Deceased-donor lobar lung transplant: A successful strategy for small-sized recipients

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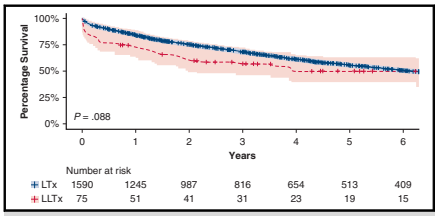
ABSTRACT

Objectives: Lobar lung transplantation (LLTx) from deceased donors is a potential solution for donor–recipient size mismatch for small sized recipients. We reviewed our institutional experience to compare outcomes after LLTx to standard lung transplantation (LTx).

Methods: We retrospectively reviewed transplants in our institution from January 2000 to December 2017. LLTx early- and long-term outcomes were compared with LTx. Additional analysis of outcomes was performed after dividing the cohort into 2 eras (era 1, 2000-2012; era 2, 2013-2017).

Results: Among the entire cohort (1665), 75 were LLTx (4.5%). Compared with LTx, LLTx were more frequently bridged to transplant with extracorporeal life support or mechanical ventilation and were transplanted in a rapidly deteriorating status (respectively, 20% vs 4.4%, $P = .001$; 22.7% vs 7.9, $P < .001$; and 41.3% vs 26.5%, $P = .013$). LLTx had longer intensive care unit and hospital lengths of stay (respectively, median 17 vs 4 days, and 45 vs 23, both $P < .001$), and greater 30-day mortality (13.3% vs 4.3%, $P = .001$) and 90-day mortality (17.3% vs 7.2%, $P = .003$). In era 2, despite a significantly greater 30-day mortality (10.8% vs 2.8%, $P = .026$), there was no significant difference in 90-day mortality between LLTx and LTx (13.5% vs 5.1%, $P = .070$). Overall survival at 1, 3, and 5 years was not significantly different between LLTx and LTx (73.2% vs 84.4%, 56.9% vs 68.4% and 50.4% vs 55.8, $P = .088$).

Conclusions: Although LLTx is a high-risk procedure, both mid- and long-term survival are comparable with LTx in all cohorts in the modern era. LLTx therefore represents a valuable surgical option for small-sized recipients. (J Thorac Cardiovasc Surg 2021;161:1674-85)



Kaplan–Meier survival comparison between LLTx and LTx.

CENTRAL MESSAGE

Lobar lung transplantation is higher risk than standard lung transplantation, yet mid- and long-term survival are comparable in modern times, and it is a valuable surgical option for small-sized recipients.

PERSPECTIVE

LLTx represents a challenging procedure due to the technical complexity and more demanding perioperative management. However, our mid- and long-term outcomes are comparable with LTx and show that LLTx remains a valuable surgical alternative for reconciling size mismatches between donors and recipients, especially those with small chest cavities and children.

See Commentaries on pages 1686 and 1687.

Lung transplantation (LTx) is a widely applied therapy for selected patients with end-stage lung failure. Although the number and outcomes of LTx are improving yearly worldwide, primary graft dysfunction (PGD), chronic graft failure, and scarcity of donors are limitations of this procedure, with the latter being the greatest impediment to offering this therapy to all patients to whom it would be of benefit.

Various strategies have been developed to increase the pool of deceased donors, such as ex vivo lung perfusion

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Abbreviations and Acronyms

CLAD = chronic lung allograft dysfunction
CPB = cardiopulmonary bypass
DCD = donation after circulatory death
ECLS = extracorporeal life support
ECMO = extracorporeal membrane oxygenation
EVLP = ex vivo lung perfusion
FEV1 = forced expiratory volume in 1 second
ICU = intensive care unit
LLTx = lobar lung transplantation
LOS = length of stay
LTx = lung transplantation
PGD = primary graft dysfunction
TLC = total lung capacity

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(EVLP),[1,2] donation after circulatory death (DCD),[3-7] optimized donor care in the intensive care unit (ICU),[8] and size-reducing surgical techniques to increase potential donors for small-sized recipients.[9-11] Among the last group, there are 2 main techniques that have been described: non-anatomic size reduction using multiple wedge resections, or lung volume reduction, and lobar lung transplantation (LLTx). Specifically, LLTx has been advocated as a potential solution for the donor-organ shortage for adults with small-sized chest cavities and children, both of whom tend to have longer waiting times.

LLTx is a more challenging and infrequently used technique that requires careful perioperative management. For that reason, the international experience with LLTx from deceased donors appears to have been relatively limited, with only a few centers having reported their results.[12,13] In this study, we reviewed our institutional experience with LLTx compared with standard LTx in the Toronto Lung Transplant Program.

METHODS

This single-center retrospective study included all lung transplants performed between January 2000 and December 2017 (total transplants = 1665; LTx = 1590 and LLTx = 75). The study was approved by the University Health Network Research Ethics Board (Coordinated Approval Process for Clinical Research ID: 18-5794). All variables were collected from our program's prospectively collected database and the patients' charts.

A comparison between the 2 study groups was performed for the entirety of the study period from 2000 to 2017. Secondary analyses were performed by dividing the study period into 2 eras: era 1 included all transplants performed from 2000 to 2012, and era 2 included transplants performed from 2013 to 2017. Other than the temporal effect of early versus later experience, there are 2 major reasons for the specific temporal differentiation. First, the program policy for intraoperative support changed from cardiopulmonary bypass (CPB) to extracorporeal membrane oxygenation (ECMO) around 2012.[14] Since 2013, the majority of transplants that require intraoperative support have been carried out on ECMO, unless a simultaneous cardiac procedure is indicated. Second, even though the EVLP technique was introduced into clinical practice in 2008, EVLP significantly increased in use for graft evaluation and recovery starting in 2012.

Patients were placed on the waiting list in 1 of 3 groups: Rapidly deteriorating (status 3), semiurgent (status 2), and standard (status 1). The designation of rapidly deteriorating occurs after clinical assessment by the transplant surgeons and respirologists and takes into account factors that increase the patient acuity, such as requirement for bridging support, admission to hospital, and rapidly worsening functional status.

All analyses were conducted using R, version 3.5.1. (R Foundation for Statistical Computing, Vienna, Austria) and SPSS, version 23 (IBM Corp, Armonk, NY). For univariate analysis comparing baseline characteristics of LLTx with LTx, P values were calculated for numerical values using a t-test or Kruskal–Wallis tests when the data are not normally distributed, and χ^2 test for categorical variables. The survival analyses sections included univariate and multivariate results: univariate results came from Kaplan–Meier curves with log-rank tests (95% confidence intervals), and multivariate results were generated from a Cox proportional hazard model. All included variables were decided a priori based on clinical expertise. All variables were tested for the proportional hazards assumption and the diagnosis variable came back as violating this assumption, so all multivariable models are stratified based on this. As some diagnoses had different hazard proportions, the Cox models were stratified based on disease.

