Pulmonary Function Changes Over 1 Year After Lobectomy in Lung Cancer

Hyun Koo Kim MD PhD, Yoo Jin Lee MSc, Kook Nam Han MD PhD, and Young Ho Choi MD PhD

BACKGROUND: This study was conducted to measure the serial changes in pulmonary function over 12 months after lobectomy in subjects with lung cancer and to evaluate the actual recovery of pulmonary function in comparison with the predicted postoperative values. METHODS: Subjects who underwent lobectomy for primary lung cancer were included in this study. In the statistical analysis, we included data from 76 subjects (52 men and 24 women; mean age, 63.4 y) who completed perfusion scintigraphy 1 week before surgery and FEV_1 and diffusion capacity of the lung for carbon monoxide (D_{LCO}) assessments preoperatively and at 1, 6, and 12 months postoperatively. RESULTS: The actual percent-of-predicted FEV_1 1 month postoperatively was 77.9% of the preoperative value, which was almost equal to the predicted postoperative value, and significantly increased to 84.3% by 6 months and 84.2% at 12 months. The actual percent-of-predicted D_{LCO} 1 month postoperatively was 81.8% of the preoperative value, which was similar to the predicted postoperative value, and also significantly increased to 91.3% at 6 months and 96.5% at 12 months. However, the actual pulmonary function test results at 1 y in subjects with COPD or in those who underwent thoracotomy or received adjuvant chemotherapy were not different from the predicted postoperative values. CONCLUSIONS: Actual pulmonary function compared with predicted postoperative values improved over time over 1 y after lobectomy. However, this improvement was not observed in subjects with COPD or in those who underwent thoracotomy or received postoperative adjuvant chemotherapy. *Key words: pulmonary function; lobectomy; lung cancer.* [Respir Care 2016;61(3):376–382. © 2016 Daedalus Enterprises]

Introduction

Lung cancer is one of the most common malignancies and is one of the leading causes of death worldwide.[1] Surgical resection has been regarded as the best treatment for controlling stage I, stage II, and part of stage III_A non-small-cell lung cancer. However, in some subjects with early stage non-small-cell lung cancer, poor respiratory function may interfere with surgery because of the increased risk for perioperative morbidity and mortality and the possibility of long-term postoperative disability secondary to respiratory insufficiency.[2] Baser et al[3] reported that 37% of subjects who had anatomically resectable lung cancers were excluded from surgical resection only because of poor lung function. Therefore, predicting postoperative pulmonary function, particularly FEV_1 and the diffusion capacity of the lung for carbon monoxide

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This research was supported by Ministry of Education, Science, and Technology Grant 20120003904; the National Research Foundation of Korea (NRF) grant, funded by the Korean government (MEST) (Grant 2012012166); and the Korean Health Technology R&D Project, Ministry of Health and Welfare, Republic of Korea (Grant A121074). The authors have disclosed no conflicts of interest.

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DOI: 10.4187/respcare.04284

(D_{LCO}), plays an important role in determining candidates for surgical resection and the extent of resection.[4]

A number of related studies have been conducted to predict pulmonary function after surgery.[5] However, reaching a definitive conclusion about predicting postoperative pulmonary function was difficult in most of these studies because they were based on small samples and short monitoring periods (3 or 6 months at the longest).[6-8] Furthermore, surgical techniques and postoperative care have steadily improved since these studies were performed.

Recently, the authors showed that actual pulmonary function results at approximately 1 month after surgery were similar to predicted postoperative pulmonary function values.[9] In addition, Brunelli et al[10] performed a prospective study of a large sample (>200 subjects) and found that actual postoperative lung function reached predicted postoperative values at 1 month after surgery and showed further improvement at 3 months after surgery. Based on these studies, we aimed to evaluate whether pulmonary function would continue to improve during the long-term follow-up after operation, and in the present study, we monitored the changes in actual postoperative lung function over 1 y after lobectomy in subjects with lung cancer and evaluated the degree of actual recovery compared with predicted postoperative values. In addition, we analyzed differences in the results according to factors including the presence or absence of COPD, surgical method (video-assisted thoracoscopic surgery [VATS] vs thoracotomy), and the use of adjuvant chemotherapy after operation.

