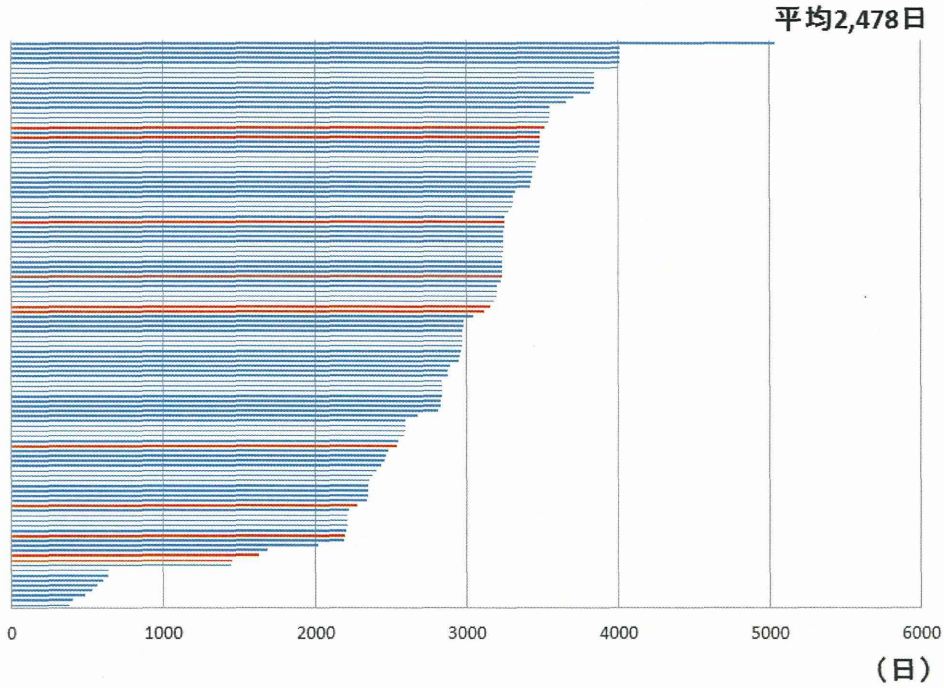


図 3. レシピエント候補者の待機期間

4．膵島移植成績（膵島移植臨床試験開始以前）

- 本邦では 2003 年に初めての臨床膵島分離が行われ、2004 年に初めて臨床膵島移植が実施されました。以降、2007 年 12 月までに 65 回の膵島分離が行われ、1 例の脳死ドナーを除く 64 回は心停止ドナーからの提供で、このうち 34 回が移植の条件を満たしていたため 18 症例（男性 5 例、女性 13 例）に対して膵島移植が行われました。膵島移植後の免疫抑制プロトコールは前述のエドモントン・プロトコールに準じて実施されました。エドモントン・プロトコールでは 1 症例に対し 3 回の移植を想定しているが、本邦では背景にあるドナー不足の影響で、18 例に対する移植回数は 1 回 8 名、2 回 4 名、3 回 6 名でした。これらの症例のうち、2 回移植の 1 例と 3 回移植の 2 例の計 3 症例で一時的にインスリン離脱を達成し、インスリン離脱の最長期間は 214 日間でした。本邦における膵島移植症例にエドモントン・プロトコールによる膵島移植の多施設共同研究における膵島生着の基準である、basal c-peptide level が 0.3 ng/ml 以上を当てはめると、初回移植後 1 年、2 年、5 年時における膵島生着率はそれぞれ 72.2%、44.4%、22.2%でした（図 4）。膵島生着率について海外の成績と比較するにあたっては、本邦での移植実施例は全て「Uncontrolled」心停止ドナーからの提供であること、本邦では移植を受けた 18 人のうち 3 回移植を受けられたレシピエントは 6 名に過ぎず、移植から次の移植までの期間が長い（0－954 日、平均 242 日）こと、などの背景を考慮する必要があると考えられます。

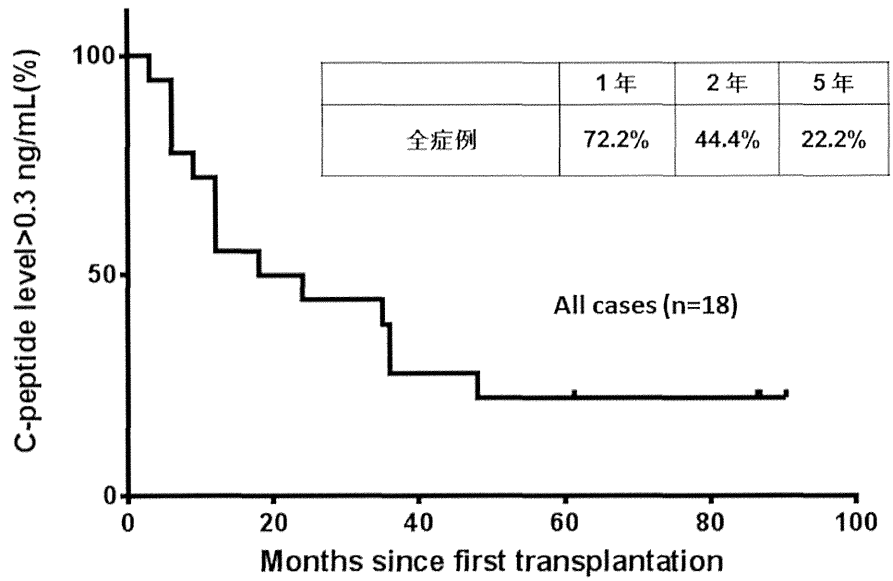


図 4. 膵島移植後生着率（200 年までの実施症例）

- 尚、膵島移植は、ドナーから膵提供を受けても、全例移植が実施できるわけではありません。実施するにあたっては、分離した膵島を移植に供するか否かについての一定の基準を満たす必要があります。膵島分離後にレシピエント体重当たり 5,000 IEQ/kg 以上の収量があり、純度 30%以上、組織量 10ml 未満、viability 70 %以上、エンドトキシン 5IU/kg 未満、グラム染色陰性などの基準を膵島分離の結果が満たした場合に膵島移植が行われます。