As data were prospectively collected, the majority of transplants were classified using the PGD definition from the 2005 International Society for Heart and Lung Transplantation consensus working group recommendations.[15]

RESULTS

Patient Demographics and Perioperative Results

Entire cohort (2000-2017). Recipient characteristics are summarized in Table 1 for the entire study period of 2000 to 2017. Patients who underwent LLTx were significantly younger and more often female than those who received LTx. The proportion of LLTx in the pediatric population (age <18 years old) was significantly greater than the proportion of LLTx in the adult transplant population (28% in pediatric [15/52] vs 3.7% in adults, $P < .001$). There was a trend toward longer time on the waiting list for LLTx (mean 205 days) compared with LTx (mean 162 days, $P = .16$).

There were no significant differences in indications for transplant when we compared the 2 groups: the most frequent diagnosis was idiopathic pulmonary fibrosis in both cohorts (36.0% in LTx vs 36.1% in LLTx); chronic obstructive pulmonary disease was a less-frequent diagnosis in LLTx, and all other diagnoses were similarly distributed in both groups (Table 1).

Single lung transplants were carried out less frequently in the LLTx group (2.7% vs 15.1%, $P = .003$). In the LLTx group, 2 patients were transplanted using a single lobe.

TABLE 1. Recipient demographics, complete study period (2000-2017)

	LTx	LLTx	*P* value
Total	1590	75	
Age, y, median [IQR]	56.0 [41.5, 62.9]	44.1 [21.2, 59.1]	<.001
Sex, n (%)			<.001
Male	916 (57.7)	14 (18.7)	
Female	674 (42.3)	61 (81.3)	
pTLC, median [IQR]	6.04 [5.05, 6.91]	4.70 [4.06, 5.17]	<.001
aTLC, median [IQR]	5.10 [3.42, 7.20]	3.20 [2.22, 4.47]	<.001
Diagnosis, n (%)			.188
IPF	574 (36.1)	27 (36.0)	
COPD	329 (20.7)	9 (12.0)	
CF	285 (17.9)	14 (18.7)	
A1-AT	64 (4.0)	1 (1.3)	
PPH	58 (3.7)	5 (6.7)	
BO	34 (2.1)	3 (4.0)	
Other restrictive disease	95 (6.0)	5 (5.3)	
Other	151 (9.5)	12 (16.0)	
Single LTx	240 (15.1)	2 (2.7)	.003
Bridging, n (%)			
MV			
No MV	1465 (92.1)	58 (77.3)	<.001
NIMV	36 (2.3)	5 (6.7)	
IMV	89 (5.6)	12 (16.0)	
ECLS	69 (4.4)	15 (20.0)	<.001
Status pre-LTx, n (%)			.013
Standard (status 1)	363 (22.9)	11 (14.7)	
Semiurgent (status 2)	803 (50.6)	33 (44.0)	
Rapidly deteriorating (status 3)	419 (26.4)	31 (41.3)	
Intraoperative support			<.001
CPB	406 (24.4)	38 (50.7)	
ECMO	265 (15.9)	26 (34.7)	
PGD 3 at 72 h			
Total, n (%)	106 (6.7)	20 (26.7)	<.001
On ECLS, n (%)	55 (3.5)	11 (14.7)	<.001
ECLS postoperative, n (%)	68 (4.3)	14 (18.6)	<.001
Hospital LOS, d median [IQR]	23 [16, 43]	45 [27, 86]	<.001
ICU LOS, d, median [IQR]	4 [2, 13]	17 [6, 33]	<.001
30-d mortality, n (%)	68 (4.3)	10 (13.3)	.001
90-d mortality, n (%)	114 (7.2)	13 (17.3)	.003

LTx, Lung transplantation; *LLTx*, lobar lung transplantation; *IQR*, interquartile range; *pTLC*, predicted total lung capacity; *aTLC*, actual total lung capacity; *IPF*, idiopathic pulmonary fibrosis; *COPD*, chronic obstructive pulmonary disease; *CF*, cystic fibrosis; *A1-AT*, alpha-1 antitrypsin deficiency; *PPH*, primary pulmonary hypertension; *BO*, bronchiolitis obliterans; *MV*, mechanical ventilation; *NIMV*, noninvasive mechanical ventilation; *IMV*, invasive mechanical ventilation; *ECLS*, extracorporeal life support; *CPB*, cardiopulmonary bypass; *ECMO*, extracorporeal membrane oxygenation; *PGD*, primary graft dysfunction; *LOS*, length of stay; *ICU*, intensive care unit.

More patients in the LLTx group required bridging using either mechanical ventilation (22.7% vs 7.9%, $P < .001$) or an extracorporeal life support (ECLS) device (20.0% vs 4.4%, $P < .001$). Moreover, LLTx were performed more frequently in patients whose status was rapidly deteriorating (41.3% vs 26.4%, $P = .013$). Intraoperative support (CPB or ECMO) was used in a significantly greater proportion of LLTx than LTx (85.3% vs 42.2%, $P < .0.001$).

The most frequent combination of transplanted lobes was right middle lobe plus right lower lobe and left lower lobe (37.3%). The second most common combination was right lower lobe and left lower lobe (12%), and the remaining patients had varying combinations of each lobe and, on occasion, lobar on one side and full lung on the other (22.6%).

LLTx recipients had significantly lower predicted total lung capacity (TLC) than LTx (Table 1). The mean actual TLC was also significantly lower in LLTx compared with LTx.

In general, our recipients are listed with an actual TLC and a predicted TLC. The donor lung is selected to match the TLC of the donor to the predicted TLC of recipient. The mean TLC ratio between donor TLC and recipient predicted TLC (TLC ratio—whole lung) was 1.61 (±0.45) in LLTx, before lung size reduction. However, as expected and intended, the mean TLC ratio between donors and recipients calculated considering only the volumes of the segments in the transplanted lobes (predicted TLC ratio—lobar) was 0.97 (±0.53).

Patients who underwent LLTx had a significantly greater likelihood of developing PGD grade 3 at 72 hours post-transplant and a significantly greater requirement for ECLS as a treatment for PGD grade 3 in the immediate postoperative period (Table 1). LLTx patients had a significantly longer ICU length of stay (LOS) and hospital LOS compared with LTx, and the 30- and 90-day mortality were significantly greater in the LLTx group (Table 1).

Multivariable logistic regression for 30-day mortality showed significantly increased risk for LLTx in older patients, redo lung transplantation, bridge to transplant using invasive mechanical ventilation, intraoperative use of CPB, and need for postoperative ECLS (Table 2). The same analyses were carried out for 90-day mortality, showing increased risk in redo lung transplant cases, intraoperative use of CPB and need for postoperative ECLS (Table 3).

