Review Article on Why is the Outcome Good? Secrets of Lung Transplantation in Japan

Roles and practice of living-related lobar lung transplantation

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Abstract: Living-donor lobar lung transplantation (LDLLT) was first performed in the USA and thereafter it was introduced in Japan in 1998 as an alternative modality to brain-dead donor lung transplantation (BDLT). Although the LDLLT procedure was employed for rapidly deteriorating patients who were hospitalized and mechanically ventilated at the time of transplantation, LDLLT demonstrated better or comparable post-transplant outcomes in comparison to BDLT. Less injured lobar grafts and a significantly shorter graft ischemic time possibly contributed to a significantly lower incidence of severe primary graft dysfunction (PGD) after LDLLT in comparison to BDLT. In standard LDLLT, patients obtained lobar grafts from two different donors, and thus most patients developed chronic lung allograft dysfunction (CLAD) only in the unilateral lung graft. This indicates that the contralateral unaffected lung graft could reserve lung function after the unilateral development of CLAD. In our transplant program, the incidence of CLAD per donor in LDLLT (14.4%) was also significantly lower in comparison to BDLT (24.7%). The 1-, 5- and 10-year survival rates after LDLLT were 90.9%, 75.5% and 57.2%, respectively, which were equivalent to those after BDLT (92.9%, 73.4% and 62.2%). The inherent surgical risk to the living donors should always be considered. In our experience, living-donor surgery was associated with a complication rate of 12.7%, and importantly, all living donors finally returned to their previous social lives. Precise functional and anatomical size matching between donor lobar graft and recipient could provide a favorable pulmonary function after LDLLT. We recently established multimodal surgical approaches, such as native upper lobe-sparing, right-to-left horizontally rotated, segmental, and single-lobe transplantation, in order to resolve the issue of size mismatch between the donor lobar graft and the recipient.

Keywords: Living donor; lobar lung transplantation; size matching; primary graft dysfunction (PGD); chronic lung allograft dysfunction (CLAD)

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Introduction

Since a first case of living-donor lobar lung transplantation (LDLLT) was successfully performed in the USA, this procedure has been employed as a major treatment strategy to save critically ill patients with end-stage lung diseases in Japan (1,2). Approximately 20 LDLLT procedures have constantly been performed annually, although the number of brain-dead donor lung transplant (BDLT) procedures has increased since the amendment of the Japanese organ transplant law in 2010 (*Figure 1*). Therefore, 270 LDLLT procedures had been conducted by the end of 2021, which accounted for 29.1% of the 928 lung transplant procedures performed in Japan. This suggests that LDLLT has remained a viable life-saving option for patients with severe respiratory disorders in Japan.