QUICK LOOK

Current knowledge

Lung cancer is one of the most common malignancies and a leading cause of death worldwide. Surgical resection is the standard of care in non-small-cell lung cancer. Poor respiratory function may preclude surgery in select patients due to the increased risk for perioperative morbidity and mortality. Long-term postoperative disability secondary to respiratory failure represents a significant cost burden.

What this paper contributes to our knowledge

Actual pulmonary function compared with predicted postoperative values improved 1 y after lobectomy. This improvement was not observed in subjects with COPD, in those who underwent thoracotomy, or those who received postoperative adjuvant chemotherapy.

Methods

Subjects who underwent lobectomy for primary lung cancer from April 2009 through January 2012 at Korea University Guro Hospital were included in this study. Subject data were prospectively collected and were analyzed. Exclusionary criteria included cancer with chest wall invasion, endobronchial cancer with post-obstructive pneumonitis, and subjects who underwent neoadjuvant chemotherapy. Patients who had any major complications or required ventilatory support that interfered with assessment of pulmonary function in the postoperative period were also excluded. This study was approved by the Ethics Committee of Korea University Guro Hospital (KUGH 2014-01-0004), and written informed consent was obtained from all subjects, in accordance with the Declaration of Helsinki.

Subjects underwent pulmonary function tests and perfusion scintigraphy within 1 week before surgery and postoperative pulmonary function tests at 1, 6, and 12 months after surgery. The pulmonary function tests were performed according to the published guidelines using a spirometer (Vmax22, SensorMedics, Yorba Linda, California).[11] The D_{LCO} was measured using the single-breath method. Spirometry and D_{LCO} results were collected after bronchodilator administration and are expressed as percentages of age, sex, and height of the subject according to the European Community for Steel and Coal prediction equations.[12]

The preoperative radionuclide quantitative lung perfusion scans were performed in all subjects with an Infinia multidetector system (GE Medical Systems, Haifa, Israel) to estimate the predicted postoperative values, as described by Ali,[13], which was our routine procedure until January 2009: (1) postoperative percent-of-predicted FEV_1 = preoperative percent-of-predicted $FEV_1 \times (100\% -$ projected percentage loss of lung function) and (2) postoperative percent-of-predicted D_{LCO} = preoperative percent-of-predicted $D_{LCO} \times (100\% -$ projected percentage loss of lung function).

Statistics

The descriptive statistics of FEV_1 and D_{LCO} measurements are presented as the mean and SD. We used paired and independent *t* tests to compare groups with normally distributed data and the Wilcoxon signed-rank test and Mann-Whitney test for non-normal data. Data analysis was performed with SPSS 20 (SPSS, Chicago, Illinois).

Results

A total of 76 subjects (52 men and 24 women) who completed FEV_1 and D_{LCO} assessments preoperatively and at 1, 6, and 12 months postoperatively were included in the statistical analysis.

The characteristics of these subjects are shown in Table 1. The mean age of the subjects was 63.4 ± 8.98 y (range, 43–80 y). The average FEV_1/FVC ratio was 0.72 ± 0.10. Seven subjects (9.2%) had COPD, 46 (60.5%) underwent resection via VATS, and 22 (29%) received adjuvant chemotherapy after surgery. The pathology was adenocarcinoma in 38 subjects (50%), squamous cell carcinoma in 30 subjects (39.5%), and other in 8 subjects (10.5%). At clinical staging, all subjects appeared node-negative; the pathologic stages were N0 in 62 subjects, N1 in 7, and N2 in 7.

