Heliyon 11 (2025) e42768

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Case report

Combining a 9-month tailored physical exercise program with osimertinib and denosumab in a patient affected by advanced NSCLC with multiple osteolytic bone lesions: A case report

Anita Borsati [a,b], Christian Ciurnelli [b], Lorenzo Belluomini [c], Marco Sposito [c], Jessica Insolda [c], Linda Toniolo [b], Ilaria Trestini [d], Daniela Tregnago [c], Michele Milella [c], Federico Schena [b], Sara Pilotto [c,*,1], Alice Avancini [c,1]

[a] Department of Medicine, University of Verona, Italy
[b] Department of Neurosciences, Biomedicine and Movement, University of Verona, Italy
[c] Section of Innovation Biomedicine - Oncology Area, Department of Engineering for Innovation Medicine (DIMI), University of Verona and University and Hospital Trust (AOUI) of Verona, Italy
[d] Dietetic Service, Medical Direction, University Hospital of Verona (AOUI), Italy

A R T I C L E I N F O

Keywords:
Physical activity
Bone metastasis
Lung cancer
Safety
Bone-targeted agents

A B S T R A C T

A 55-year-old female patient affected by an EGFR mutant NSCLC with multiple lytic bone metastases and two prior pathological fractures, undergoing treatment with osimertinib and denosumab, participated in a 9-month physical exercise program. The exercise program was performed twice a week and consisted of aerobic and strength training. Aerobic training was composed of moderate-intensity continuous training for the first 3 months and then high-intensity interval training. Strength training was performed through body-weight/elastic band exercises for the first 6 months and isotonic machines from months 6–9. Assessments, performed every 3 months, included physical fitness parameters, such as functional capacity, muscle strength, anthropometric measures, body composition, and quality of life. Functional capacity progressively improved by 80 m at month 6 and slightly decreased by 22 m at month 9. At the end of the intervention, grip strength increased in both arms, whereas the body composition showed a progressive decrease in fat mass (−3.39 kg) and an increase in muscle mass (+3.89 kg) until month 6 and then stabilization. Quality of life exhibits a great improvement in the first 3 months, especially in the physical role, emotional functioning, fatigue, pain, dyspnoea, insomnia, appetite loss, constipation, and diarrhea, and then maintained with little variations. This case suggests that a highly structured physical exercise program may be feasible, safe, and effective in patients with lung cancer and bone metastases if performed under the supervision of trained experts.

1. Introduction

About one-third of patients with advanced non-small cell lung cancer (NSCLC) present bone metastasis at diagnosis [1]. Lytic

* Corresponding author. Section of Innovation Biomedicine - Oncology Area, Department of Engineering for Innovation Medicine (DIMI), University of Verona, P. le L.A. Scuro 10, 37134, Verona, Italy.
E-mail address: sara.pilotto@univr.it (S. Pilotto).
[1] Share the co-last authorship.

https://doi.org/10.1016/j.heliyon.2025.e42768
Received 4 April 2024; Received in revised form 14 February 2025; Accepted 17 February 2025
Available online 18 February 2025

lesions, which represent the most common type of bone metastasis in NSCLC, are characterized by an activation of osteocytes, resulting in a rapid deterioration of the bone microarchitecture [2]. Metastases often deposit in the trabecular part of the bones, such as ribs, spine, pelvis, proximal/distal femur, and homers, which are usually load-bearing, leading to an elevated fragility with a consequent reduction in quality of life and high risk of morbidity [3]. Patients with NSCLC harboring epidermal growth factor receptor (EGFR) mutations are more likely to develop bone metastases, be exposed to a high risk of pain and skeletal-related events (SREs), and thus an increased risk of mortality [2]. For instance, a multicentric retrospective study including 274 patients with EGFR-mutant NSCLC reported a prevalence of 63 % of SREs, of which 28 % were considered severe, such as bone fractures (20 %), hypercalcemia (2 %), and spinal cord compression (11 %), and early occurrence of these events after the starting of tyrosine kinase inhibitors (TKIs) [4]. Specific bone-targeted agents, including denosumab, a fully human monoclonal antibody directed against receptor activator of nuclear factor-κB ligand (RANKL), are shown to be effective in delaying the time of SREs and reducing the number of SREs [5–7], with a potentially positive impact on patient's prognosis [8].

