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ORIGINAL ARTICLE

Long-term outcomes of bilateral lobar lung transplantation†

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Abstract

OBJECTIVES: Lobar lung transplantation is an option that provides the possibility of transplanting an urgent listed recipient of small size with a size-mismatched donor lung by surgically reducing the size of the donor lung. We report our short- and long-term results with bilateral lobar lung transplantation (BLLT) and compare it with the long-term outcomes of our cohort.

METHODS: Retrospective analyses of 75 lung transplant recipients who received downsized lungs with a special focus on 23 recipients with BLLT performed since January 2000. Postoperative surgical complications, lung function tests, late complications and survival were analyzed. The decision to perform lobar transplantation was considered during allocation and finally decided prior to implantation.

RESULTS: Cystic fibrosis was the most common indication (43.5%) followed by pulmonary fibrosis (35%). Median age at transplantation was 41 (range 13–66) years. Fifteen were females. Nineteen of the transplantations (83%) were done with extracorporeal membrane oxygenation (ECMO) support; 3 of them were already on ECMO prior to transplantation. There was no 30-day or in-hospital mortality. No bronchial complications occurred. The most common early complication was haematothorax (39%), which required surgical intervention. The rate of postoperative atrial arrhythmias was 30%. Forced expiratory volumes in 1 s (% predicted) at 1 and 2 years were 76 ± 23 and 76 ± 22, respectively (mean ± standard deviation). By 2-year follow-up, bronchiolitis obliterans syndrome was documented in 3 patients with a median follow-up of 1457 days. Overall survivals at 1 and 5 years were 82 ± 8 and 64 ± 11%, respectively and were comparable with those of 219 other recipients who received bilateral lung transplantation during the same period (log rank test, $P = 0.56$).

CONCLUSIONS: This study demonstrates that BLLT has short- and long-term outcomes comparable with those of standard bilateral lung transplantation. The limitation of lung transplantation due to size-mismatch, particularly in smaller recipients, could be overcome by utilizing lobar lung transplantation.

Keywords: Lung transplantation • Lobar transplantation • Size-reduced lung transplantation

INTRODUCTION

In spite of the overall increasing survival rates in lung transplantation, there is an ongoing limitation of suitable donor organs as the availability of cadaveric donor lungs has failed to increase with the rise in numbers of transplant candidates. Due to the increasing scarcity of donors, in particular for smaller and urgent recipients, advanced operative strategies have been developed [1–9]. Peripheral segmental resection is the most common method for downsizing, whereas lobar and split lung transplants are other options performed to downsize donor lungs in order to achieve an adequate match [1–8]. Oversized lung grafts can potentially lead to atelectasis and impaired airway clearance due to bronchial anatomy distortion. Undersized grafts cause lung hyperexpansion and might limit exercise tolerance due to haemodynamic compromise [10]. In 1994, Bisson *et al.* [11] reported the first cadaveric bilateral lobar lung transplantation (BLLT) in 2 recipients with cystic fibrosis. Later, other centres reported their experience with size-reduced lung transplantation, describing the short-term outcomes [1–5]. In these series, functional outcomes and overall survival rates were comparable with standard lung transplantation; however, long-term follow-up was limited. Recently, the Melbourne Group reported their long-term lung function and survival in cadaveric lobar lung transplantation [7, 8]. In this study, we report the long-term outcomes for recipients who have undergone BLLT at our institution since 2000.

MATERIALS AND METHODS

Since the beginning of our lung transplant program in 1992 to the end of December 2011, we have performed 342 lung

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transplants. There are 308 bilateral sequential, 33 single and 1 heart lung transplants that have been performed.

Since January 2000, 75 recipients received downsized lungs. Of these, 23 patients underwent BLLT with anatomical lobectomy (9% of the total lung transplantations in the study period). These recipients are the main focus of this study. The recipients who underwent bilateral standard lung transplantation without any size reduction constituted the control group only for the comparison of the overall survival with those who underwent BLLT.

Data were prospectively collected on all recipients and retrospectively analyzed. Censor date for survival was taken on 23 January 2012. The median follow-up was 40.8 (range 1.1 to 137.3) months. All patients consented to the use of lobar transplants.

