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Rationale and design of an exercise intervention for patients with cancer cachexia: protocol for a one-year follow-up prospective study (2CAPA)

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Abstract

Background The prevalence of cancer with cachexia is rising sharply. More than 80% of digestive cancer patients are affected by cancer cachexia. Cachexia leads to weight loss, and reduces quality of life, cancer treatment response and survival. Exercise could counteract the deleterious effects of cachexia. The 2CAPA study aims to assess the effectiveness of a 12-week exercise program on various symptoms associated with cancer cachexia, including food intake, body composition, physical fitness, physical activity levels, Health-Related QoL (HRQoL) and fatigue. Additionally, it seeks to examine compliance with the exercise program, identify barriers to regular exercise and determine how compliance influences physical and psychological effects. Furthermore, we will determine the maintenance of physical activity levels and the effects post-program for one year follow-up on cachexia-related symptoms.

Methods This study will include 31 cancer patients with cachexia. Participants will receive a supervised exercise program lasting 12-weeks with two sessions per week combining endurance and resistance training. Our outcomes include food intake, anthropometric parameters, physical performances, and physical activity levels, HRQoL, and fatigue, at baseline, at the end of the 12-week exercise program, and at 3-, 6- and 12- months post-intervention. Outcomes will be compared between cancer patients with cachexia and a control group of 31 non-cachectic patients.

Conclusion This study is the first prospective, monocenter, real-life investigation designed to assess the efficacy of a supervised 12-week exercise program on physical and psychological cachexia-related symptoms at the end of the program and then during a one-year follow-up. Moreover, our study will identify compliance and barriers to regular exercise for patients with cachexia. Our results will contribute to the management of cachexia-associated with cancer and provide recommendations to ensure that the program achieves the greatest possible effects and the greatest possible compliance.

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Ethics and dissemination This study was reviewed and approved by Ethics Committee of Rennes (N°2023-039). The findings will be disseminated to the scientific and medical community via publications in peer-reviewed journals and conference presentations.

Trial registration number NCT06323733, 21/03/2024.

Keywords Cancer cachexia, Exercise, Body composition, Quality of life, Compliance, Follow-up

Background

Cachexia is a complex metabolic syndrome characterized by the loss of muscle mass, with or without a loss of fat mass, which can be diagnosed by the loss of weight [1]. Cachexia affects more than 80% of digestive and lung cancer patients [2]. The development of cachexia involves alterations in gastrointestinal functions (i.e., swallowing and digestive ability), metabolic disorders and systemic inflammation induced by tumors [3]. The diagnosis and management of cachexia are major challenges because cachexia significantly reduces the HRQoL, cancer treatment response, and survival [4]. In fact, the severity of cachexia evolves along a spectrum from pre-cachexia to refractory cachexia [1], where the patient no longer responds to treatment and survival is less than three months [5].

The development of cachexia is accompanied by symptoms. Patients with cancer cachexia often experience physical symptoms such as fatigue, pain, physical deconditioning, and loss of appetite. Loss of appetite could be explained by treatment-related side effects (e.g., nausea, diarrhea), anorexia, and digestion-related pain due to tumor localization. Physical deconditioning is exacerbated in cachectic patients. It is characterized by the loss of muscle mass and strength and the loss of endurance capacity, leading to a reduction in physical activity level and a vicious cycle. All these symptoms are responsible for a significant reduction in patients' HRQoL. Moreover, patients with cancer cachexia experience psychological symptoms such as anxiety, depression, and social isolation [6, 7].

