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Review

STATE OF THE ART OF LIVING DONOR LUNG TRANSPLANTATION

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Summary

Living donor (LD) lung transplantation (LT) is a potential alternative to cadaveric LT offering favorable results to both donors and recipients. This opportunity is most commonly offered to those patients having a limited survival expectancy on the cadaveric waiting list. LDLT was popularized in Japan over the last 20 years, while being less common in European and North American countries where cadaveric donation is more available.

Donor-to-recipient size matching is crucial for LDLT in order to provide the best fitting lobar or sub-lobar grafts. Functional size matching, based on forced vital capacity (FVC), and anatomical size matching, based on 3-dimensional computed tomography volumetry, are employed to ensure that the graft falls within the limits to allow a progressive adaptation to the recipient. Standard LD LT is a sequential, bilateral, lower lobe LT. In case of an undersized match, the two native upper lobes can be spared to decrease the potential residual dead space or a right-to-left inverted LD lobar LT can be performed. On the other hand, when the graft is oversized, coping strategies include delayed chest closure, single-lobe living transplant (LT), and bilateral middle lobe or segmental LT.

The results of LDLT, in terms of of recipient survival and peri-operative mortality, are comparable to those of patients receiving a cadaveric lung transplant. LDLT is also a well-tolerated procedure for donors, considering the importance of preserving donor safety and well-being, both from a functional and psychological standpoint.

In the near future LDLT may benefit from the adoption of minimally invasive or robotic surgery techniques to decrease the invasiveness of the procedure in lung donors. Also, in the future, a larger number of patients on the waiting lists could benefit from LDLT, such as those who could develop immunological tolerance from receiving a graft from an appropriately selected donor.

In summary, LDLT is becoming a widely accepted strategy to safely expand the donor pool providing patients on the waiting list with another chance to receive a viable organ.

Key words: living donor, lung transplant, lobar lung transplant

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INTRODUCTION

Lung transplantation (LT) is an established technique used to treat patients with end stage respiratory failure. In the past decades its use has grown consistently and its outcomes have become progressively more favourable [1].

However, due to scarcity of suitable donors, time on the waiting list remains a significant burden on patients [2], despite recent improvements in donor allocation and organ procurement. In this setting, living donor (LD) LT, since its first attempts [3], can be a valid option to increase the donor pool and provide patients who cannot wait for a cadaveric donor with viable organs for transplantation. Recent studies have highlighted the positive outcomes of LD LT in terms of survival [3] of the recipient and residual lung function of the donor [4]. Moreover, this technique has been proven to be an effective treatment for several pulmonary conditions, such as restrictive, obstructive, infectious, and vascular diseases [5]. This paper is meant to give a wide perspective on the state of the art of this technique and analyse its technical aspects, results and future perspective.

DONOR SELECTION AND DONOR-TO-RECIPIENT MATCHING

Preserving donor safety is the main aim of the process of living lung donor selection. Therefore, the eligibility criteria are universally strict. A living lung donor should be in excellent health, should have an appropriate pulmonary reserve, and should accept the risks of donation without coercion [6,7]. The assessment of vascular anatomy with 3-dimensional multidetector computed tomography angiography emerged as an important part of the process of donor evaluation, but no anatomical absolute contraindications to LD LT have been reported so far [8,9].

The match between a medically and psychologically suitable donor and the recipient involves immunological issues, primarily ABO blood type compatibility, and size matching [6].

Since lobar or sub-lobar grafts are used, size matching is crucial in LD LT. A pulmonary overflow in an undersized graft vascular bed may result in pulmonary arterial hypertension and lung edema [10]. Conversely, if the graft is excessively oversized, chest closure may cause an increase in airway resistance, atelectasis, and hemodynamic instability [11]. A transplantable graft should be neither too small for the body, nor too large for the chest cavity [12]. Functional size matching, based on forced vital capacity (FVC), allows for the identification of excessively undersized grafts, which may be an eventuality especially in the context of LD LT in adults. The graft FVC may be estimated from the donor's measured FVC and the number of segments to be implanted [13,14]. Undersized grafts can be accepted provided that their total FVC is more than 45% of the recipient's predicted FVC, or more than 50% in the presence of pulmonary hypertension. On the other hand, anatomical size matching, based on 3-dimensional computed tomography volumetry, may warn of an excessive size, particularly when the recipient is a small child. The upper threshold seems to be a graft volume to recipient's chest cavity volume ratio of around 200% [7,15]. If the size discrepancy falls within the above-mentioned limits, the graft is allowed to gradually adapt to the recipient's functional requirements and anatomy, overinflating or underinflating accordingly [16].

Depending on the recipient risk to benefit ratio, strategies to modify an adverse immunological situation, or to overcome inadequate size matching or difficult anatomy may be pursued. For example, an AB0-incompatible LD LT was recently performed by the Kyoto University group after desensitization therapy [17], and various technical approaches were adopted to face size mismatch or unfavorable arterial anatomy, as well [7].

