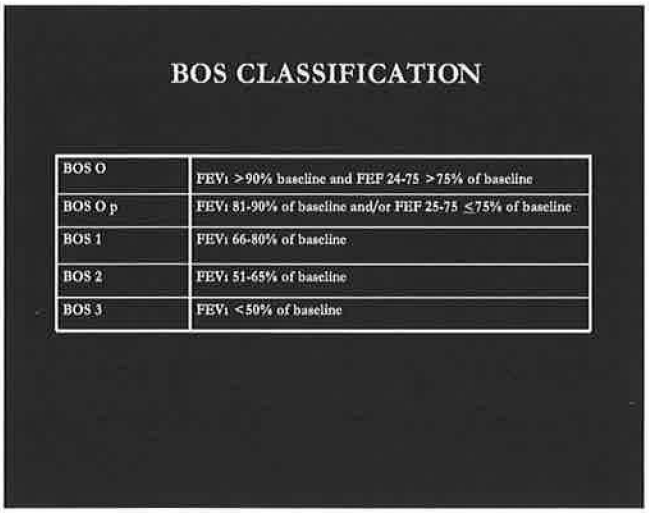
The histopathologic characteristics of bronchiolitis obliterans (B.O.) suggest that injury to the epithelial and subepithelial structures in small airways lead to excessive fibroproliferation from defective epithelial regeneration. Although the etiology is not known, this presumed injury occurs from different inflammatory insults such as ischemia- reperfusion at the time of transplant, rejection, infection, recurrent aspiration and others. B.O. is associated with the development of allospecific immune responses to graft antigens that lead to lymphocyte activation, proliferation, homing to the allograft, graft injury from cell to cell cytotoxicity, and from secretion of bioactive chemokines and cytokines.

Two excellent review articles summarize the immune mechanisms thought to be involved in bronchiolitis obliterans syndrome (BOS). [30, 31]

Bronchiolitis obliterans is a histologic diagnosis and usually is a patchy process in the lung. The histologic confirmation is difficult since the transbronchial biopsies are often not sufficiently sensitive to make the diagnosis in view of the patchy nature of this disease. [32] Bronchiolitis Obliterans Syndrome (BOS) is a clinical diagnosis manifested by decreasing lung function without another known cause.

These processes have a variable course; some patients experience a very rapid downhill course, others experience either slow progression over several years or loss of function interspersed with plateaus at which time the lung function remains stable. [33, 34] This variability in functional decline complicates the evaluation of agents used to attempt to treat this disease.

BOS is now staged according to the lung function changes. [35]



The development of BOS has been attributed to multiple risk factors; but, as in much of the lung transplant literature, the quality of information and studies is poor. Usually the studies have no control groups, utilize retrospective data, have differing therapeutic regimens, or are a single center experience. However, despite these difficulties the number and severity of acute rejection episodes and lymphocytic bronchitis/bronchiolitis do seem to correlate with the development of BOS in all of the studies. [35]

At Papworth Hospital, the hazard ratio for developing BOS was 3.40 (45% CI; 2.35, 4.94) when patients had had 3 or more acute rejections in comparison to 2 or fewer episodes of acute rejection. These rejections were considered to be A2 or higher. [36] This is similar to others reported results. Most programs still perform surveillance bronchoscopies but have not considered A1 rejection in asymptomatic patients to be a risk factor for progression to acute rejection or development of BOS. However, recently this thought process has been questioned. Both Tony Khalifah, one of the UTSW internal medicine residents, who reviewed the experience

at the Washington University Lung Transplant Program and Alan Glanville from the Sydney, Australia program felt that A1 rejection was a risk factor for BOS. [37, 38] Although the St. Louis group felt that treatment of A1 (mild) rejection lessened the likelihood of progression to A2 (moderate) rejection and the development of BOS, other studies have not corroborated their results. [35] Since augmented immunosuppresion which is associated with increased infection is usually the initial treatment of significant rejection, treatment for all mild rejections (A1) would be a significant change in approach for most programs.

Other non immune factors that may result in the injury include infection and aspiration. Unlike other solid organ transplants, the lung is continuously exposed to the environment. Assuming a minute ventilation of 6 liters at rest, a minimum of 8600 liters of air, including particulates and micro organisms, are moved through the lung each day. The lung defense system after transplant is markedly altered. The immune system is suppressed from the anti rejection meds, and the mucociliary escalator is altered. The cough reflex is absent since the lung is denervated, and the ciliary function is markedly reduced. Thus the lung becomes extremely susceptible to injury.

