Longitudinal Changes In Pulmonary Function And Patient Reported Outcomes After Lung Cancer Surgery

Sumin Shin

Ewha Womans University

Sunga Kong

Sungkyunkwan University

Danbee Kang

Sungkyunkwan University

Genehee Lee

Sungkyunkwan University

Jong Ho Cho

Samsung Medical Center

Young Mog Shim

Samsung Medical Center

Juhee Cho

Sungkyunkwan University

Hong Kwan Kim

Samsung Medical Center

Hye Yun Park (✉ hyeyunpark@skku.edu)

Sungkyunkwan University

Research Article

Keywords: non-small cell lung cancer, patients reported outcomes, pulmonary function, surgery

Posted Date: February 9th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1331424/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: Surgery is the mainstay of treatment for non-small cell lung cancer, but the decline in pulmonary function after surgery is noticeable and needs attention. The aim of this study was to evaluate longitudinal changes in pulmonary function and its integrated patient-reported outcomes (PROs) after lung cancer surgery.

Methods: The data were obtained from a prospective cohort study, Coordinate Approach to Cancer Patients' Health for Lung Cancer. Changes in forced vital capacity (FVC) and forced expiratory volume in 1s (FEV₁) 2 weeks, 6 months, and 1 year after surgery and the corresponding modified Medical Research Council (mMRC) dyspnea scale and chronic obstructive lung disease assessment test (CAT) score were evaluated. Mixed effect models were used to investigate the changes in pulmonary function and PROs.

Results: Among 620 patients, 477 (76.9%) underwent lobectomy, while 120 (19.4%) and 23 (3.7%) were treated with limited resection and bilobectomy/pneumonectomy, respectively. Both FVC and FEV₁ markedly decreased 2 weeks after surgery and improved thereafter but did not recover to baseline values. The corresponding mMRC dyspnea scale and CAT score also showed worsening immediately after surgery. The dyspnea scale was still higher, while the CAT score returned to baseline 1 year after surgery, although the breathlessness and lack of energy persisted. Patients treated with bilobectomy/pneumonectomy showed -2.3%, -6.8%, and -6.0% more decrease in FEV₁ (% predicted) compared to the patients who underwent lobectomy at each time point. Moreover, worsening quality of life including dyspnea was also robust in patients treated with pneumonectomy/bilobectomy.

Conclusions: After lung cancer surgery, pulmonary function and PROs was remarkable decreased at immediate post-operative period and improved thereafter except for dyspnea and lack of energy. The proper information on timeline of change in lung function and symptoms following lung cancer surgery could guide patient care approach following lung cancer surgery.

Trial Registration: ClinicalTrials.gov; No.: NCT03705546; URL: www.clinicaltrials.gov

Introduction

Lung cancer is the leading cause of cancer death in both men and women.[1] The median age at diagnosis of lung cancer is 70 years,[2] and more than 70% of future lung cancer cases are expected to occur in adults older than 65 years.[3] Surgery is the best treatment option for patients with early stage non-small cell lung cancer (NSCLC)[4]; the 5-year survival rate among patients with stage I NSCLC after curative resection is increased up to 70%.[5] Despite this improvement in the survival rate, a decrease in pulmonary function after surgery is inevitable. Accordingly, several studies have shown serial changes in pulmonary function after lung resection[6-9]. The lung function dropped sharply until 1 month, partly recovered at 3 months, and stabilized at 6 months after surgery[6-9]. These changes in lung function vary

depending on the extent of surgery with the reduction in forced expiratory volume in 1 s (FEV₁) being 9% and 35% after lobectomy and pneumonectomy, respectively.[7, 8]

Lung cancer survivors commonly suffer from post-treatment symptoms such as pain, dyspnea, and fatigue, negatively impacting quality of life (QOL)[10-14]. Given the importance of health-related quality of life (HRQoL) in patients with lung cancer and its prognostic impact, it is recommended to assess patient-reported outcomes (PROs)[15]. In particular, the lung cancer-specific HRQoL essential domains includes dyspnea and cough[16, 17] and several studies have found that the postoperative respiratory symptoms such as cough, dyspnea, and phlegm were more frequently observed in patients with low pulmonary function[18], resulting in a sedentary lifestyle and decreased physical function ability[19, 20]; However, the changes of PROs were measured between baseline and only one point after surgical resection and there are limited data on changes in PROs associated with changes in pulmonary function over time after surgical resection during longitudinal follow-up. Thus, we conducted a longitudinal cohort study to examine the serial changes in pulmonary function and its associated changes of PRO in NSCLC patients with curative resection.

Methods

We used data from a prospective cohort study called the Coordinated Approach to Cancer Patients' Health for lung cancer (CATCH-LUNG), which recruited patients expected to undergo curative lung cancer surgery for suspected NSCLC at Samsung Medical Center in Seoul, Korea from March 2016 to October 2018. The patients inclusion criteria were as follows: (1) expected to undergo curative lung cancer surgery for suspected or histologically confirmed NSCLC, (2) Eastern Cooperative Oncology Group performance status was either 0 or 1, (3) no problems in walking, and (4) understood the purpose of the study and agreed to participate in it. The protocols for patient enrollment and data collection have been described in a previous study.[21] The study protocol was approved by the Institutional Review Board of Samsung Medical Center (no. 2015-11-025), and written informed consent was obtained from all the participants.

Measurements

Sociodemographic and behavioral information of participants, including age, sex, body mass index, smoking status, and comorbidities, were obtained from electronic medical records. Clinical information including type of the surgical approach, pathological type of lung cancer, pathological stage, and adjuvant treatment were also collected after surgery. Pulmonary function and PROs were measured before surgery and repeated at 2 weeks (median, 2 weeks), 6 months (median, 5 months), and 1 year (median 11.2 months) after the surgery.