Indications for BLLT were cystic fibrosis ($n = 10$), pulmonary fibrosis ($n = 8$), emphysema ($n = 3$), primary pulmonary hypertension, progressive systemic sclerosis and bronchiolitis (for each $n = 1$). Sixteen patients were female, with a median age of 41 (range 13–66) years. At our centre, we follow the recently published guidelines regarding referral and selection of lung transplant candidates [12]. Organ preservation was performed with Perfadex® (Vitrolife, Gothenburg, Sweden). Before antegrade flush, 500 µg of prostaglandin E1 (Prostin VR, Upjohn, Puurs, Belgium) was injected into the pulmonary artery in all cases. We also perform retrograde flush with Perfadex® at the time of the back-table preparation.

The decision to perform size-reduced lung transplantation was made in the operating theatre during implantation based on a visual assessment of the size discrepancy after the patient having been identified as potentially needing a lobar transplantation, based on donor to recipient (D–R) height discrepancy. Our standard technique for BLLT has been to perform the surgery through two separate anterolateral thoracotomies through the fourth or fifth intercostal space.

According to our standard protocol, patients received induction therapy (antithymocyte globulin or basiliximab) and triple immunosuppressive therapy including cyclosporine, mycophenolate mofetil and prednisone. Anti-infective prophylaxis was used according to our centre's protocol described elsewhere [13]. Post-transplant management at our centre includes routine surveillance bronchoscopies with transbronchial biopsies and broncho-alveolar lavage during the first 6 months after transplant, serial laboratory lung function tests and regular outpatient clinic follow-up visits.

Predicted donor total lung capacity (litres) was measured as: for male patients = 7.99 × height in meters − 7.08 and for female patients = 6.6 × height in meters − 5.79 [14]. These were calculated and corrected for size-reduced total lung capacity (sr-TLC) with respect to size reduction. We calculated sr-TLC by using the following equation: sr-TLC = donor TLC × (1 − S × 0.0526), with S = number of resected segments [15].

Statistical analysis

Descriptive statistics was used, and data are expressed as mean ± standard deviation. The statistical analysis was performed with SPSS 20 for windows. Actuarial survival rates were calculated by the Kaplan–Meier method and compared with the log-rank test. The hazard ratio was calculated. For correlation analysis, the Pearson Correlation test was used. $P < 0.05$ was considered significant.

Surgical procedure

On the right side, in order to transplant the middle and lower lobes, an upper lobectomy was performed. The major fissure was entered, and the interlobar pulmonary artery was prepared. The upper lobe vein was dissected, tied and transected. The atrial cuff receiving both the right superior and inferior veins was preserved. The upper part of the major fissure between the upper and lower lobes and the minor fissure between the upper and middle lobes was separated with the use of a stapler. The branches of the pulmonary artery to the upper lobe were dissected, tied and divided. Transection of the bronchus was done at the distal part of the intermediate bronchus, just one ring above the middle lobe and apical segment bronchus of the lower lobe, taking great care to protect the peribronchial connective tissue (Fig. 1).

To implant only the right upper lobe, the right lower and middle lobes were resected. The major fissure was entered, and the interlobar pulmonary artery was dissected. The middle lobe artery was identified, tied and transected. The interlobar pulmonary artery was tied, preserving the posterior ascending artery to the upper lobe, and transected. The lower and the middle veins were dissected, tied and transected. The atrial cuff was preserved. The upper lobe bronchus was transected just at the level of its separation from the main bronchus. To perform upper and lower lobes, the middle lobe was resected. The middle lobe vein and artery were dissected, tied and transected. In case of parenchymal bridge between upper and middle lobe, it was separated with a stapler. The middle lobe bronchus was transected with a stapler. In this situation, before implantation of the right upper and lower lobes, the main bronchus was cut just one ring above the right upper lobe bronchus.

