SPECIAL ARTICLE

Cost Effectiveness of Lung-Volume–Reduction Surgery for Patients with Severe Emphysema

National Emphysema Treatment Trial Research Group*

ABSTRACT

BACKGROUND
The National Emphysema Treatment Trial, a randomized clinical trial comparing lung-volume–reduction surgery with medical therapy for severe emphysema, included a prospective economic analysis.

METHODS
After pulmonary rehabilitation, 1218 patients at 17 medical centers were randomly assigned to lung-volume–reduction surgery or continued medical treatment. Costs for the use of medical care, pharmacy medication, transportation, and time spent receiving treatment were derived from Medicare claims and data from the trial. Cost effectiveness was calculated over the duration of the trial and was estimated for 10 years of follow-up with the use of modeling based on observed trends in survival, cost, and quality of life.

RESULTS
Interim analyses identified a group of patients with excess mortality and little chance of improved functional status after surgery. When these patients were excluded, the cost-effectiveness ratio for lung-volume–reduction surgery as compared with medical therapy was $190,000 per quality-adjusted life-year gained at 3 years and $53,000 per quality-adjusted life-year gained at 10 years. Subgroup analyses identified patients with predominantly upper-lobe emphysema and low exercise capacity after pulmonary rehabilitation who had lower mortality and better functional status than patients who received medical therapy. The cost-effectiveness ratio in this subgroup was $98,000 per quality-adjusted life-year gained at 3 years and $21,000 at 10 years. Bootstrap analysis revealed substantial uncertainty for the subgroup and 10-year estimates.

CONCLUSIONS
Given its cost and benefits over three years of follow-up, lung-volume–reduction surgery is costly relative to medical therapy. Although the predictions are subject to substantial uncertainty, the procedure may be cost effective if benefits can be maintained over time.

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Lung-volume–reduction surgery is a new treatment for patients with severe emphysema, the value of which is, as yet, uncertain.[1-5] Because the potential clinical and economic effects of lung-volume–reduction surgery are large, a federally sponsored, multicenter, randomized, controlled trial — the National Emphysema Treatment Trial (NETT) — was initiated to evaluate the effectiveness of lung-volume–reduction surgery. This trial included a prospective, economic analysis.

METHODS

The design and methods of the NETT and the cost-effectiveness component of the trial have been described previously.[6,7] The trial design and economic analysis are briefly summarized below.

CLINICAL TRIAL

The NETT is a multicenter, randomized, controlled trial comparing lung-volume–reduction surgery with medical therapy for patients with severe emphysema. Between January 1998 and July 2002, 17 centers randomly assigned 1218 patients with severe emphysema to either lung-volume–reduction surgery or medical therapy.[8] All patients provided written informed consent, and the study was approved by the institutional review board at each center.

Before randomization, all patients underwent pulmonary rehabilitation. The primary outcome measures were overall mortality and maximal exercise capacity (on bicycle ergometry) two years after randomization. Secondary outcomes included results on the six-minute walk test[9] and lung-function tests and general health-related quality of life as measured on the Quality of Well-Being scale.[10] These outcomes were assessed at screening, after pulmonary rehabilitation (base line), at 6 months, at 12 months, and yearly thereafter.

COST-EFFECTIVENESS ANALYSIS

We conducted a cost-effectiveness analysis prospectively with the use of a societal perspective to determine the cost of lung-volume–reduction surgery plus medical therapy per quality-adjusted life-year gained[11] as compared with the cost of medical therapy alone per quality-adjusted life-year gained for patients with severe emphysema. For the cost analysis, we estimated the value of the following resources: medical goods and services, transportation to and from health care facilities, time spent by family and friends in caring for the patient, and time spent by the patient in receiving treatment. A detailed description of the cost-effectiveness analysis is presented in Supplementary Appendix 1 (available with the full text of this article at http://www.nejm.org).

Life Expectancy and Health-State Preferences

The number of quality-adjusted life-years is derived by the adjustment of survival data for health-state preferences, also known as "utilities."[12] Weights for these utilities were obtained from the self-administered version of the Quality of Well-Being questionnaire, a comprehensive measure of health-related quality of life covering acute and chronic symptoms, self-care, mobility, physical activity and functioning, and social activity. Scores for each patient are converted to utility weights, on a scale ranging from 0 (death) to 1.0 (optimal quality of life). The Quality of Well-Being scale has been used in a variety of clinical studies for medical and surgical conditions, including chronic obstructive pulmonary disease,[13] the acquired immunodeficiency syndrome, cystic fibrosis,[14] diabetes, atrial fibrillation, lung transplantation,[15] arthritis,[16] and cancer.[17]

Measurement of Resource Utilization

Information on the utilization of medical care was based on Medicare claims for study participants that were provided by the Centers for Medicare and Medicaid Services. Medicare reimbursed providers for trial-related medical care for study participants, including the screening evaluation, pulmonary rehabilitation before randomization, the surgical procedure itself, and trial-related follow-up visits after surgery. Other Medicare services included inpatient care; outpatient care provided by physicians; ambulatory laboratory, diagnostic, and radiology services; home health services; supplementary oxygen for home use; up to 100 days of care at a skilled nursing facility; and hospice care. The use of medications for emphysema on an outpatient basis (not covered by Medicare) was recorded at follow-up visits. Doses of medications were based on the usual doses for adults that are recorded in the manufacturer's package insert.[18]

Several methods were used to estimate emphysema-related utilization of nonmedical goods and services. Travel distances to care facilities were estimated with the use of software that calculated the distances traveled from the ZIP Code of the patient's residence to NETT-affiliated facilities.[19] Enrollees

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gave estimates of the weekly average number of hours of care provided to them by unpaid caregivers (family and friends). The time spent by patients in seeking medical care was estimated on the basis of Medicare records for ambulatory care and hospitalizations.

