Chapter

Lung Transplantation: A Final Option for End-Stage Interstitial Lung Diseases

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Abstract

Lung transplantation (LTx) is an established, well-recognized medical intervention for treating patients with an end-stage irreversible pulmonary disease. Such diseases include interstitial lung disease (ILD), where other standard medical options often have been proven as insufficient. Post-operative survival after LTx depends on various factors such as the general and organ-specific recipient status in addition to donor organ condition and operative technique. The prolonged survival rates obtained during the 1980s and 1990s have established LTx in the medical field. Reflecting the improvements made in the field of organ preservation, operative technique, immunosuppressants, recipient and donor organ selection and prophylactic as well as direct treatment in the wide spectrum of possible infections in the recipient. Despite LTx being the golden standard for treating end-stage irreversible ILD, with idiopathic pulmonary fibrosis (IPF) as the most common cause, post-operative outcome is greatly hampered compared to the outcome of other patient categories within LTx. This chapter will provide insight in the outcome of ILD and subsequently IFP after LTx.

Keywords: lung, transplantation, post-operative outcome, long-term follow-up, interstitial lung diseases, interstitial pulmonary fibrosis

1. Introduction

Lung transplantation (LTx) is a known medical intervention for irreversible/end stage lung diseases, where standard medical treatment has been proven to be insufficient, such as patients with end-stage interstitial lung disease (ILD) [1].

Other medical interventions for ILD are restricted to corticosteroids and cytotoxic pharmaceuticals with reports showing up to 90% of this patient group as non-responsive to pharmaceuticals [2–4].

Idiopathic pulmonary fibrosis (IPF) was the diagnosis for the first LTx among long-term surviving patients that was successful, performed in 1983 at Toronto. IPF is regularly found in recipients that have undertaken LTx for end-stage pulmonary disease [5, 6].

ILD is problematic to treat and often with poor prognosis. Especially IPF that has an outcome that is among the poorest in ILD, with a median survival of up to 3 years after time of diagnosis [7]. As IPF is an incurable disease, it has additionally been reported that if untreated presents with a 5-year survival of 30–50% [3, 4, 8, 9].

Post-operative outcome of LTx rests on several aspects, for instance general and organ specific patient status, donor graft status and operative method. The extended survival estimates attained in the 80s and 90s most probably mirror developments in graft preservation, operative practice, immunosuppressive agents, recipient/donor graft selection, and prophylactic therapies of opportunistic infections in the recipient [10].

These progressions in averting early adverse events have permitted a wider incline of indications in LTx with a steady liberalization of donor criteria. This has provided a general growth in LTx, although this quantity is yet to date constrained by donor organ scarcity. Even though numerous difficulties after LTx persist (e.g., opportunistic infections, graft rejection, and pathological relapse in the donor graft), LTx is the definitive option for candidates with advanced loss of pulmonary function triggered by advanced IPF. The quantity of LTxs achieved is principally restricted by the low availability of donor organs [11]. Survival is meager for IPF recipients when compared to basically all other pulmonary disease groups.

2. Patients and methods

2.1 Transplant procedure

Five types of Tx procedures are normally presented:

- Single lung transplantation (SLTx)
- Double lung transplantation (DLTx)
- Heart-lung transplantation (HLTx)
- Cadaveric lobar transplants (CLTx)
- Transplantation of lobes from living related donors

Throughout the course of listing a patient with ILD for LTx, the patient's indication for Tx as well as preference for DLTx or SLTx, comorbidities, operative risk, blood type, and donor specific antibodies are investigated beforehand. Both SLTx and DLTx are achieved in recipients with IPF and discussion is present yet to date whether SLTx or DLTx is the superior alternative in this specific group [12].

2.2 Recipient selection

Recipients are selected differently from center to center. In the Lund university model as an example, recipients can be selected according to the guidelines by the consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation [13]. Inclusion norms are often candidates diagnosed with chronic lung pathology who are non-responsive to other medical treatment. LTx candidates characteristically have a life expectancy of less than 18 months and are often dependent on additional oxygen present and are often physically restricted. Before entering a LTx programme, candidates usually undergo a clinical investigation that can consist of following:

a. evaluation of kidney function (GFR) by iohexol clearance;

b. immunological screening;

c. microbiological screening;

d. hematological and biochemical laboratory testing;

e. virologic screening;

f. dental examination;

g. densitometry;

h. stress test with arterial blood gas, lung scintigraphy and spirometry;

i. Doppler of the carotid arteries (>50 years);

j. CT scan of the chest and abdomen;

k. echocardiogram;

l. coronary angiography of coronary blood vessels; and

m. 24 hours pH evaluation, sometimes followed by gastroscopy.