Pulmonary function measurements, including spirometry and diffusing capacity of the lung for carbon monoxide (DLco), were performed using a Vmax 22 respiratory analyzer (SensorMedics, OH, USA) according to the American Thoracic Society/European Respiratory Society criteria.[22, 23] Absolute

values of FEV₁, forced vital capacity (FVC), and DLco were obtained, and their percent predicted values (% pred) were calculated using a representative Korean sample[24, 25] as a reference. PROs were assessed using the modified Medical Research Council (mMRC) dyspnea scale and the chronic obstructive lung disease assessment test (CAT) score. The mMRC dyspnea scale is a questionnaire consisting of five statements related to perceived breathlessness, which were classified into grade 0 to 4[26]. The CAT score consists of eight parameters, including cough, sputum, chest tightness, dyspnea, activity confidence, sleep, and energy. Scores range from 0 to 5 points, resulting in a total CAT score ranging from 0 to 40 points[27].

Statistical analysis

We used mixed effect models for longitudinal data analysis and modeled changes in absolute values of FVC and FEV₁; % pred for FEV₁ and FVC at each time point changed over time. These mixed models provided the average longitudinal change from preoperative values (with 95% confidence intervals [CI]) and allowed for random variations in longitudinal changes among participants according to normal distributions with unstructured variance-covariance matrices. Furthermore, we compared differences in the changes observed in pulmonary function in comparison to preoperative values by the type of surgery (pneumonectomy and bilobectomy, lobectomy, or segmentectomy, and wedge resection) using a mixed model that included interaction terms between the time and type of surgery.

In terms of PROs, patients with more than grade 2 mMRC dyspnea scale (I get short of breath when hurrying on the level or up a slight hill) were considered to have significant dyspnea in the current study[26]. Based on CAT total scores, patients were categorized into three groups: low ($0 \leq \text{CAT} < 10$), medium ($10 \leq \text{CAT} < 20$), and high ($20 \leq \text{CAT} \leq 40$) impact groups according to the CAT users guide (<http://www.catestonline.org>). To evaluate the change in the prevalence of mMRC dyspnea grade ≥ 2 and medium or high CAT (total score ≥ 10), we used a generalized estimating equation with binomial as family and logit as the link function. To adjust for the confounding factors, we included age, sex, stage, obesity, smoking status, cell type, type of surgery, video-assisted thoracic surgery, postoperative pulmonary complications, and adjuvant treatment. PPC was defined as any of the following conditions: (1) atelectasis requiring bronchoscopic toileting, (2) pneumonia (at least three among leukocytosis, pulmonary infiltrate or consolidation, fever [$>38^{\circ}\text{C}$], culture-positive, or use of antibiotics), (3) acute lung injury or acute respiratory distress syndrome (rate of arterial oxygen partial pressure to fractional inspired oxygen <300 and bilateral infiltrate observed on chest radiograph without evidence of congestive heart failure or volume overload), or (4) acute exacerbation of chronic obstructive pulmonary disease[28].

All reported *p* values were set at a significance level of 0.05. Statistical analyses were performed using Stata version 16 (Stata Corp., College Station, TX, USA).

Results

Patient characteristics

The mean (standard deviation) age of study participants was 61.2 (9.0) years, and the percentage of male patients was 56.5% (n = 350) (Table 1). Among the 620 eligible participants, 23 (3.7%), 477 (79.9%), and 120 (19.4%) underwent pneumonectomy/bilobectomy, lobectomy, and segmentectomy/wedge resection, respectively. All the participants completed the baseline examination, while 603 (97.3%, pneumonectomy/bilobectomy n = 21; lobectomy n = 464; segmentectomy/wedge resection n = 118), 536 (86.6%, pneumonectomy/bilobectomy n = 20; lobectomy n = 406; segmentectomy/wedge resection n = 110), and 518 (83.5%, pneumonectomy/bilobectomy n = 17; lobectomy n = 395; segmentectomy/wedge resection n = 106) completed the examination at 2 weeks, 6 months, and 1 year after surgery, respectively. Compared to patients who underwent lobectomy, pneumonectomy/bilobectomy patients were more associated with parameters like old age, male gender, smoker, squamous cell carcinoma, severe cancer stage, and receiving adjuvant treatment (Table 1).

Changes in pulmonary function

The baseline, average (standard deviation) levels of FVC, predicted FVC, FEV₁, predicted FEV₁, and DLco were 3595.1 mL, 92.9%, 2637.4 mL, 90.1%, and 89.9% and the adjusted means were 3600.3 mL, 93.2%, 2647 mL, 90.4%, and 90.5%, respectively (Table 2). FVC decreased sharply 2 weeks after surgery and increased thereafter but did not return to baseline levels (2721.4 mL, 3137.7 mL, and 3268.8 mL at 2 weeks, 6 months, and 1 year after surgery, respectively) (Table 2). Compared to the baseline, patients showed -331.6 (95% CI; -365.1, -297.3) mL less FVC at 1 year after surgery (Figure 1). Furthermore, patients showed decline in % pred FVC (95% CI) of -23.3% (-24.1, -22.5), -12.3% (-13.2, -11.4), and -8.5% (-9.4, -7.6) compared to baseline at 2 weeks, 6 months, and 1 year after surgery, respectively (Figure 1). Similar pattern were observed in FEV₁ and % pred FEV₁, and the decline in FEV₁ (95% CI) was -20.6 % (-21.3, -19.9), -10.7 (-11.5, -10) and -7.8 (-8.6, -7) at 2 weeks, 6 months, and 1 year after surgery, respectively (Table 2, Figure 1).

