

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of living donor lung transplant for end-stage lung disease

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in April 2005

Procedure names

Living lung transplantation
Living lobar lung transplantation

Specialty societies

Society of Cardiothoracic Surgeons of Great Britain and Ireland
British Transplant Society
British Thoracic Society

Description

Indications:

Lung transplants are performed in patients with non-malignant pulmonary disease that is unresponsive or minimally responsive to treatment and who have a life expectancy of less than a year. This may be the result of end-stage lung diseases, such as severe pulmonary fibrosis, cystic fibrosis, pulmonary hypertension and obliterative bronchiolitis.

The majority of live donor lung recipients are patients with cystic fibrosis. The majority of lung donors are first degree relatives who are compatible in terms of size and ABO group.

Current treatment and alternatives

Living donation is an alternative to cadaveric organ donation. The widening gap between supply of cadaveric organs and demand for organ transplant has led to the introduction of live donor transplants. Living donor transplantation increases the number of donor organs while preserving the supply of cadaveric donor lungs for patients on the waiting list.

Living donation is an option for patients for whom cadaveric transplantation is unsuitable, or those who have deteriorated clinically to the point of transplant ineligibility while waiting for a cadaveric donor. Living donation may also be an option for critically ill children, as there is a particular shortage of suitable cadaveric donors for this group.

What the procedure involves:

Living donor lung transplant requires three operations: two donor lobectomies and the recipient bilateral pneumonectomy and lung implant.

Once appropriate donors are identified, one is selected for right lower lobectomy and the other for left lower lobectomy.

In the donor procedures, under general anaesthetic a catheter is first inserted for analgesia and bronchoscopy is performed to exclude any abnormalities. The donor lung is then deflated and the chest opened. The inferior pulmonary ligament is incised and the mediastinal pleural is dissected to allow isolation of the pulmonary artery. Next the inferior pulmonary veins (and right middle lobe for a right lobectomy) are defined and any fissures are closed with a stapling device to minimise possible air leaks in the donor and the recipient. The lung is then reinflated and the pulmonary artery and vein are clamped leaving a cuff of tissue sufficient to allow successful implantation into the recipient while also allowing closure of these structures without compromise in the donor. The donor lobe is then resected and transported for transplantation into the recipient.

The recipient operation is performed under general anaesthesia through a transverse thoracosternotomy (clamshell) incision. Procedures are performed on cardiopulmonary bypass which allows simultaneous reperfusion of both lobes. Once the recipient pneumonectomies have been completed the lobes are implanted sequentially typically starting with the bronchial anastomosis. The pulmonary venous anastomosis is then performed, with the pulmonary artery anastomosis performed last. Once the second graft is implanted both lungs are inflated and the patient is weaned from cardiopulmonary bypass. Transoesophageal echocardiography and bronchoscopy are then performed to check for complications such as air leaks.

Efficacy

Recipient

In a study of 123 adult and paediatric patients who had undergone living lung transplant, 1-, 3- and 5-year survival was 70%, 54% and 45%¹. Infection was the main cause of death (33/63), followed by obliterative bronchiolitis (8/63). Overall freedom from obliterative bronchiolitis and bronchiolitis obliterans syndrome in adult recipients was reported as 98%, 82% and 76% at 1, 3 and 5 years respectively. In a non-randomised study from the same centre including some of these earlier patients outcomes were compared between living (n = 59) and cadaveric lung (n = 43) recipients who had survived more than 3 months after transplantation. The study found no significant differences between the groups in respect to survival; 1-, 3- and 5- year survival was 83%, 64% and 62% in the living lung group compared to 83%, 81% and 75% in the cadaveric recipients.² Freedom from obliterative bronchiolitis and bronchiolitis obliterans syndrome at 3 and 5 years was reported as 98% and 82% in the living lung group and 76% and 78% in the cadaveric group. Again, no significant differences were found between the groups. A true comparative analysis is difficult, however, because those receiving living lung donor transplants will often have poorer outcomes by nature of eligibility criteria (for example, underlying lung disease and preoperative severity of illness).

In a smaller study of 30 patients from a separate centre it was reported that all patients who had undergone living lung transplant were alive at a mean follow-up of

22 months.³ The higher survival rates in this study in contrast to the above studies may in part be explained by the difference in patient characteristics, in that only one patient with cystic fibrosis was included in this study.

Where pulmonary function was measured in the studies it was reported that patients who had undergone living lung transplant had improved function compared to preoperative values.

Donor

To date little information has been published on efficacy outcomes in living lung donors. In a study looking at outcomes following 253 donor lobectomies⁴ it was reported that donors who could be contacted at 1 and 2 years had reduced pulmonary function compared to preoperative values.

Specialist Advisors' opinions

The Specialist Advisors' opinions differed in respect to efficacy; while some stated that living lung recipient results appeared to be similar to those for cadaver lung transplants when performed by experienced surgeons, others expressed uncertainties about the long-term outcomes of recipients following living lung transplantation and the comparable incidence of obliterative bronchitis to those undergoing cadaveric transplant.

The Specialist Advisors also stated that donors were likely to experience loss of lung function following lobectomy.