On examining mid- and long-term survival, no significant differences were found at 1, 3 and 5 years (Figure 1). The Cox adjusted model including all patients revealed several risk factors for increased mortality: recipients bridged to transplant with invasive mechanical ventilation, intraoperative support using CPB, and need for postoperative ECLS. Conversely, intraoperative use of ECMO acts as a protective factor (Table 4).

TABLE 2. Multivariable logistic regression analysis for 30-day mortality

	Estimate (95% CI)	*P* value
Lobar LTx	1.408 (0.571-3.217)	.435
Age	1.024 (1.006-1.044)	.011
Sex (male)	0.677 (0.402-1.137)	.140
Redo LTx	4.168 (1.670-9.656)	.001
Bridge		
IMV	2.844 (1.096-7.088)	.027
NIMV	0.564 (0.029-3.277)	.601
PGD 3 at 72 h	1.085 (0.472-2.389)	.844
Rapidly deteriorating status	0.743 (0.378-1.392)	.370
Intraoperative support		
CPB	4.944 (2.746-9.256)	<.001
ECMO	1.412 (0.622-3.131)	.400
Postoperative ECLS	15.112 (7.060-32.810)	<.0001

CI, Confidence interval; *LTx*, lung transplantation; *IMV*, invasive mechanical ventilation; *NIMV*, noninvasive mechanical ventilation; *PGD*, primary graft dysfunction; *CPB*, cardiopulmonary bypass; *ECMO*, extracorporeal membrane oxygenation; *ECLS*, extracorporeal life support.

TABLE 3. Multivariable logistic regression analysis for 90-day mortality

	Estimate (95% CI)	*P* value
Lobar LTx	1.448 (0.673-2.934)	.322
Age	1.013 (1.000-1.027)	.060
Sex (male)	0.904 (0.609-1.347)	.618
Redo LTx	2.735 (1.242-5.619)	.008
Bridge		
IMV	1.383 (0.622-2.916)	.408
NIMV	0.516 (0.079-1.919)	.394
PGD 3 at 72 h	1.116 (0.549-2.174)	.754
Rapidly deteriorating status	1.106 (1.106-0.680)	1.757
Intraoperative support		
CPB	2.879 (1.873-4.452)	<.001
ECMO	1.019 (0.551-1.829)	.951
Postoperative ECLS	8.189 (4.246-15.850)	<.001

CI, Confidence interval; *LTx*, lung transplantation; *IMV*, invasive mechanical ventilation; *NIMV*, noninvasive mechanical ventilation; *PGD*, primary graft dysfunction; *CPB*, cardiopulmonary bypass; *ECMO*, extracorporeal membrane oxygenation; *ECLS*, extracorporeal life support.

One concern about LLTx is the potential technical difficulty anastomosing the recipient main bronchi with the donor lobar bronchi. In this group of LLTx patients, 26.7% had a postoperative bronchoscopy in the short- to mid-term that was reported as showing some abnormality—either cartilage protrusion, punctate dehiscence, partial stenosis, or malacia. However, only 3 patients (4%) needed endoscopic interventions: 2 unilateral dilatation with balloon and 1 stenting of the left bronchial anastomosis.

Era 1 (2000-2012) versus era 2 (2013-2017). After we divided the cohort into 2 groups (era 1, 2000-2012 and era 2, 2013-2017), there were similar demographics compared with the entire cohort. In era 1, patients who underwent LLTx were significantly younger than LTx recipients, although in era 2 this difference did not persist. LLTx recipients were more likely to be female in both eras 1 and 2.

In both eras 1 and 2, recipients of LLTx had a significantly lower predicted TLC. Although there were no significant differences between the indications for transplant when we compared LLTx and LTx in eras 1 and 2, a larger number of patients in era 2 underwent LLTx for idiopathic pulmonary fibrosis, and a smaller number of patients in era 2 underwent LLTx for cystic fibrosis. This difference is reflective of the changes in underlying disease indications for transplant experienced in our entire transplant program over those time periods.

Similar to the entire cohort, the proportion of patients who were transplanted in a rapidly deteriorating status was greater in LLTx in era 1 (34.2% vs 18.7%, $P = .02$). This difference is lost in era 2 patients (48.6% vs 37.7%, $P = .361$).

The perioperative outcomes for LLTx when divided by era were similar to the entire cohort: significantly greater likelihood of developing PGD 3 at 72 hours, significantly greater rate of ECLS use postoperatively, and significantly longer ICU and hospital LOS. In era 1, the 30- and 90-day mortality for LLTx and LTx were 15.8% versus 5.3% ($P = .018$) and 21.1% versus 8.6% ($P = .020$). In era 2, there were significant differences in 30-day mortality between the LLTx and LTx groups (10.8 vs 2.8%, $P = .026$). However, there were no significant differences in 90-day mortality (13.5% vs 5.1%, $P = .070$). The recipient characteristics in era 1 and era 2 are shown in Tables 5 and 6.

In era 1, even though the differences in survival between LLTx and LTx were more evident, they were not significant in the long-term (Figure 2). Also, in era 2, there were no significant differences in 1-, 3-, and 5-year survival between LLTx and LTx (Figure 2).

Donor Characteristics

Over the total study period (2000-2017) the majority of donors were brain dead donors (89.1%). The remainder of the donors (10.8%) were Maastricht type III DCD donors.[16] There were no differences in the use of DCD between LLTx and LTx This similar distribution was maintained over the years, with no difference in the analysis of the 2 eras. There were significant differences in donor sex when we compared LLTx and LTx. LLTx patients received a significantly lower proportion of grafts from female donors than LTx.

The mean donor predicted TLC was significantly greater in LLTx (Table 7). Comparing LLTx and LTx,

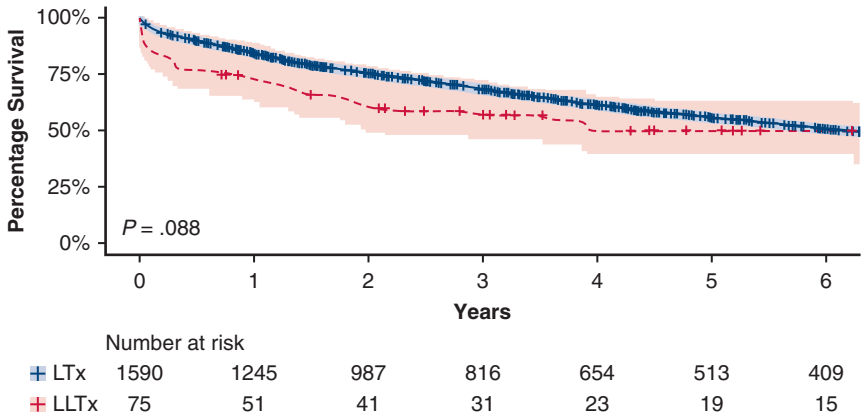


FIGURE 1. Kaplan–Meier survival curve for standard LTx and LLTx for the entire cohort (2000-2017). *LTx*, Lung transplantation; *LLTx*, lobar lung transplantation.

we found that rates of smoking history, median age, and mean last recorded oxygen tension/inspired oxygen fraction ratio were not different between the 2 study groups.

