

Current status and problems of lung transplantation in Japan

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Abstract: Lung transplantation has been performed worldwide and recognized as an effective treatment for patients with various end-stage lung diseases. Shortage of lung donors is one of the main obstacles in most of the countries, especially in Japan. Every effort has been made to promote organ donation during the past 20 years. In 2010, Japanese transplant law was revised so that the family of the brain dead donors can make a decision for organ donation. Since then, the number of cadaveric lung donor has increased by 5-fold. However, the average waiting time is still more than 800 days resulting in considerable number of deaths on the waiting list. Lung transplantation in the use of donation after cardiac death (DCD) has now been increasingly performed in Europe, Australia and North America with promising results. However, controlled death is not permitted in Japan making it difficult to accept this strategy. Use of marginal donors is one of the strategies for organ shortage. In Japan, the rate of lung usage is now well over 60% because of careful donor management by medical consultants and aggressive use of marginal donors. Living-donor lobar lung transplantation (LDLLT) has been developed to offset the mismatch between supply and demand for those patients awaiting cadaveric lung transplantation (CLT) and it is often the most realistic option for very ill patients. Between 1998 and 2015, lung transplantation has been performed in 464 patients (55 children, 419 adults) at 9 lung transplant centers in Japan. CLT was performed in 283 patients (61%) and LDLLT was performed in 181 patients (39%). The 5-year survival was 72.3% and 71.6%, respectively. Of note, only seven children received CLT. In conclusion, lung transplantation in Japan has grown significantly with excellent results but the shortage of cadaveric lung donor remains to be an important unsolved problem. LDLLT is often the only realistic option for very ill patients especially for children.

Keywords: Lung transplantation; cadaveric lung transplantation (CLT); living-donor lobar lung transplantation (LDLLT); marginal donor

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Introduction

Lung transplantation has been performed successfully worldwide since 1983 in patients with end-stage lung disease, and more than 50,000 lung transplants have been reported in The Registry of the International Society for Heart and Lung Transplantation (1). In contrast, the history of lung transplantation in Japan has had a long dark period because of the difficulty in accepting the concept of brain death. The transplant law finally became effective in October 1997 and cadaveric lung transplantation (CLT) was officially approved. However, it was somewhat a very

strict law resulting in very small practice of CLTs for the next decade. The author performed the first successful lung transplantation using living donors in 1998 at Okayama University (2). Living-donor lobar lung transplantation (LDLLT) had been the only realistic option for most patients until 2010 when the Japanese Organ Transplant Law was amended so that the family of the brain dead donors can make a decision for organ donation (3,4). The revision of the law significantly increased the number of organ donations from brain dead donors and CLT has become a more realistic option for adult Japanese patients since then (5). About 60 lung transplants, two thirds as CLT

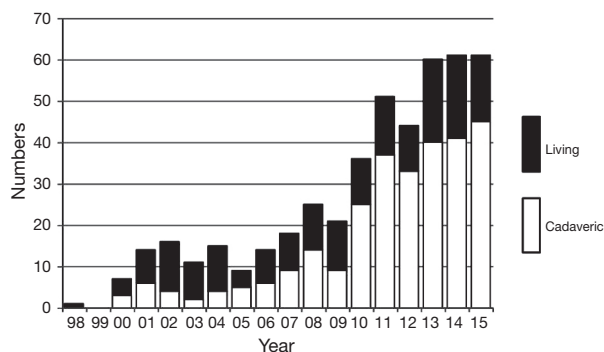


Figure 1 Annual numbers of lung transplantation in Japan [1998–2015]. In 2010, Japanese transplant law was revised so that the family of the brain dead donors can make a decision for organ donation. Since then, the number of cadaveric lung donor has increased by 5-fold. Of note, the number of living-donor lung transplantations has not decreased.

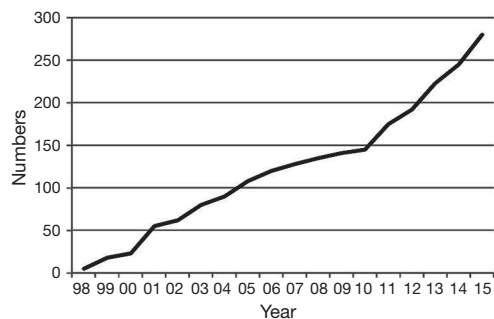


Figure 2 Number of patients on the waiting list for lung transplantation. The number of patients on the JOTN waiting list is increasing. Currently, about 300 patients are listed, however, only about 40 patients can receive CLT annually. JOTN, Japan Organ Transplant Network; CLT, cadaveric lung transplantation.