There are some advantages in LDLLT, including an ideal

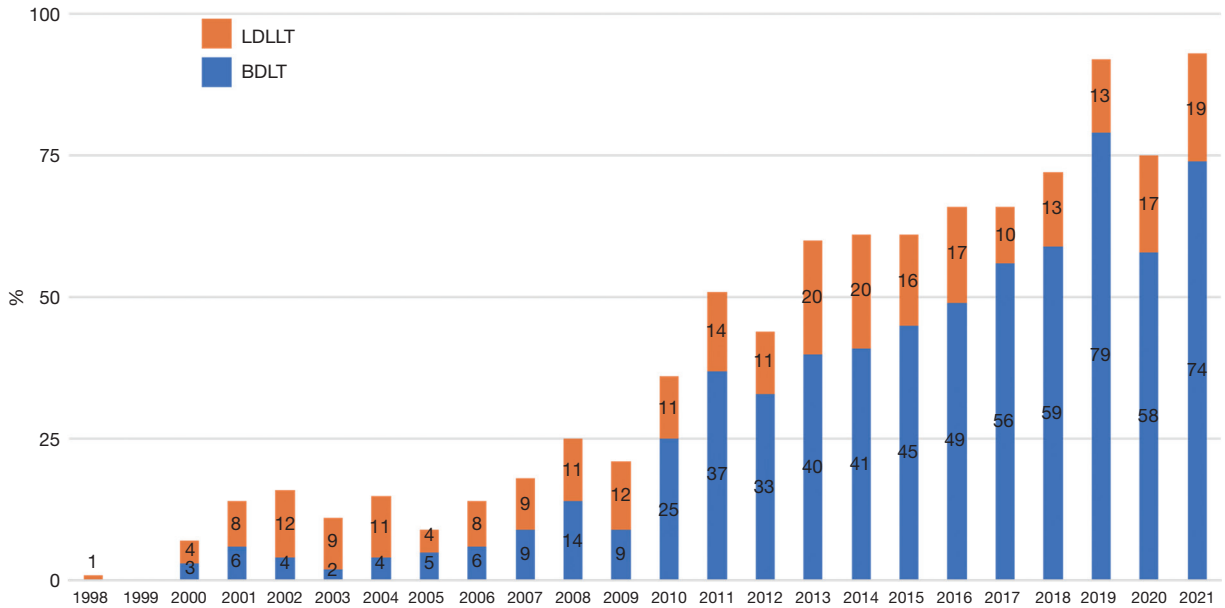

Figure 1 By the end of 2021, lung transplantation had been performed in 928 patients in Japan, including 270 LDLLT (29.1%). LDLLT, living-donor lobar lung transplantation; BDLT, brain-dead donor lung transplantation.

Table 1 Advantages and disadvantages of living-donor lobar lung transplantation

Advantages	Disadvantages
Lower HLA mismatch	Lobectomy in healthy donor(s)
Short waiting time	Difficult size matching
Scheduled operation	Three operating rooms for three teams (recipient and two donors)
Ideal graft with fewer injuries and infection	
Short ischemic time	

HLA, human leukocyte antigen.

lung graft with fewer injuries, significantly shorter graft ischemic time, and fewer human leukocyte antigen (HLA) mismatches, which can contribute to a lower incidence of severe primary graft dysfunction (PGD) and chronic lung allograft dysfunction (CLAD) after LDLLT in comparison to BDLT (*Table 1*). However, the LDLLT procedure also has some disadvantages which still need to be overcome, including difficult size matching between the lobar graft and the recipient. We recently developed multimodal surgical approaches (e.g., native upper lobe-sparing, right-to-left horizontally rotated, single-lobe, and segmental transplantation) in order to resolve the issue of graft size mismatch in recipients. This chapter will focus on roles and practice of LDLLT in our transplant program in order to elucidate a reason "why the posttransplant outcome is so good in Japan".

LDLLT recipient characteristics

In Kyoto University, recipient candidates for LDLLT should be <65 years of age and should meet the conventional BDLT criteria. Importantly, LDLLT can be indicated only for seriously ill patients and/or pediatric patients who cannot wait for the allocation of brain-dead donor lungs (3,4). Since our lung transplant program was restarted in 2008, 110 LDLLT procedures had been performed by the end of 2021. Almost 30% of the recipients were pediatric patients under 15 years of age, and more than half were female patients with significantly shorter height. LDLLT recipients were significantly younger than BDLT recipients (median age: 33 years in LDLLT *vs.* 47 years in BDLT), which might contribute to the good posttransplant outcomes in Japan. Regarding the severity of the LDLLT recipient illness, 44% of the patients were severely underweight with a body mass index (BMI) of <16.0. More than 60% of the recipients had been

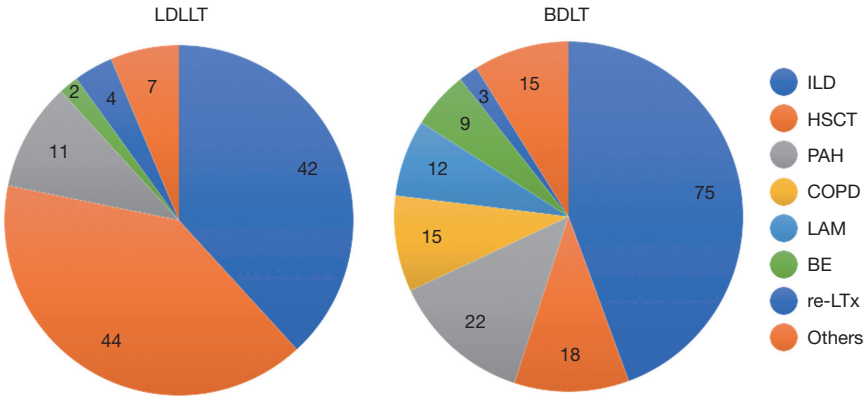

Figure 2 Indications for LDLLT and BDLT in Kyoto University. LDLLT, living-donor lobar lung transplantation; BDLT, brain-dead donor lung transplantation; ILD, interstitial lung disease; HSCT, hematopoietic stem cell transplantation; PAH, pulmonary arterial hypertension; COPD, chronic obstructive pulmonary disease; LAM, lymphangioleiomyomatosis; BE, bronchiectasis; re-LTx, re-lung transplantation.

