# NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

## INTERVENTIONAL PROCEDURES PROGRAMME

## Interventional procedures overview of lung volume reduction surgery for advanced emphysema

### *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 June 2004.

### *Procedure name*

- Lung volume reduction surgery for emphysema.

### *Procedure number*

236

### *Specialty society*

Specialist advice was sought from:

- Society of Cardiothoracic Surgeons of Great Britain and Ireland.
- British Thoracic Society

### *Description*

#### Indications

Emphysema is a chronic lung disease that is predominately caused by smoking. The walls of the air sacs (alveoli) in the lung weaken and disintegrate, leaving behind abnormally large air spaces that remain filled with air even when the patient breathes out. These air spaces may coalesce to form larger air-filled sacs called bullae. Some portions of the lung may be more affected by this disease process than others. As the disease progresses, the lungs become more enlarged, making breathing more difficult. The surface area of the alveoli is decreased, so there is less space for the exchange of oxygen and carbon dioxide. This leads to reduced levels of oxygen in the blood.

The most common symptoms of emphysema are shortness of breath (dyspnoea), coughing, fatigue and weight loss.

Emphysema often coexists with chronic bronchitis (inflammation of the bronchi). Both of these conditions may be described by the more general term of chronic obstructive pulmonary disease (COPD).

## Current treatment and alternatives

Because COPD is a heterogeneous disease that affects different patients in different ways, the management of a patient is very much guided by the symptoms and disability that the individual experiences.[1] Treatment involves a multidisciplinary approach, which includes education, exercise, breathing retraining, smoking cessation, oral and inhaled medications, oxygen therapy, and lung transplantation.

Lung volume reduction surgery may be an option for patients who experience breathlessness, and have pulmonary function tests that show severe obstruction and enlarged lungs.

## What the procedure involves

Lung volume reduction surgery (LVRS) is a palliative treatment that aims to remove the least functional part of the lungs in order to improve airflow, diaphragm and chest wall mechanics and alveolar gas exchange in the remaining portion of the lung.

A CT and perfusion scan are used to identify the diseased lung tissue. The diseased part of the lung can be accessed by various techniques including median sternotomy, video assisted thoracoscopy (VATS) for unilateral or bilateral surgery, or thoracotomy (unilateral surgery). The first two are the most common techniques. Median sternotomy involves cutting through the sternum to open the chest. The video assisted procedure involves making a number of small incisions in both sides of the chest to allow the insertion of instruments into the chest between the ribs.

The aim of the surgery is to reduce the volume of each lung by between 20 and 30%. This is done by using a surgical stapling device to cut and seal the tissue, laser ablation to shrink lung volume or a combination of both. Buttressing materials may be used along the staple line to prevent air leaks following resection. Once the tissue has been removed the lung is re-inflated and the chest closed.

## Efficacy

Evidence on efficacy indicates that in certain patients lung function, exercise performance and quality of life are improved in the short term following lung volume reduction surgery. These results have been relatively consistent across study designs and confirmed in a recent large scale randomised controlled trial comparing surgery with medical therapy.

The National Emphysema Treatment Trial found that at 24 months exercise capacity had improved in 15% (54/371) of patients in the surgery group, compared with 3% (10/378) of patients in the medical group ($p < 0.001$). Quality of life had also improved in the surgical group as compared with the medical group at 24 months (33% versus 9% $p < 0.001$).

However the trial found no difference in overall mortality between the two groups (0.11 deaths per person-year, risk ratio 1.01, $p = 0.90$), although particular subgroups were identified that appeared to have a survival advantage following the procedure.

The Specialist Advisors considered that, with proper selection, efficacy is well established.

### Safety

Among the studies, the most common complication related to lung volume reduction surgery was persistent air leak from the lung. In one study of 250 patients, 45.2% of patients (113/250) experienced prolonged air leaks lasting more than 7 days, with 8 patients (3.2%) requiring a subsequent operation. Other complications in this series included pneumonia (24/250), in-hospital mortality (12/250), myocardial infarction (5/250), deep vein thrombosis (4/250), small bowel obstruction (6/250), and phrenic nerve injury (2/250).

It should be noted that complications following lung volume reduction surgery include those that may arise from already present comorbidities as well as those that are due to the surgery.

The Specialist Advisors considered that the risks of surgery were well known. They listed the main complications as being air leaks, chest infections and respiratory failure.

## *Literature review*

### Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to lung reduction volume surgery for advanced emphysema. Searches were conducted via the following databases, covering the period from their commencement to May 2004: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and Science Citation Index. Trial registries and the Internet were also searched. No language restriction was applied to the searches.

The following selection criteria 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

### Inclusion criteria for identification of relevant studies

| Characteristic | Criteria |
|---|---|
| Publication type | Clinical studies included. Emphasis was placed on identifying good quality comparative studies.<br>Abstracts were excluded where no clinical outcomes were reported; or where the paper was a review, editorial, technical or animal study.<br>Conference abstracts were also excluded due to the difficulty in appraising methodology. |
| Patient | Patients with chronic obstructive pulmonary disease. |
| Intervention/test | Lung volume reduction surgery (by any method). |
| 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. |

### Studies included in the overview

The overview includes six studies, four of which were randomised controlled trials [2-5.] The remaining two studies were a systematic review of case-series studies on lung volume reduction surgery[6] and a recent case series with long term follow-up.[7]

Appendix A gives a list of studies not included in the data extraction tables but potentially relevant to the evidence base on this procedure.

