Project summary

Background:
Pulmonary rehabilitation (PR) is known to enhance functional capacity and quality of life (QoL) in lung cancer patients; however, its efficacy in those receiving immune checkpoint inhibitors remains unclear. This study aimed to evaluate the impact of PR on physical performance, fine motor skills, systemic inflammation, progression-free survival (PFS), and QoL in patients with stage IV lung cancer undergoing first-line immunotherapy (with or without chemotherapy).

Methods:
A total of 42 patients were randomized to either a PR group (n=18) or usual care (UC; n=24). The PR intervention consisted of 16 outpatient sessions over 8 weeks. Assessments at baseline and week 8 included: 6-minute walk test (6MWT), Short Physical Performance Battery (SPPB), isometric quadriceps force (QF), 9-Hole Peg Test (9HPT), COPD Assessment Test (CAT), Cancer-Related Fatigue Scale, EQ-5D VAS, and PFS (defined as radiographic or clinical progression or ECOG decline ≥1). Inflammatory markers were calculated using complete blood counts (NLR, PLR, LMR, SII). Twenty-four age-matched healthy controls were evaluated as reference.

Results:
Significant improvements were observed in the PR group from baseline to week 8: 6MWT (+23 ± 28 m, p=0.001), QF (+1.2 ± 1.7 kg, p=0.003), 9HPT (right: −4.5 ± 4.9 s, left: −3.5 ± 4.0 s, both p=0.001), SPPB (+0.4 ± 0.8, p=0.028), 5STS (−1.0 ± 1.4 s, p=0.004), and CAT (−2.3 ± 2.6, p=0.001). A significant reduction in NLR was also noted (p=0.004). PFS tended to be longer in the PR group but was not statistically significant. In contrast, UC participants experienced significant declines in functional measures and symptom scores. Subgroup analysis revealed that patients on combination immunotherapy had lower baseline function but demonstrated greater post-PR gains than those on monotherapy.

Conclusion:
PR significantly improves exercise capacity, muscle strength, dexterity, and QoL in stage IV lung cancer patients receiving immunotherapy, supporting its integration into oncologic care pathways.

281 words

General information

Title:
Effect of Pulmonary Rehabilitation on Functional Capacity, Quality of Life and immunotherapeutic response in Stage IV Lung Cancer Patients.

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Rationale & background information

Lung cancer remains the second most commonly diagnosed malignancy worldwide and the leading cause of cancer-related mortality across both sexes. Epidemiological projections indicate a minimum 13% increase in new lung cancer diagnoses in the coming years.[1] While targeted therapies have modestly extended overall survival—raising 1-year survival to 43% and 5-year survival to 17% of patients[2]—lung cancer remains associated with the highest symptom burden and complication rates among all cancer types, resulting in substantial reductions in health-related quality of life (HRQoL) and premature mortality.[3]

Symptoms such as dyspnea, fatigue, pain, depression, insomnia, and profound skeletal muscle weakness[4] are frequently reported. Lung cancer survivors describe up to a 45% reduction in HRQoL, with symptoms such as fatigue and breathlessness persisting chronically.[5–7] The extended duration of treatment and overlapping comorbidities frequently lead to marked deconditioning, reduced mobility, and avoidance of physical activity (PA), either due to perceived or actual intolerance to exercise.

Notably, lung cancer patients exhibit the lowest rates of physical activity among all cancer populations. A prospective study demonstrated that 36% of patients across disease stages reduced or ceased walking within 6 months of diagnosis.[8–9] This

inactivity is associated with a two-thirds decline in functional capacity and has been linked to shortened survival.[10] Despite robust evidence, physical inactivity remains prevalent.

Recent research increasingly supports that exercise is not only safe and feasible across all cancer types and stages—including advanced disease and bone metastases—but is also therapeutically beneficial.[11–19] Progressive, individualized exercise programs, particularly resistance training, have been shown to enhance muscle strength and reduce fracture risk even in patients with skeletal metastases.[20–23]

Exercise as an Adjunct in Advanced Disease

Ozalevli et al.[24] demonstrated that exercise interventions significantly alleviated pain and dyspnea in patients with terminal-stage lung cancer post-chemotherapy. Henke et al.[25] reported improvements in sleep quality, balance (secondary to peripheral neuropathy), and cognitive functioning. In animal models, daily aerobic exercise suppressed tumor progression[26] and reduced tumor incidence under anaerobic conditions.[27] Furthermore, moderate-intensity exercise enhanced macrophage and leukocyte phagocytic activity in mice with breast adenocarcinoma,[28] while Tai Chi interventions reduced chemotherapy-induced leukopenia in lung cancer patients.[29]

