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ORIGINAL ARTICLE

Effects of exercise training on exercise capacity in patients with non-small cell lung cancer receiving targeted therapy

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Abstract
Purpose Peak oxygen consumption (VO_{2peak}) is an important predictive factor for long-term prognosis in patients with non-small cell lung cancer (NSCLC). The purpose of this study was to investigate whether 8 weeks of exercise training improves exercise capacity, as assessed by VO_{2peak}, and other related factors in patients with NSCLC receiving targeted therapy.
Methods A total of 24 participants with adenocarcinoma were randomly assigned to either the control group (n=11) or the exercise group (n=13). Subjects in the exercise group participated in individualized, high-intensity aerobic interval training of exercise. The outcome measures assessed at baseline and after 8 weeks were as follows: VO_{2peak} and the percentage of predicted VO_{2peak} (%predVO_{2peak}), muscle strength and endurance of the right quadriceps, muscle oxygenation during exercise, insulin resistance as calculated by the homeostasis model, high-sensitivity C-reactive protein, and quality of life (QoL) questionnaire inventory.
Results No exercise-related adverse events were reported. After exercise training, VO_{2peak} and %predVO_{2peak} increased by 1.6 mL kg^{-1} min^{-1} and 5.3% (p<0.005), respectively; these changes were associated with improvements in circulatory, respiratory, and muscular functions at peak exercise (all p=0.001). The exercise group also had less dyspnea (p=0.01) and favorably lower fatigue (p=0.05) than baseline.
Conclusions Patients with NSCLC receiving targeted therapy have quite a low exercise capacity, even with a relatively high QoL. Exercise training appears to improve exercise capacity and alleviate some cancer-related symptoms.

Keywords Aerobic exercise · Exercise tolerance · Skeletal muscle · Quality of life

Background

Lung cancer occurs with a high incidence, and an estimated 226,160 new cases are expected in the USA in 2012 [1]. It remains the leading cause of death among all cancers worldwide. Non-small cell lung cancer (NSCLC) represents approximately 80–85% of the lung cancer cases including the most frequent subtype, adenocarcinoma [2, 3]. The recently developed targeted therapy has significantly improved the survival rate and quality of life (QoL) of these patients [4, 5]. This therapy is now employed as a first-line treatment or after first- or second-line chemotherapy. However, patients with NSCLC receiving targeted therapy may develop impaired exercise capacity because of previous anti-cancer treatment, inactivity, lung or other organ pathology, or due to the targeted therapy itself [6]. A study has also shown that Sorafenib, an anti-angiogenic agent, led to muscle loss and further physical deconditioning in patients with advanced renal cancer [7].

Poor VO_{2peak} or insufficient physical performance is associated with precautions for anti-cancer treatment, high post-operative complications, and poor long-term prognosis [8, 9]. Skeletal muscle wasting is observed in nearly half of

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patients with NSCLC [10] who might experience further exercise intolerance. Muscle wasting and limited exercise capacity are associated with inflammatory, metabolic, and neuroendocrine changes that, together, could influence patient QoL. A negative correlation between inflammation and exercise capacity has been reported in patients with NSCLC [11]. A tendency toward glucose intolerance or insulin resistance has also been observed in patients with lung cancer compared with healthy subjects [12, 13].

Exercise training has been shown to have beneficial effects on exercise capacity, functional activities, and QoL in patients with cancer [14]. However, most of the data have been reported for patients with breast cancer or mixed cancer types. Studies on patients with lung cancer and heterogeneous clinical characteristics have mostly been limited by quasi-experimental design, small sample size, and various rehabilitation programs [15–17]. No study has yet investigated the effect of exercise training on exercise capacity in patients with NSCLC receiving targeted therapy. A randomized, controlled trial was conducted to examine the effects of an 8-week, high-intensity aerobic interval training program on exercise capacity, as assessed by VO_{2peak} as the primary outcome, in patients with NSCLC receiving targeted therapy. We proposed a positive impact from training and hypothesized that the improvement would be associated with alterations in the secondary outcomes, which were muscle strength, endurance and oxygenation during exercise, insulin resistance, inflammatory response, and QoL.

Materials and methods

Participants

Subjects aged 40–75 years, with a diagnosis of adenocarcinoma for more than 4 weeks and an Eastern Cooperative Oncology Group performance status of 0 or 1, were recruited from the outpatient department of the National Taiwan University Hospital. Subjects were only included if they were medically stable and only received epidermal growth factor receptor inhibitors for ≥4 weeks. Conditions that excluded subjects from the study were a diagnosis of diabetes, an unstable condition from metastasis, primary lung disease other than lung cancer, severe cardiac or musculoskeletal conditions that might affect their participation in exercise or influence their exercise performance [18], or the inability to understand verbal or written instructions. This study was registered (NCT01136083) and approved by the Institutional Committee of Ethics (201003046R). Written informed consent was obtained from all the participants before initiating this study.

Randomization

After baseline assessment, participants were randomly assigned to either the exercise group or the control group. A computer number generator was used to assign a random order in the block of four. This allocation procedure was performed by an individual who was unaware of the purpose of this study.

Control group

The control group received the usual care, general patient education, and social phone calls every 2–3 weeks, without supervised exercise intervention. General exercise instructions with the Theraband® Elastic Band were given if the subjects in the control group specifically asked for exercise consultation.