5. 膵島移植臨床試験

- これまでの膵島移植のプロトコールでは、移植膵島の長期生着が困難であるという点が今後の一般医療化に向けての問題であると認識されました。海外では、Anti-thymocyte globulin、抗 TNFα 抗体（Etanercept）による導入療法に続いて、低容量 tacrolimus、sirolimus またはミコフェノール酸モフェチルを用いた維持療法を行う方法により、膵島移植の長期成績が改善しております。本邦でもこのプロトコールを踏襲し、多施設共同での第Ⅱ相臨床試験の実施体制が整えられました。このプロトコールは、膵島に対する自己免疫反応の抑制、拒絶反応の予防、移植直後におけるカルシニューリン阻害剤の減量、制御性 T 細胞の誘導、移植膵島に対する非特異的免疫反応の抑制などにより、移植膵島の生着率を向上させることを目的としています。臨床試験推進拠点（東北大学病院臨床試験推進センターおよび先進医療振興財団）の支援を得て質の高い臨床試験体制が整備されています。
- 膵島移植は、これまで主に心停止ドナーを対象としていましたが、改正臓器移植法施行後脳死ドナー増加と心停止ドナー減少の傾向が認められています。そのため、膵臓移植には適さないとされた脳死下提供膵を膵島移植に利用する体制の構築が必要とされ、「脳死ドナーからの膵島移植」も先進医療の枠組みで実施出来るよう厚生労働省へ申請し、2013 年 3 月に「脳死ドナーからの膵島移植」が先進医療 B として承認され、同年 4 月から運用されています。

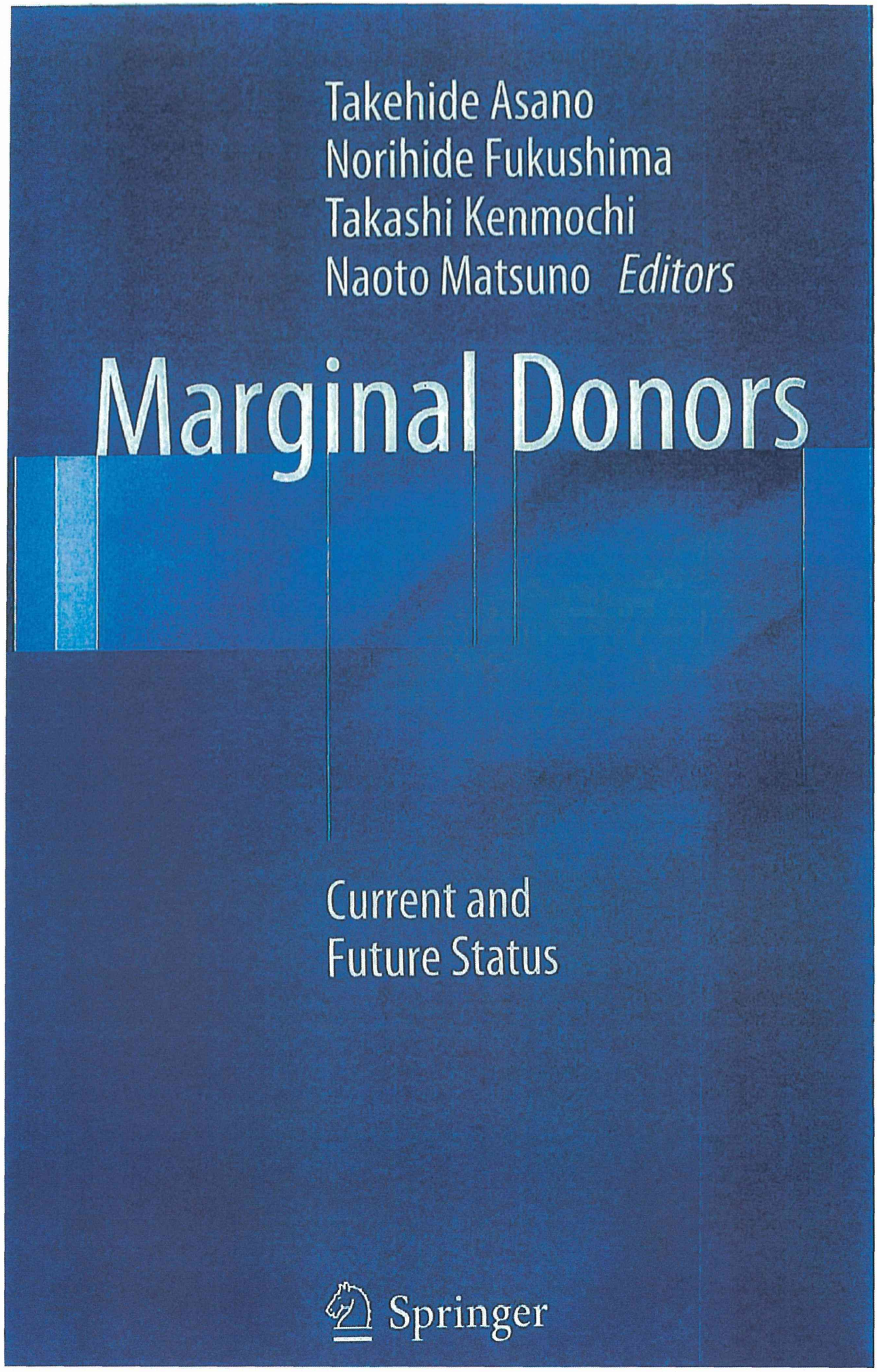
６．費　用

- 膵島移植を臨床試験として実施する場合は先進医療 B として実施され、保険適用として国が負担する部分と適用されない部分を患者さん負担で行う医療になります。現在、先進医療部分である膵島移植に関する費用は原則として、私費あるいは施設負担で実施しています。詳細は実施施設によって異なりますので、膵島移植を受ける病院の担当医師にお尋ね下さい。

７．その他

- 脳死ドナーからの膵島提供が可能となり、今後は膵島移植の成績をふまえた膵臓移植との臓器配分も重要な課題となっています。低侵襲で効果的な医療を望む１型糖尿病患者への新たな治療オプションの提示という意義に加え、提供臓器の有効利用によりドナーの意思をより活かす上でも膵島移植は重要な役割を有しています。今後も、様々な問題点が解決され、早く一般的な医療としての確立されることが望まれます。

