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ORIGINAL ARTICLE

Significance of single lung transplantation in the current situation of severe donor shortage in Japan

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Abstract
Objective Although bilateral lung transplantation is the procedure of choice internationally, single lung transplantation is preferred in Japan because of the severe donor shortage except in cases of contraindications to single lung transplantation. This study aimed to evaluate the clinical characteristics of single lung transplant recipients and outcomes of this procedure at one of the largest lung transplant centers in Japan.
Methods Between April 2002 and May 2015, 57 cadaveric lung transplantations (33 single and 24 bilateral) were performed in Kyoto University Hospital. The clinical characteristics of the lung transplant recipients and outcomes of these procedures, including overall survival and postoperative complications, were investigated.
Results Overall, the 1-, 3-, and 5-year survival rates were 86, 77, and 72 %, respectively, with a median follow-up period of 1.9 years. There was no significant difference in survival between patients who underwent single lung transplantations and those who underwent bilateral lung transplantations ($p = 0.92$). The median waiting time was significantly shorter for single lung transplant patients than for bilateral lung transplant patients ($p = 0.02$). Native lung complications were seen in 14 out of 33 patients (42 %) who underwent single lung transplantation. There was no significant difference in survival between patients with and without postoperative native lung complications.
Conclusions Single lung transplantation has been performed with acceptable outcomes in our institution. In the current situation of severe donor shortage in Japan, single lung transplantation can remain the first choice of treatment except in cases of contraindications to single lung transplantation.

Keywords Single lung transplantation · Complication · Native lung

Introduction

Lung transplantation is an established therapeutic option for various types of end-stage lung disease. Internationally, the annual rates of bilateral lung transplantation (BLT) have been increasing because of its advantages compared to single lung transplantation (SLT), that include better prognosis and absence of native lung complications [1].

However, the current situation of lung transplantation in Japan is different from the international trend. Because of the severe donor shortage in Japan, approximately 40 % of lung transplant recipients undergo living-donor lung transplantation [2–4]. In cadaveric lung transplantation, SLT is the first choice of treatment unless it is contraindicated. In fact, SLT has been more frequently performed in Japan, with SLTs accounting for 56 % of all cadaveric lung transplantations in 2014 [5].

To further understand the current situation of lung transplantation in Japan, we aimed to evaluate the clinical characteristics of single lung transplant recipients and outcomes of this procedure in our institution, in which the

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largest number of lung transplantations has been performed in Japan over the last 5 years [4].

Patients and methods

Subjects

At our institution, 116 lung transplantations (59 living-donor and 57 cadaveric) were performed between April 2002 and May 2015. Among 57 cadaveric lung transplantations, 33 patients underwent SLT (15 right and 18 left). We performed a retrospective analysis of the 33 single and 24 bilateral lung transplant recipients.

Methods

The study was approved by the institutional review board at Kyoto University. We assessed post-transplant survival and waiting time in cadaveric SLT and BLT. The patients were followed up in July 2015. Furthermore, in cadaveric SLT, native lung complications and survival were compared between patients with and without native lung complications.

Continuous data are presented as medians with ranges. Categorical data are presented as numbers and group percentages. The data were compared between groups using the Mann–Whitney *U* test and Fisher exact test. Survival was calculated using Kaplan–Meier curves. The log-rank test was used to compare survival curves. Data analysis was performed using JMP, version 12 (SAS Institute Inc., Cary, USA), and $p < 0.05$ was considered significant.

Results

The baseline characteristics of the patients who underwent cadaveric lung transplantation are described in Table 1. There were 24 male and 9 female patients who underwent SLT, with an age range of 28–60 years (median age 49 years). The patients who underwent SLT were significantly older and higher body mass index. Indications for SLT were interstitial lung disease ($n = 12$), chronic obstructive pulmonary disease ($n = 6$), lymphangioleiomyomatosis ($n = 5$), other fibrosis ($n = 4$), lung injury after hematopoietic stem cell transplantation ($n = 2$), chronic hypersensitivity pneumonia ($n = 2$), Langerhans cell histiocytosis ($n = 1$), Castleman disease ($n = 1$).