Patients are often reviewed by a multidisciplinary team before accepted for LTx. Recipient/donor matching can be based on ABO blood type and graft size.

The United Network for Organ Sharing (UNOS) has implemented a lung allocation score (LAS) in the United States. The LAS is a resolve to classify patients in most need of a LTx. The LAS is designed by means of numerous evaluations of a patient's status that approximate outcome and predicting the period of survival with or without a LTx. Application of the LAS gave rise to an improved quantity of IPF patients getting a LTx as IPF developed into the biggest and most common major indication to accept a LTx in 2007 in the United States [14]. In 2011, patients with IPF yielded the biggest proportion (46%) of candidates on the LTx wait-list in the US.

Diverse clinical methods are utilized to properly rank for LTx. Biopsy results are supportive in deciding the precise diagnosis for IPF [13, 15]. Conventionally, numerous clinicians have utilized lung function tests to decide the appropriate period of listing a ILD/IPF patient for LTx, with a report that lung function testing through diffusion pulmonary function for CO < 39% may predict early mortality [16] in addition to 6-minute walk test (6MWT) that can predict early mortality [17]. Radiologic findings are of great value in sorting ILD patients in terms of hazard. High-resolution computed tomography has shown that a greater grade of fibrosis forecasts greater risk for death [18, 19].

Patients with IPF although placed on the waiting list for LTx, such a patient is still exposed to great hazard. In history, IPF patients have the highest waiting list mortality estimates of all candidates for LTx [20, 21]. Before the LAS, candidates with IPF showed a waiting list mortality between 28 and 47% with other recipient groups presenting a waiting-list mortality at only 15% [2, 3, 22]. Due to the great risk in mortality as well as morbidity on the waiting list, it is of great interest to investigate methods to optimize this process. 15-step oximetry test, 6MWT as well as

the quantity of oxygen that the IPF recipient is dependent on have all a role to play in reflecting the risk of mortality on the waiting list [22–24]. Further improvements are needed in maintaining the well-being of this patient group in waiting for a LTx.

2.3 Donor organ selection

Matching a donor lung with a recipient can be grounded on donor/recipient height and even pulmonary volume from chest radiographs [25, 26]. The optimal grade of fit is not known and the association between donor and recipient do not have to be a perfect match, but a close match is favored in terms of size [27].

"Ideal donor criteria" are often thought of as age < 55 years, normal chest X-ray, PaO_2/FiO_2 > 300 mmHg at five PEEP, <20 pack year smoking history, lack of chest trauma and lack of aspiration/sepsis [27, 28].

2.4 Immunosuppression

Maintenance of immunoregulation depends on the center and region. With the Lund University model as an example, it has remained more or less the same during the LTx programmes inception, based on a practice of cyclosporine, corticosteroids and azathioprine or mykofenolatmofetil as a lifelong routine.

2.5 Antimicrobial and infection prophylaxis

LTx patients are at increased hazard for infectious difficulties because of subsequent features:

- High level of immunosuppression to prevent rejection
- Adversative consequences from Tx on the lung host defenses
- Persistent environmental interaction permitting microbiological agents direct admission into the graft

The probability and category of infection differs with the degree of recipient immunosuppression, timing since LTx, variety and period of anti-microbial prophylaxis in addition to the local center and regional microbiology. The most common type presented in LTx recipients are bacterial pneumonia [29, 30].

Prophylactic administration of broad-spectrum antibiotics such as carbapenem are preferred until cultures can be available and then initiate target treatment for specific infection. Antiviral therapy may be directed against CMV for recipients with positive CMV serology. Preoperative screening for CMV is performed routinely in recipients/donors. Antifungal prophylaxis may include low-dose fluconazole for Candida and sulfametoxazol/trimethoprim for *Pneumocystis carinii*. Broad-spectrum antibiotics with colistin may be utilized for Pseudomonas if present.

2.6 Follow-up

Routine follow-up after LTx is intended to avert complications or to distinguish them as soon as possible. While follow-up is most rigorous during the first year after LTx, it is necessary to proceed with a lifetime of follow-up of the LTx recipient. Pulmonary function progressively advances and typically scopes a plateau by the end of year 1 after LTx [31, 32].

