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Original Article

Long-Term Outcomes of Cadaveric Lobar Lung Transplantation: An Important Surgical Option

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Background: Cadaveric lobar lung transplantation (L-LTx) is developed to overcome donor–recipient size mismatch. Controversial short- and long-term outcomes following L-LTx have been reported compared to full-sized lung transplantation (F-LTx). This study reports long-term outcomes after L-LTx.
Methods: We reviewed patients undergoing lung transplantation (LTx) between 2000 and 2016. The decision to perform L-LTx was made based mainly on donor–recipient height discrepancy and visual assessment of donor lungs. Predicted donor–recipient total lung capacity (TLC) ratio was calculated more recently. Primary outcome was overall survival.
Results: In all, 370 bilateral LTx were performed during the study period, among those 250 (67%) underwent F-LTx and 120 (32%) underwent L-LTx, respectively. One- and 5-year survival rates were 85% vs. 90% and 53% vs. 63% for L-LTx and F-LTx, respectively (p = 0.16). Chronic lung allograft dysfunction (CLAD)-free survival at 5 years was 48% in L-LTx vs. 51% in F-LTx recipients (p = 0.89), respectively. Age, intraoperative extracorporeal membrane oxygenation (ECMO) use, intensive care unit (ICU) stay, and postoperative renal replacement therapy (RRT) were significant prognostic factors for survival using multivariate analysis.
Conclusions: Overall survival and CLAD-free survival following L-LTx were comparable to F-LTx. Given the ongoing donor organ shortage, cadaveric L-LTx remains as an important resource in LTx.

Keywords: lobar lung transplantation, lung transplantation, survival, chronic rejection

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Introduction

Lung transplantation (LTx) is an established treatment option for end-stage lung diseases. Donor shortage is still a problem and particularly threatens the small-sized and urgent candidates awaiting an appropriate organ donor. Some transplant centers developed an advanced operative technique called "downsizing" or "size reduced" LTx.[1–7] This includes peripheral wedge resections and lobar and split lung transplants to overcome size mismatch. Lobar LTx has been proposed to be an important surgical technique for those with smaller chest

cavities and restrictive lung disease, leading to potentially fewer cases of waiting-list mortality.[4] Due to its technical challenges, lobar lung transplantation (L-LTx) is not widely performed.[8]

Although publications reporting on survival after L-LTx exist, there is no published data with special focus on the incidence of CLAD in L-LTx. Chronic lung allograft dysfunction (CLAD) is the major obstacle for long-term survival in LTx.[9–15] CLAD is reported to be the most common cause of death in recipients between 1 and 5 years after LTx.[10–15]

The aim of this study is to investigate the long-term outcomes after L-LTx compared to full-sized lung transplantation (F-LTx).

Materials and Methods

Patient data are prospectively collected in our lung transplant program database starting from the first LTx conducted in November 1992. Between November 1992 and the end of September 2016, 485 patients underwent LTx at our center. Unilateral LTx, re-transplantations, and LTx performed before the year 2000 were excluded. After those exclusions, 370 patients remained for analysis and were included in the study. There were two groups, patients undergoing F-LTx (N = 250) and patients undergoing L-LTx (N = 120). The censor date for survival analysis was May 27, 2020. The decision to perform L-LTx was made prior to implantation based on donor–recipient height discrepancy and visual assessment of donor. We also calculated donor–recipient predicted total lung capacity (TLC) ratio (D-R pTLC). TLC is calculated according to standardized formula.[16] Donor lobectomies were performed on the back table prior to implantation. Primary graft dysfunction (PGD) grading is performed according to International Society for Heart and Lung Transplantation (ISHLT) consensus statement.[17] CLAD was defined as a persistent, obstructive decrease in forced expiratory volume in 1 second (FEV1) with at least 20% compared to the mean of the two best post-transplant values, in the absence of other identifiable causes.[15] Primary outcome was overall survival. Local research ethics committee approved the study (KEK Nr. 2019-00873).

