Integrating Health Status and Survival Data
The Palliative Effect of Lung Volume Reduction Surgery

Roberto Benzo¹, Max H. Farrelly², Chung-Chou H. Chang³,⁴, Fernando J. Martinez⁵, John Reilly⁶, Gerard Criner⁷, Robert Wise⁸, Barry Make⁹, James Luketich¹⁰, Alfred P. Fishman¹¹, and Frank C. Sciurba¹², for the NETT Research Group

¹Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minnesota; ²Division of General Internal Medicine, Department of Medicine, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania; ³Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania; ⁴Internal Medicine, Division of Pulmonary & Critical Care Medicine, University of Michigan, Ann Arbor, Michigan; ⁵Department of Health Services, University of California, Los Angeles, California; ⁶Division of Pulmonary and Critical Care Medicine, Department of Medicine, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania; ⁷Division of Pulmonary & Critical Care Medicine, Temple University, Philadelphia, Pennsylvania; ⁸Division of Pulmonary & Critical Care Medicine, Johns Hopkins University, Baltimore, Maryland; ⁹Division of Pulmonary Sciences, National Jewish Medical Center and Research Center, Denver, Colorado; ¹⁰Division of Thoracic and Foregut Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania; ¹¹Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Rationale: In studies that address health-related quality of life (QoL) and survival, subjects who die are usually censored from QoL assessments. This practice tends to inflate the apparent benefits of interventions with a high risk of mortality. Assessing a composite QoL-death outcome is a potential solution to this problem.

Objectives: To determine the effect of lung volume reduction surgery (LVRS) on a composite endpoint consisting of the occurrence of death or a clinically meaningful decline in QoL defined as an increase of at least eight points in the St. George’s Respiratory Questionnaire total score from the National Emphysema Treatment Trial.

Methods: In patients with chronic obstructive pulmonary disease and emphysema randomized to receive medical treatment (n = 610) or LVRS (n = 608), we analyzed the survival to the composite endpoint, the hazard functions and constructed prediction models of the slope of QoL decline.

Measurements and Main Results: The time to the composite endpoint was longer in the LVRS group (2 years) than the medical treatment group (1 year) (P < 0.0001). It was even longer in the subsets of patients undergoing LVRS without a high risk for perioperative death and with upper-lobe-predominant emphysema. The hazard for the composite event significantly favored the LVRS group, although it was most significant in patients with predominantly upper-lobe emphysema. The beneficial impact of LVRS on QoL decline was most significant during the 2 years after LVRS.

Conclusions: LVRS has a significant effect on the composite QoL-survival endpoint tested, indicating its meaningful palliative role, particularly in patients with upper-lobe–predominant emphysema.

Keywords: chronic obstructive pulmonary disease; outcome assessment; palliative care; quality of life; survival; emphysema

What This Study Adds to the Field

The choice of methods and endpoints to use in evaluating the quality of life (QoL) trajectory requires careful consideration in chronic obstructive pulmonary disease (COPD). Patients who die during the period of observation from QoL assessments are often censored, as if their outcomes were neither good nor bad (1). Censoring may inflate the apparent benefits of treatment interventions that are associated with increased mortality, such as lung volume reduction surgery (LVRS) (1). One possible solution to this problem is to use a composite endpoint that combines mortality and QoL. For our study, we created a composite endpoint that consisted of the occurrence of death or a clinically meaningful decline in QoL. We tested the effect of LVRS on the selected composite endpoint in patients with severe emphysema who participated in the National Emphysema Treatment Trial (NETT) (2, 3) to define a more meaningful representation of the benefits of the procedure on QoL (palliative effect). Some of the results of these studies have been previously reported in the form of an abstract (4).

METHODS

Database

The design and methods of the NETT have been described previously (2, 5). Briefly, the 1,218 patients with severe emphysema who partic-
We used mixed models to study the progression of QoL over time. Knowing the QoL trajectory in individuals who have different clinical characteristics and have undergone LVRS can help healthcare providers and patients weigh the risks and benefits of this type of surgery and make appropriate decisions concerning whether it should be pursued in particular cases.

