Cost effectiveness of lung-volume-reduction surgery for patients with severe emphysema

National Emphysema Treatment Trial Research Group

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of lung-volume-reduction surgery (LVRS) plus medical therapy for patients with severe emphysema. LVRS was performed using either median sternotomy or video-assisted thoracoscopic surgery.

Type of intervention
Treatment and rehabilitation.

Economic study type
Cost-utility analysis.

Study population
The study population comprised patients with severe emphysema who had not smoked for 6 months prior to enrolment, who were judged to be free of other diseases, disabilities, or circumstances likely to interfere with therapy.

Setting
The setting was a hospital. The economic study was conducted in 17 medical centres across the USA.

Dates to which data relate
The effectiveness and resource use data appear to have been gathered from January 1998 to July 2002. The price year was 2002.

Source of effectiveness data
The effectiveness evidence was derived from a single study, the details of which were published elsewhere (see Other Publications of Related Interest).

Link between effectiveness and cost data
The costing was conducted prospectively on a sub-sample of patients used in the effectiveness study.

Study sample
Sample size calculations suggested that the study was powered to detect statistically significant differences in survival rates (8%) for a rate of unplanned crossover of 30% among those assigned to medical therapy and that an overall sample of 2,500 patients (i.e. 1,250 patients per group) was required. The study was powered to detect statistically significant differences in the remaining outcome measures. Patients who were considered eligible were Medicare beneficiaries or those whose insurance carrier was willing to cover the costs of their participation in the trial. Of an initial sample of 3,777 patients, 1,218 cases were enrolled in the study. There were 608 in the LVRS group and 610 in the medical therapy group. The mean age in the LVRS group was 66.5 (+/- 6.3) years and 42% were women. The mean
age in the medical therapy group was 66.7 (+/- 5.9) years and 36% were women. It was not stated whether some patients refused to participate, or were excluded from the initial study sample for any reason.

**Study design**
This was a prospective, randomised controlled trial that was carried out in 17 medical centres. Prior to randomisation, the patients underwent 6 to 19 weeks of pulmonary rehabilitation. Subsequently, the patients were randomised to either LVRS or medical therapy using a 1:1 ratio. Details of the method of randomisation were not accurately described. The patients were followed for 3 years with outcome assessments being conducted at 6 and 12 months, and yearly thereafter. The loss to follow-up was unclear, but 157 patients in the LVRS group and 160 in the medical therapy group died. No blind assessment was performed.

**Analysis of effectiveness**
The analysis of the clinical study was conducted on an intention to treat basis. The primary health outcomes used in the effectiveness study were overall mortality and maximal exercise capacity on cycle ergometry (measured with an increment of 5 to 10 W per minute after 3 minutes of pedalling with the ergometer set at 0 W and the patients breathing 30% oxygen). The secondary health outcomes were a 6-minute health test, lung function test and three self-administered questionnaires. The questionnaires related to health-related quality of life (St. George's Respiratory Questionnaire), general quality of life (the Quality of Well-Being scale, QWB) and dyspnoea (the University California, San Diego, Shortness of Breath Questionnaire). Prognostic factors were identified using a multiple logistic regression model to take into account potential confounders, which may have occurred despite randomisation. The authors considered four sub-groups of patients based on the combination of the presence or absence of upper-lobe predominance in the distribution of emphysema and low or high maximal exercise capacity. The study groups were shown to have been comparable at baseline. However, there was a higher proportion of men in the medical therapy group.

**Effectiveness results**
The total mortality rate was 0.11% in both groups, despite a higher early mortality rate in the LVRS group.

Exercise capacity in the LVRS group improved by more than 10 W in 28% of the patients after 6 months, in 22% after 12 months, and in 15% after 24 months.

In the medical therapy group, the improvement was 4% after 6 months, 5% after 12 months, and 3% after 24 months.

The patients in the LVRS group had significantly better results than those in the medical therapy group for the remaining outcome measures.

After excluding 140 patients who were considered at high risk of death, the total mortality rate was 0.09% in the LVRS group and 0.10 in the medical therapy group, (p=0.31).

Survival was significantly improved among patients with predominantly upper-lobe emphysema and low exercise capacity, and among patients with predominantly non-upper-lobe emphysema and high exercise capacity.

**Clinical conclusions**
The effectiveness analysis showed that LVRS did not offer any survival benefit, although it appears likely that some sub-group of patients could improve survival and function.

