Transplant International

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

The number of lung transplants can be safely doubled using extended criteria donors; A single-center review

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Keywords
expanded donor pool, extended criteria donors, lung transplantation.

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Received: 2 September 2009
Revision requested: 1 October 2009
Accepted: 23 November 2009
Published online: 5 January 2010

doi:10.1111/j.1432-2277.2009.01033.x

Summary

Relaxing the standard lung donor criteria may significantly increase the reported 15% organ yield but post-transplant recipient outcome should be carefully monitored. Charts from all consecutive deceased organ donors within our hospital network were reviewed over a 2-year period. Reasons for lung refusals and number of lungs transplanted were analysed. Hospital outcome including early recipient survival was compared between standard- and extended criteria donors. Out of 283 referrals, 164 (58%) qualified as donor of any organ. The majority (65.9%) of these effective donors were declined for lung donation because of chest X-ray abnormalities (20%), age >70 years (13%), poor oxygenation (10%), or aspiration (9%). Out of 56 (34.1%) accepted lung donors, 50 transplants were performed at our center, 23 from standard criteria donors versus 27 from extended criteria donors. There were no significant differences in hospital outcome and in early survival between lung recipients from both donor groups. Lung acceptance rate (34.1%) in our donor network is 10–20% higher than reported figures. The number of lung transplants in our center doubled by accepting extended criteria donors. This policy did not negatively influence our results after lung transplantation.

Introduction

Lung transplantation is an effective treatment modality for selected patients suffering from any form of end-stage pulmonary disease [1]. As a result of the widespread success of lung transplantation, there is a persistent organ shortage with a percentage of patients not surviving the waiting period as their prospects on the thoracic waiting list are governed by the chance of receiving an organ in time [2]. Only about 15% of the multiple organ donors (MODs) have lungs suitable for transplantation when adhering to standard donor criteria [3]. In a recent analysis from the California Transplant Donor Network, more than 85% of the lungs were rejected for different reasons [4].

Previously, a lung donor was considered ideal when the following criteria were met: age <55 years, clear chest radiograph, arterial oxygen pressure (PaO_2) > 300 mmHg [on fraction of inspired oxygen (FiO_2) = 1.0 and positive end expiratory pressure (PEEP) = 5 cm H_2O], smoking history <20 pack-years, absence of chest trauma, no evidence of aspiration, absence of organisms in sputum and no purulent secretions on bronchoscopy [3,5]. An extensive review published by a working group within the International Society for Heart and Lung Transplantation (ISHLT) in 2003 concluded that these generally accepted standard donor criteria were arbitrarily chosen based on broad clinical impressions rather than solid medical evidence [6]. Meanwhile, experienced centers have liberalized their donor criteria in the last decade. In a recent multicenter study from Canada, a lung utilization rate of 23% was reported [7]. In Eurotransplant, out of 2003 deceased donors in the year 2008, 508 (25.3%) served as lung

donors [8]. This percentage is still much lower compared with other solid organs (kidney: 91.5%; liver: 77.3%; heart: 29.1%).

Numerous studies have previously reported that lungs from so called extended criteria donors, not matching these standard criteria, can be transplanted successfully [9–18]. Two reports, however, demonstrated a negative effect on hospital outcome but not on long-term survival [15,18]. A review paper on the subject recently argued for further cautious relaxation of the once-strict guidelines on deceased lung donor acceptability criteria, especially with respect to older donor age [19].

We hypothesized that the lung donor acceptance rate in our hospital network was higher than the currently reported figures as a result of our policy in the last decade to relax our donor criteria and to assess the lungs *in situ* at the donor hospital as often as possible.

The aim of this study was to review all donors reported within our hospital network over the last 2 years. The lung donor profile and acceptance rate were analysed. The outcome after lung transplantation was compared between standard- and extended criteria donors.

