Recovery of Respiratory Muscle, Physical Functions, and Dyspnea After Lobectomy for Lung Cancer

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Research Article

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Abstract

Purpose: To characterize respiratory muscle strength, physical functions, and dyspnea in patients receiving pulmonary rehabilitation following lobectomy for non-small cell lung cancer.

Methods: This retrospective study included non-small cell lung cancer patients who underwent lobectomy via video-assisted thoracoscopic surgery or posterolateral thoracotomy and pulmonary rehabilitation between September 2013 and March 2018. Maximum mouth inspiratory and expiratory pressures, 6-minute walking distance, quadriceps force, and modified Medical Research Council dyspnea scale score were evaluated before surgery, at discharge, and at post-lobectomy months 1 and 3.

Results: Data from 41 eligible patients were analyzed. At discharge, maximum mouth inspiratory and expiratory pressures, 6-minute walking distance, and modified Medical Research Council dyspnea scale score were lower than pre-operative values, but quadriceps force was unchanged. The maximum mouth inspiratory pressure and 6-minute walking distance returned to pre-operative values at post-lobectomy month 1, and maximum expiratory pressure and modified Medical Research Council dyspnea scale score improved at month 3. During sub-analysis, maximum mouth inspiratory pressure and modified Medical Research Council dyspnea scale score after video-assisted thoracoscopic surgery (n = 24) improved to pre-operative levels at post-lobectomy month 1, whereas patients in the posterolateral thoracotomy group (n = 17), it improved at 3 months.

Conclusions: After lobectomy for non-small cell lung cancer, patients undergoing pulmonary rehabilitation had their respiratory muscle strength, physical functions, and dyspnea improve to pre-operative levels at post-lobectomy month 3. Moreover, video-assisted thoracoscopic surgery may be more beneficial than posterolateral thoracotomy in the early post-operative recovery of inspiratory muscle strength and dyspnea.

Introduction

Lung resection is the standard treatment for patients with stage I or II non-small cell lung cancer (NSCLC). In Japan, the 5-year survival rate after lung cancer surgery increased from 62% in 1999 to 70% in 2004 [1]. Recently, apart from survival, there has been an increased interest in additional outcomes for patients undergoing lung resection and, as a result, “enhanced recovery after surgery” pathways are recommended for perioperative management in order to reduce complications, length of hospital stay (LOS), and treatment costs [2]. These pathways are composed of various care elements, including a strong recommendation for pulmonary rehabilitation (PR) [2].

A recent systematic review reported that pre-operative PR enhanced pulmonary function before surgery and reduced LOS and post-operative complications in patients undergoing lung resection [3]. On the other hand, patients perceive physical debility as an extremely undesirable outcome after lung resection [4], and the essential elements of physical debility include reduced exercise capacity and quadriceps force (QF), as well as dyspnea. Previous studies have found PR in patients with NSCLC initiated day 1 after lung

resection improved exercise capacity and QF to preoperative levels at 4–12 weeks [5, 6]. Moreover, respiratory muscle strength at 2 weeks after lung resection was also comparable to pre-operative levels for patients undergoing PR [7]. Studies have included various lung resection techniques such as wedge resection, segmentectomy, lobectomy, and pneumonectomy, and both post-operative pulmonary function and exercise capacity are remarkably affected by the amount of lung tissue removed [8, 9]. In order to optimize the effectiveness of PR, we need to investigate the post-operative changes in physical debility for each specific lung resection technique.

However, it remains unclear how the essential factors associated with physical debility change post-lobectomy, which is the standard treatment for an operable NSCLC, when PR is provided. The aim of the present study was, therefore, to characterize the recovery of respiratory muscle strength, physical functions, and dyspnea post-lobectomy via video-assisted thoracoscopic surgery (VATS) or posterolateral thoracotomy (PLT) in NSCLC patients undergoing pre- and post-operative PR.

Materials And Methods

Patients

Patients with clinical stage I or II NSCLC who underwent lobectomy via VATS or PLT between September 2013 and March 2018 in Tokai University Oiso Hospital were selected. They commenced supervised PR 1 week before lobectomy as standard care. Exclusion criteria included physical or mental disorders adversely influencing physical performance, post-operative death, dropping out before completing PR, radiation therapy, and a lack of PR data. The Institutional Review Board for clinical research at Tokai University approved this retrospective study (Approval Number: 17R389), and individual informed consent was waived.