Safety

Recipient

There was limited information reported on the complications in recipients following living lung transplant. In the studies that included both adult and paediatric patients, the incidence of acute rejection ranged from 0.8 to 1.5 episodes per patient.^{1,3} In a small study of 30 patients, complications following living lung transplantation included lung oedema (6/30), haemorrhage necessitating rethoracotomy (2/30) and cardiac tamponade (2/30). Tracheostomy was required in 15 patients (50%), reintubation in seven patients (23%) and re-opening of thoracotomy in three patients (10%).³

Donor

There were no reports of donor mortality in the literature following donor lobectomy. In one study it was reported that 19.8% (50/283) of donors had one or more perioperative complications following donor lobectomy.⁴ The most common complication was the need for a thoracostomy tube (15/50), either for persistent drainage or for air leaks. The most significant complication was pulmonary artery thrombosis, which occurred in two patients (0.8%). Eight patients (3.2%) also required re-operation because of bleeding (1.2%), bronchopulmonary fistula (0.4%), unresponsive pericarditis (0.4%), loculated pleural effusion (0.4%), a sterile empyema (0.4%) and a retained sponge (0.4%).

Specialist Advisors' opinions

The Specialist Advisors considered rejection (infection) and hyperexpansion of the lobar transplants leading to significant lung injury and subsequent failure in recipients to be the main complications following living lung transplant.

With respect to donors, the Specialist Advisors listed potential complications following donor lobectomy as prolonged air leak, bleeding, pleural sepsis, pulmonary embolism and bronchopleural fistula – although this was not considered a common complication. The Specialist Advisors also expressed uncertainties around the safety

of this procedure, particularly in relation to the high morbidity and psychological stress experienced by donors.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to living donor lung transplantation. Searches were conducted via the following databases, covering the period from their commencement to April 2005: Medline, Premedline, EMBASE and the Cochrane Library. Trial registries and the Internet were also searched. No language restriction was applied to the searches.

The following selection criteria (Table 1) were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies included. Emphasis was placed on identifying good-quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Patients who have had a live lobar transplantation or donor lobectomy patients.
Intervention/test	Living lung transplantation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on seven studies. Four of these studies are from the same group and some studies appear to be updated reports on the outcomes of patients treated since 1993.

Two papers are included in this overview that specifically report on the outcomes of living lung donors.^{4 5}

One abstract has been included because although it provided limited information, it does give some indication of results from a different study centre.⁶

Existing reviews on this procedure

There were no published reviews identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B details the recommendations made in each piece of guidance listed below.

Interventional Procedures

None

Technology Appraisals

None

Clinical Guidelines

NICE has published a clinical guideline 'Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care'.

Public Health

None.

Table 2 Summary of key efficacy and safety findings on living lung transplantation