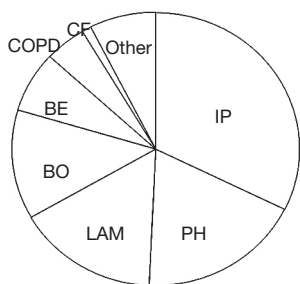


Figure 3 Indications for lung transplantation in Japan (n=464). IP, PH, LAM and BO were four major indications followed by BE. COPD and CF were rather rare indications. IP, interstitial pneumonia; PH, pulmonary hypertension; LAM, lymphangioleiomyomatosis; BO, bronchiolitis obliterans; BE, bronchiectasis; COPD, chronic obstructive pulmonary disease; CF, cystic fibrosis.

and one third as LDLLT had been performed annually during the last 3 years (Figure 1).

Cadaveric lung transplant system in Japan

There are nine certified lung transplant centers in Japan (Tohoku, Dokkyo, Chiba, Tokyo, Kyoto, Osaka, Okayama, Fukuoka and Nagasaki Universities). Following multidisciplinary assessment, a decision is made to accept or reject the patient as a potential lung transplant recipient by the Lung Transplant Evaluation Committee at each lung transplant center. Candidates accepted by the Committee are evaluated further by nationwide Central Lung Transplant Evaluation Committee. Then, the accepted candidates are registered on the waiting list for CLT of the Japan Organ Transplant Network (JOTN). The number of lung transplant candidates newly registered at JOTN has generally been increasing. Accordingly, the number of patients on the waiting list is also increasing (Figure 2). Currently, about 300 patients are listed, however, only about 40 patients can receive CLT annually. The algorithm for brain dead donor lung allocation is based primarily on accrued time on the waiting list, a situation which favors patients with slowly progressive diseases and disadvantages patients with rapidly progressive diseases. As a result, the average waiting time is still more than 800 days resulting in nearly 50% mortality rate on the waiting list.

Indications

Lung transplantation is indicated for patients with end-stage lung disease who are failing maximal medical therapy and whose life expectancy is limited. Because of the severe cadaveric donor shortage, upper age limit is set in Japan. Candidates should be less than 55 years old for bilateral lung transplantation and they should be less than 60 years old for single lung transplantation at the time of registration on JOTN waiting list.

Regarding recipient's diagnoses, interstitial lung pneumonia, pulmonary hypertension, lymphangioleiomyomatosis, and bronchiolitis obliterans were four major indications (Figure 3). Indications for lung transplant are quite distinct in Japan where cystic fibrosis is a rare disease and emphysema is not a common indication due to upper age limit. Majority patients with bronchiolitis obliterans suffered from chronic progressive pulmonary complications after hematopoietic stem cell transplantation (6,7). These patients are commonly believed to be high-risk candidates for lung

The utility ratio of the lungs of brain-dead donors in Japan (1999–2014)

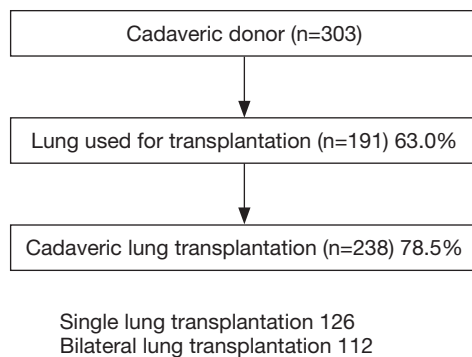


Figure 4 The utility ratio of the lungs of brain-dead donors in Japan [1999–2014]. The utility ratio of the lungs of brain-dead donors in Japan was over 63.0% and donor/recipient ratio was 78.5%.

transplantation because long term pre-transplant intake of immunosuppressant drugs often causes organ dysfunction of other organs and increases the risk of various infections.

Strategies for organ shortage

As the waiting list for lung transplantation continues to grow, use of DCD has recently begun to expand. The Maastricht workshop identified categories of donors that could be considered for DCD. Category 1: dead on arrival. Category 2: unsuccessful resuscitation, are uncontrolled donors. Spanish group utilized Category 1 donors and reported acceptable mid- and long-term survival, however, the higher rated of primary graft dysfunction and its impact on early mortality were also reported (8). Category 3: includes donors awaiting cardiac arrest, and category 4 involves cardiac arrest in a brain dead donor. Maastricht category three donors were increasingly used for lung transplantation in Europe, Australia and North America (9-13). Withdrawal of life-supporting therapy is planned in advance in the setting of an intensive care unit or operating room. After confirming circulatory arrest for the legally determined minutes, the lungs are extracted and used for transplantation. The results after category three were reported to be at least equivalent to that after brain dead donation. However, controlled death is not permitted in Japan making it difficult to accept this strategy.