Pulmonary rehabilitation

All patients received supervised PR from 1 week before lobectomy to 3 months after lobectomy (Fig. 1). The patients were instructed to perform deep inspiration using a Coach 2® Incentive Spirometer (Smith Medical Japan, Tokyo, Japan) in breathing exercises along with coughing/huffing techniques and early mobilization; patients sat out of bed and ambulated from day 1 post-lobectomy. Patients were monitored with an electrocardiographic monitor during PR, and the intensity of exercise training was graded 3–5 on a 0–10 modified Borg exertion scale.

Surgical procedure

Lobectomy was performed in the lateral position either by VATS using the two-port approach or standard PLT. The choice of lobectomy procedure was determined by the surgeon after considering the anatomy (that is, adhesions or tumor size/location), lymph nodes, and vascular health of the individual patient. In the VATS procedure, two skin incisions were made in the fourth intercostal space [10]; one was placed 3 cm posteriorly and the other 3 cm anteriorly to the inferior angle of the scapula. In the PLT procedure, a

15–20 cm incision was made on the posterolateral side of the trunk. The latissimus dorsi muscle was divided while the serratus anterior muscle was preserved.

For post-operative pain management, continuous thoracic epidural infusion of fentanyl was administered to each patient until removal of the chest drainage tube, and non-steroid anti-inflammatory drugs were used as needed thereafter.

Measurements

For patients undergoing lobectomy, the following data were routinely assessed the day before lobectomy, at discharge from the hospital, and 1 month and 3 months post-lobectomy, as the clinical outcomes of PR: forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) measured using an Autospiro AS-507 spirometer (Minato Medical Science, Tokyo, Japan) to assess the pulmonary function [11]; inspiratory and expiratory muscle strength, maximal mouth inspiratory pressure (Pimax) and expiratory pressure (Pemax) also measured using an Autospiro AS-507 spirometer [12]; and QF measured using a hand-held dynamometer (Power Track II; Nihon Medix, Chiba, Japan) [13] while patients were instructed to perform maximal isometric voluntary contraction of the right and left quadriceps at the sitting. The QF values of the right and left sides were averaged and expressed relative to the bodyweight. Additionally, 6-minute walk distance (6MWD) was measured based on the published guideline as exercise capacity [14] and dyspnea was assessed with the modified Medical Research Council (mMRC) dyspnea scale [15].

Data were collected from the medical records. The predicted values of pulmonary function, respiratory muscle strength, and 6MWD were taken from the Japanese Respiratory Society [16], the American Thoracic Society/European Respiratory Society statement [12], and the previous study of Enright PL, *et al.* [17], respectively.

Statistical analysis

The data were tested for normality using the Shapiro–Wilk test, and continuous variables were presented as means ± standard deviation or medians with interquartile range. Categorical variables were described as numbers and percentages. For the analysis of changes over time, one-way repeated measures analysis of variance (rmANOVA) or Friedman test with Bonferroni post hoc test were used depending on the normality of data distribution.

We performed the sub-group analysis by comparing the VATS group with the PLT group. To compare baseline and perioperative characteristics, unpaired-*t* or Mann-Whitney U tests were used for continuous variables, and the chi-square test was used for categorical variables. The comparisons of FVC, FEV_1, Pimax, Pemax, and 6MWD expressed relative to the predicted values and QF between the groups over time were analyzed in two-ways rmANOVA and Bonferroni post hoc test. $P < 0.05$ was considered statistically significant. All analyses were performed with IBM SPSS Statistics version 24 (IBM, Armonk, NY, USA).

Results

Of the 58 patients who underwent lobectomy for clinical stage I or II NSCLC and received PR, 17 were excluded in accordance with our inclusion criteria (Fig. 2). Data obtained from 41 patients were analyzed. The overall incidence of post-operative pulmonary complications was 7.3% including pneumonia (n = 1) and prolonged chest tube (n = 2). The numbers of patients undergoing VATS and PLT were 24 and 17, respectively, and both groups were comparable in their baseline characteristics (Table 1). With regards to perioperative characteristics, the VATS group experienced less blood loss, shorter duration of chest tube drainage, and shorter LOS compared with the PLT group (Table 2).