## Existing studies on the procedure

Three systematic reviews relevant to this topic were identified:

- Medical Services Advisory Committee *Lung volume reduction surgery* (literature search date: April 2000).
- Australian Safety and Efficacy Register of New Interventional Procedures - Surgical *Systematic review of lung volume reduction surgery: update and reappraisal* (literature search date: September 1988).
- Cochrane review. *Lung volume reduction surgery for diffuse emphysema* (Literature search date: unclear. Date of most recent substantive amendment June 1999).

In all three reviews the literature search was undertaken more than 4 years ago and hence none of these reports assess recent randomised controlled trial data, including data from the National Emphysema Treatment Trial. It was therefore decided not to incorporate the findings of these reviews into this overview.

## Table 1 Summary of key efficacy and safety findings on lung volume reduction surgery

**Abbreviations used:** LVRS – lung volume reduction surgery; NETT – National emphysema treatment trial; HRQL – Health related quality of life; FEV – forced expiratory volume; FVC – forced vital capacity; CRQ – disease specific quality of life; IQR – interquartile range; RV – residual volume; W – Watts.

| Study details | Key efficacy findings | Key safety findings | Comments |
|---|---|---|---|
| Fishman et al (2003) [2]<br><br>USA<br><br>NETT<br><br>Randomised controlled trial<br><br>January 1998 – July 2002<br><br>1218 patients underwent randomisation<br><br>608 randomised to surgery (580 actually underwent surgery)<br>• 406 median sternotomy<br>• 174 by video assisted thoracic surgery<br><br>610 randomised to medical therapy (33 underwent LVRS outside the study)<br><br>Follow-up: 29.2 months<br><br>After May 2001 patients considered to be high risk (i.e. $FEV_1$ < 20% predicted) were excluded from the study | **Outcomes reported:** 90 day mortality; total mortality<br><br>**Surgery group (95% CI)** — **Medical therapy (95% CI)**<br>90-day mortality: 48/608 7.9 (5.9–10.3) — 8/610 1.3 (0.6–2.6) p <0.001<br>Total mortality: 157/608 — 160/610 p = 0.90<br><br>The total mortality rate was 0.11 deaths per person-year in both groups<br><br>With the exclusion of patients at high risk for death from surgery according to the interim analysis, overall mortality in the surgery group was 0.09 deaths per person-year compared with 0.10 deaths per person-year in the medical therapy group (risk ratio 0.89; p = 0.31)<br><br>**Exercise capacity improvement** — **Surgery group** — **Medical therapy**<br>All patients 24 months: 54/371 (15%) — 10/378 (3%) p < 0.001<br>High risk patients: 4/58 (7%) — 1/48 (2%) p = 0.37<br><br>Exercise capacity improved by more than 10 W (on cycle ergometry) in 28%, 22% and 15% of patients in the surgery group at 6, 12 and 24 months respectively, compared with 4%, 5% and 3% of all patients. P < 0.001<br><br>**HRQL** — **Surgery Group** — **Medical therapy**<br>All patients 24 months: 121/371 (33%) — 34/378 (9%) p<0.001<br><br>High risk patients: 115/113 (37%) — 34/330 (10%) p<0.001<br><br>Patients in the surgery group were significantly more likely to have improvements than patients in the medical therapy group in the distance walked in 6 minutes (48% vs 21%), percentage of the predicted value for FEV1 (63% vs 26%), general and health-related quality of life and degree of dyspnea (69% vs 34%) at 6 months (also significant at 12 months and 24 months although fewer patients reported) | **Complications**<br>None specifically reported apart from those outlined in the efficacy section | Before randomisation eligible patients completed 6 to 10 weeks of pulmonary rehabilitation<br><br>Randomisation method not described<br><br>Study accrual rate was lower than expected<br><br>3777 patients were evaluated and 1218 patients underwent randomisation<br><br>In the surgery group 21 patients declined surgery and 7 patients were deemed unsuitable after surgery<br><br>In the medical group 33 patients underwent LVRS outside the study and 15 patients received lung transplants during follow-up<br><br>Patients who died or were missing data required for the assessment were considered not to have improved<br><br>Authors comment that those patients with predominately upper lobe disease were most likely to benefit from the procedure. |