執筆　穴澤　貴行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Contents

Chapter 7
ECD for Lung Transplantation

Yasushi Hoshikawa, Yoshinori Okada, Tatsuaki Watanabe, and Takashi Kondo

7.1 Introduction

The short supply of donor organs has been one of the most critical problems in the area of lung transplantation (LTx), and this is especially serious in Japan. One approach to attempt to address this limitation is the use of extended criteria donor (ECD) lungs. The currently accepted criteria for suitable donor lungs (Table 7.1) were instituted in the mid-1980s during the early development of clinical LTx [1]. These criteria were chosen by early transplant physicians and surgeons based on prevailing knowledge of pulmonary physiology, but were not based upon strict scientific evidence [2]. Afterward the ever-increasing number of recipients on waiting lists compelled lung transplant doctors to consider the use of ECD lungs. Liberalization of the donor selection criteria has been gradually accepted worldwide since the mid-1990s [2]. A recent large registry study of more than ten thousand LTxs performed in the USA from 1999 to 2008 revealed that at least one variance from the criteria occurred in more than a half of transplants [3]. Although results have varied among studies, outcomes of LTx using ECD lungs have generally been acceptable [4–18]. However, proper judgment is still difficult if multiple factors are defined extended and if ECD lungs are used in high-risk recipients especially who are rapidly deteriorating on the waiting list. To properly assess and optimize ECD lungs in such circumstances, a new strategy utilizing normothermic ex vivo lung perfusion (EVLP) system has been developed, and the impact of the system on LTx has been explored in several high-flow transplant centers [19, 20].

In Japan, 124 LTxs from deceased donors have been successfully performed as of the end of 2012 [21]. These transplantations achieved a 5-year patient survival rate of 72.0 % and a 10-year survival of 57.3 % [21]. To maximize the lung

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Table 7.1 Current donor lung guidelines

Age <55 years
ABO compatibility
Clear chest radiograph
PaO_2 >300 torr on FiO_2 = 1.0, PEEP 5 cm H_2O
Smoking history <20 pack-years
Absence of chest trauma
No evidence of aspiration/sepsis
No prior cardiothoracic surgery
No organisms on endotracheal aspirate gram stain
No purulent secretions on bronchoscopy

PaO_2 arterial difference in partial pressure of oxygen, FiO_2 fraction of inspired oxygen, *PEEP* positive end-expiratory pressure. Adapted from [23]

utilization rate in multiorgan donors, Japan Organ Transplant Network has operated a system involving the partnership of well-trained transplant consultant doctors and local doctors in assessing donor lungs and providing intensive care to donors since 2002 [22]. These consultant doctors tirelessly performed bronchial toileting for donors and provided advice on respiratory therapy, mechanical ventilation, infection controls, and circulatory management of donors. Since such sustained efforts by the consultant doctors in cooperation with local doctors have been made to effectively utilize ECD lungs, the lungs were used for transplantation in more than 60 % of brain-dead donors [22].

This chapter reviews definition and assessment methods of ECD lungs, studies showing outcomes of LTx using ECDs, and progress in recent research regarding ECD lungs.

7.2 Definition

The extended donor criteria are defined according to the standard criteria [23], which are as follows: age <55 years, ABO compatibility, clear chest radiograph, arterial difference in partial pressure of oxygen (PaO_2) >300 mmHg at 100 % fraction of inspired oxygen (FiO_2) and positive end-expiratory pressure (PEEP) of 5 cm H_2O, a cumulative smoking history of <20 pack-years, absence of chest trauma, no evidence of aspiration/sepsis, no prior cardiothoracic surgery, no organisms on endotracheal aspirate gram stain, and no purulent secretions on bronchoscopy (Table 7.1).

7.3 Viability Assay

To assess the viability of donor lungs, all donor criteria listed on Table 7.1 must be carefully evaluated. The most difficult judgment decisions pertain to the chest radiograph, the bronchoscopic findings, and the intraoperative assessment of the

donor lung by means of hands-on inspection and palpation [24]. These assessments cannot be performed in quantitative form and critically depend on the experience of the retrieval surgeon. We believe that the donor bronchoscopic examination is of most importance and that the findings of copious purulent secretions, which cannot be suctioned clear, and of edematous and/or reddened bronchial mucosa coincident with chest radiograph infiltrates indicating pneumonia represent strong contraindications to the use of that lung. In Japan, a transplant consultant doctors sent from one of seven lung transplant centers assesses bronchoscopic findings and chest radiograph infiltrates at several time points to evaluate if the ECD recovers from pneumonia after suitable management.

In addition to the careful evaluation of all donor criteria, consideration must also be given to the recipient's underlying disease and the severity of illness when using an ECD lung [6]. Usually, care is taken not to place organs from truly extended donors into high-risk recipients especially with pulmonary hypertension or pulmonary fibrosis with secondary pulmonary hypertension, or into other complex cases [24].

Normothermic EVLP is currently being explored to evaluate the viability of ECD lungs. This system allows the lungs after procurement to be perfused under normothermic conditions for approximately 4 h so that the lungs can be optimized as well as continually reassessed. Steen et al. were the first to create a successful EVLP evaluation system for donating after cardiac death [19] by means of Steen solution, a hyperoncotic fluid with 15 % hematocrit [25]. Cypel et al. applied this system to the clinical trial where they evaluated early post-LTx outcomes of ECD lungs which were physiologically stable during 4 h of normothermic EVLP and compared them with those of the conventionally selected lungs [20]. ECD lungs were defined by specific criteria, including pulmonary edema and a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2) less than 300 mmHg. Twenty out of 26 ECD lungs were transplanted after EVLP and demonstrated comparable incidence of primary graft dysfunction (PGD), 30-day mortality, bronchial complications, duration of mechanical ventilation, and length of stay in intensive care unit (ICU) and hospital, to 116 conventionally selected lungs. However, the clinical use of normothermic EVLP system for assessing ECD lungs has not yet been spread worldwide since Steen solution is not yet approved by the Food and Drug Administration (FDA) for use in the USA and also has not been approved for use based on pharmaceutical affairs law in most countries including Japan as of the end of 2012.

The use of biomarkers in bronchoalveolar lavage (BAL) fluids also has been explored to assess the viability of ECD lungs. Fisher and associates found that high IL-8 levels in the donor BAL were associated with poor outcomes after LTx, especially with development of severe PGD and with early recipient mortality [26]. Similarly, Kaneda and associates found that IL-6, IL-8, TNF-α, and IL-1β were risk factors for 30-day mortality, while IL-10 and IFN-γ were protective [27]. However, none of such biomarkers have yet been generally utilized in clinical transplantation.