The impact of bacterial infections on the development of BOS is controversial. [35] Whether this is a contributing factor itself or only in combination with other alloimmune factors is not clear. However, infections with CMV and the common respiratory viral (CRV) agents such as para influenza, influenza, respiratory syncytial virus, and adenovirus definitely correlate with the development of chronic rejection or BOS, but most of the studies are retrospective in design. [39, 40] Fernando Torres, one of my colleagues, when he was a fellow at the University of Colorado, noted that approximately 1/3 of the patients who were symptomatic with a documented viral infection developed an episode of acute rejection in the subsequent 90 days. [41] Their experience has been substantiated by a similar prospective study at the University of Toronto. Approximately 16% of their patients with a CRV infection developed acute rejection in 3 months as well. They also observed a decline in FEV_1 which was compatible with BOS in 18% of the patients. [39] These studies and others are certainly suggestive of the relationship between CRV and both acute and chronic rejection.

The Colorado group has aggressively treated these symptomatic patients and noted a decrease in the appearance of acute rejection and BOS. However, the total number of patients actually studied remains small.

The UTSW-St. Paul program has developed an aggressive posture in managing lung transplant patients with URI symptoms. All patients are instructed to obtain a nasal wash to detect RSV, para influenza, influenza, and adenoviral infections if they become symptomatic. If the nasal wash is positive, then the patients are treated with various anti viral regimens in an attempt to decrease the likelihood of developing rejection.

Gastro esophageal reflux is relatively common after transplant surgery, which, in part, may be related to an injury to the vagus nerve at the time of surgery. As many as 73% of the patients have esophageal probe findings compatible with significant reflux. Patients with normal esophageal pH studies had a significantly better 5 year survival (82%) than those who showed reflux. The FEV_1 increased 24% in those patients with reflux who underwent a laparoscopic fundoplication. [42] This study has prompted many centers to rethink how aggressive to be in

looking for reflux. Furthermore, if we extrapolate from the studies from the early 70's, most normal persons aspirate during sleep. Eliot Huxley noted that approximately 45% of normal individuals (medical students and residents) showed evidence of aspiration of oropharyngeal contents during one night of sleep.[43] Thus, following lung transplant, the lung becomes more vulnerable to injury since the lung defense mechanisms are physically altered, there is more evidence of reflux, and there may be decreased gastric emptying.

The other hypothetical and potential risk factors for BOS include donor age, ischemic time, reperfusion injury, and HLA mismatching.[35] In many of these cases, a single center report of association of certain factors is not substantiated by the larger ISHLT database.[5]

A variety of therapies have been used to treat BOS. None have been confirmed in large scale studies. By and large, immunosuppresion may be augmented with cytolytic therapy, the calcinurin inhibitors may be changed, mycophenolate mofetil has been utilized, Sirolimus may be included in the regimen, or total lymphoid irradiation may be considered.[44-47, 51] Photopheresis has shown some benefit in a small number of patients.[48] Studies utilizing azithromycin have shown either stabilization or improvement, but the combined total of patients is only 14![49, 50] The usual practice in most centers is to try many of these modalities in an attempt to stabilize lung function.

Inhalation of medications for lung disorders has attracted significant attention since it has the potential to deposit higher doses of medication in the lung without achieving significant blood levels. Inhaled steroids have not been of significant benefit in preventing or treating BOS. Recently, inhaled cyclosporine was evaluated in a group of 56 patients, 30 who received placebo and 26 who received CSA. There was a significant difference in survival and time of onset of BOS in the treated patients in the 48 month study period.[52] However, the FDA did not approve the drug until more patients and other centers are involved.
Overall, the outlook is bleak once bronchiolitis obliterans syndrome occurs. We utilize all of these options, some patients improve, some stabilize, but most progress.

Complications

Although respiratory failure and infections are the most common causes of death in the lung transplant population, these patients develop significant internal medicine problems that require comprehensive medical management. The most common complications are reviewed in Table 7. Some of these conditions are pre-existing but are aggravated by the immunosuppressive medications. This is essentially the case with hypertension and diabetes.