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| Study details | Key efficacy findings | Key safety findings | Comments |
|---|---|---|---|
| Goldstein et al (2003) [3]<br><br>Canada<br><br>Randomised controlled trial<br><br>55 patients with heterogeneous disease<br><br>28 patients had surgery (LVRS)<br><br>Surgery was performed by video assisted thoracic surgery or less often by median sternotomy<br><br>27 patients in the control group<br><br>Mean age: 65 years<br><br>Follow-up: 12 months | **Outcomes reported:** disease specific quality of life, 6 minute walking distance, sub-maximal cycle endurance time, and measures of pulmonary functions (FEV, FEV/FVC, residual volume, functional residual capacity and total lung capacity)<br><br>**Mortality**: Surgery group 4/28 (2 patients < 30 days); 1/27 in the medical group. All patients died of respiratory failure<br><br>**Disease specific quality of life:** A significant treatment effect in favour of LVRS was found in each of the domains. The differences between groups at 12 months with 95% CI were as follows<br>Dyspnoea 1.9 (1.3–2.6)<br>Emotional function 1.5 (0.9–2.1)<br>Fatigue 2.0 (1.4–2.6)<br>Mastery 1.8 (1.2–2.5)<br><br>**Treatment failure**: surgical treatment had a significant effect in preventing treatment failure over 12 months (hazard ratio 3.1; 95% CI 1.3–7.6). 7/28 (25%) of patients in the surgical group experienced treatment failure as opposed to 17/27 (63%) of control patients<br><br>**Baseline / 3 months / 6 months / 12 months**<br>**FEV (litres) median**<br>Surgery 0.8 / 1.0 / 1.1 / 1.0<br>Control 0.7 / 0.7 p < 0.05 / 0.7 p < 0.05 / 0.7 p < 0.05<br>**6 min walk (metres)**<br>Surgery 387 / 373 / 403 / 389<br>Control 372 / 356 / 346 p < 0.05 / 323 p < 0.05<br>**FVC (litres) median**<br>Surgery 2.3 / 2.9 / 3.0 / 2.9<br>Control 2.5 / 2.4 p < 0.05 / 2.3 p < 0.05 / 2.2 p < 0.05<br>**Residual volume (% of predicted)**<br>Surgery 228 / 184 / 191 / 192<br>Control 253 / 235 p < 0.05 / 236 p < 0.05 / 239 p < 0.05<br>**Total lung capacity (% of predicted)**<br>Surgery 142 / 129 / 133 / 149<br>Control 151 / 151 p < 0.05 / 150 p < 0.05 / 134 p < 0.05<br>Note not all outcomes are listed in this table. | **Complications**<br>**Surgery**<br>• 2 patients required prolonged ventilation<br>• 10 patients had prolonged air leakage<br>• 6 patients had benign dysrhythmias<br>• 6 patients had respiratory tract infections<br>• 6 patients had transient confusion<br>• 2 patients had small bowel ileus<br>• 2 patients had vocal cord dysfunction<br>• 1 patient had a transient ischaemic attack<br><br>**Post discharge:**<br>4 patients had subsequent admissions (colitis, pneumonia, respiratory failure, empyema) – all in the surgery group.<br><br>**Morbidities**<br>Surgery group:<br>• 1 patient had ischaemic heart disease<br>• 30 patients had respiratory infections<br><br>Control group:<br>• 1 patient had ischaemic heart disease<br>• 35 patients had respiratory infections | 328 subjects were screened for eligibility – 55 were randomised. (47 patients declined enrolment – reasons given)<br><br>Randomisation undertaken according to a random numbers table<br><br>No significant differences between the two groups<br><br>Research assistants who were blind to the patients' group allocation conducted all outcome assessments<br><br>Treatment failure was defined as death or function decline (a consistent reduction > 1 unit in any two domains in the CRQ from which they did not recover) |

**Abbreviations used:** LVRS – lung volume reduction surgery; NETT – National emphysema treatment trial; HRQL – Health related quality of life; FEV – forced expiratory volume; FVC – forced vital capacity; CRQ – disease specific quality of life; IQR – interquartile range; RV – residual volume; W – Watts.

| Study details | Key efficacy findings | Key safety findings | Comments |
|---|---|---|---|
| Geddes et al (2000) [4]<br><br>Randomised controlled trial<br><br>April 1996 – February 1999<br><br>24 patients had surgery (LVRS)<br>Bilateral lung resection was performed through median sternotomy or by thoracoscopy<br><br>Median age: 62 years<br><br>Emphysema was<br>▪ generalised in 14 patients<br>▪ upper zone in 8 patients<br>▪ lower zone in 2 patients<br><br>24 patients had medical therapy<br>Median age: 60 years<br><br>Emphysema was<br>▪ generalised in 12 patients<br>▪ upper zone in 9 patients<br>▪ lower zone in 3 patients<br><br>Follow-up: 6-12 months | **Outcomes reported:** mortality and changes in FEV, shuttle walking distance, and quality of life. Other outcomes were changes in FVC, total lung capacity, residual volume, inspiratory and expiratory mouth pressures and arterial-blood gas values<br><br>**Mortality**: Surgery group 5/24 (21%); 3/24 (12.5%) in the medical group. No significant difference in survival between groups<br>(RR:1.74; 95% CI 0.47─6.46)<br><br>**FEV (litres) median**<br>Surgery: 0.74 / 0.91 / 0.92 / 0.84<br>Medical: 0.75 / 0.70 / 0.72 / 0.74<br>p = 0.87 / p = 0.02 / p = 0.09 / p = 0.45<br><br>**Shuttle walking (metres) median**<br>Surgery: 210 / 260 / 270 / 290<br>Medical: 220 p = 0.93 / 230 p = 0.46 / 210 p = 0.44 / 205 p = 0.26<br><br>**SF-36 score median**<br>Surgery: 51 / 57 / 72 / 72<br>Medical: 50 p = 0.56 / 46 p = 0.07 / 43 p < 0.001 / 42 p = 0.01<br><br>**FVC (litres) median**<br>Surgery: 2.91 / 2.84 / 2.96 / 2.78<br>Medical: 2.81 / 2.53 / 2.58 / 2.68<br>p = 0.93 / p = 0.26 / p = 0.11 / p = 0.38<br><br>**Residual volume (% of predicted) median**<br>Surgery: 226 / 169 / 163 / 171<br>Medical: 220 p = 0.79 / 229 / 228 / 233<br>p < 0.001 / p < 0.001 / p = 0.02<br><br>**Total lung capacity (% of predicted) median**<br>Surgery: 136 / 119 / 119 / 126<br>Medical: 129 p = 0.23 / 133 / 139 / 127<br>p = 0.005 / p = 0.002 / p = 0.17 | **Complications:**<br>Surgery:<br>• Mean hospital stay was 19 days (range 8─64 days)<br>• 3 patients had a persistent air leak<br>• 2 patients had infection<br><br>Authors make no note of complications in the control group | 174 patients were initially assessed as eligible, only 48 took part in the study<br><br>Entry criteria were modified during the protocol (after the first 15 patients)<br><br>All patients were given rehabilitation prior to entry into the study<br><br>Method of randomisation was not described in the article<br><br>No blinded assessment<br><br>Small study population<br><br>Some patients in medical therapy group underwent surgery outside the trial<br><br>Not an intent to treat analysis (one patient withdrew from surgery group)<br><br>Appears to be loss to follow-up at 12 months – with only 13 patients in the surgical group and 19 in the medical group (authors do not discuss) |