### Statistical Analyses

We used discrete time analysis to describe the failure probability from the time of randomization until the occurrence of an at least eight-point increase in the total SGRQ score or death in each treatment group (the medical treatment group and the LVRS group). To compare the failure probabilities of the two treatment groups, we used the generalized Wilcoxon test.

To study the natural progression of QoL over time, we used mixed hierarchical models. We fit several functional forms, including polynomials and piecewise polynomials, to select a model that best captured the variation over time. To take possible heterogeneity among patients into account, we included random intercepts and random slopes and tested the significance of these effects.

Because the data involved missing information, we conducted a sensitivity analysis using the method of simultaneously modeling progression of QoL over time and time to missing data.

### RESULTS

#### Patient Characteristics

Of the 1,218 patients in the NETT trial, 610 received continued medical therapy, and 608 underwent LVRS. The two treatment groups had similar characteristics at baseline (i.e., after pulmonary rehabilitation but before randomization) (Table 1).

### Endpoints

In the total sample of patients, the median time to the composite event was significantly shorter in the medical treatment group (1 y) than in the LVRS group (2 y) ($P < 0.0001$) (Table 2). In three of the subsets of patients, based on emphysema distribution and exercise capacity, the difference between the medical treatment group and the LVRS group was also highly significant (Table 2).

Figure 1 shows the discrete failure functions for the composite endpoint (solid lines) and for mortality alone (dotted lines) in the total sample and in all subsets of the sample. These curves indicate that patients receiving LVRS, particularly those with upper-lobe–predominant emphysema, had combined QoL...
non-upper lobe predominant, the scores predicted by mixed models with random intercepts are shown in Table E1A of the online supplement. The ML-based likelihood ratio tests for missing data. The point estimates and the inference tests of the QoL progression were similar using these two approaches. Therefore, the modeling results of QoL progression indicated above were not sensitive to the missing information.

**DISCUSSION**

Our study demonstrated the beneficial impact of LVRS on a composite outcome that integrates QoL and survival data of patients who had severe emphysema and participated in the NETT. Although the NETT has previously demonstrated (2, 3) that LVRS offers a survival advantage to patients, we have extended these findings by observing that LVRS further offers a palliative effect in these patients by effecting a significant and clinically meaningful improvement in QoL trajectory and that this improvement is most profound in the initial year after LVRS.

To investigate the effect of missing data, we compared the results from two approaches: (1) the mixed hierarchical models and the simultaneous models of QoL progression and (2) time to missing data. The point estimates and the inference tests of the QoL progression were similar using these two approaches. Therefore, the modeling results of QoL progression indicated above were not sensitive to the missing information.
Figure 1. Probability of reaching the composite event (CE) or mortality for the lung volume reduction surgery (LVRS) or medical treatment groups. Failure functions, shown as the proportion of patients developing the event over time, in the following samples of patients: (A) All patients in the study. (B) Patients without high risk of perioperative mortality. (C) Patients without high risk for perioperative mortality, upper-lobe–predominant emphysema, and high exercise capacity. (D) Patients without high risk for perioperative mortality, upper-lobe–predominant emphysema, and low exercise capacity. (E) Patients without high risk for perioperative mortality, non–upper-lobe predominant emphysema, and high exercise capacity. (F) Patients without high risk for perioperative mortality, non–upper-lobe predominant emphysema, and low exercise capacity. Solid lines relate to the composite event, which is the occurrence of death or the occurrence of at least an eight-point increase in the total score on St. George’s Respiratory Questionnaire, whichever happened first. Gray solid lines represent the medical treatment group, and black solid lines represent the LVRS group. Dotted lines represent the previously reported results of survival analysis for the same sets of patients (n = 9) and are included for comparison. The P value in the upper left corner of each panel refers to the value found when Wilcoxon tests were used to compare the failure functions for the composite event in the medical treatment group with those in the LVRS group. The number at risk refers to the number at risk for the composite event. The failure functions are described for death alone and for the composite event.
The failure probability curves in Figure 1 document large differences between the LVRS group and the medical treatment group in the composite occurrence of death or a clinically meaningful decline in QoL. The beneficial effects of LVRS become more apparent and more pronounced with the composite endpoint analysis compared with an analysis using solely mortality as the endpoint. The benefit for the composite endpoint in the subset of patients with upper-lobe–predominant emphysema and high exercise tolerance is most noteworthy in that a beneficial effect in this group could not be identified using a mortality analysis alone (3).