7.4 Outcomes

First, several studies demonstrating the effects of the clinical use of ECDs in LTx are listed in chronological order. Kron et al. reported the efficacy of the use of 10 ECDs in LTx performed at a single center in the USA to expand the donor pool in 1993 [4]. It was the first report showing the possibility to utilize ECD lungs without an increased risk of mortality. Sundaresan et al. reported the first retrospective study comparing 44 ECDs and 89 standard donors (SDs) [5]. No differences were found between recipients of the lungs from ECDs and SDs with respect to duration of postoperative mechanical ventilation, gas exchange, and 30-day mortality. However, cardiopulmonary bypass was required more often in the ECDs than in the SDs. Gabbay et al. published their experiences in Australia with 64 ECDs and 48 SDs [2], showing no significant differences in length of ICU stay, postoperative gas exchange, 30-day mortality, and 1-, 2-, and 3-year survival between recipients of the lungs from ECDs and SDs. They found graft ischemic time was predictive of recipient gas exchange after transplantation. Bhorade et al. performed the retrospective evaluation comparing patients receiving the lungs from 52 ECDs and 61 SDs at a single center in the USA [6]. To define ECDs, the authors were the first to use following criteria: donor ventilator time >5 days and donor use of inhaled drugs (cocaine or marijuana) in addition to the previously accepted standard criteria, such as donor age, tobacco history, and abnormal chest radiograph. There were no differences in operative and early-term complications and hospital survival. Moreover, this is the first report to suggest that no alteration in lung function or 1-year survival occurs with the use of ECDs. Since the authors observed a trend toward slightly decreased pulmonary function at 1 year in single-ECD-lung recipients, they advocated to be cautious against the use of single lungs from ECDs. Pierre et al. reported the retrospective review of 128 consecutive lung or heart-lung transplants performed in Toronto comparing 63 ECDs and 65SDs [24]. This is the first to find a higher early mortality at both 30 (17.5 vs. 6.2 %, $p=0.047$) and 90 days (22.2 % vs. 7.7 %, $p=0.0391$) after transplantation using ECDs. The authors warned against using ECDs in higher-risk recipients, especially ones with pulmonary hypertension (PH), pulmonary fibrosis with PH, and cystic fibrosis with *Burkholderia cepacia* colonization. Oto et al. retrospectively reviewed 173 heart-lung and bilateral single-lung transplant recipients of whom 77 were ever smokers and 64 out of those were current smokers [7]. The authors found more than 20 pack-years was associated with impaired early oxygenation and longer ventilation time and ICU stay, but no differences in 3-year survival and incidence of death due to bronchiolitis obliterans syndrome (BOS) which is one of the major factors affecting long-term survival after LTx. Thabut et al. investigated the effect of donor characteristics on short- and long-term outcomes of a total of 785 adult patients undergoing LTx at seven centers in France [8]. The authors found donor gas exchange before harvest was significantly associated with recipient early gas exchange, duration of mechanical ventilation, and long-term survival. A nonlinear model showed a steep increase in the relative risk of death when donor PaO_2/FiO_2 before harvest was below 350 (hazard ratio 1.43; 95 % confidence interval 1.10–1.85; $p=0.01$). Lardinois et al. evaluated an

impact of ECDs, especially low PaO_2 (<250 torr) before harvesting and multiple extended criteria, on early outcomes and medium-term survival of 148 consecutive recipients at a single center in Switzerland [9]. The authors did not find any difference in early and intermediate results when they analyzed survival among the number of extended criteria. Moreover, this is the first report showing that the use of ECD lungs with a PaO_2 <250 mmHg in selected cases is not associated with an unfavorable outcome. However, the authors cautioned against the use of ECD lungs with an association of PaO_2 <300 mmHg and purulent secretions. Aigner et al. retrospectively analyzed 98 consecutive lung transplantations performed at a single center in Austria during a 2-year period of time with the lungs from 26 ECDs and 72 SDs [10]. The analysis of major outcomes in the short and the medium term did not show any differences between ECDs and SDs. Kawut et al. performed a retrospective cohort study of 51 patients undergoing LTx at a single center in the USA for 2 years [11]. This study included comprehensive data reflecting the condition of the recipient at the time of transplantation. Significant differences between recipients of 27 ECD and 24 SD lungs in several primary endpoints were shown. Recipients of ECD lungs had fewer ICU-free days, a longer time to hospital discharge, and lower spirometry at 1 year than did SD lung recipients. Donor age 55 years or older and smoking were associated with fewer ICU-free days than younger donors and nonsmokers, respectively. No differences were observed in 30-day and longer-term survival between ECDs and SDs. Luckraz et al. analyzed 362 double-lung and heart-lung transplantations performed at a single center in the UK from 50 donors with low levels of PaO_2 (<300 mmHg) and 312 donors with normal PaO_2 [12]. They observed, in the low PaO_2 group, a compromised 30-day mortality rate (22 % vs. 13 %, odds ratio = 1.92) and comparable 1- and 5-year survival when compared with the normal PaO_2 group. Botha et al. retrospectively reviewed 201 patients undergoing lung or heart-lung transplantation at a single center in the UK of whom 83 received ECD lungs [13]. Recipients of ECD lungs had a higher incidence of severe PGD (43.9 % vs. 27.4 %) and 90-day organ-specific (respiratory failure or multiorgan failure with severe PGD) mortality (15.7 % vs. 5.1 %) when compared with recipients of SD lungs. They found significantly high 30-day mortality (17 %) with ECD lungs for bilateral lung transplantation with the use of cardiopulmonary bypass. Moreover, the authors advocated current heavy smoking as a risk factor for impaired oxygenation and longer ICU stay after transplantation. De Perrot et al. compared the outcome of 60 LTxs of the lungs from donors aged 60 years or more with 407 LTxs of the lungs from younger donors, all of which were performed at a single center in Toronto for 11 years [14]. The authors found the increased age is associated with borderline risk for increased 10-year mortality (39 % vs. 16 % in the younger donor group, $p = 0.07$) and increased risk of BOS (65 % vs. 34 % in the younger donor group, $p = 0.01$). Meers et al. analyzed 50 LTxs with the lungs from 27 ECDs and 23 SDs performed at a single center in Belgium and observed a negative impact of ECDs in terms of ICU stay and the PGD rate [15]. The study of Berman et al. [16] was based on smoking donors (n = 184) and their impact on LTx performed at a single center in the UK. Over a period of 13 years, 454 patients were included. The authors found a significant association between smoking history and

