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Clinical Trial Protocol

Effects of a 12-week multicomponent exercise programme on physical function in older adults with cancer: Study protocol for the ONKO-FRAIL randomised controlled trial

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ABSTRACT

Introduction: Cancer in older adults is often associated with functional limitations, geriatric syndromes, poor self-rated health, vulnerability, and frailty, and these conditions might worsen treatment-related side effects. Recent guidelines for patients with cancer during and after treatment have documented the beneficial effects of exercise to counteract certain side effects; however, little is known about the role of exercise during cancer treatment in older adults.

Materials and Methods: This is a multicentre randomised controlled trial in which 200 participants will be allocated to a control group or an intervention group (the sample size has been calculated to detect a clinical difference of 1 point in Short Physical Performance Battery (SPPB) score, assuming an α error of 0.05, a β error of 0.20, and a 10 % loss rate). Patients aged ≥70 years, diagnosed with any type of solid cancer and candidates for systemic treatment are eligible. Subjects in the intervention group are invited to participate in a 12-week supervised multicomponent exercise programme in addition to receiving usual care. Study assessments are conducted at baseline and three months. The primary outcome measure is physical function as assessed by the SPPB. Secondary outcome measures include comprehensive geriatric assessment scores (including social situation, basic and instrumental activities of daily living, cognitive function, depression, nutritional status, polypharmacy, geriatric syndromes, pain, and emotional distress), anthropometric characteristics, frailty status, physical fitness, physical activity, cognitive function, quality of life, fatigue, and nutritional status. Study assessments also include analysis of inflammatory, endocrine, and nutritional mediators in serum and plasma as potential frailty biomarkers at mRNA and protein levels and multiparametric flow cytometric analysis to measure immunosenescence markers on T and NK cells.

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Discussion: This study seeks to extend our knowledge on exercise interventions during systemic anticancer treatment in patients over 70 years of age. Results from this research will guide the management of older adults during systemic treatment in hospitals seeking to enhance the standard of care.
Trial registration: ClinicalTrials.gov Identifier: NCT05131113, November 11, 2021.

1. Background

Motivated by the known relationship between cancer and age, a recent study sought to describe -for the first time- international trends in cancer incidence in older adults [1]. In most European countries, increases have been seen in the incidence of all cancers (excluding non-melanoma skin cancers) in adults over 50 years of age. In Spain, new cancer diagnoses have also increased, and it was estimated that approximately 60 % of all new cancers detected in 2023 would be in people older than 65 years old [2]. This increase in Spain can be attributed to demographic growth, ageing, exposure to a range of risk factors, and advances in early detection [2]. A cancer diagnosis in an older adult is often associated with functional limitations, geriatric syndromes, poor self-rated health, vulnerability, and frailty [3]; these conditions may have a negative impact on treatment-related side effects due to drug interactions [4]. On the other hand, older adults (≥65 years old) are more likely to receive lower relative dose intensities of chemotherapy treatment [5]. Moreover, the older the age, the higher the probability of completing less than 85 % of the planned or standard dose intensity, and this threshold is considered to be a clinically significant reduction [5]. Thus, evidence shows that treating older adults with cancer may be very complex, presenting a great challenge to oncology clinicians.

Age-related deterioration of the immune system is associated with greater morbidity and mortality in older adults due to, among other factors, increases in the incidence of cancer [6,7], which is attributable to a decrease in tumour immunosurveillance [8]. All cellular components of the immune system are affected by immunosenescence and some of the most notable changes occur in adaptive immunity, and especially in cytotoxic CD8+ T cells [9]. Changes in CD8+ T cells in older donors led to the identification of an immunological risk profile characterised by an inverted CD4/CD8 ratio (less than 1) and an expansion in the population of exhausted CD8+ T cells [10,11]. The other large population of cytotoxic lymphocytes are natural killer (NK) cells, components of innate immunity, and these also exhibit marked changes in their phenotype and functionality related to immunosenescence [12,13]. In this context, it is interesting to explore whether age-related risk can be reduced by modifying these biomarkers, and one approach may be to increase levels of physical activity. Specifically, the analysis of exercise training-induced changes in immunosenescence markers expressed by immune cells is crucial for understanding how such interventions might be beneficial. Some studies suggest that exercise training may have an anti-immunosenescence effect in patients with cancer, as shown by a reduction in the frequency of exhausted CD4+ T cells [14]. Other research has demonstrated that aerobic exercise training changes the frequency of CD4+ and CD8+ T cells associated with immunosenescence in middle-aged/older women at high risk of breast cancer [15].