Despite these therapeutical advances, bone metastatic disease, especially in the presence of lytic lesions, is still a major challenge for clinicians and patients. One of the most frequent concerns in these patients is related to their engagement in physical exercise due to safety issues. For instance, a survey conducted on healthcare providers working in lung cancer settings found that about 40 % of them agreed or had no opinion regarding the avoidance of performing physical exercise in the presence of bone metastases [9]. Nevertheless, physical exercise may produce important benefits in patients with lung cancer [10,11]. Whereas epidemiological evidence has observed an association between physical activity and survival [12], randomized controlled trials demonstrated the efficacy of physical exercise in increasing the physical fitness components (i.e., cardiorespiratory fitness, strength, muscle mass) and in managing different symptoms, such as anxiety, depression, fatigue, pain, and bone health [13–15]. Indeed, physical exercise, especially if dynamic, with a mechanical load, and at high impact, may produce a bone anabolic response, able to increase bone formation and decrease absorption [3]. However, most evidence derives from the early-stage disease settings. Focusing on bone metastasis, the available literature, mostly on patients affected by prostate or breast cancer, reported the safety, feasibility, and efficacy in terms of physical fitness of a structured physical exercise program [16]. Of note, these trials often excluded the frailest patients, e.g., those with bone pain, lytic metastases, prior pathological fractures, or multiple bone metastatic sites, or investigated a relatively short period-time of training (i.e., 10–17 days), proposing isometric (static) exercises [3]. Evidence in the context of lung cancer and bone metastases is even more limited. A systematic review examining the effects of exercise interventions included 221 patients with advanced lung cancer, none of whom had bone metastases [17]. Similarly, ongoing clinical trials often exclude patients with bone metastases, making the physical exercise in patients with lung cancer and bone metastases unexplored. In this still *orphan* context, we report the results of a 9-month combined physical exercise intervention performed in a patient with NSCLC affected by multiple lytic lesions and two previous pathological fractures undergoing osimertinib and denosumab.

2. Case presentation

In December 2022, a 55-year-old woman, never smoker, with no relevant comorbidities, was hospitalized due to pain in the

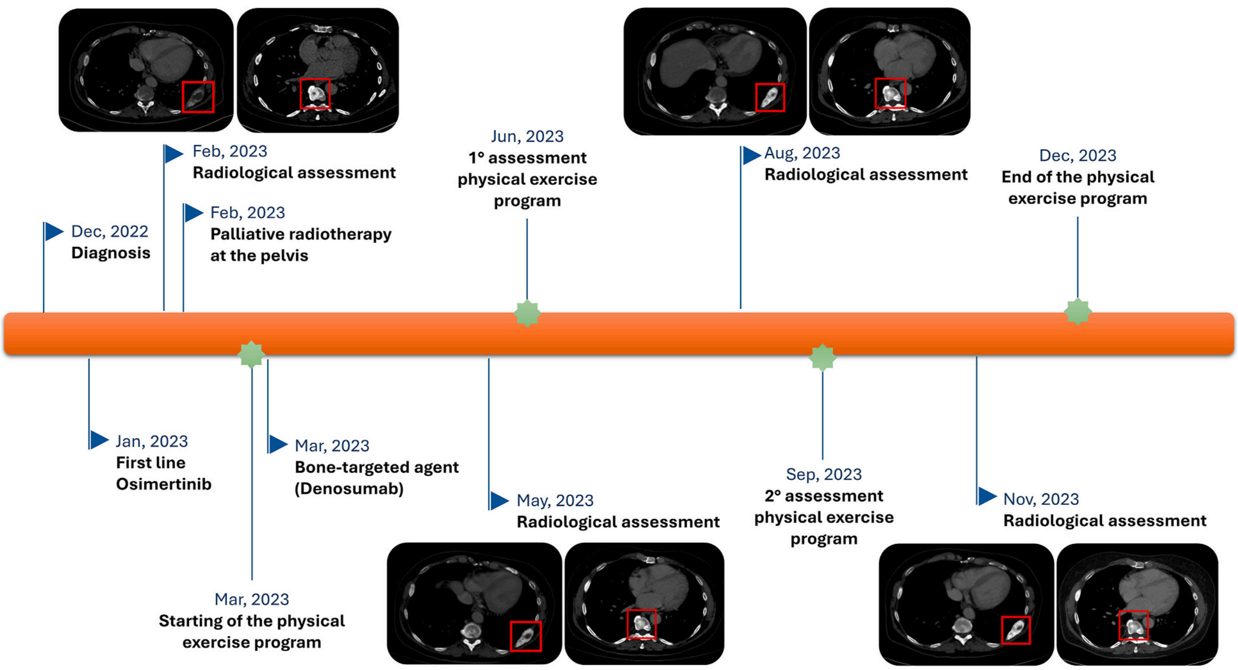

Fig. 1. Timeline of disease status and physical exercise intervention.

scapulohumeral joint and pelvis, with impairment in walking and two pathological fractures in the spine (D5 and L4). Computer tomography scan and subsequent liver needle biopsy revealed a lung adenocarcinoma with a deletion of exon 19 of EGFR (ex19del), PD-L1 negative [stage IV (cT4 N1 M1c), according to TNM classification (Fig. 1.)]. Metastatic lesions involved the liver and the bones. In detail, osteolytic bone lesions were located along the spine (D4-D6, L2-L5, S1-S5), in the ribs (II, IV, VI, X, dx; V, IX, sx), pelvis, and proximal femurs. In January 2023, she started osimertinib (80 mg/die), and in February, she underwent palliative radiotherapy to the pelvis (30Gy, 10 fractions). In March 2023, she began denosumab, 120mg every 28 days, and at the same time, she was offered the opportunity to participate in a 9-month, tailored physical exercise program at the Department of Sport Sciences of the University of Verona. In November 2023, the disease progressed, with an increase in the number and dimension of liver metastases, whereas the bone lesions became osteoblastic. The subsequent liver re-biopsy demonstrated the persistence of the EGFR ex19del without the onset of *druggable* resistance mechanisms; thus, in January 2024, the patient was enrolled in a clinical trial (testing chemo with/without osimertinib prosecution).

