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Review Article

Clinical lung transplantation in Japan: Current status and future trends

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Abstract

The first successful lung transplantation (LTx) was performed in 1983. Since then, more than 10 000 LTx have been performed in the world, with approximately 1000 new cases each year in recent years. Lung transplantation is established as the ultimate treatment for end-stage pulmonary diseases. Clinical application of LTx was delayed in Japan because of difficulty in acceptance of brain death. The Japanese Brain Death Act (JBDA) for organ transplantation was enforced in October 1997. Now, LTx from a brain-dead cadaver donor (BDCD) becomes a clinical option for end-stage lung diseases in this country. Four LTx centers were selected and the registration of candidates for LTx started in August 1998. In total, up until May 2001, 51 patients had been registered on a waiting list. Patients' diseases for LTx in Japan are different from those in the US and Europe. So far, primary pulmonary hypertension (PPH; $n = 23$), idiopathic pulmonary fibrosis/interstitial pneumonia (IPF/IIP; $n = 8$), lymphangioleiomyomatosis (LAM; $n = 7$) and bronchiectasis (BE; $n = 6$) are the major indications for LTx in Japan. Fourteen patients (27%) have died while waiting for LTx and only eight patients (14%) have received lung allografts. The BDCD are quite precious and, thus far, only 13 donors have become available after enforcement of the JBDA. Although the average utilization of BDCD for LTx was reported to be only 10–20%, positive utility of marginal donors in Japan has led to a higher rate (five of 13; 36%). Six LTx were performed from five BDCD. These included five single LTx (LAM $n = 3$; IPF/IIP $n = 2$) and one bilateral LTx (PPH $n = 1$). Because there are few BDCD in Japan, living-donor lobar LTx (LDLTx) is thought to be the optimal choice for selected patients. Eight LDLTx (BE $n = 2$; bronchiolitis obliterans $n = 2$; IPF/IIP $n = 2$; LAM $n = 1$; and PPH $n = 1$) have been performed. All recipients who received a LTx in Japan are alive and doing well at present.

Key words: brain-dead cadaver donor, bronchiectasis, idiopathic pulmonary fibrosis, living-donor lobar lung transplantation, lung transplantation, lymphangioleiomyomatosis, primary pulmonary hypertension.

Introduction

After the first successful lung transplantation (LTx) in 1983,[1] more than 10 000 LTx have been performed in the world, with approximately 1000 new cases each year in recent years.[2] Lung transplantation is established as the ultimate treatment for end-stage pulmonary diseases in developed countries, except Japan. Clinical application of LTx was delayed in Japan until the Japanese Brain Death Act (JBDA) for organ transplantation was enforced in October 1997. Major indications for LTx in Japan are quite different from those in Western countries. Six LTx from brain-dead cadaver donors (BDCDs) have been performed in Japan and LTx becomes a clinical option for end-stage lung diseases in our country. Because BDCDs are quite precious, LTx from living donors is thought to be

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an alternative choice for selected patients, as well as renal or liver transplantation, in Japan. The present review analyzes the current status and future trends of LTx in Japan.

Current status of LTx in Japan

Indication for LTx and the transplant window in Japan

Clinical organ transplantation from BDCD was not accepted for a long time in Japan. After the submission of a report from the National Brain Death Investigative Committee in 1992, the JBDA for organ transplantation was enforced in October 1997. Since then, organ transplantation from BDCD has become a real clinical option in this country. Four lung transplant centers were selected in April 1998 and registration of candidates for LTx started in August 1998.[3] The indicated lung diseases for LTx in Japan are limited to chronic advanced lung disorders for which no further medical or surgical therapies are available. Japanese criteria for LTx include a limitation of recipient age. Heart–lung and bilateral transplantation are restricted to patients under 55 years of age and single LTx is restricted to patients under 60 years of age. A Council for Lung and Heart–Lung Transplantation Organized with Related Societies approved 16 pulmonary diseases and one status (Table 1).[3] The indications for LTx include pulmonary vascular diseases, parenchyma lung diseases and diffuse pulmonary lesions due to several systemic diseases. Although survival limitation of candidates has not been clearly decided in Japan, an estimated survival of less than 2–3 years, as for candidates in Western countries, is usually accepted.[4] The transplant window means a recipient who has severe respiratory failure but does not have irreversible damage in other organ functions (Fig. 1). The transplant window must be considered in the assessment of each patient. Early registration is strongly recommended in the US because there is expected to be a wait of more than 600 days before LTx. The 6 min walk distance is thought to be a good indicator of total cardiopulmonary function.[5] However, it is difficult to assess the condition of each candidate, with a variety of pulmonary disorders, using a common standard. Therefore, international guidelines for the selection of LTx candidates based on major indications were submitted in 1998 (Table 2).[6] These guidelines are very useful and are also acceptable in our country.