Pulmonary function, respiratory muscle strength, physical functions, and dyspnea

Changes over time in pulmonary function, respiratory muscle strength, QF, 6MWD, and dyspnea are summarized in Table 3. Post-operative FVC and FEV_1 gradually increased from the day of hospital discharge to 3 months post-lobectomy, but were lower than the pre-operative values. Pimax, Pemax, and 6MWD at discharge were lower than the pre-operative values; however, QF did not change. At 1-month post-lobectomy, Pimax and 6MWD increased to the pre-operative values, while Pemax remained low. At 3-months post-lobectomy, Pemax increased to the pre-operative value. In addition, QF improved more than the pre-operative values. mMRC dyspnea worsened at discharge and 1-month post-lobectomy but improved to a pre-operative level at 3 months.

Comparison between VATS and PLT

Fig. 3 shows the results of the comparison between the VATS and PLT groups for changes in FVC, FEV_1, Pimax, Pemax, QF, and 6MWD. All parameters exhibited significant main effects of time (each $P < 0.001$). Pimax only showed a significant group-by-time interaction effect ($P = 0.031$). Specifically, Pimax at discharge was lower than the pre-operative values in both the groups. However, Pimax at 1 month and 3 months post-lobectomy was higher than that at discharge and increased to the pre-operative value in the VATS group. On the contrary, there was no difference between Pimax at discharge and 1-month post-lobectomy; however, Pimax at 3 months post-lobectomy was higher than that at discharge in the PLT group.

mMRC dyspnea exhibited significant differences between the changes over time in the VATS and PLT group using the Friedman test (each $P < 0.001$). In the VATS group, mMRC dyspnea at discharge (1 [1–2]) deteriorated when compared pre-operatively (0 [0–1]), but dyspnea at 1 month and 3 months post-lobectomy (1 [0–1] and 0 [0–1], respectively) improved to the pre-operative level. However, in the PLT group, mMRC dyspnea at discharge and 1 month post-lobectomy (2 [1–2] and 1 [1–2], respectively) became worse than the pre-operative conditions (0 [0–1]); however, it improved at 3 months (0 [0–1]) post-lobectomy.

Discussion

In patients with stage I or II NSCLC who received pre- and post-operative PR, we observed transiently impaired respiratory muscle strength and exercise capacity, as well as increased dyspnea at hospital discharge, but all conditions returned to pre-operative levels at 3 months post-lobectomy. Moreover, pre- and post-operative QFs remained stable. In a sub-analysis of the two surgical procedures, VATS showed early improvement in Pimax and dyspnea compared to PLT. These results are novel because there have been few studies reporting post-operative changes in the factors associated with physical debility in lobectomized patients undergoing PR.

In our study, post-operative FVC and FEV_1 were comparable to those in previous studies for lobectomized patients undergoing post-operative PR [8, 18]; however, post-operative FEV_1 in our study was higher than that in a report for lobectomized patients who did not undergo PR [19]. This difference might be attributable to the effect of PR. From previous studies on pulmonary function after lung resection [20–22], the difference between VATS and thoracotomy more than 2 weeks post-operation has been controversial, although VATS yielded better results than thoracotomy in the first post-operative week. The factors impacting pulmonary function recovery following lung resection are regarded as multifactorial, with total loss of the lung tissue, pain, and alterations in chest wall mechanics owing to the surgical incision being implicated [21–25]. In our study, the change in remaining pulmonary function following PLT was similar to that following VATS after about 1 week post-operation. These results indicate that improvement in remaining pulmonary function after lobectomy may be attributed to improvements in perioperative management including pain management and PR.

According to previous reports on lung resection, including wedge resection, lobectomy, and pneumonectomy, both Pimax and Pemax in the first post-operative week were lower than those in the pre-operative week [7, 21, 26]. At 1 month post-lung resection, Pimax in patients who did not perform PR remained lower than that in patients with pre-operative PR (80%–84% of pre-operative values) [18, 26], whereas Pimax in patients undergoing PR increased to the pre-operative values [18]. Meanwhile, Pemax at 1-month post-lung resection was 82%–88% of the pre-operative values regardless of whether PR was provided or not [18, 26]. At 3 months post-lung resection, both Pimax and Pemax have already improved to the pre-operative levels [18, 26]. As expected, in our study for lobectomized patients undergoing PR, Pimax at 1-month post-operation recovered to the pre-operative value, but the improvement of Pemax was delayed to 3 months post-operation. The discrepancy between the recovery of Pimax and Pemax appears to be owing to two causes. First, the value of Pemax is dependent on the lung volume because of the force-length relationship in the expiratory muscle [12], which suggests that the recovery of Pemax was strongly associated with that of the pulmonary function. Second, breathing exercises used in our study emphasized the activation of inspiratory muscles.