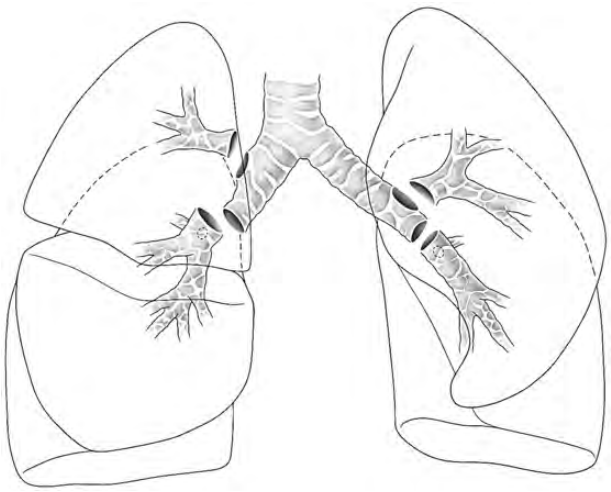


Figure 1: Bronchus transection lines during lobar transplantation. For implantation of the right middle and lower lobes, the transection of the bronchus was done at the distal part of the intermediate bronchus, just one ring above the middle lobe and apical segment bronchus of the lower lobe. For right upper lobe implantation, the upper lobe bronchus was transected just at the level of its separation from the main bronchus. For implantation of right upper and lower lobes, the main bronchus was cut just one ring above the right upper lobe bronchus. Left upper lobe implantation, immediately before implantation the upper lobe bronchus was divided at the level of its connection with the main bronchus. Left lower lobe implantation, the left lower lobe bronchus was transected just at the level of the lobar bifurcation, allowing the anastomosis to be performed preserving the bronchus of the apical segment of the lower lobe.

On the left side, to implant the left upper lobe, a left lower lobectomy was performed. The fissure was entered. The bridge between the upper and lower lobes was separated using a stapler. The interlobar pulmonary artery was dissected, tied distally to the lingula artery and transected. The lower lobe apical segment artery was dissected, tied and transected. The lower lobe vein was prepared, tied and transected. The atrial cuff was divided, leaving enough cuff tissue around the superior pulmonary vein. Just before implantation, the upper lobe bronchus was divided just at the level of its connection with the main bronchus.

To perform left lower lobe transplantation, an upper lobectomy was performed. The fissure was prepared. The bridge between the upper and lower lobes was separated using a stapler. The interlobar pulmonary artery was dissected. The lingula artery and the branches to the upper lobe were tied and divided. The superior pulmonary vein was tied and divided. The atrial cuff was preserved. The left lower lobe bronchus was transected just at the level of the lobar bifurcation, allowing the anastomosis to be performed, preserving the bronchus of the apical segment of the lower lobe.

First, the bronchial anastomosis was carried out. All dissection close to the bronchus was done using the 'minimal' or 'no touch' technique in order to keep the peribronchial tissue intact [16]. A continuous suture of the membranous wall (polydioxanone suture [PDS], 4/0) and end-to-end anastomosis with interrupted single sutures (PDS, 4/0) of the cartilaginous part were performed. Venous (atrium) and pulmonary artery anastomoses were then performed. Deairing was performed via the antegrade way.

RESULTS

The median waiting list time was 150 (range 15–1063) days. The mean ischaemic time for the right side was 256.4 ± 88.8 min and for the left side was 332.5 ± 97.9 min. The median operation time was 492 (range 275–970) min. The median mechanical ventilation time was 1 (range 1–52) days. The median intensive care unit length of stay was 14 (range 2–56) days.

The donor age was 38.5 ± 13.9 years. Twenty-one of the donors were male. The major cause of donor death was intracranial bleeding ($n = 17$). The donor's partial oxygen pressure at the time of retrieval was 40.2 ± 16.2 kPa. Donor and recipient characteristics are shown in Table 1.

In 12 transplants, we performed middle and left upper lobectomy, which were the most common types of lobectomies performed on the back table. Right upper and left lower lobectomies were performed in 4 cases. Right upper, middle and left upper lobectomies were performed in 3 transplants. The other lobectomy combinations were: left upper, middle and right upper lobectomy ($n = 1$); middle, right lower and left lower lobectomy ($n = 1$); right upper and left lower lobectomy ($n = 1$); right upper, middle and left upper lobectomy ($n = 1$).