In addition to T and NK cell markers, numerous independent studies have tried to identify biomarkers in plasma and serum that can predict, diagnose and monitor various aspects of frailty and ageing in cancer at biological and molecular levels [16–18]. These potential biomarkers include inflammatory, endocrine, and nutritional mediators. The relationship between frailty and chronic low-grade inflammation is well documented [7,19]. Frailty is related to several different physiological systems, including the musculoskeletal (sarcopenia and osteopenia), haematological (anaemia), cardiovascular, and endocrine systems. Decreased plasma levels of myostatin, insulin-like growth factor 1, dehydroepiandrosterone sulphate, and insulin resistance have also been linked to frailty and cancer cachexia [20–22]. Although the study of biomarkers of cognitive impairment in the context of frailty is still in its infancy, the best characterised marker to date is brain-derived neurotrophic factor [23]. Nonetheless, to our knowledge, there are no solid data concerning biological mechanisms that might explain potential effects of exercise during antineoplastic treatment. In addition, although a few studies have identified possible benefits of exercise in terms of treatment tolerance and chemotherapy completion rate, the impact of exercise on these outcomes remains unclear [24].

Poorer physical function before treatment is associated with lower treatment tolerance and a greater probability of not completing planned treatment [25,26], but doing exercise during chemotherapy may mitigate this association and be especially beneficial in patients with poor physical condition before treatment [26]. Benefits of exercise in counteracting treatment-related adverse effects have been also documented in recent guidelines for patients with cancer during and after treatment [27]. Nonetheless, little is known about the role of exercise during cancer treatment specifically in older adults. The feasibility of a multimodal (nutrition and exercise) intervention in older adults was evaluated in a study that included patients with advanced non-small-cell lung or pancreatic cancer receiving chemotherapy [28]. That study reported excellent feasibility and safety in this population. Cognitive function was evaluated in another feasibility study, in this case, in patients with breast and prostate cancer, and it was observed that speed-feedback therapy using a cycle ergometer could be feasible and effective [29]. Physical function has been evaluated as the primary outcome in four studies [30–33]. All of them reported significant improvements after the interventions and one that improvements were maintained to two years. These studies were heterogenous, however, in terms of the population included: patients with prostate cancer, any type of cancer, or advanced pancreatic, biliary tract, and lung cancer. The characteristics of the interventions also varied: six-week home-based walking and resistance or a technology-mediated walking and resistance intervention using Wii Fit, a 12-week combined supervised and unsupervised aerobic and resistance intervention, a one-year unsupervised multicomponent intervention, and a 12-week supervised multimodal intervention. On the other hand, a study assessing radiation-related fatigue in a home-based graduated walking programme for patients with breast cancer did not find improvements [34], while a secondary analysis evaluated effects on body composition and fitness in a three-armed study (aerobic, resistance, and control group) during radiotherapy in participants with prostate cancer ≥65 years and ≤ 65 years [35], and in the older age group, resistance exercise improved body composition (preserving lean body mass) and upper and lower body muscle strength compared with aerobic training and usual care.

Overall, evidence on exercise programmes during systemic treatment in older adults with cancer is scarce and heterogeneous and this will be among the first studies to investigate a multicomponent exercise programme in patients over 70 years of age. Specifically, the primary aim of the ONKO-FRAIL study is to assess the effect of a 12-week supervised multicomponent exercise programme on physical function in patients with cancer over 70 years old who are scheduled to receive systemic treatment. Secondary outcomes include measures related to comprehensive geriatric assessment scores, anthropometric characteristics, frailty status, physical fitness, physical activity, cognitive function, quality of life, fatigue, nutritional status, and inflammatory, frailty, and immunosenescence biomarkers.

2. Methods/Design

2.1. Study design and participants

To address the study aim, we designed a prospective, multicentre, randomised controlled trial (ClinicalTrials.gov Identifier: NCT05131113). Participants are randomly allocated to a control or an intervention group (Fig. 1). Recruitment takes place in three university hospitals: Hospital Universitario Donostia, Hospital Universitario Basurto and Hospital Universitario Araba; all in the Basque Country, in the north of Spain. Hospital Universitario Donostia will enrol 100 patients, while the other two hospitals will enrol 50 patients each. The intervention took place between January 2022 and May 2024. The assessments are conducted by research staff at baseline and after 12 weeks. This study follows the standard protocol for clinical trials in accordance with the Standard Protocol Items: Recommendations for Interventional Trials statement [36]. This research has been approved by the Research Ethics Committee of the Basque Country (code: PI2021110).

2.2. Inclusion and exclusion criteria

Patients are considered eligible for the study if they meet all of the following criteria: age $\geq$ 70 years; a diagnosis of solid cancer including breast, gynaecological, lung, pleural, digestive, urological, ear, nose or throat cancer, sarcoma, brain tumours, melanoma, or patients with a lymphoma diagnosis (requiring at least six cycles of chemotherapy) or tumours of unknown origin; and a candidate for any line of systemic treatment (chemotherapy, hormone therapy, biological therapies, or immunotherapy) provided that at least one month has elapsed since the last dose of treatment (washout period).