Exercise group

Participants in the exercise group exercised on a treadmill or cycling ergometer in the outpatient clinic three times a week for 24 sessions. Exercise training consisted of 2–5-min intervals, alternating with high intensity [80% VO_{2peak}, or a rate of perceived exertion (RPE) of 15–17], and active recovery of moderate intensity (60% VO_{2peak}, or a RPE of 11–13). Each exercise session was 30–40 min in length, including 10-min warm-up and 5-min cool-down phases, under one-to-one supervision from a physical therapist. Heart rate (HR), blood pressure, and oxygen saturation were monitored prior to, during, and after each exercise session. The exercise program, including interval intensity and duration, was adjusted by the physical therapist every 1–2 weeks based on the individual's exercise response. Adverse events that occurred during training or those reported by patients were recorded. Exercise adherence was defined as the percentage of number of sessions attended out of the total 24.

Outcome measures

The basic data for each participant were obtained from medical charts and personal interviews. Body height and weight were measured to calculate body mass index. Structured questionnaires were used to monitor habitual physical activity levels and diet throughout the study period. The testing protocol, including the assessments of VO_{2peak}, muscle strength, endurance and oxygenation during exercise, insulin resistance, inflammatory response, and QoL, was performed at baseline and after 8 weeks. All tests were performed by a blinded assessor.

Cardiopulmonary exercise testing (CPET)

Each participant underwent symptom-limited CPET on a cycle ergometer with a Vmax Series V229 gas analyzer (Vmax229; Sensor Medics, Anaheim, CA, USA). Participants began cycling at 20 W for 1 min, and the workload was increased from 5 to 20 W/min, depending on the participant's comorbidities, treatment history, or exercise response in the first minute until the peak exercise level was reached [19, 20]. Cardiometabolic and ventilatory responses, such as respiratory exchange rate (RER) and VO_{2peak}, were determined on a breath-by-breath basis, and the averages were calculated using the software over a 30-s interval. Respiratory parameters, HR, blood pressure, and the reason for termination were recorded. The percentage of predicted VO_{2peak} (%predVO_{2peak}) was calculated using a prediction equation based on sex, age, height, and weight [21].

Near-infrared spectroscopy (NIRS)

NIRS was conducted simultaneously during the CPET with a probe that included detectors, and 690- and 830-nm light sources (ISS Imagent, ISS Inc., IL, USA). The sampling frequency was set at 2 Hz. The probe was firmly attached to the skin overlying the lower third of the vastus lateralis muscle (approximately 10–12 cm above the knee joint) of the lower right limb [22], parallel to the major axis of the thigh. The levels of oxygenated and deoxygenated hemoglobin were determined. Muscle oxygenation, as assessed by oxygen saturation in the muscle (S_tO_2), was calculated as an average during a 2-min rest and at the termination of the CPET by using the following formula: (oxygenated hemoglobin content)/(oxygenated hemoglobin and deoxygenated hemoglobin content) × 100%. The relative change (ΔS_tO_2) was then determined using the following formula: $S_tO_{2peak} - S_tO_{2resting} / S_tO_{2resting} \times 100\%$.

Venous blood sample analysis

Plasma fasting glucose levels were measured using an Ektachem DT60 II chemistry analyzer (Johnson and Johnson, Rochester, NY, USA), while plasma insulin levels were measured by radioimmunoassay (INS-IRMA; Biosource Europe S.A., Nivelles, Belgium). Using a homeostatic model of insulin resistance (HOMA-IR), insulin resistance was calculated using the following formula: HOMA-IR = fasting plasma insulin level (μU/mL) × fasting plasma glucose level (mM)/22.5 [23]. High-sensitivity C-reactive protein (Hs-CRP) levels were analyzed using a Biochemical Analyzer (TBA-120FR; Toshiba, Tokyo, Japan).

Isokinetic muscle testing

Isokinetic muscle testing of the right quadriceps at a velocity of 180° s^{-1} was performed using the Biodex isokinetic dynamometer (Bioex Medical Inc., Shirley, NY, USA) after a 10-min warm-up and five submaximal knee extension repetitions from 90° of knee flexion for familiarization. Subjects then performed 25 continuous maximal knee extension repetitions to determine the peak concentric torque and total work done, which was representative of muscle strength and endurance. The test–retest reliability is 0.91 for peak torque and 0.84 for work done [24].

Assessment of QoL

The European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30, Chinese language version), with established reliability and validity, was used [25]. It consisted of global health status and QoL scales, functional scales, and specific symptom scales that included dyspnea (together with lung cancer-specific symptom QLQ-LC13) and fatigue. The raw data from the questionnaire were transformed into a score ranging from 0 to 100. A high score indicated a better QoL, except on symptom scales with high values referring to more severe symptomatic problems.

Statistical analysis

Statistical analyses were conducted using SPSS™ 13.0. A two-sided p value of <0.05 indicated statistical significance. Continuous data are shown as mean±standard deviation (SD), and dichotomous data are shown as counts (percentage). Hs-CRP data were transformed by natural logarithms. Two-way repeated measures analysis of variance was performed for each variable with time and group factors. The baseline-observation-carried-forward approach was the method applied to handle missing data. Post hoc analysis was carried out with an adjusted alpha level to determine significant interaction effects. Given the scale property, small sample size, and non-normal distribution data, non-parametric statistics were used to examine within-group effects through time and between-group effects on QoL. The Pearson correlation was used to examine the relationship between the change of exercise capacity and changes in other outcomes.