Valuation of Resources Used

The value of medical care was estimated on the basis of Medicare reimbursements for covered services, with adjustment to 2002 dollars according to the medical care component of the Consumer Price Index.[20] Costs for medications related to respiratory disease were determined on the basis of the average wholesale price for 2002, discounted by 15 percent in order to adjust for typical retail-acquisition costs, with a $2.50 dispensing fee added for each 30-day period.[21] The lowest price for available generic versions of medications was used. Costs for transportation to and from health care facilities were determined by multiplying the travel distances by the federal government's reimbursement rate per mile.[19,22] The value of time spent by family and friends in caring for patients was calculated on the basis of the average wage for workers 20 to 64 years of age, as reported by the Bureau of Labor Statistics.[23] The value of the time patients spent receiving treatment was calculated on the basis of the average wage for workers 65 years of age or older.[23] In accordance with guidelines for conducting cost-effectiveness studies,[11] costs and benefits accruing after year 1 were discounted at an annual rate of 3 percent.

STATISTICAL ANALYSIS

All analyses were conducted according to the intention-to-treat principle. Patients who were still alive at the time of a given visit but who did not complete a questionnaire were assigned a value for the Quality of Well-Being score that was half of the lowest score among all patients who completed a questionnaire at the corresponding visit.[24] In secondary analyses of patients who did not complete questionnaires, we used the mean and median values for the patient's treatment group. All analyses exclude patients who did not use Medicare as their primary insurer and those who were enrolled in Medicare+Choice plans, since no health care claims were available for these patients. The average total costs and the mean numbers of quality-adjusted life-years gained and associated 95 percent confidence intervals were determined for each treatment group with the use of the nonparametric Kaplan–Meier sample-average estimator.[25] This estimator sums over intervals of follow-up either the mean costs (for the calculation of total costs) or the mean utility weights (for the calculation of the number of quality-adjusted life-years) for patients who are alive at the beginning of the interval, weighted according to the Kaplan–Meier estimate of the probability of surviving until the beginning of the interval. All reported P values are based on two-sided tests.

Cost effectiveness was calculated as the ratio of the difference in costs between the surgery group and the medical-therapy group divided by the difference in quality-adjusted life-years gained between the two groups. Cost-effectiveness ratios were computed for the trial period (3 years of follow-up) and then projected for 5 and 10 years after randomization. To estimate long-term survival for the medical-therapy group, a log-logistic model was fitted, with the use of data from patients who survived for at least one year after randomization. Regression analysis was used to determine the relation between survival and treatment-group assignment in order to derive estimates of the parameters for the model. The relative hazard of death in the surgery group as compared with the medical-therapy group was set at observed levels for year 3 and then, in separate models, was assumed to change to 1.0 (no survival benefit) by 3 years, 5 years, and 10 years. Projected costs and Quality of Well-Being scores were based on trend lines fitted to monthly values for the surgery and medical-therapy groups during the third year of follow-up.

The nonparametric bootstrap method with 2000 replications was used to derive a 95 percent confidence interval for the incremental cost-effectiveness ratio at three years of follow-up.[26] To describe the uncertainty in the estimates of cost effectiveness at 10 years, we constructed cost-effectiveness–acceptability curves with the bootstrap method applied to projected survival and estimates of cost and quality-adjusted life-years gained for each group of patients.[27]

RESULTS

STUDY PATIENTS

Interim analysis of the NETT cohort identified a subgroup of 140 patients with a high risk of death and little chance of improved function after surgery.[24] Patients in this subgroup became ineligible for enrollment as of May 2001 and are thus excluded from the cost-effectiveness analysis. Twelve additional participants were excluded from the cost-effectiveness analysis (seven in the surgery group and five in the medical-therapy group) — three patients because they were not enrolled in Medicare, eight because they were enrolled in Medicare+ Choice plans at the time of randomization, and one because the patient's Medicare claims could not be located. The mean (±SD) Quality of Well-Being score before randomization was 0.58±0.12 in the surgery group and 0.57±0.11 in the medical-therapy group.

USE AND COSTS OF RESOURCES

During the first six months of follow-up, the mean number of inpatient hospital days was significantly higher in the surgery group than in the medical-therapy group (23.3 days vs. 3.0 days, P<0.001), as was the percentage of patients with more than 25 hospital days (26 percent vs. 3 percent, P<0.001). During the first year, the mean numbers of hospital days and days of ambulatory care per person and the total number of nursing-home admissions were significantly greater in the surgery group than in the medical-therapy group (Table 1). In contrast, during the second year, the mean numbers of hospital days and emergency-room visits per person were significantly lower in the surgery group than in the medical-therapy group (P=0.005 and P=0.04, respectively). During the third year, there were no significant differences between the two groups in the use of resources (Table 1). Use of bronchodila-

Table 1. Measures of Health Care Utilization According to Time after Randomization.*

Variable	Surgery Group		Medical-Therapy Group		P Value
	No. of Patients	Mean No. (95% CI)	No. of Patients	Mean No. (95% CI)	
0–12 Mo after randomization	531		535		
Hospital days		24.9 (22.3–27.6)		4.9 (4.0–5.8)	<0.001
Days of ambulatory care		10.3 (9.5–11.2)		8.6 (7.8–9.4)	0.005
Emergency-room visits		0.6 (0.5–0.7)		0.8 (0.6–0.9)	0.11
Hospice days		1.2 (0.0–2.7)		1.0 (0.0–2.3)	0.27
Nursing-home admissions		0.1 (0.0–0.3)		0.0 (0.0–0.1)	0.005
Claims for supplemental oxygen		6.7 (6.2–7.3)		7.2 (6.6–7.7)	0.19
13–24 Mo after randomization	407		424		
Hospital days		3.2 (2.3–4.1)		6.1 (4.5–7.6)	0.005
Days of ambulatory care		5.0 (4.4–5.6)		4.9 (4.2–5.5)	0.49
Emergency-room visits		0.5 (0.4–0.6)		0.7 (0.6–0.8)	0.04
Hospice days		1.7 (0.0–3.6)		2.2 (0.0–4.6)	0.15
Nursing-home admissions		<0.1 (0.0–0.1)		<0.1 (0.0–0.1)	0.49
Claims for supplemental oxygen		5.8 (5.2–6.4)		6.5 (5.9–7.1)	0.09
25–36 Mo after randomization	277		278		
Hospital days		4.0 (2.3–5.8)		5.2 (3.8–6.7)	0.08
Days of ambulatory care		4.5 (3.8–5.2)		4.4 (3.5–5.2)	0.43
Emergency-room visits		0.5 (0.4–0.6)		0.7 (0.5–0.8)	0.10
Hospice days		2.5 (0.3–5.2)		3.6 (0.9–6.2)	0.12
Nursing-home admissions		<0.1 (0.0–0.1)		<0.1 (0.0–0.1)	0.10
Claims for supplemental oxygen		5.9 (5.1–6.6)		5.6 (4.8–6.3)	0.39

* P values were derived by two-sided t-tests for equality of means. CI denotes confidence interval.