Exclusion criteria are Eastern Cooperative Oncology Group performance status score $\geq$ 3, advanced dementia, serious psychiatric illness, a lack of basic fluency in Basque or Spanish, inability to get up from a chair and walk independently with or without walking aids, participation in other research involving a physical exercise programme, and absolute or relative contraindications in which the risk of adverse effects outweighs the possible benefits, such as unstable angina or acute symptomatic heart failure.

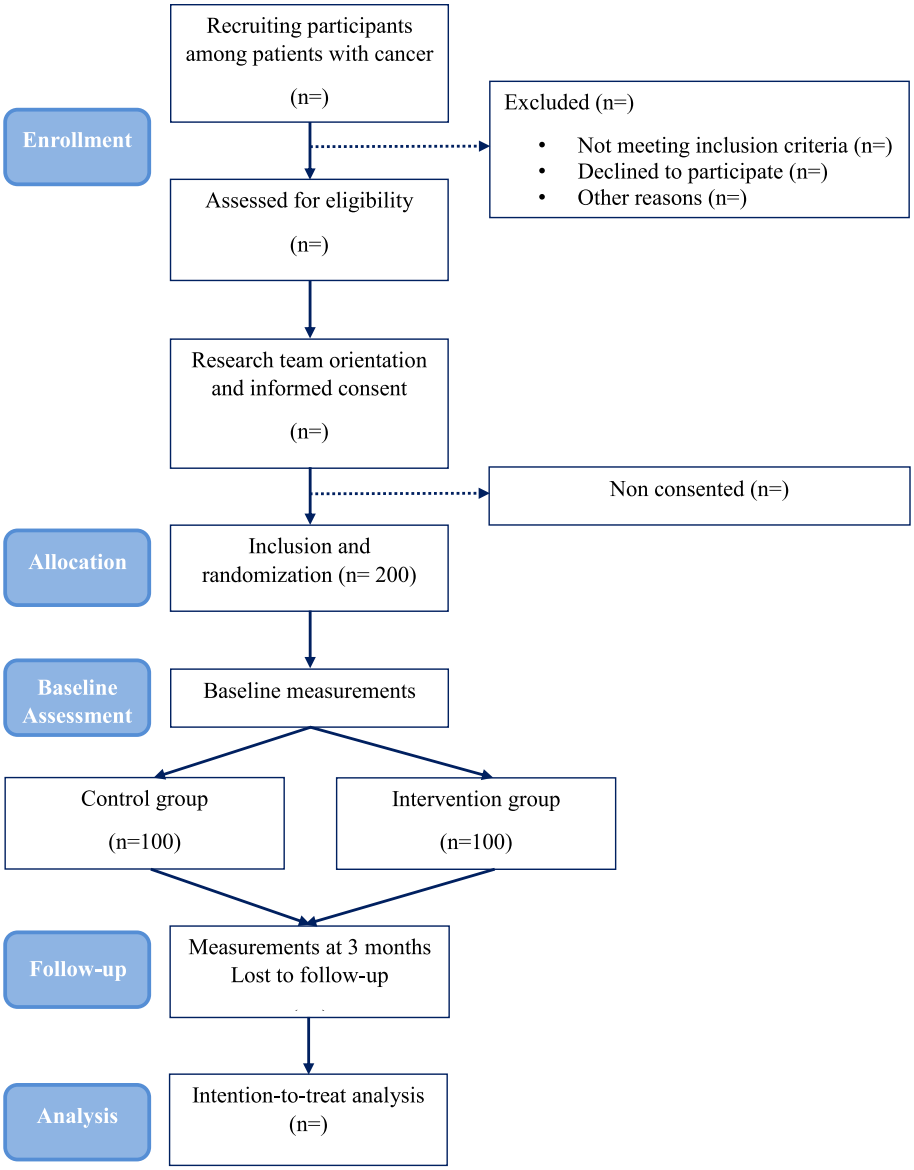

Fig. 1. Study protocol description.

2.3. Recruitment and randomisation

Lists of individuals that meet inclusion criteria are obtained from the database of each hospital. The primary recruitment strategy is through the provision of information to potential participants by their oncologist: objectives, measurement variables, and other details about the interventions are explained orally and in writing. After patients have given written informed consent, they are randomised to the control or the intervention group in blocks of four (in a 2:2 ratio). Randomisation is stratified by the recruitment centre. The allocation sequence is incorporated into the electronic case report form (ECRF). The group allocation of each participant is revealed by a member of the research team at the first visit after the initial assessments, signing of the informed consent form and registration of the participant in the ECRF. The ECRF is developed by a professional who is not a member of the current research team. No research team members have any prior knowledge of the allocation sequence; nor they are able to alter the sequence. Due to the nature of the intervention, blinding is not possible for either patients or exercise specialists who supervise the exercise sessions.