Preoperative and predicted and actual postoperative values at each time point in subjects with complete follow-up data are shown in Table 2 and Figure 1. At 1, 6, and 12 months after operation, actual percent-of-predicted FEV_1 values were 77.9, 84.3, and 84.2%, respectively, of the preoperative values. The actual percent-of-predicted FEV_1 was almost equal to the predicted postoperative value at 1 month and increased at 6 months ($P = .03$) but showed no further increase at 12 months. Actual postoperative percent-of-predicted D_{LCO} values were 81.8, 91.3, and 96.5% of the preoperative values at 1, 6, and 12 months, respectively. The actual percent-of-predicted D_{LCO} was similar to the predicted postoperative value at 1 month and increased at 6 months ($P = .01$). Compared with the percent-of-predicted FEV_1, the actual percent-of-predicted D_{LCO} showed a greater increase and approximated the preoperative value at 1 y after operation.

Figure 2 shows the comparative pulmonary function data according to the presence (7 subjects) or absence (69 subjects) of COPD. Significant improvements were observed in percent-of-predicted FEV_1 ($P = .02$) and percent-of-predicted D_{LCO} ($P < .01$) between 1 and 6 months after operation in non-COPD subjects. However, no significant recovery of pulmonary function was observed over the entire period in those with COPD. Significant differences in preoperative and predicted postoperative percent-of-predicted FEV_1 values between the 2 groups did not reduce during the 1-y follow-up after operation. On the other hand, from 6 months after operation, the actual percent-of-predicted D_{LCO} showed a dramatic improvement in non-COPD subjects compared with those with COPD.

Figure 3 shows comparative pulmonary function data according to the type of surgery (VATS in 46 subjects vs thoracotomy in 30). Significant improvements were observed in percent-of-predicted FEV_1 ($P = .02$) and percent-of-predicted D_{LCO} ($P = .01$) between 1 and 6 months after operation in subjects who underwent VATS. However, no significant improvement was observed over the

Table 1. Subject Characteristics

Variables	Values
Male/female, *n*	52/24
Age, mean ± SD y	63.4 ± 8.98
FEV_1/FVC, mean ± SD	0.72 ± 0.10
Pathology, *n* (%)	
Adenocarcinoma	38 (50.0%)
Squamous cell carcinoma	30 (39.5%)
Other	8 (10.5%)
Presence of COPD, *n* (%)	7 (9.2%)
Type of surgery, *n* (%)	
VATS	46 (60.5%)
Thoracotomy	30 (39.5%)
Adjuvant chemotherapy, *n* (%)	22 (29.0%)

VATS = video-assisted thoracoscopic surgery

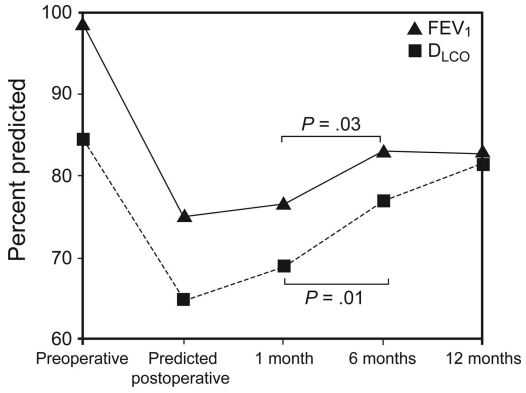

Fig. 1. Time-series graphs showing the actual postoperative percent-of-predicted FEV_1 and percent-of-predicted diffusion capacity of the lung for carbon monoxide (D_{LCO}) values at each postoperative time point relative to the preoperative and predicted postoperative values. The actual percent-of-predicted FEV_1 ($P = .03$) and percent-of-predicted D_{LCO} ($P = .01$) values significantly increased between 1 and 6 months postoperatively.