Our results show that VATS was associated with a faster recovery of Pimax compared with PLT. The difference between VATS and thoracotomy for post-operative pain has been controversial; a few studies have reported that VATS generates less pain than thoracotomy [22, 24], while another study reported that pain after VATS and thoracotomy were similar [23]. The type of surgical invasion has been suggested to affect chest wall muscle function and to reduce chest wall compliance, and VATS has an advantage over

PLT in reducing injury to the inspiratory muscles of the chest wall [27]. Thus, it was presumed that an earlier recovery of Pimax in VATS compared with PLT results from the type of surgical invasion rather than post-operative pain. Regarding Pemax, there was no difference between VATS and PLT in the post-operative recovery pattern. This probably could be attributed to their non-invasion of the abdominal muscles, which are the primary expiratory muscles, and a similar recovery pattern was observed for the lung volume in both VATS and PLT.

Our study showed that 6MWD at discharge was lower than the pre-operative values, which is similar to previous studies for the various types of lung resection [5, 28]. This could be owing to the ventilatory limitation during the early post-operative period [5]. At 3 months post-lobectomy, the exercise capacity by maximal oxygen uptake on a cardiopulmonary exercise test showed a lower value compared to the pre-operative levels without PR, and this limiting factor was primarily owing to leg muscle fatigue [9]. On the contrary, 6MWD at 1 month post-lobectomy had already improved to the pre-operative levels in our study; this is because QF after lobectomy could be kept in a state of pre-operative condition, and this effect may benefit from exercise training.

There were few studies investigating dyspnea after lobectomy, which limits physical activity and leads to poor quality of life. Our study found that dyspnea improved to the pre-operative level at 1 month post-operation in VATS and at 3 months in PLT. This differential recovery pattern could be explained based on 2 factors. First, the recovery pattern of dyspnea was like that of Pimax but not to the remaining pulmonary function. The deterioration of Pimax has been reported to worsen dyspnea in patients with chronic obstructive pulmonary disease [29]. Thus, it is possible that the change in Pimax affected dyspnea post-lobectomy. Second, a review of respiratory mechanics [25] suggested that respiratory work increases post-lobectomy because lung compliance decreases in inverse proportion to the volume resected. From this review, dyspnea post-lobectomy may be associated with the increase in the respiratory work.

This study has several limitations. First, this is a single-center retrospective study, and post-operative pain scores could not be analyzed because it was difficult to collect them from medical records alone. Second, we cannot rule out that the 6-minute walk test used as a measure of exercise capacity in our study might be a submaximal exercise test because this test is self-paced [30]. However, the relationship between 6MWD and peak oxygen uptake during cardiopulmonary exercise testing showed a moderate to strong correlation in chronic respiratory diseases [30]. Third, PR could not be followed up and compared with a control group until 3 months post-lobectomy, even though pulmonary function has been reported to improve until 12 months post-lobectomy [31]. A further longitudinal randomized controlled trial is needed to follow-up and confirm the advantage of PR on the post-operative changes of factors associated with physical debility.

Conclusion

In patients with NSCLC undergoing supervised PR from 1 week before lobectomy to 3 months after lobectomy, this study indicated that QF did not weaken, and respiratory muscle strength, exercise capacity, and dyspnea improved to the pre-operative levels at 3 months post-lobectomy. In addition, VATS may be more beneficial than PLT for early post-operative recovery of inspiratory muscle strength and dyspnea.

Declarations

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Conflicts of interest/Competing interests: The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethics approval: This retrospective study was performed in line with the principle of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Institutional Review Board for clinical research at Tokai University (Approval Number: 17R389).

Consent to participate: The individual informed consent was waived because of the retrospective design.

Consent for publication: Not applicable.

Availability of data and material: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability: Not applicable.

Authors' contributions: Tsuyoshi Ichikawa, Masanori Yokoba, Masato Katagiri, and Minoru Toyokura contributed to the conception and design of this study. Material preparation, data collection, and analysis were performed by Tsuyoshi Ichikawa, Masanori Yokoba, Yu Horimizu, Saki Yamaguchi, Akiko Kawakami, Satoru Oikawa, Haruka Takeichi, and Masato Katagiri. The first draft of the manuscript was written by Tsuyoshi Ichikawa and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline characteristics of patients