Patients and methods

Charts from all consecutive potential MODs referred within our hospital network between January 2006 and December 2007 were reviewed and the reasons for ultimately not becoming an organ donor were recorded. In effective MODs, donor demographics including age, gender, blood type, cause of brain death, smoking history, and duration of ventilation were recorded and number of rejected and accepted lungs were analysed. Post-transplant outcome parameters including use of cardiopulmonary bypass, primary graft dysfunction, length of postoperative intubation, ICU and hospital stay, hospital mortality, and survival were compared between lung recipients from standard- and extended criteria donors.

In total, 110 lung transplantations (77 double-, 27 single- and six heart–lung transplants) were performed in our center in the years 2006–2007 (Fig. 1). Sixty recipients who were transplanted during the study period with lungs recovered at hospitals outside our donor network were excluded in this study.

Data are expressed as median [range] value. Differences between donor groups were analysed with the Fisher's exact test. Survival curves were calculated with the Kaplan–Meier method and compared using the log-rank test. A P value of <0.05 was defined as level of statistical significance.

Informed consent was obtained from the recipients according to the Belgian law on patients' rights regarding data registration. Approval for analysing recorded data was waived by the institutional ethics committee on human research given the retrospective nature of the study.

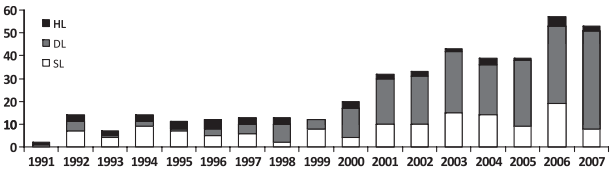

Figure 1 Number of lung transplantations performed annually at the University Hospital Gasthuisberg between 1991 and 2007 (SL, single lung; DL, double lung; HL, heart–lung).

Results

Potential donors

A total of 283 potential MODs located in 26 different hospitals were reported to our central donor coordination office during the study period. One hundred and nineteen (42%) of these did not become an effective donor of any organ for various reasons: brain death not certified (20), no consent (28), objection by the King's attorney (1), and medical contraindications against organ donation (70) including hemodynamic instability with premature cardiac arrest, sepsis, multiple organ failure and viral seropositivity for HIV, Hepatitis B or Hepatitis C.

Effective donors

One hundred and sixty-four of the referrals (58%) became effective MODs. Their median age was 52 [8–86] years. Fifty-eight percent of them were male. Most of the donors had blood group O (44%) or A (43%), followed by B (10%) and AB (3%). Fifty-five percent of the effective MODs were nonsmokers, whereas 33% were smokers, and in remaining 12%, smoking history was not documented. The cause of brain death was a cerebrovascular accident in 78 (47.6%) MODs followed by a craniocerebral trauma in 63 (38.4%), hypoxia in 22 (13.4%) and brain tumor in 1 (0.6%). Fourteen donors had suffered a chest trauma (8.5%).

Out of 164 effective MODs, 56 (34.1%) were accepted as lung donor, whereas 108 (65.9%) were rejected. The primary reasons for declining these lungs are listed in Table 1. The most frequent causes (>50%) were abnormal chest X-ray findings, older age >70 years, poor oxygenation (PO_2/FiO_2 <300 mmHg) and airway aspiration. Most of these rejected donors presented with a combination of risk factors.

Lung donors

The median age of the 56 lung donors was 48 [15–66] years and M/F ratio was 1.08. Blood type was O in 45%,

A in 43%, B in 10%, and AB in 2%. Fifty-five percent of the effective MODs were nonsmokers, whereas 27% were smokers, and smoking history was not known in 18% and thus further considered below as standard donors if not matching other extended criteria. All lungs were retrieved from heart-beating donors. The cause of brain death was craniocerebral trauma in 29 lung donors (52%) followed by a cerebrovascular accident in 23 (41%) and hypoxia in 4 (7%). Seven donors had suffered a chest trauma (12.5%). Six (11%) donors were ventilated for <24 h from hospital admission until organ recovery, while 50 (89%), 28 (49%), 21 (37%), 17 (30%), and 15 (26%) were ventilated for longer than 1, 2, 3, 4, or 5 days respectively.