The results of the HRs for the composite outcome and for the decline of at least eight points in the SGRQ (Figure 2) conclusively demonstrate the palliative effect of LVRS. These
analyses show that LVRS tends to significantly decrease the risk of developing a profound decline in QoL (HR < 1) in the total sample of patients with severe emphysema and in all subsets except those who have non–upper-lobe predominant emphysema and a high risk for perioperative mortality.

We believe that our analysis represents the longest trajectory analysis of QoL in patients with severe emphysema with or without LVRS. Other reports have documented QoL in severe emphysema from different series, including NETT, but at specific time points, without modeling QoL progression over time (9–11). The documentation of the progression of QoL in the well-screened and well-characterized NETT patient population should prove particularly helpful in understanding health status progression due to severe emphysema because this population is less confounded by the presence of comorbidities that could dominate any assessment of QoL.

Our study showed that mean SGRQ scores (observed and predicted) were stable in the medical group during the first 4 years since randomization (A). Predicted progression of total scores measured in St. George’s Respiratory Questionnaire (SGRQ) for the following samples of patients: (A) All patients in the study. (B) Patients without a high risk of perioperative mortality. (C) Patients without high risk for perioperative mortality, and with upper-lobe–predominant emphysema and high exercise capacity. (D) Patients without a high risk for perioperative mortality, upper-lobe–predominant emphysema, and low exercise capacity. (E) Patients without a high risk for perioperative mortality, non–upper-lobe predominant emphysema, and high exercise capacity. (F) Patients without a high risk for perioperative mortality, non–upper-lobe predominant emphysema, and low exercise capacity. Black lines indicate predicted total SGRQ scores for the lung volume reduction surgery (LVRS) treatment group. Gray lines indicate predicted total SGRQ scores for the medical group.
years and improved in the fifth year (Table E1 of the online supplement). That response could be explained by the survival bias effect and has been previously described with respect to lung function (12) and QoL (13) in cohorts of patients with severe COPD. Our results differ from those of the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study, which reported a decline of 3.2 points per year (14). The ISOLDE cohort was significantly less compromised than the NETT cohort, and thus the difference in response was probably influenced less by survival bias effect. In addition, our study showed that the QoL trajectory in the medical group differed significantly from that in the LVRS group (Figure 3). The LVRS group demonstrated a meaningful improvement in QoL (more than eight points) in the first year after surgery. Although this was followed by a trend toward the baseline, the trajectory for the LVRS group remained clinically and statistically different than that of the medical treatment group in the second year and throughout the 5-year period. The authors of an earlier study of patients with moderate to severe COPD found that a four-point increase was associated with a 12.9% increase in COPD-related mortality at 3 years of follow-up (13). Although the slopes of decline for the LVRS and medical treatment groups differed during the first 2 years, the slopes did not differ thereafter. These findings confirm a palliative effect of LVRS, with initial improvement of QoL and subsequent maintenance of the improvement over time.

This analysis has several limitations. First, the absence of cardiovascular comorbidities in the NETT cohort represents a limitation in terms of generalizability of the results to patients with ongoing cardiac disease. Second, the inability to blind patients to the treatment received may have affected the subjective QoL measurements and was the reason for choosing an unquestionable QoL difference of eight points as part of the composite outcome. Finally, we recognize a limitation in the assumption made in the creation of the composite outcome, which arbitrarily considered an eight-point increase in the SGRO total score as equivalent to death to make an event. Because a strong motivation for patients to undergo such serious surgery is in fact preservation of QoL, such increases in SGRO score almost certainly represent a serious negative event (13, 15). The methodology that we used to analyze time-sensitive variables that include unquestionably clinically important differences may become more accepted in the future as a practical and clinically oriented approach to time-dependent analysis of clinical trial outcomes.