Table 2. Mean Direct Medical Costs and Total Health Care–Related Costs According to Time after Randomization.*

Variable	Surgery Group		Medical-Therapy Group		P Value
	No. of Patients	Mean Cost (95% CI)	No. of Patients	Mean Cost (95% CI)	
		$		$	
0–12 Mo after randomization	531		535		
Direct medical costs		61,145 (56,069–66,220)		15,738 (14,006–17,470)	<0.001
Total costs		71,515 (65,921–77,109)		23,371 (21,056–25,686)	<0.001
13–24 Mo after randomization	407		424		
Direct medical costs		9,474 (8,260–10,688)		15,648 (12,934–18,362)	<0.001
Total costs		13,222 (11,479–14,964)		21,319 (18,004–24,635)	<0.001
25–36 Mo after randomization	277		278		
Direct medical costs		10,199 (8,161–12,236)		12,303 (9,977–14,629)	0.18
Total costs		14,215 (11,529–16,901)		17,870 (14,785–20,954)	0.08

* Costs are reported in 2002 dollars. Direct medical costs include Medicare reimbursements and pharmacy costs. Total costs include direct medical costs plus the value of the time spent by caregivers, the value of the time spent by the patient, and travel costs were. After year 1, costs were discounted by 3 percent per year. P values were derived by two-sided t-tests for equality of means. CI denotes confidence interval.

tors did not differ between the groups during any period (data not shown).

The total costs were substantially higher for patients in the surgery group than for patients in the medical-therapy group during the first 12 months after randomization, largely because of costs incurred during surgery and during the 6 months after surgery (total at 6 months, $62,753 vs. $12,932; P<0.001). During the second year, the total costs and the costs of medical care were significantly lower for patients in the surgery group; the total costs were not significantly different in the two groups during the third year (Table 2). The mean total medical cost per patient during follow-up months 7 through 36 was nearly $10,000 lower in the surgery group than in the medical-therapy group ($36,199 vs. $49,628, P<0.001), largely because patients in the surgery group had fewer hospital days during that period.

The mean total costs per person at three years were $98,952 in the surgery group and $62,560 in the medical-therapy group (P<0.001). Per-person costs for direct medical care alone were $80,818 in the surgery group and $43,689 in the medical-therapy group over the three-year period (P<0.001) (Table 2). Nonmedical costs did not differ significantly between the two groups (P=0.57; data not shown).

QUALITY-ADJUSTED LIFE-YEARS

After three years of follow-up, the mean number of quality-adjusted life-years gained was higher in the surgery group than in the medical-therapy group (1.46 vs. 1.27, P<0.001) (Table 3). The mean number of quality-adjusted life-years gained was also significantly higher in the surgery group at 12 and 24 months of follow-up (data not shown). Alternative methods of imputing missing Quality of Well-Being scores did not substantively change the results.

COST-EFFECTIVENESS RATIOS

With the exclusion of the previously described subgroup of high-risk patients, the estimated cost-effectiveness ratio for lung-volume–reduction surgery as compared with medical therapy during the three years after the initiation of treatment was $190,000 per quality-adjusted life-year gained (Table 3). When costs for direct medical care alone were considered (as they would be from the perspective of the health insurer), the cost-effectiveness ratio for surgery as compared with medical therapy remained $193,000 per quality-adjusted life-year gained.

The cost-effectiveness ratio for surgery as compared with medical therapy at 10 years was $53,000 per quality-adjusted life-year gained (Table 3). Un-

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Table 3. Total Health Care–Related Costs, Quality-Adjusted Life-Years Gained, and Estimated Cost-Effectiveness Ratios at Three Years.*

Variable	Surgery Group		Medical-Therapy Group		P Value	Incremental Cost-Effectiveness Ratio for Surgery ($)
	No. of Patients	Mean (95% CI)	No. of Patients	Mean (95% CI)		
All patients	531		535			190,000
Total costs ($)		98,952 (91,694–106,210)		62,560 (56,572–68,547)	<0.001	
Quality-adjusted life-years gained		1.46 (1.46–1.47)		1.27 (1.27–1.28)	<0.001	
Patients with predominantly upper-lobe emphysema and low exercise capacity	137		148			98,000
Total costs ($)		110,815 (93,404–128,226)		61,804 (50,248–73,359)	<0.001	
Quality-adjusted life-years gained		1.54 (1.53–1.55)		1.04 (1.03–1.05)	<0.001	
Patients with predominantly upper-lobe emphysema and high exercise capacity	204		212			240,000
Total costs ($)		84,331 (73,699–94,962)		55,858 (47,161–64,555)	<0.001	
Quality-adjusted life-years gained		1.54 (1.54–1.55)		1.42 (1.42–1.43)	<0.001	
Patients with non–upper-lobe emphysema and low exercise capacity	82		65			330,000
Total costs ($)		111,986 (93,944–130,027)		65,655 (52,075–79,236)	<0.001	
Quality-adjusted life-years gained		1.25 (1.23–1.26)		1.10 (1.09–1.12)	<0.001	

* Upper-lobe predominance of emphysema was defined according to the results on computed tomography. Exercise capacity was defined as the maximal workload on bicycle ergometry. Low exercise capacity was defined as a workload of 25 W or less for women and 40 W or less for men; a workload above these thresholds was considered to represent high exercise capacity. P values were derived by two-sided t-tests for equality of means. The results for the overall cohort exclude 140 patients previously found to be at high risk for death, 3 patients who were not enrolled in Medicare, 8 patients who were enrolled in Medicare+Choice plans, and 1 patient whose claims records were missing. Total costs include direct medical costs (Medicare reimbursements and pharmacy costs) plus the value of the time spent by caregivers, the value of the time spent by the patient, and travel costs. After year 1, costs were discounted by 3 percent per year. The incremental cost-effectiveness ratio is the cost per additional quality-adjusted life-year gained with lung-volume–reduction surgery. The subgroup of patients with non–upper-lobe emphysema and high exercise capacity is not included, because in this subgroup, surgery was associated with higher total costs and fewer quality-adjusted life-years gained than was medical therapy. CI denotes confidence interval.

der the assumption that the survival benefit from surgery lasted 3 years, the projected absolute difference in survival was less than 3 percent at 10 years (Fig. 1A). Increasing the assumed duration of the relative survival benefit from surgery (up to 10 years) changed the incremental cost-effectiveness ratio at 10 years by less than 2 percent.