Results

A total of 24 outpatients were recruited and randomized into either the exercise or the control group. A minor reallocation was made at the beginning of the study (Fig. 1): two participants

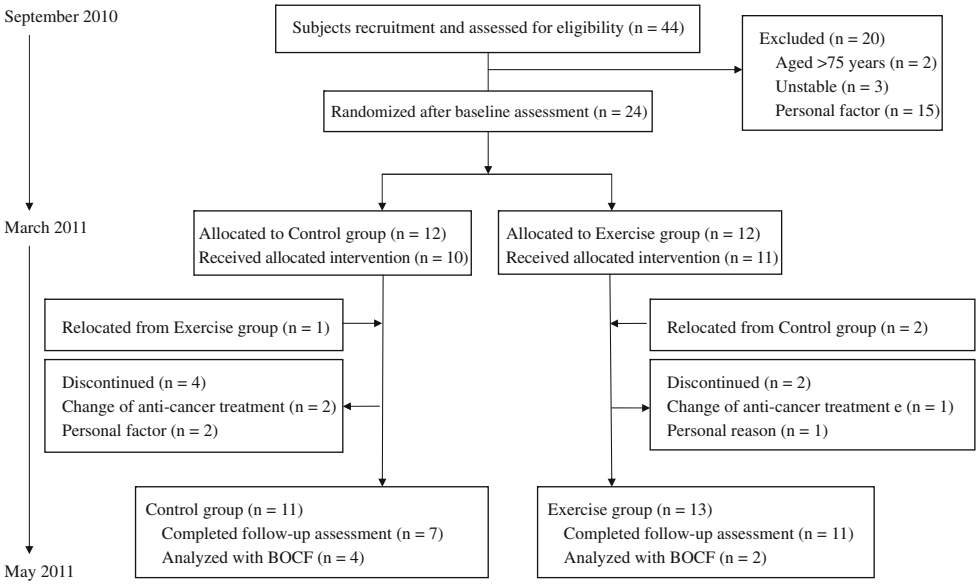

Fig. 1 Schematic flow chart of the study. *BOCF* baseline observation carried forward

were very motivated to participate in exercise training, while one who lived at a distance from the outpatient clinic wanted to be assigned to the control group right after the assignment. The exercise and control groups finally included 13 and 11 participants, respectively. None of the participants had a history of chronic obstructive pulmonary disease and most were stage IV. A total of 39.1% and 65.2% participants had had previous lung surgery and chemotherapy, respectively (Table 1). The median number of previous chemotherapy lines was 1. With regard to treatment, eight participants (five in the control group) had targeted therapy as first-line treatment, five took Iressa, one was on Tarceva, and two received Afatinib in the context of a clinical trial. In the control group, three participants took Afatinib with a previous history of receiving another targeted therapy. Six participants had brain metastasis (two in the control group) and two (both in the control group) had bone metastasis. One participant in the control group refused to perform CPET and six participants (four in the control group) declined venipuncture for laboratory testing at baseline measurement. No between-group differences in the clinical characteristics or the outcome measures were observed at baseline. All participants had a VO_{2peak} of 15.8± 4.0 mL kg^{-1} min^{-1} and %predVO_{2peak} of 49.1±9.8%, ranging from 28.6% to 59.4% as a whole group, and maintained their physical activity and diet throughout the study. Six participants did not return for the follow-up assessment. Two lacked motivation, one had a time conflict, and three participants, who switched from their original targeted therapy (one took Iressa, Tarceva, and Afatinib, respectively) to chemotherapy, refused because of concern about poor responses and disease progression.

Exercise adherence

The mean and median adherence rate of the exercise group was 71.2% and 83.3%, respectively (range 4.2–100%). An attendance rate of 75% or higher was achieved by nine participants (69.2%), with three (12.5%) attending all 24 exercise sessions. The reasons for non-attendance were mainly personal reasons, such as time limitations and family problems. Others were medically related, including fatigue, body discomforts, falling accidents at home, and hospitalization owing to pericardial effusion. However, none of these reasons were directly related to exercise training and no exercise-related adverse events were reported.

Effects of exercise training

The subjects in the exercise group showed a significant increase in VO_{2peak} (+1.6, 95% CI, 0.9–2.3 mL kg^{-1} min^{-1}, $p<0.005$) and %predVO_{2peak} (+5.3, 95% CI, 2.9–7.7%, $p<0.005$), while the values for the control group remained unchanged for both VO_{2peak} (−0.4, 95% CI, −1.2–0.4 mL kg^{-1} min^{-1}, $p=0.27$) and %predVO_{2peak} (−1.5, 95% CI, −4.2–1.3%, $p=0.28$) (Fig. 2). Similar results were found for the peak workload (+12, 95% CI, 7–16 W), and the tidal volume (0.11, 95% CI, 0.03–0.20 L), increased considerably in the exercise group and remained unchanged in the control group. Peak O_2 pulse tended to increase in the exercise group (+0.3, 95% CI, 0.0–0.7, $p=0.08$), but decreased in the control group (−0.3, 95% CI, −0.8–0.1 mL min^{-1}, $p=0.13$).

Peak torque and total work of the right quadriceps increased in all participants at the post-test. No interaction, time, or group effect was noted in the other outcomes (Table 2). The HOMA-IR and Hs-CRP remained unchanged in both groups. No between-group differences in QoL scales were found (Table 3). However, the exercise group displayed significant improvements in dyspnea and favorably decreased fatigue ($p=0.05$) compared with baseline.