Table 2. Preoperative, Predicted Postoperative, and Actual FEV_1 and D_{LCO} Values

Variables	Preoperative	Predicted Postoperative	Actual 1-Month Postoperative	Actual 6-Month Postoperative	Actual 12-Month Postoperative
FEV_1, L	2.30 ± 0.56	1.80 ± 0.48 (76.1)	1.80 ± 0.48 (77.4)	2.00 ± 0.52 (83.3)	2.00 ± 0.51 (84.6)
FEV_1, % predicted	98.50 ± 17.76	74.98 ± 14.53 (76.0)	76.70 ± 16.46 (77.9)	83.00 ± 20.18 (84.3)	82.90 ± 18.80 (84.2)
D_{LCO}, mL/min/mm Hg	14.20 ± 4.30	10.90 ± 3.34 (76.8)	11.50 ± 3.12 (80.8)	12.80 ± 4.48 (90.0)	13.60 ± 4.35 (95.6)
D_{LCO}, %	84.40 ± 9.72	64.80 ± 14.04 (76.7)	69.00 ± 16.13 (81.8)	77.00 ± 21.98 (91.3)	81.40 ± 20.14 (96.5)

Data are expressed as mean ± SD (% of preoperative value).
D_{LCO} = diffusion capacity of the lung for carbon monoxide

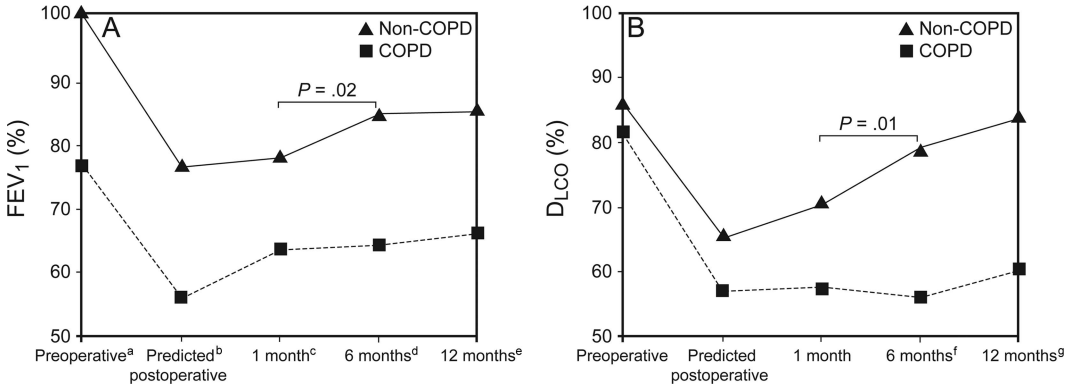

Fig. 2. A: Time-series graphs showing the actual postoperative percent-of-predicted FEV_1 values at each postoperative time point relative to the preoperative and predicted postoperative percent-of-predicted FEV_1 values in subjects with and without COPD. The actual percent-of-predicted FEV_1 values significantly increased between 1 and 6 months postoperatively only in subjects without COPD ($P = .02$). The preoperative, predicted postoperative, and actual postoperative percent-of-predicted FEV_1 values at all time points were significantly higher in subjects without COPD than in the COPD group (a, $P = .02$; b, $P = .02$; c, $P = .02$; d, $P = .01$; e, $P = .01$). B: Time-series graphs showing the actual percent-of-predicted diffusion capacity of the lung for carbon monoxide (D_{LCO}) values at each postoperative time point relative to the preoperative and predicted postoperative percent-of-predicted D_{LCO} values in subjects with and without COPD. The actual percent-of-predicted D_{LCO} values significantly increased between 1 and 6 months postoperatively only in subjects without COPD ($P < .01$). The actual postoperative percent-of-predicted D_{LCO} values at 6 and 12 months were significantly higher in subjects without COPD than in those with COPD (f, $P < .001$; g, $P < .001$).