lower 3-month survival (21 % vs. 13 % in the nonsmoking donor group, $n=240$, odds ratio 1.9, $p=0.04$) and also ICU stay for >2 days. No differences were observed in long-term survival and infection between recipients of the lungs from smoking and nonsmoking donors. Reyes et al. utilized multivariable survival methods to determine several donor factors, adjusted for recipient risk factors on 10,333 LTxs performed during a 10-year period of time in the USA [3]. Increasing number of variances was not associated with worse survival after LTx. Of donor guideline variables, a smoking history of greater than 20 pack-years appeared to be a small but statistically significant risk factor for mortality. Mortality did not significantly increase despite the use of donor lungs with an abnormal chest radiograph, age greater than 55 years, or a lower donor PaO_2 (as low as 230 mmHg). Recently, Zafar et al. retrospectively analyzed 12,045 LTxs performed over a 9-year period of time to assess the effect of donor PaO_2 at the time of procurement on graft survival [17]. Kaplan-Meier survival analysis on LTxs from 12,045 donors who had a PaO_2 of greater than 300 mmHg ($n=9,593$), of 201 to 300 ($n=582$), and of less than 200 ($n=1,830$) showed no difference in graft survival, irrespective of whether recipients had a single or double LTx. A Cox multivariable analysis of 21 donor characteristics also demonstrated that donor PaO_2 had no association with graft survival [17]. The study limitation is they did not look at the short-term or the acute events, such as development of PGD, sepsis, and 30-day mortality in these patients. Recently, Bonser et al. [18] retrospectively analyzed 1,295 LTxs performed during a 12-year period of time in the UK to assess the impact of donor smoking history on recipient early outcomes and survival. In this study, the authors estimated the effects of non-acceptance of the lungs from donors with positive smoking histories. This study showed increased 3-year mortality after adjustment for other independent factors such as recipient's age, cytomegalovirus mismatch, and increasing ischemic time (67.2 % vs. 55.7 %, $p=0.0002$, adjusted hazard ratio 1.36, 1.11–1.67) and an increased incidence of BOS associated with 510 smoking donors compared with 712 nonsmoking donors. Furthermore, recipients of the lungs from smoking donors were likely to spend longer in ICU and hospital and could derive less functional benefit from transplantation than recipients of the lungs from donors with negative smoking histories. The stratified Cox regression model revealed recipients receiving the lungs from donors with positive smoking histories had a significantly lower unadjusted hazard of death after registration than did those remaining on the list for a potential transplant from a donor with negative smoking history (HR 0.79, 95 % CI 0.70–0.91; $p=0.0004$).

In summary, although results have varied, outcomes of LTx using ECD lungs have generally been acceptable. Next, considerations regarding each extended criteria (age, P/F ratio, and smoking history) are listed below.

7.4.1 Age

Although the current guidelines for upper age limit suggest 55 years as maximum age, small-size studies with some dozens of donors have not shown a survival

disadvantage with the use of older donors [11, 28, 29]. A larger study with hundreds of LTxs has shown that increased age (of 60 years or more) is associated with borderline risk for increased 5-year mortality, increased 10-year mortality, and increased risk of BOS [14]. A recent larger registry study with more than ten thousand LTxs has demonstrated no significant increase in mortality despite the use of donor lungs with an age greater than 55 years [3].

7.4.2 Low Ratio of Pulmonary Arterial Oxygen to Fraction of Inspired Oxygen (P/F Ratio)

Although small studies demonstrated an impact with the use of donors presenting low P/F ratio on 30-day mortality (P/F ratio <300) [12] and long-term mortality (P/F ratio <350) [8], recent larger registry studies have shown no significant increase in long-term mortality despite the use of donor lungs with a lower P/F ratio [3, 17]. In the future more and more centers will utilize EVLP to assess the viability of borderline grafts with P/F ratio of 300 mmHg or lower.

7.4.3 Smoking History

Although no study has evaluated the number of pack-years of smoking history that would preclude the lungs from being transplanted, a retrospective study by Oto et al. showed more than 20 pack-years was associated with impaired early oxygenation and longer ventilation time and ICU stay, but no differences in 3-year survival and incidence of death due to BOS [7]. The study of Berman demonstrated a significant association between smoking history and lower 3-month survival and longer ICU stay, but no differences in long-term survival and infection [16]. Recent larger studies have shown increased long-term mortality (3, 18) and an increased incidence of BOS associated with smoking donors. It is of interest that a study by Bonser revealed recipients receiving the lungs from donors with positive smoking histories had a significantly lower hazard of death after registration than did those remaining on the list for a potential transplant from a donor with negative smoking history [18].

7.5 Research

Recently, approaches for an effective reconditioning of ECD lungs by means of EVLP system have been explored. Several studies have demonstrated a high incidence of thrombi in donor lungs which cause rejection of the lungs for LTx or PGD after LTx [30–33]. Motoyama et al. reported the effect of the fibrinolytic agent plasmin administered in an EVLP model of cardiac arrest rats on pulmonary vascular resistance,

dynamic compliance, and lung weight gain [34]. Plasmin administration dissolved thrombi in the rat lungs, resulting in reconditioning of the lungs as assessed by significantly decreased pulmonary vascular resistance, stable dynamic compliance, and less lung weight gain when compared with non-plasmin rats.

Although cold flush and static cold storage is the accepted standard for preservation of donor lungs in clinical transplantation, deterioration of the donated lungs still occurs. Usually, the longer the lung is kept cold and ischemic, the greater the extent of injury. To minimize this cold ischemia injury and to assess and improve ECD lungs, organ care system (OCS), a portable normothermic EVLP system, has been developed [35]. The OCS provides immediate and sustained lung recruitment starting at the donor site and substantially reduces cold ischemic time [35]. An international randomized trial is ongoing in which the impact of portable ex vivo perfusion and ventilation of donor lungs by means of the OCS on post-LTx outcomes as compared to current cold storage technique is evaluated. Interim results from this trial were presented at the International Society for Heart and Lung Transplantation (ISHLT) 33rd Annual Meeting in Montreal (http://www.transmedics.com/wt/page/pr_1366904571). The donor lungs preserved using the OCS had significantly lower incidence of severe PGD after LTx as compared to the lungs that were preserved using cold storage. In addition, other important clinical parameters like in-hospital mortality, six-month survival, rate of lung-related complications, time on mechanical ventilation, and ICU time were better in the OCS group as compared to cold storage.