SURGICAL STRATEGIES

LD LT was initially developed as single-lobe LT, with inconsistent outcomes [7,18,19]. The procedure was subsequently refined to become bilateral [20,21], with more satisfactory results[7]. Over time, further strategies have been introduced in order to optimize the donor-to-recipient matching, or to better cope with specific needs of the recipient.

In LD LT, the intraoperative use of mechanical circulatory support is systematic, for the purpose of controlled reperfusion of a lobar or sub-lobar graft. As in the setting of cadaveric LT, over the past decade, the traditional support with cardiopulmonary bypass has been largely replaced by veno-arterial extracorporeal membrane oxygenation, which appears to be associated with a reduced risk of bleeding and a lower proinflammatory potential [7,15,22].

Standard LD LT

Standard LD LT is a sequential, bilateral, lower lobe LT. Each native pneumonectomy is followed by the implantation of the ipsilateral lower lobe. Standard LD LT implies the availability of two lobar donors (LD), each contributing a right or a left lower lobe, respectively [7]. Importantly, each lower lobe must be adequately size matched.

Strategies to avert an excessively undersized graft-to-recipient match

When the total estimated graft FVC is less than 60% of the recipient's predicted FVC, but more than 40%, the native upper lobes, or segments of the upper lobes, may be spared. As a consequence, the intrathoracic dead space would be reduced, whereas the pulmonary vascular bed would be increased. Only if the recipient's lung is not infected may this technique be considered [3,7,15,23]. Despite an accurate patient selection, native upper lobe complications may occur, but favorable outcomes have been reported so far [24].

An alternative option may be represented by right-to-left inverted LD lobar LT. Since the right lower lobe is generally 20-25% larger than the left lower lobe, the donor right lower lobe, rotated 180° on its longitudinal axis, may be implanted in the recipient's left chest cavity instead of the donor left lower lobe [3,7,15,25]. The same strategy may be adopted when the anatomy of the donor interlobar pulmonary artery would make a left lower lobectomy technically demanding [3,7,15].
Importantly, these techniques may be combined to achieve the best possible size matching [3].

Strategies to avert an excessively oversized graft-to-recipient match

When standard LD LT is contraindicated due to an excessively oversized graft-to-recipient match, possible alternative strategies include delayed chest closure, single-lobe living transplant (LT), and bilateral middle lobe or segmental LT [3,7]. If even single-lobe LT resulted in an excessively oversized match, size-reduction and/or simultaneous contralateral pneumonectomy could be considered [3,7,25]. On the other hand, bilateral middle lobe LT involves the right-to-left inverted technique, and its feasibility depends on the presence of a single arterial, venous, and bronchial branch [3,25,26]. Finally, in bilateral segmental LT from two LD, either the right basal segment and the left lower lobe, or the right basal segment and the inverted right S6 segment may be used [3,26]. Bilateral segmental LT may also be performed from a single LD, whose left lower lobe may be split into its superior and basal segments, to be implanted in the recipient's left and right chest cavities, respectively, the latter after being rotated [27].

Single LD LT

In a context, like Japan, characterized by a limited access to deceased organ transplantation, single LD LT may represent the last resort when only one suitable LD is available, and the recipient is too sick to wait for a deceased donor. Under these circumstances, transplant outcomes were reported to be acceptable, although inferior to those of standard LD LT [12,15]. In the same setting, single LD LT, with or without contralateral pneumonectomy, may be a strategy to avert an excessively oversized graft-to-recipient match, as previously mentioned [3,7,25]. On the other hand, patients with a previous allogeneic hematopoietic stem cell transplant appeared to benefit more from single LT from the same LD than from bilateral deceased donor LT, probably due to immunological reasons [28,29]. Two of the authors recently reported a successful case of pediatric single-lobe LT after hematopoietic stem cell transplantation from the same LD, characterized by immune tolerance as an effect of full donor chimerism. This was the first case of LD LT in Italy, and an almost unique case in Europe as well [30].