SECONDARY COST-EFFECTIVENESS ANALYSIS BASED ON PREOPERATIVE PREDICTORS OF OUTCOME

Post hoc analyses in the clinical study, including the 1078 patients remaining after the exclusion of the 140 high-risk patients, suggested differential relative benefits from lung-volume–reduction surgery in four subgroups of patients defined according to combinations of two base-line characteristics — the presence or absence of upper-lobe predominance in the distribution of emphysema on computed tomography and low or high maximal exercise capacity after pulmonary rehabilitation (low capacity being defined as a workload of ≤25 W for women and ≤40 W for men and high capacity as a workload above these thresholds).[8] In the subgroup of patients who had emphysema without upper-lobe predominance and who had high exercise capacity, patients assigned to lung-volume–reduction surgery had significantly higher mortality than patients assigned to medical therapy, had reduced quality-adjusted survival, and had higher costs.

Of the remaining three subgroups, patients with predominantly upper-lobe emphysema and low exercise capacity had the most favorable cost-effectiveness ratio for surgery at three years ($98,000 per quality-adjusted life-year gained) (Table 3). Although the average total health-related costs were higher

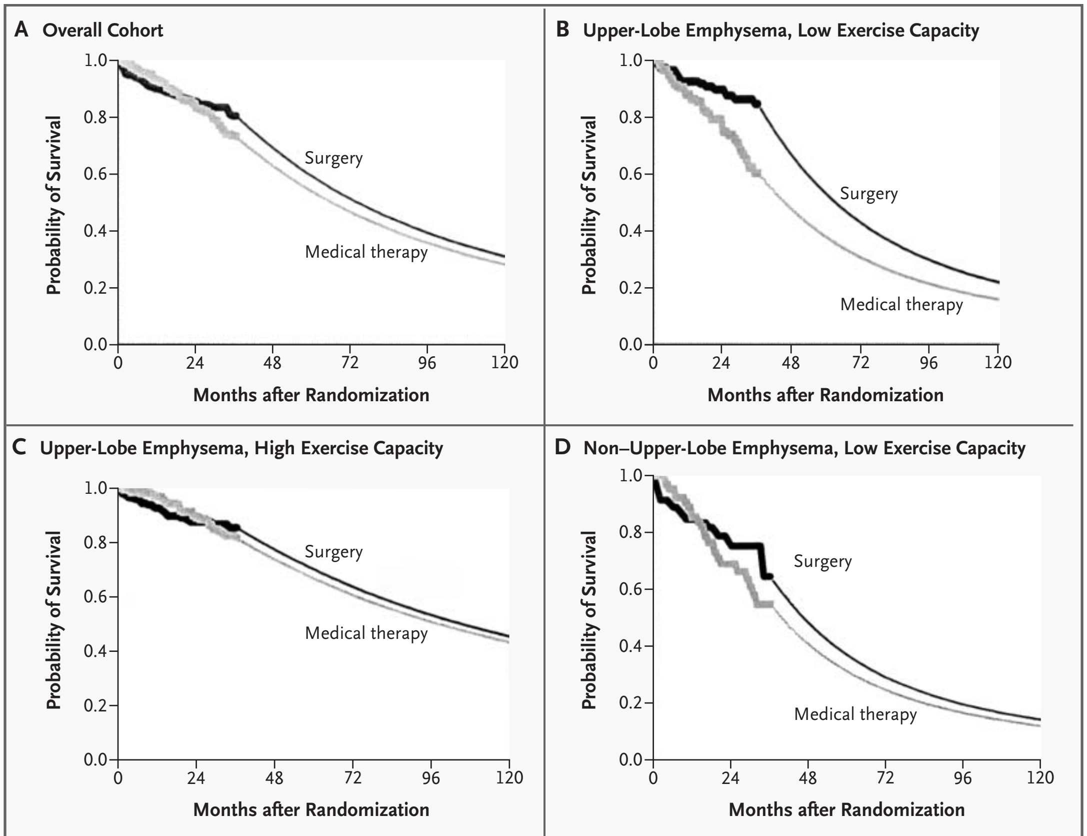

Figure 1. Cost-Effectiveness–Acceptability Curves at 3 Years (Panel A) and 10 Years (Panel B) for Lung-Volume–Reduction Surgery as Compared with Medical Therapy for All Patients and for Three Subgroups with Significantly Improved Clinical Outcomes (Reduced Mortality, Improved Quality of Life, or Both) in the Surgery Group.

The curve represents the probability that lung-volume–reduction surgery is associated with a cost per quality-adjusted life-year gained that is lower than the corresponding cost-effectiveness ratios (the ceiling ratios) shown on the x axis. The value of the ceiling ratio at a probability of 0.5 is the median cost per quality-adjusted life-year gained for lung-volume–reduction surgery. Solid horizontal lines denote 95 percent confidence limits for the projections. The results exclude 140 patients previously found to be at high risk for death, 3 patients who were not enrolled in Medicare, 8 patients who were enrolled in Medicare+Choice plans, and 1 patient whose claims records were missing. Upper-lobe predominance of emphysema was defined according to the results on computed tomography. Exercise capacity was defined as the maximal workload on bicycle ergometry. Low exercise capacity was defined as a workload of 25 W or less for women and 40 W or less for men; a workload above these thresholds was considered to represent high exercise capacity.

in this subgroup than in the cohort as a whole, the relative improvement in quality-adjusted survival in the surgery group as compared with the medical-therapy group was greater in this subgroup, resulting in improved cost effectiveness. The estimated cost-effectiveness ratio over the three-year follow-up period was much less favorable in the two remaining subgroups of patients — those with predominantly upper-lobe emphysema who had high exercise capacity ($240,000 per quality-adjusted life-year gained) and those with non–upper-lobe emphysema who had low exercise capacity ($330,000 per quality-adjusted life-year gained) (Table 3).