We believe that the inclusion of QoL in assessments of LVRS provides further support for the role of this surgical intervention in the clinical care of patients with severe emphysema. QoL measures are highly relevant to patient choices and confirm the rationale for using LVRS as a palliative tool. Our findings are relevant for recommending LVRS for patients with upper-lobe–predominant emphysema and in particular those with high exercise capacity, a subset of patients in whom the survival benefits may be marginal but in whom the combined survival and QoL benefits are pronounced.

Conflict of Interest Statement: R.B. received up to $1,000 in consultancy fees from Medacorp. M.H.F. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. C.C.H.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. F.J.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. R.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. G.C. received $1,001 to $5,000 from GlaxoSmithKline, and $1,001 to $5,000 from Aersi in industry-sponsored grants for research studies. R.W. received $5,001 to $10,000 for serving on an advisory board for BIP, $10,001 to $50,000 as a consultant for GlaxoSmithKline, $10,001 to $50,000 as a consultant for Novartis, $1,001 to $5,000 as a consultant for Schering Plough, $10,001 to $50,000 as a consultant for AstraZeneca, $10,001 to $50,000 as a consultant for Boehringer Ingelheim, $5,001 to $10,000 as a consultant for Genentech, and $5,001 to $10,000 as a DSMB from Medimmune; more than $100,001 from BIPI, more than $100,000 from GlaxoSmithKline, and more than $100,000 from Forest in industry-sponsored grants; and $5,001 to $10,000 as a DSMB member from Aventis, Mclntire fees; received Institutional–Clinical Trial $295,000 for clinical study, $100,000 per year for 5 years for data management from Accuracy, Institutional–Clinical Trial $375,982 over 3 years from Angiodynamics (Rita Medical), Institutional–Nonclinical trial $50,000 over 3 years from OncoTech, Inc, $10,000 to $50,000 Institutional–nonclinical trial ending June 2008 from Axcan, and Institutional–nonclinical trial $150,000 per year for 3 years (2005–2008) from Stykere; and $350,000 for fellowship training, renewed yearly, institutional from U.S. Surgical/Covidien. A.P.F. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. F.C.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