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第 1 章

肺移植の概要

1 肺移植の歴史と海外の現状

a. 肺移植のスタートと惨憺たる草創期の成績

肺移植の臨床第1例目は，1963年に米国ミシシッピー大学のHardyらにより，治療抵抗性の重篤な肺炎によって呼吸不全に陥った58歳の男性に対し，左片肺移植を実施したものである．この患者は術後18日目に腎不全で死亡したものの，移植肺は期待通りに機能し，拒絶反応の徴候もなかったと報告された[1]．肺移植については，神経支配を失って反射機構を喪失した移植肺が正常に機能するものかどうかという点が初期には大きな問題であったが，動物実験やこの第1例目の経験によって，呼吸機能が保たれることが示され，肺移植にとって大きな一歩になったものといえる．

その後，1978年までの15年間に世界で38例の肺移植実施例の報告がみられるが，その予後はきわめて厳しく，1968年にDermonらが実施した右片肺移植の10ヵ月生存が最長という惨憺たるものであった(**図1**)．その死因やグラフト機能廃絶の原因としては，10例が術後早期の呼吸不全，11例が感染症，15例が拒絶反応，9例が気管支吻合部合併症であった．術後早期の呼吸不全は現在でいうところの虚血再灌流障害を主因とする移植肺機能不全に該当するものであろう．この結果から，

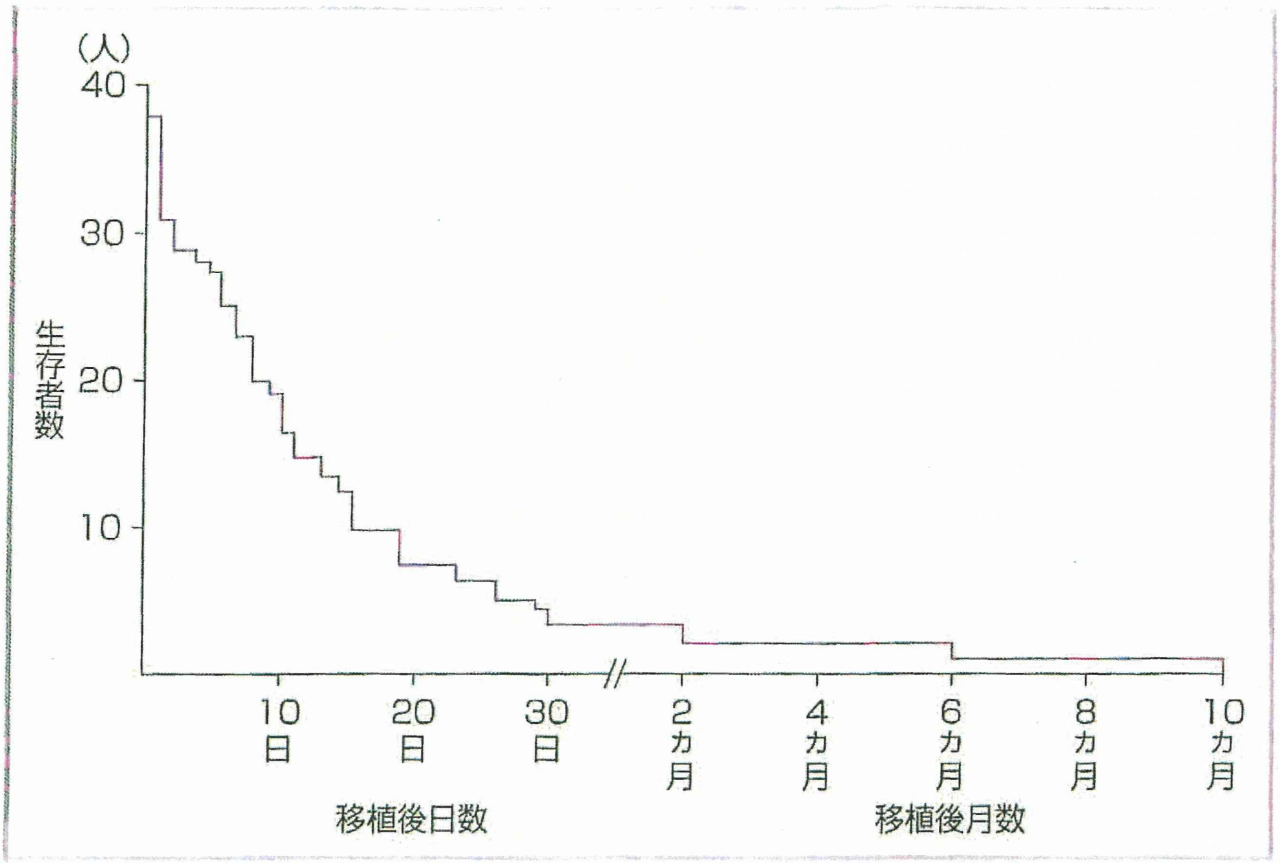

図1　肺移植最初の38例の予後

[藤村重文ほか：移植 15: 190-196, 1980 より引用]

感染症，拒絶反応，気管支吻合部合併症が解決すべき大きな問題点として浮かび上がってきたが，有効な打開策が見出せないまま，その後新しい免疫抑制薬が登場するまで一時期肺移植は実施されなくなった．

b. 新しい免疫抑制薬の登場で第2のスタートへ

1978年以降にCalneらによって腎臓，膵臓，肝臓移植へのシクロスポリンの臨床応用成功例が報告され[2, 3]，肺移植への導入の前にReitzらによって3例の心肺同時移植例が1982年に報告された[4]．3例中1例は4日目に死亡したものの，他の2例は1例が急性拒絶反応を乗り切り，もう1例は拒絶反応を認めず，それぞれ10ヵ月と8ヵ月良好な状態で生存しているというものである．肺移植へのシクロスポリンの導入はトロント大学のCooperらによってなされ，気管支吻合部合併症予防のための有茎大網弁による気管支吻合部被覆法の導入と相まって長期生存例を得ることが可能となった[5]．さらに1988年には両肺移植手技が