Table 1 Indications for lung transplantation in Japan

Primary pulmonary hypertension
Idiopathic pulmonary fibrosis
Chronic emphysema
Bronchiectasis
Sarcoidosis
Lymphangioleiomyomatosis
Eisenmenger's syndrome
Other type of interstitial pneumonia*
Bronchiolitis obliterans
Pneumoconiosis
Pulmonary eosinophilic granuloma
Diffuse panbronchiolitis
Chronic thromboembolic pulmonary hypertension
Multiple pulmonary arteriovenous fistula
α_1-Antitrypsin deficiency emphysema
Cystic fibrosis
Progressive pulmonary disease that are approved by a council†

*Interstitial pneumonia except for idiopathic pulmonary fibrosis.

†The Council for Lung and Heart-Lung Transplantation Organized with Related Societies in Japan.

Registration for LTx in Japan

Candidates for LTx from BDCD must be registered on the Japan Organ Transplant Network (JOTNW) waiting list.

Table 2 International guidelines for the selection of lung transplant candidates

Chronic obstructive lung disease
$FEV_1 < 25\%$ predicted
$P_aCO_2 \leqq 55$ mmHg
Cor pulmonale
Bronchiectasis, cystic fibrosis
$FEV_1 \leqq 30\%$ predicted
$P_aCO_2 > 55$ mmHg, $P_aO_2 < 55$ mmHg
Increasing numbers of hospitalizations
Rapid fall in FEV_1
Massive hemoptysis
Increasing cachexia
Idiopathic pulmonary fibrosis
$VC < 60$–70% predicted
$DLCO/VA < 50$–60% predicted
Mandatory early referral (rapid progression)
Pulmonary hypertension
NYHA III–IV (despite optimal treatments, including PGI_2
CI $\leqq 2.0$ /min per m^2
RAP > 15 mmHg
mPAP > 55 mmHg
Eisenmenger's syndrome
Severe, progressive symptoms
NYHA III–IV (despite optimal treatments)

FEV1, forced expiratory volume in 1 s; VC, vital capacity; DLCO/VA, diffusion capacity of carbon monoxide corrected for alveolar volume; CI, cardiac index; RAP, right atrial pressure; mPAP, mean pulmonary pressure.