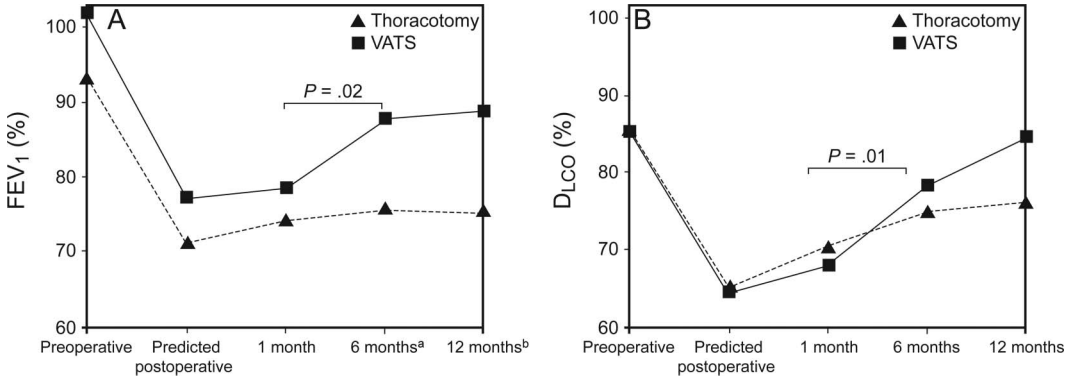

Fig. 3. A: Time-series graphs showing the actual percent-of-predicted FEV_1 values at each postoperative time point relative to the preoperative and predicted postoperative percent-of-predicted FEV_1 values in subjects who underwent video-assisted thoracoscopic surgery (VATS) versus open thoracotomy. The actual percent-of-predicted FEV_1 values significantly increased between 1 and 6 months postoperatively only in subjects who underwent VATS ($P = .02$). The actual postoperative percent-of-predicted FEV_1 values at 6 and 12 months were significantly higher in those who underwent VATS compared with the thoracotomy group (a, $P < .01$; b, $P < .01$). B: Time-series graphs showing the actual postoperative percent-of-predicted diffusion capacity of the lung for carbon monoxide (D_{LCO}) values at each time point relative to the preoperative and predicted postoperative percent-of-predicted D_{LCO} values in subjects who underwent VATS versus open thoracotomy. The actual percent-of-predicted D_{LCO} values significantly increased between 1 and 6 months postoperatively only in subjects who underwent VATS ($P = .01$), but overall, the percent-of-predicted D_{LCO} values were not significantly different between the 2 groups.

entire period in the thoracotomy group. From 6 months after operation, the actual percent-of-predicted FEV_1 showed significant improvement after VATS versus thoracotomy, although the actual percent-of-predicted D_{LCO} showed no difference between the 2 groups during the 1-y follow-up after operation.

Figure 4 shows the comparative pulmonary function data between subjects receiving adjuvant chemotherapy (22 subjects) or not (54 subjects). Significant improvements were observed in percent-of-predicted FEV_1 ($P = .02$) and percent-of-predicted D_{LCO} ($P = .02$) between 1 and 6 months after operation in the non-adjuvant group. However, no significant improvement was observed over the entire period in the adjuvant group. From 6 months after operation, the actual percent-of-predicted FEV_1 showed significant improvement in the non-adjuvant group compared with the adjuvant group, and the actual percent-of-predicted D_{LCO} showed significant improvement in the non-adjuvant group compared with the adjuvant group at 1 y after operation.

