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Feasibility of an early versus delayed rehabilitation intervention in patients with lung cancer on cancer-related fatigue: a pilot RCT

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ABSTRACT

Background: Cancer-related fatigue (CRF) reduces physical performance and quality of life (QoL). Some authors suggest including moderate-intensity physical exercise to manage CRF; however, the optimal timing to offer rehabilitation remains unclear. The primary aim is to investigate the feasibility of a pulmonary rehabilitation (PR) program, including physical exercise and educational sessions, for lung cancer patients undergoing cancer treatments; secondary objectives are to investigate its effect on CRF, physical performance, and QoL.
Methods: This randomized controlled trial enrolls 40 patients with stage II or III non-small-cell lung cancer undergoing chemotherapy, radiotherapy, or immunotherapy. Patients are randomly assigned to one of two groups: Group A (early-PR) begins PR after enrollment, at the beginning of non-surgical therapies, while Group B (delayed-PR) begins PR for 3 months after enrollment. The PR program consists of two education sessions focused on CRF management and eight supervised exercise sessions, including aerobic, strengthening, stretching, and breathing exercises, combined with home exercises. CRF, QoL, activity level, and endurance are assessed at the baseline (T0) and at 3 and 6 months (T1–T2). One year after T0, survival is assessed along with the CRF, QoL, and activity level (T3). Feasibility will be assessed at 3 and 6 months.
Clinical Trial Registration: www.clinicaltrials.gov identifier is NCT06051136.

PLAIN LANGUAGE SUMMARY

What is this article about?
Many patients with lung cancer experience severe exhaustion (cancer-related fatigue, CRF), which makes it difficult to perform daily activities and lowers their quality of life. Physical exercise is an effective way to manage this fatigue, but it is not yet clear what is the best time to begin a rehabilitation program during cancer treatment. This study investigates whether a pulmonary rehabilitation (PR) program, which includes physical exercise and practical advice, is feasible and safe to implement for lung cancer patients undergoing treatment.
What are the expected results of this study?
This clinical trial involves 40 patients with non-small-cell lung cancer receiving anticancer therapies. Patients are divided into two groups: one starts rehabilitation immediately, while the other starts 3 months later. The program consists of eight supervised exercise sessions (aerobic, strength, breathing exercises) and two informational sessions focused on managing fatigue. We expect to demonstrate that the program is feasible (i.e. patients can complete it) and that by comparing the two groups, we will identify which timing of rehabilitation (early versus delayed) leads to better outcomes.
What do the results of this study mean?
The findings of the study regarding the feasibility and effect of PR will provide crucial information for clinical practice. The results will help doctors and rehabilitation specialists understand when and how to offer rehabilitation support to patients with lung cancer. This knowledge is essential for developing evidence-based intervention to improve patients' energy levels, physical function, and quality of life during their cancer treatment.

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KEYWORDS
Rehabilitation; lung neoplasm; chemotherapy; radiotherapy; fatigue; pulmonary rehabilitation; education

1. Introduction

Lung cancer is the first most commonly diagnosed cancer worldwide with almost 2.5 million new cases, accounting for 12.4% of all cancers globally diagnosed in 2022 [1]. In Europe, the incidence of lung cancer was 319.236 new cases in 2022 [2].

Patients affected by this disease experience disabling symptoms caused by cancer itself as well as cancer treatments, such as dyspnea and fatigue, which reduce physical performance and quality of life (QoL) [3,4].

Cancer-related fatigue (CRF) is experienced by 90% of patients undergoing chemotherapy and 57% of patients undergoing

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Article highlights

- A randomized controlled trial (RCT) design and blinded evaluators and statisticians reduce bias in assessing the feasibility and effect of the pulmonary rehabilitation program.
- The study involves a long-term follow-up, up to 12 months after enrollment.
- The assessment of quality of life and fatigue provides a comprehensive understanding of the intervention's effects on the patient's overall well-being.
- The results will help researchers plan feasible rehabilitation interventions and self-management strategies to face cancer-related fatigue during the care journey of lung cancer patients.

resection [5]. CRF is one of the main symptoms affecting cancer patients, it is often reported from the diagnosis, and it continues during the course of the disease [6].

The European Society of Medical Oncology (ESMO) recommends physical activity, including moderate-intensity aerobic exercise and muscle strengthening, to manage CRF and improve QoL [7]. Moreover, the American College of Sports Medicine (ACSM) guidelines support the important role of physical exercise in improving the survival of cancer patients [8].

Furthermore, physical exercise associated with educational sessions offered to patients and/or caregivers was deemed to be more effective than pharmacological treatment alone in reducing CRF in cancer patients [7,9].

According to previous studies [10,11] and the authoritative guidelines from ESTRO and ESMO [12], physical exercise is suggested as a beneficial support for lung cancer patients undergoing concomitant chemotherapy and radiotherapy. The goal of these exercise interventions is to improve CRF and to counteract side effects of anti-tumor therapies, including the loss of strength and muscle mass.

Some studies conducted on this specific population during active treatment reported an inverse correlation between the level of physical activity and CRF [13]. Furthermore, these findings highlight the negative impact that CRF has on QoL and on the psycho-physical well-being of individuals [3,13].

Physical exercise may improve physical and respiratory performance [14,15], reducing the severity of symptoms and improving QoL in lung cancer patients [15,16].