Mechanistic Pathways

Moderate-intensity aerobic exercise limits reactive oxygen/nitrogen species (ROS/RNS) production, upregulates antioxidant gene expression, mitigates DNA damage, and attenuates inflammation—mechanisms involved in both carcinogenesis and tumor progression.[30]

Endocrine Modulation:
Aerobic activity (>30 min/session) influences endocrine pathways implicated in cancer progression. Elevated insulin, estrogen, and IGF-1—linked to obesity, menopause, and hormone therapy—facilitate tumorigenesis and recurrence.[31–34] Exercise counteracts this by directly modulating hormone levels and indirectly through adipose tissue reduction.[35]

Immunologic Activation:
Exercise enhances immune surveillance via increased activity of natural killer (NK) cells—critical in early tumor elimination.[36] Furthermore, exercise induces elevations in lymphocyte and leukocyte counts, which can reduce infection risk during chemotherapy and hematopoietic stem cell transplantation.[37]

Inflammatory Biomarkers:
Exercise has been shown to downregulate pro-inflammatory cytokines (e.g., TNF-α, IL-6), C-reactive protein (CRP), and intercellular adhesion molecule-1 (ICAM-1)—all implicated in lung carcinogenesis and adverse prognosis in non-small cell lung cancer (NSCLC).[38–42] Reduction in these biomarkers correlates with improved survival and decreased cardiopulmonary complications.

Muscular Implications

Cancer-related muscle wasting—sarcopenia—is multifactorial, arising from tumor metabolism, inflammatory milieu, and therapeutic toxicity.[43–45] Even prior to treatment, patients may experience a 1.5 kg reduction in lean mass, progressing to >11 kg loss over extended therapies (>6 months).[44] Resistance training programs (2–3 sessions/week, moderate intensity) have been shown to reverse muscle atrophy, enhancing both strength (12–35% improvement) and lean body mass.[46–47] Proper supervision is essential, particularly in patients with lymphedema or comorbidities.[48]

Cardiorespiratory Fitness

Cardiopulmonary toxicity is common among lung cancer patients, with VO_2max reductions of up to 36%.[2] Chemotherapy alone can result in a 9.7% VO_2max decline within 12 weeks—equivalent to a decade of physiologic aging.[2] Anemia (Hb <12 g/dL in females, <13 g/dL in males) affects up to 100% of patients and is a key contributor to reduced aerobic capacity.[41] Aerobic exercise improves VO_2max by up to 11%, offsetting treatment-induced deconditioning. Optimal intensity should be individualized based on dyspnea thresholds.[25]

Exercise and QoL / Treatment Toxicity

Fatigue prevalence in lung cancer ranges from 37–78%, often correlating with elevated CRP levels.[50] Exercise reduces CRP and improves fatigue, hemoglobin levels, and hematopoietic function—even during bone marrow transplantation.[51] Physical activity also stimulates hematopoietic growth factor release, counteracting chemotherapy-induced anemia.[51]

Prehabilitation and Surgical Outcomes

Preoperative exercise improves physiological reserve and may reclassify inoperable patients as surgical candidates.[25–53] Targeted respiratory training reduces postoperative atelectasis by 25%.[25] Exercise testing (e.g., VO_2peak, 6MWT) has emerged as a superior predictor of postoperative complications compared to spirometry alone.[52–54] Distances <12 meters during pre-op tests correlate with a twofold increase in postoperative morbidity and mortality.

Although physical activity has been shown to enhance chemotherapy and surgical outcomes, its role in augmenting immunotherapy efficacy is underexplored. Preliminary studies suggest that exercise-induced stimulation of NK cells may potentiate immunotherapeutic responses, particularly in lung and breast cancers.[55] Given the overlap between exercise-mediated immunomodulation and immunotherapy mechanisms, a synergistic effect is biologically plausible and warrants further investigation.

To the best of our knowledge, this is the first study to investigate the effects of a structured respiratory rehabilitation program in a homogeneous cohort of lung cancer patients, both in terms of disease stage and treatment regimen

Aim of the Study

Consequently, the aim of this study is to investigate the impact of structured exercise interventions on quality of life and immunotherapeutic response in patients with stage IV lung cancer.

Hypotheses:

1. PR programme will significantly improve functional capacity, overall HRQoL and alleviate treatment-related side effects—particularly fatigue and physical deconditioning.
2. PR programme will enhance immunotherapy efficacy, as reflected by extended progression-free survival (PFS), and modulation of relevant biomarkers (e.g., decreased inflammation indices).
3. Exercise will lead to improvements in muscular strength in this patient population.

