Lung Volume Reduction Surgery for Severe Emphysema

Description

Lung volume reduction surgery (LVRS) is proposed as a treatment option for patients with severe emphysema who have failed optimal medical management. The procedure involves the excision of diseased lung tissue, and aims to reduce symptoms and improve quality of life.

Background

Lung volume reduction is a surgical treatment for patients with severe emphysema involving the excision of peripheral emphysematous lung tissue, generally from both upper lobes. The precise mechanism of clinical improvement for patients undergoing lung reduction surgery has not been firmly established. However, it is believed that elastic recoil and diaphragmatic function are improved by reducing the volume of diseased lung. In addition to changes in chest wall and respiratory mechanics, the surgery is purported to correct ventilation perfusion mismatch and improve right ventricular filling.

Research on LVRS has focused on defining the sub-group of patients most likely to benefit from the procedure. Potential benefits of the procedure e.g., improvement in functional capacity and quality of life must be weighed against the potential risk of the procedure e.g., risk of post-operative mortality.

Regulatory Status

Lung volume reduction surgery is a surgical procedure and, as such, is not subject to regulation by the U.S. Food and Drug Administration.

Related Policies

7.01.128 Endobronchial Valves
Policy

*LThis policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Lung volume reduction surgery as a treatment for emphysema may be considered medically necessary in patients with emphysema who meet ALL of the following criteria*:

- Predominantly upper lobe emphysema with hyperinflation and heterogeneity (i.e., target areas for removal)
- Forced expiratory volume in one second (FEV-1):
  - For patients who are younger than 70 years of age, the FEV-1 must be no more than 45% of the predicted value.
  - For patients who are 70 years of age or older, the FEV-1 must be no more than 45% of the predicted value and greater than or equal to 15% of the predicted value.
  - Marked restriction in activities of daily living despite maximal medical therapy
  - Age younger than 75 years
  - Acceptable nutrition status; i.e., 70–130% of ideal body weight
  - Ability to participate in a vigorous pulmonary rehabilitation program
  - No coexisting major medical problems that would significantly increase operative risk
  - Willingness to undertake risk of morbidity and mortality associated with LVRS
  - Abstinence from cigarette smoking for at least 4 months

Lung volume reduction surgery is considered investigational in all other patients.

*patient selection criteria are based on the National Emphysema Treatment Trial (NETT)

Policy Guidelines

The following additional criteria, also from the NETT trial, may provide further information in determining whether a patient is a candidate for lung volume reduction surgery:

- PaO2 on room air greater than or equal to 45 mm Hg (greater than or equal to 30 mm Hg at elevations of 5,000 feet or higher)
- PaCO2 on room air less than or equal to 60 mm Hg (less than or equal to 55 mm Hg at elevations of 5,000 feet or higher)
- Post-rehabilitation 6-minute walk of at least 140 m, and able to complete 3 min. unloaded pedaling in exercise tolerance test.
Rationale

Randomized Controlled Trials

National Emphysema Treatment Trial (NETT)

The NETT was a large multicenter prospective randomized controlled trial (RCT) comparing lung volume reduction surgery (LVRS) to optimal medical therapy. Two-year findings were published in 2003 by Fishman and colleagues. (1) The trial included 1,218 patients, and the analysis was intention to treat, reporting on of all randomized patients. The primary outcomes included total, 30-day, and 90-day mortality and maximal exercise capacity. Secondary outcomes included pulmonary function, the distance walked in 6 minutes, and self-reported health-related quality of life and general quality of life.

