Long-Term Follow-Up of High-Risk Patients in the National Emphysema Treatment Trial

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Background. The National Emphysema Treatment Trial (NETT) was a randomized clinical trial designed to compare lung volume reduction surgery (LVRS) with maximal medical care for patients with severe emphysema. The trial was halted early for a subgroup of patients with severe lung disease. We report longer term follow-up for this high-risk subgroup.

Methods. In a randomized clinical trial, patients with moderate to severe emphysema were assigned to LVRS plus maximal medical care or to maximal medical care alone and followed prospectively for vital status over 15 years. We focus on 140 high-risk patients. Quality of life data were available through 6 years of follow-up and were assessed using the University of California, San Diego Shortness of Breath Questionnaire and the Self-Administered Quality of Well-Being Scale.

Results. Through the first 3 years of follow-up, surgical patients in the high-risk subgroup had a significantly higher probability of death. However, the mortality curves crossed and there was a trend favoring surgical treatment through the remainder of the follow-up. The log-rank test suggested that the 2 groups were not significantly different \((p = 0.95)\) in survival. Quality of life data suggested an advantage of LVRS through the first 5 years of follow-up \((p < 0.01)\). The combined quality-adjusted survival model favored the medical group for the first few years of follow-up and favored the LVRS group after 4 years.

Conclusions. The NETT was stopped early for high-risk patients with severe lung disease. Longer term follow-up suggests that surgical patients in this high-risk subgroup ultimately achieved comparable outcomes. The high risk of death within 30 days of the surgery may discourage use of the procedure for high-risk patients despite the potential for better long-term outcomes.

The National Emphysema Treatment Trial (NETT) was a randomized clinical trial evaluating lung volume reduction surgery (LVRS). The trial randomly assigned adults with moderate to severe emphysema to either LVRS plus maximal medical care or to maximal medical care alone. The study demonstrated that LVRS improved survival in selected subgroups of patients. In particular, patients with predominantly upper lobe emphysema who, at baseline, had low exercise capacity experienced greater improvements in life expectancy and quality of life [1].

One of the complicating findings in the NETT was the observation of harmful outcomes for some subsets of patients. An earlier report identified a group of high-risk patients who experienced an increased probability of short-term mortality after LVRS [2]. These patients, who comprised about 13.6% of the NETT cohort, had \(FEV_{1.0} \) values that were less than 20% of the predicted and either a very low carbon monoxide diffusing capacity or homogeneous emphysema. For patients in this subgroup, the 30-day mortality rate was 16% in comparison with no deaths (0%) in the medical therapy group. The overall mortality rate was almost 4 times higher in the LVRS group in comparison with the medical group (relative risk \([RR] = 3.9; 95\% \) confidence interval \([CI] = 1.9 to 9.0) with 0.43 deaths per person-year for the LVRS group versus 0.11 deaths per person-year among medical care patients. After 6 months, about a third of patients who had completed and survived surgery had improvements in 6 minute walking distance in comparison with only about 4% in the medical care only group. Quality of life showed little change and was equivalent in the 2 groups.

In response to these early findings, the trial was halted for this high-risk subgroup. However, evaluation of high-risk patients randomly assigned to LVRS or to maximal medical care continued. In this paper we report long-term follow-up for the high-risk group. The analysis focuses on 3 different but related outcomes: (1) the primary outcome of life expectancy; (2) the secondary outcome of health-related quality of life among survivors; and (3) an index that combines survival and quality of life.
Material and Methods

Subjects

The NETT included 746 male and 472 female volunteers with an average age of 64 years at baseline. Participants were studied at 1 of 17 approved NETT sites. The inclusion criteria were the following: (1) radiographic evidence of bilateral emphysema; (2) severe airflow obstruction and hyperinflation; and (3) completion of pulmonary rehabilitation. Exclusion criteria were the following: (1) a broad range of medical conditions that place patients at risk for perioperative morbidity or mortality; (2) emphysema felt to be unsuitable for LVRS; and (3) medical conditions or other circumstances that make it likely that the patient would be unable to complete the trial. The exclusion criteria relating to cardiologic issues were based upon the work of Goldman and colleagues [3]. All participants provided written informed consent to participate and the study protocol was approved by the Institutional Review Boards (IRBs) of each of the 17 participating centers. The Coordinating Center, the Johns Hopkins Bloomberg School of Public Health provided oversight over all participating institutions and did not accept data from any center without an active approval (Johns Hopkins Institutional Review Board, approved protocol number H34.02.01.29.A1). A more detailed description of the NETT methodology is available elsewhere [4].