From these 56 donors, the following lungs were recovered in total: 42 double lungs, nine paired single lungs (all twin lungs were transplanted at another center), and five unpaired single lungs (four contused contralateral lungs were not accepted by other transplant teams and one normal contralateral lung could not arrive in time at the recipient center because of bad weather conditions).

Standard versus extended criteria donors

Donors were divided into standard (25) and extended donors (31) according to the criteria listed in Table 2. The majority of extended donors had a smoking history >20 pack years (12/31) or abnormalities on chest X-ray (10/31). On the other hand, oxygenation index was below 300 mmHg in only 2/31 accepted lungs. The number of donors that met one, two or three extended criteria is also presented in Table 2. Only a minority of donors (8/31 or 25.8%) were accepted with more than one extended criterion.

The extended criteria were comparable between accepted single and double lungs. The number of donors with one, two or three extended criteria was also comparable between single and double lungs [Table 2]. There were more single lungs in the extended donor group (11/14) and more double lungs in the standard group (22/42), but the difference did not reach statistical significance ($P = 0.06$). The chest X-rays were abnormal in all the six single lungs that were transplanted at our center from the extended group (Table 2).

Table 1. Primary reason for nonacceptance of donor lungs in 164 effective multiple organ donors.

Reason	*n*	%
Abnormalities on chest X-ray	32	20
Age >70 years	21	13
PaO_2/FiO_2 <300 mmHg	17	10
Aspiration	15	9
Smoking history	7	4
Donor after cardiac death	4	2
Infectious risk	3	2
Intrinsic lung disease	3	2
Lung emboli	2	1
Hemodynamic instability	1	0.6
Prolonged ventilation	1	0.6
Not documented	2	1
Total	108	65.9

Lung transplants

From 56 lung donors, four double lungs and two unpaired single lungs were transplanted elsewhere in Eurotransplant. Outcome data in these six recipients were not available and these donors were therefore excluded in the outcome analysis.

In total, 50 lung transplants were performed at our center, 23 from standard- and 27 from extended criteria donors. By accepting these nonstandard criteria donors, we have doubled the lung utilization rate and thus the number of lung transplantations performed during the study period [50 transplants from 158 (164 − 6) donors (31.6%) instead of 23 (14.5%)].

The median age of recipients from extended criteria donors (56 [28–69] years) did not differ from the standard donor group (54 [15–65] years); $P = 0.31$. Also the indication for transplantation did not differ between both donor groups; $P = 0.75$ (Table 3). The median age in the single lung recipients (61 [40–69] years) was older compared to double lung recipients (55 [15–65] years); ($P < 0.0001$).

Recipient outcome

Cardiopulmonary bypass

There was no difference in the intraoperative use of cardiopulmonary bypass (eight out of 50 transplants)

Table 2. Criteria in 31 extended lung donors.

Criteria	Total (31)*	SL (11)*	DL (20)*	*P*-value
Smoking history >20 pack years	12	5	7	NS
Abnormalities on chest X-ray	10	6	4	NS
Age >55 years	9	1	8	NS
Chest trauma	7	3	4	NS
PaO_2/FiO_2 <300 mmHg	2	1	1	NS
Total criteria	40	16	24	NS
Single criterion	23	6	17	NS
Two criteria	7	5	2	NS
Three criteria	1	0	1	NS

*Number of extended donors.
SL, single lung; DL, double lung; NS, not significant.

Table 3. Indication for transplantation in 50 recipients comparing both donor groups.

