

Short-term inpatient-based high-intensive pulmonary rehabilitation for lung cancer patients: is it feasible and effective?

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Background: This study was conducted to develop a preoperative in-hospital short-term rehabilitation program for surgical lung cancer patients, and investigate its feasibility, potential cost benefit and effectiveness on outcome measures including reduction of postoperative pulmonary complications (PPCs) and postoperative length of stay.

Methods: A 7-day inpatient-based high-intensive rehabilitation regimen was performed between March 01, 2014 and June 30, 2015. It was combined with inspiratory muscles training (IMT) and aerobic endurance training and was tested in an enriched cohort study with 939 lung cancer patients undergoing lobectomy in a regional thoracic unit.

Results: Finally, 939 patients were divided into pulmonary rehabilitation (PR) group (n=197) and non-PR (NPR) group (n=742), according to whether they received the 7-day preoperative in-hospital systematic rehabilitation. The PR group had a shorter total length of stay (14.7 ± 4.0 vs. 16.7 ± 6.2 days, $P<0.001$) as well as postoperative length of stay (6.2 ± 3.3 vs. 8.3 ± 5.6 days, $P<0.001$) than the NPR group. Lower incidences of total PPCs (18.3%, 36/197 vs. 26.1%, 194/742, $P=0.022$), pneumonia (11.2%, 22/197 vs. 17.3%, 128/742, $P=0.024$) and atelectasis (6.6%, 13/197 vs. 12.3%, 91/742, $P=0.038$) were found in the PR group compared with NPR group. Meanwhile, a multivariable analysis of risk to PPCs, atelectasis and pneumonia, revealed that the PR intervention was the independent risk factor of the occurrence of the PPCs (OR =0.57, 95% CI: 0.47 to 0.93, $P=0.033$) and atelectasis (OR =0.49, 95% CI: 0.26 to 0.91, $P=0.024$).

Conclusions: The study showed the effectiveness of this systematic and high-intensive PR combining IMT and aerobic exercise in reductions of the length of stay and occurrence of PPCs without increase in in-hospital cost, suggesting the potential of this rehabilitation pattern as a practicable strategy performed preoperatively in surgical lung cancer patients.

Keywords: Pulmonary rehabilitation (PR); cost-benefit analysis; lung cancer; lobectomy

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Introduction

Malignant tumors have been the most health-threatening and death-causing disease to humans with the morbidity rate of lung cancer ranking first among all tumors in China since about 600,000 people were attacked in 2010 and 480,000 of them died (1,2). Lung cancer continues to be a difficult disease with a high mortality and symptom burden, in part because of frequent lung comorbidities, even the survivors often remain symptomatically and functionally limited. Surgery is the optimal treatment of early-stage lung cancer, when the pre-malignant or early lesions are amenable to resection and cure (3,4). Postoperative pulmonary complications (PPCs) are the leading cause of morbidity and mortality after lung resection surgery for lung cancer patients, let alone the burden of PPC on the patients (5). Thus, any intervention to reduce PPCs will have a valuable impact on clinical and cost-effectiveness outcomes.

In the last several decades, exercise and physical activity have arisen rapidly as therapeutic options for obstructive lung disease and lung cancer. To date, exercise has shown effectiveness to relieve symptoms, increase exercise tolerance, improve quality of life, and potentially reduce length of stay and postoperative complications, as growing evidence supports activity's benefit in primary and secondary cancer prevention (6). However, the lack of evidence-based consensus as to how and when to implement the pulmonary rehabilitation (PR) regimen has aroused numerous researches focusing on it (7).

Based on this, we performed a study to develop, refine and examine the feasibility of a systemic-intensive preoperative rehabilitation combined with inspiratory muscle training (IMT) and endurance exercise, which may play an impactful role on improving cardiopulmonary intolerance and the sequential reduction of PPC rate.

Methods

Study subjects and grouping

We retrospectively collected 939 surgical patients with lung cancer between the year between March 1, 2014 and June 30, 2015, following the inclusion/exclusion criteria listed below. Inclusive criteria: patients who (I) were diagnosed as primary non-small cell lung cancer (NSCLC); (II) with age ≥ 50 years old; (III) received lung cancer lobectomy ultimately. Exclusive criteria: (I) not primary NSCLC pathologically; (II) did not undergo lobectomy, including sub-lobectomy, pneumonectomy, etc.; (III) received

preoperative chemoradiotherapy.