2.4. Control group

The control group receives usual care. To standardise the physical activity recommendations that oncologists or haematologists provide, a basic manual on physical activity is given and explained to patients allocated to this group. The guide encourages them to be active and avoid prolonged sedentary time and also includes some basic safety recommendations.

2.5. Intervention group

Patients in the intervention group are invited to take part in a 12-week supervised moderate-intensity multicomponent exercise programme designed to maintain physical function. Supervision is performed by exercise specialists (trainers), who receive standardised instructions from the research team, to ensure identical execution of the multicomponent exercise programme in all three settings. The multicomponent exercise intervention involves balance, resistance, and aerobic training. The technical content of the programme is based on a specific literature review [27,31,37–39] as well as the authors' knowledge and field experience (Table 1). The intervention has been designed in accordance with the most recent exercise guidelines for cancer survivors [27] and the guidelines for older adults established by the American College of Sport Medicine (ACSM) [37]. The multicomponent exercise programme has specific goals and a standardised framework (combination and sequence of exercises), but the objectives are individualised based on the fitness level of each patient. Objectives are adapted in response to illness, injury, or physical symptoms.

One-hour supervised sessions are conducted twice a week, with an interval of at least 48 h between training sessions (Table 2). Exercise sessions are carried out in groups of up to four participants when recruitment allows. Each session begins with a brief 5-min warm-up (range-of-motion exercises for the neck, shoulders, hips, knees, and ankles). The second part is balance training (10 min), which consists of exercises with progressive difficulty levels, starting by decreasing arm support along with decreasing the base of support and increasing the complexity of the movements, to challenge the patients' balance as they progress. Three types of exercises are performed: (i) static balance, (ii) dynamic balance, and (iii) dynamic balance exercises with interaction with other members of the group or the trainer.

The third part of each session is resistance training (25 min) involving six exercises targeting the major upper and lower body muscle groups and using free weights or body weight. The first week of the intervention mainly serves to familiarise participants with the resistance exercises. Then, in week 2 and again in week 6, the intensity of each exercise is tailored to the patient's fitness level using Brzycki's formula for estimating an individual's one-repetition maximum (1-RM), to ensure an adequate training stimulus. In general, the exercises should be performed at moderate intensity. From week 2 to week 5, exercises are performed with loads of 60 % of 1-RM, and if these are well tolerated, after the second 1-RM estimate at week 6, loads are increased to 70 % of 1-RM at week 7 and maintained until week 12, seeking to achieve additional benefits. Since this is a vulnerable population whose health status may deteriorate, and because we can expect variability in patients' exercise tolerance over the course of the programme due to their cancer treatment, the intensity of each exercise is adapted based on the intensity of exertion as perceived by the patient using an OMNI scale (range: 0 to 10) [40], maintaining the intensity between 4 and 5. If the rating of perceived exertion is >5, the load should be decreased by 10 % for that and following sessions, while if it is <4, the load can be increased by 10 %, with the aim of keeping the training in the moderate intensity range. Finally, for patients with bone metastasis, 1-RM testing is not performed for exercises that load regions with bone metastasis; in these cases, the multicomponent exercise programme is adapted based on the site of bone metastases as set out in Table 3.

Sessions continue with aerobic training consisting of a moderate-intensity continuous cycle training lasting 10 min per session for the first 8 weeks, and 15 min from week 9 to week 12. The aerobic training protocol is individually tailored to the patient's fitness level using the Maximal Short Exercise Capacity and estimated peak power output (Wpeak) as determined at baseline with the Steep Ramp Test [41]. The training is performed at 60 % of Wpeak, when patients report being physically active; and otherwise at 50 % (physically inactive). Patients wear a monitor to track their heart rate. Safety precautions for this monitoring have been established: if patients present tachycardia at rest,

Table 1
Physical exercise intervention's technical content.

	12 weeks	
	Weeks 1–6	Weeks 7–12
Balance (10 min)	Progressive difficulty starting with decreasing arm support along with decreasing base of support.	
Resistance (25 min)	6 Exercises: 2 sets, 10–15 repetitions at 40–60 % of 1RM.	6 Exercises: 2–3 sets, 8–12 repetitions at 70 % of 1RM.
Aerobic training (10–15 min)	10 min moderate-intensity continuous training at 50–60 % of Wpeak.	15 min moderate-intensity continuous training at 50–60 % of Wpeak.

Table 2
Programation of the intervention for the 7th week.