Extended			Standard		
	n	%		*n*	%
Emphysema	16	59.3	Emphysema	12	52.2
Cystic fibrosis	4	15	Cystic fibrosis	7	30.4
Pulmonary fibrosis	3	11	Pulmonary fibrosis	2	8.7
PPH	2	7.4	PPH	1	4.3
Others	2	7.4	Others	1	4.3
Total	27	100	Total	23	100

PPH, primary pulmonary hypertension.
There were no significant differences between both donor groups ($P = 0.75$).

between both donor groups (3/23 in standard vs. 5/27 in extended donor group; $P = 0.71$).

Primary graft dysfunction

Primary graft dysfunction in the first 48 h after transplantation is shown in Fig. 2. Apart from slightly higher grade dysfunction at T24 in the extended group ($P < 0.04$), no significant differences were seen between both donor groups at other time intervals.

Duration of intubation

No significant differences were found in the length of intubation between both donor groups (3 [1–8] days in standard vs. 3 [1–12] days in extended donor group; $P = 0.50$).

Length of ICU and hospital stay

Recipients from standard donors had a significantly shorter stay in the ICU compared with extended donors (4 [2–4] days vs. 7 [2–76] days respectively; $P < 0.03$).

However, no significant differences was seen in length of hospital stay between both donor groups (27 [14–41] days in standard vs. 30 [13–128] days in extended donor group; $P = 0.06$).

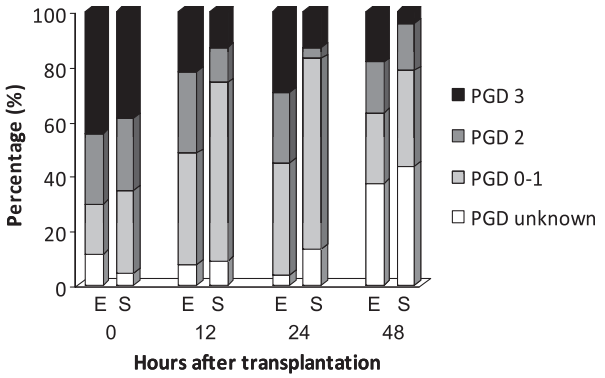

Figure 2 Primary graft dysfunction (PGD) as defined by the International Society for Heart and Lung Transplantation working group [1] in the first 48 h after lung transplantation. No significant differences were found between donor groups at any time interval except at T24 ($P < 0.04$). PGD unknown: the grade could not be defined for patients with missing data at T0 or in extubated patients at T12-T48. E: extended donors; S: standard donors.

Hospital mortality

Four patients have died in hospital (8%), one in the standard donor group (1/23) vs. three in the extended donor group (3/27); $P = 0.61$. The cause of death in these recipients is listed in Table 4. In one recipient (no. 5), death was directly related to a problem in the donor lung. His 35-year-old traumatic donor ventilated for 64 h was classified as extended because of an infiltrate in the left lower lobe on chest X-ray believed to be related to his chest trauma. Beside slight emphysematous changes, no other macroscopic abnormalities were discovered at recovery. The graft, however, was colonized with Aspergillus contributing to the death of the recipient from Aspergillus sepsis and acute rejection 76 days after the transplantation. Two patients developed severe brain damage after a technically difficult transplant procedure resulting in death after 2 weeks. One more patient died in hospital from multiple organ failure after 120 days.

Table 4. Cause of death in 6/50 lung recipients transplanted from local donors between January 2006 and December 2007.

Patient	Age (years)	Sex	Lung disease	LTx type	Time to death (days)	Cause of death	Extended donor criterion
1	45	M	Sarcoidosis	DL	535	BOS	Age >55 years
2	65	F	Emphysema	SL	391	BOS	Smoking >20 years
3	69	M	Fibrosis	SL	120*	MOF	Abnormal X-ray
4	56	F	Emphysema	DL	14*	Brain damage	Smoking >20 years
5	54	M	Emphysema	DL	76*	Aspergillus + AR	Abnormal X-ray
6	49	F	Emphysema	DL	14*	Brain-dead	None

*In-hospital death.
M, male; F, female; SL, single lung; DL, double lung; LTx, lung transplantation; BOS, Bronchiolitis Obliterans Syndrome; AR, acute rejection; MOF, multiple organ failure.