Changes of PROs

Both mMRC and CAT scores decreased at 2 weeks after surgery, and were alleviated over time (Table 3, Figure 1). The prevalence of mMRC dyspnea grade ≥ 2 group was increased by 15.2, 3.3, and 2.1-times that of baseline at 2 weeks, 6 months, and 1 year after surgery, respectively. The prevalence of CAT score ≥ 10 group also increased by 6.0 and 1.4-times that of baseline at 2 weeks and 6 months after surgery, respectively, although the CAT score was fully recovered at 1 year (e-Table 1). Individual changes in CAT levels are listed in Table 4. Two weeks post-surgery, all domains except the amount of phlegm, were significantly worse than the baseline; only breathlessness walking upstairs and lack of energy domains of CAT persisted 1 year after surgery.

Impact of surgical extent on pulmonary function and PROs

The levels of pulmonary function were similar regardless of the type of surgery (Table 2). In patients with pneumonectomy/bilobectomy, FVC were decreased as compared to baseline (-1195.6 mL, -999.6 mL, and -770.1 mL at 2 weeks, 6 months, and 1 year after surgery, respectively). Furthermore, patients with

segmentectomy/wedge resection were -670.1 mL, -244.4 mL, and -164.7 mL at 2 weeks, 6 months, and 1 year after surgery, respectively (Table 2, Figure 2). Compared to the change from baseline in % pred FVC in patients with lobectomy, pneumonectomy/bilobectomy resection patients showed -5.5%, -11.0%, and -9.7% decreased % pred FVC, while segmentectomy/wedge resection patients had 6.3%, 5.9%, and 4.4% less decrease in % pred FVC at 2 weeks, 6 months, and 1 year after surgery, respectively. The patterns observed for FEV₁ and % pred FEV₁ were similar to those observed for FVC. Compared to the change from baseline in % pred FEV₁ in lobectomy patients, pneumonectomy/bilobectomy and segmentectomy/wedge resection patients showed -2.2%, -6.8%, and -6.0% more and 6.3%, 5.6%, and 4.5% less decrease at 2 weeks, 6 months, and 1 year after surgery, respectively.

Pneumonectomy/bilobectomy resection patients had the highest mMRC dyspnea grade among the three groups, but it was not statistically significant 1 year after surgery (Table 3). The odd ratio for CAT score >10 were significantly higher after pneumonectomy/bilobectomy as compared to that after lobectomy or limited resection 2 weeks after surgery; however, this difference was not statistically significant 6 months and 1 year after surgery (e-Table 1).

Discussion

In this study, we investigated changes in pulmonary function and PROs over one year after lung cancer surgery. We demonstrated that all parameters of lung function, dyspnea scale, and CAT score noticeably worsened 2 weeks after surgery. During the follow-up period, lung function and PROs partly recovered, but not returned to baseline. The pattern of alteration of PROs was found to be closely linked to changes in pulmonary function. Although the CAT score was fully recovered 1 year after surgery, the breathlessness and energy domains deteriorated. Lung function decline, with worsening PROs including dyspnea, was robust in patients with pneumonectomy or bilobectomy. To our knowledge, this is the largest prospective cohort study with repeated (over 1 year) evaluation of pulmonary function and PROs after lung cancer surgery.

Surgical resection offers the best long-term survival results in patients with resectable NSCLC, but it also leads to the loss of lung parenchyma, with a subsequent impairment of pulmonary function and worsening of PROs[7, 29]. Immediately after surgery, the FVC and FEV₁ were dramatically decreased with worse PROs including dyspnea. The proportion of patients with a dyspnea scale >2 was only 2.4% at baseline, while it increased to 26.3% two weeks after surgery. The CAT score also showed a similar pattern, with significant increase (more than double; 6 to 13) 2 weeks after surgery. The loss of pulmonary function was evidently correlated with the amount of lung resection; at postoperative 2 weeks, the decline in % pred FVC and FEV₁ was 17% and 15.5% after limited resection, 23.3% and 21.7% after lobectomy, and 28.8% and 24% after pneumonectomy or bilobectomy, respectively. Furthermore, after limited resection, more than 18% of patients also suffer from dyspnea with a profound decrease in pulmonary function in the early postoperative period.

Six months after surgery, the decline in lung function and worsened PROs were partially recovered, consistent with the results of previous studies[6-9]^{29,30}. Previously, lung function parameters at different time points over 1 year period were found to be significantly restored 3-6 months after surgical resection[8, 30, 31]. Due to surgical incision and pain, pulmonary function could be impaired more than expected in the early postoperative period. Furthermore, time is required to overcome the postoperative residual pleural space (occupied by pleural fluid), achieve lung expansion, and displace the mediastinum and diaphragm[32]. Previous studies have shown that the physical functioning and QoL restored to baseline levels after lung cancer surgery, except in patients with pneumonectomy[33, 34]; although few symptoms were relieved, a large proportion of patients still suffered from dyspnea. In the present study, approximately 8% of the patients showed significant dyspnea 6 months after surgery, which was robust in pneumonectomy cases.

One year after surgery, the mean FVC and FEV₁ loss were mitigated regardless of the surgical extent; the FVC and FEV₁ loss were 4.1% and 4%, 8.5% and 8.4%, and 18.2% and 14.4% after limited resection, lobectomy, and pneumonectomy/bilobectomy, respectively. Approximately 5% of the patients showed significant dyspnea, and the proportion was not significantly associated with the extent of surgery. Other symptoms such as cough, sputum, chest tightness, confidence, and home activities were not significantly observed after 1 year, but the lack of energy persisted.