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Study goals and objectives

The aim of the study is to investigate the impact of a Pulmonary rehabilitation programme on quality of life , functional capacity and immunotherapeutic response in patients with metastatic lung cancer.

Primary outcome measure

Functional capacity measured using the 6-minute walk test (6MWT) at baseline and after completion of the 8-week pulmonary rehabilitation program.

Secondary outcome measures

1.Fine motor dexterity measured using the 9-Hole Peg Test (9HPT) at baseline and two months post-intervention. 2.Functional capacity measured using the Short Physical Performance Battery (SPPB), and isometric quadriceps force (QF) measured using a strain gauge Myometer device (MIE, Medical Research LTD, Leeds, UK) at baseline and two months post-intervention. 3.Quality of life measured using the COPD Assessment Test (CAT), the Cancer-Related Fatigue Scale (CFS), and the EQ-5D VAS scale, at baseline and two months after completion of the rehabilitation program. This document is an unpublished preview, not for official use 4. Blood inflammatory biomarkers (NLR, PLR, LMR, SII) measured using complete blood counts at baseline and two months post-intervention . 5.Progression-free survival (PFS) assessed using radiological progression and/or significant clinical decline (e.g., new or worsening respiratory symptoms or ECOG performance status decline ≥1) at baseline and four months post-intervention.

Study design

This single-centre interventional randomized control open-label trial, assessed the effect of a PR programme consisting of 16 out-patient sessions on, functional capacity, quality of life, progression free survival (PFS) and immunotherapy effectiveness in stage IV non-small cell lung cancer (NSCLC) patients receiving immunotherapy as first line treatment with or without chemotherapy. The study took place from December 2021 to September 2024 at Sotiria Hospital, in Athens, Greece. Patients were eligible if they were >35 years, receiving immunotherapy as primary treatment, had not undergone thoracic surgery and were able to walk 6 minutes without walking aids. Exclusion criteria included history of cognitive or neuromuscular disorders, musculoskeletal impairments affecting walking ability and inability to read and understand Greek language. Furthermore, patients with ECOG performance status ≥2, unstable cardiac disease, dyspnoea classified as NYHA class II-IV, recent cerebrovascular event, thrombocytopenia (platelet count<50,000/μ L), low hemoglobin levels (<10.0g/dl) or high risk of pathological fracture were also excluded. Healthy individuals had clear medical history. Informed written consent was obtained from all patients prior to any assessment. The investigations were carried out according to the rules of the Declaration of Helsinki of 1975 and the study was approved by the Hospital Ethics Committee (Protocol ID-11622/30.4.20).

Study population

Patients with stage IV lung cancer treated with immunotherapy, with or without chemotherapy and healthy age matched participated in this study.

Methodology

Participants with lung cancer, were stratified based on their baseline functional capacity, as measured by the 6-minute walk test (6MWT), using a threshold of 351 meters. Those who walked ≤351 meters were classified as “lower-functioning,” and those who walked >351 meters as “higher-functioning.” This stratification was implemented to ensure balanced allocation across functional levels. Within each stratum, participants were randomly assigned in a 1:1 ratio to the intervention group (PR) or the usual care group (UC) using a computer-generated randomization list.

Assessments

Lung function, functional capacity, fine motor dexterity, QoL and blood biomarkers were assessed at baseline and after 8 weeks. Functional capacity. was assessed via the six-minute walk test (6MWT), the SPPB test and the isometric quadriceps force (QF). Fine motor dexterity was assessed via 9 Hole-Peg Test (9HPT) and QoL was assessed via CAT questionnaire, HADS, EQ-5D-VAS scale and cancer related fatigue scale (CFS scale). To evaluate potential predictors of response and overall prognosis, a panel of peripheral blood biomarkers was assessed at baseline and after 8 weeks. Progressive Free Survival (PFS) was also estimated.

Pulmonary function test

Standard spirometry was conducted using a metabolic cart (Vmax Encore 22; Sensor Medics, Yorba Linda, CA, USA) with the "fast inspiratory maneuver". Static lung volumes were assessed through the multiple nitrogen washout technique (Vmax Encore 22 apparatus) . The diffusing capacity of the lungs for carbon monoxide (DLco) was measured using the single-breath

technique (Vmax Encore 22 apparatus). Predicted values for spirometry, static lung volumes, and DLCO were based on the European Community for Coal and Steel guidelines .