**Abbreviations used:** LVRS – lung volume reduction surgery; NETT – National emphysema treatment trial; HRQL – Health related quality of life; FEV – forced expiratory volume; FVC – forced vital capacity; CRQ – disease specific quality of life; IQR – interquartile range; RV – residual volume; W – Watts.

| Study details | Key efficacy findings | | | | Key safety findings | Comments |
|---|---|---|---|---|---|---|
| | **$PaCo_2$ (mm Hg) median** | | | | | |
| | Surgery | 37 | 38 | 37 | 41 | |
| | Medical | 38 p = 0.78 | 37p = 0.47 | 38 p = 0.39 | 38 p = 0.70 | |
| | **$PaO_2$ (mm Hg) median** | | | | | |
| | Surgery | 74 | 76 | 71 | 77 | |
| | Medical | 70 p = 0.36 | 75 p = 0.92 | 73 p = 0.92 | 68 p = 0.08 | |
| | **Carbon monoxide diffusing capacity (% of predicted) median** | | | | | |
| | Surgery | 36 | 42 | 42 | 45 | |
| | Medical | 37 p = 0.66 | 36 p = 0.68 | 37 p = 0.32 | 35 p = 0.11 | |
| | **Mouth inspiratory pressure (cm of water) median** | | | | | |
| | Surgery | 64 | 83 | 80 | 75 | |
| | Medical | 68 p = 0.41 | 62 p = 0.04 | 58 p = 0.02 | 63 p = 0.02 | |
| | **Mouth expiratory pressure (cm of water) median** | | | | | |
| | Surgery | 69 | 70 | 69 | 66 | |
| | Medical | 81 p = 0.46 | 76 p = 0.14 | 74 p = 0.33 | 71 p = 0.44 | |

**Abbreviations used:** LVRS – lung volume reduction surgery; NETT – National emphysema treatment trial; HRQL – Health related quality of life; FEV – forced expiratory volume; FVC – forced vital capacity; CRQ – disease specific quality of life; IQR – interquartile range; RV – residual volume; W – Watts.