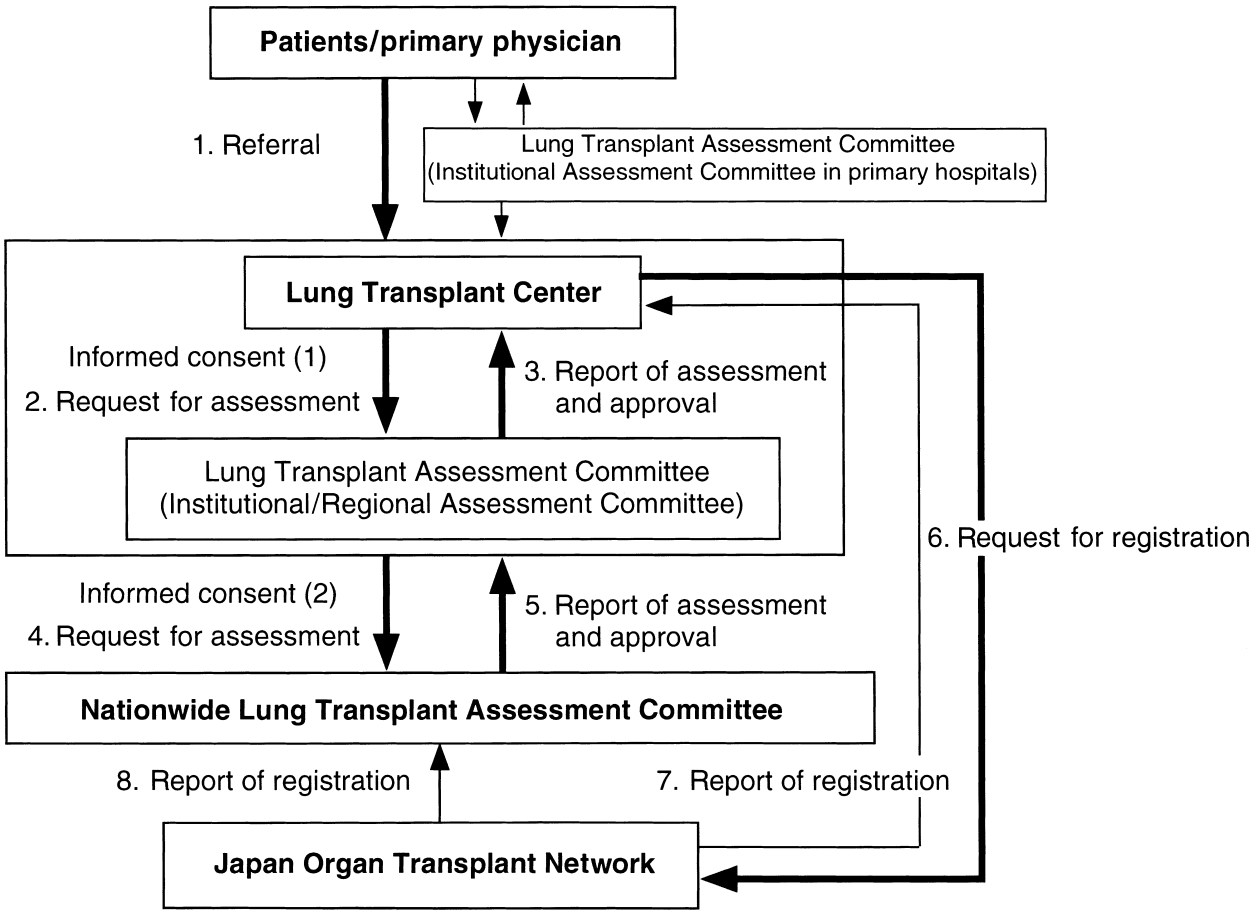

Fig. 1 Process of registration on waiting list for lung transplantation with the Japan Organ Transplant Network (JOTNW). During this process, informed consent is obtained at least twice from patients and their families.

The process of registration requires two different appraisals by LTx assessment committees, which are an institutional/regional committee and a nationwide committee (Fig. 2).[3] In addition, the validity of LTx for each candidate must be confirmed ethically by the institutional ethics committee. Thus, in Japan, it takes 2 or 3 months for the assessment and the process of registration to be completed. During this process, informed consent is obtained from candidates and their family.

Analysis of waiting patients for LTx

From August 1998 to March 2001, 51 candidates were accepted and registered on the waiting list. Only eight patients (16%) have received lung allografts during this period and 14 patients (27%) have already died (Fig. 3). Major causes for LTx candidates are primary pulmonary hypertension (PPH) in 23 cases (45.1%), idiopathic pulmonary fibrosis/interstitial pneumonia (IPF/IIP) in eight cases (15.7%), lymphangioleiomyomatosis (LAM) in seven cases (13.7%) and bronchiectasis (BE) in six cases (11.8%). The disease entities in Japan are quite different from those in Western countries (Fig. 4).[2] Juvenile emphysema, cystic fibrosis and α_1-antitrypsin-deficient emphysema are major indications in the international registry; in contrast, there are very few cases with these diseases in Japan.[7,8] All eight patients who received LTx are alive and doing well; in contrast, the survival of the other patients who could not have LTx is limited (Fig. 5). These prognoses for patients who do not undergo LTx vary according to primary disease. The prognosis for PPH is best, with a 2 year survival for over 80% of cases. The prognosis for IPF/IIP is worst and all candidates with IPF/IIP had died within 1 year if they could not receive LTx (Fig. 5).