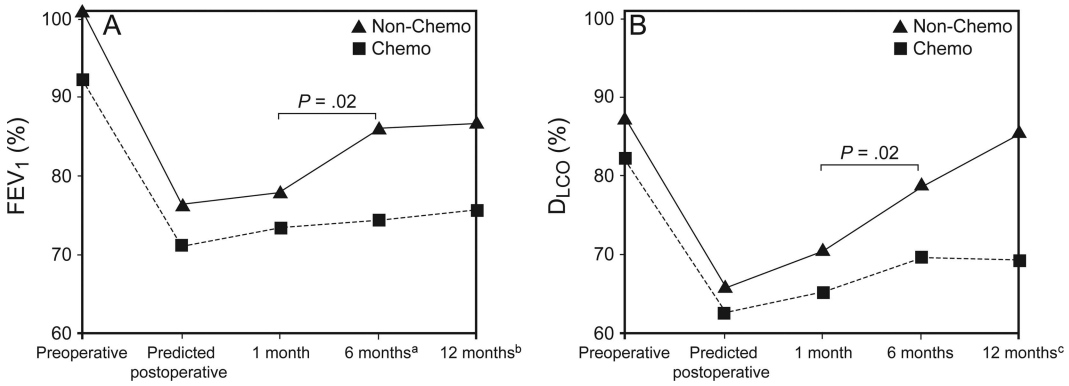

Fig. 4. A: Time-series graphs showing the actual postoperative percent-of-predicted FEV_1 values at each time point relative to the preoperative and predicted postoperative percent-of-predicted FEV_1 values in subjects who underwent adjuvant chemotherapy versus those who did not. The actual percent-of-predicted FEV_1 increased significantly between 1 and 6 months postoperatively only in the non-chemotherapy group ($P = .02$). The actual postoperative percent-of-predicted FEV_1 values at 6 and 12 months were significantly higher in the non-chemotherapy group than in the chemotherapy group (a, $P = .02$; b, $P = .02$). B: time-series graphs showing the actual postoperative percent-of-predicted diffusion capacity of the lung for carbon monoxide (D_{LCO}) values at each time point relative to the preoperative and predicted postoperative percent-of-predicted D_{LCO} values in subjects receiving and not receiving chemotherapy. The actual percent-of-predicted D_{LCO} values significantly increased between 1 and 6 months postoperatively only in the non-chemotherapy group ($P = .02$). The actual postoperative percent-of-predicted D_{LCO} value at 12 months was significantly higher in the non-chemotherapy group versus the chemotherapy group (c, $P < .01$).

Discussion

Predicted postoperative pulmonary function in patients undergoing major pulmonary resection for lung cancer plays an important role in determining operability and predicting quality of life after surgery. In particular, FEV_1 and D_{LCO} are useful predictors of postoperative mortality and complications.[14,15] In a previous study,[9] we showed that predicted postoperative pulmonary function was similar to the actual postoperative value at 1 month after surgery, and Brunelli et al[10] demonstrated that actual postoperative lung function improved to an even greater extent at 3 months after surgery. Based on these findings, we wanted to know how much and for how long pulmonary function would continue to be recovered after major pulmonary resection in lung cancer patients.

In the present study, we found that actual percent-of-predicted FEV_1 was similar to the predicted value at 1 month after surgery, significantly increased to 1.11 times the predicted postoperative value at 6 months after surgery, and remained at approximately the same level (84.0% of the preoperative value) until 12 months after surgery. The actual percent-of-predicted D_{LCO} was not different from the predicted value at 1 month after surgery but significantly increased to 1.19 times the predicted postoperative value at 6 months and eventually reached 1.26 times the predicted postoperative value by 12 months (97.2% of the preoperative value). These results indicate that the postoperative percent-of-predicted D_{LCO} exhibits greater recovery compared with FEV_1, which is similar to the findings reported by Brunelli et al.[10] This finding may be explained by pulmonary vascular and hemodynamic compensatory mechanisms.[16]

Several authors have reported that the percent-of-predicted FEV_1 in COPD subjects was decreased to a lesser extent or even improved after surgical resection compared with the percent-of-predicted FEV_1 in non-COPD subjects,[17-19] and the difference was more prominent at the early phase (1–3 months) after surgery.[10,20] This might be attributed to the similar effect of lung volume reduction surgery for subjects with bullous emphysema. Further, it has also been noted that the actual postoperative percent-of-predicted D_{LCO} in subjects with COPD shows a marked increase with improvement of the ventilation/perfusion ratio.[17-19] In the present study, the actual percent-of-predicted FEV_1 had a tendency to exceed the predicted postoperative value in subjects with COPD (1.13 times the predicted postoperative value) at 1 month after surgery ($P = .06$), but these values did not increase thereafter; meanwhile, the actual percent-of-predicted D_{LCO} in COPD subjects showed no improvement, reaching only 73.5% of the preoperative value (1.05 times the predicted postoperative value) at 1 y after surgery. This inconsistency with the previous results may be due to the small number of COPD subjects ($n = 7$) in our study. On the other hand, the actual percent-of-predicted FEV_1 in the non-COPD group was similar to the predicted postoperative value (1.01 times the predicted postoperative value) at 1 month after surgery, significantly increased to 1.11 times the predicted postoperative value at 6 months, and remained at approximately the same level at 12 months (85.1% of the preoperative value). The actual percent-of-predicted D_{LCO}