After baseline evaluation all participants completed comprehensive pulmonary rehabilitation. A second assessment was completed after rehabilitation and prior to randomization.

Treatment Groups

After extensive screening and completion of pulmonary rehabilitation for eligible subjects, patients were randomly assigned to LVRS or to maximal medical therapy. Maximal medical therapy included state of the art medical management of advanced emphysema. The LVRS was achieved using a median sternotomy approach (406 patients) or by means of video-assisted surgery (174 patients). In this paper we focus on 140 participants who were later assessed for eligibility.

<table>
<thead>
<tr>
<th>Group</th>
<th>Assessed for Eligibility</th>
<th>Excluded</th>
<th>Randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk Patients</td>
<td>140</td>
<td>2559</td>
<td>1218</td>
</tr>
<tr>
<td>Non High Risk Patients</td>
<td>1078</td>
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<td></td>
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</table>

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Medical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocated</td>
<td>Allocated</td>
</tr>
<tr>
<td>Refused surgery</td>
<td>Crossed-over</td>
</tr>
<tr>
<td>Received surgery</td>
<td>Received treatment</td>
</tr>
<tr>
<td>69</td>
<td>70</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Follow-up for Quality of Life*</th>
<th>Follow-up for Quality of Life*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analyzed for Year 1 Visit</td>
<td>Analyzed for Year 1 Visit</td>
</tr>
<tr>
<td>For quality of life</td>
<td>For quality of life</td>
</tr>
<tr>
<td>37</td>
<td>49</td>
</tr>
<tr>
<td>For quality adjusted survival</td>
<td>For quality adjusted survival</td>
</tr>
<tr>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Analyzed for Year 4 Visit</td>
<td>Analyzed for Year 4 Visit</td>
</tr>
<tr>
<td>For quality of life</td>
<td>For quality of life</td>
</tr>
<tr>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>For quality adjusted survival</td>
<td>For quality adjusted survival</td>
</tr>
<tr>
<td>59</td>
<td>45</td>
</tr>
</tbody>
</table>

*See details in Table 2
classified into a subgroup identified by the Data and Safety Monitoring Board as being at high risk of short-term mortality after LVRS with little chance of functional improvement. Seventy patients were assigned to LVRS and 70 to maximal medical care. One of the patients in the LVRS group declined surgery but is included in that group by the intention to treat principle.

Quality of Life Data Collection
Data collection for NETT subjects began in October, 1997. The NETT randomizations began in January 1998 and ended in July 2001. The quality of life assessments were collected at all visits. The final quality of life forms were collected by mail between December 31, 2003 and June 30, 2004. Based on date of randomization, the follow-up time for quality of life data collection of NETT patients varied from 2.0 to 6.5 years. As a result, not all quality of life measures were assessed for patients in the later phases of the trial (due to right censoring). The NETT created time windows for follow-up visits and mapped the forms into them. In this paper, we will include analyses of the quality of life measures from pre-rehabilitation, post-rehabilitation (or baseline before randomization), and follow-up visits 0.5, 1, 2, 3, 4, 5, and 6 years after randomization. Two instruments were used to assess quality of life; the University of California San Diego (UCSD) Shortness of Breath Questionnaire (SOBQ) and the Self-Administered Quality of Well-Being Scale (QWB-SA).

University of California San Diego Shortness of Breath Questionnaire
The SOBQ was used as a symptom-specific quality of life indicator. It is self-administered and asks subjects to rate their breathlessness for 21 various daily activities (plus 3 overall items) on a 6-point scale from none at all (0) to severe (4) to maximal or unable to do because of breathlessness (5) [5]. For activities that they do not typically perform, respondents are expected to estimate their breathlessness for that activity. The 21 activities of daily living (ADLs) are grouped according to factor analysis into 4 categories of ADLs: rest and light ADLs (factor 1), 8 questions; moderate ADLs (factor 2), 5 questions; walking (factor 3), 4 questions; and strenuous ADLs (factor 4), 4 questions. The score on each of the 24 items is summed to produce a total score (range of 0 to 120).