Use of marginal donors is one of the strategies for organ shortage. For example, we successfully performed bilateral

lung transplantation from a donor with ruptured right main bronchus by a trauma (14). A medical consult system has been established in Japan to maintain various organ conditions suitable for the subsequent donation. The utility ratio of the lungs of brain-dead donors in Japan (Figure 4) is indeed over 60% and it is much higher than that reported in the USA (approximately 20%). Bilateral lung transplantation has been increasingly performed in most of the centers knowing that its long term survival is better than that of single lung transplantation (1). However, single lung transplantation has been chosen more often than bilateral lung transplantation in Japan to maximize the number of transplantation by sharing the scarce donor (5,15). As a result, donor/recipient ratio was approaching 80%.

LDLLT has been performed as a life-saving procedure for critically ill patients who are unlikely to survive the long wait for cadaveric lungs (3,4,16,17). Although LDLLT was initially performed in the USA (18), its use has decreased there because of the recent change by the Organ Procurement and Transplantation Network to an urgency/benefit allocation system for cadaveric donor lungs. For the past several years, reports on LDLLT almost exclusively have been from Japan, where the average waiting time for a cadaveric lung is still more than 800 days. Because only two lobes are implanted, appropriate size matching between the donor and recipient is important in LDLLT. It is often inevitable that small grafts are implanted. Excessively small grafts may cause high pulmonary artery pressure, resulting in lung edema. We have developed lobar sparing transplantation (19) and right to left inverted transplantation (20) for undersize graft. On the other hand, the adult lower lobe might be too big for small children. The use of oversized grafts could cause high airway resistance, atelectasis and hemodynamic instability by the time of chest closure. To overcome these problems, we have developed several techniques including single lobe transplantation with or without contralateral pneumonectomy (21,22), delayed chest closure (23), and downsizing the graft (24).

Comparison between CLT and LDLLT

Advantages and disadvantages of LDLLT compared to CLT are summarized in Table 1. In general, the ischemic time for LDLLT is much shorter than CLT. Although only two lobes are transplanted, LDLLT seems to be associated with less frequent primary graft failure. We believe that using a “small but perfect graft” is a great advantage in LDLLT.

Table 1 Comparison between LDLLT and CLT

Variables	LDLLT	CLT
Waiting time	Short	Long
Schedule	Controllable	Uncontrollable
Ischemic time	Short	Long
Graft size	Unmatched	Matched
Primary graft failure	Infrequent	10–20%
Infection transmitted from graft	Infrequent	Frequent
Number of teams	3	2
Bronchial complication	Rare	5%
Chronic rejection	Often unilateral	Major cause of death

LDLLT, living-donor lobar lung transplantation; CLT, cadaveric lung transplantation.

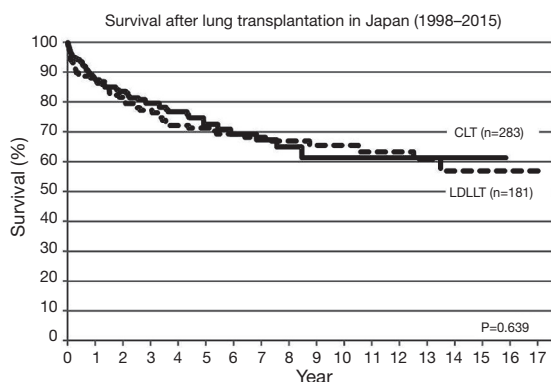


Figure 5 Survival after lung transplantation in Japan [1998–2015]. Lung transplantation has been performed in 464 patients at nine lung transplant centers in Japan. CLT was performed in 283 patients (61%) and LDLLT was performed in 181 patients (39%). Survival was similar between the two transplant procedures. The 5-year survival was 72.3% and 71.6%, respectively ($P=0.639$). CLT, cadaveric lung transplantation; LDLLT, living-donor lobar lung transplantation.