This report was conducted according to the Declaration of Helsinki and Good Clinical Practice and reported following case report (CARE) guidelines [18]. The authors obtained the patient's consent for publication of clinical data, and her personal details were anonymized.

2.1. *Exercise intervention*

The supervised training sessions were conducted by an experienced trainer with a master's degree in preventive and adaptive physical activity and expertise in exercise oncology, and performed at facilities of the Department of Sport Science, University of Verona. The exercise prescription was designed following the current exercise guidelines for patients with cancer of the American College of Sports Medicine [14], considering the indications for bone metastatic lesions [19]. In particular, the following recommendations for bone metastases were adopted: *i)* limit exercises that directly load the bone metastatic sites (e.g., avoid trunk flexion/extension/rotation), *ii)* educate the patient to the right movements and control the postural alignment, *iii)* prefer the gravity vs. antigravity activities, *iv)* increase the balance to prevent falls and *v)* monitor pain level during each session and stop the activity if pain raised.

The overall training was organized in 3 macrocycles (every 3 months) to achieve specific aims (Fig. 2.).

The first 3 months focused on improving the patient's general physical condition, such as walking impairment, coordination, and symptom management. The patient attended two weekly sessions, one supervised at the gym and one at home with written instructions, lasting approximately 60 minutes. Sessions started with a warm-up, including dynamic stretching exercise (5 minutes), and continued with aerobic and strength training, concluding with a cool-down, comprising balance and static stretching activities (5 minutes). Aerobic training comprised moderate-intensity continuous training on a treadmill or walking (for the home-based sessions), starting at 10 minutes and increasing by 5 minutes every two weeks, reaching 25 minutes. The intensity was monitored using the CR-10 Borg Scale and set at 3–5 RPE. Strength training included five body-weight or elastic-band exercises (i.e., leg extension, shoulder bench press, calf raises, pulley, leg curl, biceps curl, and triceps extension), performed in 2–3 sets of 8–12 repetitions at moderate intensity (i.e., 3–5 RPE). Exercises were adjusted based on patient capability, focusing on the correct technique. Abdominal exercises were

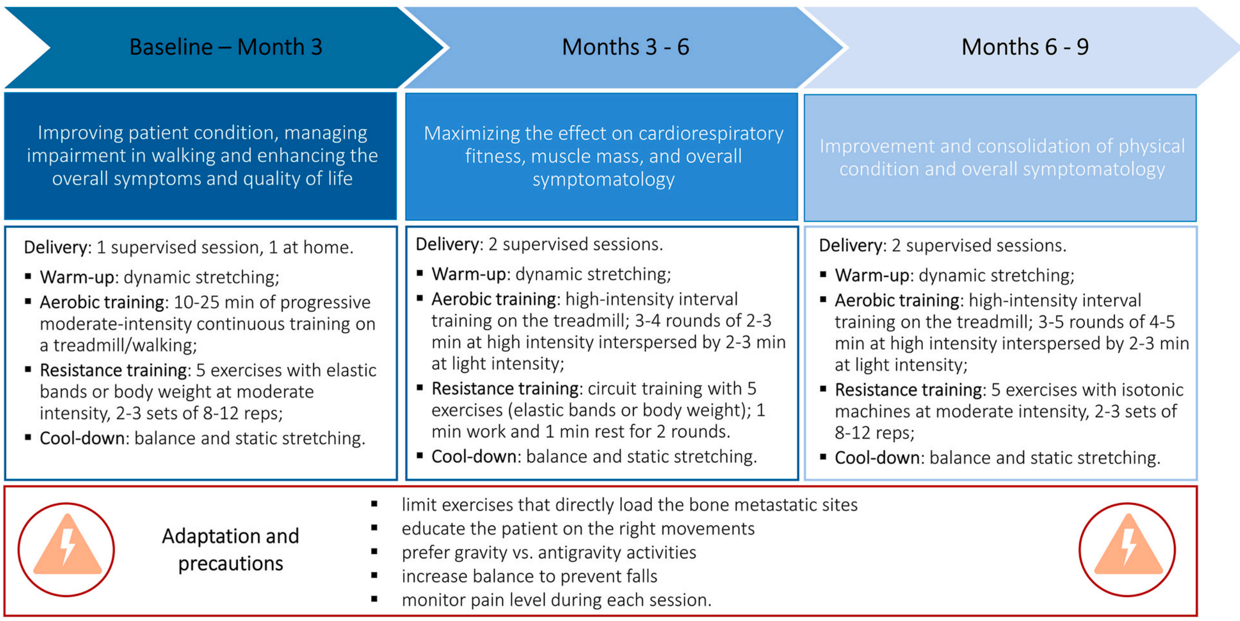

Fig. 2. Physical exercise prescription and adaptation for the 9 months of training.

excluded to reduce vertebral compression or fracture risk.