Quality of Life Measurement: QWB-SA
The QWB-SA combines preference-weighted values for symptoms and functioning; QWB-SA data can be combined with survival data to estimate quality-adjusted life expectancy. In the NETT, QWB-SA was the metric employed in the cost-effectiveness analysis.

Table 1. Characteristics of the High-Risk Patientsa at Baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Surgery (n = 70)</th>
<th>Medical Therapy (n = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at randomization, years</td>
<td>63.1 ± 6.8</td>
<td>64.2 ± 6.1</td>
</tr>
<tr>
<td>Race or ethnic group, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>68 (97)</td>
<td>64 (91)</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>2 (3)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>18 (26)</td>
<td>19 (27)</td>
</tr>
<tr>
<td>Male</td>
<td>52 (74)</td>
<td>51 (73)</td>
</tr>
<tr>
<td>FEV1 after bronchodilator use– % of predicted</td>
<td>17.1 ± 2.5</td>
<td>17.3 ± 2.4</td>
</tr>
<tr>
<td>RV after bronchodilator use, % of predicted</td>
<td>267.4 ± 57.1</td>
<td>274.5 ± 55.7</td>
</tr>
<tr>
<td>DLCO, % of predicted</td>
<td>20.5 ± 8.9</td>
<td>19.8 ± 7.5</td>
</tr>
<tr>
<td>PaO2, mm Hg</td>
<td>60.7 ± 8.6</td>
<td>60.0 ± 9.3</td>
</tr>
<tr>
<td>PaCO2 mm Hg</td>
<td>46.8 ± 6.4</td>
<td>47.2 ± 6.0</td>
</tr>
<tr>
<td>Perfusion ratiob</td>
<td>0.27 ± 0.15</td>
<td>0.24 ± 0.17</td>
</tr>
<tr>
<td>Distribution of emphysema, n (%)c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneous</td>
<td>24 (34)</td>
<td>22 (31)</td>
</tr>
<tr>
<td>Homogeneous</td>
<td>46 (66)</td>
<td>48 (69)</td>
</tr>
<tr>
<td>Maximal workload on bicycle ergometry, W</td>
<td>28.0 ± 17.5</td>
<td>24.2 ± 14.9</td>
</tr>
<tr>
<td>Distance walked in 6 minutes, (feet)</td>
<td>1038.2 ± 300.7</td>
<td>993.9 ± 264.1</td>
</tr>
<tr>
<td>Average daily score on Quality of Well-Being questionnaired</td>
<td>0.58 ± 0.12</td>
<td>0.54 ± 0.12</td>
</tr>
</tbody>
</table>

a High-risk patients were those with a forced expiratory volume in 1 second (FEV1) that was no more than 20% of their predicted value and either a homogeneous distribution of emphysema on computed tomographic scanning or a carbon monoxide diffusing capacity (DLCO) that was no more than 20 percent of their predicted value. 

b The perfusion ratio was derived from the radionuclide perfusion scan. c The distribution of emphysema was based on scores assigned subjectively to each of the three zones in each lung. d The quality of well-being scale where 0 is equivalent to death and 1.0 indicates perfect health without symptoms. For details see reference 1.


PaO2 = partial pressure of oxygen, arterial; PaCO2 = partial pressure of carbon dioxide, arterial.
Preference weights for the QWB were obtained from ratings by 856 people from the general population. These judges rated the desirability of health conditions in order to place each on the continuum between death (0) and optimum health (1.0). Symptoms are assessed by questions that ask about the presence or absence of different symptom complexes. Functioning is assessed by a series of questions designed to record functional limitations over the previous 3 days, within 3 separate domains (mobility, physical activity, and social activity). The 4 domain scores are combined into a total score that provides a numeric point-in-time expression of well-being that ranges from zero (0) for death to 1 (1.0) for asymptomatic optimum functioning. In this analysis, the value 0.0 was inserted for each follow-up that was missed because a patient had died. The QWB has been used in numerous clinical trials and studies to evaluate medical and surgical therapies in conditions including chronic obstructive pulmonary disease [6] and other chronic illnesses [7].