Statistical Analysis

IBM SPSS version 25 (SPSS IBM, Armonk, New York, USA) was used for statistical analysis. Data are presented as median and interquartile range (IQR, 25%–75%). Categorical variables were compared using chi-square tests. Mann–Whitney test was used to compare continuous variables. Results of the multivariable linear or logistic regression analysis were adjusted for potential confounders such as recipient age, renal replacement therapy (RRT), and intraoperative extracorporeal membrane oxygenation (ECMO) use. Independent risk factors were identified by a step-wise backward regression analysis. Kaplan–Meier Method (log rank test) was used to calculate unadjusted survival rate and CLAD-free survival. A p value less than 0.05 was considered as the threshold for statistical significance.

Results

In this series, L-LTx constituted 32% (120/370) of all LTx performed in this study cohort. **Table 1** shows the recipient and donor characteristics of the study cohort. Gender and underlying diagnosis were statistically different between the two groups. D-R pTLC and donor and recipient height difference was also significantly different between the two groups.

There was a very significant correlation between D-R pTLC ratio and donor-recipient height difference ($r = 0.873$, $p = 0.000$, Pearson correlation test).

Perioperative data are given in **Table 2**. L-LTx group needed more intraoperative ECMO use. Operation time and intensive care unit (ICU) stay were longer in the L-LTx group. In addition, L-LTx required more RRT, and the overall postoperative complication rate was higher. PGD Grade 2 and 3 at T48 was significantly higher in L-LTx recipients compared to F-LTx recipients.

In our series, 19 left upper lobe and 40 left lower lobe implantations were performed. On the right side, 25 middle and right lower lobe, 112 right upper lobe and right lower lobe and 11 right upper lobe and middle lobe implantations were performed.

We observed higher rates of tracheotomy, complications related to ECMO and critical illness neuromyopathy in L-LTx recipients (**Table 3**).

The rate of urgent listed recipients was 11.6% (N = 14) in L-LTx and 7.2% (N = 18) in F-LTx groups.

Early bronchial anastomosis complication occurred in one patient in the L-LTx group. Cartilage inversion in the anastomosis on the left side was corrected surgically after 24 hours following transplantation. As a late complication in three cases in the L-LTx group, bronchial stump insufficiencies (back table lower lobectomy, bronchial closure with stapler) leading to empyema were

Table 1 Recipient and donor characteristics

	L-LTx (N = 120)	F-LTx (N = 250)	p Value
Age (years)	53 (43,58)	58 (50,60)	0.1
Sex (F/M)	71/49	101/149	0.001
Waiting list time (d)	190 (22,301)	328 (143,626)	0.1
CRP at LTx	12 (6,29)	3 (2,6)	0.2
Diagnosis			0.001
CF	46 (38.3)	81 (32.4)	
COPD	21 (17.5)	89 (35.6)	
IPF	38 (31.6)	37 (14.8)	
PAH	5 (4.1)	15 (6)	
OTH	10 (8.3)	28 (11.2)	
CMV (D/R) neg/pos	30 (25)	57 (22.8)	0.3
BMI (kg/m^2)	20.5 (18.3,29.4)	23 (20.5,26.8)	0.3
R-Height (cm)	165 (159,172)	173 (168,182)	0.001
R-Weight (kg)	56 (51,85)	71 (58,86)	0.01
FEV1 preop (L)	0.8 (0.6,1.36)	0.85 (0.68,2.29)	0.6
FEV1 preop (%)	30 (25,44)	30 (20,65)	0.1
Donor characteristics			
Sex (F/M)	24/96	116/134	0.001
Age (years)	54 (45,58)	53 (45,71)	0.6
Height (cm)	180 (175,185)	172 (170,178)	0.001
Weight (kg)	80 (70,85)	70 (60,80)	0.001
PaO_2-FiO_2 ratio (kPa)	47.1 (36.8,62.6)	44.7 (34.7,58.8)	0.3
D-R height difference (cm)	11.5 (6,19)	2 (-3,7)	0.001
D-R pTLC	1.24 (1.09,1.47)	1.02 (0.93,1.09)	0.001
Donor type			0.6
DBD	115	236	
DCD	5	14	