	Total sample (n = 41)	VATS group (n = 24)	PLT group (n = 17)	*P*-value
Age (years)	69 ± 7	70 ± 7	68 ± 6	0.393
Sex (male)	15 (37)	6 (25)	9 (53)	0.102
Body mass index (kg/m^2)	22 ± 4	22 ± 4	23 ± 3	0.633
Chronic obstructive pulmonary disease	6 (15)	2 (8)	4 (24)	0.175
Smoking status				0.375
Never-smokers	25 (61)	16 (67)	9 (53)	
Current or former smokers	16 (39)	8 (33)	8 (47)	
ECOG-PS				0.560
0	38 (93)	23 (96)	15 (88)	
1	3 (7)	1 (4)	2 (12)	
FVC (% predicted)	93 ± 13	91 ± 14	97 ± 12	0.148
FEV_1 (% predicted)	93 ± 15	92 ± 16	94 ± 14	0.691

Values are presented as means ± standard deviation or medians [interquartile range] or numbers (%). ECOG-PS: Eastern Cooperative Oncology Group Performance Status; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; PLT: posterolateral thoracotomy; VATS: video-assisted thoracoscopic surgery. *P*-value was shown as the results of comparison for VATS versus PLT.

Table 2. Perioperative characteristics of patients

	Total sample (n = 41)	VATS group (n = 24)	PLT group (n = 17)	*P*-value
Lobectomy site				0.101
Right upper lobe	21 (51)	11 (46)	10 (59)	
Right middle lobe	3 (7)	3 (13)	0 (0)	
Right lower lobe	6 (15)	5 (21)	1 (6)	
Left upper lobe	9 (22)	3 (13)	6 (35)	
Left lower lobe	2 (5)	2 (8)	0 (0)	
Pathological stage				0.024
IA	29 (71)	21 (88)	8 (47)	
IB	8 (20)	3 (13)	5 (29)	
IIA	3 (7)	0 (0)	3 (18)	
IIB	1 (2)	0 (0)	1 (6)	
Histological type				0.944
Adenocarcinoma	36 (88)	21 (88)	15 (88)	
squamous cell carcinoma	5 (12)	3 (12)	2 (12)	
Duration of lobectomy (min)	207 [186–229]	213 [191–233]	200 [183–227]	0.404
Blood loss (mL)	64 [30–111]	43 [23–68]	100 [69–135]	0.002
Duration of chest tube (days)	3 [3–4]	3 [3–4]	4 [3–5]	0.021
Post-operative initial walking (days)	1 [1–1]	1 [1–1]	[1–1]	0.487
Length of hospital stay (days)	10 [9–13]	10 [9–11]	12 [10–14]	0.030
Length of post-operative hospital stay (days)	8 [7–10]	7 [6–9]	9 [8–10]	0.045

Values are presented as medians [interquartile range] or numbers (%). PLT: posterolateral thoracotomy; VATS: video-assisted thoracoscopic surgery. *P*-value was shown as the results of comparison for VATS versus PLT.

Table 3. Changes in pulmonary function, respiratory muscle strength, quadriceps force, exercise capacity, and dyspnea before and after lobectomy in all patients

	Before lobectomy	Discharge	1 month after lobectomy	3 months after lobectomy	*P*-value
FVC (L)	2.72 ± 0.79	1.96 ± 0.54*	2.11 ± 0.57*,†	2.29 ± 0.57*,†,§	< 0.001
FVC (% predicted)	93 ± 14	68 ± 12*	73 ± 11*,†	79 ± 11*,†,§	< 0.001
FEV_1 (L)	2.08 ± 0.57	1.50 ± 0.43*	1.64 ± 0.48*,†	1.78 ± 0.49*,†,§	< 0.001
FEV_1 (% predicted)	93 ± 15	68 ± 13*	73 ± 14*,†	79 ± 14*,†,§	< 0.001
Pimax (cmH_2O)	59 ± 20	46 ± 19*	58 ± 21†	65 ± 25†,§	< 0.001
Pimax (% predicted)	101 ± 33	79 ± 30*	99 ± 32†	112 ± 36†,§	< 0.001
Pemax (cmH_2O)	85 ± 38	53 ± 23*	70 ± 33*,†	82 ± 33†,§	< 0.001
Pemax (% predicted)	107 ± 35	69 ± 23*	89 ± 32*,†	107 ± 37†,§	< 0.001
QF (% bodyweight)	43 ± 13	40 ± 12	44 ± 13†	47 ± 14*,†	< 0.001
6MWD (m)	433 ± 85	379 ± 84*	425 ± 73†	450 ± 79†,§	< 0.001
6MWD (% predicted)	91 ± 17	80 ± 17*	89 ± 15†	94 ± 16†,§	< 0.001
mMRC dyspnea scale score	0 [0–1]	1 [1–2]*	1 [0–2]*,†	0 [0–1]†,§	< 0.001