From months 3–6, the patient attended two weekly supervised sessions at the gym facility. This phase aimed to maximize improvements in cardiorespiratory fitness and muscle mass and reduce symptomatology. Whereas warm-up and cool-down remained the same, aerobic training was replaced with aerobic interval training performed in 3–4 rounds of 2–3 minutes at higher intensity, i.e., 5–7 Borg Scale, interspersed by 2–3 minutes at a light intensity, i.e., 1–2 Borg Scale. The strength component was conducted using circuit training of five body-weight or elastic bands exercises. Maximal repetitions of each exercise were performed for 1 min consecutively, followed by a one-minute break, and the circuit was repeated twice per session.

Months 6–9 were dedicated to further improvement in the physical components. The aerobic interval training was re-proposed, increasing the number of rounds (i.e., 3–5) and the duration of intervals performed at high intensity to 4–5 minutes. In this phase, there was a transition to isotonic machines for five exercises, performed in 2–3 sets of 8–12 repetitions at moderate to somewhat vigorous intensity (i.e., 3–6 RPE).

In each training phase, to ensure safety and optimal intensity, RPE and pain levels were recorded during and after aerobic training, as well as after each set of strength exercises. Adjustments (i.e., treadmill incline, elastic band resistance, or machine weights) were made when the perceived intensity deviated from the target. Examples of sessions for each phase are provided in the Supplementary Material.

Table 1
Absolute scores of physical fitness and health-related parameters.

Variable	At baseline	At 3 months	At 6 months	At 9 months
Physical fitness				
Functional capacity (m)	403	440	483	461
Heart rate (bpm)	146	148	146	149
Rate of perceived exertion (CR0-10)	6	5	5	5
Handgrip strength (kg)				
Left arm	16.5	19	21.5	22
Right arm	22	24	28	24
Anthropometric values				
Body weight (kg)	64.80	64.40	65.40	66.00
BMI (kg/m^2)	25.90	25.80	25.90	26.10
Waist (cm)	91	91.5	89.4	98
Hip (cm)	100	94	95	102
Waist-hip ratio (cm)	0.91	0.97	0.94	0.96
Body composition				
Fat mass (kg)	21.90	20.61	18.51	19.27
Fat-free mass (kg)	42.90	43.79	46.89	46.73
Muscle mass (kg)	40.70	41.60	44.55	44.40
Back scratch (cm)				
Left arm	−13.5	−13	−9	−13
Right arm	4.5	7.5	6	3.5
Chair sit and reach (cm)				
Left leg	−17.5	−10	−12	−6
Right leg	−17	−10	−11	−5
Patient-reported outcomes				
Quality of life (score 0–100)				
Physical functioning	66.67	80	73.33	80
Role functioning	33.33	100	100	100
Emotional functioning	33.33	91.67	91.67	75
Cognitive functioning	100	100	100	83.33
Social functioning	66.67	66.67	100	83.33
Global health status	50	66.67	83.33	50
Fatigue	77.78	11.11	11.11	33.33
Nausea/vomiting	33.33	0	0	0
Pain	83.33	16.67	0	16.67
Dyspnea	33.33	0	0	0
Insomnia	33.33	0	33.33	33.33
Appetite loss	33.33	0	0	0
Constipation	33.33	0	0	0
Diarrhea	66.67	0	0	33.33
Financial problems	33.33	0	33.33	33.33
Physical activity level (min/week)				
Light	0	540	0	0
Moderate	0	60	420	240
Vigorous	0	0	0	0
Total	0	600	420	240

2.2. Assessments

Physical fitness and patient-reported outcomes were assessed at baseline, 3 months, 6 months, and 9 months. To minimize subjective bias, assessments at each time point were performed by the same exercise specialist, a researcher at the University of Verona who had prior training in these operating procedures and who was not involved in the patient's training.

Socio-demographic information was collected at baselines using a self-administered questionnaire, whereas safety and feasibility of exercise were monitored throughout the study. A series of evaluations were proposed to assess physical fitness. Blood pressure, heart rate, and oxygen saturation were recorded at the beginning of the assessment and before starting the physical tests.

Anthropometric parameters, which included height, weight, waist, and hip circumferences, were measured using standardized tools and following World Health Organization procedures [20]. Body composition, including fat mass, fat-free mass, and muscle mass, was estimated using a bioelectrical impedance scale (Tanita RD-545 HR).