When the subgroup of patients with significantly higher mortality and costs was excluded from the analysis and the most conservative estimates of the survival benefit from surgery were used (Fig. 1B, 1C, and 1D), the projected cost-effectiveness ratios over 10 years of follow-up were $21,000 per quality-adjusted life-year gained among patients with predominantly upper-lobe emphysema who had low exercise capacity and $54,000 per quality-adjusted life-year gained among patients with predominantly upper-lobe emphysema who had high exercise capacity. Among patients with non–upper-lobe emphysema and low exercise capacity, surgery was associated with lower costs than medical therapy and a higher number of quality-adjusted life-years gained. The cost-effectiveness–acceptability curves (Fig. 2A and 2B) reveal substantial uncertainty in these estimates, especially for the group with predominantly upper-lobe emphysema and high excercise capacity and the group with non–upper-lobe emphysema and low exercise capacity.

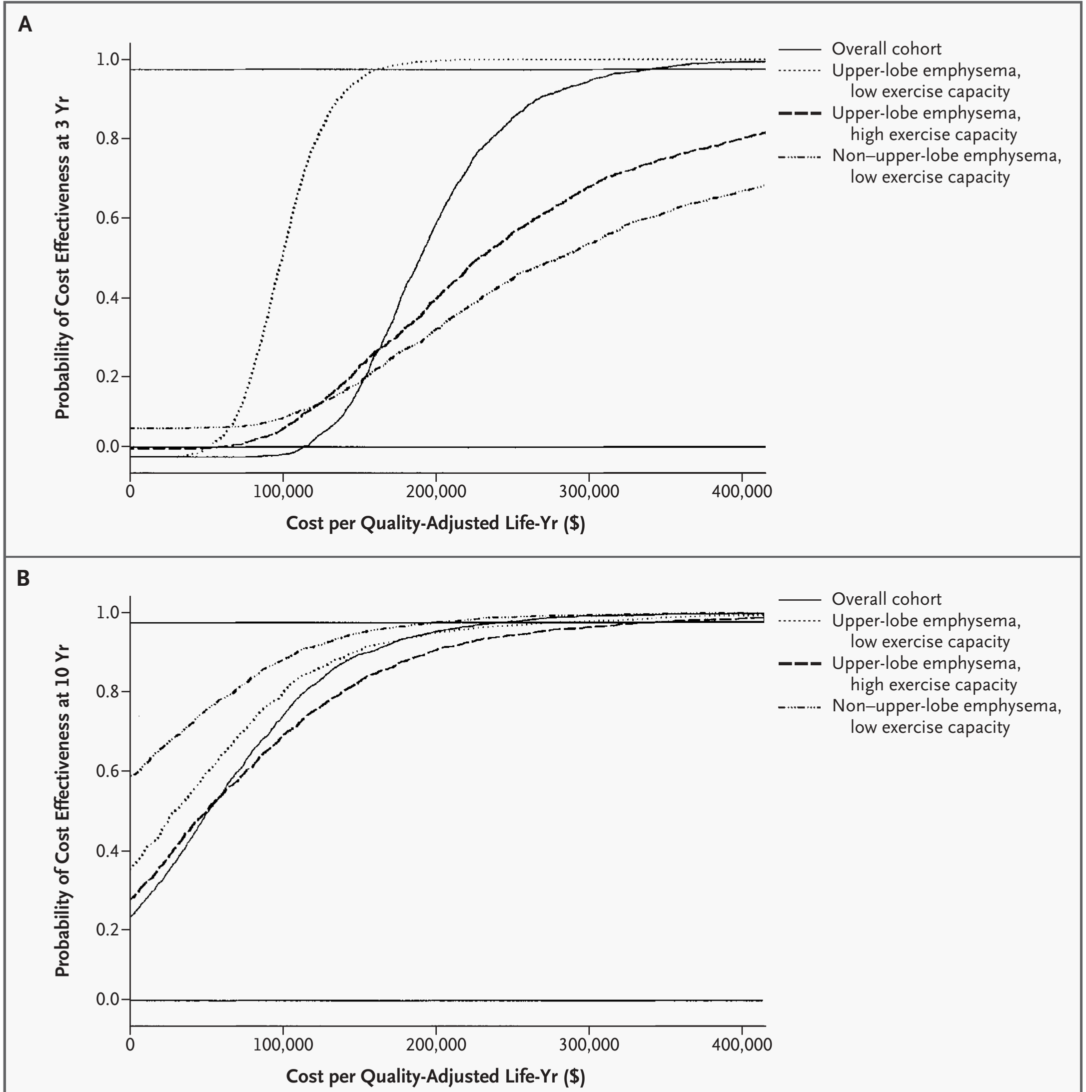

Figure 2. Observed Survival Curves (Thick) and Extrapolated Survival Estimates (Thin) under the Assumption of a Relative Hazard of Death of 1.0 at Three Years.

The results exclude 140 patients previously found to be at high risk for death, 3 patients who were not enrolled in Medicare, 8 patients who were enrolled in Medicare+Choice plans, and 1 patient whose claims records were missing. Upper-lobe predominance of emphysema was defined according to the results on computed tomography. Exercise capacity was defined as the maximal workload on bicycle ergometry. Low exercise capacity was defined as a workload of 25 W or less for women and 40 W or less for men; a workload above these thresholds was considered to represent high exercise capacity.

DISCUSSION

Many experts propose that the cost effectiveness of lung-volume–reduction surgery should be considered in relation to the outcomes and costs for other medical and surgical procedures.[28-30] Over the observation period in our study, the cost-effectiveness ratio for surgery as compared with medical therapy was relatively unfavorable because of the costs of the surgical procedure and the number of adverse clinical outcomes, very long periods of hospitalization, and a greater number of nursing-home admissions during the first few months after surgery.

The effect of lung-volume–reduction surgery on the national health care budget is uncertain, but it could be substantial. Fewer patients were enrolled in the trial than expected, and about 32 percent of those who began to undergo screening were ultimately determined to be eligible. Nevertheless, if 1 percent of the estimated 2 million persons with emphysema were potentially eligible for lung-volume–reduction surgery, national health expenditures for this procedure (excluding those for initial screening and the costs of pulmonary rehabilitation) might range from $100 million to $300 million per year, depending on patients' interest in the procedure and their suitability for it after pulmonary rehabilitation.