Values are presented as means ± standard deviation or medians [interquartile range]. *P*-value was shown as the results of one-way repeated measures analysis of variance or Friedman test. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; mMRC: modified Medical Research Council; Pemax: maximal mouth expiratory pressure; Pimax: maximal mouth inspiratory pressure; QF: quadriceps force; 6MWD: 6-minute walk distance. $^{*}P < 0.05$, $^{†}P < 0.05$, and $^{§}P < 0.05$ for comparison before lobectomy, discharge, and 1-month post-lobectomy, respectively.

Figures

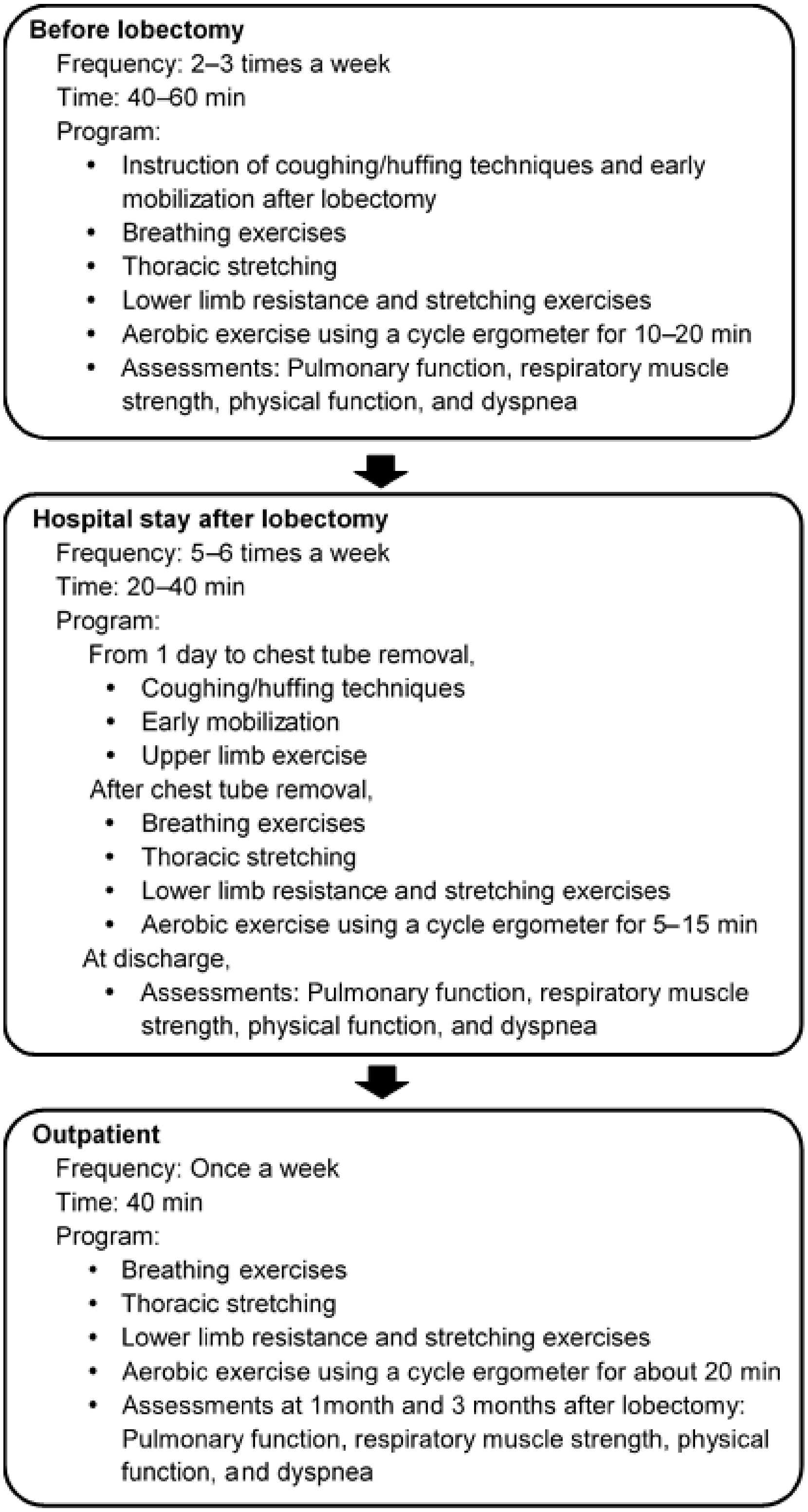

Figure 1

Flow diagram of pulmonary rehabilitation from 1 week before lobectomy to 3 months after lobectomy.