According to Rickly and Jones's procedure, flexibility was evaluated using the back scratch test and the chair sit and reach test [21]. For the back scratch test, the distance or overlap between the middle fingers of the hands behind the back was measured. For the chair sit-and-reach test, the patient sat on the edge of a chair, extending one leg forward while reaching toward the toes. Two attempts were performed for each test, with instructions to stretch without pain.

Upper muscle strength was measured using a handgrip strength test with a calibrated dynamometer, following the International Organization for Standardization-certified procedure [22]. The patient was seated in a straight-backed chair with feet flat on the floor, shoulder adducted and neutrally rotated, elbow flexed at 90°, and forearm and wrist in a neutral position. Five attempts were performed per hand, with each contraction held for 2–4 seconds [22].

The *"Six Minutes Walking Test"* was used to estimate cardiorespiratory fitness, according to the protocol of the American Thoracic Association [23]. The patient was instructed to walk as far as possible in a 20-m hallway at their own pace. Standardized encouragement was provided at regular intervals, and oxygen saturation, rate of perceived exertion, and heart rate were measured at the test's conclusion [23].

Quality of life was explored using the Italian version of the European Organization for Research and Treatment of Cancer Quality of Life and Core Questionnaire (EORTC QLQ C-30), containing 30 items designed to assess cancer-specific QoL, symptom burden, and functional scales [24]. Current physical exercise behavior was evaluated using Godin's Shepard Leisure Time Exercise Questionnaire, comprising three items to determine the frequency and duration of vigorous, moderate, or light activities in a typical week [25].

Circulatory parameters were extracted from medical records at baseline, 3, 6, and 9 months. Intervention feasibility was assessed by calculating: *i)* attendance, i.e., the number of attended exercise sessions out of the scheduled sessions, *ii)* compliance, defined as the ratio of the total completed volume compared to the prescribed one, *iii)* tolerance, corresponding to the patient's perceived Rate of Perceived Exertion (RPE) in comparison to the prescribed intensity, and *iv*) safety, evaluated as the number of adverse events linked to exercise intervention, following the Common Terminology Criteria for Adverse Events, version 5.0 [26].

3. Results

During the 9-month of training, no adverse events of any grade related to exercise were registered. Overall attendance was 90 % (65/72), and the main reasons for missed sessions were hospital appointments (n = 4) and fever (n = 3). Between months 6–9, a dose reduction in the strength training was necessary due to knee pain, whereas the HIIT required a dose reduction in two sessions due to excessive fatigue during the last 3 months of the program. Tolerability was optimal without pain in the bone metastatic lesions during the training activity.

Physical fitness and patient-reported results are shown in Table 1. Briefly, improvement in functional capacity was observed at 3 (+9.2 %), 6 (+19 %), and 9 (+14.3 %) months, compared to baseline value. A progressive increase in the upper limb strength was observed for both arms until it reached +27.2 % for the right arm and +33.3 % for the left arm. Whereas lower limb flexibility gradually improved over the months, the back scratch test remained stable, with little variations during the time points. Body weight and anthropometric measures increased over the 9 months. Body composition analysis showed a reduction of fat mass (−15.4 %) and a considerable increase in fat-free mass (+9.3 %) and muscle mass (+9.4 %) from baseline to month 6, which remained stable until month 9. Several domains of quality of life improved especially from baseline to month 3, such as physical (66.7 vs. 80.0 points), role (33.3 vs. 100.0 points), and emotional (33.3 vs. 91.7 points) functioning, fatigue (77.8 vs. 11.1 points), pain (83.3 vs. 16.7 points), dyspnea (33.3 vs. 0.0 points), insomnia (33.3 vs. 0.0 points), appetite loss (33.3 vs. 0.0 points), constipation (33.3 vs. 0.0 points), and diarrhea (66.7 vs. 0.0 points). Few variations in these domains were observed during the other time points, with a little worsening at month 9, probably due to the concurrent disease progression. The total amount of physical activity, especially that performed at moderated intensity, increased from baseline to months 3 and 6 (0 vs. 420 min/week) and slightly decreased at month 9 (420 vs. 240 min/week). Circulatory parameters (Supplementary Materials) did not exhibit any significative changes and remained within the normality range, apart from hemoglobin (at baseline, months 3, 6, and 9), platelets (at months 6 and 9), leukocytes (at month 9), lymphocytes (at baseline, month 3 and 6), calcium (at baseline and month 3), which resulted below the normality range and AST and ALP at month 9 which were above the range.

4. Discussion

Herein, we have reported that a 9-month, highly structured, and supervised physical exercise program, including aerobic and strength training, is safe, feasible, and effective in increasing physical fitness and ameliorating the quality of life of a patient affected by

NSCLC with multiple osteolytic bone lesions. Indeed, no adverse events were observed during the training period, and the attendance, compliance, and tolerability results highlight the feasibility of this type of intervention. These findings are particularly crucial given the relevant safety concerns limiting both the clinical management and physical exercise promotion in this population. In addition, to the best of our knowledge, no prior data were available for patients with multiple lytic lesions.