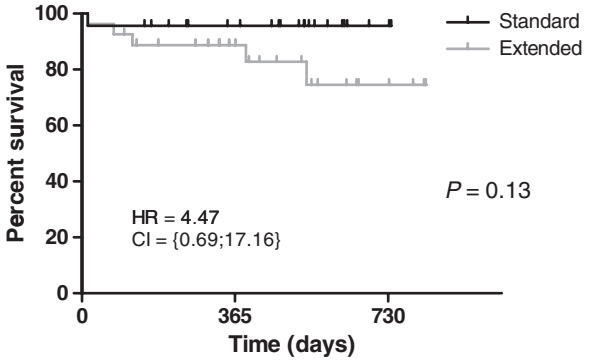

Figure 3 Actuarial survival comparing patients transplanted with lungs from standard versus extended criteria donors. No significant difference was found. (HR, hazard ratio; CI, confidence interval).

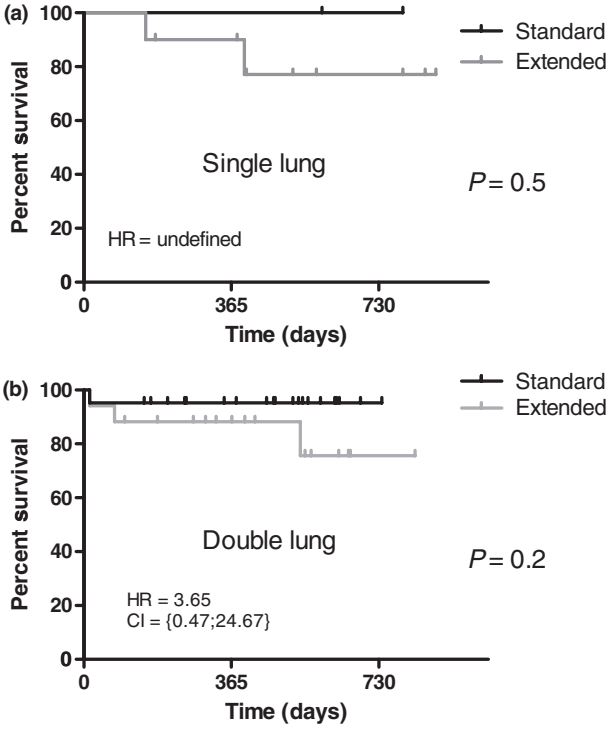

Figure 4 Actuarial survival in (a) single lung recipients; (b) double lung recipients comparing standard versus extended donors. No significant differences were found (HR, hazard ratio; CI, confidence interval).

Survival

Two more patients in the extended group have died from bronchiolitis obliterans syndrome in the second year after the transplant (Table 4).

The overall survival in the 50 lung recipients was 92.0% at 1 year and 84.2% at 2 years. Survival in patients transplanted with lungs from standard versus extended donors is compared in Fig. 3. No significant difference was found between both groups (95.7% vs. 88.7% at 1 year and 95.7% vs. 74.5% at 2 years respectively; $P = 0.1329$).

The survival in single and double lung recipients from standard versus extended donors is compared in Fig. 4a and b respectively. There were no significant differences in survival for both transplant types between donor groups ($P = 0.5$ and $P = 0.2$, respectively).

Survival with lungs transplanted from extended donors did not differ significantly between single versus double lung recipients (77.1% vs. 75.6% at 2 years respectively); (Fig. 4a versus 4b).

Discussion

In this study, we have found that the lung acceptance rate in our transplant center in the last 2 years was 34.1%. The number of lung transplants in our center doubled by accepting donors that did not match the preset ideal criteria [3,5]. A higher prevalence of primary graft dysfunction at 24-h post-transplant and a longer stay in the ICU were found in recipients from extended criteria donors. However, this liberal policy did not seem to have a significant negative impact on hospital outcome or late survival in our lung recipients.