The 1-, 3-, and 5-year post-transplant survival rates for all cadaveric lung transplant patients were 86, 77, and 72 %, respectively, with a median follow-up period of 1.9 years. There was no statistically significant difference in 3-year survival between patients who underwent cadaveric SLT and those who underwent BLTs (79 vs 80 %, $p = 0.92$) (Fig. 1). The median waiting time was significantly shorter for SLT patients than for BLT patients (645 vs. 813 days, $p = 0.02$) (Fig. 2).

Regarding native lung complications, 16 native lung complications occurred in 14 of 33 SLT patients (42 %) (Table 2). These complications included pneumothorax ($n = 7$), pneumonia ($n = 4$), overinflation ($n = 3$), and exacerbation of the original disease ($n = 2$). Native lung

Table 1 Clinical features of cadaveric lung transplant patients

	SLT		BLT		*p* value
Number of patients	33		24		
Female	9 (27.3 %)		12 (50.0 %)		0.1
Age	49 (28–60)		32.5 (8–55)		<0.001
BMI	21.0 (16.1–30.5)		17.65 (11.4–24.5)		0.006
Indications for LT	ILD	12 (36.4 %)	Bronchiectasis	7 (29.2 %)	
	COPD	6 (18.2 %)	Lung injury after HSCT	5 (20.8 %)	
	LAM	5 (15.2 %)	PAH	4 (16.7 %)	
	Other fibrosis	4 (12.1 %)	COPD	3 (12.5 %)	
	Lung injury after HSCT	2 (6.0 %)	LAM	3 (12.5 %)	
	CHP	2 (6.0 %)	ILD	1 (4.2 %)	
	LCH	1 (3.0 %)	Other fibrosis	1 (4.2 %)	
	Castleman disease	1 (3.0 %)			

SLT single lung transplantation, *BLT* bilateral lung transplantation, *BMI* body mass index, *LT* lung transplantation, *ILD* interstitial lung disease, *COPD* chronic obstructive pulmonary disease, *LAM* lymphangioleiomyomatosis, *HSCT* hematopoietic stem cell transplantation, *CHP* chronic hypersensitivity pneumonitis, *LCH* langerhans cell histiocytosis, *PAH* pulmonary arterial hypertension

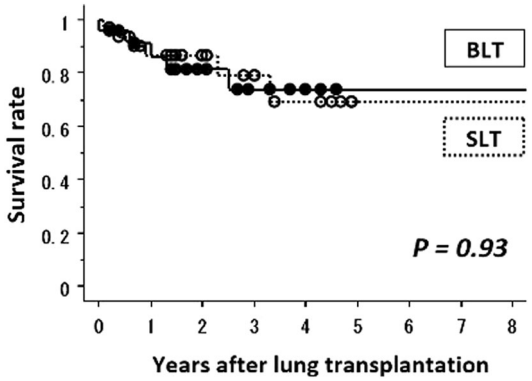

Fig. 1 Survival curve for patients who underwent single lung transplantation (SLT) and bilateral lung transplantation (BLT) ($p = 0.92$)

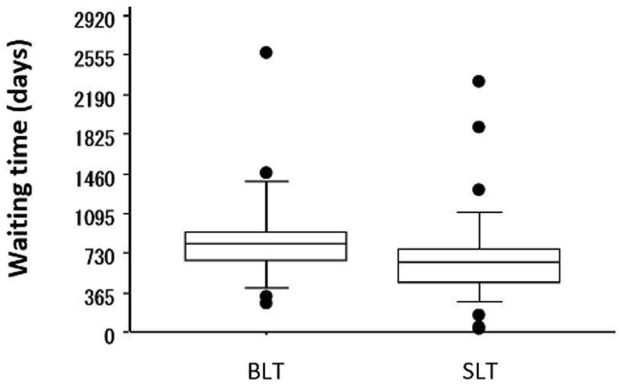

Fig. 2 Median time on the waiting list for single lung transplant recipients and bilateral lung transplant recipients (645 vs. 813 days, $p = 0.02$)