Beyond its safety profile, our intervention improved the overall patient's condition, especially in terms of functional capacity, muscle strength, and body composition. Functional capacity increased by 80 m during the first 6 months of training and slightly decreased to month 9, resulting in an overall improvement of 58 m. Comparable findings have been reported in two meta-analyses [15, 17]. The first, investigating the effects of physical exercise on functional capacity in patients with NSCLC post-lung resection, demonstrated a mean increase in walking distance of 57 m (95 % CI: 34–80 m), and the second, focusing on patients with advanced lung cancer, reported a mean improvement of 63.33 m (95 % CI: 3.70–122.96 m). Although some factors, including, for instance, the occurred disease progression, may have contributed to a decrease in the walked maters from months 6–9, the overall improvement from baselines can be considered clinically relevant. Indeed, functional capacity has been identified as a key prognostic factor in metastatic NSCLC, with every 50-m increase linked to a 13 % reduction in mortality risk [27].

The intervention also led to significant gains in handgrip strength, with increases of 5.5 kg in the right arm and 2 kg in the left arm, alongside notable body composition remodelling. Over the 9-month period, fat mass decreased while muscle mass increased by over 4 kg. Such changes are particularly valuable given the prognostic role of muscle mass and strength in metastatic NSCLC patients. In this sense, sarcopenia is a recognized prognostic factor for overall response rate and overall survival in patients with metastatic lung cancer [28]. To reinforce the data observed by the body composition analyses, the anthropometric measures revealed a gain in body weight, waist, and hip circumferences, which progressively increased at the different time points, especially until month 6. Additionally, also flexibility improved during the intervention, particularly in the lower limbs, with both legs showing an increase of 11 cm. This improvement is highly significant given the physical limitations and reduced mobility often caused by lytic metastases in the spine, pelvis, and femurs and their consequence on overall quality of life. In the upper limbs, variations were observed across assessments, with general maintenance of flexibility in the left arm despite the pain reported at diagnosis.

While our findings are preliminary and require further validation, some plausible mechanisms underlying the synergistic benefits of denosumab and exercise contribution to bone health warrant discussion. Since denosumab has demonstrated to reduce the incidence of SREs in patients with NSCLC, it is possible that its administration, concomitant with physical intervention, could have contributed to guaranteeing the safety of the exercise programs. On the other hand, since the mechanical stimuli induced by physical exercise are well-recognized factors in increasing bone mineral density and content, it may be hypothesized that our intervention may have had a synergistic effect with osimertinib and the bone-targeted agent in improving the overall bone health and maybe the remineralization of the lytic lesions, how highlighted in the radiological images. Additionally, the bone metastases tumor microenvironment is highly influenced by the interplay between bone cells, immune cells, and cancer cells, and the combination of anticancer therapy, denosumab, and exercise may theoretically contribute to interrupting the "vicious cycle" of bone metastases. Although these observations are purely speculative and need to be further explored, the combination of physical exercise with denosumab may offer additional benefits for these patients.

The last consideration concerns the impact on quality of life. The presence of bone metastases inevitably has a negative impact on functioning and some symptoms, such as pain, which may occur in up to 80 % of these patients [2]. In our case, the prolonged physical exercise program resulted in substantial improvements across several quality-of-life domains, including a marked reduction in pain and fatigue levels, enhancement in global health status, and functioning domains. While these clinical benefits are expected from treatment with osimertinib in combination with denosumab in a patient with EGFR-mutant NSCLC, a wealth of evidence supports the additional role of physical exercise in mitigating cancer and treatment-related side effects and enhancing quality of life [13]. Notably, in our case report, these improvements occurred early, in the first 3 months of the exercise program, then stabilized in the following period, and some of them worsened at month 9, such as almost all the outcomes assessed. While these fluctuations cannot be fully explained, it is plausible that factors such as disease progression, a reduction in exercise dose, and the onset of new symptoms may have played a role. This may underscore the importance of tailoring exercise interventions to accommodate changes in treatment plans and symptom profiles. This may be particularly important in patients with metastatic NSCLC, where multiple therapies are often administered concurrently to manage bone metastasis-related morbidities.

Of note, the exercise intervention led to notable gains in the patient's psychological well-being, e.g., emotional and cognitive functioning. This is in line with the current literature [29] and further strengthens the positive effect of exercise on moods also in patients affected by bone metastases. The improvement in psychological well-being may have clinical implications since it has been demonstrated to be fundamental in increasing compliance with treatments [30]; thus, modalities, such as physical exercise, to enhance it are relevant. Further, balanced mental well-being may also favor the patients' adherence to an exercise program, probably enhancing their possibility of benefiting.