Patients were divided into PR group and non-PR group, according to whether they received the 7-day preoperative in-hospital systematic rehabilitation. Inclusive criteria for rehabilitation included a ≥ 20 pack-year smoking history, body mass index ≥ 28 , forced expiratory volume in 1s percentage (FEV₁%) $\leq 60\%$, chronic obstructive pulmonary disease (COPD), asthma or airway hyper reactivity, which were considered as risk factors of the occurrence of PPCs. Patients were excluded if they had any of the following exclusion criteria: (I) refusal to participate; (II) contraindications for the physical rehabilitation including myocardial infarction or cerebrovascular accident (<1 year), unstable angina pectoris, aneurysm, haemoptysis (<90 d), musculoskeletal or mental disorders. Finally, we enrolled 294 patients into rehabilitation regimen, 65 patients met exclusion criteria, 32 patients refused to participate in regimen and 37 did not complete.

Preoperative PR program

Education

Lung cancer nurse specialists performed the education sessions for the participants, including teaching the normative inhalation exercise and abdominal exercise, supervising them to completing the daily exercise sessions in ward, and sequentially making records. Physiotherapists trained and supervised the patients to perform the daily endurance exercise in the rehabilitation training center.

Rehabilitation regimen

IMT exercise

IMT exercise was performed in the in-patient ward, including: (I) abdominal breathing training: diaphragm muscles could be strengthened through this exercise (twice a day, with 15–20 minutes each turn). The patient inhaled slowly to the maximum lung capacity through nose, and held the breath for a short time, then exhaled slowly through tips with his abdominal muscles tighten; (II) inspiration exercise: a simple respiratory training device (Voldyne 2500, Sherwood Medical Supplies, St Louis, MO, USA) was used for the training. The patient was guided to exhale calmly at beginning, and then deeply inhaled through the suction nozzle in the training device, and after holding for several seconds, then exhaled slowly. Training pattern lasted three times a day, 20-minute each turn.

Aerobic endurance training

The device Nu-Step (Inc. Ann Arbor, Michigan, USA) was used in rehabilitation training center. The patients adjusted the resistance gear range according to their own speed and power at first, and then increased the resistance range progressively. During the training, procedure must be stopped if patients had any obvious discomfort, such as shortness of breath, dyspnea or exhaustion. Patients were allowed to have a rest until his/her condition can withstand the subsequent training. This pattern lasted 30 mins daily.

Rehabilitation expense

During the rehabilitation regimen, the patients were charged for \$28, consisting of \$8 for daily special nursing care and ¥20 for Nustep exercise. This charging standard was established and approved by the hospital and provincial health bureau in 2013.

Data collection

This study was a retrospective and single-center study of consecutive patients underwent lung cancer lobectomy at the Department of Thoracic Surgery of West China Hospital of Sichuan University between March 1, 2014 and June 30, 2015. The ethics committee gave its approval (number: 2015-176) for the publication of this study with a waiver of informed consent. Clinical data were collected by well-trained coordinators using a hospital database.

Statistical analysis

Demographic data were presented as follows: continuous variables as mean and standard deviation (mean \pm SD), binary variables as frequencies and proportions. The continuous variables were compared by Student's *t*-test, and discrete variables were analyzed using the Chi-square test or Fisher exact test. A multivariable analysis of risk factors of PPCs, pneumonia and atelectasis were analyzed, using the binary logistic regression, variables analyzed included age, gender, smoking status, COPD, diabetes, hypertension or/and coronary disease, early tumor stage (stage I), surgical approach, operation time, amount of bleeding during the operation, FEV₁, postoperative predicted FEV₁% (ppoFEV₁%), Dlco, postoperative predicted Dlco% (ppoDlco%), whether rehabilitation or not. All results were considered significant at *P*<0.05. Statistical analyses were performed using SPSS software V.21.0 (SPSS Inc., Chicago, IL, USA).