Table 1 Clinical characteristics of the control and exercise groups in patients with NSCLC receiving targeted therapy

	Control (n=11)	Exercise (n=13)
Age (years)	58.5±8.2	61.0±6.3
Male (n)	7 (63.6)	5 (38.5)
Smoking status (n)		
Current or quit less than 6 months	1 (9.1)	0 (0.0)
Ever	3 (27.3)	2 (15.4)
Never	7 (63.6)	11 (84.6)
Body mass index (kg/m^2)	23.1±2.6	22.6±2.4
Time since diagnosis (years)	2.8±2.4	2.6±2.1
Stage (n)		
III A	1 (9.1)	1 (7.7)
III B	0 (0.0)	2 (15.4)
IV	10 (90.9)	10 (76.9)
Targeted therapy type (n)		
Iressa	3 (27.2)	5 (38.5)
Tarceva	4 (36.4)	7 (53.8)
Afatinib	4 (36.4)	1 (7.7)
Length of targeted therapy period (months)	7.2±7.1	11.0±11.2
Previous therapy (n)		
Chemotherapy	5 (45.6)	10 (76.9)
Radiotherapy	5 (45.5)	8 (61.5)
Lobectomy	3 (27.3)	2 (15.4)
Bilobectomy	1 (9.1)	1 (7.7)
Wedge resection	0 (0.0)	2 (15.4)
Brain operation	0 (0.0)	4 (30.8)
Comorbidity (n)		
Hypertension	3 (27.3)	6 (46.2)
Dyslipidemia	1 (9.1)	2 (15.4)
Coronary artery disease	1 (9.1)	0 (0.0)
Peripheral vascular disease	0 (0.0)	1 (7.7)

Data presented as mean±standard deviation or count (percentage)
NSCLC non-small cell lung cancer

Relationship between changes in outcome measures after exercise intervention

The improvement in %predVO_{2peak} was strongly associated with increases in the peak workload (r=0.95), minute ventilation (r=0.63), tidal volume (r=0.64), and O_2 pulse (r=0.64) (all p=0.001). A significant, moderate correlation was found between improvement in the %predVO_{2peak} and role functioning (r=0.41) in QoL among all correlations made with changes in muscle function, insulin resistance, inflammatory response, and QoL. A moderate, negative correlation was noted between the symptoms of dyspnea and cognitive (r=−0.48) and social functioning QoL (r=−0.49). The increase in emotional functioning QoL was also moderately related to an amelioration in fatigue (r=−0.51).

Discussion

This study is the first to investigate the training effect on exercise capacity, muscle function, insulin resistance, inflammatory response, and QoL in patients with NSCLC at advanced stages who were receiving targeted therapy. It provides basic information about the functional capacity, muscular strength/endurance, and QoL of these patients. Patients in the exercise group exhibited significant improvements in exercise capacity that were associated with ameliorations in circulatory, respiratory, and muscular functions. Decreased dyspnea was also noted. Patients in the control group showed no changes in the outcomes of interest, except for a small improvement in fatigue with no between-group significant differences.

Our patients, who had a diagnosis of NSCLC and received only targeted therapy, had low %predVO_{2peak} despite relatively few symptoms, and acceptable QoL, which was consistent with our clinical impression. Patients with NSCLC whose activity level at diagnosis was decreased have been shown to have higher risks of mortality [26]. VO_{2peak} was shown to be an important factor affecting survival in lung cancer patients without resection [8]. If VO_{2peak} >13.9 mL kg^{-1} min^{-1}, a mortality rate decrease by 4% was associated with 1.0 mL kg^{-1} min^{-1} increments in VO_{2peak}. Maintaining exercise capacity or keeping active can prevent sedentary-related disorders, and improve daily activity and independence. Exercise training is suggested to improve exercise capacity in patients with NSCLC [16, 17, 27, 28]. Some single-group studies have shown improvements in VO_{2peak} by 1.7–2.9 mL kg^{-1} min^{-1} through exercise training in operable lung cancer patients [27–30]. Our study also supports the positive impact of exercise training on VO_{2peak} for inoperable patients or for those with an advanced stage of NSCLC.

Following 8 weeks of exercise training, our patients displayed improvements in VO_{2peak}, with a 10.5% improvement by 1.6 mL kg^{-1} min^{-1} increments. The VO_{2peak} of patients waiting for lung resection increased by 15–20% after training [28, 30], while an improvement of only 11.3% was noted in patients after lung resection [29]. Similarly, our patients without and with lung resection had 12.2% and 6.7% improvements in VO_{2peak}, respectively. Whether this phenomenon relates to targeted therapy or whether reduced lung volume weakens the effects of exercise remains unclear. Moreover, patients with breast cancer receiving chemotherapy were reported to show an improvement of approximately 40% in VO_{2peak} after a 10-week training program [31]. Lesser increases in VO_{2peak} for patients with NSCLC following exercise training were

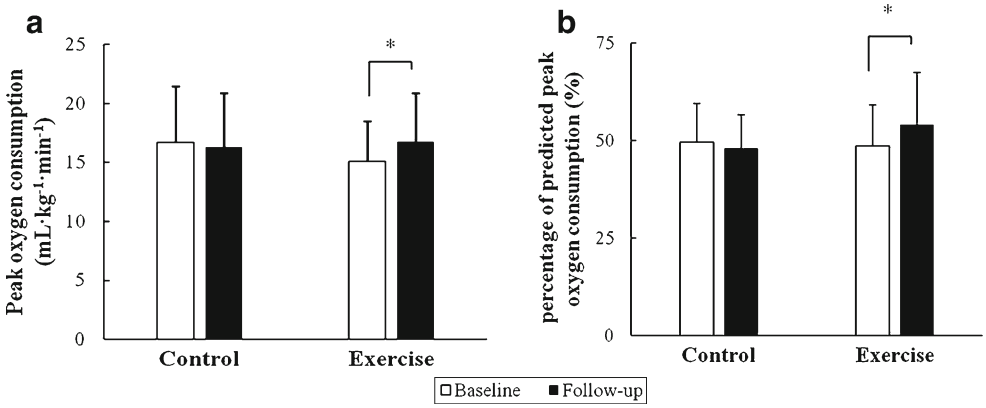

Fig. 2 Effects of exercise training on **a** peak oxygen consumption and **b** percentage of predicted peak oxygen consumption. *$p<0.05/2$

noted in a previous study consisting of both continuous and interval training [27–29], as well as in the present study. Longer training periods may be required to achieve further improvements in exercise capacity in patients with NSCLC.