The type of exercise found to be most effective to manage CRF and reduce the side effects of cancer therapies consists of aerobic exercise associated with muscle-strengthening exercise, performed at moderate intensity, according to recommendations and guidelines [12,17].

Researchers investigating the best modality to provide exercise for lung cancer patients agree in proposing outpatient and home programs, or a combination of both to facilitate adherence to exercise sessions [18,19].

Furthermore, there is evidence on safety, feasibility, and effectiveness of the treatment provided in telerehabilitation, which can integrate with rehabilitation programs carried out in person [20,21].

Nevertheless, to date, there is no precise indication on the best time frame to propose physical exercise during active cancer therapies, considering toxicity, side effects, and frequency of anti-tumor therapy schedule [16,22,23].

Preliminary evidence supports the safety and effectiveness of exercise in lung cancer patients both in the pre- and post-surgical phases [24,25] and during and after treatments [26]. Unfortunately, despite this evidence, many patients remain sedentary or poorly active [5]. These individuals often experience both physical and environmental barriers which prevent them from performing physical activity [27].

Of course, the health status determined by the toxicity and side effects of concomitant anti-cancer therapies must be considered and can negatively influence cancer patients' lifestyle [3,28].

Additionally, the demanding treatment path (such as the frequency of radiotherapy sessions) can decrease the tolerability and hinder the adherence to exercise sessions.

Therefore, given the already demonstrated benefits of physical exercise on CRF in lung cancer patients, the phase in which exercise is best tolerated remains to be investigated [22].

The aim of this study is to explore the timing of rehabilitation intervention for patients undergoing non-surgical cancer treatments and to determine the most feasible in terms of tolerability and adherence to the protocol.

Therefore, we propose a monocentric, interventional, two-arm pilot RCT (OVER-CRF, the abbreviation means "overcome cancer-related fatigue"). This study aims to investigate the feasibility of an experimental pulmonary rehabilitation (PR) program for lung cancer patients undergoing active cancer treatments (chemotherapy and/or radiotherapy and/or immunotherapy, possibly associated with surgery). The feasibility of providing PR early (in the first 3 months of oncological treatment) will be compared with that of a delayed schedule (after 3 months from the beginning of oncological treatment).

2. Materials and methods

2.1. Aims

2.1.1. Primary objective

To verify the adherence to the PR program proposed at the beginning of non-surgical lung cancer treatments or 3 months later (early or delayed). The delayed PR will be the control arm.

2.1.2. Secondary objective

- To evaluate the recruitment rate, the adherence to home sessions, the treatment failure (overall and due to causes), survival 12 months after enrollment, and the intervention safety;
- To investigate clinical outcomes, such as the CRF, QoL, physical performance, and the level of physical activity in the first 12 months after enrollment.

2.2. Setting

OVER-CRF is a pilot RCT conducted at the Local Health Authority of Azienda USL-IRCCS of Reggio Emilia, in Northern Italy.

Inclusion criteria: patients with a new diagnosis of stage II or III non-small-cell lung cancer (NSCLC), candidates for non-surgical cancer therapies (chemotherapy and/or radiotherapy and/or immunotherapy); prognosis ≥12 months; informed consent signed. Surgery is not an exclusion criterion, but patients will be enrolled at the beginning of non-surgical cancer therapies or at least 1 month after surgery.

Exclusion criteria: obstacles to participate in PR programs (clinical conditions that contraindicate moderate physical exercise, preexisting serious physical disabilities, serious/important cognitive or sensitive deficits, and serious psychiatric disorders); stage IV NSCLC, the presence of lung metastases from another tumor, cerebral metastases, and bone metastases with fracture risk; patients considered for surgery alone; language barrier.

2.3. Intervention

Patients will be randomized into two experimental groups: A (early PR) and B (delayed PR).

Group A will perform PR just after enrollment and carry out eight sessions supervised by a physiotherapist during the 3months of the intervention and two therapeutic educational group sessions. The exercise supervised sessions will be planned every 7–14 days and completed within 3 months.

The physiotherapists who will provide the rehabilitation intervention have specific expertise in pulmonary and cancer rehabilitation.

The supervised PR sessions will be tailored to the patients' conditions and delivered according to specific exercise guidelines for cancer [29]. The RP program will include aerobic, muscle-strengthening, flexibility, and respiratory exercises (see Table 1).

Moderate-intensity aerobic exercise will be proposed two to three times per week, and muscle strength training two times per week, according to the recommendation of the guidelines for cancer survivors [17]. Respiratory exercises will be performed every day.

The details of the progression of each exercise component are the following:

- Progressive aerobic exercise: 20–30 minutes of aerobic activity at moderate intensity, with a target intensity of 60–80% estimated maximum heart rate (% HRmax). The duration of aerobic exercise will increase from 20 to 30 minutes over 12 weeks, increasing by 5 minutes every 4 weeks.
- Progressive resistance exercise: muscle strength training at moderate intensity ranging from 8 to 15 repetitions, for 2–4 sets for each exercise. The progression of exercise intensity will change over the weeks based on the participant's compliance and performance, increasing the weight, number of sets, and repetitions.
- Respiratory exercises: the progression will change by increasing the number of repetitions and the type of exercise.

The progression of exercise intensity and difficulty is adjusted to the patient's compliance, performance, and perception of physical effort, ensuring safety and tolerability.

The RP program and educational sessions will last approximately 60 minutes, 30 minutes if the session is delivered in telerehabilitation.