Primary endpoints

The occurrence of PPCs was the main endpoint of the study. The PPCs in 30 days were identified and recorded. PPCs included (I) pneumonia; (II) prolonged air leak (≥ 7 days); (III) atelectasis; (IV) pleural effusion requiring drainage; (V) acute respiratory distress syndrome (ARDS); (VI) respiratory failure; (VII) mechanical ventilation ≥ 48 hours postoperatively; (VIII) pulmonary embolism; (IX) empyema. Pneumonia is defined as at least 3 of the following: leukocytosis $>12,000/\text{mm}^3$ or $<3,000/\text{mm}^3$, temperature $>38^\circ\text{C}$, purulent sputum, persistent infiltrate on chest roentgenogram, or pathogenic microorganisms from endotracheal aspirate. Also, we used Clavien-Dindo complication classification system to analyze the PPCs, and the PPCs reaching Clavien-Dindo grade II–V were included in final analysis (8).

Results

Completion status

Patients (*n*=939) (mean age: 58.7 \pm 9.4 years; range, 50–87 years) were divided into PR group (*n*=197) and non-PR group (*n*=742), according to whether they performed the 7-day preoperative in-hospital systematic rehabilitation. There was no significant difference between the groups in their preoperative characteristics, and the baseline data were listed in *Table 1*. Regarding to the duration of rehabilitation regimen, 17 (8.6%, 17/197) in the PR group perform the PR program for 1–3 days, 20 (10.2%, 20/197) for 4–6 days, and 160 (81.2%, 160/197) completed the regimen. Among the 197 patients who agreed and finally participated in the rehabilitation regimen, 37 (18.8%, 37/197) did not completed the 7-day rehabilitation plan due to various reasons: 7 (18.9%, 7/37) required for advancing the surgery, 9 (24.3%, 9/37) perceived lack of benefit, 11 (29.7%, 11/37) could not endure the high-intensive regimen, 7 (18.9%, 7/37) considered time/expense cost and suspended, and 3 (8.1%, 3/37) for other reasons (*Table 2*).

Clinical characteristics

The PR group had a shorter total length of stay (14.7 \pm 4.0 *vs.* 16.7 \pm 6.2 days, *P*<0.001) as well as postoperative length of stay (6.2 \pm 3.3 *vs.* 8.3 \pm 5.6 days, *P*<0.001) than the NPR group. However, no difference was found in the preoperative in-hospital stay (8.6 \pm 1.9 *vs.* 8.4 \pm 1.8 days, *P*=0.230) between the groups. The details can be seen in *Table 2*.

Table 1 Baseline of the two groups

Characteristics	PR group, n=197	NPR group, n=742	P
Age, mean ± SD	58.5±9.6	58.8±9.3	0.564
Gender			
Men	116 (58.9)	406 (54.7)	0.295
FEV ₁ , L	2.2±0.6	2.3±0.5	0.059
ppoFEV ₁ %	69.9±17.5	69.3±18.4	0.676
Dlco, mL/min/mmHg	21.7±5.0	22.2±5.0	0.231
ppoDlco%	72.2± 23.3	71.4±24.6	0.684
Comorbidities			
Hypertension or/and coronary disease	10 (5.0)	37 (5.0)	0.959
Current smoking status	50 (25.4)	176 (23.7)	0.628
COPD	22 (11.2)	92 (12.4)	0.638
Diabetes	13 (6.6)	49 (6.6)	0.998
Clinical stage			0.524
Stage I	102 (51.8)	350 (47.2)	
Stage II	69 (35.0)	303 (40.8)	
Stage III	24 (12.2)	81 (10.9)	
Stage IV	2 (1.0)	8 (1.1)	
Surgical approach			
VATS	122 (61.9)	489 (65.9)	0.298
Open	75 (38.1)	253 (34.1)	
Duration of drainage	4.2±2.8	4.5±2.5	0.110
Average time of in-hospital stay, day	14.7±4.0	16.7±6.2	<0.001
Preoperative, day	8.6±1.9	8.4±1.8	0.230
Postoperative, day	6.2±3.3	8.3±5.6	<0.001

Data are shown as number (%) or mean ± standard deviation. PR, pulmonary rehabilitation; NPR, non-pulmonary rehabilitation; FEV₁, forced expiratory volume in one second; ppoFEV₁, postoperative predicted FEV₁. Dlco, diffusion capacity for carbon monoxide of the lung; COPD, chronic obstructive pulmonary disease; VATS, video assisted thoracic surgery.