At the time of data analysis, 371 (30%) patients had been followed up for a total of 24 months. Primary findings of the Fishman et al. study are summarized below:

<table>
<thead>
<tr>
<th></th>
<th>90-day mortality (%)</th>
<th>Total mortality (no death/total)</th>
<th>Improvement in Exercise Capacity at 24 mo (%)**</th>
<th>Improvement in Quality of Life at 24 mo (%) ***</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>1.3</td>
<td>7.9</td>
<td>160/610</td>
<td>157/608</td>
</tr>
<tr>
<td>High-risk patients*</td>
<td>0</td>
<td>28</td>
<td>30/70</td>
<td>42/70</td>
</tr>
<tr>
<td>Upper lobe emphysema with low exercise capacity</td>
<td>3.3</td>
<td>2.9</td>
<td>51/151</td>
<td>26/139</td>
</tr>
<tr>
<td>Upper lobe emphysema with high exercise capacity</td>
<td>0.9</td>
<td>2.9</td>
<td>39/213</td>
<td>34/206</td>
</tr>
<tr>
<td>Non-upper lobe emphysema, low exercise capacity</td>
<td>0</td>
<td>8.3</td>
<td>28/84</td>
<td>26/65</td>
</tr>
<tr>
<td>Non-upper lobe emphysema, high exercise capacity</td>
<td>0.9</td>
<td>10.1</td>
<td>27/109</td>
<td>14/111</td>
</tr>
</tbody>
</table>

* High risk is defined as those with a forced expiratory volume in 1 second that was 20% or less of the predicted value and either homogeneous emphysema on computed tomography or a carbon monoxide diffusion capacity that was 20% or less of the predicted value

** Improvement in exercise capacity in patients followed up for 24 months after randomization was defined as an increase in the maximal workload of more than 10 W from the patient's post-rehabilitation baseline value

*** Improvement in health-related quality of life in patients followed up for 24 months after randomization was defined as a decrease in the score on the St George's Respiratory Questionnaire of more than 8 points (on a 100-point scale) from the patient's post-rehabilitation baseline score
Conclusions drawn from these data include:

- Overall, lung volume reduction surgery increases the chance of improved exercise capacity but does not confer a survival advantage over medical therapy; the functional benefits of lung volume reduction surgery come at the price of increased short-term mortality and morbidity.
- There is a survival advantage for patients with both predominantly upper lobe emphysema and low baseline exercise capacity. This survival advantage appears to be due to the very high mortality and marked progressive functional limitation of those treated medically.
- Patients considered at high risk and those with non-upper lobe emphysema and high baseline exercise capacity are poor candidates for lung volume reduction surgery.

In 2006, a follow-up analysis of data from NETT was published; there was a median follow-up of 4.3 years compared to 2.4 years in the initial full report. (2) Seventy percent of randomized patients participated in the extension of follow-up conducted in 2003, and 76% participated in the mailed quality-of-life data collection in 2004. The analysis was done on an intention-to-treat basis including all 1,218 randomized patients. Median follow-up was 4.3 years.

Overall, LVRS showed a mortality benefit compared to medical therapy. During follow-up, 46.5% (283/608) patients in the lung volume reduction surgery (LVRS) group and 53.1% (324/610) patients in the medical therapy group died (relative risk [RR]: 0.85, p=0.02). However, the long-term mortality benefit was limited to the subgroup of participants who had predominately upper lobe emphysema and low exercise capacity (those found in the initial report to benefit from LVRS) (RR=0.57, p=0.01). Moreover, in this subgroup of patients (n=290), compared to medical therapy, those in the LVRS group were also more likely to have an improvement in exercise capacity throughout 3 years of follow-up testing (p<0.01) and to have an 8-point improvement in quality of life through 4 years of follow-up testing (p=0.003).

In the subgroup of patients with predominately upper lobe emphysema and high exercise capacity (n=419), there was not a survival benefit associated with LRVR, but there was a significantly higher improvement in exercise capacity over 3 years (p<0.001) and quality of life over 4 years (p=0.003 in year 4). Patients with non-upper lobe emphysema, and either high or low exercise capacity, did not significantly benefit from surgery in terms of mortality rates, exercise capacity or quality of life. A limitation of the long-term follow-up study was that fewer than 80% of surviving NETT participants took part in the study extension.