Abbreviations used: COPD – chronic obstructive pulmonary disease; FVC – forced vital capacity; FEV – forced expiratory volume; SpO ₂ – oxygen saturation; OB - obliterative bronchiolitis; BOS – bronchiolitis obliterans syndrome																																																																						
Study details		Key efficacy findings		Key safety findings	Comments																																																																	
Bowdish et al. (2005) ² Non-randomised comparative study California, USA January 1993 – September 2002 125 adult patients who have undergone transplantation - 59 patients living-donor (originally 79) - mean age 27.5 years - primary indication cystic fibrosis (95%) - mean follow-up 4.1 years - 43 cadaveric recipients (originally 46) - mean age 45.2 years - primary indications COPD (33%) - mean follow-up 3.5 years Inclusion criteria: All patients fulfilled the criteria for cadaveric lung transplantation and were listed with the United Network for Organ Sharing. Living lobar lung transplantation recipients were selected primarily on the basis of a deteriorating clinical status and the expectation that a cadaveric donor would not become available.		Efficacy outcomes measured: Survival, pulmonary function (forced vital capacity, forced expiratory volume and mid-forced expiratory flow), exercise testing Survival – no significant differences between groups p=0.32. <table><tr><th>Group</th><th>Living donor</th><th>Cadaveric</th></tr><tr><td>1 year</td><td>83%</td><td>83%</td></tr><tr><td>3 years</td><td>64%</td><td>81%</td></tr><tr><td>5 years</td><td>62%</td><td>75%</td></tr></table> Causes of death <table><tr><td>Pneumonia</td><td>10 (42%)</td><td>4 (36%)</td></tr><tr><td>Sepsis</td><td>5 (21%)</td><td>3 (27%)</td></tr><tr><td>Bronchiolitis obliterans syndrome</td><td>3 (12%)</td><td>1 (9%)</td></tr><tr><td>Non-compliance</td><td>1 (4%)</td><td>2 (18%)</td></tr><tr><td>Other</td><td>5 (21%)</td><td>1 (9%)</td></tr><tr><td>Total</td><td>24</td><td>11</td></tr></table> Pulmonary function <table><tr><th>FVC</th><th>Living donor</th><th>Cadaveric</th></tr><tr><td>1 month</td><td>42.5%</td><td>54.3%</td></tr><tr><td></td><td>63.6%</td><td>74.2% (12 mths)</td></tr><tr><td></td><td>(6mths)</td><td>mths)</td></tr></table> FEV <table><tr><td>1 month</td><td>46.9%</td></tr><tr><td>6 months</td><td>64.5%</td></tr></table> Exercise: Assessed at a mean interval of 2.1 years after transplantation <table><tr><td>Maximum workload</td><td>163 watts</td><td>169 watts</td></tr><tr><td>Heart rate</td><td>84.6%</td><td>80.4%</td></tr></table>		Group	Living donor	Cadaveric	1 year	83%	83%	3 years	64%	81%	5 years	62%	75%	Pneumonia	10 (42%)	4 (36%)	Sepsis	5 (21%)	3 (27%)	Bronchiolitis obliterans syndrome	3 (12%)	1 (9%)	Non-compliance	1 (4%)	2 (18%)	Other	5 (21%)	1 (9%)	Total	24	11	FVC	Living donor	Cadaveric	1 month	42.5%	54.3%		63.6%	74.2% (12 mths)		(6mths)	mths)	1 month	46.9%	6 months	64.5%	Maximum workload	163 watts	169 watts	Heart rate	84.6%	80.4%	Complications recipient: Freedom from bronchiolitis obliterans syndrome. <table><tr><th></th><th>Living</th><th>Cadaveric</th></tr><tr><td>1 year</td><td>98%</td><td>100%</td></tr><tr><td>3 years</td><td>85%</td><td>100%</td></tr><tr><td>5 years</td><td>79%</td><td>78%</td></tr></table> Complications donor: not reported			Living	Cadaveric	1 year	98%	100%	3 years	85%	100%	5 years	79%	78%	Only patients who survived more than 3 months were included in this cohort. Authors note that initial survival was significantly lower in the living donor patients than it was in the cadaveric recipients p=0.009 (introduces selection bias) Living donor patients were younger, more likely to have cystic fibrosis and more likely to be hospitalised at the time of transplantation (p<0.001) Difficult to make comparisons between groups due to significant differences. Error in table 2 in the paper, which lists the causes of death. All patients received triple immunosuppressive therapy. Data not always reported consistently. Small sample sizes at distant time points.
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Study details	Key efficacy findings	Key safety findings	Comments																																						