Exercise intolerance in patients with lung cancer was affected by multiple factors that were mainly related to tumor pathology or respiratory limitations. The reasons for terminating CPET in our patients at baseline included dyspnea (47.8%), leg fatigue (26.1%), HR ≥90% of age-predicted maximal HR (17.4%), as well as other symptoms (4.3%). A previous study suggested that high intensity exercise may ameliorate exercise intolerance due to ventilation

Table 2 Effects of exercise training on exercise testing, blood analysis, and isokinetic muscle testing in patients with NSCLC receiving targeted therapy

	Control (n=10)		Exercise (n=13)		p value		
	Baseline	Follow-up	Baseline	Follow-up	Time×group effect	Time effect	Group effect
Exercise testing at end-point							
VO_{2peak} (mL kg^{-1} min^{-1})	16.7±4.8	16.3±4.6	15.1±3.4	16.8±4.1	<0.005	–	–
%predVO_{2peak} (%)	49.5±9.9	48.0±8.4	48.7±10.1	54.0±13.5	<0.005	–	–
Work load (W)	85±25	80±24	72±25	84±25	<0.005	–	–
RER	1.22±0.11	1.22±0.13	1.24±0.09	1.23±0.38	0.61	0.56	0.57
O_2 pulse (mL min^{-1})	8.0±2.1	7.7±2.1	6.9±2.1	7.3±2.1	0.03	–	–
Minute ventilation (L min^{-1})	40.4±10.4	38.9±9.4	38.9±9.0	40.5±13.3	0.24	1.00	0.98
Tidal volume (L)	1.35±0.32	1.33±0.33	1.12±0.30	1.23±0.38	0.045	–	–
Heart rate (bpm)	127±11	130±15	134±11	139±12	0.55	0.13	0.09
Heart rate predict (%)	79.4±4.2	81.0±8.0	84.2±8.5	87.7±9.2	0.55	0.12	0.06
Systolic blood pressure (mmHg)[a]	167±24	169±21	171±11	181±16	0.33	0.10	0.33
Diastolic blood pressure (mmHg)[a]	72±6	95±10	78±10	15±10	0.31	0.56	0.34
ΔS_tO_2 (%)[b]	−14.0±10.0	−10.4±10.4	−6.2±12.4	−8.2±7.9	0.25	0.73	0.22
Venous blood sample analysis[c]							
HOMA	1.71±0.73	1.84±0.76	2.82±1.26	2.73±1.26	0.62	0.93	0.06
Hs-CRP (mg L^{-1})	2.29±2.01	7.33±11.66	6.21±7.67	5.30±9.21	0.20	0.74	0.50
Isokinetic muscle testing[d]							
Peak torque (N m)	61.4±19.3	67.0±20.2	55.7±18.1	61.2±13.9	0.97	<0.005	0.43
Total work done (J)	1,496.8±454.0	1,660.6±496.2	1,366.2±413.1	1,485.1±455.7	0.59	<0.005	0.41

Data presented as mean±standard deviation

NSCLC non-small cell lung cancer, *VO_{2peak}* peak oxygen consumption, *%predVO_{2peak}* percentage of predicted peak oxygen consumption, *RER* respiratory exchange rate, *ΔS_tO_2* relative change of muscle oxygenation from baseline, *HOMA-IR* homeostatic model assessment of insulin resistance, *Hs-CRP* high-sensitive C-reactive protein

[a] n (control/exercise)=10/11

[b] n (control/exercise)=9/12

[c] n (control/exercise)=7/11

[d] n (control/exercise)=11/13

Table 3 Effects of exercise training on the quality of life in patients with NSCLC receiving targeted therapy

	Control (n=11)		Exercise (n=13)		p value		
	Baseline	Follow-up	Baseline	Follow-up	Within-group effect		Between-group effect
					Control	Exercise	
Global health status and QOL	62.1±14.1	65.2±15.3	73.1±14.5	78.2±16.1	0.34	0.17	0.45
Physical functioning	90.3±12.1	87.9±11.9	93.8±6.9	92.3±6.6	0.26	0.17	0.88
Role functioning	90.9±15.6	90.9±15.6	96.2±7.3	96.1±7.3	0.10	0.47	0.08
Emotional functioning	85.6±17.1	85.6±13.0	88.5±12.5	91.7±12.3	0.23	0.14	0.06
Cognitive functioning	84.8±11.7	84.8±11.7	83.3±11.8	87.2±13.9	0.23	0.35	0.22
Social functioning	89.4±21.4	87.8±21.7	88.5±19.7	91.0±12.9	0.14	0.73	0.23
Dyspnea[a]	15.2±14.3	13.6±14.6	9.6±10.7	3.8±5.5	0.06	0.01	0.06
Fatigue	26.3±20.0	17.2±18.2	14.5±13.9	9.4±11.9	0.01	0.05	0.30

Data presented as mean±standard deviation

NSCLC non-small cell lung cancer, *QOL* quality of life

[a] Combined item with QLQ-C30 and LC13

limitations in patients with lung disease [32]. Our study showed that exercise-induced improvements in exercise capacity were associated with an increase in O_2 pulse, minute ventilation, and tidal volume, but not with improvements in O_2 extraction in the muscles. Instead, enhanced oxidative or metabolic abilities of mitochondria in the muscles [33–35] may be a possible mechanism. More efficient energy metabolism with similar O_2 delivery and extraction might lead to better exercise performance.