There were no differences seen in the use of EVLP between the 2 groups; however, in era 1, EVLP was used significantly more for LLTx than LTx. This statistical difference is lost in era 2.

Best Forced Expiratory Volume in the First Second (FEV1) After Transplant and Chronic Lung Allograft Dysfunction (CLAD)

For the mean best FEV1 comparison between LLTx and LTx, pediatric recipients were excluded because pulmonary functional tests (PFTs) after transplant are not routinely performed in this group. Mean best FEV1 achieved after transplant was significantly lower in LLTx than LTx (mean 1.65 L [±0.52] vs 2.67 L [±0.86], $P < .001$). No significant differences were found between the 2 groups regarding the development of chronic lung allograft dysfunction (CLAD) at any time point (Figure 3). Considering only patients diagnosed with CLAD and excluding those who had no pulmonary functional tests, there were no differences in the time to onset of CLAD between LLTx and LTx (mean 1366.56 days [±1110] vs 1094.58 days [±978], $P = .193$).

TABLE 4. Adjusted Cox model for survival among all patients (stratified by diagnosis)

	HR (95% CI)	*P* value
Lobar LTx	1.109 (0.783-1.570)	.5594
Age	1.011 (1.004-1.019)	.0041
Sex (male)	1.092 (0.941-1.267)	.2484
Redo LTx	1.788 (1.134-2.820)	.0123
Bridge		
ECLS	1.573 (0.980-2.524)	.6801
IMV	1.534 (1.046-2.249)	.0285
NIMV	1.528 (0.961-2.428)	.0729
Single LTx	1.121 (0.905-1.388)	.2959
Rapidly deteriorating status	1.001 (0.820-1.223)	.991
Intraoperative support		
CPB	1.189 (1.007-1.403)	.0405
ECMO	0.739 (0.559-0.976)	.0333
Postoperative ECLS	3.755 (2.793-5.048)	<.0001

HR, Hazard ratio; *CI*, confidence interval; *LTx*, lung transplantation; *ECLS*, extracorporeal life support; *IMV*, invasive mechanical ventilation; *NIMV*, noninvasive mechanical ventilation; *CPB*, cardiopulmonary bypass; *ECMO*, extracorporeal membrane oxygenation.

DISCUSSION

Several strategies have been implemented to mitigate the scarcity of suitable donor organs for lung transplantation. In addition to EVLP,[1,2] DCD donors,[3-7] and improvements in donor care in the ICU,[8] lobar lung transplantation from deceased donors has been performed for small-sized adults and pediatric recipients.[12,17-22] In this study, we reviewed our institutional experience with LLTx in comparison with our outcomes for LTx.

Lobar separation in the LLTx setting is routinely performed on the back table, usually after preparing the recipient hilum for implantation. Performing back-table lobectomies can be challenging and time-consuming, with important technical considerations. First, the recipient bronchial division and preparation must be precise, ensuring that sufficient proximal bronchial wall is available to perform an anastomosis while avoiding extensive peribronchial dissection to minimize the risk of anastomotic ischemia. Also, transplanting lobes with a blind bronchial stumps has traditionally been avoided (such us an upper lobe with a lower lobe bronchial stump) due to concerns about poor bronchial healing and bronchial dehiscence in the post-operative immunocompromised setting. However, recent series have shown good outcomes in the presence

TABLE 5. Recipient characteristics in era 1 (2000-2012)

	LTx	LLTx	*P* value
Total	940	38	
Age, y, median [IQR]	53.6 [38.9, 61.4]	24.6 [16.2, 49.7]	<.001
Sex			<.001
Male	527 (56.1)	8 (21.1)	
Female	413 (43.9)	30 (78.9)	
pTLC, median [IQR]	5.73 [4.95, 6.67]	4.41 [3.62, 4.86]	<.001
aTLC, median [IQR]	5.50 [3.60, 7.40]	3.17 [2.09, 4.10]	<.001
Diagnosis (%)			.052
IPF	290 (30.9)	9 (23.7)	
COPD	212 (22.6)	4 (10.5)	
CF	203 (21.6)	12 (31.6)	
A1-AT	44 (4.7)	0	
PPH	35 (3.7)	2 (5.3)	
BO	23 (2.4)	2 (5.3)	
Other restrictive disease	49 (5.2)	1 (2.6)	
Other	84 (8.9)	8 (21.0)	
Single LTx	124 (13.2)	0 (0)	.032
Bridging (%)			.014
MV			
No MV	880 (93.6)	31 (81.6)	
NIMV	21 (2.2)	2 (5.2)	
IMV	39 (4.2)	5 (13.2)	
ECLS	22 (2.3)	5 (13.2)	
Status pre-LTx (%)			.020
Standard (status 1)	239 (25.4)	4 (10.5)	
Semiurgent (status 2)	525 (55.9)	21 (55.3)	
Rapidly deteriorating (status 3)	176 (18.7)	13 (34.2)	
Intraoperative support			<.001
CPB	368 (37.6)	35 (92.1)	
ECMO	7 (0.7)	1 (2.6)	
PGD 3 at 72 h			
Total, n (%)	34 (3.6)	8 (21.1)	<.001
On ECLS, n (%)	24 (2.6)	7 (18.4)	<.001
ECLS postoperative, n (%)	26 (2.8)	9 (23.6)	<.001
Hospital LOS, d, median [IQR]	23.0 [16.0, 42.0]	40.5 [24.0, 77.5]	.003
ICU LOS, d, median [IQR]	4.0 [2.0, 14.0]	14.0 [7.0, 30.5]	<.001
30-d mortality, n (%)	50 (5.3)	6 (15.8)	.018
90-d mortality, n (%)	81 (8.6)	8 (21.1)	.020

LTx, Lung transplantation; *LLTx*, lobar lung transplantation; *IQR*, interquartile; *pTLC*, predicted total lung capacity; *aTLC*, actual total lung capacity; *IPF*, idiopathic pulmonary fibrosis; *COPD*, chronic obstructive pulmonary disease; *CF*, cystic fibrosis; *A1-AT*, alpha-1 antitrypsin deficiency; *PPH*, primary pulmonary hypertension; *BO*, bronchiolitis obliterans; *MV*, mechanical ventilation; *NIMV*, noninvasive mechanical ventilation; *IMV*, invasive mechanical ventilation; *ECLS*, extracorporeal life support; *CPB*, cardiopulmonary bypass; *ECMO*, extracorporeal membrane oxygenation; *PGD*, primary graft dysfunction; *LOS*, length of stay; *ICU*, intensive care unit.