The practices include:

- Follow-up with a (trained) nurse coordinator
- Check-ups by a pneumonologist
- Chest X-ray
- Spirometry
- (Bronchoscopy)
- Selected hematological testing to supervise the immunosuppressive serum levels

There are also possibilities for the LTx recipient to be undergo follow-up from the home, such as daily home spirometry. This form of monitoring has been associated with earlier detection of chronic forms of rejection [33–37].

3. Outcomes after LTx

3.1 Survival

Outcome after LTx can be evaluated founded on numerous different measures: survival, quality of life, physiologic changes and cost benefit [38, 39]. Survival is feasibly the most objective calculation of outcome. The International Society for Heart and Lung Transplantation (ISHLT) has created a registry of survival estimates from international data that have become a benchmark for the field [40, 41]. According to the 2017 ISHLT registry report, the median survival for all adult LTx recipients is 6 years [38]. Nevertheless, it is uncertain if survival benefit is primarily connected to the type of procedure or the underlying LTx patient's features that does the impact. A report that assessed the influence of patient age and procedure on the survival outcome of patients with IPF showed that SLTx recipients younger than 60 years displayed a survival benefit over DLTx in the same age category [6].

The influence of the diagnostic type of recipient on survival after LTx has been studied expansively [38, 42, 43]. The primary major indication is habitually connected to age. Furthermore, specific diagnostic groups have a greater hazard of complications during LTx and primary graft dysfunction (PGD). Nevertheless, patients with COPD have the most superior first-year survival but then again a worse 10-year survival compared to other recipient groups such as pulmonary hypertension, sarcoidosis, and alpha-1 antitrypsin deficiency patients [38]. Those with IPF have the lowest 10-year outcome when compared to all other diagnostic groups.

Multiple report that have studied the post-LTx survival for IPF patients showed that 1-year survival range from 68 to 80%, 3-year survival from 50 to 61% and 5-year survival between 32 and 59%, with earlier LTx periods even tend to have worse outcome than recent LTxs performed [44–48]. There are various reports in post-LTx survival from monocentric data from Europe, North America as well as Brazil and Australia that show corresponding survival data for 1-year survival data ranging between 25 and 87% while 5-year survival has showed between 33 and 63% [22, 49–58].

3.2 DLTx versus SLTx

SLTx was the typical Tx type for recipients with IPF for several years and survival outcomes were analogous to other diagnostic groups within LTx [2, 5, 6, 22]. Though, a major proportion of IPF recipients are presently undergoing DLTx [59–61].

In 2011, almost half of all IPF patients where DLTxs while the other half where almost entirely SLTxs [62]. More than 60% of LTxs in 2014 for IPF recipients was DLTx while in 1991 this number was only 15% [60]. This alteration in trend is not entirely clear but it has been proposed that probable factors are better operative technique in addition to improved pulmonary function and survival for DLTx.

IPF patients that underwent DLTx has shown significantly better survival for DLTx versus SLTx, where survival has improved for DLTx patients with IPF compared to SLTx patients in this patient category [63]. Especially if IPF patients manage to survive beyond the 10-year mark, with attributed survival benefits in DLTx [64]. However it has also been reported that IPF patients that underwent DLTx do have an increased mortality risk in the early postoperative period [47]. In addition, when adjusting for risk factors in such analyses for DLTx vs. SLTx among IPF patients, no difference in outcome has been shown [65]. Other single centers such as from the US and Australia and data from the ISHLT from the period of 1994 to 2004 showed no difference in outcome regarding DLTx vs. SLTx for IPF patients [53, 66–68]. Interestingly, European centers has been able to show in contrast from the literature that SLTx has the ability to yield survival benefit for IPF patients than DLTx [69].

Living donor lobar LTx has been proposed as an option for LTx candidates with end-stage IPF with low probability to survive the entire period on the waiting list for standard donor LTx [70].

3.3 Ventilator support, intensive care and postoperative stay

Few studies have reported data on the early period in hospital stay post-LTx. One single center in Sweden however has reported ventilator support, intensive care unit stay and overall post-operative stay until discharge for all types of LTx recipients including IPF recipients [71]. This report showed that the median time for ventilator support after LTx was 2 days while for IPF patients that required almost 3 days. The same pattern followed for intensive care unit time after LTx, showing a median of over 6 days for all recipients while PF patients had a median of 8 days. Finally, the total time of hospital stay after LTx was a median of 43 days in all recipients while IPF patients had one of the longest at 46 days.