The PR group spent average \$142 for the rehabilitation regimen, and had a higher preoperative cost compared with NPR group (\$579.2±\$211.5 vs. \$438.6±\$206.3, P<0.001). But no significantly difference was found in the average in-hospital cost between the two groups (\$7,131.8±\$2,316.6 vs. \$7,266.4±\$1,615.0, P=0.347). Respectively, the postoperative

Table 2 Rehabilitation regimen and completion status

Variables	Exercise intervention
Components	
IMT	Abdominal exercise: 20 breaths/ session, 3 times a day for 7 days Inhalation exercise (spirometer): 20 min/session, 3 times a day for 7 days
Endurance exercise	Nustep: 30 min, once a day for 7 days
Completion status	1~3 days: 17 (8.6) 4~6 days: 20 (10.2) Completing: 160 (8.2)
Reasons for not completing the regimen (n=37)	
Requiring for advancing the surgery	7 (18.9)
Perceived lack of benefit	9 (24.3)
Could not endure the high-intensive regimen	11 (29.7)
Consideration of time/expense cost	7 (18.9)
Other reasons	3 (8.1)

IMT, inspiratory muscles training.

expense (P=0.001), post-ward cost (P=0.001), post-care cost (P=0.001), post-drug cost (P=0.004) in the PR group were significantly lower than in the NPR group (Table 3).

PPC rate

Pneumonia (14.9%, 140/939), atelectasis needing bronchoscope (11.1%, 104/939) and air leak ≥7 days (8.3%, 78/939) were the leading PPCs presented after the surgery in 30 days. Lower incidences of total PPCs (18.3%, 36/197 vs. 26.1%, 194/742, P=0.022), pneumonia (11.2%, 22/197 vs. 17.3%, 128/742, P=0.024) and atelectasis (6.6%, 13/197 vs. 12.3%, 91/742, P=0.038) were found in the PR group, compared with in NPR group (Table 4).

Furthermore, we performed a multivariable analysis of risk to PPCs, pneumonia and atelectasis with variables including age, gender, smoking status, COPD, diabetes, hypertension or/and coronary disease, early tumor stage (stage I), surgical approach, operation time, amount

Table 3 In-hospital expense between the groups

Variables	PR group (\$)	NPR group (\$)	P
Total expense	7,131.8±2,316.6	7,266.4±1,615.0	0.347
Preoperative costs	579.2±211.5	438.6±206.3	<0.001
Ward expense	118.4±34.7	115.3±32.0	0.236
Care expense	53.3±15.6	51.9±14.4	0.234
Rehabilitation expense	142.0±32.5	0	<0.001
Surgery related expense	5,602.5±2,211.1	5,751.0±1,495.5	0.270
Postoperative costs	949.3±462.6	1,076.8±524.9	0.001
Drug expense	379.1±211.3	444.8±201.0	0.004
Ward expense	112.0±57.0	131.0±100.4	0.001
Care expense	67.2±35.9	78.6±60.2	0.001

PR, pulmonary rehabilitation; NPR, non-pulmonary rehabilitation.

of bleeding during the operation, FEV₁, ppoFEV₁%, Dlco, ppoDlco%, whether rehabilitation or not. The PR intervention (OR =0.57, 95% CI: 0.47 to 0.93, P=0.033) and operation time (OR =1.01, 95% CI: 1.00 to 1.02, P=0.043) were the independent risk factors to the occurrence of PPCs. Meanwhile, FEV₁ (OR =2.93, 95% CI: 1.12 to 7.68; P=0.029) value was the independent factor for pneumonia, and the PR intervention (OR =0.49, 95% CI: 0.26 to 0.91, P=0.024), early tumor stage (OR =0.58, 95% CI: 0.37 to 0.89, P=0.014) and COPD (OR =2.22, 95% CI: 1.16 to 4.25, P=0.016) for atelectasis (*Table 5*).