Starnes et al (2004) ¹ Case series California, USA January 1993 – December 2002 123 patients - 84 adults mean age 27 years - 39 paediatric mean age 13.9 years Main Indications: 108 (84.4%) patients with cystic fibrosis 5 (3.9%) patients with pulmonary hypertension 5 (3.9%) patients with idiopathic pulmonary fibrosis 3 patients with primary graft failure after lobar transplantation 83 (67.5%) patients were hospitalised at the time of transplantation 22 (17.9%) patients were ventilator dependent at the time of transplantation Mean follow-up: 3.0 years Inclusion criteria: All patients fulfilled the criteria for cadaveric lung transplantation and were listed with the United Network for Organ Sharing. Living lobar lung transplantation recipients were selected primarily on the basis of a deteriorating clinical status the expectation that a cadaveric donor would not become available.	Efficacy outcomes measured: Survival Survival <table><tr><td>1 year</td><td>70%</td></tr><tr><td>3 years</td><td>54%</td></tr><tr><td>5 years</td><td>45%</td></tr></table> No significant differences between adult and paediatric patients p=0.65. Causes of death <table><tr><td></td><td>N=63</td></tr><tr><td>Infection</td><td>33 (52.4%)</td></tr><tr><td>Bronchiolitis obliterans syndrome*</td><td>8 (12.7%)</td></tr><tr><td>Graft dysfunction</td><td>5 (7.9%)</td></tr><tr><td>Emboli/thrombi</td><td>4 (6.3%)</td></tr><tr><td>Cerebral oedema</td><td>3 (4.8%)</td></tr><tr><td>Malnutrition</td><td>2 (3.2%)</td></tr><tr><td>Other</td><td>8 (12.7%)</td></tr><tr><td>Total</td><td>63</td></tr><tr><td>- within 30 days</td><td>15</td></tr><tr><td>- between 30 days and 1 year</td><td>22</td></tr><tr><td>- more than 1 year</td><td>26</td></tr></table> * all BOS cases occurred after 1 year 45 adult deaths and 18 paediatric deaths	1 year	70%	3 years	54%	5 years	45%		N=63	Infection	33 (52.4%)	Bronchiolitis obliterans syndrome*	8 (12.7%)	Graft dysfunction	5 (7.9%)	Emboli/thrombi	4 (6.3%)	Cerebral oedema	3 (4.8%)	Malnutrition	2 (3.2%)	Other	8 (12.7%)	Total	63	- within 30 days	15	- between 30 days and 1 year	22	- more than 1 year	26	Complications recipient: Rejection episodes, freedom from BOS. Overall incidence of rejection was 0.8 episodes per patient. Of the 100 episodes in 67 patients, 72% were unilateral and 28% were bilateral 12% of episodes were grade 3 53% of episodes were grade 2 35% of episodes were grade 1 22 (33%) of the 67 recipients with rejection had multiple episodes. Freedom from BOS OB was pathologically confirmed in 17 patients (9 adult and 8 paediatric patients) <table><tr><td></td><td>Adults</td></tr><tr><td>1 year</td><td>98%</td></tr><tr><td>3 years</td><td>82%</td></tr><tr><td>5 years</td><td>76%</td></tr></table> Complications donor: HLA mismatches No relationship between HLA mismatches and outcomes.		Adults	1 year	98%	3 years	82%	5 years	76%	Same group as ² Two patients underwent retransplantation for BOS Limited efficacy outcomes reported. Subgroup analysis conducted – found predictors of death, patients on ventilators preoperatively had significantly worse outcomes.
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Study details	Key efficacy findings	Key safety findings	Comments																														
Date et al (2004)^{3,7} Case series Japan October 1998 – April 2004 30 patients (24 adults, 6 children) - 10 patients primary pulmonary hypertension - 7 patients idiopathic interstitial pneumonia - 5 patients bronchiolitis obliterans - 3 patients bronchiectasis - 2 patients lymphangioleiomyomatosis - 1 patient cystic fibrosis - 1 patient Eisenmenger syndrome - 1 patient multiple bullae 5 patients (17%) were ventilator dependent 26 patients (87%) were hospital bound. Mean age was 30.4 years (range 8-55 years) Follow-up: mean 22.2 months (range 1-66 months) Inclusion criteria: Patients fulfilled the criteria for conventional bilateral lung transplantation. Only accepted critically ill patients and relatives within the second degree or a spouse as living donors. IP Overview: living lung donor transplant	Efficacy outcomes measured: Survival, pulmonary function (forced vital capacity, forced expiratory volume) Authors report that all recipients are alive at a maximum follow-up of 66 months. Both FVC and FEV had improved at 12 months. FVC reached 71.8% of predicted value at 1 year	Complications recipient: <table><tr><td>Lung oedema</td><td>6 (20%)</td></tr><tr><td>Transient peroneal nerve palsy</td><td>3 (10%)</td></tr><tr><td>Renal dysfunction</td><td>3 (10%)</td></tr><tr><td>Haemorrhage necessitating rethoracotomy</td><td>2 (6.7%)</td></tr><tr><td>Cardiac tamponade</td><td>2 (6.7%)</td></tr><tr><td>Kinking of the pulmonary artery</td><td>2 (6.7%)</td></tr><tr><td>Haemolytic anaemia</td><td>2 (6.7%)</td></tr><tr><td>Transient phrenic nerve palsy</td><td>2 (6.7%)</td></tr><tr><td>Massive haemoptysis</td><td>1 (3.3%)</td></tr><tr><td>Tracheostomy</td><td>15 (50%)</td></tr><tr><td>Reintubation</td><td>7 (23%)</td></tr><tr><td>Rethoracotomy</td><td>3 (10%)</td></tr><tr><td>Continuous haemodiafiltration</td><td>3 (10%)</td></tr><tr><td>Extracorporeal membrane oxygenation</td><td>1 (3%)</td></tr><tr><td>Bronchiolitis obliterans syndrome (BOS)</td><td>4 (13.3%)</td></tr></table> Authors note the incidence of acute rejection was 1.5 episodes per patient. Complications donor: Authors note that 'all donors have returned to their previous lifestyles'⁷ However in the discussion section note that two donors required rethoracotomies.	