This study has revealed that exercise training is beneficial in alleviating dyspnea, even for patients with mild symptoms. A small change in dyspnea [36] is significant for patients with lung cancer. Patients in the exercise group may be accustomed to breathing difficulty during high intensity exercise [31], thus resulting in a longer test and higher VO_{2peak} measurement. However, in this study, no direct relationship was found between a change in exercise capacity and dyspnea. Instead, the decreases in dyspnea were moderately associated with improvements in cognitive and social functioning QoL. Through the interactions with the study personnel and patient education, participants in the exercise group may learn to better cope with their symptoms. Interestingly, a similar finding was observed with the correlation between a reduction in fatigue and improvements in emotional functioning, rather than exercise capacity. Multiple and complex factors, including tumor progression, underlying comorbidities, social participation, or even personal characteristics, may affect the level of fatigue perceived by patients. Progressive fatigue has been reported to be associated with severe pain and depression in advanced cancer patients [37]. Not all of the participants had a high degree of fatigue, although a favorable improvement was observed in the exercise group. The participants were mostly high in emotional functioning; however, one person in the control group was taking an anti-depressant throughout the study. Further studies are needed to investigate other disease impacts and/or the training effect on the QoL. Moreover, a ceiling effect may exist and contribute to the insignificant findings given that most of our subjects were relatively high functioning.

This study did not reveal the effects of exercise training on muscle strength, endurance, insulin resistance, or inflammatory response. Previous studies reported no change in muscle strength in patients with NSCLC after resection or at an advanced stage following combined aerobic and resistance exercise [15, 38]. The specificity or loading of the training type may contribute to this finding. Alternatively, the isokinetic test performed at 180° s^{-1} used in this study may not have been sensitive enough to detect the effects of our intervention. Nearly all participants in the control group asked for exercise consultation. This may partly explain the insignificant between-group differences observed, although none of the participants adhered to it based on their reports at follow-up. In patients with advanced lung cancer, HOMA-IR was greater than in those with limited lung cancer [39]. An in vitro study also indicated that insulin might play a direct role in tumor angiogenesis of adenocarcinoma [40]. CRP was primarily associated with tumor size in patients with NSCLC who had the potential of being cured by resection [41]. CRP is also considered a survival predictor in inoperable patients with NSCLC [42, 43]. Although the underlying mechanisms of insulin resistance, inflammatory response, and tumor angiogenesis remain uncertain, exercise training does not appear to regulate these complex relationships efficiently in conjunction with targeted therapy.

There were several limitations of this study. Our findings may be limited for generalization because of the relatively small sample size and also due to the inclusion criteria specifying that only patients who were medically stable and who had received targeted therapy for at least 1 month could be enrolled in the study. In addition, we did not define the maximal length of targeted therapy as one of the inclusion criteria. Difficulty in recruiting subjects for exercise training in the lung cancer population has been reported, especially among outpatients [16, 27–29, 38]. A high rate of decline-to-participate and higher-than-average dropout rates were noted, possibly weakening the effects of the exercise training and contributing to our insignificant results. The training protocol appeared to be safe with no adverse events were reported; however, motivation remained as the major issue needing to be addressed with oncology rehabilitation. Heterogeneity has been noted in the existing studies investigating exercise training for patients with lung cancer. Given that survival rate is improved by targeted therapy, more studies should be undertaken to verify the benefits of exercise and to uncover the underlying mechanisms.

In conclusion, patients with NSCLC receiving targeted therapy have quite a low exercise capacity despite having a high QoL. Interventions aimed at normalizing this patient population with respect to daily living are important in oncology rehabilitation. Subjects who participated in an 8-week exercise training significantly improved in exercise capacity, which was associated with improvements in the parameters of circulatory, respiratory, and muscle functions. Marked decreases in dyspnea and a favorable trend of lessening fatigue were also noted after training. Exercise training appears to be safe and effective for patients with NSCLC receiving targeted therapy. Future randomized, controlled studies with larger sample sizes are therefore warranted.

Conflict of interest All authors claimed no disclosure and had full control of all primary data. All authors agree to allow the journal to review data if requested.