POST-LUNG TRANSPLANT MORBIDITY
(Cumulative Prevalence in Survivors)

Outcome	1 Year	5 Years
Hypertension	51.1%	85.9%
Renal Dysfunction	25.7%	39.4%
Creatinine <2.5 mg/dl	16.2%	22.7%
Creatinine >2.5%	7.6%	12.8%
Chronic Dialysis	1.9%	3.2%
Renal Transplant	0.0%	0.7%
Hyperlipidemia	17.7%	46.8%
Diabetes	21.5%	30.9%
Bronchiolitis Obliterans	9.4%	34.4%

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TABLE 7

The immunosuppressive regimen has changed in many programs in the last few years. According to the ISHLT registry, in the last 4 years, cyclosporine was utilized in 23% of the patients at one year and 29% at 5 years. Tacrolimus was utilized in 62% of the patients at one year and 52% at 5 years.[5] This probably reflects the change in immunosuppresion over the last 5 years with more programs favoring Tacrolimus. This change may impact the complication rates since Tacrolimus has been associated with a mildly higher incidence of diabetes.

The UTSW-St. Paul program still utilizes cyclosporine and azathioprine as first line drugs.[53] If clinical rejection occurs, is seen on surveillance bronchoscopy, or the lung function is deteriorating, then we then switch the cyclosporine to Tacrolimus and azathioprine to mycophenolate mofetil.

Hypertension is clearly related to the calcineurin inhibitors and the use of prednisone. It is seen in 51% of the patients at one year and 86% at 5 years.[5] Thus most of the patients are prescribed anti hypertensive medications. Some of anti hypertensive medications interfere with the metabolism of tacrolimus and cyclosporine. For instance, the addition of calcium channel blockers may result in markedly elevated levels of cyclosporine or tacrolimus. Angiotensin converting enzyme inhibitors may worsen renal function in these patients.[53]

Diabetes occurs in 21.5% of the patients at one year and 31% at 5 years. This percentage may reflect the Cystic Fibrosis population's impact on pancreatic function. Diabetes is not listed as a significant risk factor in lung transplantation survival at one year, but the relative risk for mortality with diabetes at 5 years is 1.27 (95% confidence interval 1.05-1.52) even though these patients have been carefully screened for any vascular and renal disease which would preclude transplantation.[5] In a review of the transplants performed up to 2003 at UTSW-St. Paul, we too noted a poorer survival in patients who had diabetes prior to transplant in comparison to those who had normal glucose tolerance and those who developed diabetes after the transplant.

Hyperlipidemia is a significant medical problem in the transplant population. It occurs in 18% of the patients at one year and 47% at 5 years.[5] Most of the patients have only increased cholesterol; but with the use of sirolimus, elevated triglycerides also become a problem.[52] The impact of the calcineurin inhibitors on cholesterol metabolism is significant. In a review of our

CF population who have been transplanted, the cholesterol level was very low reflecting the severity of their illness and their poor nutritional status, but post transplant there was no difference in the cholesterol and triglyceride levels between the CF and non CF patients. The CF patients were also significantly younger than the COPD and ILD patients and would have been expected to have lower lipid values.

Renal dysfunction, a significant finding in the lung transplant population, is clearly related to the calcineurin inhibitors and the other medications utilized for prophylaxis of infections, to hypertension, to diabetes mellitus and to their underlying diseases. Thus, the medication regimen of most lung transplant patients include the anti rejection medications, trimethoprim / sulfamethoxazole to prevent Pneumocystis carinii pneumonia, an anti viral medicine, and anti hypertensive agents. The medications, themselves, could easily explain the loss of renal function.

Renal dysfunction is seen in 25% of the patients at one year and 39% at 5 years. Approximately 13% of the patients have a serum creatinine >2.5 and 3% are on dialysis 5 years after transplantation..[5] This degree of renal dysfunction occurs despite the careful screening of these patients pre-op and the requirement of a creatinine clearance of 65 ml/min. to be eligible for a lung transplant.