All values are presented as N (%) or median (Interquartile range: 25%–75%). BMI: body mass index; CF: cystic fibrosis; CMV: cytomegalovirus; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; d: days; D: donor; DBD: donation after brain death; DCD: donation after circulatory death; D-R pTLC: donor (D)-recipient (R) predicted total lung capacity (TLC) ratio; F: female; FEV1: forced expiratory volume in 1 second; FiO_2: fraction of inspired oxygen; F-LTx: full sized lung transplantation; IPF: idiopathic pulmonary fibrosis; kPa: kilopascal; L: liter; L-LTx: lobar lung transplantation; M: male; OTH: other; PAH: pulmonary arterial hypertension; PaO_2: arterial oxygen partial pressure; R: recipient

treated surgically using either omentum or muscle flap interposition. In the F-LTx group, we observed bronchial anastomosis complications in three cases, all of which were treated surgically early in the postoperative period.

Multivariate analysis of risk factors for mortality demonstrated that recipient age, intraoperative ECMO use, ICU stay, and RRT were risk factors for mortality in all patients (**Table 4**). Surgical procedure itself was not a risk factor.

30-d (96% vs. 97%) and 90-d survival rates (89% vs. 94%) were comparable between the groups (L-LTx vs. F-LTx).

One- and 5-year survival rates were 85% vs. 90% and 53% vs. 63% for L-LTx and F-LTx, respectively (p = 0.16) (**Fig. 1**).

Median time to CLAD was 1096.5 days (IQR, 319, 2432) for L-LTx and 1290 days (IQR, 531, 2444) for F-LTx groups. CLAD-free survival at 5 years was 48% in L-LTx and 51% in F-LTx recipients (p = 0.89). During the study period, CLAD Stage 3 occurred in 54 recipients in L-LTx and in 110 in F-LTx recipients (p = 0.2).

Discussion

L-LTx is an additional option utilized in limited number of centers to overcome organ shortage, particularly in small recipients and urgent cases.[1–8] The gap between suitable donor lungs and the number of patients on the waiting list urged transplant centers to search for alternative strategies such as use of extended criteria donors organs,

Table 2 Perioperative characteristics and outcome of the recipients

	L-LTx	F-LTx	p-value
Intraoperative ECMO	76 (63)	108 (43)	0.001
Bridge to LTx			0.3
ECMO	11 (9.1)	14 (5.6)	
Intubated	1 (0.8)	2 (0.8)	
Tracheotomy	1 (0.8)	–	
ILA	2 (1.6)	2 (0.8)	
PreTx-Postop ECMO	7 (5.8)	5 (2)	
Intra-Postop ECMO	9 (7.5)	6 (2.4)	
Postop ECMO	–	6 (2.4)	
Total Op time (min)	420 (390,470)	415 (380,474)	0.006
Intubation Time (d)	1 (1,15)	1 (1,1)	0.08
ICU time (d)	12 (3,31)	2 (1,3)	0.01
RRT	19 (16)	21 (8)	0.04
PGD			
PGD2 T24	9 (13)	16 (13)	0.09
PGD2 T48	5 (7)	14 (11)	0.04
PGD2 T72	3 (4)	10 (8)	0.07
PGD3 T24	15 (22)	12 (10)	0.09
PGD3 T48	17 (25)	12 (10)	0.04
PGD3 T72	16 (23)	12 (10)	0.07
Surgical complication	59 (49)	95 (38)	0.04
Re-exploration for bleeding	16	18	0.1
30-d mortality	6 (5)	10 (4)	0.7
90-d mortality	13 (11)	17 (7)	0.7
CLAD free survival (d)	1096.5 (319,2432)	1290 (531,2444)	0.89

All values are presented as N (%) or median (interquartile range: 25%–75%). CLAD: chronic lung allograft dysfunction; d: days; ECMO: extracorporeal membrane oxygenation; F-LTx: full-sized lung transplantation; ICU: intensive care unit; ILA: interventional lung assist device; L-LTx: lobar lung transplantation; Op: operation; PGD: primary graft dysfunction; Pre-Tx: pretransplantation; Postop: postoperative; RRT: renal replacement therapy