Our high acceptance rate results from relaxing the donor criteria in the last decade. On the other hand, we believe that our policy to send an experienced surgeon to the donor hospital to assess the lungs *in situ* as often as possible has contributed to this result although we have no firm data to support this. This strategy is logistically feasible because two members of the staff are on call for transplants simultaneously and because the distances between our transplant center and the 26 referring donor hospitals in our network are all within 1-h car drive. More lungs were often found to be less marginal and thus transplantable after assessment *in situ* than originally believed at the time of organ offer. This policy resulted in an increase from 12 transplants/year on average before 2000 to more than 50 per year in the last 2 years (Fig. 1).

Our lung donor acceptance rate of 34% is more than double the rate of 15% published by Ware *et al.* in 2002 based on data from the Californian Transplant Donor Network [4] and one-half more than the figure (23%) reported in a recent multicenter study from Canada [7]. Our center also surpasses the mean lung donor yield in Eurotransplant in 2008 by more than one-third [8]. Belgium with a population of approximately 10.7 million and 94 new procedures in the year 2007 is the country with the highest lung transplant rate per inhabitant (8.8 pmp) in Eurotransplant and in the world. Donor figures, however, should be interpreted with caution as

donor demographics may well vary from one donor region to another and different centers may calculate and report figures in a different manner. First, the moment of data recording during the donor process may differ. Some lungs classified as marginal based on parameters (e.g. oxygenation) recorded at the time of donor offer may well turn into perfect lungs when atelectasis is completely removed with ventilation in an open chest during organ recovery. Secondly, the denominator may differ amongst studies. We have only used effective organ donors (including kidney-only donors) as denominator because other offers never resulted in an organ donor for various reasons and thus lung donation was never discussed with a member of the lung transplant team. If we add the 70 potential donors that were turned down because of general medical contraindications to the 164 effective MODs, then our lung donor yield would drop from 34.1% to 23.9%.

When we compared the current lung donor profile (2006–2007) with the one in the first 2 years of our lung transplant program (1991–1992), we noticed that the median age rose from 34 to 48 years, the number of donors ventilated for more than 5 days increased from 8% to 26%, and the percentage of traumatic cause of brain death decreased from 69% to 52% [20]. Moreover, the lung acceptance rate increased nearly fivefold from as low as 7% to 34.1% nowadays.

Some of the MODs that were turned down for lung donation by one member of our team may well have been accepted by another member. We acknowledge that the acceptance of a donor lung is very subjective as demonstrated in this study by the overlap in criteria between marginal lungs that were rejected (Table 1) and those that were accepted (Table 2). However, it should be stated that most of the declined donors had more extended lung criteria than those whose lungs were accepted.

There are no evidence-based rules to define how far we can extend the criteria before the donor lung becomes unacceptable for transplantation [19]. We believe that a heavily consolidated pulmonary graft as a result of food aspiration or pneumonia is quite different in terms of operative risk as compared with a contused or edematous lung. The infected graft may rapidly lead to sepsis in the recipient especially when extracorporeal support is needed to adequately oxygenate the recipient in case of primary graft failure. In contrast, contusion and edema may rapidly resolve in the early post-transplant period with increased ventilatory settings. Twelve donors (21%) in our study had a smoking history of more than 20 years. Gas exchange was reported to be poorer and mechanical ventilation prolonged in recipients of lungs from current heavy smokers [18]. Ten lung donors (18%) had infiltrations on chest X-ray. In an earlier study, Shumway pointed out that small pulmonary infiltrates *per se* are not an absolute contraindication [10]. It is well known that some X-ray abnormalities may be related to retained secretions and atelectasis that can be easily corrected. Professional early donor management including bronchoscopic toilet and improved ventilatory settings may result in a higher acceptance rate of donor lungs initially rejected [3,12,14,21,22]. Nine of our lung donors (16%) were older than 55 years. Previous studies have reported a negative effect of donor age on outcome, especially when combined with longer graft ischemic times [3,19], although this effect is no longer seen in the ISHLT registry data for many years [1]. Only two lung donors (4%) had a PaO_2/FiO_2 ratio below 300 mmHg. In a study by Thabut *et al.*, recipients of donor lungs with such a PaO_2/FiO_2 ratio demonstrated poorer gas exchange within the first 6-h post-transplantation as well as a prolonged mechanical ventilation and a decreased long-term survival [23]. Luckraz *et al.* also found a higher 30-day mortality when donor PaO_2/FiO_2 ratio was between 225 and 300 mmHg although no difference was noted in long-term outcome [24].