Nineteen (83%) of the transplantations were performed with extracorporeal membrane oxygenation (ECMO) support. Three recipients were on ECMO preoperatively and one had tracheostomy. Two of the 3 patients who were on ECMO preoperatively required postoperative ECMO and 2 recipients who had intraoperative ECMO also required ECMO postoperatively.

Atrial fibrillation (30%) and haemothorax requiring reoperation (39%) were the most common early postoperative complications. In 14 recipients, we performed tracheotomy. Primary graft dysfunction developed in 3 patients. One patient developed oesophageal perforation and intracranial bleeding. She survived both complications. One recipient was reoperated on postoperative day 3 due to venous anastomotic stricture. We did not observe any bronchial complication. Late complications were rare. In 2 patients, we observed lymphocel at the site of inguinal ECMO cannulation. Pericostal suture insufficiency ($n = 1$), spinocellular carcinoma ($n = 3$), vulva carcinoma ($n = 1$) and mechanic ileus (laparotomy, laparoscopy) ($n = 2$) were the other late complications.

Lung function testing at 3, 6, 12, 24 and 36 months revealed % predicted forced expiratory volume in 1 s (FEV1; mean ± SD) of 74.5 ± 23.8, 75.3 ± 20.7, 76.8 ± 23.5, 76.5 ± 22 and 71.3 ± 18.5, respectively (Fig. 2).

There was a statistically significant correlation between the donor sr-TLC (estimated TLC from donor adjusted to the number of segments resected) and the % predicted recipient FEV1 at 3 months (Pearson's correlation coefficient (r) = 0.485, $P = 0.04$).

Postoperative % TLC, % predicted FEV1 at 3, 6 and 12 months significantly correlated with donor–recipient (D–R) height

Table 1: Recipient and donor characteristics

Recipient height (cm)	159.5 ± 8.8
Recipient weight (kg)	56.3 ± 17.2
Donor height(cm)	180 ± 8.2
Donor weight (kg)	79.4 ± 15.9
D–R height difference (cm)	20.5 ± 13.6
D–R weight difference (kg)	23.1 ± 23.9
Donor-predicted TLC (l)	7.2 ± 0.8
sr-TLC (l)	4.4 ± 0.7
Recipient preoperative actual TLC (l)	3.8 ± 1.4
Recipient preoperative predicted TLC (%)	82.4 ± 31.8
Recipient preoperative FEV1 (l)	1.2 ± 0.75
Recipient preoperative predicted FEV1 (%)	40.7 ± 23.3
Recipient postoperative TLC (l)	3.6 ± 0.5
Recipient postoperative predicted TLC (%)	71.8 ± 18.6
D–R TLC difference (l)	3.2 ± 1.4
Number of resected segments (median)	6 (range 6–12)

Data are expressed as mean ± standard deviation. D–R: donor to recipient; TLC: total lung capacity; sr-TLC: donor total lung capacity corrected for size reduction; FEV1: forced expiratory volume in 1 s.

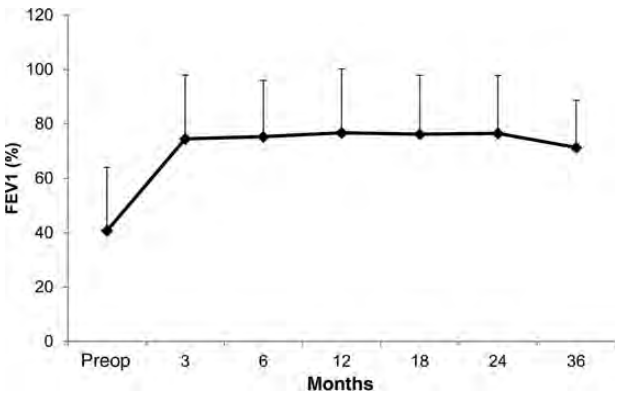


Figure 2: The line graph shows the long-term lung function evolution for the cohort during 36 months following the BLLT. Forced expiratory volume in 1 s % predicted (FEV1%) improved during the 2-year period. Error bars show standard deviation.

difference ($r = 0.564$, $P = 0.02$; $r = 0.479$, $P = 0.04$; $r = 0.531$, $P = 0.01$; $r = 0.611$, $P = 0.007$).