With the intense immunosuppression regimen, malignancy is a significant issue in the post transplant patients. Careful pre-op and post-op screenings are important in the care of these patients. Skin cancers are the most common cancer in the long term survivors accounting for 50% of the tumors at 5 years. Overall 4% of the transplant patients develop some type of malignancy at 1 year and 13% at 5 years. Post transplant lymphoproliferative disease is the most common tumor at one year and accounts for approximately 24% of the tumors at 5 years.[5]

The UTSW-St. Paul Program has had 14 patients (10%) develop a malignancy in the post operative period if skin cancers are excluded. The types of tumors seen have been head and neck (2), lung (1), PTLD (3), GIST (1), carcinoid (1), rectal (1), vulvar (1), and colon (4). The mean age of the patients developing malignancies was 44.1 $\pm$17.7 years, but the mean age of the CF patients with a malignancy was 25.6 $\pm$11.8 years. Six of the 50 CF patients who have undergone transplantation at UTSW-St. Paul have developed a cancer and 50% of their tumors have been colon cancers. All of these colon cancer patients were less than 44 years of age. This has prompted us to perform colonoscopies in all of the CF patients despite their young age.

Lung Allocation System

In 1999, the Department of Health and Human Services issued a directive to UNOS to examine organ distribution policies and to institute changes that would direct organs to those who were most in need.[54] Lungs had been allocated to patients only based on their length of time on the waiting list. The severity or type of illness had no bearing on patients receiving a lung. This allocation system was further questioned in an analysis of the UNOS data from 1992-94. In this retrospective study of 2419 patients, 21% of the patients died while waiting for a transplant. Further analysis of the data revealed that 29% of the CF patients and 33% of the IPF patients

died while waiting for a transplant but only 11% of the COPD patients died waiting for a transplant. During that same time period, 48% of the CF and PF patients and 66% of the COPD patients were transplanted. Approximately 11% of the patients died from transplant related complications. The mortality rate 1 year after transplant was 19%. There was not a significant difference in survival among the CF, PF, or COPD patients one year after transplant. Thus, the CF and PF patients had a higher mortality rate while on the waiting list than one year after transplant, but the COPD patients had a higher one year mortality rate after transplant than while on the waiting list. [55] This study, most importantly, did not address quality of life issues which are difficult to quantitate. Furthermore, the previous allocation system encouraged some programs to list patients before they truly needed to be transplanted just to attain time on the waiting list.

More recently, the UNOS lung allocation subcommittee analyzed Cox regression models with transplant in a time dependent covariate to compare the mortality of lung transplantation with the mortality of remaining on the wait list in the patients listed between 1995-2001, a more recent time period. The overall mortality (not just one year mortality) was significantly lower for CF patients who had been transplanted (HR 0.8:p <0.05), but the Pulmonary Fibrosis patients also had a lower mortality at one year (HR 0.7; p <0.05) but not overall. This difference between the one year mortality and total mortality in IPF probably reflects the increased mortality related to surgical problems in this group. In other words, if the PF patients made it to 3 months, then their survival curves improved. The COPD patients who had been transplanted had a higher overall and 1 year mortality (HR 1.2; p <0.001, HR 2.0, p <0.001). [56] These two studies have very similar conclusions about the impact of transplant on survival in the COPD population.

None of these survival statistics, however, addressed quality of life issues. As can be seen from the ISHLT data, approximately 85% of the patients report no activity limitation at one year and 5 years. (Figure 7) As another measure of activity, the ISHLT collects information on employment status of the transplanted patients. At one year approximately 30% of the patients are working full or part time, and at 5 years approximately 40% of the patients were working. [5] The UTSW-St. Paul experience basically found that patients did not return to the work force if they were not working prior to the transplant.

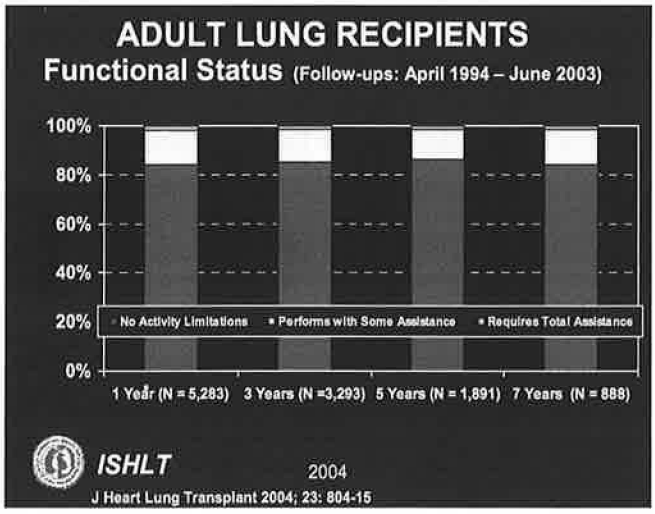

FIGURE 7

Thus, with the questions of who really benefits from a transplant, a new lung allocation system was implemented in April 2005.