overinflation was identified as displacement of the mediastinal line on chest computed tomography. The typical appearance of overinflation and pneumothorax is shown in Figs. 3 and 4, respectively. All infectious complications were successfully treated with intravenous antibiotics. Among the 7 patients with pneumothorax after SLT, 5 were treated with video-assisted thoracoscopic wedge resection. Three of the 5 patients underwent video-assisted thoracoscopic surgery after pleurodesis. Two cases of exacerbation of the original disease were included in our study. One is an acute exacerbation in a patient with interstitial lung disease and the other is an exacerbation of chylothorax in a patient with lymphangioleiomyomatosis. Acute exacerbation of interstitial lung disease was successfully treated with steroid pulse therapy. Exacerbation of chylothorax was also treated with fat-restricted diet. Of the 14 patients with native lung complications among the 33 patients who underwent SLT, 3 patients were dead at the time of data collection. Two patients died of chronic lung allograft dysfunction 40 and 8 months after transplantation, and the other died of post-transplantation lymphoproliferative disorder 3 months after transplantation. However, the primary cause of death in these patients was not related to native lung complications. Survival was not significantly different between patients with and without native lung complications (Fig. 5).

Discussion

The present study shows that SLT was associated with acceptable outcomes in our institution, and that the median waiting time was significantly shorter for SLT patients. While the 3-year post-transplant survival rates for patients who underwent SLT was approximately 60 % in the 2014 registry of the International Society for Heart and Lung Transplantation, it was 79 % in the present study [1]. Native lung complications were seen in 14 out of 33 patients who underwent SLT, but there was no significant difference in survival between the patients with and without postoperative native lung complications.

Since SLT has an advantage over BLT from the viewpoint of organ donation, SLT is the preferable procedure in Japan where there is severe donor shortage. Approximately 40 % of the patients on the waiting list died without receiving a lung transplant between May 1994 and July 2014 in Japan [5]. Our findings of about 5 months shorter waiting time for SLT might provide a solution to this problem of deaths due to donor shortage in Japan. However, BLT is the standard procedure used internationally because of its advantages compared to SLT that include higher survival rates and absence of native lung complications [1, 6]. According to the 2014 registry of the International Society for Heart and Lung Transplantation, the number of BLT procedures performed is three times more than that of SLT [1]. This trend might be strongly related to the difference in the severity of donor shortage between Japan and other countries.

In our series, SLT accounted for 60 % of all cadaveric lung transplantations. No statistical difference in survival was observed between patients who underwent SLT and those who underwent BLT in our institution. Moreover, there was no difference in survival between patients with and without native lung complications. Although the incidence of native lung complications was similar to that previously reported, the survival rates were different from those previously reported [1, 7, 8]. One explanation for this difference in survival rates might be the absence of fatal native lung complications in our series [7, 8]. In contrast to our study, Venuta et al. [7] showed that the primary cause of death was native lung complications in 50 % of patients with native lung complications. According to previous reports, infectious and malignant native lung complications

Table 2 Native lung complications

	Indication for LT	Age	Gender	Native lung complications	Time of onset after LT	Treatment	Follow-up period after LT (months)	Outcome
1	COPD	55	Male	Overinflation	5 months	Follow up	24	Alive
2	COPD	50	Male	Overinflation	6 months	Follow up	40	Dead
3	COPD	56	Male	Overinflation, Pneumonia	6 months, 1 month	Follow up, Medical treatment	55	Alive
4	ILD	36	Male	Pneumonia	1 day	Medical treatment	2	Alive
5	LAM	41	Female	Pneumonia	1 year 1 month	Medical treatment	40	Alive
6	ILD	60	Male	Pneumonia, Exacerbation of IPF	8 months, 9 months	Medical treatment, Medical treatment	18	Alive
7	LAM	41	Female	Exacerbation of LAM	1 year 8 months	Medical treatment	52	Alive
8	CHP	43	Male	Pneumothorax	Before surgery	VATS	6	Alive
9	ILD	53	Male	Pneumothorax	17 days	VATS	58	Alive
10	ILD	28	Male	Pneumothorax	3 months	Follow up	18	Alive
11	ILD	50	Male	Pneumothorax	6 months	VATS	16	Alive
12	Other fibrosis	31	Female	Pneumothorax	1 year 4 months	VATS	34	Alive
13	Lung injury after HSCT	29	Male	Pneumothorax	2 months	Follow up	8	Dead
14	Lung injury after HSCT	48	Male	Pneumothorax	2 months	VATS	5	Dead