TABLE 6. Recipient characteristics in era 2 (2013-2017)

	LTx	LLTx	*P* value
Total	650	37	
Age, y, median [IQR]	58.3 [46.3, 65.2]	56.7 [37.9, 60.3]	.063
Sex (%)			<.001
Male	389 (60.0)	6 (16.2)	
Female	259 (40.0)	31 (83.8)	
pTLC, median [IQR]	6.51 [5.25, 7.11]	5.00 [4.53, 5.35]	<.001
aTLC, median [IQR]	4.50 [3.20, 6.70]	3.20 [2.30, 4.70]	<.001
Diagnosis (%)			.745
IPF	284 (43.7)	18 (48.7)	
COPD	117 (18.0)	5 (13.5)	
CF	82 (12.6)	2 (5.4)	
A1-AT	20 (3.1)	1 (2.7)	
PPH	23 (3.5)	3 (8.1)	
BO	11 (1.7)	1 (2.7)	
Other restrictive disease	46 (7.1)	3 (8.1)	
Other	67 (10.3)	4 (10.8)	
Single LTx	116 (17.8)	2 (5.4)	.194
Bridging (%)			.004
MV			
No MV	585 (90.0)	27 (73.0)	
NIMV	15 (2.3)	3 (8.1)	
IMV	50 (7.7)	7 (18.9)	
ECLS	49 (7.5)	10 (27.0)	<.001
Status pre-LTx (%)			.361
Standard (status 1)	124 (19.2)	7 (18.9)	
Semiurgent (status 2)	278 (43.1)	12 (32.4)	
Rapidly deteriorating (status 3)	243 (37.7)	18 (48.7)	
Intraoperative support			.005
CPB	38 (5.5)	3 (8.1)	
ECMO	258 (37.6)	25 (67.6)	
PGD 3 at 72 h			
Total (%)	72 (11.1)	12 (32.4)	.001
On ECLS (%)	31 (4.8)	4 (10.8)	.112
ECLS postoperative (%)	42 (6.5)	5 (13.5)	.098
Hospital LOS, median [IQR]	25 [17, 47]	46 [32, 97]	<.001
ICU LOS, median [IQR]	4 [2, 11]	18 [5, 33]	<.001
30-d mortality, n (%)	18 (2.8)	4 (10.8)	.026
90-d mortality, n (%)	33 (5.1)	5 (13.5)	.070

LTx, Lung transplantation; *LLTx*, lobar lung transplantation; *IQR*, interquartile; *pTLC*, predicted total lung capacity; *aTLC*, actual total lung capacity; *IPF*, idiopathic pulmonary fibrosis; *COPD*, chronic obstructive pulmonary disease; *CF*, cystic fibrosis; *A1-AT*, alpha-1 antitrypsin deficiency; *PPH*, primary pulmonary hypertension; *BO*, bronchiolitis obliterans; *MV*, mechanical ventilation; *NIMV*, noninvasive mechanical ventilation; *IMV*, invasive mechanical ventilation; *ECLS*, extracorporeal life support; *CPB*, cardiopulmonary bypass; *ECMO*, extracorporeal membrane oxygenation; *PGD*, primary graft dysfunction; *LOS*, length of stay; *ICU*, intensive care unit.

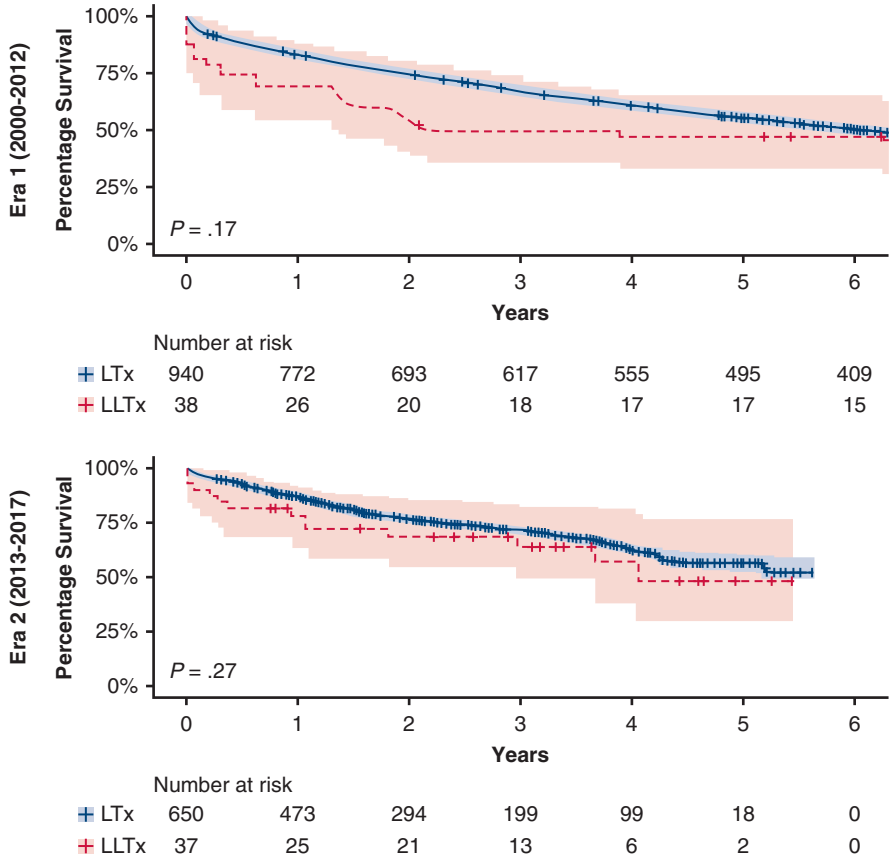


FIGURE 2. Kaplan–Meier survival curve for standard LTx and LLTx. *LTx*, Lung transplantation; *LLTx*, lobar lung transplantation.

of bronchial stumps.[23] Second, back-table vascular dissection and division of the donor vessels can be more challenging as the vessels are empty, in contrast to the usual blood-filled vessels with which surgeons are familiar. For those reasons, plus the more demanding perioperative management that these patients require, the majority of LLTx are usually performed in experienced large-volume lung transplant centers.

The size mismatch between the lobar graft bronchus and the recipient's main stem bronchus may be a concern in LLTx. Achieving a tension-free anastomosis is a critical technical point to prevent airway complications. In this series, the rate of airway complications requiring endoscopic intervention was 4.0% (3/75), remarkably less than other reported series ranging from 12% to 16%.[17,18,21]

Our LLTx technique does not differ substantially from our standard LTx bronchial anastomosis, with the use of running absorbable monofilament suture (4-0 PDS, polydioxanone; Ethicon, Inc, Somerville, NJ) for the membranous wall and interrupted non-absorbable sutures (3-0 or 4-0 PROLENE; Ethicon) for the cartilaginous wall. The size mismatch is addressed by suture width correction with each stitch to create a conical end-to-end anastomosis. Telescoping the anastomosis is not usually performed unless size mismatch is prohibitive, although on occasion the anastomosis naturally telescopes. In addition, the bronchial anastomosis is routinely covered with peribronchial tissue from the donor and the recipient. In addition to proper donor-lung preservation and these technical details, gentle manipulation of the airway when performing the anastomosis should be ensured in all lung transplants, but especially in the LLTx cases to avoid traumatizing the bronchial tissue and provide optimal healing conditions.