The goals of the new system are: 1. to reduce the deaths on the waiting list, 2. to increase the transplant benefit for the recipients, and 3. to insure an efficient and equitable allocation of organs. To achieve these goals, the prospective recipients are prioritized based on the risk of death without a transplant versus the survival after a transplant. Thus waiting time is no longer a factor, the only consideration in the old system. [57]

The factors now utilized to predict survival on the waiting list include forced vital capacity, systolic pulmonary artery pressure, oxygen use, age of the patient, body mass index, insulin dependent diabetes, functional status (NYHA), 6 minute walk distance, ventilator use, pulmonary capillary wedge pressure, and diagnosis.

To predict the benefit of transplantation, a transplant benefit measure is determined. The post transplant survival measure is the expected number of days lived during the first year post transplant. The wait list urgency measure is the expected number of days lived without a transplant during an additional year on the waiting list. The transplant benefit measure is the difference between the post transplant survival measure and the waitlist urgency measure. The actual lung allocation score is designed to be the difference between the transplant benefit measure and the wait list urgency measure. This score is then normalized to a range from 0-100. Thus with this new allocation system both urgency and post transplant survival factor into the score or benefit of transplantation. The score is dynamic since it can be updated at any time, as patients worsen or improve.

Although these efforts are directed to insure that those patients who will benefit most receive the donated lungs, the major problem is the number of organs available for transplantation. The number of patients transplanted over the past few years has remained essentially the same because of the number of organs available. [5] The number of lung transplants performed in the U.S. last year was 1173, and the number of patients presently waiting for a lung transplant is 3536. [28] The wait list number may actually decrease since time on the waiting list is no longer a factor, and thus patients no longer will be listed solely to accumulate time.

As discussed previously, the long term survival results now appear to favor bilateral lung transplantation. Should this be adapted universally, the number of patients actually transplanted may decrease since only one person will be receiving a transplant rather than two persons.

The lung is the most fastidious of the organs to transplant. Brain death has a significant impact on the lung function. Although the criteria for "acceptable" lungs have been liberalized, only 18% of the lungs available from donors are used, in contrast to 74% of the kidneys and 92% of the livers. [28] Newer preservation solutions have allowed longer graft ischemic times. Some programs have utilized non heart beating donors. There have been too few patients to determine how viable an option this will become. [58]

Living lobar lung transplantation has been proposed to address the urgency for the shortage of organs for those urgently needing a transplant. Bilateral lobar transplantation has been accomplished in a small group of patients mainly with CF. There have been no reported mortalities among the donors, but the morbidity is significant. Perioperative complications occur in 7-49% of the donors. In this procedure, the patient receives a lobe from each donor. The results are surprisingly good, and the actual survival was similar to the ISHLT survival for bilateral lung transplantation. Although this procedure has the potential to "rescue" small young patients, it should be reserved only for those critically ill.

Summary

Thus, lung transplantation has matured over the last 15 years on this campus and nationwide. Although survival has improved which is probably related to more experience and better preservation solutions, the relentless deterioration in lung function continues. This decline in lung function is secondary to chronic rejection which should be the focus of our efforts. Transplantation offers an improved quality of life and survival in patients with pulmonary fibrosis and CF. Further analysis on the impact of transplantation in patients with COPD, the 4th leading cause of death, will be necessary. The new lung allocation system should benefit those most likely in need.

The success of our program is related to the individuals involved. Dr. W. Steves Ring has provided the leadership since the inception of thoracic organ transplantation program at St. Paul in 1998. I want to acknowledge the surgical expertise team of Drs. Michael Wait, Michael Dimaio, Dan Meyer and Michael Jessen, the excellent support of Pat Kaiser and the transplant coordinators, and all of the consultants who help in the evaluation and care of these patients. Special acknowledgment is deserved for Dr. Fernando Torres who has been an integral and key member of the team and to Dr. Joseph Viroslav who has given us back up, support, and perspective.

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