Postoperative impairment of pulmonary function has been reported as an indicator of dyspnea[18]. The presence of dyspnea was associated with a low level of QoL, including physical, social and role function[12, 35]. The relationship between subjective symptoms and objective pulmonary function has been reported among patients with chronic lung disease[36-38], but rarely reported for lung cancer patients postoperatively. In a previous study, respiratory symptoms were significantly more common in the presence of moderate to severe pulmonary dysfunction[18]; postoperative symptoms, such as dyspnea, are often ignored and underestimated. Despite the symptoms, medication usage has not been commonly reported, and only 18% of the patients used bronchodilators[18]. Several previous studies have shown that exercise programs are effective in improving exercise capacity, symptoms, and QOL after lung cancer surgery[39, 40], but the clinical application of exercise programs is still limited. To our knowledge, this is the largest prospective study to show the longitudinal changes in PROs related to lung function decline postoperatively. Our data showed the nature of pulmonary function changes and symptoms over 1 year after lung cancer surgery and found that the most deteriorated PROs and pulmonary function reduction occurred at 2 weeks, which could be targets for intervention. Deterioration of pulmonary function and related-symptoms could be relieved or mitigated with integrated programs, including medication and rehabilitation, and future research is required to establish interventions to improve pulmonary function and patient discomfort.

There were several limitations to the present study. As it was conducted only in patients at a tertiary hospital, the results might not represent the different settings. In addition, few patients dropped out during the follow-up and hence, changes in pulmonary function could be overestimated if those patients

showed worse performance. Finally, the surgical procedures largely depended on the tumor characteristics, and the differences in baseline characteristics by surgical procedure were unavoidable.

Conclusions

In conclusion, our study showed longitudinal changes in pulmonary function and integrated PROs in a large prospective cohort after lung cancer surgery. Lung function and PROs improved over time, but patients suffered from dyspnea and various discomfort in the early postoperative period independent of the extent of surgery. Thus, physicians are required to stay attentive regarding lung function decline and associated symptoms after surgery, and support patients as the lung function and QOL is expected to improve with time. Further studies are needed to establish an intervention program for such patients.

List Of Abbreviations

Non-small cell lung cancer (NSCLC)

Forced expiratory volume in 1s (FEV₁)

Quality of life (QOL)

Health-related quality of life (HRQoL)

Patient-reported outcomes (PROs)

Diffusing capacity of the lung for carbon monoxide (DLco)

Forced vital capacity (FVC)

modified Medical Research Council (mMRC)

Chronic Obstructive Lung Disease Assessment Test (CAT)

Percent predicted values (% pred)

Declarations

Conflict of interest statement

The authors declare no conflict of interests.

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of Samsung Medical Center (no. 2015-11-025), and written informed consent was obtained from all the participants.

Consent for publication

Not applicable

Availability of data and materials

The data will not be shared with a reason.

Competing interests

The authors declare that they have no competing interests

Funding

This work was supported by grants from the National Research Foundation of Korea (NRF) funded by the Korean government(MSIP) (No. 2017R1A2B2006435and 2019R1H1A2039761)

The role of the funding body is in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Author contributions: S.S., S.K., C.J. and H.Y.P. drafted the manuscript. All authors listed have provided substantial contributions to the conception, design, data acquisition, analysis, or interpretation of this work, and all authors participated in revising the manuscript after critical review.

Acknowledgments

Not applicable

References

1. Collaboration GBoDC: **Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study.** *JAMA Oncology* 2017, **3**:524-548.
2. Howlader N NA, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). : **SEER Cancer Statistics Review, 1975-2016, National Cancer Institute.** . *SEER Cancer Statistics Review, 1975-2016, National Cancer Institute Bethesda, MD, https://seercancer.gov/csr/1975_2016/, based on November 2018 SEER data submission, posted to the SEER web site* 2019, **April 2019**.
3. Smith BD, Smith GL, Hurria A, Hortobagyi GN, Buchholz TA: **Future of cancer incidence in the United States: burdens upon an aging, changing nation.** *J Clin Oncol* 2009, **27**:2758-2765.
4. Howington JA, Blum MG, Chang AC, Balekian AA, Murthy SC: **Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians**

evidence-based clinical practice guidelines. *Chest* 2013, **143**:e278S-e313S.

5. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WEE, Nicholson AG, Groome P, Mitchell A, Bolejack V, et al: **The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer.** *Journal of Thoracic Oncology* 2016, **11**:39-51.
6. Gu Z, Wang H, Mao T, Ji C, Xiang Y, Zhu Y, Xu P, Fang W: **Pulmonary function changes after different extent of pulmonary resection under video-assisted thoracic surgery.** *Journal of thoracic disease* 2018, **10**:2331-2337.
7. Bolliger CT, Jordan P, Soler M, Stulz P, Tamm M, Wyser C, Gonon M, Perruchoud AP: **Pulmonary function and exercise capacity after lung resection.** *Eur Respir J* 1996, **9**:415-421.
8. Win T, Groves AM, Ritchie AJ, Wells FC, Cafferty F, Laroche CM: **The effect of lung resection on pulmonary function and exercise capacity in lung cancer patients.** *Respir Care* 2007, **52**:720-726.
9. Larsen KR, Svendsen UG, Milman N, Brenøe J, Petersen BN: **Cardiopulmonary function at rest and during exercise after resection for bronchial carcinoma.** *Ann Thorac Surg* 1997, **64**:960-964.
10. Fitch MI: **Exploring Experiences of Survivors and Caregivers Regarding Lung Cancer Diagnosis, Treatment, and Survivorship.** *J Patient Exp* 2020, **7**:193-199.
11. Lowery AE, Krebs P, Coups EJ, Feinstein MB, Burkhalter JE, Park BJ, Ostroff JS: **Impact of symptom burden in post-surgical non-small cell lung cancer survivors.** *Support Care Cancer* 2014, **22**:173-180.
12. Hechtner M, Eichler M, Wehler B, Buhl R, Sebastian M, Stratmann J, Schmidberger H, Gohrbandt B, Peuser J, Kortsik C, et al: **Quality of Life in NSCLC Survivors - A Multicenter Cross-Sectional Study.** *J Thorac Oncol* 2019, **14**:420-435.
13. Yang P, Cheville AL, Wampfler JA, Garces YI, Jatoi A, Clark MM, Cassivi SD, Midthun DE, Marks RS, Aubry MC, et al: **Quality of life and symptom burden among long-term lung cancer survivors.** *J Thorac Oncol* 2012, **7**:64-70.
14. Ostroff JS, Krebs P, Coups EJ, Burkhalter JE, Feinstein MB, Steingart RM, Logue AE, Park BJ: **Health-related quality of life among early-stage, non-small cell, lung cancer survivors.** *Lung Cancer* 2011, **71**:103-108.
15. Gridelli C, Perrone F, Nelli F, Ramponi S, De Marinis F: **Quality of life in lung cancer patients.** *Annals of Oncology* 2001, **12**:S21-S25.
16. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M: **The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials.** EORTC Study Group on Quality of Life. *Eur J Cancer* 1994, **30A**:635-642.