Besides its design as a single-case report, other limitations must be acknowledged. First, the lack of follow-up data reduces our ability to evaluate the long-term sustainability of the observed benefits. Another limitation could be related to the body composition assessment tool. Indeed, the bioimpedance analysis is practical, but the model used in this case report did not have a validation article, even if it is largely utilized in the research context. For this reason, although all the indications, e.g., clothing and hydration, have been adopted, the findings related to body composition should be taken with caution.

The patient included in this study represents a typical clinical scenario, reflecting the complexity of managing NSCLC with bone metastases. NSCLC is the second most commonly diagnosed cancer worldwide, with an increasing incidence among women. Notably, approximately 30 % of patients present with bone metastases at diagnosis, and at least one SRE occurs, often necessitating radiotherapy or managing pathologic fractures [31]. Proper SRE management is thus crucial in improving outcomes for these patients.

When promoting exercise programs, it is important to acknowledge individual differences and adapt interventions to the unique conditions of each patient. For example, in early-stage NSCLC, where surgery combined with systemic therapies offers the best chance of a cure, exercise programs should focus on prehabilitation to optimize surgical readiness and post-surgical rehabilitation to restore functional capacities. Conversely, in patients with advanced or inoperable NSCLC, the primary goals of exercise interventions shift toward prolonging survival, mitigating treatment side effects, and improving quality of life. In cases of metastatic disease, the exercise program must also consider the number, location, and severity of bone lesions, as these factors influence both the safety and the objectives of the intervention. Furthermore, patient-specific factors such as age, presence of comorbidities, and the type of treatment being received (e.g., targeted therapies, immunotherapy, or chemotherapy) are critical in tailoring the exercise program to maximize its effectiveness while minimizing risks.

Future research should focus on expanding the sample size and adopting a more robust design, such as a randomized controlled trial, to enhance the generalizability and reliability of the findings. Such studies should also include extended follow-up periods to assess the durability of the intervention's effects over time.

To conclude, we found that a highly structured and supervised physical exercise program was safe, feasible, and effective in increasing the physical condition of a patient with NSCLC affected by multiple osteolytic lesions. The supervision by a trained exercise specialist may be the key to ensuring the safety of the intervention, as well as the improvements in both physical fitness and quality of life. Our patient reported in her testimony: "*With these personalized exercises, I returned to walk … I never thought I would walk normally again. I think that this program helped me to manage my pain level; I have reduced the assumption of analgesic and opioid drugs … I feel stronger and safer in my movements*" (The patient).

CRediT authorship contribution statement

Anita Borsati: Writing – review & editing, Writing – original draft, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Christian Ciurnelli:** Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Investigation, Data curation. **Lorenzo Belluomini:** Writing – review & editing, Visualization, Validation, Resources, Data curation. **Marco Sposito:** Writing – review & editing, Visualization, Resources, Data curation. **Jessica Insolda:** Writing – review & editing, Visualization, Data curation. **Linda Toniolo:** Writing – review & editing, Visualization, Validation, Resources, Data curation. **Ilaria Trestini:** Writing – review & editing, Visualization, Validation. **Daniela Tregnago:** Writing – review & editing, Visualization, Validation. **Michele Milella:** Writing – review & editing, Visualization, Supervision, Resources, Project administration, Data curation. **Federico Schena:** Writing – review & editing, Visualization, Supervision, Resources, Project administration, Formal analysis. **Sara Pilotto:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Alice Avancini:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Ethic statement

Written informed consent was obtained from the patient for the publication of all her data and images included.

Data and code availability statement

Data will be made available on request. For requesting data, please write to the corresponding author.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Sara Pilotto reports a relationship with AstraZeneca that includes: speaking and lecture fees. Sara Pilotto reports a relationship with Eli Lilly that includes: speaking and lecture fees. Sara Pilotto reports a relationship with Bristol-Myers Squibb that includes: speaking and lecture fees. Sara Pilotto reports a relationship with Merck & Co Inc that includes: speaking and lecture fees. Sara Pilotto reports a relationship with Takeda Oncology that includes: speaking and lecture fees. Sara Pilotto reports a relationship with Amgen that includes: speaking and lecture fees. Sara Pilotto reports a relationship with Novartis that includes: speaking and lecture fees. Sara Pilotto reports a relationship with Roche that includes: speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2025.e42768.