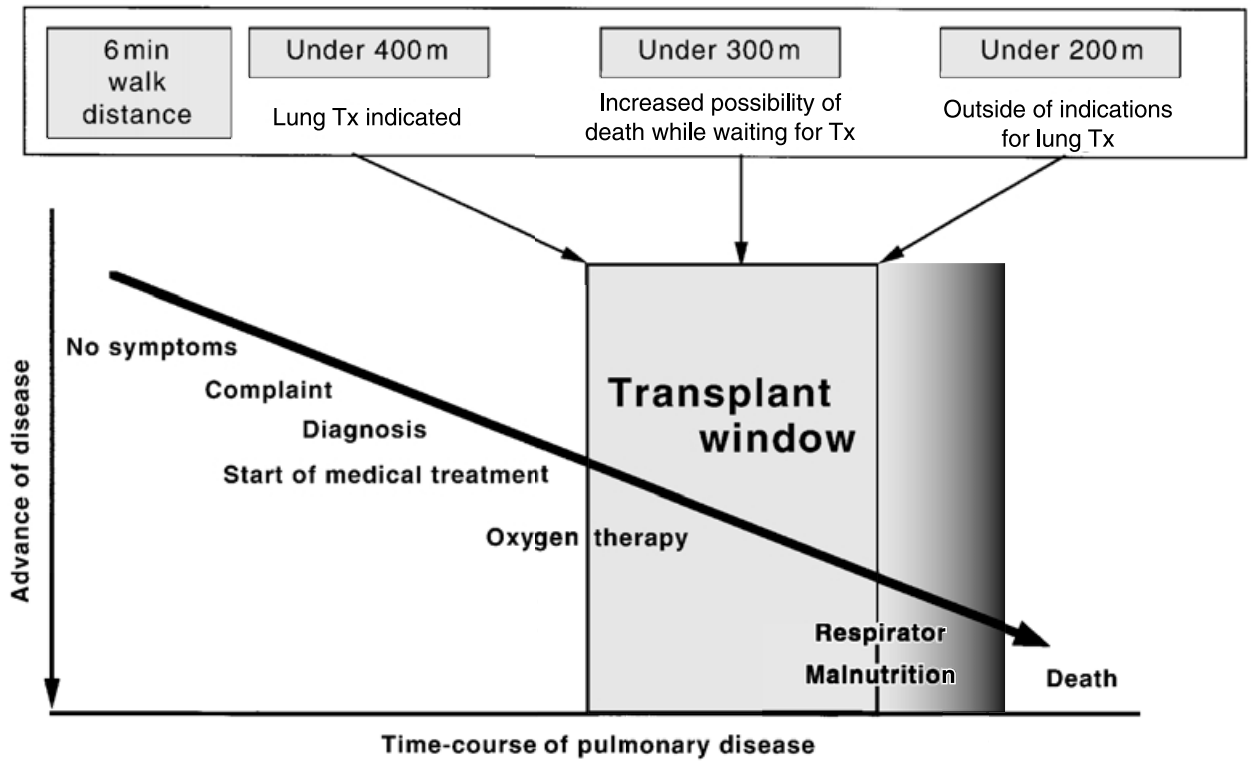

Fig. 2 Transplant (Tx) window and 6 min walk distance. In Japan, the transplant window is thought to be more to the right side than its correct position, as indicated in this figure.