Lung oedema	6 (20%)	Transient peroneal nerve palsy	3 (10%)	Renal dysfunction	3 (10%)	Haemorrhage necessitating rethoracotomy	2 (6.7%)	Cardiac tamponade	2 (6.7%)	Kinking of the pulmonary artery	2 (6.7%)	Haemolytic anaemia	2 (6.7%)	Transient phrenic nerve palsy	2 (6.7%)	Massive haemoptysis	1 (3.3%)	Tracheostomy	15 (50%)	Reintubation	7 (23%)	Rethoracotomy	3 (10%)	Continuous haemodiafiltration	3 (10%)	Extracorporeal membrane oxygenation	1 (3%)	Bronchiolitis obliterans syndrome (BOS)	4 (13.3%)	Authors mention that patients are consecutive. Method of outcome assessment: Patients were given a diary to note daily pulmonary function, digital saturation, body temperature, body weight, blood pressure and heart rate. This was sent to a coordinator every month. Routine assessment was performed at 6 months, 12 months and then annually. One paediatric patient had a single lung transplanted. Limited efficacy outcomes were reported.
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Starnes et al (1999)⁸ Non randomised comparative study California, USA 1993 - 1998 25 paediatric patients - 14 patients had living lung (10 cystic fibrosis and 4 had primary pulmonary hypertension) 11 patients had cadaveric surgery (4 patients with cystic fibrosis and 3 with primary pulmonary hypertension, 3 with congenital heart disease and 1 with pulmonary arteriovenous malformation) Inclusion criteria: No documentation of medication non-compliance, children had to have follow-up for at least one year and the ability to performed pulmonary function testing. Follow-up: 2 year follow-up was available for 15 patients.		Key outcomes assessed: survival, pulmonary function (FVC, FEV) and exercise testing. <table><tr><td>Survival</td><td>Living donor</td><td>Cadaveric</td></tr><tr><td>1 year</td><td>85%</td><td>79%</td></tr><tr><td>2 years</td><td>77%</td><td>67%</td></tr></table> FVC <table><tr><td>12 months</td><td>Living donor</td><td>Cadaveric</td></tr><tr><td>24 months</td><td>84*</td><td>80*</td></tr><tr><td></td><td>88.4</td><td>53.0</td></tr></table> FEV <table><tr><td>12 months</td><td>73*</td><td>67*</td></tr><tr><td>24 months</td><td>74.5</td><td>38.6</td></tr></table> FEF <table><tr><td>12 month</td><td>60*</td><td>49*</td></tr><tr><td>24 months</td><td>62.7</td><td>30.9</td></tr></table> SpO₂ <table><tr><td>12 months</td><td>95.7</td><td>88.5</td></tr><tr><td>24 months</td><td>98.4</td><td>96.6</td></tr></table> * numbers are approximates read from graphs Authors report that that except for one cadaveric lung recipient, all paediatric lung transplant patients returned to school within one year after transplantation.		Survival	Living donor	Cadaveric	1 year	85%	79%	2 years	77%	67%	12 months	Living donor	Cadaveric	24 months	84*	80*		88.4	53.0	12 months	73*	67*	24 months	74.5	38.6	12 month	60*	49*	24 months	62.7	30.9	12 months	95.7	88.5	24 months	98.4	96.6	Complications recipient: Living lung recipients 7/14 (50%) patients had 12 episodes of acute rejection with the maximum grade of rejection (severity) being 2. (0.9 episodes per patient) At both 1 and 2 years there were no cases of bronchiolitis obliterans syndrome (BOS) in living lung recipients. Cadaveric recipients 8/11 (73%) patients had 24 episodes of acute rejection with the maximum grade of rejection (severity) being 4. (2.1 episodes per patient) At 1 year there were 9/11 cases of bronchiolitis obliterans syndrome (BOS) in cadaveric recipients. At 2 years 6 out of 7 patients had been diagnosed with BOS. 3 cases of lymphoproliferative disease. Complications donor: not reported	Same study group as ² All the children who underwent living lung surgery were also listed for cadaveric organs – given living lung because of disease severity. Original study group was 28 patients – however three patient excluded because of repeated medication non-compliance. Small number of patients have 2 year follow-up.
Survival	Living donor	Cadaveric																																							
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Kozower et al (2005)⁶ Non randomised comparative study Washington, St Louis USA 1991 - 2004 39 paediatric patients that underwent re-transplantation - 13 living donor (mean age 17.3 years) - 26 cadaveric (mean age 13.2 years)		Key outcome measures – hospital mortality, freedom from bronchiolitis obliterans <table><tr><td>Group</td><td>Living donor</td><td>Cadaveric</td></tr><tr><td>Hospital mortality</td><td>1 (7.7%)</td><td>11 (42.3%)</td></tr><tr><td>Freedom from OB at 3 years</td><td>90%</td><td>46%</td></tr></table>		Group	Living donor	Cadaveric	Hospital mortality	1 (7.7%)	11 (42.3%)	Freedom from OB at 3 years	90%	46%	Complications recipient: not reported Complications donor: not reported	Retrospective review Abstract only – limited information.																											
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Freedom from OB at 3 years	90%	46%																																							