**Modelling**
The long-term cost-effectiveness of the study interventions was evaluated using a log-logistic model to extrapolate survival data from the trial (3-year period) to a time horizon of 5 or 10 years. A regression analysis was conducted to determine the relationship between survival and treatment-group assignment in order to derive estimates of the
parameters for the model. It was assumed that the relative hazard of death in the surgery group, compared with the medical therapy group, was set at observed levels for year 3. Further details of the model were not reported.

Measure of benefits used in the economic analysis
The summary benefit measure used in the economic analysis was the quality-adjusted life-years (QALYs). These were calculated by combining survival data from the primary study with the utility values derived from the QWB scores. A 3% annual discount rate was used since the benefits were estimated over more than 2 years.

Direct costs
The costs incurred after the first year were discounted using an annual rate of 3%. The unit costs were not reported separately from the quantities of resources used. The health services included in the economic evaluation were medical goods and services, and transportation to and from health care facilities. Medical goods and services included pulmonary rehabilitation, the surgical procedure itself, medication, inpatient and outpatient care, ambulatory laboratory, diagnostic and radiology services, home health services, supplementary oxygen for home use, a skilled nurse facility and hospice care. The cost/resource boundary adopted was that of Medicare (or the patient insurer). The costing was conducted on a sub-group of patients (from which high-risk patients were excluded) who had been included in the effectiveness study. Resource use and the unit costs were estimated using actual data derived from Medicare records, reimbursement rates and average wholesale prices. The lowest price for the available generic versions of the medications was used. Transportation costs were estimated on the basis of travel distances and tariffs were based on government reimbursement per mile. All costs were inflated to 2002 values using the consumer price index.

Statistical analysis of costs
The statistical significance of the differences between the two study groups was tested using standard statistical analyses of the costs and resources used. The average total costs were estimated using the non-parametric Kaplan-Meier sample-average estimator.

Indirect Costs
The indirect costs were included because a societal perspective was adopted. The time spent by family and friends (unpaid caregivers) in caring for the patient, and the time spent by the patient in receiving treatment were included in the analysis. The value of time spent by family and friends was calculated on the basis of the average wage for workers aged 20 to 64 years. The value of the time patients spent receiving treatment was calculated on the basis of the average wage for workers aged 65 years or older. Both wages were estimated from the Bureau of Labor Statistics. The unit costs were not analysed separately from the quantities of resources used. The price year was 2002.

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analyses were not conducted. However, the relative hazard of death was assumed to change to 1.0 (no survival benefit) by 3, 5 and 10 years. The non-parametric bootstrap method with 2,000 replications was used to derive a 95% confidence interval (CI) for the incremental cost-effectiveness ratio (ICER) at 3 years of follow-up. To further deal with uncertainty, the authors constructed a cost-effectiveness acceptability curve, with the bootstrap method applied to projected survival and estimates of costs and QALYs.

Estimated benefits used in the economic analysis
After 3 years, the mean number of QALYs gained was 1.46 in the LVRS group and 1.27 in the medical therapy group, (p<0.001). Similar results were obtained at 12 and 24 months. The authors stated that alternative methods of imputing missing QWB scores had no impact on the estimated QALYs.
Cost results
In the first year, the mean number of hospital days was 24.9 (95% CI: 22.3 - 27.6) in the LVRS group and 4.9 (95% CI: 4 - 5.8) in the medical therapy group, (p<0.001). The corresponding figures in the second year were 3.2 (95% CI: 2.3 - 4.1) and 6.1 (95% CI: 4.5 - 7.6), (p=0.005), and in the third year, 4 (95% CI: 2.3 - 5.8) and 5.2 (95% CI: 3.8 - 6.7), (p=0.08).

The mean total cost per person at 3 years was $98,952 in the LVRS group and $62,560 in the medical therapy group, (p<0.001).

In the first year, the mean total costs were $71,515 (95% CI: 65,921 - 77,109) in the LVRS group and $23,371 (95% CI: 21,056 - 25,686) in the medical therapy group, (p<0.001). The corresponding figures in the second year were $13,222 (95% CI: 11,479 - 14,964) and $21,319 (95% CI: 18,004 - 24,635), (p<0.001), and in the third year, $14,215 (95% CI: 11,529 - 16,901) and $17,870 (95% CI: 14,785 - 20,954), (p=0.08).

The difference in costs was largely due to the direct medical care costs, as the non-medical costs did not differ significantly between the two groups.