Week day physical exercise program	Tuesday	Thursday
Warm-up (5 min)	Range of motion for different joints	
Balance training (10 min)	One legged stand 3 sets 10 s (supported, unsupported, with uneven surface or with eyes closed) Walk on a line forward and backward. Passing a ball while maintaining the tandem position.	
Resistance training (25 min)	Squad 70 % 2 sets 8–12 rep	Squad 70 % 2 sets 8–12 rep
	Lunge 70 % 2 sets 8–12 rep	Leg abduction 70 % 2 sets 8–12 rep
	Hip extension 70 % 2 sets 8–12 rep	Leg extension 70 % 2 sets 8–12 rep
	Calf raise 70 % 2 sets 8–12 rep	Calf raise 70 % 2 sets 8–12 rep
	Push-up 70 % 2 sets 8–12 rep	Standing row with resistance band 70 % 2 sets 8–12 rep
	Overhead lifting of dumbbells 70 % 2 sets 8–12 rep	Shoulder external rotations with resistance band 70 % 2 sets 8–12 rep
Aerobic training (10–15 min)	Cycling: 15 min moderate-intensity continuous training at 50–60 % of Wpeak.	
Cooling-down (5 min)	Stretching, breathing and relaxing exercises.	

Table 3
Adaptations to the prescribed exercise programme based on the site of bone metastases[d e].

Metastasis site	Resistance exercise			Aerobic exercise		Flexibility
	Upper	Trunk	Lower	WB	NWB	Static
Pelvis	√	√	√[b]		√	√
Axial skeleton (lumbar)	√		√		√	√[c]
Axial Skeleton (thoracic/ribs)	√[a]		√	√	√	√[c]
Proximal humerus		√[a]	√	√	√	√[a]
Proximal femur	√	√	√[b]		√	√
All regions	√[a]		√[b]		√	√[c]

√ = Target region considered appropriate.
WB: weight bearing (e.g., walking), *NWB:* non-weight bearing (e.g., cycling).
[a] Exclusion of shoulder flexion/extension/abduction/adduction - inclusion of elbow flexion/extension.
[b] Exclusion of hip extension/flexion - inclusion of knee extension/flexion.
[c] Exclusion of spine/flexion/extension/rotation.
[d] Galvão DA, Taaffe DR, Cormie P, et al. Efficacy and safety of a modular multi-modal exercise program in prostate cancer patients with bone metastases: A randomised controlled trial. BMC Cancer. 2011;11:517. https://doi.org/10.1186/1471-2407-11-517.
[e] Hiensch, A. E., Monninkhof, E. M., Schmidt, M. E., Zopf, E. M., Bolam, K. A., Aaronson, N. K., … & May, A. M. (2022). Design of a multinational randomised controlled trial to assess the effects of structured and individualised exercise in patients with metastatic breast cancer on fatigue and quality of life: the EFFECT study. Trials, 23 (1), 1–14.

bradycardia on exertion, or their heart rate exceeds 90 % of their heart rate maximum (220-age) during exercise, the exercise is stopped, and the trainer contacts the ONKO-FRAIL team/medical services. As in the resistance exercises, seeking to keep the training in the moderate intensity range, the intensity of the aerobic training is adapted based on the intensity of exertion as perceived by the patient using an OMNI scale, maintaining the intensity between 4 and 5, decreasing the load by 10 % for ratings >5 and increasing it for ratings <4. Alternatives for aerobic training have been established for participants who for whatever reason cannot use the bicycle: i) standing, with or without hand support, alternately flexing the hip and knee of one leg and then the other, imitating the movement of static running, ii) standing, taking a lateral step with one leg while the homolateral upper limb is abducted to 90° and vice versa, iii) and seated or standing, performing an exercise routine agreed with the patient. These alternative options can be combined to reach 10–15 min of training, with a rating of 4–5 on the OMNI scale as a reference. These patients also wear a monitor to track their heart rate. In patients with bone metastasis, osteoporosis or pain, high impact is avoided. In such cases, the oncologist should be informed to confirm the safety of the proposed exercises. Sessions end with a 5-min cool down with stretching, breathing and relaxation exercises.

The multicomponent exercise programme also includes recommendations for aerobic training at moderate intensity (for example, walking), as other authors have done [42], taking a rating of 4–5 on the OMNI scale as a reference to achieve the target intensity. The trainer makes recommendations to each patient individually concerning the minutes of aerobic training to achieve the following week, with the aim of reaching at least 150 min/week as recommended in the cancer population [43,44].

Programme attendance may be discontinued due to injury, hospitalisation, or any other health-related event. The assessment for restarting exercise depends on the functional impact of the illness and any limits on physical activity that may be recommended by the patient's healthcare professionals. Regardless of the week of the intervention in which discontinuation might occur, every restart is carried out in a supervised and progressive manner.

The multicomponent exercise programme is based on a pilot study in which we successfully collected preliminary data to accurately confirm the adherence to and safety of the intervention, refine the outcome assessments, and optimise the organisational infrastructure [45].