The two educational sessions, designed for both patients and their caregivers, will focus on the management of CRF and the promotion of an active lifestyle (see Table 2). These sessions will encourage participants to share their experiences and develop essential skills to enhance their QoL during and after cancer treatment.

A booklet containing a personalized home-based exercise program will be delivered to the patients. This booklet includes images and detailed explanations to support the unsupervised execution of the exercises, along with a summary of the contents of the therapeutic educational sessions.

Patients will be invited to complete a diary of unsupervised home-based exercises. This diary will be reviewed by the physiotherapist during supervised sessions to identify any difficulties encountered, serving as a weekly verification and motivational mechanism.

In-person and educational sessions will be conducted at the Physical Medicine and Rehabilitation Unit of Santa Maria Nuova Hospital of Reggio Emilia.

After the first in-person exercise session, the other sessions may be delivered in telerehabilitation if the patient requires it.

To prompt adherence, the physiotherapist will plan PR sessions based on the patient's needs and the agenda of their hospital appointments for visits or therapies.

Group B (delayed PR) will begin the program 3 months after enrollment, using the same PR protocol as Group A.

During the trial, all therapies and medical checkups are permitted in order to monitor the patient's health status. If the clinical conditions worsen or an adverse event occurs, the PR program will be modified or suspended after consultation with a physiatrist/oncologist/pulmonologist.

2.4. Outcome

2.4.1. Primary outcome

According to the literature, patient adherence is considered sufficient when it is >70% [29]. We decided to consider "adherent" a patient who attend to at least 70% of the supervised PR sessions for the relevant allocation group.

2.4.2. Secondary outcomes

(1) Evaluation of the recruitment rate by calculating the number of subjects participating in the study;
(2) Number of treatment failures, related causes, and number of sessions carried out;
(3) Survival (patients surviving 12 months after enrollment in the two intervention arms);
(4) Safety: the research group will report adverse events related to the PR program in the 3 months of intervention (falls, fractures, muscle pain, exertional dyspnea, acute inflammation of the muscle-skeletal structures,

Table 1. PR individual program offered to patients in the OVER-CRF study.

Type of exercise	Duration	Exercises	Repetitions and series	Tools used	Parameters to monitor
Aerobic exercise	From 20 to 30 minutes	Exercise bike at an intensity equal to 60–80% of maximum heart rate	/	Oximeter or heart rate monitor	Heart rate Borg Scale Applied resistance
Muscle strengthening	From 20 to 30 minutes	Lower limbs. Feet pushes (plantiflexion) in standing position, sit and/or in supine position with elastic band. Knee extension sitting (with/without graduated anklets). Wall squats (with/without weights). Isometric knee contraction in supine position of the knee on the table. Hip extension lying on the table or in standing position. Cat stretch/quadrupedal position with hip extension (with/without anklets). Hip adductors in supine position, sitting, standing position (with/without exercise bands and/or anklets). Hip abductors in supine position, sitting, standing position (with/without exercise bands and/or anklets). Hip flexion in supine or standing position (with/without exercise bands and/or anklets). Leg-press (machine) Leg extension Trunk: Crunches Bridge exercise Plank (with elbows and feet supported) Spinal erectors in supine, prone position or sitting (with/without exercise bands and/or anklets Upper Limbs: Shoulder abduction, adduction, flexion, intra/extra rotation (with/without weights and/or exercise bands)	Repetition: 8–15 Series: 2–4 Note: for isometric exercise hold position from 20 to 60 seconds	Gym machines Graduated anklets (Little) Weights Exercise bands Ball/ Cushion	Weight Number of repetitions/series Correct technique/errors Speed Breathing Posture Borg Scale
Respiratory exercises	From 10 to 20 minutes	Diaphragmatic breathing PEP bottle Flow incentive spirometer	PEP: 5–10 repetitions, 2–3 times per day Spirometer: 3–5 repetitions, 2–3 times per day	PEP bottle Flow incentive spirometer	Number of repetitions/series Correct technique/errors Speed Breathing Posture Borg Scale

Note: All sessions include an initial period of 5 minutes of warm-up consisting of light-intensity aerobic activity and 5 minutes of cool-down consisting of flexibility/stretching or light-intensity aerobic activity based on the patient's preferences/needs.

Table 2. Main themes included in therapeutic educational group sessions in the OVER-CRF study.

First session: evidence-based strategies to enhance physical well-being and overall QoL.	
Goal Setting	Help participants to set realistic short- and long-term goals to enhance self-awareness and manage their daily activities more effectively.
Problem Solving	Help patients to identify obstacles, solutions and to evaluate results.
Physical Activity	Through a brainstorming session, participants will explore the benefits of physical exercise, such as reducing therapy side effects, strengthening muscles, managing joint pain, and improving mental health.
Assistive Devices and Orthoses	Guidance on the use of walking aids and supportive devices to enhance mobility and reduce disability.
Breathing Techniques and Relaxation	Practice diaphragmatic breathing and body-scan relaxation exercises to manage stress and fatigue.
Second session: managing CRF.	
Goal Setting	Help participants to set realistic short- and long-term goals to enhance self-awareness and manage their daily activities more effectively.
Problem Solving	Help patients to identify obstacles, solutions, and to evaluate results. Help patients to plan strategies to include physical activity in everyday life.
Understanding Fatigue	Explore the causes and symptoms of CRF, including physical, emotional, and psychological factors. Through a brainstorming session, participants will share their experiences and discuss strategies to manage fatigue effectively.
Effective Communication	Teach patients how to ask for help and express their needs to caregivers and healthcare professionals, using role-playing techniques to improve communication skills.
Relaxation Techniques	Practice diaphragmatic breathing and guided relaxation exercises, such as body scan and visualization, to reduce stress and promote well-being.
Respiratory Exercises	Introduce specific breathing exercises, including the PEP bottle technique and the use of an incentive spirometer, to improve respiratory function and alleviate fatigue-related symptoms.