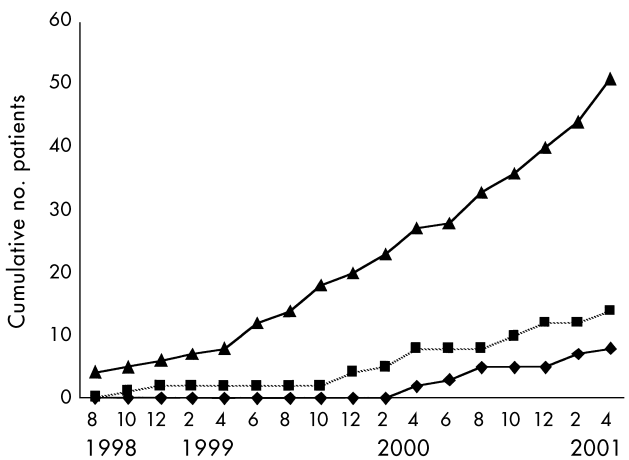

Fig. 3 Proliferation of lung transplant candidates on the Japan Organ Transplant Network (JOTNW) waiting list ($n = 51$). (▲), number of patients on the waiting list ($n = 51$); (■), number of deaths ($n = 14$; 27%); (◆), number of lung transplants ($n = 8$; 16%).

Lung transplantation from BDCD

The first LTx from BDCD were performed at Osaka University and Tohoku University as left and right two single LTx from the same donor on March 2000.[9,10] Six LTx from BDCD have been performed in Japan (Table 3). The types of procedure include single LTx in five cases and bilateral LTx in one case; the primary diseases are LAM in three cases, IPF/IIP in two cases and PPH in one case. All patients who have received LTx are alive and well and several recipients have already returned to an active life without oxygen therapy.

Brain dead and living donors

It is estimated that approximately 7000 brain deaths occur every year in Japan;however, only less than 10 cases a year will be available for LTx based on our experience to date. The donation may be quite limited, because the JBDA for organ transplantation requires a written will for a person to donate his/her organs, which is estimated only 10% of the population have. A donor card campaign and education about organ transplantation

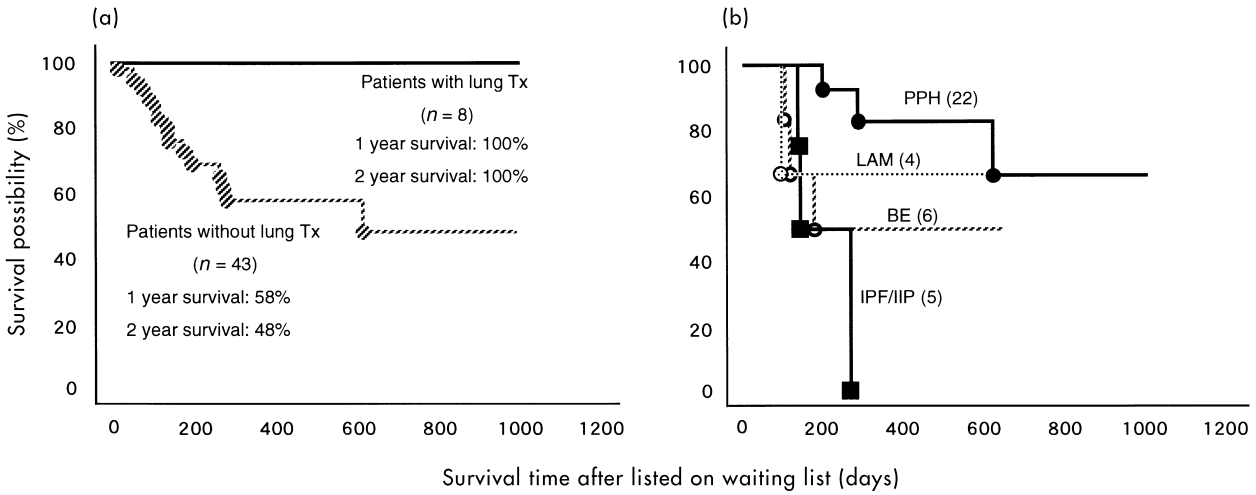

Fig. 4 Survival possibility for lung transplant candidates. (a) Survival with or without lung transplantation ($n = 51$). The survival of eight patients who received lung transplantation (Tx) was significantly better than that of the remaining 43 patients who did not receive lung Tx. (b) Survival without lung Tx of major indications ($n = 37$). PPH, primary pulmonary hypertension; IPF/IIP, idiopathic pulmonary fibrosis/interstitial pneumonia; LAM, lymphangioleiomyomatosis; BE, bronchiectasis. Survivals vary according to primary diseases. The 1 year survival for patients with PPH is over 80%; in contrast, all patients with IPF/IIP without lung transplantation died within 1 year.