Our program's approach to intervention for airway complications post-transplant takes into account the degree of abnormality of the airway and the clinical status of the patient. For those patients with severe anatomic abnormalities (eg, large area dehiscence, very tight stenosis preventing bronchoscopic examination) and resulting clinical consequences (eg, mediastinal abscess or large air leak, atelectasis of the stenotic lobe), intervention is performed. We prefer to attempt endoscopic intervention before reoperation. All patients with minor abnormalities and no clinical consequences are monitored endoscopically until resolution.

TABLE 7. Donor characteristics

	LTx	LLTx	*P* value
Donor type, all patients (%)			
BDD	1422 (89.5)	65 (86.7)	.560
DCD-III	167 (10.5)	10 (13.3)	
Donor type, era 1 (%)			1
BDD	888 (94.5)	36 (94.7)	
DCD-III	52 (5.5)	2 (5.3)	
Donor type, era 2 (%)			.703
BDD	534 (82.3)	29 (78.4)	
DCD-III	115 (17.7)	8 (21.6)	
Sex, n (%)			<.001
Male	824 (52.0)	59 (78.7)	
Female	761 (48.0)	16 (21.3)	
TLC, mean [SD]	6.07 [1.30]	7.07 [1.28]	<.001
Smoking history (%)			.546
Yes	758 (53.5)	35 (58.6)	
No	659 (46.5)	25 (41.4)	
Age, mean, y [SD]	45.0 [17.3]	43.3 [17.3]	.460
Pao_2/Fio_2, mean [SD]	407.5 [100.3]	410.9 [124.5]	.711
EVLP, all patients (%)			.155
Yes	251 (15.8)	17 (23.3)	
No	1339 (84.2)	58 (76.7)	
EVLP, era 1, n (%)			.044
Yes	58 (6.2)	6 (15.8)	
No	882 (93.8)	32 (84.2)	
EVLP, era 2, n (%)			.977
Yes	193 (29.7)	11 (29.7)	
No	457 (70.3)	26 (70.3)	

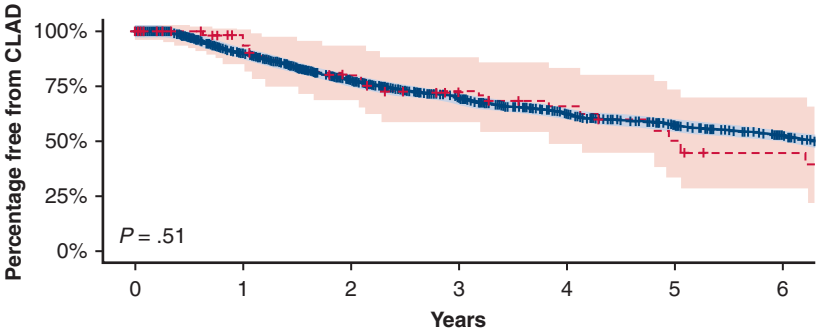
LTx, Lung transplantation; *LLTx*, lobar lung transplantation; *BDD*, brain death donor; *DCD-III*, death cardiac donor type III Maastricht classification; *TLC*, total lung capacity; *SD*, standard deviation; Pao_2, arterial oxygen tension Fio_2, inspired oxygen fraction; *EVLP*, ex vivo lung perfusion.

Donor and recipient size matching is calculated using a combination of donor predicted TLC and recipient predicted TLC as well as visual inspection of recipient chest cavity intraoperatively.[12] It has been previously reported from registry studies that TLC ratios between the donor and recipient from 0.5 to 1.3 might have less risk of death in the first year after transplantation. However, that risk rises when TLC ratio is over 1.3.[24] In addition, extremely oversized grafts may also result in thoracic tamponade and atelectasis of basal segments predisposing to infectious complications. Conversely, a lower risk of PGD grade 3 has been associated with oversized allografts.[25] At our center, when the donor TLC is up to 1 L greater than the recipient predicted TLC, non-anatomic size reduction is considered. When the donor TLC is more than 1 L larger than the recipient predicted TLC, we consider performing LLTx. This decision is usually made preoperatively but can also be made intraoperatively at the time of examination of the chest cavity and graft size. In our study, the mean TLC ratio for the LLTx patients would have been 1.61 but the mean TLC ratio for LLTx (lung volume actually transplanted) was 0.97, reflecting effective amelioration of the size-mismatch between donor and recipient. Therefore, LLTx can be a good solution when there is a considerable size-mismatch, especially if the TLC ratio of the donor full lung and recipient predicted TLC is approaching 2.

Significantly more patients who underwent LLTx in era 1 were transplanted in a rapidly deteriorating status. This, plus the greater rate of PGD grade 3 at 72 hours and postoperative requirement for ECLS in both eras, may explain the greater early mortality in all cohorts. The incidence of PGD grade 3 and need for postoperative ECLS are comparable with other published series of LLTx[12,13] and explain the longer ICU and hospital LOS. However, in our series, we have shown improvements in outcomes when only the modern era is considered. In era 2, although early mortality and PGD grade 3 is still significantly greater in LLTx, long-term survival for LLTx is not significantly different than LTx. Although the proportion of patients who were considered rapidly deteriorating in era 2 was greater than era 1, it was not significantly greater than the proportion of rapidly deteriorating patients in era 2 who underwent LTx. Earlier in our experience, we transplanted patients who were bridged to transplant using mechanical ventilation or ECLS less frequently overall. Thus, compounding the risk of a technically demanding procedure with a complex, high-risk recipient may have contributed to worse outcomes in the LLTx group in the early era. As our program experience has grown, both with ECLS and transplantation of more complex patients, our success with LLTx has improved to be comparable with LTx in the long term, despite the fact that the acuity of the entire modern cohort has increased. Several additional factors might have contributed to this improvement in survival in era 2, such as the implementation of EVLP assessment, the near-routine use of ECMO in the intraoperative setting, and the use of prophylactic postoperative ECLS support.

The use of EVLP for evaluating, reconditioning, and treating otherwise-unsuitable organs was implemented and standardized in our program in 2008.[1,2] It is difficult to discern the true extent of impact of EVLP in the LLTx setting. However, since EVLP has been increasingly used over time irrespective of the type of transplantation, the sequelae of this practice change may be that better quality grafts with predictable function are being used in all recipients.