Table 3. Timeline of assessment.

Evaluations	T0 (Baseline)	T1 (3 months after T0)	T2 (6 months after T0)	T3 (phone call, 12 months after T0)
FACIT-FS	X	X	X	X
EORTC QLQ-C30	X	X	X	X
6MWT	X	X	X	
IPAQ-SF	X	X	X	X
Sessions adherence (supervised)		X	X	
Independently physical activity	X	X	X	
Survival				X
Recruitment rate	X			
Dropout		X	X	X
Safety		X	X	X

hematomas, etc.) and through the detection of falls or fractures that occurred between T2 and T3;

(5) Clinical outcomes: CRF will be evaluated through the Functional Assessment of Chronic Illness-Fatigue Scale (FACIT-SF), QoL by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC-QLQ-C30), and physical performance by 6-Minute Walk Test (6MWT);

(6) The level of physical activity will be assessed through International Physical Activity Questionnaire – Short Form (IPAQ-SF) Scale;

(7) Adherence to home-based exercise will be assessed by self-reported exercise diary filled in by patients.

The outcomes will be evaluated by blind assessors who do not directly deliver the intervention.

Moreover, baseline information will be collected for each participant, including age, sex, marital status, household composition, education level, occupation, and smoking habits.

(Table 3 shows the timeline of assessment; Figure 1 shows the timeline of the intervention)

2.5. Sample size

There is no available literature about the feasibility of a combined intervention (physical exercise + therapeutic education) in lung cancer patients during adjuvant therapies. Since this is a pilot study, a sample size calculation was not performed, according to "CONSORT 2010 statement: extension to randomised pilot and feasibility trials" [30]. The research group aims to enroll 40 participants because they think it is a large enough sample to inform them about the feasibility of the PR during cancer treatments in lung cancer patients.

2.6. Recruitment strategies

Enrollment will last 24 months.

Healthcare professionals involved in lung cancer multidisciplinary groups (oncologist, radiotherapist, pulmonologist, physiatrist, physiotherapist, etc.) will screen patients for eligibility criteria.

Eligible patients will be referred to the physiatrist, who will visit them, provide detailed information about the study, and obtain informed consent.

The baseline (T0) assessment will be conducted at the beginning of anti-tumor treatments, specifically within 30 days from the non-surgical treatment proposal (chemotherapy, radiotherapy, and/or immunotherapy) made by the multidisciplinary lung cancer group or the relevant specialists, following tumor typing.

For patients undergoing surgery, enrollment will be postponed to at least 1 month after the procedure to prevent

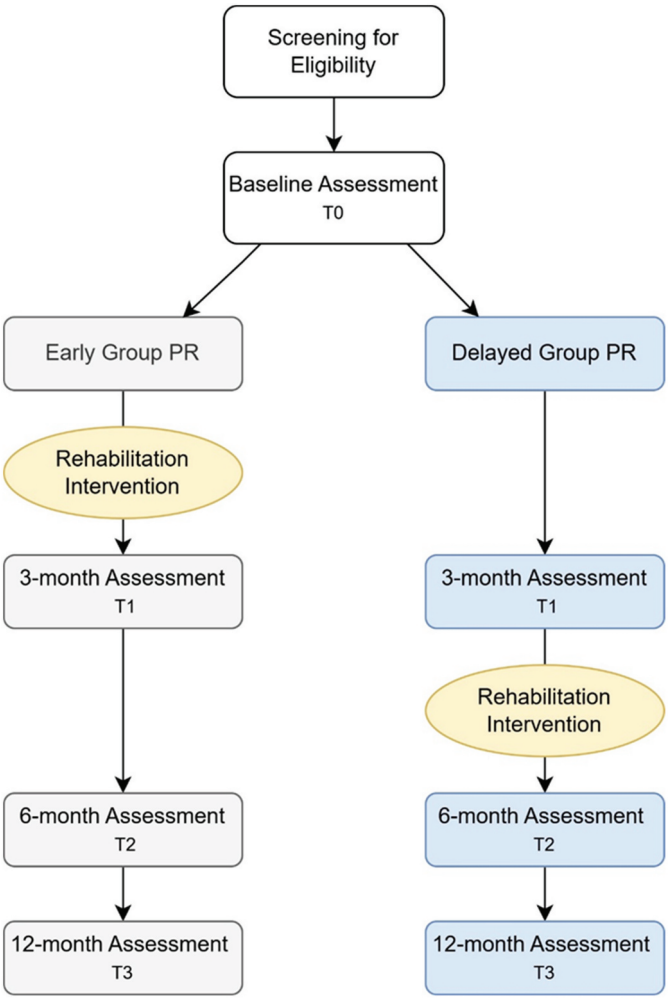

Figure 1. Flow chart of the study.

evaluation biases caused by temporary decline in functional performance and post-operative pain.

Any refusals to participate in the study will be recorded, reporting the related reasons.