Functional capacity

Patients performed the 6MWT at a pre-marked 30-metre hospital corridor according to the ATS guidelines (ATS 2002). Patients were asked to walk at their own pace for six minutes and try to cover as much distance as possible during that time. Total distance covered during the 6MWT was recorded at the end of the test. Self-reported dyspnea and leg fatigue were recorded at rest and at the end of the 6MWT using the 1-10 Borg scale . The Short Physical Performance Battery Test (SPPB) was also performed to provide additional data regarding functional capacity.

Quality of life, peripheral muscle strength and body composition analysis

Quadriceps muscle force (QF) was evaluated using a strain gauge Myometer device (MIE, Medical Research LTD, Leeds, UK). Quality of life, symptom severity, and levels of anxiety and depression were assessed using the CAT, EQ-5D-5L, HADS and Cancer related Fatigue Scale (CFS).

The 9-hole peg test

Fine motor function both in the dominant and non-dominant hand was assessed as described by Kellor et al., 1971. Prior to the assessment, a familiarization trial was conducted. The time spent during pick up of pegs and their placement into the pegboard one by one, as well as time spent during pegs removal from pegboard was recorded .

Blood Biomarkers

Peripheral Blood biomarkers, included ratios derived from complete blood counts and systemic inflammation indices, including Neutrophil-to Lymphocyte Ratio (NLR), Platelet to-Lymphocyte Ratio (PLR), Lymphocyte to Monocyte Ratio (LMR), Lactate Dehydrogenase (LDH). Serum albumin and systemic immune-inflammation index (SII - Platelet count x Neutrophil count) / LymPhocyte count)) were calculated. Blood samples for immune biomarker analysis were collected at two time points: baseline (prior to the intervention) and immediately following the 8-week exercise intervention. Measuring at baseline and immediately post-intervention allows for capturing the peak immunomodulatory effects of exercise. Delayed sampling, risks missing clinically relevant changes.

PFS-Progression free survival

PFS was estimated 4 months following baseline assessment. According to international guidelines from the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN)), radiological evaluations (typically via chest CT) are recommended every 6–12 weeks to assess tumor response or progression during immunotherapy. Consequently the four-month window includes two full months post-intervention, during which time disease progression can typically be detected.

Clinical deterioration, our defined event, was assessed using a combination of radiological progression based on RECIST 1.1 criteria [31] and significant clinical decline (e.g., new or

worsening respiratory symptoms or ECOG performance status decline ≥1). Clinical status was evaluated through in-person visits and review of medical records.

Intervention

Patients in the PR group completed 16 supervised exercise training sessions consisting of 30 minutes of high intensity interval aerobic exercise on an electromagnetically braked cycle ergometer (Cateye Ergociser, ECI600; Osaka, Japan) and 30 minutes of resistance training, balance training, gait training and breathing exercises. The initial aerobic exercise intensity was set at 100% of the baseline peak work rate (WRpeak) predicted through 6MWT. Throughout each session, dyspnoea and leg discomfort were assessed using the modified Borg scale , and heart rate (HR) and oxygen saturation (SpO_2%) were continuously monitored via a portable pulse oximeter (Beurer PO 35, Beurer GmbH, Ulm, Germany). Cycling intensity was progressively increased by 5–10% of the baseline estimated WRpeak if dyspnoea and leg discomfort were ≤4 on the Borg scale, otherwise it remained unchanged. Patients in the usual care group were encouraged to be active during daily activities. Participants in the UC group did not receive any intervention but underwent all scheduled assessments at baseline and two months post-enrollment, while they attended a one-hour informational session regarding the role of physical exercise in managing their chronic illness.

Safety considerations

No risk anticipated from our intervention. However, as these patients have a long-term condition they are closely monitored by the study oncologist. During each visit, patients who underwent the intervention were monitored for vital signs, including blood pressure, heart rate, oxygen saturation and body temperature.

Follow-up

Patients were followed up for two months after the study completion, to record any potential adverse events and survival rate from the study investigators.

Data management and statistical analysis

Calculation of sample size within each group was based on a study comparing exercise training to usual care in patients with lung cancer. Using the mean difference in 6-minute walk distance (48 meters) between intervention group and control group, and standard deviation (SD) (44 meters), an alpha significance level of 0.05 (2-sided) and 90% power, a minimum total sample size of 36 patients was calculated to be sufficient to detect significant differences in the distance covered during the 6 minute walk test between intervention and usual care groups. To compensate for possible attrition at 30%, a total sample size of 47 was required. Forty-eight patients were recruited to achieve equal allocation between the two groups.