17. Ediebah DE, Coens C, Zikos E, Quinten C, Ringash J, King MT, Schmucker von Koch J, Gotay C, Greimel E, Flechtner H, et al: **Does change in health-related quality of life score predict survival? Analysis of EORTC 08975 lung cancer trial.** *Br J Cancer* 2014, **110**:2427-2433.
18. Sarna L, Evangelista L, Tashkin D, Padilla G, Holmes C, Brecht ML, Grannis F: **Impact of respiratory symptoms and pulmonary function on quality of life of long-term survivors of non-small cell lung cancer.** *Chest* 2004, **125**:439-445.
19. Solberg Nes L, Liu H, Patten CA, Rausch SM, Sloan JA, Garces YI, Cheville AL, Yang P, Clark MM: **Physical activity level and quality of life in long term lung cancer survivors.** *Lung Cancer* 2012, **77**:611-616.
20. Pozo CL, Morgan MA, Gray JE: **Survivorship issues for patients with lung cancer.** *Cancer Control* 2014, **21**:40-50.
21. Lee H, Kim HK, Kang D, Kong S, Lee JK, Lee G, Shin S, Cho J, Zo JI, Shim YM, Park HY: **Prognostic Value of 6-Min Walk Test to Predict Postoperative Cardiopulmonary Complications in Patients With Non-small Cell Lung Cancer.** *Chest* 2020, **157**:1665-1673.
22. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CPM, Gustafsson P, et al: **Standardisation of spirometry.** *European Respiratory Journal* 2005, **26**:319-338.
23. **American Thoracic Society. Single-breath carbon monoxide diffusing capacity (transfer factor). Recommendations for a standard technique—1995 update.** *American Journal of Respiratory and Critical Care Medicine* 1995, **152**:2185-2198.
24. Choi JK, Paek D, Lee JO: **Normal Predictive Values of Spirometry in Korean Population.** *trd* 2005, **58**:230-242.
25. **Normal Predicted Values of Single-Breath Diffusing Capacity of the Lung in Healthy Nonsmoking Adults FAU - Park, Jeong Ok FAU - Choi, In Seon FAU - Park, Kyung Ok.** *Korean J Intern Med* 1986, **1**:178-185.
26. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA: **Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease.** *Thorax* 1999, **54**:581-586.
27. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Leidy NK: **Development and first validation of the COPD Assessment Test.** *European Respiratory Journal* 2009, **34**:648-654.
28. Shin S, Park HY, Kim H, Kim HK, Choi YS, Kim J, Um S-W, Chung MJ, Kim H, Kwon OJ, et al: **Joint effect of airflow limitation and emphysema on postoperative outcomes in early-stage nonsmall cell lung cancer.** *European Respiratory Journal* 2016, **48**:1743.

29. Lima LN, da Silva RA, Gross JL, Deheinzelin D, Negri EM: **Assessment of pulmonary function and quality of life in patients submitted to pulmonary resection for cancer.** *J Bras Pneumol* 2009, **35**:521-528.
30. Kim SJ, Lee YJ, Park JS, Cho YJ, Cho S, Yoon HI, Kim K, Lee JH, Jheon S, Lee CT: **Changes in pulmonary function in lung cancer patients after video-assisted thoracic surgery.** *Ann Thorac Surg* 2015, **99**:210-217.
31. Yokoba M, Ichikawa T, Harada S, Naito M, Sato Y, Katagiri M: **Postoperative pulmonary function changes according to the resected lobe: a 1-year follow-up study of lobectomized patients.** *J Thorac Dis* 2018, **10**:6891-6902.
32. Miserocchi G, Beretta E, Rivolta I: **Respiratory mechanics and fluid dynamics after lung resection surgery.** *Thorac Surg Clin* 2010, **20**:345-357.
33. Brunelli A, Socci L, Refai M, Salati M, Xiume F, Sabbatini A: **Quality of life before and after major lung resection for lung cancer: a prospective follow-up analysis.** *Ann Thorac Surg* 2007, **84**:410-416.
34. Balduyck B, Hendriks J, Lauwers P, Van Schil P: **Quality of life evolution after lung cancer surgery: a prospective study in 100 patients.** *Lung Cancer* 2007, **56**:423-431.
35. Poghosyan H, Sheldon LK, Leveille SG, Cooley ME: **Health-related quality of life after surgical treatment in patients with non-small cell lung cancer: a systematic review.** *Lung Cancer* 2013, **81**:11-26.
36. Martinez TY, Pereira CA, dos Santos ML, Ciconelli RM, Guimaraes SM, Martinez JA: **Evaluation of the short-form 36-item questionnaire to measure health-related quality of life in patients with idiopathic pulmonary fibrosis.** *Chest* 2000, **117**:1627-1632.
37. Mahler DA, Faryniarz K, Tomlinson D, Colice GL, Robins AG, Olmstead EM, O'Connor GT: **Impact of dyspnea and physiologic function on general health status in patients with chronic obstructive pulmonary disease.** *Chest* 1992, **102**:395-401.
38. Ruffin RE, Wilson DH, Chittleborough CR, Southcott AM, Smith B, Christopher DJ: **Multiple respiratory symptoms predict quality of life in chronic lung disease: a population-based study of Australian adults.** *Qual Life Res* 2000, **9**:1031-1039.
39. Avancini A, Sartori G, Gkoutakos A, Casali M, Trestini I, Tregnago D, Bria E, Jones LW, Milella M, Lanza M, Pilotto S: **Physical Activity and Exercise in Lung Cancer Care: Will Promises Be Fulfilled?** *The oncologist* 2020, **25**:e555-e569.
40. Codima A, das Neves Silva W, de Souza Borges AP, de Castro G, Jr.: **Exercise prescription for symptoms and quality of life improvements in lung cancer patients: a systematic review.** *Support Care Cancer* 2021, **29**:445-457.