Abbreviations used: COPD – chronic obstructive pulmonary disease; FVC – forced vital capacity; FEV – forced expiratory volume; BOS – bronchiolitis obliterans syndrome

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Study details	Key efficacy findings	Key safety findings	Comments																																																																		
Bowdish et al (2004) ⁴ California, USA January 1993 and December 2002 253 donor lobectomies - 127 right lobectomy - 126 left lobectomy Mean age 36.5 years (range 18-56 years) 123 living lung recipients Follow-up: unclear Inclusion criteria: Age between 18 and 55, no history of thoracic procedures on the side to be donated, and excellent general health. Preference is given to donors larger than the recipient.	Efficacy outcomes measured: pulmonary function (donor) Authors note initial 1 and 2 year postoperative pulmonary function testing demonstrated an average decrease of 17% in forced vital capacity, 15% in forced expiratory volume in one second and 16% in total lung capacity from preoperative values. Recipient outcomes are reported in ¹	Complications donor Estimated blood loss 216 ± 174ml Length of stay 9.4±4.8 days No perioperative or long-term mortality. 203 (80.2%) donors had no perioperative complications. 50 (19.8%) had one or more perioperative complications. <table><tr><th>Complications</th><th>N</th><th></th></tr><tr><td>Intraoperative complication</td><td>9</td><td>3.6%</td></tr><tr><td>- sacrifice of right middle lobe</td><td>4</td><td>1.6%</td></tr><tr><td>- re-implantation of right middle lobe</td><td>3</td><td>1.2%</td></tr><tr><td>- blood loss requiring transfusion</td><td>1</td><td>0.4%</td></tr><tr><td>- persistent supraventricular tachycardia</td><td>1</td><td>0.4%</td></tr><tr><td>Complication requiring re-operation</td><td>8</td><td>3.2%</td></tr><tr><td>- bleeding</td><td>3</td><td>1.2%</td></tr><tr><td>- sterile empyema</td><td>1</td><td>0.4%</td></tr><tr><td>- retained sponge</td><td>1</td><td>0.4%</td></tr><tr><td>- loculated pleural effusion</td><td>1</td><td>0.4%</td></tr><tr><td>- bronchopulmonary fistula</td><td>1</td><td>0.4%</td></tr><tr><td>- pericardiectomy</td><td>1</td><td>0.4%</td></tr><tr><td>Perioperative complication</td><td>38</td><td>15.0%</td></tr><tr><td>- thoracostomy tube</td><td>15</td><td>5.9%</td></tr><tr><td>- required additional tube</td><td>7</td><td>2.8%</td></tr><tr><td>- pulmonary artery thrombosis</td><td>2</td><td>0.8%</td></tr><tr><td>- pericarditis</td><td>4</td><td>1.6%</td></tr><tr><td>- arrhythmias</td><td>3</td><td>1.2%</td></tr><tr><td>- minor epidural-related complications</td><td>2</td><td>0.8%</td></tr><tr><td>- bronchoscopy for lobe collapse</td><td>1</td><td>0.4%</td></tr><tr><td>- required readmission</td><td>4</td><td>1.6%</td></tr></table>	Complications	N		Intraoperative complication	9	3.6%	- sacrifice of right middle lobe	4	1.6%	- re-implantation of right middle lobe	3	1.2%	- blood loss requiring transfusion	1	0.4%	- persistent supraventricular tachycardia	1	0.4%	Complication requiring re-operation	8	3.2%	- bleeding	3	1.2%	- sterile empyema	1	0.4%	- retained sponge	1	0.4%	- loculated pleural effusion	1	0.4%	- bronchopulmonary fistula	1	0.4%	- pericardiectomy	1	0.4%	Perioperative complication	38	15.0%	- thoracostomy tube	15	5.9%	- required additional tube	7	2.8%	- pulmonary artery thrombosis	2	0.8%	- pericarditis	4	1.6%	- arrhythmias	3	1.2%	- minor epidural-related complications	2	0.8%	- bronchoscopy for lobe collapse	1	0.4%	- required readmission	4	1.6%	Same study group as ² Further analysis was performed to determined variables that might predict the occurrence of perioperative complications. - donation of the right lower lobe was associated with an increased risk of perioperative complications. Authors note the importance of appropriate donor screening and selection. Authors note some donor efficacy outcomes in the discussion section. Authors note the difficulty assessing the long-term outcomes and functional effects of lobar donation i.e. motivation when there has been death of recipient and distance in that many donors live far away from the medical centre and are reluctant to return for routine follow-up evaluation.
Complications	N																																																																				
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Study details	Key efficacy findings	Key safety findings	Comments
Battafarano et al (2000) ⁵	Outcomes measured: survival	Complications donor	Retrospective review. Authors note that cases were consecutive.
Washington, USA	Recipient survival	24 donors had no perioperative complications	
July 1994 – February 200	Survival	Major complications	10 patients had previously undergone transplantation.
62 donors for paediatric recipients	1 year 63.7%	Pleural effusions necessitating drainage 4	
	Causes of death	Bronchial stump fistulas 3	
	Infection (sepsis) 3	Haemorrhage necessitating transfusion 1	
	Primary graft failure 7	Permanent phrenic nerve injury 1	Little detail provided on the characteristics of donors or recipients.
Recipient characteristics (n=31)	Cerebral haemorrhage 1	Atrial flutter 1	
26 patients with cystic fibrosis	Sudden cardiac death 1	Bilobectomy 1	
2 patients with idiopathic bronchiolitis obliterans	Total 12	Bronchial stricture 1	
2 patients with pulmonary hypertension	Two additional patients died 3.5 years after transplant	12 major complications in 10 donors	Authors note the difficulty assessing the long-term outcomes and function effects of lobar donation
1 patients with pulmonary arteriovenous malformation		Minor complications	
		Persistent air leaks 9	
16 recipient patients were hospitalised at time of transplants		Pericarditis 9	
Follow-up: unclear		Pneumonia 8	
		Arrhythmia 7	
Inclusion criteria: potential donors with no significant medical or psychological contraindications were considered suitable donor candidates.		Hypotension 4	
		Atelectasis 3	
		Ileus 3	
		Subcutaneous emphysema 3	
		Urinary tract infection 2	
		Localised pleural effusion 2	
		Transfusion 2	
		<i>Clostridium difficile</i> colitis 1	
		Breast implant rupture 1	
		Severe contact dermatitis 1	
		55 minor complications in 38 donors	