Donor-predicted TLC also significantly correlated with D–R height ($r = 0.755$, $P = 0.0001$) and weight ($r = 0.587$, $P = 0.003$) difference.

sr-TLC correlated with the number of transplanted segments ($r = 0.659$, $P = 0.001$). There was a significant negative correlation between the number of transplanted segments and D–R height and weight difference ($r = -0.568$, $P = 0.005$).

There was no 30-day mortality. Early mortality within the 90 days was 8.6% ($n = 2$). The causes of these deaths were sepsis ($n = 1$) and multiorgan failure ($n = 1$). One of them was on ECMO 4 weeks prior to transplantation and the other patient had multi-resistant *Pseudomonas aeruginosa*. The causes of death among the other 6 patients who died to date were multiorgan failure and cytomegalovirus disease ($n = 1$), organizing pneumonia ($n = 1$), respiratory failure ($n = 3$) and unknown ($n = 1$).

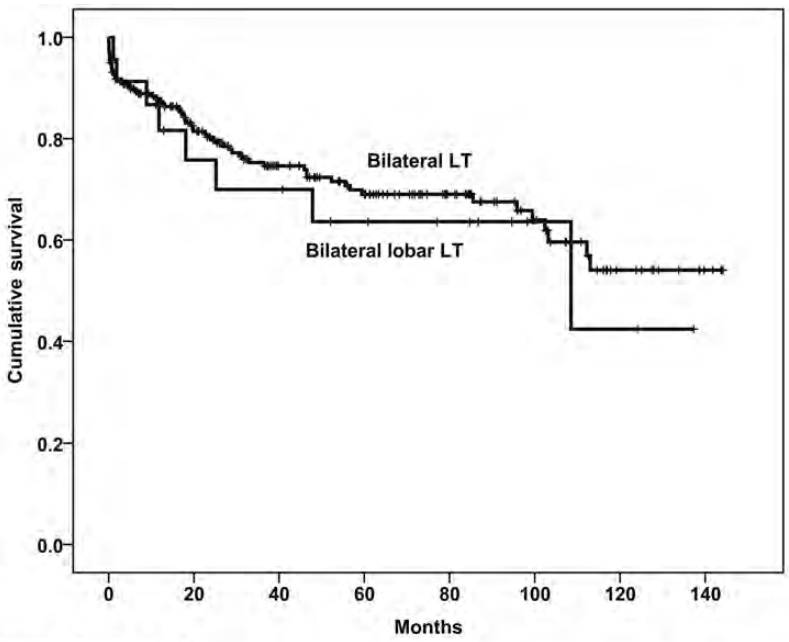
By 2-year follow-up, bronchiolitis obliterans syndrome (BOS) was documented in 3 patients with a median follow-up of 1457 (range 113–4178) days. BOS Stage 3 developed in 2 and BOS Stage 2 in 1 recipient. In the first 2 recipients, the percent fall in best FEV1 was 30.4 and 41.2, respectively. In the one with BOS Stage 2, the percent fall in best FEV1 was 59.1. By 3-year follow-up, 1 recipient developed BOS Grade 1 and another 2, potential BOS leading to FEV1 values of 70.2, 82.4 and 88.6% of their respective previous best FEV1 values determined according to standard definitions.

Survival analysis showed no significant difference between BLLT and standard bilateral lung transplantation (hazard ratio = 0.808, 95% confidence interval 0.387–1.686; Fig. 3). The estimated 1- and 5-year survival rates in BLLT were 82 ± 8 and 64 ± 11% compared with 88 ± 2 and 69 ± 3% in bilateral lung transplantation (BLT) ($P = 0.56$).

DISCUSSION

Reducing the size of an oversized lung graft either by non-anatomical resection or by lobectomy is one of the methods to increase the donor pool, particularly for small recipients in case of a donor–recipient size mismatch. However, it is not routinely performed in many transplant centres. Optimal size matching is important because of the potential problems that might occur following the use of oversized grafts [1–4, 7, 8]. Previous experimental studies have shown the adverse effects of oversized grafts on chest mechanics, atelectasis of the graft and pulmonary haemodynamics [10]. In a canine model of bilateral living donor lobar lung transplantation, both pulmonary vascular resistance and peak airway pressure were significantly increased after the chest closure due to the overcrowding phenomena in animal lung grafts that did not undergo size reduction, whereas little change was observed in those that underwent size reduction [10].