**Statistical Analysis**

We ascertained survival status as of June 2013. The Kaplan-Meier survival curves were compared by the log-rank test. The 95% confidence intervals for the median survival times were constructed using the method of Brookmeyer and Crowley [8].

The UCSD SOBQ scores were analyzed only for the survivors. The QWB-SA quality-adjusted survival analysis was based on available data with imputation of 0.0 for deceased participants. We analyzed these longitudinal data using the analysis of response profiles approach [9]. The mean response profiles model included the indicator variables for treatment groups, visit times, and the interaction terms of treatment groups and visit times. The variance covariance matrix among repeated measures had an unstructured pattern in this model. The average quality of life score, change from baseline score, treatment effect, corresponding 95% CIs, and p values at each visit were estimated and tabulated for both groups. The unadjusted group means and standard errors were also included in the table for comparison.

![Fig 2. Long-term survival by group. (LVRS = lung volume reduction surgery.)](image)
Table 3. Unadjusted and Response Profile Model-Based Estimates for University of California San Diego Shortness of Breath Questionnaire Total Scores

<table>
<thead>
<tr>
<th>Visit (Year)</th>
<th>Treatment Group</th>
<th>Unadjusted Mean (SE)</th>
<th>Raw Score Mean (SE)</th>
<th>95% CI</th>
<th>Treatment Effect Mean (SE)</th>
<th>95% CI</th>
<th>p Value</th>
<th>Change From Baseline Mean (SE)</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.25</td>
<td>LVRS</td>
<td>70.44 (2.03)</td>
<td>70.44 (2.14)</td>
<td>[66.22-74.66]</td>
<td>-1.97 (3.03)</td>
<td>[-7.94-3.99]</td>
<td>0.52</td>
<td>2.23 (2.20)</td>
<td>[-2.09-6.55]</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>Medical</td>
<td>72.41 (1.97)</td>
<td>72.41 (2.14)</td>
<td>[68.19-76.63]</td>
<td>-0.66 (2.20)</td>
<td>[-3.66-4.98]</td>
<td>0.77</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>LVRS</td>
<td>68.21 (1.80)</td>
<td>68.21 (2.14)</td>
<td>[63.99-72.43]</td>
<td>-3.54 (3.03)</td>
<td>[-9.51-2.42]</td>
<td>0.24</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medical</td>
<td>71.76 (1.73)</td>
<td>71.76 (2.14)</td>
<td>[67.53-75.97]</td>
<td>-0.29 (2.20)</td>
<td>[-6.55-6.95]</td>
<td>0.78</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>LVRS</td>
<td>55.45 (2.99)</td>
<td>56.47 (2.54)</td>
<td>[51.46-61.47]</td>
<td>-17.67 (3.55)</td>
<td>[-24.64-10.70]</td>
<td>0</td>
<td>-11.75 (2.59)</td>
<td>[-16.84-6.65]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Medical</td>
<td>73.38 (2.52)</td>
<td>74.14 (2.47)</td>
<td>[69.28-78.99]</td>
<td>-15.5 (3.65)</td>
<td>[-22.67-8.32]</td>
<td>0</td>
<td>-6.26 (2.76)</td>
<td>[-11.68-0.84]</td>
<td>0.02</td>
</tr>
<tr>
<td>1</td>
<td>LVRS</td>
<td>59.7 (4.03)</td>
<td>61.95 (2.71)</td>
<td>[56.61-67.28]</td>
<td>-18.11 (4.17)</td>
<td>[-27.01-10.60]</td>
<td>0</td>
<td>-7.01 (2.98)</td>
<td>[-12.87-1.15]</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Medical</td>