RESULTS

In the field of living lung transplantation, it is of paramount importance to achieve an optimal clinical result both for the donor and for the recipient. Despite the limited number of procedures carried out worldwide, the results are favorable. In his series, Nakajima et al reported that the post-operative mortality in the first 30 days from the transplant was 2%, and the in-hospital mortality rate was 7%; during this timeframe the most frequent causes of in-hospital death were primary graft dysfunction (PGD), disseminated intravascular coagulation, aspiration pneumonitis, and sepsis [15]. These results are confirmed by the paper of Starnes at al reporting similar proportions of peri-operative mortality and complications [5]. Regarding long term survival, as recently reported by the pioneering Kyoto group, the 1-, 5- and 10-year survival rates for LD LT recipients were 90.9, 75.5 and 57.2%, respectively, after LD LT [31]. The University of Southern California team presented a report of 123 patients (39 paediatrics) who underwent LDLT from 1991 to 2004 and whose survival rates at one, three, and five years were 70, 54, and 45%, respectively [32]. Starnes et al described the survival in the LDLT recipients at 1, 3, and 5 years to be 70, 54, and 45%, respectively [5]. Also the Okayama University reported similar outcomes [33]. In particular, regarding the paediatric population, the reported outcome by Tanaka et al. in term of 5-year and 10-year survival rates was 87.7 and 75.1%, respectively [34]. The Saint Luis group reported similar survival rates [35]. In the paediatric population the 5-year and 10- year chronic lung allograft disfunction (CLAD)-free survival rates were 78.8 and 60.0%, respectively [34]. The Japanese Society of Lung and Heart–Lung Transplantation reported the long-term outcomes of 270 LDLT recipients operated between 1998 and 2021 at 9 Japanese transplant centres and the 3-, 5-, and 10-year survival rates were 80.0, 74.1 and 62.7% [36]. The incidence of CLAD per donor in LD LT varies from 14%, as reported by Nakajima et al. [31], to 56.7%, as described by Sugimoto et al. [33]. Is it interesting to note that CLAD usually develops unilaterally [37], giving a potential advantage to the recipient due to the unaffected contralateral graft that may act as a reservoir. This is probably due to the limited HLA mismatch. Indeed, in Japan, where most of these procedures are conducted, living donor candidates are selected within third degree relatives or spouse.
The outcome of the donor is equally important as that of the recipient. Individuals who decide to donate a lung lobe can experience severe psychological distress; for this reason, aside from the mandatory physical tests, a thorough psychological assessment is mandatory. In Japan, patients who decided to donate a pulmonary lobe scored higher on health-related quality of life (HRQOL) tests than the general population, suggesting that living lung donor

lobectomy may not adversely affect long-term HRQOL in many individuals[3 8]. However, pre- and post-operative psychological issues, such as anxiety and ethical issues, have been reported in LDLT; risk factors include donor age (< 40 years), recipient age (< 18 years), high lung allocation score of the recipient (≥ 50) and recipient death [38]. Regarding surgical post-operative complications, a cooperative study by the University of Southern California and the Washington University reported complications in 18% of donors, the most frequent being arrythmia; in particular, 2.2% of the donors underwent reoperation and 6.5% had early rehospitalization [39]. The Kyoto University group described a slightly higher complication rate of 28% in their series of donors, the most frequent one being pneumothorax after chest tube removal that required repositioning of a pleural drainage [40]. Post operative lung function of the donors is an important part of post operative quality of life, in 2015 Chen et al outlined a FVC and FEV1 that reach up to 90% of the pre-operative value one year after donor lobectomy [40]. These data are in accordance with the previous experience from the Massachusetts General Hospital group [41]. A possible explanation for this phenomenon is compensatory lung growth, due to mechanical stress of the remaining tissue, a well-known process in animal models [42]. A special interest has been drawn to the growth of the donor lung in children, in this setting opposing results have emerged: the Kyoto group demonstrated substantial growth [34], on the other hand, the USC group did not find aby evidence for growth [43], clearly more studies will be needed.

FUTURE PERSPECTIVES

The use of LDLT is largely affected by the local organ donation and procurement policies. Therefore, the future development of LD LT may vay coinsiderably among different countries and allocation systems..

In Japan, where the access to deceased organ transplantation is more difficult than in western countries, LD LT is an established procedure and successful, high volume programs are available [9]. Many techniques were developed to tailor the graft to the recipient's needs. The donor operation has remained quite unchanged over time. Considering the recent improvements in patient care allowed by robotic-assisted thoracic surgery, robotic LD lobar lung donation may reasonably represent the next step in the future of LD LT.

By contrast, in western countries, LD LT has little past and almost no present. Deceased donor lung donation, by means of innovative strategies for lung procurement, preservation, and reconditioning, allowed to significantly increase the donor pool [44]. The Japanese experience is a valuable framework for those transplant programs who are embarking in LDLT. In selected situations, LD LT could be even preferred to deceased donor LT, representing a source of unique advantages, like the possible tolerance of a graft from the same LD in patients with a previous allogeneic hematopoietic stem cell transplant [30].

CONCLUSIONS

LD LT was developed in the United States and gained widespread diffusion in Japan. At this time, generally speaking, it is mostly an underused resource. Although the procedure is undoubtedly more complex than deceased donor LT, excellent donor and recipient outcomes were reported in expert hands. Therefore, a reasonable use of LD LT, adapted to specific cases, could be a potential tool to safely expand the lung donor pool.

Conflict of interest statement

The authors declare no conflict of interest.

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CS, PA, CM, BA: contributed to the design and implementation of the paper and to the writing of the manuscript.

Ethical consideration

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