hospitalized due to the progression of respiratory disorders and required long-term steroid use prior to transplantation. Patients under preoperative mechanical respiratory support accounted for 12.7% of all the LDLLT recipients and these patients were significantly younger with a median age of 7 years (range, 6–50 years). Furthermore, most ventilator-dependent patients were intubated after LDLLT was scheduled, and thus the duration of preoperative mechanical respiratory support was relatively short (median: 17 days; range, 3–41 days) in these patients, which indicated that the patients could maintain their ability to undergo adequate physiotherapy after transplantation (5). Two patients—a 6-year-old boy and 57-year-old woman had been preoperatively managed under ECMO support for 6 and 104 days, respectively—required a bridge to LDLLT with the use of veno-venous extracorporeal membrane oxygen (ECMO) (6,7). The increased severity of the LDLLT recipient illness, including severe malnutrition, long-term steroid use, hospitalization at the time of transplantation, and bridge to transplantation with the use of a ventilator or ECMO, have been listed as risk factors for post-transplant mortality according to the registry and consensus reports from the International Society for Heart and Lung Transplantation (8,9).

Various lung diseases, including restrictive, obstructive, infectious and vascular lung diseases, were indicated for lung transplantation in our program (*Figure 2*). Although cystic fibrosis was the most indication for LDLLT in USA, cystic fibrosis was rarely observed in Japan. Furthermore, chronic obstructive lung disease was not a common indication for lung transplantation in Japan. Pulmonary graft-versus-host disease (GVHD) following hematopoietic stem cell transplantation (HSCT) (40.0%) and interstitial lung disease (38.2%) were presented as two major indications for LDLLT. Patients who suffered from pulmonary GVHD after HSCT were reported to be high-risk candidates for lung transplantation, according to the data collected from six transplant centers in Japan (10). However, the patients who received the graft from the same living donor as for HSCT could show significantly better prognosis.

Operative characteristics of LDLLT

In standard LDLLT, right and left lower lobar grafts retrieved from two healthy donors are implanted in a recipient as a whole lung, following right and left pneumonectomy. Therefore, cardiopulmonary support is absolutely required during the LDLLT procedure in order to control the blood flow within the implanted lobar grafts: veno-arterial ECMO is basically utilized in the majority of adult transplant cases, whereas cardiopulmonary bypass is employed for pediatric transplantation and/or the cases that require cardiac repair such as closure of an atrial septal defect at the same time (11-13).

Bilateral LDLLT requires three surgical teams for a recipient and two donors and a back-table team, and each team member can communicate closely to identify the appropriate timing to retrieve the donor

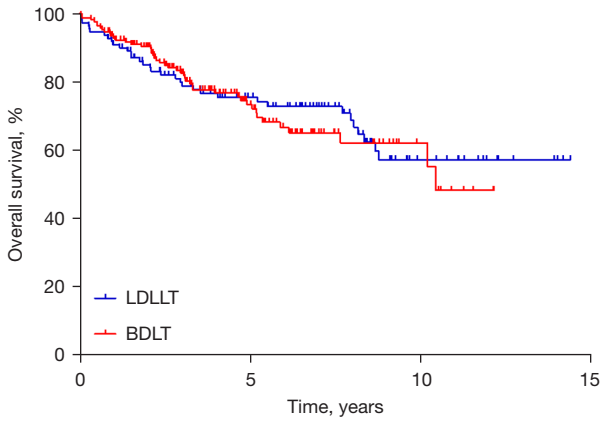

Figure 3 In Kyoto University, the 1-, 5- and 10-year survival rates were 90.9%, 75.5% and 57.2%, respectively, after LDLLT (n=110) and 92.9%, 73.4% and 62.2% after BDLT (n=169). LDLLT, living-donor lobar lung transplantation; BDLT, brain-dead donor lung transplantation.

lung grafts in order to minimize the graft ischemic time (*Table 1*). Therefore, the median graft ischemic time in LDLLT was 153 minutes (range, 80–301 minutes), which was significantly shorter than that in BDLT (median: 498 minutes; range, 242–780 minutes) according to our experience.