Physiotherapists will also record the performance status (ECOG), cancer stage, and clinical data regarding the diagnosis and the treatment path (date of the multidisciplinary discussion, possible date of surgery, start and type of oncological treatment, hemoglobin, etc.).

This information will be collected through direct requests to the patient and/or a caregiver or obtained from computerized medical records.

2.7. Allocation

Subjects will be allocated with simple randomization between the two arms according to a 1:1 ratio.

Randomization will be conducted online through the company software, which will generate allocation assignments based on a block randomization list of four, previously prepared by the Clinical Studies and Statistics Unit of Azienda USL-IRCCS of Reggio Emilia.

Due to the nature of the rehabilitation intervention, blinding of the treating physical therapist and the patients was not feasible. The outcome evaluator, however, is an independent physical therapist who does not perform the intervention and is not involved in baseline assessments, randomization, or data analysis. Therefore, a single-blind design was implemented, ensuring that the evaluators at T1, T2, and T3, as well as those analyzing the data, will be blinded to the patient's group assignment.

2.8. Rating scales

A blinded evaluator will administer these rating scales:

– FACIT-FS

It is a 13-item measure that assesses self-reported fatigue and its impact upon daily activities and function. The score ranges from 0 to 52. The higher the score, the less fatigue the patient experiences. The FACIT-FS is part of the widely validated measurement system, and the scale has been formally validated in various languages (including Italian), demonstrating excellent reliability and construct validity within the cancer patient population [31]. The Minimal Clinically Important Difference (MCID) for the FACIT-F scale was estimated at three points [32].

– EORTC QLQ-C30

It is a 30-item instrument designed to measure QoL in all cancer patients, evaluating various dimensions: five functional scales (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, pain, and nausea), and a global measure of health state. The remaining six single-question scales assess symptoms: dyspnea, loss of appetite, sleep disturbances, constipation, diarrhea, and the perceived economic impact of treating the disease. The EORTC QLQ-C30 is generally considered to have good reliability, as evidenced by high internal consistency and strong test–retest reliability. This scale has also a strong evidence supporting its content, construct, and criterion validity. These metrics support the use of the EORTC QLQ-C30 as a consistent, stable, and well-validated measure of quality of life in cancer patients [33,34]. The MCID for the EORTC QLQ-C30 scale was estimated between 5 and 10 points [35].

– 6MWT

It has been widely used to reliably assess submaximal physical function in patients with cancer [36]. This test measures the distance that a patient can quickly walk in a corridor of at least 30 meters in a period of 6 minutes. Furthermore, the number of stops during the route, saturation and heart rate before and after the test, respiratory fatigue, and muscle fatigue are measured. The MCID for the 6MWT in lung cancer patients was estimated to be 42 meters [37].

– IPAQ-SF

It is a questionnaire used to estimate the amount of physical activity performed by patients during the 7 days before assessment. The patients indicate weekly frequency and average duration of vigorous and moderate physical activity and walking (during work or leisure) and the number of hours spent sitting per day.

Furthermore, to evaluate the degree of physical activity carried out, IPAQ uses Metabolic Equivalent of Tasks (METs), which have a different value depending on the effort practiced and allow activities of different intensity to be added together [38]. The IPAQ-SF has been widely used in epidemiological studies for cross-national monitoring of physical activity and inactivity and has demonstrated acceptable psychometric properties, including good reliability and validity in the general adult population, which supports its utility in clinical settings [39]. Furthermore, its feasibility and reproducible use have been demonstrated in Italian cohorts with chronic conditions [40,41], making it a suitable tool for assessing physical activity levels in this population.

The data collection forms will be stored at the Rehabilitation and Physical Medicine Department of Azienda USL-IRCCS of Reggio Emilia.

In the event of dropout, the date and reason for leaving the study protocol will be recorded, including withdrawal of informed consent, worsening clinical conditions, death, loss of motivation to participate, unavailability, loss to follow-up, or other specified reasons.

Signed informed consent forms and data collection records will be securely stored at Rehabilitation Unit, accessible only to authorized researchers. Digital data collection files and other sensitive documents will be protected by password security measures.

2.9. Data analysis

The Clinical and Statistical Study Unit of the Azienda USL-IRCCS of Reggio Emilia will carry out the statistical analysis (to explore primary and secondary objectives) using the SAS System or R System. Since the small sample size, for each percentage determined, the exact bilateral confidence interval will be calculated according to the Clopper–Pearson approach, ensuring a confidence level of at least 95%.

The statistical analysis of the variables reported in secondary outcomes will be descriptive, with a tabular representation of average, median, minimum, maximum, remarkable percentiles, and central tendency index (with 95% CI), chosen on the basis of the distribution characteristics of the variables in question.

Adherence will be calculated as the ratio between the number of sessions completed and the number of sessions scheduled. Patients will be classified as "adherent" to the protocol if they complete ≥70% of the planned sessions.

The improvement in CRF will be evaluated taking into account the changes in the FACIT-FS score exceeding MCID in the two groups (difference of at least three points between the score recorded before and after the intervention for each patient).

The improvement in QoL will be evaluated taking into account the changes in EORTC-QLQ-C30 score exceeding MCID in the two groups (difference of at least five points between the score recorded before and after the intervention for each patient).

Physical performance will be evaluated taking into account the changes in 6MWD in the two groups (difference of at least 42 meters between the score recorded before and after the intervention for each patient, as reported by Granger [37]).