A longer-term view is preferable for cost-effectiveness analyses.[31] Our 10-year estimates required mathematical modeling based on extrapolation of the 3-year trial data. These models are based on assumptions that may not be realized. The 10-year estimates suggest that the cost effectiveness of lung-volume–reduction surgery may approach recognized thresholds if the moderate benefits observed during the trial are sustained.[32] We arrived at the relatively favorable results for long-term cost effectiveness using the most conservative estimates for survival (an absolute benefit of <3 percent for surgery), cost, and quality of life at 10 years. Nevertheless, the estimates of long-term cost effectiveness are characterized by substantial uncertainty. We caution that extended follow-up of patients enrolled in the NETT is necessary in order to derive more precise estimates of the long-term cost effectiveness of lung-volume–reduction surgery.

Post hoc subgroup analyses were conducted to identify characteristics of persons who are more likely to have favorable clinical and survival outcomes after surgery. Among patients with predominantly upper-lobe emphysema who had low exercise capacity, lung-volume–reduction surgery was associated with significant improvements in survival and functional outcomes as compared with medical therapy. The cost-effectiveness ratio for lung-volume–reduction surgery for patients who met both of these criteria was more favorable than that for patients who met only one of the criteria and was superior to that for the entire cohort. The very high level of uncertainty regarding the cost effectiveness of lung-volume–reduction surgery in the subgroups that met only one of the two clinical criteria precludes the drawing of any conclusion regarding the cost effectiveness of the procedure for such patients.

Cost-effectiveness ratios for other types of thoracic surgery as compared with medical therapy include (in 2002 dollars) $8,300 to $64,000 per quality-adjusted life-year gained for coronary-artery bypass surgery,[33-35] $130,000 to $220,000 per quality-adjusted life-year gained for lung transplantation,[36,37] $65,000 per quality-adjusted life-year gained for heart transplantation,[38] and $47,000 per quality-adjusted life-year gained for the implantation of a cardioverter–defibrillator in a survivor of cardiac arrest with a low cardiac ejection fraction.[35,39]

Our analysis has limitations. Medical and nonmedical costs that patients incurred as part of their screening and pulmonary rehabilitation before randomization and administrative costs associated with the maintenance of a center that performs lung-volume–reduction surgery were not included. Although screening and pulmonary rehabilitation increase the cost of treatment, they do not influence the incremental analysis because they are applied equally to both groups. Medicare copayments and deductibles paid by patients for NETT-related services were not included in the analysis. The amounts of these payments varied from center to center and from service to service and thus were extremely difficult to quantify. Clinical trials also necessarily involve more intensive monitoring of patients than does typical clinical practice.[40]

Optimal use of limited health care resources depends on accurate economic information and systematic analysis of new forms of medical technology. Joint sponsorship by the Centers for Medicare and Medicaid Services permitted parallel collection of Medicare claims for trial participants, thus maximizing the accuracy of the economic data. Modeling is necessary in cost-effectiveness analyses in order to help decision makers consider the long-term effects of the adoption of new medical techniques. The per-patient cost of the adoption of lung-volume–reduction surgery will be high in the short run. The effect of the use of such surgery on national health care expenditures will depend on the fraction of the estimated 2 million persons with emphysema who meet the criteria for eligibility and are willing to undergo the procedure, which at present is unknown. The extent of experience of the participating clinical centers also influenced the economic outcomes in this trial. Health care payers should consider clinical experience as well as the criteria for selection of patients when establishing reimbursement policies for lung-volume–reduction surgery.

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APPENDIX

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COSTS

Medical Costs

Monthly costs for medical care were derived from Medicare-claims records and pharmacy costs provided by the Centers for Medicare and Medicaid Services (CMS). Data on Medicare costs were retrieved from the data bases of inpatient, outpatient, physician, hospice, and skilled-nursing–facility claims. Claims specific to the National Emphysema Treatment Trial (NETT) were identified by CMS through an internal procedure (DemoID30) and provided in a separate data base. Monthly costs were converted to June 2002 dollars with the use of the seasonally adjusted monthly U.S.-city average Consumer Price Index (CPI) for medical care. Series Id CUSR0000SAM data extracted from the CPI Web site were used.[1]

Pharmacy costs were estimated for medications related to chronic obstructive pulmonary disease. The use of oral corticosteroids, inhaled corticosteroids, and bronchodilators was reported by patients at base line and at follow-up clinic visits. Patients could indicate the use of up to six different bronchodilators. Costs for each medication were assigned on the basis of the average wholesale price listed in the *Red Book*[2]: $1.64 for oral corticosteroids, $85.17 for inhaled corticosteroids, and $44.15 for each bronchodilator. A monthly dispensing fee of $2.50 was added for each medication. Monthly use of medication was assumed to remain constant between visits.

Nonmedical Costs

Nonmedical costs were estimated on the basis of costs associated with the time spent by caregivers, the time spent by the patient, and travel distance. Patients reported the weekly number of caregiver-hours at base line, at follow-up visits, and through telephone surveys. Weekly hours were multiplied by four to estimate the monthly hours of caregiver time. For monthly caregiver-hours during months without surveys, we used the average of values from the previous questionnaire and the next questionnaire.

The caregiver-hours for the month of the patient's death were prorated according to the number of days in the month that the patient was alive. Estimates of monthly costs for caregivers were generated by multiplying the number of caregiver-hours by the median usual weekly earnings of full-time workers 20 to 64 years of age receiving wages or a salary during the third quarter of 2002 ($626, without seasonal adjustment).[3] A 35-hour workweek was assumed.

The cost of the time patients spent receiving treatment was estimated on the basis of utilization data from Medicare claims. The total monthly time for each patient was estimated by adding eight hours for each day spent in the hospital, emergency room, outpatient clinic, skilled nursing facility, or hospice. Monthly costs for patients' time were then calculated by multiplying the monthly number of hours by the median usual weekly earnings of full-time workers 65 years of age or older receiving wages or a salary during the third quarter of 2002 ($501, without seasonal adjustment).[3] A 35-hour workweek was assumed.