also showed continuous improvement in non-COPD subjects after surgery and reached 97% of the preoperative value (1.27 times the predicted postoperative value).

VATS is associated with faster recovery of pulmonary function after surgery because of its reduced invasiveness, which reduces postoperative pain, impairment of respiratory muscles, and damage to the thoracic wall.[21-25] In the present study, the recovery of actual pulmonary function after VATS was not different from that after thoracotomy at 1 month after operation. However, the actual percent-of-predicted FEV_1 in the VATS group significantly increased at 6 months after operation to 1.14 times the predicted postoperative value and eventually reached 89.0% of the preoperative value at 12 months (1.20 times the predicted postoperative value), whereas it did not increase significantly in the thoracotomy group. Although there were no significant differences overall in the percent-of-predicted D_{LCO} values between the 2 groups, the actual percent-of-predicted D_{LCO} in the VATS group had recovered significantly to 91.8% of the preoperative value (1.22 times the predicted postoperative value) at 6 months and continued to increase to 99.2% of the preoperative value (1.32 times the predicted postoperative value) at 12 months, whereas there was no significant improvement of the actual percent-of-predicted D_{LCO} observed in the thoracotomy subjects (82.2% of the preoperative value at 1 month to 89.1% at 12 months).

Adjuvant chemotherapeutic agents for non-small-cell lung cancer are known to have various adverse effects, including dyspnea, cough, wheezing, chest tightness, and hypersensitivity reaction.[14,26,27] Approximately 10% of subjects who receive chemotherapy exhibit pulmonary toxicity, which mainly manifests as a parenchymal lung injury, such as pneumonitis or interstitial lung disease.[14,15,26,28,29] This toxicity might present as airway or pleural disease or in various other ways.[15,29] Therefore, adjuvant chemotherapy after major lung resection can affect the recovery of pulmonary function. In the present study, the actual percent-of-predicted FEV_1 significantly increased to 85.9% of the preoperative value (1.11 times the predicted postoperative value) at 12 months in subjects who did not receive adjuvant chemotherapy, whereas the increase was not significant in the adjuvant group (79.0% of the preoperative value at 1 month to 81.9% at 12 months). The actual percent-of-predicted D_{LCO} in the non-adjuvant group showed a marked recovery to 98.4% of the preoperative value (1.29 times the predicted postoperative value) at 12 months, whereas no significant improvement of the actual percent-of-predicted D_{LCO} was observed in the adjuvant group (79.6% at 1 month to 83.9% at 12 months). This result demonstrates the negative effect of adjuvant chemotherapy on pulmonary function recovery after operation and is compatible with the findings of previous studies. This study had limitations, including the small number of subjects and the uneven distribution for subgroup analysis, especially for the presence of COPD.

Conclusions

In conclusion, the actual pulmonary function after surgery improved above the level of the predicted postoperative values for 1 y. The postoperative predicted values are an underestimate of the actual lung function recovery over a period of 1 y. This has clinical implications because this underestimation may lead to curative resection being withheld in marginal candidates. Therefore, the systematic use of exercise testing should be considered.[16] However, this improvement was not observed in subjects with COPD, subjects who underwent thoracotomy, or those who received postoperative adjuvant chemotherapy. The result of this study should be useful for the determination of surgical candidates, of the extent of resection, and of the strategy of postoperative pulmonary care.

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