In 2010, Sanchez and colleagues published an analysis of data from the National Emphysema Treatment Trial further examining factors associated with a positive outcome after LVRS. (3) The analysis focused on patients with upper lobe predominance and a heterogeneous distribution of emphysema defined as a difference in severity of emphysema in any 2 zones of the lung of at least 2 points on a 0-to-4 severity scale. Of the 1,218 patients enrolled in the study, 511 patients (42%) met both of these criteria; 261 were in the LVRS group, and 250 were in the medical therapy group. Using Kaplan-Meier analysis, the 3-year survival rate was 81% in patients receiving LVRS and 74% for those the medical group, p=0.05. At 5 years, the estimated survival rate was significantly higher in the LVRS group than the medical therapy group, 70% versus 60%, p=0.02. Maximal exercise capacity, another NETT primary outcome, was a mean of 49 watts in the LVRS group and 38 watts in the
medical therapy group at 1 year, p<0.001. At 3 years, the values in the two groups were 43 and 38 watts, respectively, and the between-group difference was not statistically significant.

A 2014 study by Kaplan et al reported on long-term outcomes in high-risk patients from the NETT trial. (4) In this subgroup of 140 randomized patients, the mortality rate was higher in the LVRS group than the medical therapy group for the first 4.4 years but longer term survival did not differ significantly in the 2 groups. Median survival was 2.14 years (95% confidence interval [CI], 1.20 to 4.07) in the LVRS group and 3.12 years (95% CI, 2.79 to 4.27) in the medical therapy group (p>0.05).

**Systematic Reviews**

Additional RCTs evaluating LVRS for treating emphysema have been published, and 2 meta-analyses of RCTs have been published. (5, 6) Each meta-analysis included 8 RCTs published between 1999 and 2006. However, the NETT accounted for about 75% of the patients in both meta-analyses, limiting the usefulness of the findings of the pooled analyses. In the more recent meta-analysis, pooled analyses found a significantly higher odds of mortality in the medical therapy group compared to LVRS at 3 months (odds ratio [OR]: 5.16, 95% confidence interval [CI]: 2.84 to 9.35) and no statistically significant difference between groups in mortality at 12 months (OR: 1.05, 95% CI: 0.82 to 1.33). (6) The authors did not conduct sub-group analyses e.g., by location of emphysema, exercise capacity, or heterogeneity of emphysema.

**Selected RCTs (other than NETT) are summarized below:**

Hillerdal and colleagues conducted a multicenter study in Sweden evaluating LVRS that was published in 2005. (7) Eligibility criteria included age 75 years or younger, forced expiratory volume in one second (FEV-1) of no more than 35% of predicted normal value; excessive hyperinflation with a residual volume of at least 200% of predicted, with radiologic signs of emphysema and decreased mobility of the diaphragm. Participants were required to successfully complete a 6-week physical training program. Of the 114 patients eligible for the initial training (of 304 evaluated), 3 were unable to complete the program, and 5 died before completion; the remaining 106 patients were randomized to continued physical training alone (n=53) or LVRS plus continued physical training for 3 months post-surgery (n=53). A total of 42 (79%) patients in the surgery group and 43 (81%) in the physical training group were followed for 1 year; intention-to-treat analysis was used. The primary outcome was health status according to the Swedish version of the Short-Form General Health Survey (SF)-36 instrument and the disease-specific St. George’s Respiratory Questionnaire (SGRQ). Both instruments have scores ranging from 0 to 100; in the SF-36, 100 represents the best health status and in the SGRQ, 100 represents poor health status. For both instruments, the minimally important clinical difference was defined as 4 scale points. In an analysis adjusting for age and sex, there was a significant difference in the score on the SGRQ at 6 months (mean difference of 14.3 points) and 12 months (mean difference of 14.7 points), favoring the LVRS group. The total score on the SF-36 at follow-up was not reported. At 12 months, there was significantly more improvement in 6 of the 8 SF-36 subscales in the LVRS group compared to the physical training group. The researchers only reported mean difference in the scales, not the proportion of patients who achieved a certain level of improvement. Mortality was a secondary outcome. There were 7 deaths in the LVRS group (13%) and 2 deaths in the physical training group (4%); this difference was not statistically significant (p=0.5), but
the study was likely underpowered for this outcome. Six of the deaths in the LVRS group were caused by respiratory failure and pneumonia; the seventh patient died suddenly at home. Respiratory failure was also the cause of the 2 deaths in the physical training group. The authors point out that the baseline SGRQ scores were lower than in the NETT (59 versus 53, respectively), suggesting a more severely impaired population. The study did not examine patient outcomes according to upper-lobe predominance or initial exercise capacity.