<td>76.59 (2.39)</td>
<td>77.45 (2.43)</td>
<td>[72.65-82.23]</td>
<td>0.64 (2.48)</td>
<td>[0.80-10.57]</td>
<td>0.02</td>
<td>8.26 (3.00)</td>
<td>[2.35-14.15]</td>
<td>0.01</td>
</tr>
<tr>
<td>2</td>
<td>LVRS</td>
<td>56.87 (4.04)</td>
<td>61.2 (2.94)</td>
<td>[55.41-66.98]</td>
<td>-18.11 (4.17)</td>
<td>[-27.01-10.60]</td>
<td>0</td>
<td>-7.01 (2.98)</td>
<td>[-12.87-1.15]</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Medical</td>
<td>79.45 (3.65)</td>
<td>80.01 (2.96)</td>
<td>[74.19-85.83]</td>
<td>0.64 (2.48)</td>
<td>[0.80-10.57]</td>
<td>0.02</td>
<td>8.26 (3.00)</td>
<td>[2.35-14.15]</td>
<td>0.01</td>
</tr>
<tr>
<td>3</td>
<td>LVRS</td>
<td>55.71 (3.26)</td>
<td>62.84 (3.38)</td>
<td>[56.18-69.49]</td>
<td>-13.24 (4.78)</td>
<td>[-22.63-3.85]</td>
<td>0.01</td>
<td>-5.37 (3.42)</td>
<td>[-12.09-3.15]</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>Medical</td>
<td>71.29 (5.35)</td>
<td>76.09 (3.37)</td>
<td>[69.45-82.71]</td>
<td>-13.24 (4.78)</td>
<td>[-22.63-3.85]</td>
<td>0.01</td>
<td>4.33 (3.41)</td>
<td>[-2.36-11.02]</td>
<td>0.20</td>
</tr>
<tr>
<td>4</td>
<td>LVRS</td>
<td>64.21 (4.74)</td>
<td>56.63 (6.43)</td>
<td>[43.99-69.25]</td>
<td>-32.55 (11.93)</td>
<td>[-55.98-9.11]</td>
<td>0.01</td>
<td>5.71 (4.04)</td>
<td>[-2.23-13.64]</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>Medical</td>
<td>76.57 (6.72)</td>
<td>89.17 (10.05)</td>
<td>[69.43-108.91]</td>
<td>-13.24 (4.78)</td>
<td>[-22.63-3.85]</td>
<td>0.01</td>
<td>8.23 (5.56)</td>
<td>[-2.70-19.16]</td>
<td>0.14</td>
</tr>
<tr>
<td>5</td>
<td>LVRS</td>
<td>56 (11.33)</td>
<td>73.92 (4.01)</td>
<td>[66.04-81.80]</td>
<td>-6.06 (6.84)</td>
<td>[-19.50-7.38]</td>
<td>0.38</td>
<td>-11.59 (6.44)</td>
<td>[-24.25-1.07]</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>Medical</td>
<td>99.5 (0.50)</td>
<td>79.98 (5.54)</td>
<td>[69.09-90.87]</td>
<td>-13.24 (4.78)</td>
<td>[-22.63-3.85]</td>
<td>0.01</td>
<td>17.42 (10.06)</td>
<td>[-2.34-37.18]</td>
<td>0.08</td>
</tr>
</tbody>
</table>

CI = confidence interval; LVRS = lung volume reduction surgery; SE = standard error of the mean.
Results

A CONSORT diagram showing the flow of participants is given in Figure 1. Characteristics of the high-risk subgroup are summarized in Table 1. The LVRS and medical groups were approximately equivalent at baseline. The frequency of observed and missed observations within the treatment groups at all follow-up is presented in Table 2.

Virtually all participants (96% in LVRS group, 97% in the medical group) died by the 14-year follow-up. As expected, mortality was initially higher in the LVRS group, but the curves crossed around 4.4 years of follow-up with the survival rate of about 35% (Fig 2). Although not statistically significant, long-term survival favored the surgery group. Median survival in the LVRS group was 2.14 years (95% CI 1.20 to 4.07) in comparison with 3.12 years (95% CI 2.79 to 4.37) in the medical group. Using the log-rank test, differences between groups in survival for the total duration of follow-up were nonsignificant (p = 0.95).