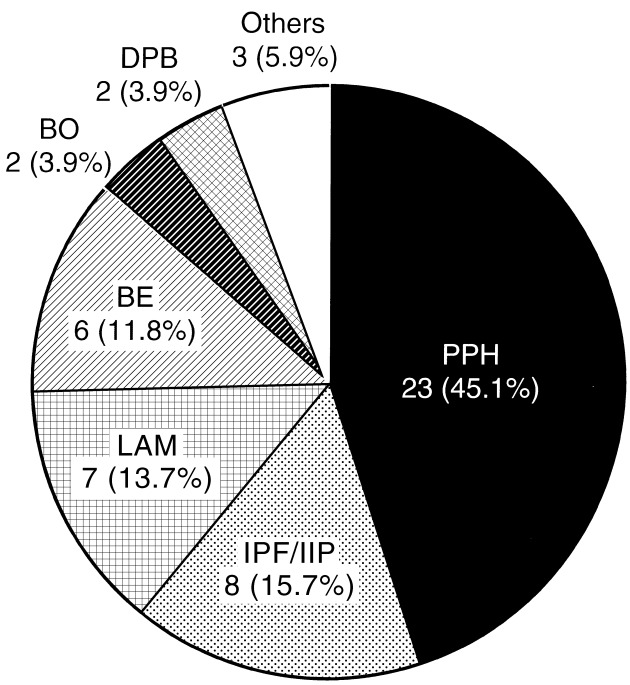

Fig. 5 Composition of pulmonary diseases of lung transplant candidates in Japan ($n = 51$). DPB, diffuse panbronchiolitis; BO, bronchiolitis obliterans; BE, bronchiectasis; PPH, primary pulmonary hypertension; IPF/IIP, idiopathic pulmonary fibrosis/interstitial pneumonia; LAM, lymphangioleiomyomatosis.

are quite necessary to increase the number of donors. The lung is very susceptible to damage in the process of drain death and during management with a ventilator. Lung edema, aspiration and pneumonia disturb the utilization of lung allografts. The utilization of BDCD for LTx is generally lower than for kidney, liver and heart allografts. The average BDCD utilization for LTx is only 10–20%.[11] Utilization of lungs in the US was 13% according to the United Network for Organ Sharing (UNOS) 1998 report (http://www.unos.org; Fig. 6). Because organ shortages are serious in Western countries, the criteria for lung donors have been relaxed to expand donor pools.[4,12–14] At present, the upper age limit has been extended to 65 years. Unilateral chest shadow on chest X-ray films, a small amount of purulent airway secretion and detection of bacteria from airway secretion of donors are no longer contraindications for LTx. These are called marginal donors. It was reported that number of lung donors increased 1.4–2.0-fold after utilization of marginal donors.[13,15–17] We have attempted to use marginal donors aggressively and could use lung grafts in five of 13 BDCD (36%) (Table 4).

Living-donor lobar transplantation

Living-donor lobar LTx (LDLTx) was introduced as an alternative method to expand donor pools. The first LDLTx

applied to an infant used one lobe in 1990.[18] Thereafter, double-lobar transplantation from two living was donors developed and applied to adult patients.[19–21] Because BDCD is not frequent in Japan, LDLTx is chosen as another option more frequently in Japan than in the US.