The percentage of patients exceeding the MCID on the FACIT-FS, EORTC QLQ-C30, and 6MWT scales will also be calculated for both allocation groups.

Adverse events will be summarized in lists and tables, categorized into homogeneous classes where applicable.

To promote participants' retention and adherence to the intervention, participants are required to fill out a daily diary reporting their home-based exercise program. During the in-person session, the participants will return this diary where they can report critical issues and difficulties encountered.

In the case of dropout, the date and reason for leaving the protocol are recorded (withdrawal of informed consent, worsening of clinical conditions, death, loss of motivation to participate in the study, not available, loss to follow-up, and others).

Missingness issues will not be foreseen on the primary outcome; statistical analyses for secondary outcomes will be performed on a complete case basis.

2.10. Patient and public involvement

No patients or associations were involved in the design or conduct of the study. However, the development of the rehabilitative intervention was based on a thorough literature review, and the priorities of patients were collected by the specialists during clinical practice.

3. Conclusions

The findings of the study will provide crucial information for clinical practice, enriching published data on the feasibility of rehabilitation support during cancer treatments for lung cancer patients. Based on both clinical considerations and results from the current work, the research group will set up a properly powered RCT to explore efficacy of rehabilitation on patients' energy levels, physical function, and quality of life during lung cancer treatment. The results are essential for developing evidence-based interventions and will help oncologists and rehabilitation specialists understand when and how to offer rehabilitation programs to patients with lung cancer.

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Author contributions

SF, FZ, FF, PC, SCavuto, MD, CM, and SCosti contributed to study conceptualization and design, providing input into the development of the protocol. SF, CM, MD, BB, and SCosti analyzed the literature on lung cancer rehabilitation intervention and self-management support, to set up therapeutic education sessions. SF, AP, MM, MBG, and CM drafted the manuscript, and all authors revised it critically and approved the final version for publication.

Disclosure statement

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Ethical declaration

The study was approved by the Ethics Committee Area Vasta Emilia Nord, Azienda USL-IRCSS of Reggio Emilia, Italy, with the number 345/2022/SPER/AUSLRE. All study participants will be informed in detail of the aims and objectives of the study by the PI. Each participant has the right to withdraw their membership in the study at any time. All data collected are restricted by Ethics Committee of the Vast Northern Emilia (Italy) in order to protect participant privacy. The data will be available from the corresponding author, on reasonable request, with the permission of Azienda USL-IRCCS of Reggio Emilia, Italy. The study will be conducted in accordance with this protocol along with any amendments introduced and authorized, as well as the ethical principles of the Declaration of Helsinki. In terms of dissemination strategy, the research group aims to publish in scientific peer-reviewed journals and conference presentations; OVER-CRF protocol will enable the research group to share with clinicians and other research groups patients timeline assessments and intervention description. The expected impact for this study is the development of a useful and acceptable physical exercise program integrated into lung cancer care for patients receiving oncological therapies and radiotherapy, to be explored in a powered future RCT. The authors will provide the dissemination of the study results through publication in international scientific journals, preferring an open-access practice to improve the access and reproducibility of its outcomes.

Access to clinical documentation: The investigators will collect only the data specified in the form (personal and clinical data) by reviewing clinical documentation available from the Physical and Rehabilitation Medicine, Pneumology, Provincial Medical Oncology, and Radiotherapy Units at Azienda USL – IRCCS di Reggio Emilia. The collected information will be strictly limited to the data outlined in the form and will be used exclusively for the implementation of educational and rehabilitation interventions.

To ensure the privacy of all participants, the following measures will be implemented:

- Participant-related documents will be securely stored and will not contain the individual's name in clear text. Instead, an identification code, known only to the researchers, will be used.
- Data will be presented and published in aggregate form, ensuring that no information can be traced back to individual patients or healthcare professionals.

The data collected in the study will be processed and stored in accordance with the provisions of GDPR 679/2016, Legislative Decree 196/2003, as amended by Legislative Decree 101/2018, and the Provision of the Guarantor for the Protection of Personal Data n. 146/2019.

The collection of data and the results provided by the study have exclusively research purposes in the clinical field and are kept with absolute confidentiality at the AUSL-IRCCS of Reggio Emilia under the responsibility of the promoter and the investigators involved, in compliance with the provisions of the ethics medical and professional and to what is established by law for the processing of personal data for statistical and scientific purposes. The documentation will be retained and made available for any inspections required by regulatory authorities.

Data management aspects: The data will be collected via the paper CRF tool and processed and managed electronically via the e-CRF sheet with a software prepared by the Informatics and Telematics Technologies Service (STIT) of the AUSL-IRCCS of Reggio Emilia, which guarantees data management in compliance with the provisions of GDPR 679/2016, Legislative Decree 196/2003 and subsequent amendments, and the Measure of the Guarantor for the Protection of Personal Data n. 146/2019.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–263. doi: 10.3322/caac.21834
2. European Cancer Information System. Estimates of cancer incidence and mortality in 2022, for all countries. [cited 2025 Mar 12]. [Online]. Available from: https://ecis.jrc.ec.europa.eu/explorer.php?0-0$1-All$2-All$4-1,2$3-22$6
3. Chabowski M, Polanski J, Jankowska-Polańska B, et al. Quality of life of patients with lung cancer. Oncotargets Ther. 2016;1023:1023. doi: 10.2147/OTT.S100685
4. Iyer S, Roughley A, Rider A, et al. The symptom burden of non-small cell lung cancer in the USA: a real-world cross-sectional study. Support Care Cancer. 2014;22(1):181–187. doi: 10.1007/s00520-013-1959-4
5. Avancini A, Sartori G, Gkountakos A, et al. Physical activity and exercise in lung cancer care: will promises be fulfilled? Oncologist. 2020;25(3):555–569. doi: 10.1634/theoncologist.2019-0463
6. Berger AM, Mooney K, Alvarez-Perez A, et al. Cancer-related fatigue, version 2.2015. J Natl Compr Canc Netw. 2015;13(8):1012–1039. doi: 10.6004/jnccn.2015.0122