The unadjusted and response profile model-based estimates for the UCSD SOBQ are summarized in Table 3 and Figure 3. Lower scores on the SOBQ indicate better health outcomes. The groups did not differ at baseline and both groups experienced a nonsignificant improvement after rehabilitation. A significant advantage favoring the surgical group appeared at the 6-month, 1-, 2-, 3-, and 4-year follow-ups (p < 0.01). The differences were primarily explained by more rapid declines in health among the medical group subjects. When focusing exclusively on the SBOQ measure that considers only survivors, the surgical group achieves better average outcomes.

Analysis for the QWB quality-adjusted survival analysis is shown in Table 4 and Figure 4. The surgery and medical groups were comparable at baseline. Both the LVRS group and medical group increased QWB scores after rehabilitation (indicating improved quality of life), although the changes were not statistically significant. For the first 3 years of follow-up, the medical group achieved better outcomes than the surgery group (p < 0.05 through year 1 only). After year 3, outcomes were superior for the surgery group, although the differences were not statistically significant.

An analysis of QWB scores unadjusted for deaths produced outcomes similar to the UCSD SOBQ. After baseline the surgical group obtained better outcomes in all years, although the differences were statistically significant only for years 2, 3, and 4 (p < 0.05) (data not shown).

Comment

The NETT had an early stop for a subgroup of high-risk patients with severe lung disease. As a result of this finding, LVRS was identified as too risky for patients in this category. This study considers longer term follow-up of the high-risk group. We used 3 different outcomes: survival, dyspnea among survivors, and quality-adjusted survival using an index that combines survival with health-related quality of life. Each of these measures tells a somewhat different story about the effects of surgical treatment. The survival results suggest that shortly after enrollment of high-risk patients was terminated, outcomes began to change. With longer term follow-up, the curves crossed with outcomes in the surgical group appearing nonsignificantly superior to those patients in the medical arm. The dyspnea outcome for those who survived surgery significantly favored surgery. The combined QWB index favored medical care for the first year but then became nonsignificant for longer term follow-up. After the fourth year, both quality of life and survival demonstrated a nonsignificant trend in favor of surgery.

Our study was limited to only 140 high-risk patients and we did not have the statistical power to identify factors associated with a higher probability of survival after surgery. Among the 140 patients, only 53 survived to year 4. Although we could not reliably evaluate risk factors in this small group, previous studies have explored predictors of operative mortality in the NETT. Overall, the incidence of operative mortality in the trial was 5.5%. In addition, major pulmonary complications occurred in 29.8% of the patients. The only consistent prognostic factor for death within 90 days of surgery was non-upper lobe emphysema determined from a radiologist’s evaluation. There was also a trend toward greater 90-day mortality among older patients. Factors associated with major pulmonary morbidity 30 days after surgery included older age, lower FEV1, and lower percent of predicted diffusing capacity. Baseline quality of life scores did not predict 90-day survival or pulmonary complications. With the exception of age and non-upper lobe
Table 4. Unadjusted and Response Profile Model Based Estimates for Self-Administered Quality of Well-Being Scale Average Scores