In 2006, Miller and colleagues published a study with data from 5 centers in Canada. (8) Eligibility criteria included: age between 40 and 79 years; disabling dyspnea; FEV-1 of no more than 40% of predicted; diffusing capacity no more than 60%; and total lung capacity no more than 120% or residual volume no less than 200%. After eligibility screening, medical therapy was optimized, and then patients were randomized to LVRS (n=32) or continued medical therapy (n=30). The researchers had originally planned to enroll 350 individuals, but due to the low proportion of screened individuals who were eligible, they stopped recruitment when only 18% of their target was met (467 individuals were screened to identify 62 who were eligible). Thus, the study may have been underpowered to detect differences in outcomes between groups. None of the randomized patients were lost to follow-up, and analysis was intention to treat. The overall 2-year survival rate was similar in the two groups; there were 5/32 (16%) deaths in the LVRS group and 4/30 (13%) deaths in the medical therapy group (p=0.935). At 3 and 6 months, there was a significantly higher change from baseline in FEV-1 in the LVRS group compared to the medical therapy group, but there was a non-significant difference between groups in FEV-1 at 12 and 24 months. The mean difference in FEV-1 at 24 months was 0.06 liters.

In 2013, Agzarian et al published long-term results of the CLVRS trial. (9) Fifty-two of 62 randomized patients (84%) were available for the long-term follow-up 8 to 10 years after treatment. One patient was excluded before surgery and 9 others were lost to follow-up. The proportion of patients surviving 5 and 10 years was 46% and 7%, respectively, in the LVRS group and 25% and 0% in the control group. According to Kaplan-Meier survival analysis, median survival was 63 months in the LVRS group and 47 months in the control group; the difference between groups was not statistically significant (p=0.20).

In 2015, Clarenbach et al reported an RCT in 30 patients scheduled for LVRS. (10) The trial compared patients who were immediately treated with LVRS to patients who were treated after a 3-month waiting period. The primary outcomes were a physiologic measures (endothelial function) assessed by flow-mediated dilatation of the brachial artery at 3 months (2.9; 95% CI, 2.1 to 3.6; p<0.001) and C-reactive protein (p=NS). In the group treated with immediate LVRS, the secondary outcome of FEV1 improved by 29%. There were no significant differences between groups for the 6-minute walk test or levels of daily activity at 3 months. This trial included patients who had LVRS for either upper-lobe or lower-lobe disease, the latter being an indication not supported by the results of NETT.

Nonrandomized Comparative Studies
In 2014, Decker et al reviewed data on 538 patients from the Society of Thoracic Surgeons (STS) database who received LVRS and compared these data with those of the 608 NETT participants randomized to the surgery group.11 None of the patients in the STS database had an FEV1 less than 20% of predicted or a carbon monoxide diffusing capacity less than 20% of predicted; thus, these
patients would not have been considered high risk in NETT. And, about 10% of patients in the STS database had previous cardiothoracic surgery and 1.5% had lung cancer, both exclusion criteria in NETT. Overall, the mortality rate within 30 days of LVRS did not differ significantly between the STS database (5.6%) and NETT (3.6%; p=0.113). When database findings were compared with non-high-risk NETT participants, the 30-day mortality rate was significantly higher among patients in the STS database (5.6%) than NETT patients (2.2%; p=0.005). This study was descriptive and did not propose patient selection criteria for LVRS.