| Study details | Key efficacy findings | Key safety findings | Comments |
|---|---|---|---|
| Pompeo et al (2000) [5]<br><br>Italy<br><br>Randomised controlled trial<br><br>January 1996─January 1999<br><br>30 patients underwent video-assisted thoracopcopic reduction pneumoplasty – unilateral or bilateral<br><br>30 patients underwent a structured supervised exercise rehabilitation program<br>(3 patients withdrew due to dissatisfaction with improvement)<br><br>Mean follow-up: 24 months | **Outcomes reported:** FEV, maximal exercise capacity, physiological assessment, respiratory muscle strength<br><br>Absolute changes between pre-treatment and last post-treatment measures<br><br>**Outcomes** / **Surgery (%)** / **Medical (%)** / **P value**<br>Dyspnea index: -1.52 (-46%) / -0.4 (-12%) / < 0.0001<br>FEV: 0.46 (53%) / 0.01 (1%) / < 0.0001<br>FVC: 0.42 (17%) / -0.04 (2%) / < 0.0001<br>Residual volume: -1.4 (-25%) / 0 (0%) / < 0.0001<br>Maximal inspiratory pressure ( mmHg): 21 (42%) / 11 (20%) / 0.07<br>Maximal expiratory pressure (mm Hg): 5 (6%) / 2 (2%) / 0.12<br>$PaO_2$ (mm Hg): 5 (7%) / 2 (3%) / < 0.002<br>$PaCo_2$ (mm Hg): -1.3 (-3%) / -0.3 (-1%) / 0.55<br>6 minute walk test: 93 (24%) / 31 (8%) / < 0.0002<br>Incremental treadmill test: 1.52 (223%) / 0.48 (60%) / < 0.0001<br><br>There was a more significant improvement in dyspnea index, $PaO_2$, 6 minute walking test and incremental walk test after surgical than medical therapy<br><br>The 6 minute walking test and the incremental treadmill test changed significantly during the follow-up in both groups, whereas the FEV changes significantly only in the surgical group<br><br>Surgical group there were improvements in time with the 6 minute test and incremental test in comparison to the medical group which peaked at 3 months<br><br>**Long-term follow-up: (additional 24 months)**<br>Surgical arm: 2 patients underwent rehabilitation; 2 patients died and 1 patient required hospitalisation<br><br>Medical arm: 4 patients died, 12 patients underwent surgery; 5 patients required hospitalisation | **Complications:**<br>**Surgery:**<br>Nineteen nonfatal complications occurred in 16 patients (3 patients had 2 complications)<br>• 11 cases of prolonged air leaks<br>• 3 cases of atrial fibrillation<br>• 2 cases of pneumonias<br>• 1 case empyema<br>• 1 transient ischemic attack<br>• 1 transient Horner's syndrome<br><br>Late complications<br>• 1 patient had persistent intercostals neuralgia<br>• 1 patient pneumonia<br>• 1 patient had loculated pneumothorax requiring reoperation<br><br>2 deaths:<br>• 1 patient died in hospital death due to pneumonia<br>• 1 patient died after 4 months due to pneumonia and respiratory failure<br><br>Medical arm:<br>• 1 patient died respiratory failure | Randomised by computer<br><br>No patient in the surgical arm underwent preoperative or postoperative rehabilitation<br><br>237 patients were screened – 125 ineligible/112 eligible. 52 patients refused randomisation, 60 were randomised and 55 completed the 6-month study (unclear if those refusing randomisation were any different)<br><br>Authors report no difference in baseline characteristics between surgical and medical arm<br><br>Small number of patients |

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| Study details | Key efficacy findings | Key safety findings | Comments |
|---|---|---|---|
| Young et al (1999) [6]<br><br>Systematic review of case-series<br><br>Literature review: 1975–1999.<br><br>Lung volume reduction surgery (reduction pneumoplasty of pneumectomy) defined as multiple lung resections and/or placations of diseased lung tissue to reduce lung volume. The following techniques and approaches were all included: open or closed procedure, unilateral or bilateral procedure, laser ablation, stapling or both<br><br>Studies were excluded that reported on less than 3 months follow-up<br><br>19 studies met the inclusion and exclusion criteria<br><br>All included studies were case series | **Outcomes reported:** mortality; lung function, six minute walking distance, quality of life, dyspnoea, length of hospital stay, supplemental oxygen<br><br>**Mortality:** (data available on n = 567 patients)<br>The interquartile range (IQR) for early mortality (defined as hospital deaths or deaths occurring within 30 days) was 0 – 6%.<br>The interquartile range for late mortality (defined as hospital deaths or deaths occurring after more than 30 days) at 3–6 months was 0–8%<br>Late mortality at 2 years was estimated as between 0–3%<br><br>**Lung function:** (data available on 925 patients)<br>At baseline FEV1 was 0.64-0.731 (IQR) which rose to 0.91-1.07 3-6 months after surgery (difference of 0.23-0.36).<br>FEV as a percentage of the predicted value was presented for 806 patients. Baseline measurement were 24–28%; improving to 35–41% (difference 9–13%)<br><br>**Six minute walking distance (486 patients – 10 studies)**<br>The baseline distance covered by study participants was 241–290 m (IQR). This rose to 306–424 m after treatment (difference 32–96 m)<br><br>**Quality of life (187 patients – 4 studies)**<br>Authors note that although only limited data were presented in the studies, improvements in quality of life were observed across all studies and measurement tools<br><br>**Dyspnoea (12 studies)**<br>All studies reported improvement following surgery<br><br>**Length of hospital stay (668 patients)**<br>Varied between 13–18 days<br><br>**Supplemental oxygen (487 patients)**<br>In the short-term (3–6 months) the reduction in the percentage of patients requiring supplemental oxygen either continuously or on exertion was 16–42% | **Complications:**<br>See efficacy section – no other details reported. | Good quality systematic review – methods well described<br><br>Inclusion and exclusion criteria clearly stated – authors also undertook quality assessment<br><br>Authors note that in many studies LVRS may have also included a component relating to preoperative pulmonary rehabilitation – may confound results<br><br>Lack of standardised outcome measures in some of the studies<br><br>Variation in surgical technique – evolving over time<br><br>Authors note high degree of consistency among the studies in terms methodological quality<br><br>Results are most likely to be prone to bias in case of mortality and quality of life |