Discussion

This study developed and refined a preoperative short-term and integrated rehabilitation program combining IMT with endurance exercise, and validated its effectiveness on reducing PPCs rate as well as in-hospital stay, on the premise of not increasing the in-hospital expense, and all with the primary aim of optimizing and enhancing recovery and physical status of patients undergoing curative lung cancer surgery. Compared with rehabilitation at home, the adherence of this in-hospital PR pattern might be higher, under the guidance and supervision of the trained nurses and physiotherapists. Unlike other researches mainly aiming at the effectiveness of IMT for lung cancer patients (9-11), this main intervention treatment in this study was a modified preoperative PR program combining with IMT and aerobic endurance

Table 4 PPCs rate in 30 days between the PR and NPR groups

Outcome variables	PR group, n=197	NPR group, n=742	P
PPCs rate	36 (18.3)	194 (26.1)	0.022
Grade II			
Pneumonia	22 (11.2)	128 (17.3)	0.024
Atelectasis needing bronchoscope	13 (6.6)	91 (12.3)	0.038
Air leak ≥7 days	16 (8.1)	62 (8.4)	0.916
Pleural effusion needing drainage	14 (7.1)	49 (6.6)	0.802
Grade III			
Bronchopleural fistula	4 (2.0)	13 (1.8)	0.766
Mechanical ventilation >48 h	8 (4.1)	27 (3.6)	0.781
Empyema	6 (3.0)	30 (4.0)	0.517
Grade IV			
Respiratory failure or ARDS	4 (2.0)	8 (1.1)	0.289
Pulmonary embolism	2 (1.0)	5 (0.7)	0.922
Back to ICU	4 (2.0)	7 (0.9)	0.256
Grade V			
Death	2 (1.0)	4 (0.5)	0.611

Data are shown as number (%). PPCs rate was defined as PPCs with Clavien-Dindo grade over level II (grade II-V). PPCs, postoperative pulmonary complications; PR, pulmonary rehabilitation; NPR, non-pulmonary rehabilitation; ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

training. Inspiratory training has a long history of research, especially among patients with COPD, asthma, or poor lung function. It has been proven effective for improving inspiratory muscle strength and endurance, functional exercise capacity and dyspnea symptoms (12,13). In addition, the aerobic endurance training under the guidance of physical therapist, is consider as a safe and effective strategy aiming at tumor patients (14).The American Cancer Society recommends that adults with cancer engage in at least 150 minutes of moderate-intensity aerobic exercise and two sessions of resistance exercise per week (15), as they have been proposed as alternative training modality for resistance training on multi-gym equipment, helping to represent the disease severity and clinically relevant exercise-tolerance in pediatric pulmonary arterial hypertension, improving

Table 5 Multivariable analysis of risk to PPCs, pneumonia and atelectasis*

PPC categories	Variables	OR (95% CI)	P
PPCs	PR intervention	0.57 (0.47–0.93)	0.033
	Operation time	1.01 (1.00–1.02)	0.043
Pneumonia	FEV ₁ value	2.93 (1.12–7.68)	0.029
	PR intervention	0.62 (0.38–1.02)	0.061
Atelectasis	PR intervention	0.49 (0.26–0.91)	0.024
	COPD	2.22 (1.16–4.25)	0.016
	Early tumor stage	0.58 (0.37–0.89)	0.014

*, variables analyzed included age, gender, smoking status, COPD, diabetes, hypertension or/and coronary disease, early tumor stage (stage I), surgical approach (open/VATS), operation time, amount of bleeding during the operation, FEV₁, ppoFEV₁%, Dlco, ppoDlco%, whether rehabilitation or not. PPCs, postoperative pulmonary complications; PR, pulmonary rehabilitation; FEV₁, forced expiratory volume in one second; COPD, chronic obstructive pulmonary disease.

cardiopulmonary coordination ability, as well as exercise tolerance (16-18). We hypothesized that a shorter-term intensive treatment combining IMT with aerobic endurance training to lung cancer patients could be a better strategy compared with conventional care.