In Japan, after the first LDLTx at Okayama University in 1998,[22] eight LDLTx have been performed (Table 5). All LDLTx were double-lobar transplantation from two living donors and each donor provided a right or left lower lobe. Primary diseases of the recipients were BE in two

Table 3 Lung transplantation from brain-dead cadaver donors in Japan

Case no.	Date of Tx	Donor	Recipient	Method of LTx	Transplant center
1	29/3/2000	Female,* 20s (Tokyo)	Female, 30s, LAM	Single LTx (right)	Tohoku University
2	29/3/2000	Female,* 20s (Tokyo)	Female, 40s, IPF/IIP	Single LTx (left)	Osaka University
3	8/7/2000	Female, 10s (Fukuoka)	Female, 40s, LAM	Single LTx (left)	Tohoku University
4	8/1/2001	Male, 30s (Tokyo)	Male, 40s, IPF/IIP	Single LTx (right)	Tohoku University
5	21/1/2001	Female, 50s (Kanagawa)	Female, 30s, LAM	Single LTX (left)	Osaka University
6	19/3/2001	Male, 20s (Nara)	Male, 20s, PPH	Bilateral LTx	Osaka University

*Case 1 and 2 were transplanted with a right or left lung graft from the same donor.

Tx, transplant; LTx, lung transplant; LAM, lymphangioleiomyomatosis; IPF/IIP, idiopathic pulmonary fibrosis/interstitial pneumonia, PPH, primary pulmonary hypertension.

Table 4 Organ transplantation from brain-dead cadaver donors in Japan ($n = 13$) from October 1997 to April 2001

Donated organ	No. utilized donors	No. transplanted organs	No. transplantations
Kidney	12	23	23
Liver	11	11	12*
Pancreas	3	3	3
Heart	10	10	10
Lung	5	7	6

*Including two cases of split liver transplantation from the same donor.

Table 5 Lung transplantation from living donors in Japan

Case no.	Date of Tx	Donor	Recipient	Transplant center
1	28/10/1998	Mother, 40s Sister, 20s	Female, 20s, BE	Okayaka University
2	12/1/2000	Brother, 20s Brother, 20s	Male, 30s, BE	Osaka University
3	10/5/2000	Mother, 50s Brother, 20s	Female, 20s, BO*	Okayaka University
4	25/7/2000	Father, 50s Mother, 50s	Female, 20s, IPF/IIP	Tohoku University
5	18/10/2000	Mother, 50s Brother, 20s	Female, 20s, LAM	Okayaka University
6	5/1/2001	Father, 50s Mother, 50s	Female, 10s, PPH	Okayaka University
7	28/2/2001	Husband, 30s Sister, 30s	Female, 30s, IPF/IIP	Okayaka University
8	27/3/2001	Father, 30s Mother, 30s	Male, 10s, BO**	Okayaka University

*Post-bone marrow transplantation (Tx); **due to Steven–Johnson syndrome.

LAM, lymphangioleiomyomatosis; IPF/IIP, idiopathic pulmonary fibrosis/interestitial pneumonia; PPH, primary pulmonary hypertension; BO, bronchiolitis obliteraus.