In 1994, Bisson *et al.* [11] reported the first lobar lung transplantation in 2 cystic fibrosis patients. They transplanted left lower lobe and right lower and middle lobes. In 1997, Couetil *et al.* [5] published their series of 7 cases with bipartitioning of the left lung. They reported a median survival of 19 months with good exercise tolerance and lung function. Aigner *et al.* [17] from the Vienna Group published the largest series in 2004 with 18 lobar lung transplantations. They reported 80% 3-month survival with only one bronchial complication seen in the lobar



Number of patients at risk

Months	0	12	24	36	60	120
BLT	219	172	137	114	81	13
BLLT	23	16	13	12	9	2

Figure 3: Actuarial survival rates calculated by the Kaplan–Meier method and compared using the log-rank test did not show any difference between BLLT ($n = 23$) and standard bilateral lung transplantation ($n = 219$), $P = 0.56$.

transplant group. Similar short-term results following lobar transplantation have been reported [4, 9]. The Melbourne Group recently published their long-term results in lobar lung transplantation [7, 8]. In their first publication, they reported on 5 bilateral, and in their most recent report, they extended their series to 23 lobar transplants in which 13 underwent BLLT. They reported similar overall survival rates in the lobar lung transplant group compared with the standard lung transplant group [8]. Our results presented here support the similar overall survival rates.

For optimal size matching, different methods have been proposed, such as donor–recipient difference or ratio in body weight and height [1–3]. In addition, chest circumference and chest X-ray vertical and transverse dimensions have been used [1]. The use of donor and recipient total lung capacity for optimal size matching has also been reported [2–5, 17]. Small differences in the lung graft size can be managed by stapler resection or peripheral non-anatomical wedge resection. Generally, on the right-side middle lobe and on the left side, the lingula are the preferred lobes for resection [2]. This technique of size reduction has been reported to lead to ∼10–15% downsizing not only in height but also in the anterior–posterior diameter since the upper lobe rotates towards the lower lobe [17]. We use D–R height difference to identify a possible size reduction. In our series, the D–R height difference ranged from 0 to 47 cm (mean 20.5 cm). The recipient with 0 cm height difference had idiopathic pulmonary fibrosis (IPF) and he was on ECMO for 4 weeks prior to transplantation. If we consider this group of patients with IPF, due to small chest cavity, enlarged heart on the left side and increased mediastinal fat amount, the need for size-reduced lung transplantation can be anticipated even with a lower D–R height discrepancy.

The use of cardiopulmonary bypass (CPB) or ECMO has been advocated by some centres in order to prevent reperfusion injury of the first transplanted lobe [8, 9, 17]. The utilization rate of CPB or ECMO of the recent series varied between 56 and 100% [8, 9, 17]. In our series, ECMO was used intraoperatively in 83% ($n = 19$), whereby 3 patients were already on ECMO prior to transplantation. To protect the first transplanted lobe, especially if the pulmonary artery pressure is high or in case of marginal donor lung, we do not hesitate to perform the operation with ECMO. In addition to this concept, our recipient population characteristics (IPF, $n = 8$) also explain the high rate of ECMO use during transplantation.

Lobectomy for size reduction can be performed on the back table or after implantation. The advantages of back-table lobectomy are saving time, because it can be performed simultaneously with recipient preparation for transplantation by a separate surgeon, and by preventing a big size mismatch the view of the hilum is not impaired [8]. On the other hand, it can be technically difficult to perform the back-table lobectomy as the vessels are not distended by blood, which makes the dissection more difficult [8]. On the other hand, lobectomy following engraftment may be difficult to perform due to the large size of the lung within a small chest cavity [8]. Manipulation of the recently perfused lung with reperfusion injury is another disadvantage of postimplantation lobectomy as it may cause more injury to the transplanted lung. As previously reported by others [6–9, 17], we also perform donor lung lobectomy on the back table immediately before the implantation because of the advantages mentioned above.