2.6. Outcome measures

Primary and secondary outcomes are assessed at baseline and after 12 weeks (Table 4). Completing the assessments is expected to take approximately 75 min per participant. In addition, blood samples are collected from all patients at both visits for the analysis of inflammatory, frailty, and immunosenescence biomarkers. Blood sample collection takes place in the morning following an overnight fast. Sociodemographic data are assessed at baseline with a study-specific questionnaire. Medical data are retrieved from medical records.

The primary outcome is differences in physical function between control and intervention groups measured by changes in the ordinal summary score of the Short Physical Performance Battery (SPPB) [46]. The SPPB includes tests of static balance, gait speed and lower extremity strength. The score for each test is given in a categorical manner (0–4) based on run time intervals. Overall, the maximum SPPB score is 12 (4 points in each test). It has proven to be a valid instrument for predicting disability, institutionalisation, and mortality in older adults [46]. A 1-point change in SPPB score has been shown to be of clinical relevance and represent a substantial meaningful change. Further, a 1-point change was reported to be able to identify changes in the ability to walk a block, the ability to climb a flight of stairs, or any self-perceived change in mobility [47].

Secondary outcome measures include scores obtained as part of a comprehensive geriatric assessment measuring social situation (an abbreviated version of Gijón's Social-Familial Evaluation Scale) [48]; basic activities of daily living (Barthel Index) [49]; instrumental activities of daily living (Lawton Instrumental Activities of Daily Living Scale) [50]; cognitive function (Pfeiffer's Short Portable Mental Status Questionnaire test) [51]; depression (Geriatric Depression Scale-Short Form) [52]; nutritional status (Mini Nutritional Assessment-Short Form) [53]; polypharmacy (number of chronic medications taken); geriatric syndromes (immobility and pressure ulcers; instability and falls; urinary and faecal incontinence; dementia and acute confusional syndrome; malnutrition; alterations in sight and hearing; constipation, faecal impaction; depression/insomnia); pain (Visual Analogue Scale, VAS) [54]; and emotional distress (Distress Thermometer) [55]. Anthropometric data collected include weight, height, waist, hip and calf circumferences, and bioelectrical impedance [56]. Resting heart rate, and systolic and diastolic blood pressures also are measured. Frailty is assessed using the G8 scale [57] and Fried Frailty Phenotype [58]. Physical fitness is determined by the 8 Foot Up and Go Test [59], and Steep Ramp test [60]. In addition, physical activity level is assessed using a patient reported outcome measure (PROM), the Godin-Shephard Leisure-Time Physical Activity Questionnaire [61], and recorded with an accelerometer (GT3X, Actigraph LLC, Pensacola, FL, USA). Patients wear an accelerometer on their hip using a belt for 7 days, both at baseline and after 12 weeks, to assess sedentary time, physical activity and its different intensities (light, moderate, vigorous and very vigorous), step counts and sleep efficiency. Cognitive function is measured with the Montreal Cognitive Assessment (MoCA) [62] and the Cognitive Failures Questionnaire (CFQ) [63]. Other relevant outcomes also assessed by PROMs are quality of life (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQ]-Core 30 and its sub-scales) [64], fatigue (EORTC QLQ-12-item cancer related fatigue [FA12]) [65] and nutritional status (Short Nutritional Assessment Questionnaire) [66].

For the biomarker analysis, blood samples are collected as previously indicated and they are processed by the Basque Biobank to obtain plasma, serum, and peripheral blood mononuclear cells. Frailty and inflammatory biomarkers, including insulin-like growth factor 1, myostatin, brain-derived neurotrophic factor, dehydroepiandrosterone sulphate, vitamin D, C-reactive protein, and cytokines (such as IL-1b, IL-6,

Table 4
Overview of outcomes and time point of data collection.

Outcomes	Instrument	Study period		
		Enrolment	Initial assessment	Follow-up at 3 months
Enrolment				
Eligibility screen	–	X		
Informed consent	–	X		
Primary outcome				
Physical function	Short Physical Performance Battery		X	X
Secondary outcomes				
Comprehensive geriatric assessment	Social situation: Abbreviated Gijón Scale		X	
	BADL: Barthel Index		X	X
	IADL: Lawton's test		X	
	Cognitive function: Pfeiffer test		X	X
	Depression: Yesavage test-short form		X	X
	Nutritional status: MNA-SF test		X	X
	Polypharmacy		X	X
	Geriatric syndromes		X	
	Pain: Visual Analogue Scale		X	X
	Emotional distress: The Distress Thermometer		X	X
Anthropometric data	Body weight		X	X
	Height		X	X
	Waist, hip and calf circumference		X	X
	Bioelectrical impedance		X	X
	Resting heart rate and blood pressure		X	X
Frailty	G8 scale		X	X
	Fried frailty Phenotype		X	X
Physical fitness	8 Foot Up and Go Test		X	X
	Steep Ramp test		X	X
Physical activity	Accelerometer		X	X
	Godin-Questionnaire		X	X
Cognitive assessments	Montreal Cognitive Assessment		X	X
	Cognitive Failures Questionnaire		X	X
Quality of life	EORTC QLQ-C30		X	X
Fatigue	EORTC QLQ-FA12		X	X
Nutrition	SNAQ		X	X
Satisfaction with exercise intervention[*]	Self-developed questionnaire			X
Biomarker analysis			X	X
Sociodemographic and medical data				
Sociodemographic parameters	Self-developed questionnaire		X	
Medical history	Medical records		X	X
Cancer progress and treatment over the course of the study	Medical records		X	X
Cancer characteristics and treatment history	Medical records		X	X
Adverse events	CTCAE, reports of patients, trainers, physicians or medical records		X	X