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| Study details | Key efficacy findings | Key safety findings | Comments |
|---|---|---|---|
| Ciccone et al (2003) [7]<br><br>January 1993 – June 2000<br><br>Case series<br><br>250 consecutive patients<br><br>Inclusions and exclusion criteria clearly defined<br><br>249 procedures were performed through a median sternotomy<br>1 case was done through a bilateral muscle-sparing thoracotomy<br><br>Mean age: 62 years<br><br>Mean follow-up: 4.8 years. (range 1.8–9.1 years)<br>Follow-up was completed for all but one patient | **Outcomes reported:** mortality, pulmonary function studies, exercise testing and quality of life assessment.<br><br>**Mortality:** 96/250 (38.4%) of patients died, 65.6% due to respiratory failure. Kaplan-Meier estimate of survival at 5 years was 67.7% (n = 108).<br><br>**FEV (litres) mean** 0.7 ± 0.2 (Baseline n = 249); 1.1 ± 0.5 (6 months n = 231); 1.0 ±0.5 (1 year n = 225); 0.8 ±0.5 (5 years n = 106)<br>**% of predicted** 25%; 39%; 38%; 30%<br><br>After 6 months the mean change from preoperative values was 54%. After 5 years the mean change was 7%<br><br>**RV mean** 5.9 ± 1.4; 4.0 ±1.2; 4.1± 1.3; 4.8 ± 1.8<br>**% of predicted** 282%; 189%; 193%; 222%<br><br>After 6 months the mean reduction was 30%, by 5 years the mean reduction was 14%.<br>**RV/total lung capacity** 72 ± 7; 57 ± 9; 58 ± 10; 66 ± 11<br><br>**Diffusion lung capacity of carbon monoxide (mean)** 9.1 ± 3.7; 10.4 ± 4.6; 10.3 ±4.3; 8.6 ± 4.2<br>**% predicted** 34%; 39%; 39%; 34%<br><br>**6 minute walking (metres)** 919 ± 335; 1345 ± 315; 1341 ± 310; 1154 ± 348<br><br>**PaCo2 (mmHg)** 42 ± 6; 39 ± 5; 39 ± 5; 42 ± 6<br>**PaO2 (mmHg)** 64 ± 9; 72 ± 10; 72 ± 11; 69 ± 11<br><br>**Supplemental oxygen**<br>continuously 60.8%; 11.3%; 12.4%; 22.6%<br>during exercise 83.6%; 50.2%; 56.4%; 80.0%<br><br>**Dyspnea improved (not all pts)** -; 88%; 79%; 42%<br>**SF-36 improved** -; 96%; 94%; 79%<br><br>18 patients subsequently underwent lung transplantation. | **Complications**<br>All morbidity (138 patients 55.2%)<br>• 113 patients (45.2%) had prolonged air leak (> 7 days)<br>• 24 patients (9.6) pneumonia<br>• 18 patients (7.2%) reintubation<br>• 10 patients (4%) tracheostomy<br>• 6 patients (2.4%) small bowel obstruction or ileus<br>• 5 patients (2%) myocardial infarction<br>• 4 patients (1.6%) deep vein thrombosis<br>• 2 patients (0.8%) caecal perforation<br>• 2 patients (0.8%) phrenic nerve injury<br><br>Subsequent operation (18 patients 7.2%)<br>Re-exploration<br>• 8 patients (3.2%) prolonged air leak<br>• 3 patients (1.2%) bleeding<br>• 6 patients (2.4%) gastrointestinal complications<br>• 1 patient (0.4%) coronary artery bypass grafting<br><br>10 patients (4%) 90-day mortality<br>All attributed to respiratory failure, except 1 due to pulmonary embolism<br>12 patients (4.8%) in-hospital mortality | Aim was report on long-term outcomes<br><br>Patients judged suitable for surgery were enrolled in a preoperative pulmonary rehabilitation programme<br><br>Quality of life measured by either the Nottingham Health Profile, Short-36 Item Short-form health survey<br><br>Authors note that as longitudinal data with a shrinking cohort of observable patients is prone to bias (not all patients had five follow-up assessments) – authors compared results from patients with complete follow-up at 5 years with all patient data – no observable differences |

## Validity and generalisability of the studies

- The studies include patients who had undergone a variety of surgical techniques to reduce lung volume. There have been some studies to suggest that the type of operation has an influence on the efficacy and/or safety of the procedure.[8]
- Baseline characteristics also differed among the studies. In the case of the NETT study the protocol was amended in 2001 to exclude certain patients considered high risk. Earlier studies may therefore have less favourable outcomes.
- Some of the studies include patients who have undergone a preoperative and/or postoperative rehabilitation programme. This may act as a confounder.
- Very few studies report on long term outcomes. This is important given the suggestion that benefits of LVRS seem to be maximal at 6 months, declining thereafter towards presurgical values.
- Few studies used validated tools to assess outcomes and in most of the randomised controlled trials there was a lack of blinded assessment.
- Although subgroup analysis was undertaken in a number of studies it was unclear whether this was established a priori.

## Specialist advisors' opinions

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

- While $FEV_1$ does tend to decline towards baseline values at 3-5 years following surgery, this has to be viewed against the inherent decline in lung function that occurs with age.
- The procedure appears to be beneficial for a subgroup of patients.
- Risks of surgery are well established; uncertainties pertain to selection for surgery.
- LVRS is undertaken relatively infrequently, and performed in a small number of specialist units in the UK.

## Analysis of potential literature

- There is a significant body of literature on this procedure and it is difficult to determine the most appropriate studies to accurately reflect the efficacy and safety profile of this procedure.
- While the majority of studies are case-series studies there have been several randomised controlled trials evaluating LVRS. Four of the randomised controlled trials are outlined in the data extraction tables; three have been excluded and are listed in Appendix A. These studies were of much weaker methodological quality than the other four randomised controlled trials but they may still add to the evidence base on this procedure.
- There have been no randomised controlled trials comparing LVRS with lung transplantation but there have been reports of case series of the effectiveness of LVRS in patients on a transplant waiting list.
- In general complications were reported in more detail in the non-randomised studies in comparison with the randomised studies, many of the non-randomised studies also seemed to have longer term follow-up.