Travel costs were estimated on the basis of the number of miles traveled from the patient's home to study clinics and satellite rehabilitation centers. Patients provided their home ZIP Code at base line and at follow-up visits. Patients may have been assigned to attend additional rehabilitation sessions that took place at satellite centers. ZIP Codes were linked to a data set at SAS Institute (Cary, N.C.) that contains information on longitude and latitude for the ZIP centroid. The Great Circle Distance Formula was used to estimate the distance in miles between ZIP Codes. A cost of $0.365, based on the federal mileage-reimbursement rate as of January 21, 2002, was accrued for each mile traveled.[4] Travel costs were assigned to the month in which the travel occurred. Additional rehabilitation sessions were assumed to have taken place during the first month after randomization.

QUALITY OF WELL-BEING SCORES

Quality of Well-Being scores were recorded at base line and at follow-up clinic visits. Monthly Quality of Well-Being scores were estimated on the assumption that scores remained constant between clinic visits. Missing scores for a visit were imputed as half the lowest score for all patients who filled out a form at the corresponding visit. Quality of Well-Being scores were imputed only if the patient survived beyond the end of the period during which that visit was to occur. Quality of Well-Being scores were assumed to remain constant between forms. Table A1 summarizes the monthly Quality of Well-Being scores for all patients not at high risk and among subgroups of patients not at high risk who were alive at the start of the period, according to the time after randomization.

INCREMENTAL COST-EFFECTIVENESS RATIOS

Uncertainty in Incremental Cost-Effectiveness Ratios

To depict uncertainty in the estimates of cost effectiveness, cost-effectiveness–acceptability curves were constructed according to the bootstrap method as applied to projected survival and the estimates of cost and quality-adjusted life-years gained for each patient. The curve represents the probability that lung-volume–reduction surgery is associated with a cost per quality-adjusted life-year gained that is lower than the corresponding cost-effectiveness ratios (ceiling ratios) shown on the x axis. The value of the ceiling ratio at a probability of 0.5 is the median cost per quality-adjusted life-year gained for lung-volume–reduction surgery.

Extrapolation to Estimate Incremental Cost-Effectiveness Ratios to 10 Years

Incremental cost-effectiveness ratios were extrapolated out to 10 years with the use of assumptions about survival, accrual of costs, and future Quality of Well-Being scores. Models were fitted to observed trends in these variables and then used to predict the results at 10 years of follow-up.

Analysis of Trends in Survival

In an effort to estimate long-term survival more accurately, the log-logistic model was fitted to survival data from only those patients who survived for at least one year. Several models were tried; the log-logistic model provided the best fit to the observed data, according to expert opinion. Regression analysis was used to determine the relation between survival and censoring information for survivors and treatment-group assignment in order to derive estimates of the parameters to be used in the model. Monthly survival data were extrapolated beyond three years with the use of the intercept and regression parameters for the log-logistic model.

Because in some subgroups there was a survival advantage for lung-volume–reduction surgery as compared with medical therapy at three years, several models were constructed for all groups to predict outcomes under alternative assumptions of the duration of the relative survival benefit. In the base case, point estimates for the relative survival advantage were first set at observed levels for year 3 (for example, the relative risk of death among all patients, excluding the high-risk subgroup, was 0.89 [P=0.31]). In separate models, the relative hazard of death was then assumed to change to 1.0 (no benefit) at years 3, 5, and 10. Changes in the relative hazard over time were modeled as a linear function, starting from 3 years after randomization and continuing until the date specified (3, 5, or 10 years). Future costs and quality-adjusted life-years were discounted by three percent per year.

Analysis of Trends in Mean Costs and Quality of Well-Being Scores

A least-squares linear-regression model was used to estimate the mean costs and Quality of Well-Being scores. The model analyzed the mean costs and Quality of Well-Being scores, with time (in months after randomization) as the predictor. Mean costs and Quality of Well-Being scores from year 3 were used for the regression analysis. Regression parameters were estimated separately for the surgery group and the medical-therapy group. The regression estimates for the intercept and time from randomization for mean costs were $635.74 and $28.87 (P=0.22) for the surgery group and $1,515.23 and $17.05 (P=0.48) for the medical-therapy group. The regression estimates for the intercept and time from randomization for mean Quality of Well-Being scores were 0.478 and 0.002 (P=0.11) for the surgery group and 0.440 and 0.000 (P=0.69) for the medical-therapy group. Figures A1 and A2 show mean costs and Quality of Well-Being scores and their fitted linear-regression curves, respectively.

Alternative Assumptions Regarding Duration of Survival Benefit

Increasing the duration of the relative survival benefit from surgery to 5 years and then to 10 years had very little effect on the incremental 10-year cost-effectiveness ratio for surgery as compared with medical therapy (Table A2).

Sensitivity Analysis of the Discount Rate

The effect of varying the discount rate applied to costs and quality-adjusted life-years gained on the 10-year incremental cost-effectiveness ratios was examined with a sensitivity analysis. Discount rates are applied per year. Discount rates of 0, 3, 5, and 10 percent were analyzed. Table A3 reports the 10-year cost-effectiveness ratios at the different discount rates, assuming a relative hazard of death of 1.0 at year 3 as the base case.

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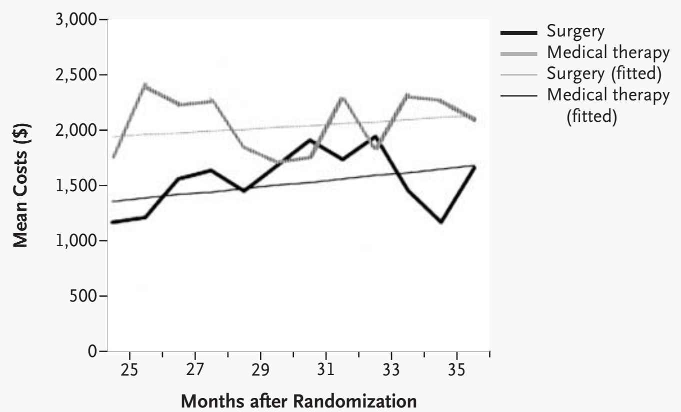

Figure A1. Mean Costs and Fitted Linear-Regression Curves for 25 to 36 Months after Randomization in the Surgery Group and the Medical-Therapy Group.

The high-risk subgroup and 12 patients with no Medicare claims were excluded from the analysis.