Validity and generalisability of the studies

- Most of the published evidence on living donor lung transplantation comes from one group (Department of Cardiothoracic Surgery, University of Southern California Keck School of Medicine and Children's Hospital Los Angeles) and it may therefore be difficult to generalise these results to other centres or surgeons.
- Most of the studies from the above centres include a percentage of the same patients as the authors continue to publish reports on patients treated since 1993.
- However, in the most recent publication from this group ² the authors have only reported on those recipients surviving more than 3 months after transplantation. This introduces a selection bias (death-censored analysis) and results should be interpreted within this context.
- Within each study and between studies patient characteristics varied; for example, inclusion of both adult and paediatric patients and the ratio of cystic fibrosis to other indications. There is some suggestion that these differences might explain some of the discrepancy between reported survival among the studies ³ (range 70% at 1 year to 100% at a mean follow-up of 22 months).
- Three studies included in Table 2 provided data on receipt outcomes following both living donor lung and cadaveric transplantation. A true comparative analysis is difficult, however, because those receiving living lung donor transplants by nature of eligibility criteria will often have poorer outcomes.
- To date very little information has been published on long-term donor outcomes such as pulmonary function and psychological well-being.
- Quality of life has not been addressed in any of the studies from the perspective of either the recipient or the donor.

Specialist advisors' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College.

Below is a summation of the opinions given by the following.

Mr Robert Bonser, Professor Corris, Professor Dark, Professor Wallwork, Mr Wilson

- This is a procedure that is being done in a few centres in the UK.
- All transplant centres submit results to the International Society of Heart Lung Transplantation (ISHLT) and in the UK to the UK Cardiothoracic Audit.
- Procedure would only be appropriate in a small number of patients eligible for lung transplant.
- There is considerable debate regarding the risk to the donor versus the outcome of the recipient.
- Selection of both recipients and donors is important.
- Living lung donor transplantation is a complex and intensive procedure (as it involves three operations) – must be undertaken by an experienced team.

Issues for consideration by IPAC

Related audits or registries:

The National Audit of Intrathoracic Transplantation was established in 1995 to monitor the outcomes of cardiopulmonary transplantation in the UK. The audit is funded by the National Specialist Commissioning Advisors Group (NSCAG) at the Department of Health, through the Royal College of Surgeon's Clinical Effectiveness Unit (CEU). Data collection is coordinated through the UK Transplant Support Service Authority (UKTSSA). The audit currently has funding until March 2006.
www.rcseng.ac.uk/research/ceu/projects/proj_intrathoracic.html

The ISHLT International Registry for Heart and Lung Transplantation provides data on global thoracic organ transplantation. Every country performing a minimum specified level of heart/heart–lung/lung transplantation is invited to submit data to the Registry. The Annual ISHLT Registry Report includes survival data, risk factor data, and other outcome data in heart/heart–lung/lung transplantation for a variety of demographic criteria, including age, status at transplantation, NYHA class at transplantation, and indication for transplantation. www.isHLT.org

There is limited information available on the ISHLT Registry website regarding living lung transplantation. The information that is available relates to donor outcomes, and reports that survival 1 year post-transplant for donors is 73% (CI 61.8–84.1).

References

- 1 Starnes VA, Bowdish ME, Woo MS et al. (2004) A decade of living lobar lung transplantation: Recipient outcomes. *Journal of Thoracic and Cardiovascular Surgery* 127(1):114–22.
- 2 Bowdish ME, Pessotto R, Barbers RG et al. (2005) Long-term pulmonary function after living-donor lobar lung transplantation in adults. *Annals of Thoracic Surgery* 79(2):418–25.
- 3 Date H, Aoe M, Sano Y et al. (2004) Improved survival after living-donor lobar lung transplantation. *Journal of Thoracic and Cardiovascular Surgery* 128(6):933–40.
- 4 Bowdish ME, Barr ML, Schenkel FA et al. (2004) A decade of living lobar lung transplantation: Perioperative complications after 253 donor lobectomies. *American Journal of Transplantation* 4(8):1283–8.
- 5 Battafarano RJ, Anderson RC, Meyers BF et al. (2000) Perioperative complications after living donor lobectomy. *Journal of Thoracic and Cardiovascular Surgery* 120(5):909–15.
- 6 Kozower BD, Sweet SC de la, Morena M. et al. (2005) Living donor lobar lung transplantation improves survival following lung re-transplantation in children. *Journal of Heart and Lung Transplantation* 24; ; SUPPL: 2498.
- 7 Date H, Aoe M, Nagahiro I et al. (2003) Living-donor lobar lung transplantation for various lung diseases. *Journal of Thoracic and Cardiovascular Surgery* 126(2):476–81.
- 8 Starnes VA, Woo MS, MacLaughlin EF et al. (1999) Comparison of outcomes between living donor and cadaveric lung transplantation in children. *Annals of Thoracic Surgery* 68(6):2279–84.

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Appendix A: Additional papers on living lung transplantation not included in summary table 2

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table. It is by no means an exhaustive list of potentially relevant studies.