Patterson らによって報告されたが，当時気管支吻合は左右の気管支ではなく気管で行われており，また，肺静脈は左房での吻合，肺動脈は主幹部での吻合と，いわば心肺同時移植の心臓のみを省いた手技となっていた．気管での吻合では吻合部の血流不足による合併症の発生頻度が高かったため，必ず有茎大網による被覆が併施されていた[6]．しかし，その後の経験から，吻合は左右の気管支として有茎大網弁による吻合部被覆は原則実施せず，肺静脈は左右の左房カフ，肺動脈は左右の肺門主幹部での吻合，というように手技が変遷した．心肺同時移植においても，気管支の吻合が左右の主幹に変更されたが，手術手技，術後管理，免疫抑制などの進歩によるためか，昨今ではまた気管での吻合に吻合法を戻しているようで，その際，もはや有茎大網弁による吻合部の被覆は行っていないということである．

3. 先行する肺移植の国際登録

1981 年に国際心肺移植学会が設立され，この学会によるシクロスポリン導入以後の肺移植の国際登録がスタートした．以来，毎年年次報告をしているが，2013 年の年次報告では，2012 年 6 月までの世界各地の 177 実施施設からの 43,428 件の成人肺移植と 43 施設からの 1,875 件の小児肺移植の実施登録例について詳細な分析がなされている[7]．年間の成人肺移植実施数は毎年増加しており，2011 年は登録開始以来最多の 3,640 件が登録されたと報告されている．同学会のホームページ[8]で提供されている最新のデータでは，さらに登録数は増加していることが分かる（**図 2**）．術式別実施数から，1990 年代半ば以降の実施数の増加は両肺移植の実施数増加によるものであることも分かる．

成人例全例の移植後 50％生存期間は 5.6 年である．ただし，移植後 1 年を経過した例における 50％生存期間は 7.9 年であることから，移植後早期の成績の改善が全体の成績改善のための今後の重要な課題といえる．1 年生存率が 79％，5 年生存率が 53％，10 年生存率が 31％という移植成績にここ数年あまり大きな変化はない（**図 3**）[7]．