One potential problem in LLTx is that reperfusion edema may occur in an exaggerated fashion in the first graft during the implantation of the second graft, due to the comparatively reduced vascular bed that is receiving the recipient's full cardiac output in comparison to a full lung. It is thus imperative to perform LLTx using intraoperative cardiopulmonary support, which has been



Number at risk

LTx	1552	1124	835	669	520	405	320
LLTx	60	40	30	19	15	10	7

	1-year	95% CI	3-year	95% CI	5-year	95% CI
LTx	90%	88.4, 91.6	68.5%	65.9, 71.4	54.6%	51.5, 57.9
LLTx	98.2%	94.9,1	78.6%	67.7, 91.5	51.9%	36.6, 73.6

FIGURE 3. Kaplan–Meier curve of chronic lung allograft dysfunction-free survival for standard LTx and LLTx for the entire cohort (2000-2017). *CLAD*, Chronic lung allograft dysfunction; *LTx*, lung transplantation; *LLTx*, lobar lung transplantation; *CI*, confidence interval.

supported in the literature.[12] Intraoperative ECLS may be avoided if the lobar graft is implanted second after a full-sized lung has been implanted on the contralateral side. In our institution, routine intraoperative support changed from CPB to ECMO in 2012.[14] Benefits from the use of ECMO in the intraoperative scenario have been widely addressed and published by our group and others[14,26-30] and include shorter mechanical ventilation time, decreased ICU and hospital LOS, and decreased requirement for blood transfusion. In addition, a survival benefit in patients transplanted with elective intraoperative ECMO has been reported.[27] In the present

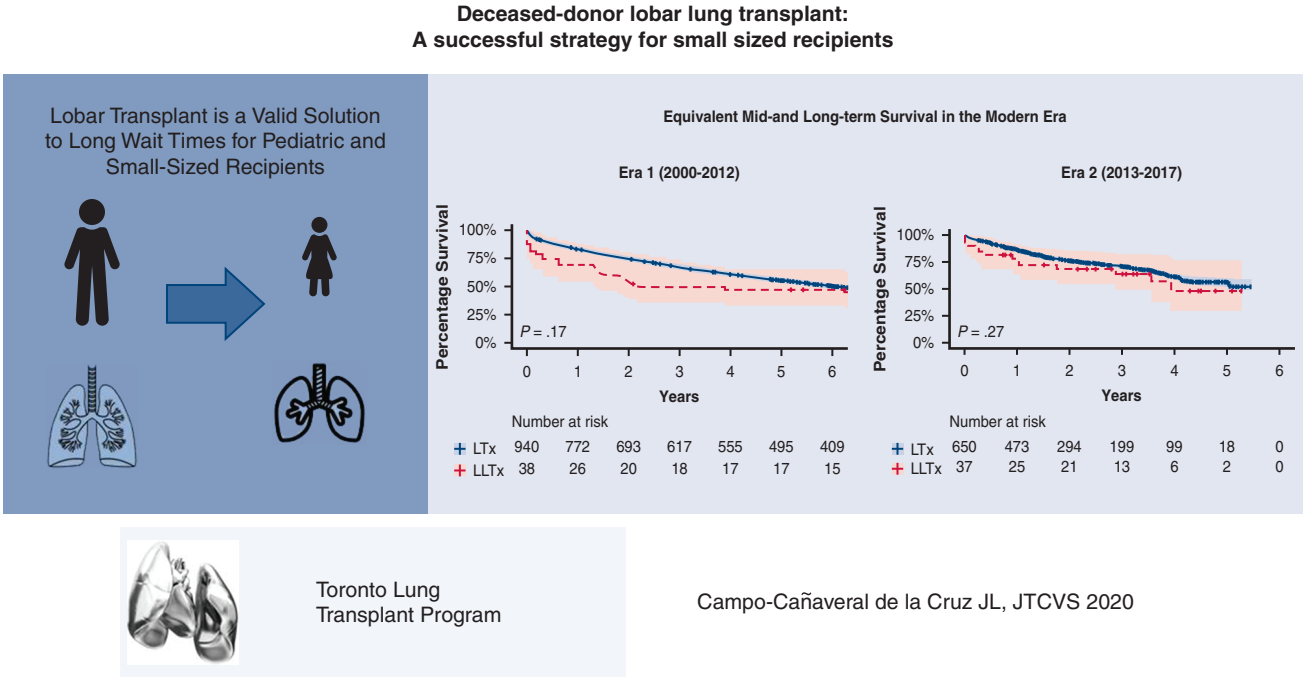


FIGURE 4. Lobar lung transplant should be considered a valid option for pediatric and small-sized recipients, as they have longer times on the waiting list. Survival has improved in the modern era, with equivalent 90-day and long-term survival when compared with standard bilateral lung transplant. *LTx*, Lung transplantation; *LLTx*, lobar lung transplantation.

study, according to the Cox model analysis, the use of CPB appeared to have a negative impact on overall survival, which supports the change from CBP to ECMO in the LLTx setting.

This study has several limitations. First, it is a single-center retrospective observational cohort analysis. The relatively small number of patients lowers the statistical power, which may explain the null findings. Second, evolution and changes over time in immunosuppressive and antibiotic therapies, surgical technique, donor and recipient selection criteria, and management of complications are not specifically addressed. However, we partially overcame this limitation by analyzing the cohort by eras, given that use of EVLP assessment, as a milestone in lung transplantation, and ECMO as intraoperative support, have been 2 significant implementations in the program and may have impacted the LLTx outcomes.

CONCLUSIONS

In summary, small-sized recipients have prolonged waiting times and greater waitlist mortality due to shortage of small-sized donor organs. LLTx is a potential solution to address these factors. Although LLTx recipients represent a greater-risk population among lung transplant patients and have greater early mortality, mid- and long-term survival are comparable with standard LTx in our cohort (Figure 4). Therefore, LLTx should be considered a valid surgical alternative to reconcile the size-mismatch between donors and recipients in small-sized adults and pediatric patients in experienced high-volume centers.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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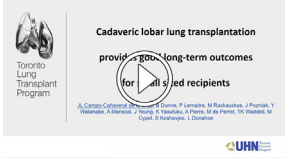

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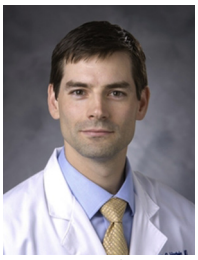
Key Words: lung transplant, lobar lung transplant, size matching

Discussion

Presenter: Dr Jose Luis Campo-Cañaveral de la Cruz



Dr Matthew G. Hartwig *(Durham, NC)*. Thank you, Dr de la Cruz, for providing your paper well in advance, and for an excellent presentation today. I'm very pleased to have the opportunity to discuss the Toronto Lung Transplant experience. With this difficult dilemma for trying to optimize outcomes in our short-statured, diminutively sized chest cavity recipients, I think this is an important question for our community, but it's one that's very challenging to answer from the data, as you showed. This is one of the largest, if not the largest, series, but it still remains challenged by low numbers. For example, you see a loss in the statistical difference in survival in the later era–it's very few patients. Clinically, it seems that those patients struggle much more perioperatively. My first questions are slightly philosophical. Unlike in the setting of single-lung transplantation, where you are actually increasing the use rate, or maximizing the number of transplants done, in this procedure, you are dramatically downsizing a lung for it to fit into a smaller recipient without actually increasing the donor pool or the number of transplants that we perform. Do you think it's ethically appropriate if there's a difference in survival? Or if there's a greater risk to the recipients, is it ethically appropriate to use this strategy to simply redirect a usable organ to a smaller recipient?