Which lobes should be resected or which lobes should be implanted may differ depending on patient characteristics. This depends on the disparity of the size mismatch, the condition of the graft and the preference and experience of the implantation team. Upper lobectomy is technically easier, because the remaining lower lobe results in a configuration that is similar to the whole lung [9, 17]. However, if the lower lobes are consolidated or contused, it is preferable to perform lower lobectomy on both sides. In our series, 83% of the recipients had upper lobectomies performed, and implantation of the remaining lungs was performed without any problem.

The rate of bronchial anastomotic complications was 5.5 and 13% in the two recent series reporting lobar lung transplantation [8, 17]. In our series, we have not observed any bronchial anastomotic complications. Bronchial ischaemia is reported to be a significant risk factor for the development of airway complications [16]. The viability of the donor bronchus is initially dependent upon retrograde low-pressure collaterals derived from the pulmonary artery since bronchial arterial circulation is lost during the harvest of the donor lungs [18]. To prevent ischaemic bronchial complications, we transect the bronchus as distally as possible, which reduces the part of donor bronchus at risk for ischaemia (Fig. 1). Additionally, we do not grasp the bronchus with the forceps during implantation, thus preventing tissue damage [6, 16].

The survival rate of our BLLT was comparable with that of standard BLT. Although the estimated survival rate was better for BLT at 1 and 5 years, the difference was not statistically significant. The reasons for this observation may be related to the condition of some recipients prior to transplantation: We had 3 patients on ECMO and 1 on ventilator prior to transplantation, as well as a large proportion of other very sick recipients, especially with IPF diagnosis, frequently with a rapid deterioration immediately prior to transplantation so they were unable to wait for a size-matched or an ideal organ.

In conclusion, we have shown that BLLT has short- and long-term outcomes comparable with those of standard bilateral lung transplantation. The limitation of lung transplantation due to size-mismatch, particularly in smaller adults and paediatric recipients, could be overcome by utilizing lobar lung transplantation.

Conflict of interest: none declared.

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EDITORIAL COMMENT

Merits of cadaveric lobar lung transplantation

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Keywords: Lobar transplant • Donor–recipient discordance • Lung downsizing

Potential lung transplant recipients of small stature and those with reduced pleural space, for example, with pulmonary fibrosis, typically have a longer waiting time for donor lungs of suitable size. Cadaveric lobar lung transplantation (CLLT) has been increasingly employed to expand the donor pool for such patients who might not survive the lengthy wait for a whole lung donor. Subsequent to the initial reports of successful lobar transplantation by Bisson *et al.* [1, 2] two decades ago, centres including Vienna [3], Spain [4], France [5] and more recently Australia [6] have reported their experience. The present series from the University Hospital, Zurich [7] is a valuable addition to the existing literature. These studies suggest that CLLT has a long-term survival comparable with lung transplantation. We have selectively performed more than 20 CLLT at our institution in the adult lung transplant programme and have also found favourable results (unpublished data).

Strategies to downsize donor lungs in the presence of donor–recipient (D–R) size discordance include either parenchymal wedge resection or anatomical lobectomy. Lobectomy can either be performed before (back table) or after implantation. CLLT, in the true sense, refers to the strategy of back-table lobectomy and implantation of a single lobe of the donor left lung or one or two lobes of the donor right lung. The initial reported experience of CLLT was described using the split donor left lung as it was felt to be technically easier. The donor left lower lobe was placed in the recipient's left side and donor left upper lobe in the recipient's right side. Ideally, in such a situation, the right lung can go to a different recipient. However, this requires tremendous co-ordination between the organ procurement organizations and availability of appropriate recipients. More commonly, the decision to downsize lungs is made intraoperatively after both lungs are received by the recipient centre. Nevertheless, knowing that CLLT is a viable option makes it easier to accept lungs from larger donors for small-statured recipients with higher acuity.

Unfortunately, due to the relative urgency of transplant, recipients deemed candidates of CLLT may be at higher risk and have more haemodynamic instability during the reperfusion phase.