BADL, Basic activities of daily living; IADL, Instrumental activities of daily living; MNA-SF, Mini Nutritional Assessment - Short Form; EORTC, European Organisation for Research and Treatment of Cancer; QLQ, Quality of Life Questionnaire; FA, fatigue; SNAQ, Simplified Nutritional Appetite Questinnaire; CTCAE, Common Terminology Criteria for Adverse Events.

[*] Only for the intervention group.

IL-8, tumour necrosis factor alpha and interferon gamma), are analysed by multiplex enzyme-linked immunosorbent assay in serum or plasma samples. Markers of frailty at the gene expression level are evaluated by quantitative polymerase chain reaction in mRNA samples derived from peripheral blood mononuclear cells (PBMCs). PBMCs are also used for the phenotypical study of the two most important subpopulations of cytotoxic lymphocytes: CD8+ T cells and NK cells. We perform multiparametric flow cytometric experiments and markers of immunosenescence are analysed, such as the expansion of exhausted CD8+ T cells and the CD4/CD8 ratio.

An assessment of the intervention and factors related to adherence to the multicomponent exercise programme are also carried out. The intervention is followed up and data are gathered concerning adverse events associated with the intervention, satisfaction with the intervention, and results related to beliefs, barriers, facilitators and self-efficacy in relation to physical exercise.

2.7. Safety assessments

All adverse events possibly related to exercise or study measurements are recorded. Patients in both groups are asked by the research staff about exercise- and study measurement-related adverse events in a standardised manner during the follow-up visit. Moreover, patients assigned to the intervention group are asked by their trainer, before and after each exercise session, whether any potentially exercise-related adverse events have occurred during or since the last supervised session that have: i) required talking to a physician or other health professional, ii) produced any worsening of health or well-being, or iii) occurred during or after physical exercise and required altering or prematurely terminating the training or should be referred to a clinician.

In addition to exercise-related events, treatment-related adverse events will also be monitored and recorded throughout the study period. Adverse events occurring during cancer treatment will be recorded and classified according to the Common Terminology Criteria for Adverse Events (CTCAE), specifically when grade III or IV toxicity is observed. In addition, information will be gathered on any treatment suspension due to toxicity, dose reduction of the initially planned regimen, and the percentage of treatment completed relative to the prescribed therapeutic scheme during the intervention period. Cases of treatment discontinuation due to disease progression or death, as well as any hospitalizations

occurring during treatment, will also be documented. Treatment-related adverse events will be classified according to the treating oncologist's assessment. This information will be used to explore the potential influence of the multicomponent intervention on treatment tolerance and completion.

2.8. Power and sample size

The sample size has been calculated to detect substantial clinical difference (1-point) in SPPB score [47]. Assuming an α error of 0.05, β error of 0.20, and 10 % of losses during the study, it has been estimated that a total of 200 patients are needed (100 in the control group and 100 in the intervention group) to detect a 1-point difference between groups, assuming a standard deviation of 2.4.

2.9. Statistical analysis

Continuous data will be presented as means and standard deviations (SD) when normally distributed, and otherwise, as medians and interquartile ranges (IQR). Categorical data will be presented as frequencies (n) and percentages (%). Baseline comparisons between groups will be performed with the *t*-test or Wilcoxon rank sum test for continuous variables, depending on their distribution. The chi-square test will be used for categorical variables. The corresponding paired tests will be implemented for pre-post comparisons. If no baseline differences are detected between groups, the effect of the intervention will be tested as a direct between-group comparison of the differences observed in the main and secondary outcomes. On the other hand, if baseline differences are found, generalised models will be fitted, adjusting for these differences. The outcome of these models will be the pre-post differences; nonetheless, depending on the distribution of the differences on certain occasions, binary outcomes may be used (improved/not improved). Linear and logistic regression models, respectively, will be fitted in such cases. Analyses will be conducted according to both the intention-to-treat (ITT) principle, including all randomised participants, and a per-protocol (PP) approach restricted to those who attend at least 70 % of the supervised exercise sessions. This will allow assessment of the impact of the intervention on study outcomes while accounting for participants' adherence. The SAS software (2016 by SAS Institute Inc., Cary, NC, USA) will be used for data analysis.