Synthesis of costs and benefits
An incremental cost-effectiveness analysis was conducted to combine the costs and benefits of the two study interventions.

After 3 years of treatment, the incremental cost per QALY gained with LVRS relative to medical therapy was $190,000. This cost became $193,000 when only the direct costs were considered (perspective of the health insurer).

After 10 years of treatment, the cost per QALY was $53,000.

Variations in the duration of survival benefits did not affect the estimated ICER.

A sub-group analysis revealed that in the group of those who had emphysema without upper-lobe predominance and who had high exercise capacity, patients in the LVRS had significantly higher mortality, reduced quality-adjusted survival, and had higher costs than patients assigned to medical therapy. At 3 years, the ICER was $98,000 among those with predominantly upper-lobe emphysema and low exercise capacity, $240,000 among with predominantly upper-lobe emphysema and high exercise capacity, and $330,000 among those with non-upper-lobe emphysema and low exercise capacity.

When patients with significantly higher mortality and costs were excluded, the ICERs fell dramatically. However, the cost-effectiveness acceptability curve analysis revealed substantial uncertainty in the decision to adopt LVRS strategies.

Authors' conclusions
Due to the uncertainty surrounding the results of the analysis, it was difficult to draw any conclusion about the cost-effectiveness of lung-volume-reduction surgery (LVRS) in comparison with standard medical therapy. The sub-group analysis indicated the patients who might receive the greatest benefits from the intervention. However, even in specific groups of patients, the costs borne by the society were likely to be high.

CRD COMMENTARY - Selection of comparators
Medical therapy alone was selected as the basic comparator because it represented the standard strategy for treating patients with severe emphysema. It was also selected since the aim of the study was to evaluate the additive value of LVRS. The authors of the primary study stated that there were available strategies (i.e. laser ablation or lung plication) that were considered to be alternatives to LVRS, but there was a large consensus that LVRS was more effective and thus recommended. You should decide whether medical therapy alone represents a valid comparator in your own setting.
Validity of estimate of measure of effectiveness
The analysis of effectiveness used a randomised clinical trial, which was appropriate for the study question. The design, rationale and results of the effectiveness study were reported elsewhere (see Other Publications of Related Interest). The study sample was heterogeneous and appears to have been representative of the study population. The internal validity of the analysis was further enhanced by several factors. First, power calculations that took into account the crossover rate were performed. Second, with the exception of the percentage of men, the study groups were shown to have been comparable at baseline. Third, the method of sample selection was reported, the length of follow-up was explicitly stated. Fourth, the basis of the analysis was intention to treat and the authors took into account potential confounding factors. Finally, the study was multi-centred and sub-group analyses were conducted. A blind assessment was not feasible due to the characteristics of the study intervention (surgery versus no surgery). The loss to follow-up was unclear, and it was not stated whether any patients were excluded from the initial study sample or refused to participate.

Validity of estimate of measure of benefit
The summary benefit measure used in the economic analysis was the QALY. This was appropriate to estimate the impact of the study interventions on quality and quantity of life. The method used to elicit utility weights was reported. The use of QALYs enables the benefits of the LVRS to be compared with those associated with other health interventions. Appropriate discounting was performed due to the long time horizon of the analysis.

Validity of estimate of costs
The perspective adopted in the study was explicitly reported. It appears that all the relevant cost components have been included in the analysis. The authors recognised that some categories of costs were not considered, but it was stated that the impact of their inclusion would have been negligible because these costs were incurred equally in both study groups. Only limited details of the cost analysis were provided. The price year was mentioned, thus making reflation exercises in other settings possible. However, the unit costs were not given and the data on resource use were not reported. Sensitivity analyses were not performed on the economic data and the cost estimates were specific to the study setting. Statistical tests were conducted on the cost and quantities.

Other issues
The authors did not compare their findings with those from other studies. They also did not address the issue of the generalisability of the study results. Sensitivity analyses were not conducted and details on the costs/resources were not provided. Thus, it appears difficult to replicate the study in other settings. The issue of uncertainty was dealt with by performing a bootstrap analysis, but this did not help to obtain more sound results. The authors used an analytical model to consider the long-term costs and benefits of LVRS, which was necessary to capture all the economic and clinical implications of the study procedures. The authors presented their results for the main sample, as well as for all the sub-groups of patients considered in the article.

Implications of the study
The authors suggested that decision makers should take into account "clinical experience as well as the criteria for selection of patients when establishing reimbursement policies for lung-volume-reduction surgery".

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Other publications of related interest


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