References

1. Siegel R, Naishadham D, Jemal A (2012) Cancer statistics, 2012. CA Cancer J Clin 62(1):10–29. doi:10.3322/caac.20138
2. D'Addario G, Felip E (2009) Non-small-cell lung cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 20(Suppl 4):68–70. doi:10.1093/annonc/mdp132
3. Herbst RS, Heymach JV, Lippman SM (2008) Lung cancer. N Engl J Med 359(13):1367–1380. doi:10.1056/NEJMra0802714
4. Sanford M, Scott LJ (2009) Gefitinib: a review of its use in the treatment of locally advanced/metastatic non-small cell lung cancer. Drugs 69 (16):2303–2328. doi:10.2165/10489100-000000000-00000
5. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, Campos D, Maoleekoonpiroj S, Smylie M, Martins R, van Kooten M, Dediu M, Findlay B, Tu D, Johnston D, Bezjak A, Clark G, Santabarbara P, Seymour L (2005) Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 353(2):123–132. doi:10.1056/NEJMoa050753
6. Jones LW, Eves ND, Haykowsky M, Freedland SJ, Mackey JR (2009) Exercise intolerance in cancer and the role of exercise therapy to reverse dysfunction. Lancet Oncol 10(6):598–605. doi:10.1016/S1470-2045(09)70031-2
7. Antoun S, Birdsell L, Sawyer MB, Venner P, Escudier B, Baracos VE (2010) Association of skeletal muscle wasting with treatment with sorafenib in patients with advanced renal cell carcinoma: results from a placebo-controlled study. J Clin Oncol 28 (6):1054–1060. doi:10.1200/JCO.2009.24.9730
8. Jones LW, Watson D, Herndon JE 2nd, Eves ND, Haithcock BE, Loewen G, Kohman L (2010) Peak oxygen consumption and long-term all-cause mortality in nonsmall cell lung cancer. Cancer 116 (20):4825–4832. doi:10.1002/cncr.25396
9. Win T, Jackson A, Sharples L, Groves AM, Wells FC, Ritchie AJ, Laroche CM (2005) Cardiopulmonary exercise tests and lung cancer surgical outcome. Chest 127(4):1159–1165. doi:10.1378/chest.127.4.1159
10. Baracos VE, Reiman T, Mourtzakis M, Gioulbasanis I, Antoun S (2010) Body composition in patients with non-small cell lung cancer: a contemporary view of cancer cachexia with the use of computed tomography image analysis. Am J Clin Nutr 91 (4):1133S–1137S. doi:10.3945/ajcn.2010.28608C
11. Jones LW, Eves ND, Mackey JR, Peddle CJ, Haykowsky M, Joy AA, Tankel K, Courneya KS, Reiman T (2008) Systemic inflammation, cardiorespiratory fitness, and quality of life in patients with advanced non-small cell lung cancer. J Thorac Oncol 3(2):194–195. doi:10.1097/JTO.0b013e318160f36b
12. Heber D, Chlebowski RT, Ishibashi DE, Herrold JN, Block JB (1982) Abnormalities in glucose and protein metabolism in non-cachectic lung cancer patients. Cancer Res 42(11):4815–4819
13. Yoshikawa T, Noguchi Y, Doi C, Makino T, Nomura K (2001) Insulin resistance in patients with cancer: relationships with tumor site, tumor stage, body-weight loss, acute-phase response, and energy expenditure. Nutrition 17(7-8):590–593
14. Galvao DA, Newton RU (2005) Review of exercise intervention studies in cancer patients. J Clin Oncol 23(4):899–909. doi:10.1200/JCO.2005.06.085
15. Arbane G, Tropman D, Jackson D, Garrod R (2011) Evaluation of an early exercise intervention after thoracotomy for non-small cell lung cancer (NSCLC), effects on quality of life, muscle strength and exercise tolerance: randomised controlled trial. Lung Cancer 71(2):229–234. doi:10.1016/j.lungcan.2010.04.025
16. Andersen AH, Vinther A, Poulsen LL, Mellemgaard A (2011) Do patients with lung cancer benefit from physical exercise? Acta Oncol 50(2):307–313. doi:10.3109/0284186X.2010.529461
17. Riesenberg H, Lubbe AS (2010) In-patient rehabilitation of lung cancer patients—a prospective study. Support Care Cancer 18 (7):877–882. doi:10.1007/s00520-009-0727-y
18. Thompson WR, Gordon NF, Pescatello LS (2010) ACSM's guidelines for exercise testing and prescription. Williams & Wilkins, Philadelphia
19. Jones LW, Eves ND, Haykowsky M, Joy AA, Douglas PS (2008) Cardiorespiratory exercise testing in clinical oncology research: systematic review and practice recommendations. Lancet Oncol 9 (8):757–765. doi:10.1016/S1470-2045(08)70195-5
20. Jones LW, Eves ND, Mackey JR, Peddle CJ, Haykowsky M, Joy AA, Courneya KS, Tankel K, Spratlin J, Reiman T (2007) Safety and feasibility of cardiopulmonary exercise testing in patients with advanced cancer. Lung Cancer 55(2):225–232. doi:10.1016/j.lungcan.2006.10.006
21. Fairbarn MS, Blackie SP, McElvaney NG, Wiggs BR, Pare PD, Pardy RL (1994) Prediction of heart rate and oxygen uptake during incremental and maximal exercise in healthy adults. Chest 105 (5):1365–1369