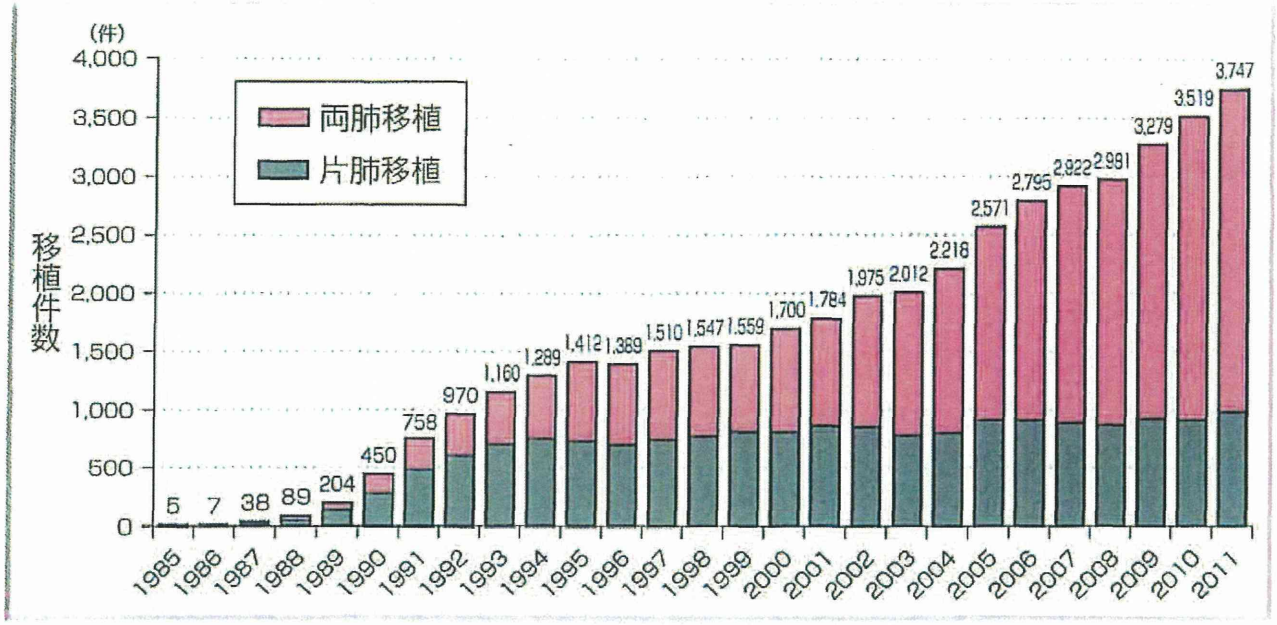

図 2　国際登録における世界の脳死肺移植実施数

［国際心肺移植学会（ISHLT）ホームページ．〈http://www.ishlt.org/〉（2014/6）より引用］

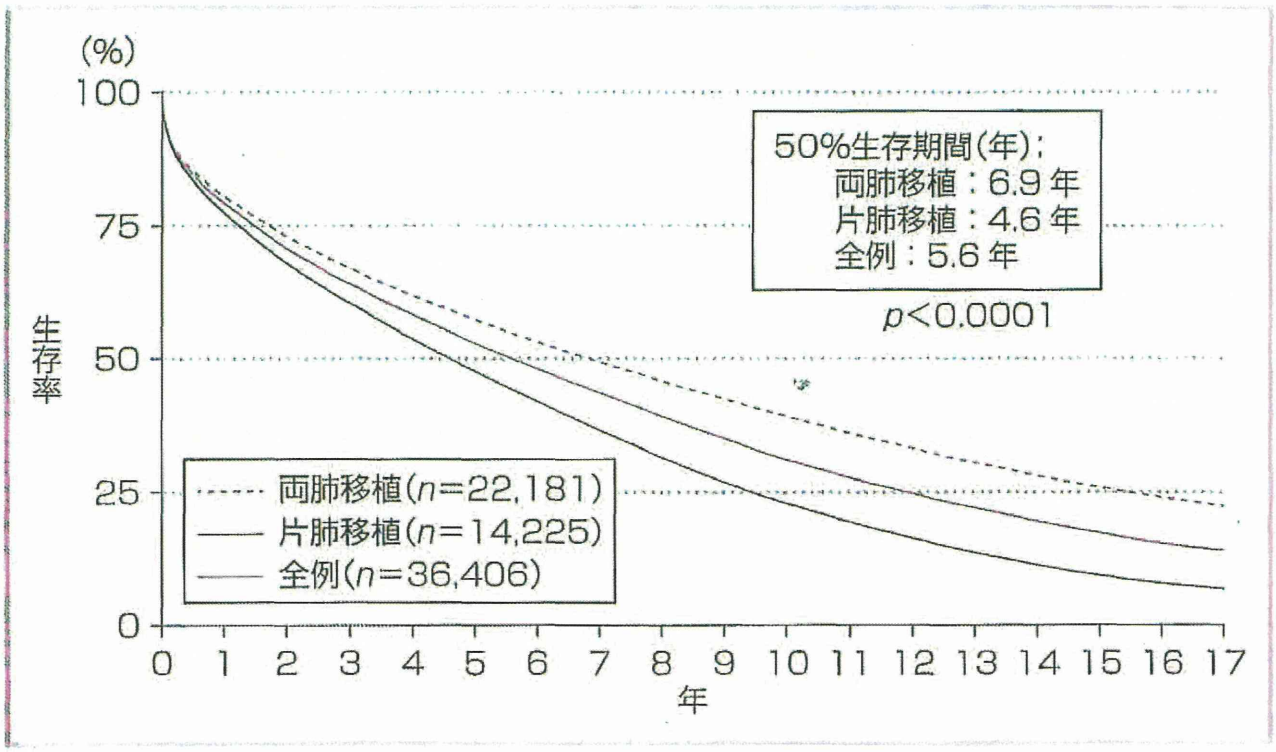

図 3　国際登録における世界の脳死肺移植実施成績

［Yusen RD, et al: J Heart Lung Transplant 32: 965-978, 2013 より引用］

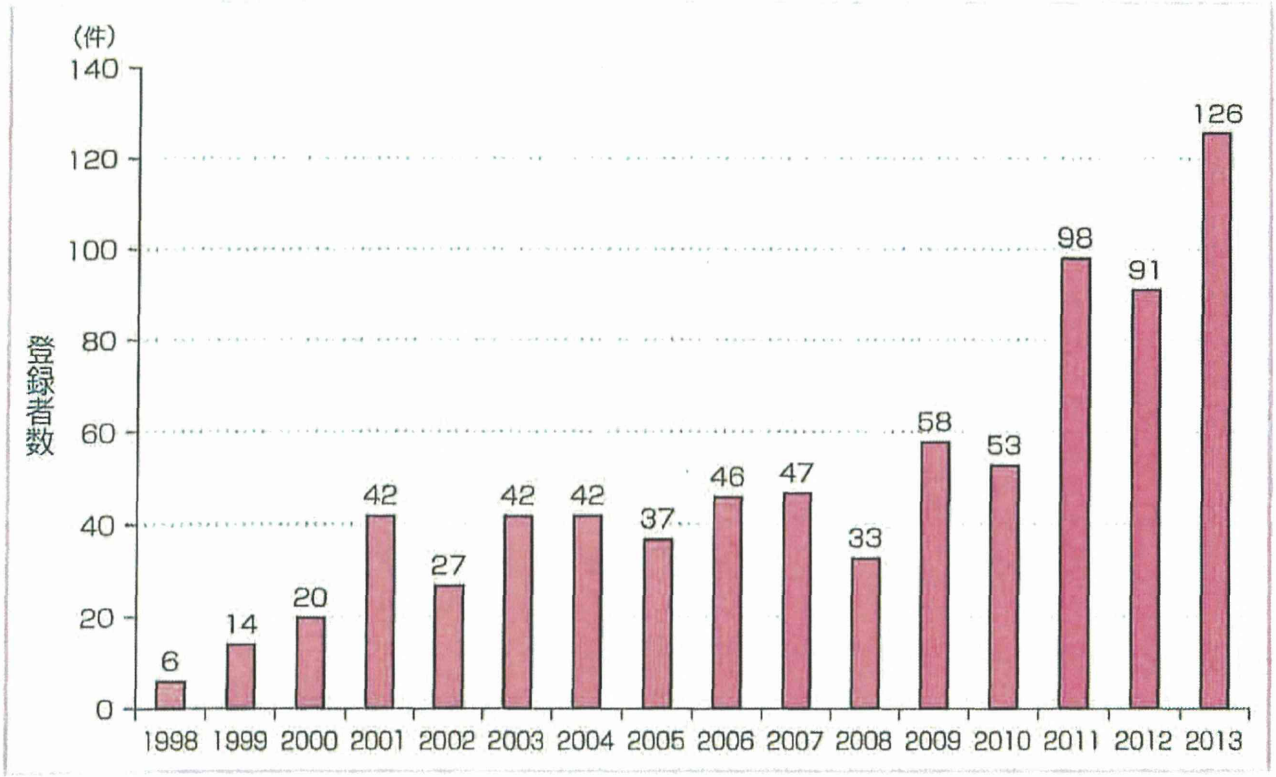

図4　わが国における脳死肺移植希望登録者数の年次推移

[日本肺および心肺移植研究会ホームページ：レジストリーレポート．〈http://www2.idac.tohoku.ac.jp/dep/surg/shinpai/pg185.html〉(2014/6) より引用]

3 日本の肺移植の現状と課題

a. わが国の肺移植のスタート

日本では，1998年4月に4つの肺移植実施施設が認定され，日本臓器移植ネットワークへのレシピエント候補者の登録が同年8月に開始された．以来年ごとに徐々に増加し，年間50～60人の登録者数となっていたが，2010年7月の改正臓器移植法の施行によって脳死肺移植実施数が急増すると登録希望者数も倍増し，2013年には年間120人を超えた（図4）[11]．

一方，脳死下での臓器提供は改正臓器移植法の施行までは年間平均7件程度ときわめて少なく，肺移植を希望して臓器移植ネットワークに登録をしても肺移植実施まで相当長期間の待機を強いられる現実があった．このため，日本では脳死肺移植よりも生体肺移植の実施が先行するということになり，肺移植実施第1例目は1998年10月に岡山大学病院