The studies that report post-LTx in hospital time and need of medical resources suggest that LTx in IPF patients has been associated with substantial resource use.

3.4 Cause of death and complications

Among IPF patients who underwent a LTx in the United States (1987–2009), the principal cause of death was infection or sepsis causing almost a quarter of the deaths of IPF recipients [2, 22, 47, 50, 55, 65, 68, 72, 73], followed by bronchiolitis obliterans syndrome (BOS)/chronic rejection [74].

As infection is the number one cause regarding complications, others causes include hemodynamic instability, kidney failure, myopathy, bleeding, and reoperation [75]. Almost a tenth of all LTx recipients may experience airway complications [76]. Malignancy is a long-term complication that almost a third of IPF patients may experience at 10 years after LTx [77]. In addition it is more common with lung embolisms in IPF patients with over a quarter of all patients in this category [49].

3.5 Rejection

PGD, a form of acute rejection is a severe complication that is a risk for all LTx recipients which include ILD patients. The background for this pathology depends on several factors though ischemia-reperfusion injury is assumed to be the main instrument of this pathology [78]. The incidence has been reported to be between 10 and 25% [78, 79]. Nonetheless, PGD in ILD patients are significantly more associated with worse mortality in the early outcome, whilst in the long-term is has been associated with increased risk of a form of chronic rejection as BOS [80]. Despite pulmonary hypertension recipients having a higher incidence of ischemia-reperfusion injury, recipients with IPF have a higher probability of experiencing ischemia-reperfusion injury than COPD patients, putting them at greater hazard of experiencing PGD [81].

BOS, a form of chronic lung allograft dysfunction, is the biggest factor hampering long-term outcome. Regrettably, it is likewise a common obstacle in LTx, where LTx recipients in general experience an incidence of almost 30% after 2 years and three quarters of recipients experience this pathology after 10 years [77, 82]. Recipients with IPF have a greater hazard of contracting PGD and therefore a greater hazard of BOS, where it is proposed that this patient group have steeper deterioration in lung function and greater risk of mortality than recipients without IPF that has been exposed to BOS [83, 84].

4. Conclusions

LTx is a well-known treatment strategy for an extensive number of irreversible end-stage pulmonary disease, including ILD with focus on IPF. There is yet to date a great gap among patients that is qualified and patients that are admitted for a LTx. IPF patients have a greater mortality on the waiting list versus other major indications. A great share of IPF patients decease before the possibility of undergoing LTx. This makes it important to prioritize this patient population for LTx as the need is unfortunately not met. IPF patients have been linked to greater risk of complications than other patient groups in parameters such as time in the intensive care unit, time in mechanical ventilator and in hospital time. It is still not entirely clear whether a SLTx or a DLTx is of greatest benefit to a IPF patient. The most recent trend has been in favor for DLTx rather than SLTx. It has been suggested that the increased survival in IPF patients is due to DLTx while on the other hand the data is conflicting. It is possible that a more accurate survival benefit is resulted among different subcategories of IPF candidates whilst on the other hand certain IPF candidates may not yield any survival benefit at all from a DLTx where greater understanding is required.

The application of the LAS has reduced the time on the waiting list and improved survival by yielding precedence for patients that are in the greatest need for a LTx. The implementation of the LAS gave rise to the IPF patient category to even surpass COPD as the greatest indication to undergo LTx. However, carrying out LTx in candidates with a greater LAS score does result in more extensive use of medical resources.

There is no curative treatment for IPF patients with a miserable prognosis. Up-to-date strategies for the inclusion of LTx candidates endorse that suitable IPF patients ought to be recruited for LTx at the earliest. IPF recipients show the worst outcome of all LTx patients in addition to the donor pool being hampered by the scarcity of donor organs. It is therefore essential that qualified ILD patients and above all IPF patients get selected for LTx in order to attain favorable long-term outcomes.

Conflict of interest

The authors declare that they have no competing interests.

Declarations

None declared.

Acronyms and abbreviations

LTx	lung transplantation
ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
SLTx	single lung transplantation
DLTx	double lung transplantation
HLTx	heart-lung transplantation
CLTx	cadaveric lobar transplants
UNOS	The United Network for Organ Sharing
LAS	lung allocation score
6MWT	6-minute walk test
ISHLT	The International Society for Heart and Lung Transplantation
PGD	primary graft dysfunction
BOS	bronchiolitis obliterans syndrome

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