Tables

Table 1 Clinical and surgical characteristics of the study participants

	Type of surgery				P value
	Overall (N=620)	Segmentectomy, Wedge resection (n=120, 19.4%)	Lobectomy (n=477, 76.9%)	Pneumonectomy, Bilobectomy (n=23, 3.7%)	
Characteristic					
Age, years	61.2 (9.0)	59.6 (9.2)	61.5 (9.0)	63.2 (7.8)	0.07
Sex, male	350 (56.5)	63 (52.5)	268 (56.2)	19 (82.6)	0.03
Body mass index, kg/m ²	24.0±2.9				
Smoking status, ever smoker	319 (51.5)	54 (45.0)	247 (51.8)	18 (78.3)	0.01
Comorbidities					
COPD ^a	140 (22.8)	26 (21.7)	106 (22.2)	8 (34.8)	0.22
Hypertension	211 (34.0)	31 (25.8)	170 (35.6)	10 (43.5)	0.08
Diabetes mellitus	92 (14.8)	14 (11.7)	73 (15.3)	5 (21.7)	0.39
Cardiovascular disease	16 (2.6)	4 (3.3)	12 (2.5)	0	0.64
Cell type, adenocarcinoma	513 (82.7)	111 (92.5)	394 (82.6)	8 (34.8)	<0.01
Pathologic stage					<0.01
I	451 (72.7)	116 (96.7)	330 (69.2)	5 (21.7)	
II	96 (15.5)	2 (1.7)	83 (17.4)	11 (47.8)	
III	70 (3.0)	2 (1.7)	62 (13.0)	6 (26.1)	
IV	3 (3.2)	0	2 (0.4)	1 (4.4)	
Surgical approach (VATS, %)	490 (79.0)	112 (93.3)	373 (78.2)	5 (21.7)	<0.01
PPC, yes	49 (7.9)	10 (8.3)	36 (7.6)	3 (13.0)	0.62
Adjuvant treatment, yes	149 (24.0)	3 (2.5)	131 (27.5)	15 (65.2)	<0.01

The values in the table are presented as mean ± standard deviation or n (%).

COPD, chronic obstructive pulmonary disease; *VATS*, video-assisted thoracic surgery; *PPC*, postoperative pulmonary complications.

^aCOPD is defined as a pre-bronchodilator FEV1/FVC < 70%.

Table 2 Changes in pulmonary function from baseline to 2 weeks, 6 months, and 1 year after surgery

	Before surgery	2 weeks after surgery	6 months after surgery	1 year after surgery
Overall				
FVC (mL)				
Adjusted mean (SE)	3600.3 (21.2)	2721.4 (21.5)	3137.7 (23.1)	3268.8 (24.8)
Change from baseline (95% CI) ^a	Reference	-879 (-910.3, -847.6)	-462.6 (-495.4, -429.8)	-331.6 (-365.4, -297.7)
FVC, % predicted				
Adjusted mean (SE)	93.2 (0.5)	70.9 (0.5)	81.6 (0.5)	85.2 (0.6)
Change from baseline (95% CI) ^a	Reference	-23.3 (-24.1, -22.5)	-12.3 (-13.2, -11.4)	-8.5 (-9.4, -7.6)
FEV ₁ (mL)				
Adjusted mean (SE)	2647 (16.7)	2033.1 (16.9)	2318.3 (17.9)	2395.2 (18.9)
Change from baseline (95% CI) ^a	Reference	-613.9 (-636.2, -591.6)	-328.7 (-352, -305.3)	-251.7 (-275.7, -227.8)
FEV ₁ , % predicted				
Adjusted mean (SE)	90.4 (0.5)	69.8 (0.5)	79.6 (0.6)	82.6 (0.6)
Change from baseline (95% CI) ^a	Reference	-20.6 (-21.3, -19.9)	-10.7 (-11.5, -10)	-7.8 (-8.6, -7)
DLco, % predicted				
Adjusted mean (SE)	90.5 (0.6)	79.2 (4.5)	77.5 (0.6)	78.3 (0.6)
Change from baseline (95% CI) ^a	Reference	-11.3 (-20.1, -2.4)	-13 (-14, -12)	-12.2 (-13.2, -11.2)
Type of surgery				
FVC (mL)				
Adjusted mean (SE)				
Segmentectomy, wedge resection	3648 (49.2)	2977.9 (50)	3403.6 (52.8)	3483.3 (56.4)
Lobectomy	3596.2 (24.2)	2678.7 (24.6)	3102.5 (26.3)	3242 (28.1)
Pneumonectomy,	3394.4	2198.8 (119.8)	2394.8	2624.3