The duration of the PR vary with the range from 3 days to 12 weeks in different studies (9,19,20). In China, a short in-hospital PR regimen is considered to be a more feasible and appropriate, for the deficiencies in basic-level hospitals and the primary care system make it infeasible and impracticable for patients to rehabilitate either at home or in community hospitals. Also, lung cancer patients generally spend 7–10 days preparing for surgery in China, including completing the diagnosis process, finishing surgery-related examinations, because of the inadequate equipment and technical skills in basic institutions. Considering that the length of the regimen to fit with cancer waiting time targets and surgery should not be delayed due to the program, one-week time is a time plot that could be accepted before operations as a longer duration maybe weaken the patient-compliance. Hence, with our previous experience, we set a unified duration of 7-day intensive PR for all PR group patients as this appropriate duration may achieve the efficiency of PR, and also balance the contradiction of patient-compliance as well as patient-economic-support. According to the results, 81.2% participants finally

completed the 7-day regimen, suggesting the favorable compliance of the patients and the feasibility of this PR pattern. Additionally, we recorded the reasons why the patients did not complete the PR regimen: among the 37 who did not finish the regimen, 29.7% of them could not endure the high-intensive regimen, which also indicated the practicability of this regimen, though further prospective research is currently needed to confirm the view.

We wished that the PR program was sustainable in the current cost-sensitive era, as a cost-effective strategy for the lung cancer patients. The results revealed that there was no increased expenditure in the total in-hospital cost in the PR group compared with the routine group, though the PR group expensed \$142 for the regimen. Moreover, a significant reduced postoperative expense as well as drug, ward, care cost was observed. These economic findings suggested that this rehabilitation model did not increase the economic burden to the participants. Potential explanations for these findings may include fewer PPCs and sequentially better postoperative recovery occurred in the intervention group, which led to shorter postoperative hospital stay, reduced use of medication and medical care and, consequently, lower in-hospital expenses.

Another essential issue was PPCs rate. PPCs significantly contribute to overall perioperative morbidity and mortality rates. However, whether the PR can reduce the rate of PPCs is still unclear (6,20-23), with controversies including exercise duration, suitable or optimal scheduling and content of the exercise. Our results revealed lower occurrences of PPCs, pneumonia and atelectasis, suggesting the effectiveness of this rehabilitation pattern in reducing the PPCs rate. Moreover, the multivariable analysis of risk revealed the PR intervention as independent risk factor for the occurrence of PPCs and atelectasis, providing meaningful evidence of the effectiveness, though for pneumonia, the intervention was not the independent risk factor. Due to the 7-day high-intensive and normative IMT and endurance exercises, the cardiopulmonary endurance of the participants would be enhanced, which might better tolerate the surgery and present better postoperative status or outcomes. Also, shorter average post-length of stay and expense were found in the PR group, revealing the physical and economic benefits the regimen provided for the patients.

This study may be brought to the forefront of further studies regarding the PR program as the concept of enhancing the patients' physical and respiratory health prior to lung surgery is vitally important to the patients. However,

some limitations exist which are inevitably ignored, as this is a retrospective cohort study with all the subjects from a single medical center. Firstly, as this was an exploratory study, we mainly selected risk factors based on the National Expert Consensus and Guidelines for Thoracic Surgery (2012) and a combination of literature review and empiric analysis. Secondly, this rehabilitation regimen did have some contraindications, including myocardial infarction or cerebrovascular accident within 1 year, unstable angina pectoris, aneurysm, recent history (<90 days) of hemoptysis, high risk of severe arrhythmia, musculoskeletal or mental disorders, which meant that the population with these contraindications was not included in the PR group. Hence, it was difficult to discuss the impact of this difference between the groups, which may limit the generalization of the conclusions. Thirdly, baseline FEV₁ parameter presented a marginally statistical significant difference (P=0.059) between PR and NPR groups. The reasons of this tendency may be that patients with poorer lung function would more likely to participant in the PR regimen as they might be more interest in the benefit from the PR. This bias may confound the results, and further affect the conclusion. Fourth, with regard to in-hospital expense, we did not specially analyze the PPC-related cost, which might be more convictive to suggest the cost-effectiveness of this PR program. In addition, we merely collected the data of PPCs after surgery in 30 days, without their long-term outcome. Furthermore, to better evaluate the effectiveness of the program in the enhancement of cardiopulmonary endurance, some instruments, for example, 6 min walk test or CPET (cardiopulmonary exercise test) should be used in our further study.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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