Members of the NETT Research Group are as follows: Office of the Chair of the Steering Committee, University of Pennsylvania, Philadelphia, PA: Alfred P. Fishman, MD (Chair); Betsy Ann Bozzarello, Ameena Al-Amin, Clinical centers: Baylor College of Medicine, Houston, TX: Marcia Katz, MD (Principal Investigator); Carolyn Wheeler, RN, MSN (Principal Investigator); Elizabeth Hung, MD; Peter Samard, PhD, RPT; Philip Cagle, MD; James Carter, MD; Sophia Chatziioannou, MD; Karla Conejo-Gonzales; Kimberly Dubose, RRT; John Haddad, MD; David Hicks, RPT; Neil Kleiman, MD; Mary Milburn-Barnes, CRT; Chinh Nguyen, RPT; Michael Reardon, MD; Joseph Reeves-Vietes, MD; Stephen Shamos, MD; Amir Shashalkanhe, MD; Owen Wilson, PhD; Christine Young PT; Rafael Espada, MD (Principal Investigator 1996–2002); Rose Butanda (1999–2001); Minnie Elliot (2002); Pamela Fox, MD (1999–2001); Katherine Hale, MD (1998–2000); Everett Hood, MD (1998–2000); Anthony Jahn (1998–2000); Satish Jhingran, MD (1998–2001); Karen King, RPT (1998–1999); Charles Miller III, PhD (1996–1999); Imran Nizami, MD (Co-Principal Investigator, 2000–2001); Todd Friender–Koff (1999–2000); Jeanie Ricketts (1998–2000); Jo Rodarte, MD (Co-Principal Investigator 1996–2000); Robert Teague; MD (Clinical Investigator); John Wilkins, MD (1998–1999). Brigham and Women’s Hospital, Boston, MA: John Reilly, MD (Principal Investigator); David Sugarbaker, MD (Co-Principal Investigator); Carol Fanning, RRT (Principal Clinical Coordinator); Simon Body, MD; Sabine Duffy, MD; Vladimir Furtmenger, MD; Anne Furr, MD, PhD; Philip Hoooper, MD; EP; Andetta Hunskar, MD; Francine Jacobson, MD; Marilyn Moj, MD; Susan Peterson, RRT; Roger Russell, MD; Diane Saunders; Scott Swanson, MD (Co-Principal Investigator 1996–2001). Cedars-Sinai Medical Center, Los Angeles, CA: Rob McKenna, MD (Principal Investigator); Zab Mohsenifar, MD (Co-Principal Investigator); Carol Geega, RN (Principal Clinical Coordinator); Mammon Biring, MD; Susan Clark, RN, MN; Jennifer Cutler, MD; Robert Frantz, MD; Peter Julian, MD; Michael Lewis, MD; Jennifer Minkoff-Rau, MSW; Valentina Yegian, BS, CPTF; Malcolm DeCamp, MD (Principal Investigator); James Stoller, MD (Co-Principal Investigator); Yvonne Meli, RN, NC (Principal Clinical Coordinator); John Apostolakis, MD; Daryl Atwell, MD; Jeffrey Chapman; MD; Pierre Devilliers, MD; Rade Dwek, MD; Erik Kraenzler, MD; Rosemary Land, LSW; Nancy Kurz, RN, BS, CPTF; Scott Mathison, MD; Kevin McCarrick, RRT; CPTF; Amy Meya, MD; Moulay Meziane; MD; Omar Minai, MD; Mindi Steiger, RPTF; Kenneth White, RPTF; Janet Maurer, MD (Principal Investigator, 1996–2001); Terri Durr, RN (2000–2001); Charles Heann, DO (1998–2000); Susan Lubeli, PA-C (1999–2000); Peter O’Donovan, MD (1998–2003); Robert Schilt, DO (1998–2002); Columbia University, New York, NY in consortium with Long Island Jewish Medical Center, New Hyde Park, NY: Mark Ginsburg, MD (Principal Investigator); Byron Thomashow, MD (Co-Principal Investigator); Patricia Jellen, MSN, RN (Principal Clinical Coordinator); John Austin, MD; Matthew Bartels, MD; Yahya Berken, MD; Patricia Berkoski, MS, RRT (Site coordinator, LJ); Frances Brogan, MSN, RN; Amy Chong, BS, CRT; Glenda DeMecaro, BSN; Angela DiMango, MD; Sandy Do, MS, PT; Bessie Kachulis, MD; Arfa Khan, MD; Bened Merts, MD; Mitchell O’Shea, BS, R, CPTF; Gregory Pearlmutter, MD; Leonard Rouskas, MD; Steven Scharf, RN; Stephen Schuman (Principal Investigator, 1998–2002); Maria Shiau, MD; Paul Simonelli, MD; Kim Stavrolakes, MS, PT; Donna Tsang, BS; Denise Vitoljovic, MS, PT; Chun Yip, MD; Mike Martinaos, MD (1996–2001); Kerin McKeon, BS, R, CPTF (1998–1999); Jacqueline Peffer, MPH, PT (1997–2002); Case University Medical Center, Durham, NC: Neil MacIntyre, MD (Principal Investigator); R Duane Davis, MD (Co-Principal Investigator); John Howe, RN (Co-Principal Clinical Coordinator); R. Edward Coleman, MD; Rebecca Crouch, RPT; Dora Greene; Kathrin Grichnik, MD; David Harpole, Jr, MD; Alan Krichman, RRT; Huffman, MD; John Key, MD; Susan Rinaldi, MD; Richard Sabatino, MD; Tina Shrestha, MD; Joan Shulman, RN, BSN; Cheryl Smith, MD; Lora Smith, BSN; Stephen Stitzer, MD; Ludeca Storz, MD; John Tarkowski, MD, PhD; John Vasko, MD; William Wheeler, RN, BSN (Principal Clinic Coordinator); Elaine Wheeler, RRT, RPFT; Neal Whey, RPTF; Janet Maurer, MD (Principal Investigator, 1996–2001); Terri Durr, RN (2000–2001); Charles Heann, DO (1998–2000); Susan Lubeli, PA-C (1999–2000); Peter O’Donovan, MD (1998–2003); Robert Schilt, DO (1998–2002).