22. Austin KG, Daigle KA, Patterson P, Cowman J, Chelland S, Haymes EM (2005) Reliability of near-infrared spectroscopy for determining muscle oxygen saturation during exercise. Res Q Exerc Sport 76 (4):440–449
23. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC (1985) Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28(7):412–419
24. Wilcock A, Maddocks M, Lewis M, Howard P, Frisby J, Bell S, El Khoury B, Manderson C, Evans H, Mockett S (2008) Use of a Cybex NORM dynamometer to assess muscle function in patients with thoracic cancer. BMC Palliat Care 7:3. doi:10.1186/1472-684X-7-3
25. Chie WC, Yang CH, Hsu C, Yang PC (2004) Quality of life of lung cancer patients: validation of the Taiwan Chinese version of the EORTC QLQ-C30 and QLQ-LC13. Qual Life Res 13(1):257–262
26. Blanchon F, Grivaux M, Asselain B, Lebas FX, Orlando JP, Piquet J, Zureik M (2006) 4-year mortality in patients with non-small-cell lung cancer: development and validation of a prognostic index. Lancet Oncol 7(10):829–836. doi:10.1016/S1470-2045(06)70868-3
27. Jones LW, Eves ND, Peddle CJ, Courneya KS, Haykowsky M, Kumar V, Winton TW, Reiman T (2009) Effects of presurgical exercise training on systemic inflammatory markers among patients with malignant lung lesions. Appl Physiol Nutr Metab 34(2):197–202. doi:10.1139/H08-104
28. Jones LW, Peddle CJ, Eves ND, Haykowsky MJ, Courneya KS, Mackey JR, Joy AA, Kumar V, Winton TW, Reiman T (2007) Effects of presurgical exercise training on cardiorespiratory fitness among patients undergoing thoracic surgery for malignant lung lesions. Cancer 110(3):590–598. doi:10.1002/cncr.22830
29. Jones LW, Eves ND, Peterson BL, Garst J, Crawford J, West MJ, Mabe S, Harpole D, Kraus WE, Douglas PS (2008) Safety and feasibility of aerobic training on cardiopulmonary function and quality of life in postsurgical nonsmall cell lung cancer patients: a pilot study. Cancer 113(12):3430–3439. doi:10.1002/cncr.23967
30. Bobbio A, Chetta A, Ampollini L, Primomo GL, Internullo E, Carbognani P, Rusca M, Olivieri D (2008) Preoperative pulmonary rehabilitation in patients undergoing lung resection for non-small cell lung cancer. Eur J Cardiothorac Surg 33(1):95–98. doi:10.1016/j.ejcts.2007.10.003
31. MacVicar MG, Winningham ML, Nickel JL (1989) Effects of aerobic interval training on cancer patients' functional capacity. Nurs Res 38(6):348–351
32. Butcher SJ, Jones RL (2006) The impact of exercise training intensity on change in physiological function in patients with chronic obstructive pulmonary disease. Sports Med 36(4):307–325
33. Daussin FN, Zoll J, Dufour SP, Ponsot E, Lonsdorfer-Wolf E, Doutreleau S, Mettauer B, Piquard F, Geny B, Richard R (2008) Effect of interval versus continuous training on cardiorespiratory and mitochondrial functions: relationship to aerobic performance improvements in sedentary subjects. Am J Physiol Regul Integr Comp Physiol 295(1):R264–272. doi:10.1152/ajpregu.00875.2007
34. Tjonna AE, Lee SJ, Rognmo O, Stolen TO, Bye A, Haram PM, Loennechen JP, Al-Share QY, Skogvoll E, Slordahl SA, Kemi OJ, Najjar SM, Wisloff U (2008) Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. Circulation 118(4):346–354. doi:10.1161/CIRCULATIONAHA.108.772822
35. Wisloff U, Stoylen A, Loennechen JP, Bruvold M, Rognmo O, Haram PM, Tjonna AE, Helgerud J, Slordahl SA, Lee SJ, Videm V, Bye A, Smith GL, Najjar SM, Ellingsen O, Skjaerpe T (2007) Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. Circulation 115(24):3086–3094. doi:10.1161/CIRCULATIONAHA.106.675041
36. Osoba D, Rodrigues G, Myles J, Zee B, Pater J (1998) Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 16(1):139–144
37. Kilgour RD, Vigano A, Trutschnigg B, Hornby L, Lucar E, Bacon SL, Morais JA (2010) Cancer-related fatigue: the impact of skeletal muscle mass and strength in patients with advanced cancer. J Cachex Sarcopenia Muscle 1(2):177–185. doi:10.1007/s13539-010-0016-0
38. Temel JS, Greer JA, Goldberg S, Vogel PD, Sullivan M, Pirl WF, Lynch TJ, Christiani DC, Smith MR (2009) A structured exercise program for patients with advanced non-small cell lung cancer. J Thorac Oncol 4(5):595–601. doi:10.1097/JTO.0b013e31819d18e5
39. Petridou ET, Sergentanis TN, Antonopoulos CN, Dessypris N, Matsoukis IL, Aronis K, Efremidis A, Syrigos C, Mantzoros CS (2011) Insulin resistance: an independent risk factor for lung cancer? Metabolism. doi:10.1016/j.metabol.2010.12.002
40. Rensing KL, Houttuijn Bloemendaal FM, Weijers EM, Richel DJ, Buller HR, Koolwijk P, van der Loos CM, Twickler TB, von der Thusen JH (2010) Could recombinant insulin compounds contribute to adenocarcinoma progression by stimulating local angiogenesis? Diabetologia 53(5):966–970. doi:10.1007/s00125-010-1687-y
41. Jones JM, McGonigle NC, McAnespie M, Cran GW, Graham AN (2006) Plasma fibrinogen and serum C-reactive protein are associated with non-small cell lung cancer. Lung Cancer 53(1):97–101. doi:10.1016/j.lungcan.2006.03.012
42. Scott HR, McMillan DC, Forrest LM, Brown DJ, McArdle CS, Milroy R (2002) The systemic inflammatory response, weight loss, performance status and survival in patients with inoperable non-small cell lung cancer. Br J Cancer 87(3):264–267. doi:10.1038/sj.bjc.6600466
43. Forrest LM, McMillan DC, McArdle CS, Angerson WJ, Dunlop DJ (2003) Evaluation of cumulative prognostic scores based on the systemic inflammatory response in patients with inoperable non-small-cell lung cancer. Br J Cancer 89(6):1028–1030. doi:10.1038/sj.bjc.6601242