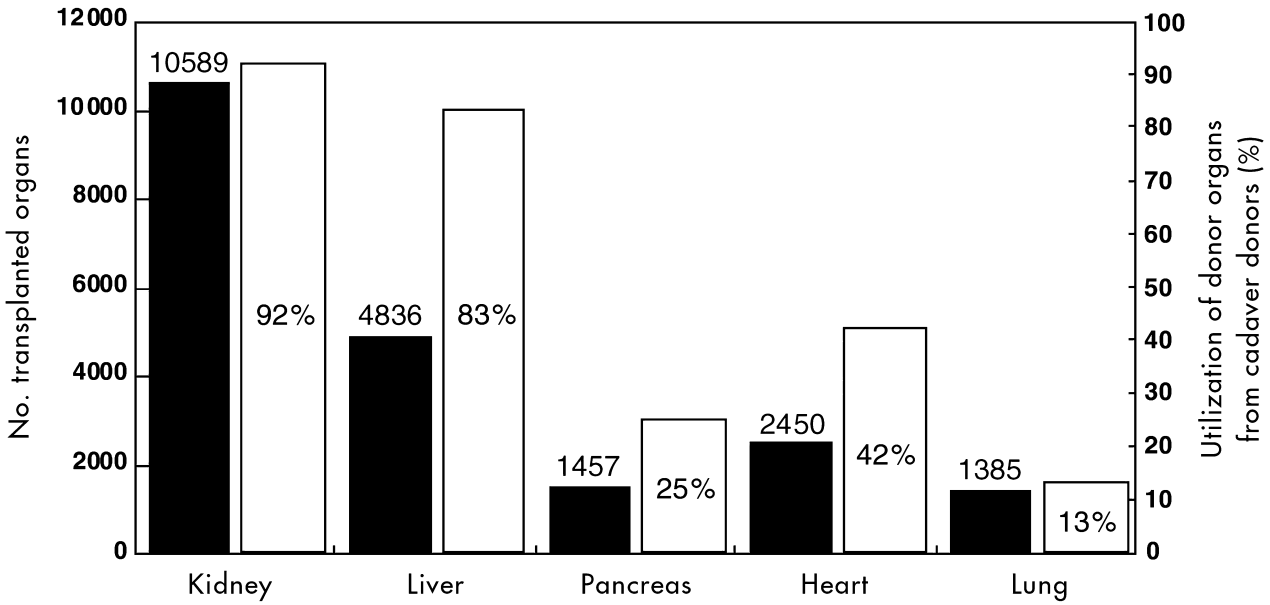

Fig. 6 Organ utilities of brain dead cadaver donors for transplantation in the US (from the United Network for Organ Sharing (UNOS) and Organ Procurement and Transplantation Network (OPTN) 1998 report; http://www.unos.org). (■), number of donors of each organ; (□), number of organs utilized.

cases, bronchiolitis obliterans in two cases, IPF/IIP in two cases, LAM in one case and PPH in one case. All patients who received LDLTx are alive and well. Living-donor organ transplants have been mainstreams in renal and liver transplantation in Japan because of a severe donor shortage. The same trend may develop for LTx. However, the cumulative number of LDLTx is only less than hundreds in the world; at present, LDLTx is still a developing and experimental treatment for terminal respiratory disorders and the advantages and disadvantages of LDLTx should be carefully considered.[21,23–26] The benefits of LDLTx are: (i) scheduled and well-prepared operations; (ii) excellent donor assessment and condition; (iii) short graft ischemic time; and (iv) mild rejection compared with cadaver transplantation because of minor HLA mismatch between blood relatives. In contrast, the disadvantages and risks of LDLTx are: (i) surgical risks for two living donors; (ii) 10–20% loss of donor lung function; (iii) difficulty of the LDLTx operation compared with cadaver LTx; and (iv) a limit to the lung volume that can be donated. Universal guidelines for donors for LDLTx have not yet been established.[25,26] We have restricted living donors to family members, from 19 to 60 years of age, with compatible blood types. Transplant lung volume is the most important restrictive factor. Using our criteria, the estimated volume of donor lobes must be more than 50% predicted vital capacity of the recipient.

Prospects for LTx and problems to be solved

The beginning of LTx in Japan is more than 10 years behind the US; nevertheless, early excellent results were obtained, possibly because initial transplant centers were restricted to four well-prepared and advanced hospitals. After a successful beginning, acceptable intermediate results will be most important to establish LTx as a clinical option for end-stage lung diseases in the Japanese community. In order to achieve this, the establishment of a management system of far-distant transplant patients is essential. Prompt and precise communication between recipients, local hospitals and transplant centers can be maintained with telephone, fax and especially with the internet. Early detection and measures against chronic rejection are keys for long survival and for maintaining good allograft function. In addition, Japanese health insurance shall cover LTx and immunosuppressive drugs as early as possible. Many patients cannot be considered as candidates for economic reasons. Lung transplantation for children is also a subject to be considered,

because, at present, only living related LTx is a possible transplant option for children in Japan. Utilization of BDCD under 15 years of age, split lobar transplantation from adult lung allograft and down-sizing LTx must be considered in LTx for children and infants.[27–29]

Finally, expansion of the donor source is the most important and urgent problem. Clinical lung preservation longer than 8 h and clinical utilization of lung allografts from cardiac arrest donors will be acceptable goals in the near future. Both have been already established in animal experiments and clinical trials are underway.[30] Thereafter, xenotransplantation and/or artificial lungs will be appear on the horizon as the next goals to be solved in the 21st century.

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