Table 3 Detailed list of complications occurred in the study groups

	L-LTx	F-LTx	p Value
Tracheotomy	41 (34)	51 (20.4)	0.01
Thoracic Hernia	2 (1.6)	8 (3.2)	0.5
Lymphocele	9 (7.5)	13 (5.2)	0.3
Phrenic nerve injury	1 (0.8)	4 (1.6)	0.4
Hemothorax	24 (20)	24 (9.6)	0.1
Pleural effusion	6 (5)	21 (8.4)	0.1
Pneumothorax	4 (3.3)	12 (4.8)	0.1
Bronchus anastomotic complications (overall)	4 (3.3)	3 (1.2)	0.15
– Early	1 (0.8)	3 (1.3)	
– Late*	3 (2.5)	–	
Abdominal complications	8 (6.6)	26 (10.4)	0.5
Critical illness neuromyopathy	12 (10)	9 (3.6)	0.02
ECMO complications	13 (10.8)	8 (3.2)	0.01

All values are presented as N (%). *Bronchus anastomotic complication that occurred after discharge of the patient. ECMO: extra-corporeal membrane oxygenation; F-LTx: full sized lung transplantation; L-LTx: lobar lung transplantation

Table 4 Multivariate analysis of risk factors for mortality

Variable	Relative risk	95% CI	p Value
Recipient age	1.022	1.013–1.032	0.001
Intraoperative ECMO use	1.34	1.010–1.777	0.04
ICU stay	1.01	1.004–1.016	0.003
RRT	1.66	1.052–2.620	0.03

ECMO: extra-corporeal membrane oxygenation; ICU: intensive care unit; RRT: renal replacement therapy

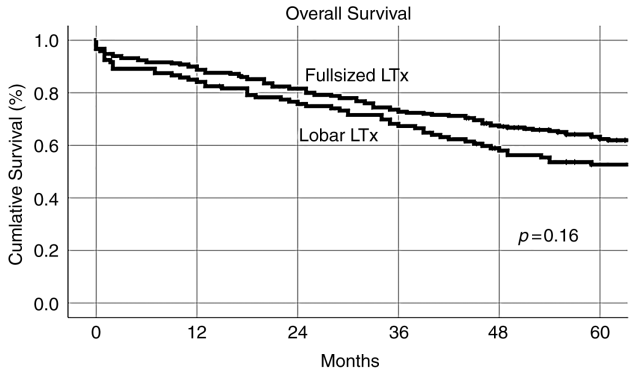

Fig. 1 Kaplan–Meier survival curve showing the overall survival between F-LTx and L-LTx. One- and 5-year survival rates were comparable between the two study groups (p = 0.16). F-LTx: full-sized lung transplantation; L-LTx: lobar lung transplantation

utilization of donation after circulatory death (DCD) donors, assessment and reconditioning of the so-called "marginal" lung in ex vivo lung perfusion system.[18–21)]

In our center, the rate of L-LTx consists one-third of our transplant population. Compared to series from Vienna, which reported 14% L-LTx, ours is approximately two times more than Vienna Group.[2)] One explanation might be the 34% rate of CF recipients and when we add the fibrosis recipients, this ratio goes up to 70% of our total cohort. As expected, these patients are generally small or they have a restricted thorax cavity (fibrosis patients). In Switzerland, we have patient-based allocation (Swiss Organ Allocation System [SOAS]) since May 2007. Before May 2007, the allocation system was center based. In both of those systems, there are no limitations for donor size during listing. In this system, we have "Urgent" status, which gives the recipient priority to get the first available donor lung, such as bridged to transplantation on ECMO and/or intubated patient. In our series, urgent-listed patients in L-LTx group were higher than F-LTx group.