**Observational Studies**
In 2012, Baldi et al conducted a retrospective analysis that included longer term follow-up than had been reported in the RCTs discussed above. The study included 52 emphysema patients who had LVRS between 1993 and 2000. (12) The 5-year survival rate was 73% and the 12-year survival rate was 20%. Eleven (21%) of 52 patients underwent lung transplantation a mean of 52 months after LVRS. In a multivariate model, 2 variables were statistically associated with patient survival: preoperative pulmonary arterial pressure (hazard ratio [HR], 2.11; 95% CI, 0.99 to 4.45) and upper-lobe distribution of emphysema (HR=2.43; 95% CI, 1.10 to 5.36).

**Ongoing and Unpublished Clinical Trials**
A search of ClinicalTrials.gov in June 2016 did not identify any ongoing or unpublished trials that would likely influence this review.

**Practice Guidelines and Position Statements**
The American Thoracic Society issued a statement on lung volume reduction surgery in 1996. (13) This was before publication of the National Emphysema Treatment Trial findings; at the time, the Society stated that LVRS appeared to be helpful in some, but not all, patients with advanced emphysema. No updated statement was identified.

**U.S. Preventive Services Task Force Recommendations**
Not applicable.

**Summary of Evidence**
For individuals who have upper-lobe emphysema who receive lung volume reduction surgery (LVRS), the evidence includes randomized controlled trials (RCTs). Relevant outcomes are overall survival, symptoms, functional outcomes, quality of life, and treatment-related mortality. Findings from the National Emphysema Treatment Trial (NETT), a multicenter RCT, suggest that LVRS is effective at reducing mortality and improving quality of life in select patients with severe emphysema. In subgroup analysis, LVRS offered a survival advantage only in patients not considered high risk who had predominately upper-lobe emphysema and low initial exercise capacity. Patients with upper-lobe emphysema, regardless of initial exercise capacity, experienced significant improvement in exercise capacity and quality of life after LVRS. Other, smaller RCTs have generally had similar findings, though they have tended to be underpowered for some outcomes and did not stratify by distribution of emphysema. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.
For individuals who have non-upper-lobe emphysema who receive LVRS, the evidence includes subgroup analysis of a large RCT. Relevant outcomes are overall survival, symptoms, functional outcomes, quality of life, and treatment-related mortality. In the subgroup analysis of NETT, LVRS offered a survival advantage only in patients who had predominately upper-lobe emphysema. For the subgroup with predominately non-upper-lobe emphysema, NETT did not find significant mortality advantages or symptom improvement with LVRS. Although NETT had positive findings for the study population as a whole, given the surgical risks, additional data are needed to confirm the net health outcome in patients with non-upper-lobe emphysema. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Medicare National Coverage**

Effective for services performed on or after January 1, 2004, Medicare will only consider LVRS reasonable and necessary for patients with severe upper lobe predominant emphysema or severe non-upper lobe emphysema with low exercise capacity who meets all of the following requirements:

(14)