CHP chronic hypersensitivity pneumonitis, *COPD* chronic obstructive pulmonary disease, *HSCT* hematopoietic stem cell transplantation, *ILD* interstitial lung disease, *LAM* lymphangioleiomyomatosis, *LT* lung transplantation, *VATS* video-assisted thoracoscopic surgery

Fig. 3 Native lung overinflation occurred in 56-year-old man with chronic obstructive pulmonary disease 6 months after left single lung transplantation. Chest computed tomography shows a mediastinal shift to the left

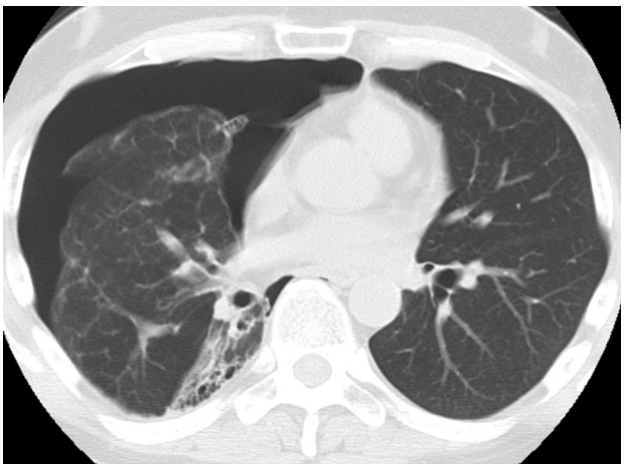

Fig. 4 Right pneumothorax occurred in 50-year-old man with interstitial lung disease 6 months after left single lung transplantation. Chest computed tomography shows pneumothorax of the native right lung

could lead to severe outcomes [7–10]. Another explanation for this difference in survival rates might be that the ISHLT registration data or the data from Venuta et al. included the old cases [1, 7]. The 2014 registry of the International Society for Heart and Lung Transplantation showed that survival of SLT from 1999 to 2008 was much better than

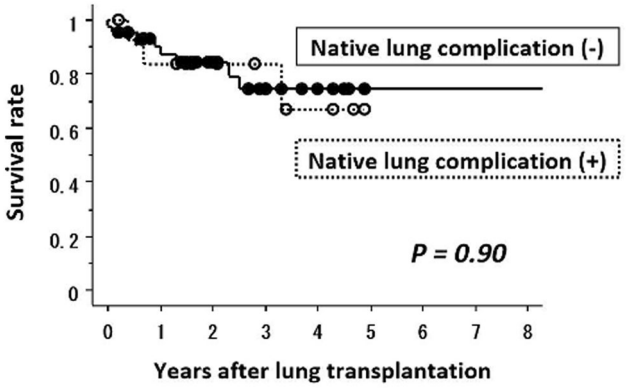

Fig. 5 Survival curve for patients with native lung complications and those without native lung complications ($p = 0.86$)

that from 1990 to 1998. Furthermore, careful preoperative patient selection including donor and recipient and postoperative management might possibly be the main potential key factors for the good outcome of SLT in our institution. For example, we periodically monitored various serum markers, such as cytomegalovirus (CMV) and Epstein-Barr Virus DNA PCR testing, CMV viral antigen (C7-HRP), aspergillus antigen, β-D-Glucan, and gamma globulin levels, postoperatively in all cases [11].

There are several limitations to our study. First, although this study was performed at one of the largest lung transplant centers in Japan, it is a single institutional study. Furthermore, the number of patients included in this study was small and the median follow-up period was short. Recently, the number of lung transplantations has increased considerably in Japan; therefore, a nation-wide study with a larger sample size and longer follow-up time might be expected in the future.

Conclusion

SLT has been performed with acceptable outcomes in our institution. Although we noted native lung complications in almost 40 % of single lung transplant recipients, there were no lethal complications. In the current situation of severe donor shortage in Japan, SLT can be the first choice of treatment except in cases of contraindications to SLT.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

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