bilobectomy	(116.5)		(125.6)	(136.5)
P values	0.15	< 0.01	< 0.01	< 0.01
Change from baseline (95% CI) ^a				
Segmentectomy, wedge resection	Reference	-670.1 (-739, -601.2)	-244.4 (-315.4, -173.4)	-164.7 (-237.9, -91.5)
Lobectomy	Reference	-917.4 (-952.1, -882.7)	-493.6 (-530.2, -457)	-354.2 (-391.8, -316.6)
Pneumonectomy, bilobectomy	Reference	-1195.6 (-1358.3, -1032.9)	-999.6 (-1165.9, -833.3)	-770.1 (-949.4, -590.8)
P for interaction		< 0.01	< 0.01	< 0.01
FVC, % predicted				
Adjusted mean (SE)				
Segmentectomy, wedge resection	93.4 (1.1)	76.4 (1.1)	87.1 (1.2)	89.3 (1.3)
Lobectomy	93.3 (0.5)	70 (0.5)	81 (0.6)	84.7 (0.6)
Pneumonectomy, bilobectomy	88.9 (2.6)	60.2 (2.7)	65.6 (2.8)	70.8 (3.1)
P values	0.25	< 0.01	< 0.01	< 0.01
Change from baseline (95% CI) ^a				
Segmentectomy, wedge resection	Reference	-17 (-18.6, -15.4)	-6.4 (-8.1, -4.7)	-4.1 (-5.9, -2.3)
Lobectomy	Reference	-23.3 (-24.1, -22.5)	-12.3 (-13.2, -11.4)	-8.5 (-9.4, -7.6)
Pneumonectomy, bilobectomy	Reference	-28.8 (-32.6, -24.9)	-23.3 (-27.3, -19.3)	-18.2 (-22.5, -13.9)
P for interaction		< 0.01	< 0.01	< 0.01
FEV ₁ (mL)				
Adjusted mean (SE)				
Segmentectomy, wedge resection	2677.9 (38.9)	2206.5 (39.4)	2485.5 (41.1)	2537.4 (43.4)
Lobectomy	2647.2 (19.1)	2004.8 (19.3)	2295.1 (20.4)	2376.9 (21.6)

Pneumonectomy, bilobectomy	2449.9 (92.1)	1669.6 (94.3)	1872.2 (97.9)	1981.1 (104.7)
P values	0.08	< 0.01	< 0.01	< 0.01
Change from baseline (95% CI) ^a				
Segmentectomy, Wedge resection	Reference	-471.3 (-520.9, -421.8)	-192.4 (-243.4, -141.4)	-140.5 (-192.8, -88.2)
Lobectomy	Reference	-642.4 (-667.4, -617.5)	-352.1 (-378.4, -325.8)	-270.3 (-297.2, -243.5)
Pneumonectomy, Bilobectomy	Reference	-780.3 (-897.4, -663.3)	-577.7 (-697.2, -458.2)	-468.8 (-596.9, -340.7)
P for interaction		< 0.01	< 0.01	< 0.01
FEV ₁ , % predicted				
Adjusted mean (SE)				
Segmentectomy, Wedge resection	90.3 (1.2)	74.8 (1.2)	84.2 (1.3)	86.3 (1.3)
Lobectomy	90.6 (0.6)	68.9 (0.6)	79 (0.6)	82.2 (0.7)
Pneumonectomy, Bilobectomy	85.2 (2.9)	61.3 (3)	66.8 (3)	70.8 (3.2)
P values	0.19	< 0.01	< 0.01	< 0.01
Change from baseline (95% CI) ^a				
Segmentectomy, Wedge resection	Reference	-15.5 (-17.1, -13.8)	-6 (-7.7, -4.3)	-4 (-5.8, -2.1)
Lobectomy	Reference	-21.7 (-22.6, -20.9)	-11.6 (-12.5, -10.7)	-8.4 (-9.4, -7.5)
Pneumonectomy, Bilobectomy	Reference	-24 (-27.8, -20.1)	-18.4 (-22.4, -14.5)	-14.4 (-18.9, -10)
P for interaction		< 0.01	< 0.01	< 0.01

^aAdjusted for age, sex, stage, obesity, smoking status, cell type, type of surgery, video-assisted thoracic surgery, postoperative pulmonary complications, and adjuvant treatment.

CI, confidence interval; DLco, diffusing lung capacity of the lung for carbon monoxide; FEV₁, forced expiratory volume in 1 s; FVC, forced expiratory vital capacity; SE, standard error

Table 3 Changes in patient reported outcome from baseline to 2 weeks, 6 months, and 1 year after surgery

	Before surgery	2 weeks after surgery	6 months after surgery	1 year after surgery
Overall				
mMRC dyspnea scale				
Adjusted mean (SE)	0.25 (0.03)	1.05 (0.03)	0.53 (0.03)	0.42 (0.03)
Change from baseline (95% CI) ^a	Reference	0.81 (0.74, 0.88)	0.28 (0.21, 0.36)	0.17 (0.1, 0.24)
CAT total score				
Adjusted mean (SE)	5.97 (0.23)	12.77 (0.24)	7.29 (0.25)	6.22 (0.25)
Change from baseline (95% CI) ^a	Reference	6.79 (6.3, 7.29)	1.32 (0.8, 1.84)	0.24 (-0.29, 0.77)
Type of surgery				
mMRC				
Adjusted mean (SE)				
Lobectomy	0.24 (0.03)	1.09 (0.03)	0.55 (0.03)	0.42 (0.03)
Pneumonectomy, Bilobectomy	0.13 (0.14)	1.44 (0.15)	0.83 (0.16)	0.65 (0.17)
Segmentectomy, Wedge resection	0.27 (0.06)	0.82 (0.06)	0.36 (0.07)	0.34 (0.07)
P values	0.67	< 0.01	< 0.01	0.22
Change from baseline (95% CI) ^a				
Lobectomy	Reference	0.85 (0.76, 0.93)	0.3 (0.22, 0.39)	0.17 (0.09, 0.26)
Pneumonectomy, Bilobectomy	Reference	1.31 (0.95, 1.67)	0.78 (0.41, 1.16)	0.52 (0.13, 0.91)
Segmentectomy, Wedge resection	Reference	0.55 (0.39, 0.71)	0.1 (-0.06, 0.26)	0.07 (-0.09, 0.24)
P for interaction		< 0.01	< 0.01	0.11
CAT total score				
Adjusted mean (SE)				
Lobectomy	5.83	13.09 (0.28)	7.42 (0.28)	6.28 (0.27)