2.10. Trial status

The trial started in January 2022 and finished in May 2024. Amendments to the protocol were made due to a lower recruitment rate. Eligibility criteria were extended to include patients with lymphoma (June 2022). In addition, patients with any stage of solid cancer were included, instead of only those with advanced cancer (May 2023).

2.11. Ethics approval and consent to participate

This study has been approved by the Research Ethics Committee (CEIm) of the Basque Country (code: PI2021110) and was being conducted in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent prior to their participation.

3. Discussion

This study aims to investigate the effects on physical function of a supervised and multicomponent exercise programme in patients over 70 years of age undergoing systemic treatment.

The few exercise-based interventions that have included older patients during systemic treatment are heterogeneous regarding the frequency, intensity, time, and type of exercise [67]. In the light of this, the exercise programme analysed in this study was designed in accordance with the latest exercise guidelines for cancer survivors [27] and the guidelines for older adults of the American College of Sports Medicine [37]. The programme includes balance, resistance, and aerobic exercises. In addition, it is supervised due to the importance of supervision in this population to ensure a moderate intensity and good technique in the exercises, minimising the risk of falls [68]. Only two randomised controlled trials that include only older patients during systemic treatment have been supervised [29,33], the others having been unsupervised [28,30,32,34] or mixed [31]. There are data confirming that supervised exercise programmes achieve better results than unsupervised programmes in terms of improving quality of life, physical function and depressive symptoms [69]. Although home-based interventions have been associated with better adherence in older adults than supervised regimens [70], in this population, it is also essential to create a social network to provide supportive relationships [71]. A qualitative interview study that enrolled adults over 65 years old with advanced cancer identified social interactions as a motivator in relation to structured exercise, participants preferring group-based exercise [72]. The present study runs the multicomponent exercise programme in groups of up to four participants when recruitment allows.

To the best of our knowledge, this study will be the first randomised controlled trial with a supervised and multicomponent exercise intervention conducted in patients ≥70 years old undergoing systemic cancer treatment. This age group is underrepresented in clinical trials [73] and it is known that being >70 years old is a major factor underlying nonparticipation in studies [74].

Furthermore, we will perform an in-depth study of biomarkers that may help us to better understand the effect of exercise training in older adults with cancer. Specifically, we focus on the study of immune cell-associated immunosenescence markers as well as frailty and inflammatory soluble mediators present in plasma and gene expression markers derived from PBMCs. It has been described elsewhere that moderate physical exercise alters the levels of senescent immune cells [14,15], and considering that immunosenescence decreases tumour immunosurveillance [8], this may help to explain any beneficial effects observed.

The timing of the intervention in this project seeks to take advantage of an opportunity to improve the quality of the care around the time of diagnosis, which corresponds to a "teachable moment" when patients are interested in changing their lifestyle to improve their health [75]. Several limitations should be recognized. One limitation of this study could be the heterogeneity of the sample due to the inclusion of several types and stages of cancer and treatments. Additionally, it is not possible to achieve blinding of trainers and participants due to the structure of this study. Moreover, outcome assessors for the SPPB and the comprehensive geriatric assessment are not blinded to group allocation due to logistical constraints across the participating hospitals. However, standardised protocols and assessor training have been implemented to ensure consistency and minimize potential measurement bias.

With the expected increase in the number of older adults with cancer and the emerging evidence of the benefits of exercise in cancer survivors, it is imperative to conduct more research in relation to exercise in older patients throughout the cancer trajectory. This study could provide new knowledge on exercise interventions during systemic treatment in patients over 70 years of age. If the exercise programme described in the present study proves to have positive effects, we should prescribe individualised exercise programmes to older adults during systemic treatment in hospitals in order to enhance the standard of care.

Consent for Publication

Not applicable.

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Authors' Contributions

LB is the principal investigator of the study. AR-L, JGM, BL-SV, NTA, IZE, FBR, MMC, KV, JI, HA, MP, JB and LB have made substantial contributions to the conception and design of the trial. JGM, BL-SV, NTA, IZE and LB conduct the recruitment. JG-G, HA and MMZR conduct the intervention, evaluation of the subjects and data-collection. JG-G, AR-L, MMRZ, FBR, MMC, IG, AA, DO, KV, HA, JB and LB manage data. JG-G, HA, FBR and MMC have drafted the manuscript. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

The authors have no competing interests to declare.

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Data Availability

Data can be obtained from the corresponding author upon reasonable request.

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