•• **This paper presents the official, most authoritative (NCCN) Guidelines for the management and diagnosis of CRF, providing the standard definition and criteria used in clinical and research settings.**

7. Fabi A, Bhargava R, Fatigoni S, et al. Cancer-related fatigue: ESMO clinical practice guidelines for diagnosis and treatment. Ann Oncol. 2020;31(6):713–723. doi: 10.1016/j.annonc.2020.02.016

•• **This paper provides the authoritative ESMO Clinical Practice Guidelines, setting the gold standard for the diagnosis and management of CRF. It specifically recommends physical activity (aerobic and resistance) and psychosocial interventions for CRF control in cancer patients.**

8. Patel AV, Friedenreich CM, Moore SC, et al. American college of sports medicine roundtable report on physical activity, sedentary

behavior, and cancer prevention and control. Med Sci Sports Exerc. 2019;51(11):2391–2402. doi: 10.1249/MSS.0000000000002117

•• **This is a crucial ACSM Roundtable Report that synthesizes the current evidence and provides authoritative guidelines and recommendations on the role of physical activity in preventing many types of cancer and for improving longevity among cancer survivors.**

9. Mustian KM, Alfano CM, Heckler C, et al. Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: a meta-analysis. JAMA Oncol. 2017;3(7):961. doi: 10.1001/jamaoncol.2016.6914

•• **This high-impact meta-analysis provides strong evidence comparing different interventions for CRF, highlighting the efficacy and therapeutic relevance of exercise.**

10. Zhang LL, Wang SZ, Chen HL, et al. Tai Chi exercise for cancer-related fatigue in patients with lung cancer undergoing chemotherapy: a randomized controlled trial. J Pain Symptom Manage. 2016;51(3):504–511. doi: 10.1016/j.jpainsymman.2015.11.020
11. Salhi B, Huysse W, Van Maele G, et al. The effect of radical treatment and rehabilitation on muscle mass and strength: a randomized trial in stages I–III lung cancer patients. Lung Cancer. 2014;84(1):56–61. doi: 10.1016/j.lungcan.2014.01.011
12. De Ruysscher D, Faivre-Finn C, Nackaerts K, et al. Recommendation for supportive care in patients receiving concurrent chemotherapy and radiotherapy for lung cancer. Ann Oncol. 2020;31(1):41–49. doi: 10.1016/j.annonc.2019.10.003

• **This paper is relevant for outlining comprehensive supportive care strategies, providing crucial context for the integration of physical exercise and the management of CRF during concurrent oncological treatment.**

13. D'Silva A, Gardiner PA, Boyle T, et al. Associations of objectively assessed physical activity and sedentary time with health-related quality of life among lung cancer survivors: a quantile regression approach. Lung Cancer. 2018;119:78–84. doi: 10.1016/j.lungcan.2018.03.010
14. Rutkowska A, Jastrzebski D, Rutkowski S, et al. Exercise training in patients with non–small cell lung cancer during in-hospital chemotherapy treatment: a randomized controlled trial. J Cardiopulm Rehabil. 2019;39(2):127–133. doi: 10.1097/HCR.0000000000000410
15. Edbrooke L, Aranda S, Granger CL, et al. Multidisciplinary home-based rehabilitation in inoperable lung cancer: a randomised controlled trial. Thorax. 2019;74(8):787–796. doi: 10.1136/thoraxjnl-2018-212996
16. Singh B, Spence R, Steele ML, et al. Exercise for individuals with lung cancer: a systematic review and meta-analysis of adverse events, feasibility, and effectiveness. Semin Oncol Nurs. 2020;36(5):151076. doi: 10.1016/j.soncn.2020.151076
17. Campbell KL, Winter-Stone K, Wiskemann J, et al. Exercise guidelines for cancer survivors: consensus statement from international multidisciplinary roundtable. Med Sci Sports Exerc. 2019;51(11):2375–2390. doi: 10.1249/MSS.0000000000002116

•• **This key international consensus statement provides comprehensive, evidence-based guidelines critical for designing safe and effective exercise interventions for cancer survivors, and represents a guide for health-care professionals.**