Exercise is known to either maintain or enhance the physical condition of early-stage cancer patients [8]. However, patients with cancer cachexia have specific characteristics, which could influence the effects of exercise. Exercise programs can be physically demanding, which could reduce compliance [9] or accentuate fatigue or weight loss through increased energy expenditure [10]. Fear of accentuating weight loss limits exercise prescription to patients with cancer cachexia and limits the possibility of studying the effects of exercise in these patients [11, 12]. Despite this, recently, it has been suggested that exercise has the potential to help maintain or slow the loss of physical function in cancer cachexia patients [13–15]. More precisely, a recent systematic study, including 12 studies involving 898 cachectic patients, concluded that exercise interventions appear to be safe and acceptable and improve muscle strength and body stature (weight and BMI) and composition (lean mass, muscle mass and fat mass) [15]. The effects on functional performance and quality of life are mitigated [15]. More evidence is needed to confirm the effects of exercise for cachectic patients on physical outcomes and patients reported outcomes (PROs, i.e., HRQoL, cancer-related fatigue) [16]. The effects could be distinguished according to medical characteristics (type of cancer, stage, treatments, stage of cachexia) and physical and psychological characteristics at baseline [15, 17, 18]. Furthermore, it is important to identify the compliance and barriers to exercise in order to improve its implementation in the management of cancer-cachexia [19]. Therefore, there is a lack of guidelines supporting the implementation and effectiveness of exercise for cancer patients with cachexia.

This trial (2CAPA) will be the first French interventional study to assess the efficacy of a 12-week exercise program to mitigate cachexia-related symptoms including food intake, body composition, physical fitness, physical activity levels, HRQoL and fatigue.

A second objective of the 2CAPA trial will be to evaluate patients' compliance (number of sessions, fidelity to exercise duration and intensity), identify barriers to regular exercise and determine how compliance influences the effects of the exercise program on cachexia-related symptoms. Furthermore, this study will aim to determine the maintenance of physical activity levels and the evolution of cachexia-related symptoms for one year follow-up post-intervention.

Methods and design

Study objectives and design

The 2CAPA study will be an observational study of cancer patient-matched cohorts and will aim to assess the efficacy of a supervised 12-week APA program on cachexia symptoms; food intake, body composition (weight, lean mass, muscle mass and fat mass), physical condition (endurance, strength, balance), and physical activity and sedentary levels, HRQoL (global QoL, fatigue, physical functioning, appetite, and pain), and cancer-related fatigue. The secondary aim will be to assess the compliance to exercise program and barriers that could affect compliance, and to explore how compliance may impact

the magnitude of the observed effects. The third objective will be to determine the maintenance of physical activity levels and the effects of exercise for 1 year follow-up (at the 3-months, 6-months and 12-months follow-ups assessments) on cachexia symptoms.

In summary, this study aims to assess the effectiveness of a 12-week exercise program on various parameters affected by cancer-related cachexia and identify barriers to regular participation to exercise program. Patient behavior and outcomes will then be assessed during a one-year post-program follow-up.

The 2CAPA study is a prospective study conducted in a sport and medicine center. The study is promoted by the University of Rennes 2 (Rennes, France).

Ethics and regulatory considerations

Written informed consent will be obtained from all patients. The current study will be conducted in compliance with the revised version of the Declaration of Helsinki as outlined in the European Directive, along with adherence to the Code de Santé Publique specific to France.

The protocol has been submitted for formal approval by the Ethics Committee. Approval has been granted by the Ethics Committee of Rennes (N°2023-039), and the study is registered on ClinicalTrials.gov (Trial registration: NCT06323733).

Characteristics of participants

Inclusion and exclusion criteria:

Participants must meet the following eligibility criteria: (1) age ≥ 18 years, (2) diagnosis of cancer cachexia according to Fearon's criterion [1]. The agreed diagnostic criterion for cachexia are weight loss greater than 5% over past 6 months (in absence of simple starvation), or weight loss greater than 2% with a BMI < 20 kg/m2, or appendicular skeletal muscle index consistent with sarcopenia (< 7.26 kg/m2 for males and < 5.45 kg/m2 for females) combined with any degree of weight loss > 2%. Weight variations will be self-reported by patients and reported by their oncology department, (3) undergoing treatment or within 1 year post-treatment (of any type), with or without metastasis, (4) Eastern Cooperative Oncology Group Performance status ≤ 2, (5) life expectancy ≥ 3 months, (6) willingness to actively participate throughout the study, (7) ability to engage in supervised exercise program as certified by their oncologist, (8) valid health insurance affiliation, (9) proficiency in reading, writing, and understanding French.