(0.27)

Pneumonectomy, Bilobectomy	8.48 (1.27)	12.55 (1.3)	8.75 (1.34)	6.96 (1.31)
Segmentectomy, Wedge resection	6.08 (0.54)	11.61 (0.55)	6.55 (0.55)	5.78 (0.54)
P values	0.12	0.02	0.12	0.2
Change from baseline (95% CI) ^a				
Lobectomy	Reference	7.26 (6.69, 7.83)	1.59 (1, 2.18)	0.45 (-0.15, 1.05)
Pneumonectomy, Bilobectomy	Reference	4.07 (1.53, 6.61)	0.27 (-2.46, 3.00)	-1.52 (-4.31, 1.27)
Segmentectomy, Wedge resection	Reference	5.54 (4.43, 6.64)	0.47 (-0.67, 1.61)	-0.3 (-1.48, 0.89)
P for interaction		< 0.01	0.17	0.25

^aAdjusted for age, sex, stage, obesity, smoking status, cell type, type of surgery, video-assisted thoracic surgery, postoperative pulmonary complications, and adjuvant treatment.

CAT, chronic obstructive pulmonary disease assessment test; *CI*, confidence interval; *mMRC dyspnea scale*, modified Medical Research Council dyspnea scale; *SE*, standard error

Table 4 Change in COPD assessment test from baseline to 2 weeks, 6 months, and 1 year after surgery

	Before surgery	2 weeks after surgery	6 months after surgery	1 year after surgery
Cough frequency				
Adjusted mean (SE)	0.82 (0.05)	2 (0.05)	0.96 (0.06)	0.68 (0.06)
Change from baseline (95% CI) ^a	Reference	1.18 (1.05, 1.31)	0.15 (0.01, 0.28)	-0.14 (-0.27, 0.00)
Amount of phlegm				
Adjusted mean (SE)	0.83 (0.05)	0.89 (0.05)	0.77 (0.05)	0.67 (0.05)
Change from baseline (95% CI) ^a	Reference	0.05 (-0.06, 0.16)	-0.06 (-0.18, 0.05)	-0.16 (-0.27, -0.04)
Chest tightness				
Adjusted mean (SE)	0.5 (0.05)	1.3 (0.05)	0.5 (0.05)	0.47 (0.05)
Change from baseline (95% CI) ^a	Reference	0.8 (0.68, 0.91)	-0.01 (-0.12, 0.11)	-0.04 (-0.15, 0.08)
Breathlessness walking upstairs				
Adjusted mean (SE)	1.28 (0.06)	2.85 (0.06)	1.97 (0.06)	1.79 (0.07)
Change from baseline (95% CI) ^a	Reference	1.57 (1.43, 1.71)	0.7 (0.55, 0.84)	0.52 (0.37, 0.66)
Home activities limited				
Adjusted mean (SE)	0.05 (0.03)	0.64 (0.03)	0.16 (0.04)	0.1 (0.04)
Change from baseline (95% CI) ^a	Reference	0.59 (0.51, 0.68)	0.12 (0.03, 0.21)	0.06 (-0.04, 0.15)
Not confident leaving home				
Adjusted mean (SE)	0.08 (0.04)	1.26 (0.04)	0.23 (0.05)	0.15 (0.05)
Change from baseline (95% CI) ^a	Reference	1.19 (1.07, 1.3)	0.16 (0.04, 0.28)	0.08 (-0.04, 0.2)
Sleep disturbance				
Adjusted mean (SE)	0.96 (0.06)	1.56 (0.07)	0.86 (0.07)	0.86 (0.07)
Change from baseline (95% CI) ^a	Reference	0.6 (0.44, 0.75)	-0.1 (-0.26, 0.06)	-0.42 (-0.58, -0.25)
Lack of energy				

Adjusted mean (SE)	1.49 (0.06)	2.5 (0.06)	1.84 (0.06)	1.8 (0.06)
Change from baseline (95% CI) ^a	Reference	1 (0.87, 1.14)	0.35 (0.21, 0.49)	0.31 (0.17, 0.46)

^aAdjusted for age, sex, stage, obesity, smoking status, cell type, type of surgery, video-assisted thoracic surgery, postoperative pulmonary complications, and adjuvant treatment.

COPD, Chronic obstructive pulmonary disease; *CI*, confidence interval; *SE*, standard error.

Figures

Figure 1

Change in pulmonary function and patient reported outcomes by postoperative time CAT, Chronic obstructive pulmonary disease assessment test; FEV₁, forced expiratory volume in 1 s; FVC, forced expiratory vital capacity; mMRC dyspnea scale, modified Medical Research Council dyspnea scale.

Figure 2

Change in pulmonary function and patient reported outcomes by type of surgery and postoperative time CAT, Chronic obstructive pulmonary disease assessment test; FEV₁, forced expiratory volume in 1 s; FVC, forced expiratory vital capacity; mMRC dyspnea scale, modified Medical Research Council dyspnea scale

**P* for interaction (*P* < 0.01) between type of surgery (reference: lobectomy) and time after adjustment for age, sex, smoking status, obesity, stage, cell type, type of surgery, video-assisted thoracic surgery, postoperative pulmonary complications, and adjuvant treatment.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supplementarytable.docx](#)