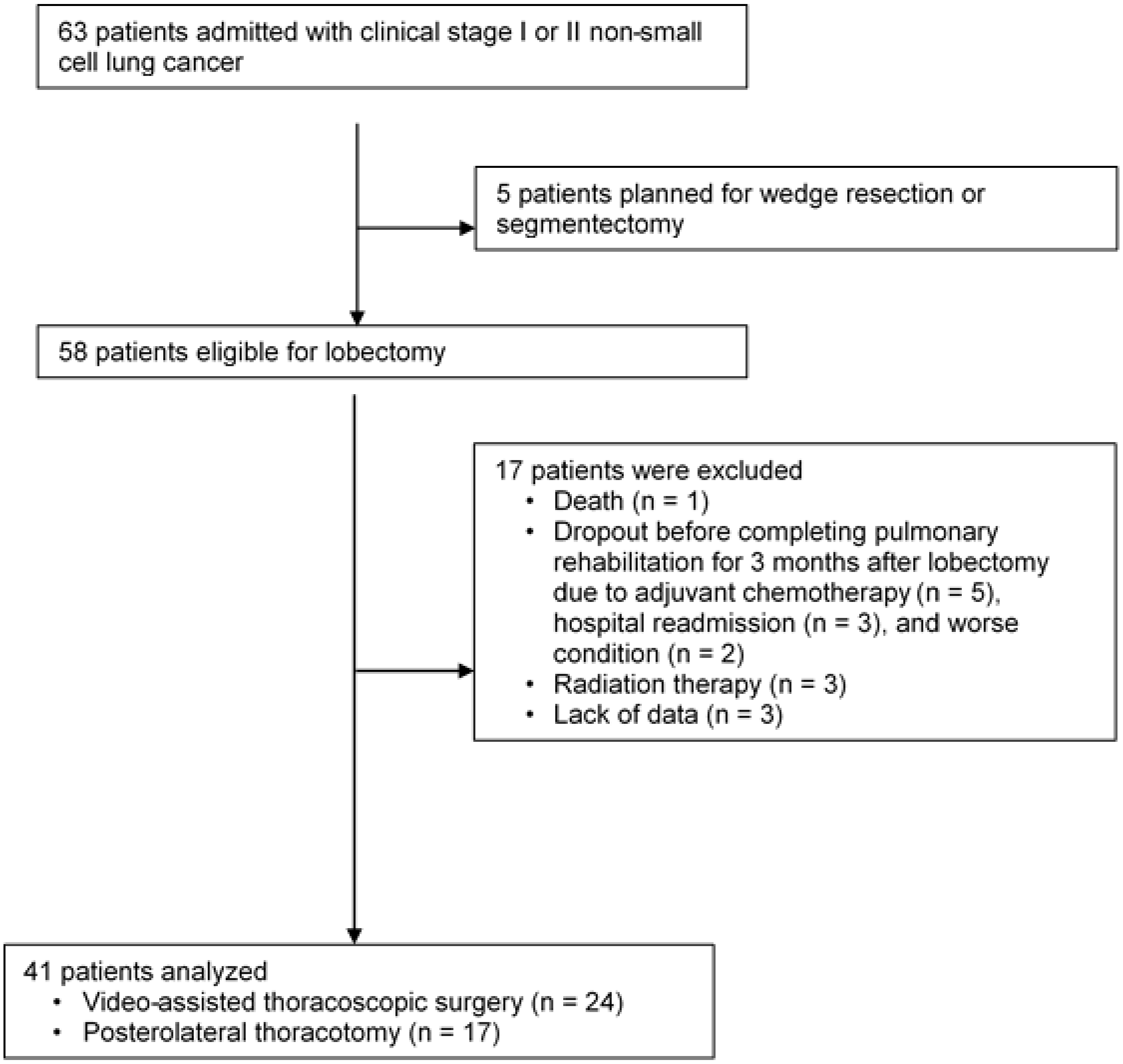

Figure 2

Study flow diagram.