18. Hoffman AJ, Brintnall RA, Brown JK. Home-based exercise: promising rehabilitation for symptom relief, improved functional status and quality of life for post-surgical lung cancer patients. J Thorac Dis. 2014;6(6):632–640. doi: 10.3978/j.issn.2072-1439.2014.06.08
19. Ferreira V, Lawson C, Carli F, et al. Feasibility of a novel mixed-nutrient supplement in a multimodal prehabilitation intervention for lung cancer patients awaiting surgery: a randomized controlled pilot trial. Int J Surg. 2021;93:106079. doi: 10.1016/j.ijsu.2021.106079
20. Dennett A, Harding KE, Reimert J, et al. Telerehabilitation's safety, feasibility, and exercise uptake in cancer survivors: process evaluation. JMIR Cancer. 2021;7(4):e33130. doi: 10.2196/33130
21. Ji W, Kwon H, Lee S, et al. Mobile health management platform–based pulmonary rehabilitation for patients with non–small cell lung cancer: prospective clinical trial. JMIR Mhealth Uhealth. 2019;7(6):e12645. doi: 10.2196/12645
22. Bade BC, Thomas DD, Scott JB, et al. Increasing physical activity and exercise in lung cancer: reviewing safety, benefits, and application. J Thorac Oncol. 2015;10(6):861–871. doi: 10.1097/JTO.0000000000000536
23. Medysky ME, Bland KA, Neil-Sztramko SE, et al. Attention to the principles of exercise training in exercise studies of persons with lung cancer: a systematic review. J Aging Phys Act. 2021;29(6):1042–1052. doi: 10.1123/japa.2020-0269
24. Cavalheri V, Burtin C, Formico VR, et al. Exercise training undertaken by people within 12 months of lung resection for non-small cell lung cancer. Cochrane Database Syst Rev. 2019;6(6):CD009955. doi: 10.1002/14651858.CD009955.pub3
25. Tenconi S, Mainini C, Rapicetta C, et al. Rehabilitation for lung cancer patients undergoing surgery: results of the PUREAIR randomized trial. Eur J Phys Rehabil Med. 2021;57(6):6. doi: 10.23736/S1973-9087.21.06789-7
26. Paramanandam VS, Dunn V. Exercise for the management of cancer-related fatigue in lung cancer: a systematic review: cancer-related fatigue in lung cancer. Eur J Cancer Care (Engl). 2015;24(1):4–14. doi: 10.1111/ecc.12198
27. Granger CL, Connoly B, Denehy L, et al. Understanding factors influencing physical activity and exercise in lung cancer: a systematic review. Support Care Cancer. 2017;25(3):983–999. doi: 10.1007/s00520-016-3484-8
28. Montazeri A, Milroy R, Hole D, et al. How quality of life data contribute to our understanding of cancer patients' experiences? A study of patients with lung cancer. Qual Life Res. 2003;12(2):157–166. doi: 10.1023/A:1022232624891
29. Driessen EJ, Peeters ME, Bongers BC, et al. Effects of prehabilitation and rehabilitation including a home-based component on physical fitness, adherence, treatment tolerance, and recovery in patients with non-small cell lung cancer: a systematic review. Crit Rev Oncol Hematol. 2017;114:63–76. doi: 10.1016/j.critrevonc.2017.03.031
30. Eldridge SM, Chan CL, Campbell MJ, et al. Consort 2010 statement: extension to randomised pilot and feasibility trials BMJ. BMJ. 2016;355:i5239. doi: 10.1136/bmj.i5239
31. Yellen SB, Cella DF, Webster K, et al. Measuring fatigue and other anemia-related symptoms with the functional assessment of cancer therapy (FACT) measurement system. J Pain Symptom Manage. 1997;13(2):63–74. doi: 10.1016/s0885-3924(96)00274-6
32. Cella D, Eton DT, Lai J-S, et al. Combining anchor and distribution-based methods to derive minimal clinically important differences on the functional assessment of cancer therapy (FACT) anemia and fatigue scales. J Pain Symptom Manage. 2002;24(6):547–561. doi: 10.1016/S0885-3924(02)00529-8
33. Groenvold M, Klee MC, Sprangers MA, et al. Validation of the EORTC QLQ-C30 quality of life questionnaire through combined qualitative and quantitative assessment of patient-observer agreement. J Clin Epidemiol. 1997;50(4):441–450. doi: 10.1016/s0895-4356(96)00428-3
34. Aaronson NK, Ahmedzai S, Bergman B, et al. The European organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365–376. doi: 10.1093/jnci/85.5.365
35. Maringwa JT, Quinten C, King M, et al. Minimal important differences for interpreting health-related quality of life scores from the EORTC QLQ-C30 in lung cancer patients participating in randomized controlled trials. Support Care Cancer. 2011;19(11):1753–1760. doi: 10.1007/s00520-010-1016-5
36. Schmidt K, Vogt L, Thiel C, et al. Validity of the six-minute walk test in cancer patients. Int J Sports Med. 2013;34(7):631–636. doi: 10.1055/s-0032-1323746
37. Granger CL, Holland AE, Gordon IR, et al. Minimal important difference of the 6-minute walk distance in lung cancer. Chron Respir Dis. 2015;12(2):146–154. doi: 10.1177/1479972315575715
38. Guidelines for data processing and analysis of the international physical activity questionnaire (IPAQ)-short and long forms. 2005. [Online]. Available from: www.ipaq.ki.se

39. Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003;35(8):1381–1395. doi: 10.1249/01.MSS.0000078924.61453.FB
40. Minetto MA, Motta G, Gorji NE, et al. Reproducibility and validity of the Italian version of the international physical activity questionnaire in obese and diabetic patients. J Endocrinol Invest. 2018;41(3):343–349. doi: 10.1007/s40618-017-0746-3
41. Natalucci V, Villarini M, Emili R, et al. Special attention to physical activity in breast cancer patients during the first wave of COVID-19 pandemic in Italy: the DianaWeb cohort. J Pers Med. 2021;11(5):381. doi: 10.3390/jpm11050381