Participants with lung Ca, were randomized in a 1:1 ratio to the intervention (I) or usual care group (UC). To ensure balance in key baseline characteristics, stratified randomization was applied based on patients' functional capacity as assessed by the 6-Minute Walk Test (6MWT). Participants were categorized according to walking distance (<351 meters or ≥ 351 meters). The 351-meter cut-off point for the 6MWT was selected based on previous studies

indicating its prognostic relevance in stratifying patients by baseline functional capacity. Randomization was performed by independent staff.

Data presented as mean±SD unless otherwise stated. Normal distribution of the data was checked with the Shapiro-Wilk test. Comparisons of baseline characteristics between the two patient groups and the healthy individuals were made using one-way ANOVA. Within each group patients were divided into two sub-groups based on the treatment received (i.e. single or combined treatment). Two-way ANOVA with repeated measures was applied to detect differences between the two groups and the four sub-groups across different time points. The LSD post hoc correction method was used where appropriate. Progression- free survival was defined as the time from the date of treatment initiation to the date of documented disease progression or death. Disease progression was assessed radiologically based on scheduled imaging evaluations every 8 to 12 weeks. Following the two-month intervention, participants were monitored for an additional two months, resulting in a total four months follow-up period. The rationale for this follow-up duration is based on the standard clinical oncology protocols for patients with advanced non-small cell lung cancer (NSCLC) undergoing immunotherapy. Kaplan-Meier survival analysis was used to estimate PFS distributions four months following baseline assessment. Group comparisons were performed using the log-rank test. A p value <0.05 was considered significant. Statistical analysis was performed using IBM SPSS 22 statistical software.

Quality assurance

All investigators had GCP certificates.

Expected outcomes of the study

The findings of this study underscore the therapeutic potential of structured exercise programs as a complementary component in the multidisciplinary management of patients with advanced lung cancer receiving immunotherapy as first line treatment. Larger-scale trials are essential to determine the broader applicability and potential clinical integration of exercise interventions in the supportive care of individuals with advanced lung cancer receiving immunotherapy. Given the observed improvements, future research should focus on multicentre randomised controlled trials with larger, stratified cohorts to confirm PR efficacy. Moreover, integration of exercise-based rehabilitation into routine oncology care pathways may offer a low-cost, non-pharmacological strategy to mitigate functional decline and systemic inflammation. Implementation studies are needed to evaluate the adherence, and long-term impact of such interventions in real-world settings.

Dissemination of results and publication policy

We are planning to publish our data as a manuscript in a peer-review journal. Additionally, a brief report with the anonymized outcomes of the study, will be circulated among the participants of the study.

Duration of the project

The first patient's first visit was on 6 December 2022.
The last patient's last visit was on 10 October 2024.

Problems anticipated

A major anticipated challenge in the study was the potential for low recruitment rates. To mitigate this, targeted strategies were employed, including the delivery of educational sessions to oncologists within the affiliated oncology department to enhance study engagement, as well as direct, face-to-face communication with eligible patients during their routine hospital visits for treatment. These interactions aimed to inform patients thoroughly about the study objectives and procedures, address potential concerns, and encourage participation

Project management

- Christiana Lekka, conceive and designed the research, collected, analyzed and interpreted the data investigated, wrote the methodology.
- Chynkiamis Nikolaos, conceive and designed the research, collected, analyzed and interpreted the data investigated, wrote the methodology and supervised the study
- Konstantinos Surigos, designed the research and supervised the study
- Athanasios Kotsakis, designed the research and supervised the study
- Emmanouil Saloustros, designed the research and supervised the study

Ethics

No ethical concerns were expected in this study, as all procedures were part of the typical management of these patients according to national and international guidelines.

Informed consent forms

All participants signed the informed consent form. In fact, two different consent forms were used in this study; one for the patients and one for the healthy participants (attached along with this document). No official translation of the documents was required as all participants were able to read and write Greek.

Research protocol: part 2

Budget

This study was funded by the Special Account of Research Grants of the University of Thessaly, as part of the operating framework of the University of Thessaly Innovation, Technology Transfer Unit and Entrepreneurship Center "One Planet Thessaly", under the “Scholarship Grants to University of Thessaly Doctoral Candidates”.

Other support for the project

No other funding was received for this project

Collaboration with other scientists or research institutions

N/A

Links to other projects

N/A

Curriculum Vitae of investigators

The CV of the Principal investigator and each co-investigator are enclosed /attached in separate documents.

Other research activities of the investigators

Principal investigator was not involved in any other projects during the period of this study.

Financing and insurance

N/A