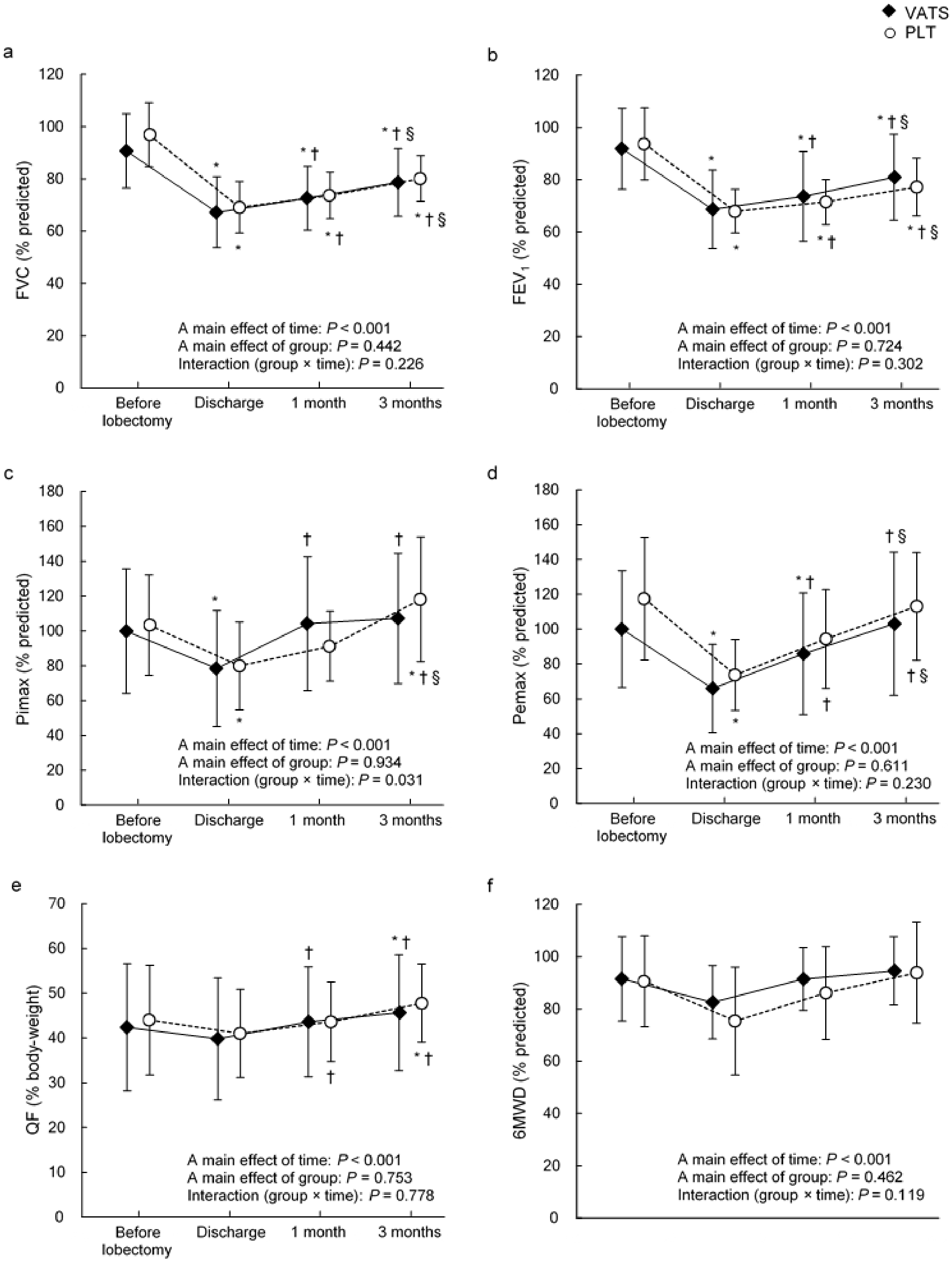

Figure 3

Differences between video-assisted thoracoscopic surgery (VATS) and posterolateral thoracotomy (PLT) over time for pulmonary function, respiratory muscle strength and physical functions. (a) Forced vital capacity (FVC), (b) forced expiratory volume in 1 s (FEV1), (c) maximal mouth inspiratory (Pimax) and (d) expiratory (Pemax) pressures, (e) quadriceps force (QF), and (f) 6-minute walk distance (6MWD). *P <

0.05, †P < 0.05, and §P < 0.05 for comparison before lobectomy, discharge, and 1-month post-lobectomy using the Bonferroni post hoc test, respectively.