References

[1] M. Kuchuk, et al., The incidence and clinical impact of bone metastases in non-small cell lung cancer, Lung Cancer 89 (2) (2015) 197–202.
[2] B.J. Knapp, S. Devarakonda, R. Govindan, Bone metastases in non-small cell lung cancer: a narrative review, J. Thorac. Dis. 14 (5) (2022) 1696–1712.
[3] A. Avancini, et al., Exercise and bone health in cancer: enemy or ally? Cancers 14 (24) (2022).
[4] M. Lagana, et al., High prevalence and early occurrence of skeletal complications in EGFR mutated NSCLC patients with bone metastases, Front. Oncol. 10 (2020) 588862.
[5] D. Henry, et al., Delaying skeletal-related events in a randomized phase 3 study of denosumab versus zoledronic acid in patients with advanced cancer: an analysis of data from patients with solid tumors, Support. Care Cancer 22 (3) (2014) 679–687.
[6] J. Chen, et al., Meta-analysis of clinical trials to assess denosumab over zoledronic acid in bone metastasis, Int. J. Clin. Pharm. 43 (1) (2021) 2–10.
[7] D.H. Henry, et al., Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma, J Clin Oncol 29 (9) (2011) 1125–1132.
[8] G.V. Scagliotti, et al., Overall survival improvement in patients with lung cancer and bone metastases treated with denosumab versus zoledronic acid: subgroup analysis from a randomized phase 3 study, J. Thorac. Oncol. 7 (12) (2012) 1823–1829.
[9] S. Pilotto, et al., Exercise in lung Cancer, the healthcare providers opinion (E.C.H.O.): results of the EORTC lung cancer Group (LCG) survey, Lung Cancer 169 (2022) 94–101.
[10] A. Avancini, et al., Physical activity and exercise in lung cancer care: will promises Be fulfilled? Oncologist 25 (3) (2020) e555–e569.
[11] V. Cavalheri, C.L. Granger, Exercise training as part of lung cancer therapy, Respirology 25 (Suppl 2) (2020) 80–87.
[12] J.A. Sloan, et al., Impact of self-reported physical activity and health promotion behaviors on lung cancer survivorship, Health Qual. Life Outcome 14 (2016) 66.
[13] A. Avancini, et al., Integrating supportive care into the multidisciplinary management of lung cancer: we can't wait any longer, Expert Rev. Anticancer Ther. 22 (7) (2022) 725–735.
[14] K.L. Campbell, et al., Exercise guidelines for cancer survivors: consensus statement from International multidisciplinary roundtable, Med. Sci. Sports Exerc. 51 (11) (2019) 2375–2390.
[15] V. Cavalheri, et al., Exercise training undertaken by people within 12 months of lung resection for non-small cell lung cancer, Cochrane Database Syst. Rev. 6 (6) (2019). CD009955.
[16] S. Weller, et al., Exercise for individuals with bone metastases: a systematic review, Crit. Rev. Oncol. Hematol. 166 (2021) 103433.
[17] C.J. Peddle-McIntyre, et al., Exercise training for advanced lung cancer, Cochrane Database Syst. Rev. 2 (2) (2019). CD012685.
[18] J.J. Gagnier, et al., The CARE guidelines: consensus-based clinical case reporting guideline development, Glob. Adv. Health Med. 2 (5) (2013) 38–43.
[19] K.L. Campbell, et al., Exercise recommendation for people with bone metastases: expert consensus for health care providers and exercise professionals, JCO Oncol Pract 18 (5) (2022) e697–e709.
[20] O. de Onis, den Broeck, Chumlea, Martorell, for the WHO Multicentre Growth Reference Study Group, Measurement and standardization protocols for anthropometry used in the construction of a new international growth reference, Food and Nutrition Bullettin 25 (1) (2004).
[21] R.E. Rikli, C.J. Jones, Development and validation of criterion-referenced clinically relevant fitness standards for maintaining physical independence in later years, Gerontol. 53 (2) (2013) 255–267.
[22] E. Innes, Handgrip strength testing: a review of the literature, Aust. Occup. Ther. J. (1999) 120–140.
[23] Society, A.T., ATS statement: guidelines for the six minute walk test, Am. J. Respir. Crit. Care Med. 166 (1) (2012).
[24] N.K. Aaronson, 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. 85 (5) (1993) 365–376.
[25] S. Amireault, et al., The use of the Godin-Shephard Leisure-Time Physical Activity Questionnaire in oncology research: a systematic review, BMC Med. Res. Methodol. 15 (2015) 60.
[26] Institute, N.C., Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, 2022.
[27] L.W. Jones, et al., Prognostic significance of functional capacity and exercise behavior in patients with metastatic non-small cell lung cancer, Lung Cancer 76 (2) (2012) 248–252.
[28] I. Trestini, et al., Body composition derangements in lung cancer patients treated with first-line pembrolizumab: a multicentre observational study, J Cachexia Sarcopenia Muscle 15 (6) (2024) 2349–2360.
[29] M. Quist, et al., The impact of a multidimensional exercise intervention on physical and functional capacity, anxiety, and depression in patients with advanced-stage lung cancer undergoing chemotherapy, Integr. Cancer Ther. 14 (4) (2015) 341–349.
[30] P. Theofilou, H. Panagiotaki, A literature review to investigate the link between psychosocial characteristics and treatment adherence in cancer patients, Onco Rev. 6 (1) (2012) e5.
[31] D. Santini, et al., Natural history of non-small-cell lung cancer with bone metastases, Sci. Rep. 5 (2015) 18670.