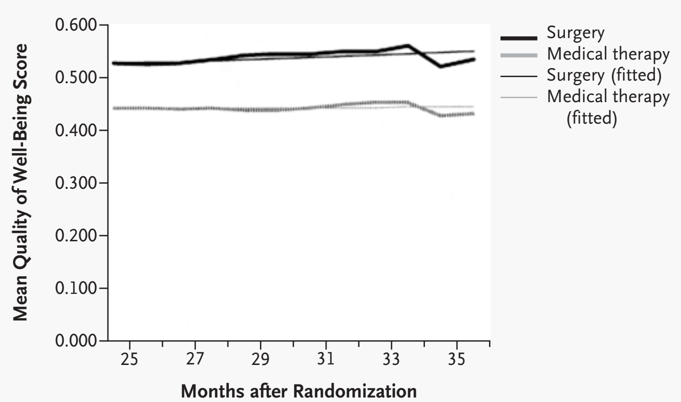

Figure A2. Mean Quality of Well-Being Scores and Fitted Linear-Regression Curves for 25 to 36 Months after Randomization in the Surgery Group and the Medical-Therapy Group.

The high-risk subgroup and 12 patients with no Medicare claims were excluded from the analysis.

Table A1. Monthly Quality of Well-Being Scores for Patients without High Risk, According to Period.*

Variable	Surgery Group			Medical-Therapy Group			P Value
	No. of Patients	Mean (±SD) Score	Median Score	No. of Patients	Mean (±SD) Score	Median Score	
All patients							
0–6 Mo	531	0.576±0.113	0.570	535	0.559±0.112	0.550	0.01
7–12 Mo	465	0.563±0.161	0.583	483	0.483±0.183	0.524	<0.001
13–24 Mo	407	0.549±0.179	0.571	424	0.463±0.200	0.513	<0.001
25–36 Mo	277	0.530±0.177	0.553	278	0.444±0.192	0.497	<0.001
Patients with predominantly upper-lobe emphysema and low exercise capacity							
0–6 Mo	137	0.566±0.119	0.551	148	0.528±0.116	0.524	0.007
7–12 Mo	125	0.587±0.156	0.597	127	0.441±0.187	0.471	<0.001
13–24 Mo	108	0.564±0.176	0.576	109	0.397±0.199	0.459	<0.001
25–36 Mo	79	0.545±0.172	0.554	65	0.369±0.189	0.429	<0.001
Patients with predominantly upper-lobe emphysema and high exercise capacity							
0–6 Mo	204	0.585±0.112	0.585	212	0.577±0.106	0.572	0.440
7–12 Mo	182	0.572±0.162	0.596	196	0.518±0.165	0.553	0.002
13–24 Mo	159	0.560±0.181	0.595	182	0.509±0.179	0.542	0.009
25–36 Mo	102	0.548±0.174	0.572	130	0.470±0.186	0.517	0.001
Patients with non–upper-lobe emphysema and low exercise capacity							
0–6 Mo	82	0.548±0.109	0.542	65	0.534±0.109	0.523	0.431
7–12 Mo	69	0.508±0.146	0.539	61	0.454±0.188	0.509	0.070
13–24 Mo	61	0.492±0.186	0.506	49	0.434±0.193	0.505	0.111
25–36 Mo	40	0.485±0.195	0.528	27	0.481±0.156	0.501	0.929

* Quality of Well-Being scores range from 0 to 1, with higher scores indicating a higher quality of life. The period was measured in months from randomization. High-risk patients and 12 patients with no Medicare claims were excluded from the analysis. Subgroups were defined according to characteristics at the time of randomization. The numbers of patients given are the numbers of patients who were alive at the start of the period. P values were calculated by the test for equality of means, with the use of Student's t-test with equal variances. Low exercise capacity was defined as a base-line maximal workload of 25 W or less for women and 40 W or less for men; a workload above these thresholds was considered to represent high exercise capacity.

Table A2. **Cost-Effectiveness Ratios for Lung-Volume–Reduction Surgery as Compared with Medical Therapy, under Alternative Time Horizons and Assumptions Regarding Duration of Survival Benefit from Surgery.***

Survival-Benefit Assumption	5 Years			10 Years		
	Mean No. of Quality-Adjusted Life-Years	Mean Total Costs	Incremental Cost-Effectiveness Ratio for Surgery	Mean No. of Quality-Adjusted Life-Years	Mean Total Costs	Incremental Cost-Effectiveness Ratio for Surgery
			$			$
Relative hazard of death = 1.0 after 3 yr						
Surgery	2.17	128,879	88,000	3.30	194,502	53,000
Medical therapy	1.77	94,013		2.49	150,925	
Relative hazard of death = 1.0 after 5 yr						
Surgery	2.18	129,218	87,000	3.33	195,887	54,000
Medical therapy	1.77	94,013		2.49	150,925	
Relative hazard of death = 1.0 after 10 yr						
Surgery	2.18	129,367	86,000	3.37	198,129	54,000
Medical therapy	1.77	94,013		2.49	150,925	

* Future costs and benefits were discounted by 3 percent per year. The duration of the relative survival benefit from surgery was modeled as a linear function, from 3 years after randomization to the date specified (3, 5, or 10 years). Survival in the medical-therapy group was modeled with the use of a log-logistic distribution.

Table A3. Ten-Year Cost-Effectiveness Ratios with Discount Rates Applied.*

Discount Rate	10-Yr Incremental Cost-Effectiveness Ratio for Surgery ($)
All patients	
0.00	49,000
0.03	53,000
0.05	57,000
0.10	65,000
Patients with predominantly upper-lobe emphysema and low exercise capacity	
0.00	16,000
0.03	21,000
0.05	25,000
0.10	34,000
Patients with predominantly upper-lobe emphysema and high exercise capacity	
0.00	51,000
0.03	54,000
0.05	56,000
0.10	61,000
Patients with non–upper-lobe emphysema and low exercise capacity	
0.00	–46,000
0.03	–38,000
0.05	–31,000
0.10	–14,000

* High-risk patients and 12 patients with no Medicare claims were excluded from the analysis. Subgroups were defined according to characteristics at the time of randomization. Low exercise capacity was defined as a baseline maximal workload of 25 W or less for women and 40 W or less for men; a workload above these thresholds was considered to represent high exercise capacity. In this case, a negative cost-effectiveness ratio indicates that the cost of surgery per quality-adjusted life-year gained was lower than the cost of medical therapy per quality-adjusted life-year gained.