**Table 2. Medicare Criteria**

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Criteria</th>
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<tbody>
<tr>
<td><strong>History and physical examination</strong></td>
<td>Consistent with emphysema</td>
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<tr>
<td></td>
<td>BMI ≤31.1 kg/m² (men) or ≤32.3 kg/m² (women)</td>
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<td></td>
<td>Stable with ≤20 mg prednisone (or equivalent) daily</td>
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<tr>
<td><strong>Radiographic</strong></td>
<td>High Resolution Computer Tomography (HRCT) scan evidence of bilateral</td>
</tr>
<tr>
<td></td>
<td>emphysema</td>
</tr>
<tr>
<td><strong>Pulmonary function (pre-rehabilitation)</strong></td>
<td>Forced expiratory volume in one second (FEV₁) ≤45% predicted ≥15% predicted if age ≥70 years</td>
</tr>
<tr>
<td></td>
<td>Total lung capacity (TLC) ≥100% predicted post-bronchodilator</td>
</tr>
<tr>
<td></td>
<td>Residual volume (RV) ≥150% predicted post-bronchodilator</td>
</tr>
<tr>
<td><strong>Arterial blood gas level (pre-rehabilitation)</strong></td>
<td>PCO₂ ≤60 mm Hg (PCO₂ ≤55 mm Hg if 1-mile above sea level)</td>
</tr>
<tr>
<td><strong>Cardiac assessment</strong></td>
<td>PO₂ ≥45 mm Hg on room air ( PO₂ ≥30 mm Hg if 1-mile above sea level)</td>
</tr>
<tr>
<td></td>
<td>Approval for surgery by cardiologist if any of the following are present: Unstable angina; left-ventricular ejection fraction (LVEF) cannot be estimated from the echocardiogram; LVEF &lt;45%; dobutamine-radiouclide cardiac scan indicates coronary artery disease or ventricular dysfunction; arrhythmia (&gt;5 premature ventricular contractions per minute; cardiac rhythm other than sinus; premature ventricular contractions on EKG at rest)</td>
</tr>
<tr>
<td><strong>Surgical assessment</strong></td>
<td>Approval for surgery by pulmonary physician, thoracic surgeon, and anesthesiologist post-rehabilitation</td>
</tr>
<tr>
<td><strong>Exercise</strong></td>
<td>Post-rehabilitation 6-min walk of ≥140 m; able to complete 3 min unloaded pedaling in exercise tolerance test (pre- and post-rehabilitation)</td>
</tr>
<tr>
<td><strong>Consent</strong></td>
<td>Signed consents for screening and rehabilitation</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>Plasma cotinine level ≤13.7 ng/mL (or arterial carboxyhemoglobin ≤2.5% if using nicotine products)</td>
</tr>
<tr>
<td><strong>Preoperative</strong></td>
<td>Nonsmoking for 4 months prior to initial interview and throughout evaluation for surgery</td>
</tr>
<tr>
<td><strong>Consent</strong></td>
<td>Signed consents for screening and rehabilitation</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>Plasma cotinine level ≤13.7 ng/mL (or arterial carboxyhemoglobin ≤2.5% if using nicotine products)</td>
</tr>
<tr>
<td><strong>Preoperative</strong></td>
<td>Must complete assessment for and program of preoperative services in preparation</td>
</tr>
</tbody>
</table>
diagnostic and therapeutic program adherence for surgery

ECG: electrocardiogram; LVEF: left ventricular ejection fraction; Med: medical; Surg: surgical; Tx: treatment

There are additional criteria specifying eligible facilities.

References


<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Reason</th>
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<tr>
<td>December 2011</td>
<td>New Policy</td>
<td>Policy updated with literature search. Rationale substantially revised. Reference 5 added; Reference 8 changed to NICE; other references renumbered or removed. No change in policy statements.</td>
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<tr>
<td>March 2013</td>
<td>Update Policy</td>
<td>Policy updated with literature search. Reference 8 added; other references renumbered. No change in policy statements.</td>
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<tr>
<td>September 2015</td>
<td>Update Policy</td>
<td>Policy updated with literature review through April 27, 2016; reference 10 added; policy statements unchanged.</td>
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</table>

**Keywords**

Emphysema, Lung Volume Reduction Surgery
Lung Volume Reduction Surgery, Emphysema

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on September 16, 2016 and is effective October 15, 2016.

Signature on File
Deborah M. Smith, MD, MPH