Early post-LDLLT outcomes

Living-donor lobar grafts are small but ideal with fewer injuries—which can exacerbate the ischemia-reperfusion induced lung injury after lung transplantation—in comparison to brain-dead donor lungs, in which injuries are frequently observed due to trauma, infection, gastric aspiration and neurogenic pulmonary edema (14,15). Furthermore, the graft ischemic time of the living-donor is significantly shorter than that of the brain-dead donor, as described previously. Therefore, LDLLT can prevent severe ischemia-reperfusion injury, which is identified as a main cause of PGD and associated with an increase in the risk of acute rejection and CLAD (15). Actually PaO_2/FiO_2 just after reperfusion was significantly better in LDLLT (median 492 mmHg; range, 65–692 mmHg), in comparison to BDLT (median: 307 mmHg; range, 70–653 mmHg), and the incidence of grade 3 PGD within 72 hours after LDLLT was reported to be 12.2%, which was significantly lower than that after BDLT (38.9%) (16,17). The other early post-transplant outcomes were equivalent between LDLLT and BDLT in our experience: ECMO support was applied in 10.9% of the post-LDLLT patients; and the 30-day mortality and the in-hospital mortality rates after LDLLT were 1.8% and 5.5%, respectively. The causes of in-hospital death after LDLLT included PGD, disseminated intravascular coagulation, aspiration pneumonitis, and sepsis.

Long-term outcomes after LDLLT

HLA matching between donor and recipient is not considered at the time of donor selection in LDLLT and BDLT. However, in our program, living-donor candidates should be relatives within the third degree or a spouse, and thus HLA mismatch between the donor and recipient was reported to be significantly lower in LDLLT in comparison to BDLT (*Table 1*) (16). Furthermore, we recently reported that *de novo* donor-specific antibodies after LDLLT developed in 6.8% of patients, which was a significantly lower rate in comparison to after BDLT (19.4%) (16). Therefore, the incidence of CLAD per donor in LDLLT (14%) is currently significantly lower than that in BDLT (25%) in our program. In conventional bilateral LDLLT, a recipient obtains right and left lobar grafts donated from different living-donors, and thus CLAD due to rejection typically occurs in the unilateral lung graft after LDLLT. This unilateral CLAD development can help the contralateral unaffected lobar graft function as a reservoir in LDLLT (18).

In Kyoto University, 110 LDLLT procedures and 169 BDLT procedures were performed between 2008 and 2021. The 1-, 5- and 10-year survival rates were 90.9%, 75.5% and 57.2%, respectively, after LDLLT, and 92.9%, 73.4% and 62.2% after BDLT (*Figure 3*). The major causes of late death after LDLLT included CLAD, infection, and malignancy (breast cancer, bladder cancer, gastric cancer and post-transplant lymphoproliferative disorders).

Living-donor surgery outcome

The eligibility criteria for living donation in our program were previously described (3,4). Donor surgery was conducted in 204 living donors between 2008 and 2021. Median donor surgical time was 282 minutes and median blood loss was 80 mL during donor surgery. Of those,

26 donors (12.7%) experienced postoperative complications, such as pneumothorax (n=10), pleural effusion (n=9), pleuritis (n=2), chylothorax (n=2), hemothorax (n=1), empyema (n=1) and wound dehiscence (n=1). All donors were discharged alive and eventually returned to their previous regular lifestyles (19,20). Median length of hospital stay was 16 days.

Lobar graft size match in LDLLT recipient

In standard LDLLT, only right and left lower lobes retrieved from living donors are implanted as a whole lung in a single recipient. Therefore, precise assessment is mandatory for size matching between the living-donor lobar graft and recipient. Functional size matching is important for an undersized lobar graft, whereas anatomical size matching is important for an oversized lobar graft.

We can obtain the real pulmonary function data from a living donor but not from a brain-dead donor, which enables us to evaluate the functional size to allow for an accurate match in LDLLT. For functional size matching, graft forced vital capacity (FVC) can be estimated based on the donor's measured FVC and the number of implanted pulmonary segments. Our acceptable lower threshold of the total FVC of the two grafts is 45–50% of the recipient predicted FVC (2). For anatomical size matching, the volumes of the oversized lung graft and recipient chest cavity are measured by 3-dimensional computed tomography (3D-CT) volumetry (21). Our upper threshold of the graft volume is considered to be 200% of the recipient's chest cavity volume (7).

We previously reported that when the size matching between the living-donor lobar graft and recipient was precisely evaluated, LDLLT recipients showed an equivalent post-transplant pulmonary function and exercise tolerance to BDLT patients who received bilateral whole lungs (22). According to our recent data, the median graft FVC was preoperatively estimated to be 64% of the recipient predicted FVC, and the post-LDLLT pulmonary function steadily improved to around 67% of the recipient predicted values over the first two years after transplantation.