Experienced centers have recently reported the incidence of bronchial complications in CLT to be about 5%. Contraindications to CLT include current high-dose systemic corticosteroid therapy because it may increase airway complications, although low-dose pre-transplantation corticosteroid therapy is acceptable. We have accepted high-dose systemic corticosteroid therapy in LDLLT. Excellent bronchial healing was observed in spite of high-dose steroid use (25). Various factors, such as short donor bronchial length, high blood flow in the small grafts implanted, well preserved lung parenchyma with short ischemic time, may

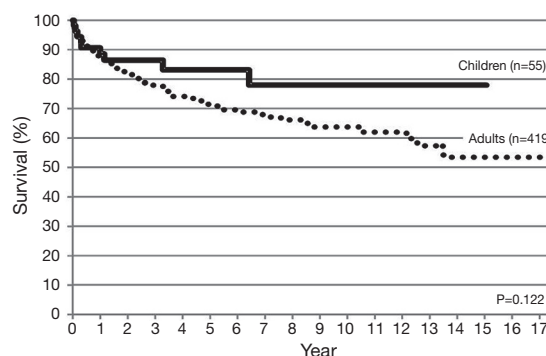


Figure 6 Survival after lung transplantation in Japan (adults vs. children). Although the number of pediatric patients was small, pediatric lung transplant recipients showed a trend toward better long-term survival than adult recipients.

contribute to better oxygen supply to the donor bronchus resulting in excellent bronchial healing in LDLLT.

Chronic allograft dysfunction (CLAD) including bronchiolitis obliterans syndrome (BOS) has been the major obstacle after CLT. Theoretically, human leukocyte antigen (HLA) similarity in cases of blood related donation may be beneficial, but the role of HLA mismatches may be more complicated when two different donor lobes are implanted into one recipient in bilateral LDLLT. Transplanting two lobes obtained from two different donors appears to be beneficial in the long term because the contralateral unaffected lung may function as a reservoir in case of unilateral BOS (26). The question remains whether patients receiving LDLLT will have less CLAD than those receiving CLT.

Results after lung transplantation

Between 1998 and 2015, lung transplantation has been performed in 464 patients (55 children, 419 adults) at nine lung transplant centers in Japan. CLT was performed in 283 patients (61%) and LDLLT was performed in 181 patients (39%). The 5-year survival was 72.3% and 71.6%, respectively (*Figure 5*). Among 55 pediatric patients, only 7 children (12.7%) received CLT and 48 children (87.3%) received LDLLT. Although the number of pediatric patients was small, pediatric lung transplant recipients showed a trend toward better long-term survival (*Figure 6*). Among 283 patients receiving CLT, single lung transplantation was performed in 149 patients (52.7%) and bilateral lung transplantation was performed in 134 patients (47.3%). The survival was similar between the two procedures (*Figure 7*).

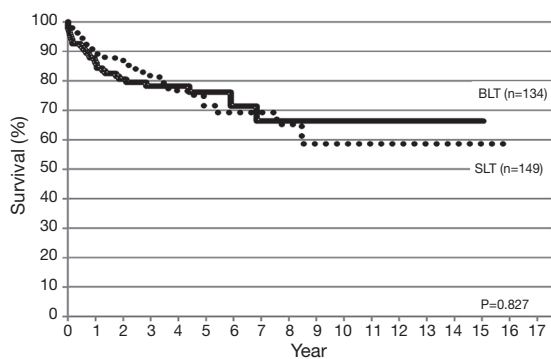


Figure 7 Survival after cadaveric lung transplantation in Japan (single vs. bilateral). Among 283 patients receiving cadaveric lung transplantation, single lung transplantation (SLT) was performed in 149 patients (52.7%) and bilateral lung transplantation (BLT) was performed in 134 patients (47.3%). The survival was similar between the two procedures.

Summary

Lung transplantation in Japan has grown significantly with excellent results but the shortage of cadaveric lung donor remains to be an important unsolved problem. The average waiting time is more than 800 days and the mortality rate on the waiting list is nearly 50%. Use of marginal donor, medical consults system, and single lung transplantation result in high utilization ratio of the lungs of brain-dead donors. Despite the aggressive use of marginal lungs and single lung transplantation by Japanese lung transplant centers, the overall survival of recipients in Japan (5-year survival, approximately 70%) is generally better than that reported by the International Society for Heart and Lung Transplantation registry (5-year survival, approximately 50%). LDLLT is often the only realistic option for very ill patients, especially for children. Although LDLLT patients are in worse preoperative condition than CLT patients, LDLLT patients demonstrates survival rates similar to CLT patients (17).

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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