Although in our study a comparable outcome was found between the extended and the standard donor group, the apparent differences may become significant with larger numbers and longer follow up. Three out of 27 recipients died in hospital in the extended donor group versus 1/23 recipients in the standard donor group (Table 4). One death in the extended group was directly related to an unrecognized Aspergillus infection in the donor. The two other recipients died from other problems not directly related to the quality of the donor lung. There was also no significant difference in late deaths between both groups ($P = 0.13$) although survival appeared lower (Fig. 3) in recipients who received lungs from an extended donor as a result of two patients dying from bronchiolitis obliterans in the second year (Table 4).

In this study, single lung recipients were older than those of the double-lungs recipients. Although not observed in this study, survival after single- in relation to double lung transplantation is reported to be lower for both obstructive [25] and restrictive [26] lung diseases. This difference in survival is believed to be related to the older recipient age and related co-morbidity. Postoperative care may also be more challenging in single lung recipients in case of ventilation-perfusion mismatch. These patients, therefore, as well as recipients with primary or associated pulmonary hypertension should receive perfect lungs from the start. We believe that lungs from extended donors should preferentially be allocated to low-risk patients listed for double lung transplantation (e.g. emphysema). More extended criteria lungs were transplanted in older emphysema patients (16/28 or 57%)

when compared with younger cystic fibrosis patients (4/11 or 36%) (Table 3).

This study suffers from several limitations. First, there were a few incomplete data as a result of the retrospective nature of the study. Smoking history was not documented in 18% of our lungs donors and the number of pack-years was often not recorded. Second, the number of patients in each donor group was limited and a longer study period with more local donors would have given a more powerful statistical analysis. Furthermore, there was no follow up in six recipients who were transplanted at other centers with lungs coming from our donor hospital network. Finally, there was only a short follow-up in the recipients, so the impact of using extended donor lungs on long-term outcome and on the development of bronchiolitis obliterans is still to be investigated.

In conclusion, lung donor acceptance rate (34.1%) in our network is 10–20% higher than the currently reported figures. The acceptance of extended criteria donors doubled the number of lung transplants in our center. This policy did not significantly influence hospital outcome and early survival in our lung recipients, but longer follow-up is needed. We believe that lungs from extended donors should preferentially be allocated to low-risk patients listed for double lung transplantation.

Conference

Presented at the 16th European Conference on General Thoracic Surgery of the European Society of Thoracic Surgeons, Bologna, 8–11 June 2008.

Authorship

CM and DVR: designed the study. CM: collected data. CM and DVR: wrote the paper. GMV: WC, HD, PDL, PN and TL: took care of patients reported in the study and reviewed the paper.

Funding

The work was supported by grant OT/03/55 from Katholieke Universiteit Leuven. Dirk Van Raemdonck is a senior clinical investigator supported by the Fund for Research-Flanders (G.3C04.99).

Acknowledgements

The authors acknowledge the help from our transplant coordinators (Dirk Claes, Joachim de Roey, Bruno Desschans, Frank Van Gelder, Dirk Van Hees, Glen Van Helleputte) in collecting donor data. Special thanks go to Shana Wauters, MSc for help with data analysis.

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