Article title	Number of patients/ follow-up	Comments/Reasons for non-inclusion
Barr ML, Baker CJ, Schenkel FA, Bowdish ME, Bremner RM, Cohen RG et al. (2001) Living donor lung transplantation: Selection, technique, and outcome. <i>Transplantation Proceedings</i> 33(7-8):3527–3532.	97 patients (recipients)	Starnes study group. Looking at outcomes of patients enrolled 1993–2000
Barr ML, Schenkel FA, Cohen RG, Barbers RG, Fuller CB, Hagen JA et al. (1998) Recipient and donor outcomes in living related and unrelated lobar transplantation. <i>Transplantation Proceedings</i> 30(5):2261–3.	60 patients (recipients)	Starnes study group. Looking at outcomes of patients enrolled 1993–1998.
Barr ML, Schenkel FA, Cohen RG, Chan KM, Marboe CC, Hagen JA et al. (1996) Bilateral lobar transplantation utilizing living related donors. <i>Artificial Organs</i> . 20(10):1110–11.	20 patients (recipients)	Starnes study group. Looking at outcomes of patients with cystic fibrosis.
Cohen RG, Barr ML, Schenkel FA, DeMeester TR, Wells WJ, Starnes VA et al. (1994) Living-related donor lobectomy for bilateral lobar transplantation in patients with cystic fibrosis. <i>Annals of Thoracic Surgery</i> 57(6):1423–8.	7 patients (recipients) 14 donors	Starnes study group. Brief report on outcomes of patients with cystic fibrosis and donor outcomes.
Cohen RG, Starnes VA (2001) Living donor lung transplantation. <i>World Journal of Surgery</i> . 25(2):244–50.	137 patients (recipients)	Starnes study group. Looking at outcomes of patients enrolled 1993–2001
Couetil J-P, Tolan MJ, Loulmet DF, Guinvarch A, Chevalier PG, Achkar A et al. (1997) Pulmonary bipartitioning and lobar transplantation: A new approach to donor organ shortage. <i>Journal of Thoracic and Cardiovascular Surgery</i> . 113(3):529–537.	7 patients 1993 - 1994	Preliminary report of authors. 6 patients alive after 10–27 months after operation.
Starnes VA, Barr ML, Cohen RG, Hagen JA, Wells WJ, Horn MV et al. (1996) Living-donor lobar lung transplantation experience: Intermediate results. <i>Journal of Thoracic and Cardiovascular Surgery</i> . 112(5):1284–91.	38 patients (recipients)	Starnes study group. Looking at outcomes of patients enrolled 1993–1996.
Starnes VA, Barr ML, Schenkel FA, Horn MV, Cohen RG, Hagen JA et al. (1997) Experience with living-donor lobar transplantation for indications other than cystic fibrosis. <i>Journal of Thoracic & Cardiovascular Surgery</i> . 114(6):917–22.	8 patients (recipients)	Starnes study group. Looking at outcomes of patients other than those with cystic fibrosis enrolled 1993–1997
Woo MS, MacLaughlin EF, Horn MV, Wong PC, Rowland JM, Barr ML et al. (1998) Living donor lobar lung transplantation: the pediatric experience. <i>Pediatric Transplantation</i> 2(3):185-90.	17 patients (recipients)	Starnes study group. Looking at only paediatric outcomes in patients enrolled 1993–1998.
Sano Y, Date H, Nagahiro I et al. (2005) Relationship between anti-ABO antibody production and hemolytic anemia after minor ABO-mismatched living-donor lobar lung transplantation. <i>Transplantation Proceedings</i> Vol. 37: 1372.	28 patients (recipients)	Technical issues more than safety and efficacy issues. Formatted: Danish

Appendix B: Related NICE guidance for living lung transplantation

Guidance	Recommendation
Interventional Procedures	Not applicable
Technology Appraisals	Not applicable
Clinical Guidelines	Relates to lung transplantation (not specifically living lung transplantation): Patients with severe COPD who remain breathless with marked restrictions of their activities of daily living despite maximal medical therapy should be considered for referral for assessment f for lung transplantation bearing in mind co morbidities and local surgical protocols. Considerations include: Age FEV1 PaCO₂ Homogeneously distributed emphysema on CT scan Elevated pulmonary artery pressures with progressive deterioration
Public Health	Not applicable

Appendix C: Literature search for living lung transplantation

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in EMBASE, Current Contents, PreMedline and all EMB databases.

Search strategy used in Medline

1. lung transplantation/
2. living donors/
3. 1 and 2
4. (lobar adj3 transplant\$.tw.
5. ((living or live) adj5 lung\$ transplant\$.tw.
6. (living related adj3 (lung\$ or lobar) adj3 transplant\$.tw.
7. donor lobectomy\$.tw.
8. or/3-7
9. limit 8 to humans
10. lung\$.tw.
11. lung/
12. 1 or 10 or 11
13. 9 and 12

For all other databases a simple search strategy using the key words in the title was employed.

Procedure number: 292	Procedure Name: Live lung transplant	
Databases	Version searched (if applicable)	Date searched
The Cochrane Library	2005 Issue 1	14/04/2005
Embase	1980 to 2005 Week 15	14/04/2005
Medline	1966 to April Week 1 2005	14/04/2005
Premedline	13 April 2005	14/04/2005
CINAHL	1982 to April Week 2 2005	14/04/2005
British Library Inside Conferences (limited to current year only)	1993 to date	14/04/2005
National Research Register		18/04/2005