Dr Jose Luis Campo-Cañaveral de la Cruz *(Madrid, Spain)*. It is a difficult question, but I do think with these numbers we can go ahead with a lobar transplant even though we don't optimize the donor pool. Especially in our more recent experience, the results are getting better and better. It all depends on where the problem is. If you don't have an important donor shortage, the ethical problem is not that big.

Dr Shaf Keshavjee *(Toronto, Ontario, Canada)*. We're fixing that problem. That's a really important point. I think Matt's point was that if we just take 2 lower lobes and throw away 2 upper lobes, have we disadvantaged 2 single-lung transplant patients? The first problem we are trying to address is that we have kids and small-statured individuals who are waiting a year and a half, while we have everybody else done in 2 weeks, so that's the challenge we are facing. Also, we are starting to be a bit more creative. We are doing 2 lower lobes and 2 upper lobes as 2 separate double-lung transplants from 1 donor. We've done the left-lung split operation with the lower lobe and upper lobe. I think that if you can get your teams together and do it, it is a lot of work and operating rooms going at the same time. You can be creative and do it. But you remember your bad cases, and that's why we started looking at it and said, "We'd better just see if this is still a good thing to be doing."

Dr Hartwig. That's great to maximize the use. Another option could be to think about allocation strategies. For example, in the United States increasing a lung allocation score for someone of small stature might be other ways to address this without having to piecemeal together for the parts. Your choice in lobar combinations in the manuscript, which I don't think you discussed in detail during the presentation, was very heterogeneous and included patients in whom you did a lung and a lobe, patients where you took various and sundry lobes, and there didn't seem to be a lot of method to the selection as described in the manuscript. Based on your experience, is there an optimal technical combination of lobes in this situation?

Dr Campo-Cañaveral de la Cruz. That's a great question. The most frequent combination was right middle and right lower lobe on the right side, and left lower lobe on the left side. I think that the final decision is made when you see the chest cavity of the recipient. If you see that what fits better is the left upper, you go ahead with the

left upper. But I think, after reviewing this experience, that the combination that we used most frequently was the one that fits better with the chest cavity of the recipient. As far as I know, there is no other specific anatomical reason, apart from the fact that sometimes one lobe fits better in one chest cavity.

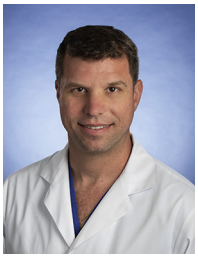
Dr Hartwig. So it's a case-by-case decision.

Dr Campo-Cañaveral de la Cruz. Yes, also using the total lung capacity donor–recipient combination.

Dr Keshavjee. For the analysis and the matching, we left out the ones who got a whole lung and half a lung, since that's really one and a half single-lung transplants. We really, in the survival and outcomes, are comparing 2 lobes, to double lungs.

Dr Hartwig. It wouldn't seem right not to ask you a question around ex vivo lung perfusion (EVLP) for the Toronto program. Now you talk about the advent of EVLP, and that's sort of helped determine some of your era delineation. Did you do any downsizing while on the EVLP, and if so was this technically easier that doing it on the back table or after implantation? If you did do any downsizing on the EVLP device, did it impact the assessment of the lung, the assessment period, or were there other implications for this strategy when combining the EVLP with pneumo-reduction?

Dr Campo-Cañaveral de la Cruz. Reviewing the database, there are no data that address that matter.



Dr Marcelo Cypel *(Toronto, Ontario, Canada)*. We always perform the anatomical down-sizing on the back table.

Dr Campo-Cañaveral de la Cruz. The assessment of EVLP is for the full-size lung, or the 2 lungs, and we go ahead on the back table with the lobar partition.

Dr Hartwig. This is wonderful work and a great presentation, thank you.

Dr Kenneth R. McCurry *(Cleveland, Ohio)*. I'll just ask you one technical question. How do you handle the bronchus?

Dr Campo-Cañaveral de la Cruz. The bronchus is one of the critical parts in the lobar transplantation, and all of the complications that can be avoided for that particular anatomical part are extremely important. You know that Toronto General has extensive experience in lung transplants, so the technical issues for the bronchial anastomosis have been exactly the same for many, many years, and the complications are very low. I have to say that the only technical thing is to manipulate as least as you can the bronchus on the back table during the dissection, giving the stump as much tissue as you can, and then a gentle manipulation during the anastomosis. You can cover the anastomosis or not. Another technical point is to address the discrepancy between the donor and the recipient. Sometimes it's not easy, and the anastomosis telescopes itself. I would say that perfect technical manipulation of the bronchus is one of the key parts.

Dr Thomas Egan *(Chapel Hill, NC)*. Technical question, but when you are splitting and using upper lobes and lower lobes, did you have trouble with either the middle lobe artery being too low or lingular branches being too low so that you had to sacrifice the lingula or middle lobe?

Dr Campo-Cañaveral de la Cruz. Again, looking at the database, I didn't see the reason why the middle lobe is preserved or sacrifice, but I would say that sometimes yes.

Dr Keshavjee. I can answer that, actually, because that's one of the things you lose in the database. The answer is yes and yes, so sometimes it just doesn't work. We want to keep as much lung as possible and sometimes you just end up having to sacrifice it, depending on where the artery comes off, so it's a challenge. I think Jose was asked a question from probably one of the most experienced lung transplant surgeons in the world, but the question that you asked, Ken, was the bronchus issue. I know most of the Japanese surgeons who do live donor transplants have experience in this, but if you're going to split and use both lobes, then you want to kind of keep that carina between the 2 lobes. If you actually split it, sometimes you lose structure because you don't have the spur. If you're only doing one lobe and are trying to preserve the spur at the lobar carina, it gives it a much better structure when you're putting a small bronchus into the main bronchus. When you are splitting it the other way, you just do what you can. Sometimes you end up sewing something that seems like membranous bronchus all the way around, and again I think it's important to correct on every bite and kind of splay it out. The other thing that is pleasantly surprising but predictable from the anatomy is the blood supply to the bronchus at that level is predominately (80% or 90%) pulmonary so it's less vulnerable than an anastomosis than a main bronchus.

Dr Campo-Cañaveral de la Cruz. Just a quick addition to that, when you're doing upper-lobe implantations, we always do the anastomosis in the upper-lobe bronchus, and not in the main bronchi avoiding leaving a stump, so it's always possible to anastomose directly the upper lobe orifice.