New strategies for size mismatch in LDLLT

We developed various living-donor lung transplant techniques in order to resolve the serious issue of graft size mismatch in LDLLT recipients, such as tall adult patients and small pediatric patients.

Strategies for undersized graft

We developed two procedures of "native upper lobe-sparing transplant" and "right-to-left horizontally rotated transplant" to manage undersized lung graft (23,24).

When we employ sparing transplant procedure, the recipient native lung should not be infected. The transplant techniques are similar to standard LDLLT as previously reported (25). One of the benefits of this strategy is that the spared upper lobes can decrease the intrathoracic dead space for the undersized graft so that the implanted small graft can function more efficiently (26).

In right-to-left horizontally rotated transplant procedure, we can implant a right lower lobe that is approximately 5% larger, instead of the left lower lobe into the recipient's left chest cavity (24,27). There are some important points in this procedure: bronchial anastomosis is performed in the graft bronchus and the recipient's left upper bronchus, which indicates that the recipient left lower bronchial stamp is left closed. Therefore, we carefully dissect the tissues surrounding the recipient left bronchus in order to maintain the bronchial artery circulation and prevent postoperative bronchopleural fistula. Pulmonary artery (PA) anastomosis is also carefully performed behind the bronchus in order to avoid PA twisting and kinking. The graft pulmonary vein (PV) is connected to the recipient's superior PV or left appendage.

Strategies for oversized graft

Single-lobe transplantation is employed mainly for small pediatric patients with various types of lung disease, including severe pulmonary arterial hypertension (13,28-31). In this procedure, a single lobe with an FVC of >60% and a CT volume of <200% should be implanted in order to prevent severe PGD after transplantation (32).

We recently developed a novel technique of bilateral living-donor segmental lung transplantation, using a basal segmental and/or an S6 segmental grafts (7). The procedure of implanting segmental grafts requires more advanced techniques in comparison to implanting of lobar grafts in LDLLT. As previously described, the S6 segmental vessels are very small; thus, vascular anastomosis should be

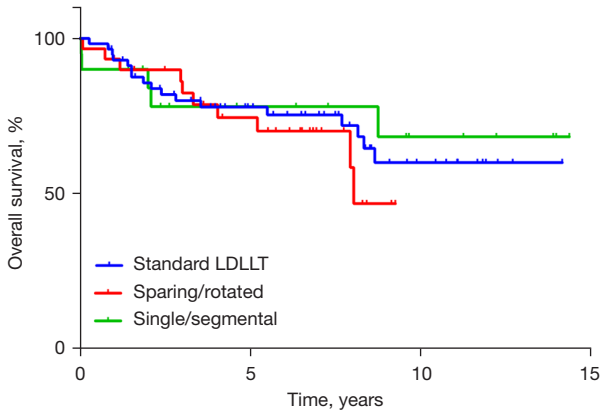

Figure 4 In Kyoto University, the 1- and 5-year survival rates were 93.0% and 77.9%, respectively, after standard LDLLT, 93.3% and 70.1% after native upper lobe-sparing and/or right-to-left horizontally rotated transplants, and 90.0% and 78.0% after single-lobe or segmental transplants. LDLLT, living-donor lobar lung transplantation.

meticulously performed in order to prevent poor venous drainage with graft congestion after transplantation (7).

Regarding segmental graft preparation, it is better for the intersegmental plane to be completely divided *in vivo* in the donor using electrocautery so that the residual adjacent segments can fully expand in the donor and the implanted segmental grafts can expand in the recipient to acquire the maximum pulmonary function.

Outcomes after novel living-donor lung transplantation

According to our recent data, almost half of the living-donor lung transplant procedures were performed as non-standard LDLLT procedures (e.g., native upper lobe-sparing, right-to-left horizontally rotated, single-lobe, and segmental transplantation). These novel transplant procedures had the potential to overcome the extensive graft size mismatch in tall adult or small pediatric patients who had been previously considered ineligible for LDLLT. The 1- and 5-year survival rates were 93.3% and 70.1%, respectively, after sparing and/or rotated transplants and 90.0% and 78.0% after single-lobe or segmental transplants, which were equivalent to those after standard LDLLT (93.0% and 77.9%) (*Figure 4*).

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Footnote

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