## Issues for consideration by IPAC

NICE has recently issued a guideline on chronic obstructive pulmonary disease.

The following recommendations were made about lung volume reduction surgery. [1]

- Patients with severe COPD who remain breathless with marked restrictions of their activities of daily living despite maximal medical therapy (including

rehabilitation), should be referred for consideration of lung volume reduction surgery if they meet all of the following criteria:

- FEV1 more than 20% predicted
- PaCO2 less than 7.3 kPA
- Upper lobe predominant emphysema
- TlCo more than 20% predicted.

The evidence statements associated with this piece of guidance are listed in Appendix C of this overview.

There is also a UK trial on lung volume reduction surgery.

## *References*


1 Managing stable COPD. *Thorax* 2004; 59(90001):39i–130.

2 Fishman A, Martinez F, Naunheim K, Piantadosi S, et al. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *New England Journal of Medicine* 2003; 348(21):2059–73.

3 Goldstein RS, Todd TR, Guyatt G, Keshavjee S, et al. Influence of lung volume reduction surgery (LVRS) on health related quality of life in patients with chronic obstructive pulmonary disease. *Thorax* 2003; 58(5):405–10.

4 Geddes D, Davies M, Koyama H, Hansell D, et al. Effect of lung-volume-reduction surgery in patients with severe emphysema. *New England Journal of Medicine* 2000; 343(4):239–45.

5 Pompeo E M. Reduction pneumoplasty versus respiratory rehabilitation in severe emphysema: A randomized study. *Annals of Thoracic Surgery* 2000; 70(3):948–54.

6 Young J, Fry-Smith A, Hyde C. Lung volume reduction surgery (LVRS) for chronic obstructive pulmonary disease (COPD) with underlying severe emphysema. [Review] [54 refs]. *Thorax* 1999; 54(9):779–89.

7 Ciccone AM, Meyers BF, Guthrie TJ, Davis GE, et al. Long-term outcome of bilateral lung volume reduction in 250 consecutive patients with emphysema.[comment]. *Journal of Thoracic & Cardiovascular Surgery* 2003; 125(3):513–25.

8 National Emphysema Treatment Trial Research Group. Safety and efficacy of median sternotomy versus video-assisted thoracic surgery for lung volume reduction surgery. *The Journal of Thoracic and Cardiovascular Surgery* 2004; 127:1350–60.

# Appendix A: Additional studies not included in the summary tables

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

| Study title | Number of patients/ Follow-up | Comments | Direction of conclusions |
|---|---|---|---|
| Criner GJ, Cordova FC, Furukawa S, Kuzma AM, et al. Prospective randomized trial comparing bilateral lung volume reduction surgery to pulmonary rehabilitation in severe chronic obstructive pulmonary disease. *American Journal of Respiratory & Critical Care Medicine* 1999; 160(6):2018-27. | 37 patients<br>3 months | Randomised controlled trial<br>Number of patients lost to follow-up<br>Limited reporting on outcomes | LVRS offers some benefit – longer terms studies are needed. |
| Goodnight WS, Jones J, Baaklini W, Soltero E, et al. Lung volume reduction surgery (LVRS) in patients with severe emphysema: 1 year follow-up. *American Journal of Respiratory and Critical Care Medicine* 2001; 163:A486. | 49 patients<br>6 months | Randomised controlled trial<br>Abstract | Do not have access to details |
| Lofdahl C-G, Hillerdal G, Strom K. Randomised controlled trial of volume reduction surgery: preliminary results up to 12 months. *American Journal of Respiratory & Critical Care Medicine* 163, A486. 2000. Abstract | 54 patients<br>12 months | Randomised controlled trial<br>Abstract | Do not have access to details |
| Hillerdal GL. Volume reducing surgery in pulmonary emphysema compared to exercise training: a randomised study. *European Respiratory Journal* 2001; 18(Suppl 33):355s. | 54 patients<br>12 months | Randomised controlled trial<br>Abstract | Same study as above. |
| Wilkens H, Demertzis S, Konig J, Leitnaker CK, et al. Lung volume reduction surgery versus conservative treatment in severe emphysema. *European Respiratory Journal* 2000; 16(6):1043-9. | 57 patients<br>18 months | Non randomised comparative study | LVRS is more effective than conservative treatment. |
| Munro PE, Bailey MJ, Smith JA, Snell GI. Lung Volume Reduction Surgery in Australia and New Zealand. Six Years On: Registry Report. Chest 2003; 124(4):1443-50 | 529 patients | Registry data – voluntary | Improvements in lung function, exercise capacity appear to be maintained for 3 years |
| Fischel RJ, McKenna RJ, Jr, Gelb A, Singh N, et al. Insight on emphysema--the first 300 cases of surgical treatment. *Western Journal of Medicine* 1998; 169(2):74-7. | 300 patients<br><br>6 months | Case series | Limited data. |
| Yusen RD, Lefrak SS, Gierada DS, Davis GE, et al. A prospective evaluation of lung volume reduction surgery in 200 consecutive patients. *Chest* 2003; 123(4):1026-37. | 200 patients<br><br>5 years | Case series | In selected patients, LVRS resulted in substantial beneficial effects. |