L-LTx as a technique is not new and has been first published by Bisson et al.[22)] in the early 1990s. Other than to adapt a large size graft for a small recipient, this method also gives the opportunity to resect a lobe due to an unexpected pathology, such as total consolidated lung.[2)]

L-LTx is a technically challenging procedure requiring an experienced surgeon to perform a lobectomy on the back table.[1,2)]

Decision when to perform L-LTx differs among the centers. Donor–recipient difference or ratio in body weight and height,[1,23,24)] chest circumference and chest X-ray vertical and transverse dimensions,[25)] and the use of donor and recipient TLC for optimal size matching have been reported.[2,26,27)] Slama and co-workers from Vienna reported that a TLC size discrepancy of less than 20% could be corrected by wedge resection alone, whereas a size reduction of 20%–60% requires L-LTX.[2)] However, final decision is made during the LTx procedure.[1,2)] Although the international standard in most centers for donor–recipient size matching is based on D-R pTLC ratio,[8)] in our center we mainly use height difference between donor and recipient. We also calculate pTLC ratio for our databank prospectively. As we demonstrated a significant correlation between donor–recipient height difference and D-R pTLC ratio, we believe that it is also possible and reliable to decide size mismatch with donor–recipient height difference.

ECMO use has been recommended to prevent reperfusion injury of the first-transplanted lobe.[1–6)] The utilization rate of ECMO in published series varied between 32% and 70%.[2–5)] Despite the use of intraoperative ECMO, the occurrence rate of PGD rate in published reports could be as high as 54%.[2,4,5)] We observed 23% PGD 3 at T72 in L-LTx group. As the etiology of PGD is multifactorial, it is difficult to speculate only with the type of surgery combined with intraoperative ECMO use for high incidence of PGD in those series. In our series, we used ECMO in 63%. A higher intraoperative ECMO use rate might be expected, but when the first side is full-sized transplantation and only the second side an L-LTx,

the ECMO might be omitted. For bilateral L-LTx, ECMO implementation is recommended at the beginning of the transplantation.[2] In addition, routine practice of implanting the second lobe on ECMO to avoid over perfusion of the first implanted lobe has been reported.[6]

Technical complications, such as bronchial anastomotic problems, kinking of vascular anastomoses, and remaining pleural dead space might occur.[1,2] The rate of bronchial anastomotic complications was 5.5% and 13%, respectively, in the two recent series reporting L-LTx.[3,23] Early anastomotic problems occurred only in one patient in our L-LTx Group, which was corrected surgically 24 hours following the transplantation. The other three cases had bronchus stump insufficiency leading to empyema, all of which occurred late and after discharge of the recipients from the hospital. All of these cases were treated surgically by decortication and covering the stump with either omentum or thoracic muscle. Although all lobar combinations can be used in L-LTx, it is extremely important not to leave a bronchus stump by resecting the right lower lobe for implantation of the upper and middle lobes.[2,4] On the left side, we also recommend not to leave a bronchus stump with stapler to make the anastomosis main-to-main bronchus: Lobar bronchus should be implanted to the recipient main bronchus.

Overall survival rates from different centers showed comparable results comparing L-LTx and F-LTx groups.[4,5] However, the Vienna Group, in their recent publication including 138 recipients, reported inferior survival in the L-LTx group compared to the F-LTx group.[2] We observed comparable survival between L-LTx and F-LTx groups as also reported from other centers.[4,6]

CLAD is reported to be the most common cause of death in recipients between 1 and 5 years after LTx.[9] CLAD has an obstructive phenotype known as bronchiolitis obliterans syndrome (BOS).[10,11] PGD is one of the risk factors for the development of CLAD.[15] Increased rate of PGD has been reported from some centers after L-LTx[2,4,5] that may contribute to the development of CLAD.[15] We observed a higher PGD Grade 2 and 3 at T48 in L-LTx recipients compared to F-LTx recipients. Despite high PGD grade observed in L-LTx group, CLAD-free survival was comparable between the two groups.

One of the limitations of our study is that we did not have the phenotypes of CLAD for the groups. The other limitation might be that we did not calculate the D-R pTLC ratio routinely at the beginning of the study.

In conclusion, in our series, overall and CLAD-free survival following L-LTx was comparable to F-LTx. Given the ongoing donor organ shortage, cadaveric L-LTx in our hands remains a viable option, in particular, for small and urgently listed LTx candidates.

Disclosure Statement

No conflicts of interest to disclose for any authors.

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