<table>
<thead>
<tr>
<th>Visit (Year)</th>
<th>Treatment Group</th>
<th>Unadjusted Mean (SE)</th>
<th>Raw Score</th>
<th>Treatment Effect</th>
<th>Change From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean (SE)</td>
<td>95% CI</td>
<td>Mean (SE)</td>
<td>95% CI</td>
</tr>
<tr>
<td>-0.25</td>
<td>LVRS</td>
<td>0.54 (0.02)</td>
<td>0.54 (0.03) [0.489–0.59]</td>
<td>0.05 (0.04) [–0.02–0.12]</td>
<td>0.17</td>
</tr>
<tr>
<td>-0.25</td>
<td>Medical</td>
<td>0.49 (0.01)</td>
<td>0.49 (0.03) [0.44–0.54]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>0</td>
<td>LVRS</td>
<td>0.58 (0.01)</td>
<td>0.58 (0.03) [0.52–0.63]</td>
<td>0.04 (0.04) [–0.04–0.11]</td>
<td>0.33</td>
</tr>
<tr>
<td>0</td>
<td>Medical</td>
<td>0.54 (0.01)</td>
<td>0.54 (0.03) [0.49–0.59]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>0.5</td>
<td>LVRS</td>
<td>0.36 (0.03)</td>
<td>0.36 (0.03) [0.31–0.42]</td>
<td>–0.08 (0.04) [–0.15––0.01]</td>
<td>0.03</td>
</tr>
<tr>
<td>0.5</td>
<td>Medical</td>
<td>0.45 (0.02)</td>
<td>0.45 (0.03) [0.39–0.49]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1</td>
<td>LVRS</td>
<td>0.32 (0.04)</td>
<td>0.32 (0.03) [0.26–0.37]</td>
<td>–0.1 (0.04) [–0.17––0.02]</td>
<td>0.01</td>
</tr>
<tr>
<td>1</td>
<td>Medical</td>
<td>0.41 (0.02)</td>
<td>0.41 (0.03) [0.36–0.46]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>LVRS</td>
<td>0.25 (0.03)</td>
<td>0.25 (0.03) [0.20–0.30]</td>
<td>–0.06 (0.04) [–0.13––0.01]</td>
<td>0.11</td>
</tr>
<tr>
<td>2</td>
<td>Medical</td>
<td>0.30 (0.03)</td>
<td>0.31 (0.03) [0.26–0.36]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>LVRS</td>
<td>0.21 (0.03)</td>
<td>0.22 (0.03) [0.16–0.27]</td>
<td>0.02 (0.04) [–0.06–0.09]</td>
<td>0.64</td>
</tr>
<tr>
<td>3</td>
<td>Medical</td>
<td>0.20 (0.03)</td>
<td>0.20 (0.03) [0.14–0.25]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>LVRS</td>
<td>0.12 (0.03)</td>
<td>0.15 (0.03) [0.09–0.20]</td>
<td>0.06 (0.04) [–0.02–0.13]</td>
<td>0.17</td>
</tr>
<tr>
<td>4</td>
<td>Medical</td>
<td>0.07 (0.03)</td>
<td>0.10 (0.03) [0.04–0.15]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>LVRS</td>
<td>0.06 (0.03)</td>
<td>0.11 (0.03) [0.05–0.17]</td>
<td>0.06 (0.05) [–0.03–0.16]</td>
<td>0.20</td>
</tr>
<tr>
<td>5</td>
<td>Medical</td>
<td>0.03 (0.02)</td>
<td>0.05 (0.04) [–0.03–0.12]</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

CI = confidence interval; LVRS = lung volume reduction surgery; SE = standard error of the mean.
predominance, preoperative risk factors remain difficult to identify [10].

It is important to emphasize that the NETT was not strictly a comparison between medical management and surgery. Both groups completed pulmonary rehabilitation and both groups received maximal medical care. The LVRS group received surgery in addition to high-quality medical intervention. It may be more appropriate to consider the trial an evaluation of the incremental value of surgery.

The results of this study are limited for a variety of reasons. The surgery was performed in well-established academic medical centers and we do not know if these results generalize to a wider range of practice sites. Participants in the study were volunteers for a very challenging and difficult clinical trial and may not be representative of the broader range of patients with emphysema. Since the completion of NETT, surgical techniques have evolved and we cannot assure that the techniques used in the study are the same as those currently employed in surgical practice. Similarly, any significant improvements in medical management would not be reflected in these results. The quality of life data are limited because there was significant missing data in the later follow-up. Although we have 14 years of mortality data, quality of life data were available for a maximum of 6 years, and several fewer years for right censored patients.

The statistical analysis has several limitations. The log-rank test does not have sufficient statistical power in many circumstances. Further, there were only 70 high-risk patients in each of the arms of the trial. As a result, there was insufficient statistical power to detect subtle differences that may have faded favoring surgery in the late years of the study.

We do not believe that these results will have a significant effect on current clinical practice. Lung volume reduction surgery remains extremely high risk for patients with severe emphysema comparable with the high-risk group participants. However, the results suggest that the risk-to-benefit analysis for high-risk patients is not as one-sided as revealed in the early analysis from the National Emphysema Treatment Trial.

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References