# Appendix B Ongoing/unpublished trials on lung volume reduction surgery

| Study name | Study details | Status |
|---|---|---|
| UK lung volume reduction surgery trial | Prospective multicentre randomised trial comparing the clinical and cost effectiveness of surgery to medical therapy including pulmonary rehabilitation.<br><br>5 UK trial centres (Papworth, Birmingham, Liverpool, Leicester and Sheffield) | Unclear if complete. |
| Canadian lung volume reduction surgery trial (CLVR) | Randomised trial of optimal medical management followed by surgery compared with medical management alone. | Aiming to recruit 350 patients. |

# Appendix C: NICE guidance on lung volume reduction surgery [1]

| **The full guidance states**<br><br>'Although lung surgery is an important option for some patients with COPD, a systematic literature search and formal critical appraisal process was not undertaken in this area due to the time limitations within the guideline development process. However a MEDLINE and Cochrane Database search and a selective review of frequently cited papers and key review articles was undertaken.'…<br><br>**Evidence statements** | ***Evidence grade*** |
|---|---|
| LVRS improves FEV1 (1b) | (1b) |
| The effect seems to be maximal at 6 months and thereafter there is variable but significant decline towards presurgical values | (1b) |
| LVRS improves walking distance | (1b) |
| LVRS improves quality of life | (1b) |
| Overall LVRS does not appear to have any effect on long term survival (see results of subgroups below) | (1b) |
| LVRS results in an unacceptable high mortality in patients who have<br>A low forced expiratory volume in 1 second ( < 20% predicted)<br>And either non-upper lobe predominant emphysema or a very low transfer factor ( < 20% predicted) | (1b) |
| With the exclusion of patients at high risk for death from surgery according to the interim analysis, overall mortality in the surgery group was 0.09 death per person years, as compared with 0.10 death per person year in the medical therapy group (risk ratio, 0.89; p = 0.31); exercise capacity after 24 months had improved by more 10W in 16% of patients in the surgery group as compared with 3% of patients in the medical therapy groups (p < 0.0001). | (1b) |
| Among patients with predominately upper-lobe emphysema and low exercise capacity, mortality was lower in the surgery group than in the medical-therapy group (risk ration for death, 0.47; p = 0.005). Among patients with non-upper-lobe emphysema and high exercise capacity, mortality was higher in the surgery group than in the medical-therapy group (risk ration 2.06; p = 0.02). | (1b) |
| Clinically and statistically significant benefits of LVRS on mortality, exercise capacity and SGRQ were seen in patients with upper lobe emphysema and low exercise capacity. LVRS led to increased mortality and deterioration in exercise capacity in patients with non-upper lobe emphysema and high exercise capacity. Some benefits were seen in patients with upper lobe emphysema and high exercise capacity and in patients with non-upper lobe emphysema and low exercise capacity but these were less marked. | (1b) |

# Appendix D: Literature search for lung volume reduction surgery

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.

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

| # | Search History |
|---|---|
| 1 | (lung$ adj volume$).mp. [mp = title, abstract, cas registry/ec number word, mesh subject heading] |
| 2 | (lung$ adj volume$ adj reduc$ adj surg$).mp. [mp = title, abstract, cas registry/ec number word, mesh subject heading] |
| 3 | (lung$ adj2 reduc$).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading] |
| 4 | LVRS.tw. |
| 5 | exp Pneumonectomy/ |
| 6 | pneumoplasty.mp. |
| 7 | pneumectomy.mp. |
| 8 | pneumonoplasty.mp. |
| 9 | or/1-8 |
| 10 | emphyse$.tw. |
| 11 | pulmonary emphysema.mp. or exp Pulmonary Emphysema/ |
| 12 | chronic obstructive pulmonary disease.mp. or exp Pulmonary Disease, Chronic Obstructive/ |
| 13 | COPD.tw. |
| 14 | (obstruct$ adj3 (lung$ or respirat$ or pulmonar$) adj3 disease$).mp. |
| 15 | or/10-14 |
| 16 | 9 and 15 |
| 17 | exp Randomized Controlled Trials/ |
| 18 | randomized controlled trial.pt. |
| 19 | exp Random Allocation/ |
| 20 | exp Double-Blind Method/ |
| 21 | exp Single-Blind Method/ |
| 22 | clinical trial.pt. |
| 23 | exp Clinical Trials/ |
| 24 | or/17-23 |
| 25 | (clinic$ adj trial$1).tw. |
| 26 | ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. |
| 27 | exp PLACEBOS/ |
| 28 | placebo$.tw. |

| | |
|---|---|
| 29 | randomly allocated.tw. |
| 30 | (allocated adj2 random).tw. |
| 31 | or/25-30 |
| 32 | 24 or 31 |
| 33 | 32 and 16 |
| 34 | exp Intraoperative Complications/ |
| 35 | exp Postoperative Complications/ |
| 36 | or/34-35 |
| 37 | or/1-4 |
| 38 | 37 and 15 |
| 39 | 38 and 36 |