As far as possible, we will match cachectic patients with non-cachectic patients. Matching will be based on gender, age, type of cancer, stage and treatment. Patients will constitute the non-cachectic group if they do not show weight loss or weight loss below the thresholds defined by Fearon [1]. Patients with hormone-dependent cancers (i.e. breast and prostate cancers) will not be included in the non-cachectic group because of hormone therapy on body composition. These non-cachectic patients will be used to compare the effects of the exercise intervention on physical and psychological outcomes. Moreover, the compliance and barriers to exercise program and the maintenance to physical activity levels during follow-up will be compare between cachectic and non-cachectic patients. This comparison will participate to identify potential specific needs of cachectic cancer patients.

Participants will be deemed ineligible if they: (1) exhibit central nervous system involvement with neurological deficits restricting walking, (2) are concurrently participating in another exercise intervention study, (3) are pregnant, or (4) are under legal or administrative detention/ deprived of liberty by judicial or administrative decision.

Sample size

The estimated number of participants needed to achieve the study objectives is determined through sample size calculations. Our primary outcome will be the HRQoL, assessed through the EORTC QLQ-C30 questionnaire. Musoro et al. (2020) identified the minimally important differences (MIDs) for interpreting the EORTC QLQ-C30 in patients with advanced colorectal cancer, ranging from 6 to 18 for improvement and − 11 to -5 for deterioration [20]. The MID for the subscale global quality of life is 8.43 points in within-group analysis. With a MID of 8.43 points, a standard deviation of 10 points, an alpha risk of 0.05, and a statistical power of 0.8, we will need to recruit 23 patients with cancer cachexia. Based on previous studies, we anticipate a 30% dropout rate [12, 21, 22], and our target recuitment will be 31 patients with cancer cachexia. We will recruit as many non-cachectic patients as necessary to obtain a matched sample.

Recruitment

Patients can join the program spontaneously or after receiving information at the hospital. At the hospital, patients diagnosed with cancer cachexia will undergo eligibility screening by clinicians within the Digestive Tract Diseases department of Rennes University Hospital (CHU Rennes, France). Clinicians will identify suitable participants and refer them to the sports-medical center SPORMED (Rennes, France), located outside the hospital, where the sessions will take place. A practice setting outside the hospital can encourage engagement and enable the study of the effects of exercise by being as close as possible to people's real-life conditions [23]. The physiotherapist at the sports-medical center will provide participants with information about the possibility and benefits of exercise. Additionally, the physiotherapist will

Table 1 Trial timeline and data collection schedule for the study

	Inclusion	Post-intervention	3-month follow-up (W12 ± 14 days)	6-month follow-up (W24 ± 14 days)	12-month follow-up (W48 ± 28 days)
Informed consent	X				
Socio demographic and clinical data					
• Socio demographic data	X				
• Medical data	X				
Physical evaluations					
• Body composition	X	X	X	X	X
• Food intake	X	X	X	X	X
• Physical fitness (6MWT, 30STS, handgrip, OLS)	X	X	X	X	X
Patient-reported outcomes					
• Quality of life (EORTC QLQ-C30)	X	X	X	X	X
• Fatigue (MFI-20)	X	X			
• Physical activity level (IPAQ-SF)	X	X	X	X	X
• Stages of change	X	X	X	X	X
• Exercise beliefs (CESS)	X	X			

Legend: W: week, 6MWT: six-minute walk test, 30STS: 30-second sit-to-stand test, OLS: one-leg stand test, QLQ-C30: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30, MFI-20: Multidimensional Fatigue Inventory, IPAQ-SF: International Physical Activity Questionnaire Short Form, CESS: Cancer Exercise Stereotypes Scale.

guide patients to the sports-medical center SPORMED (Rennes, France), where the sessions will take place. Patients enrolled in the exercise program will then receive both oral and written information about the trial. All participants will be required to sign and provide an informed consent form.

Inclusion of the first patients began in December 2022. To date, 90 people have been approached, 85 consented to take part in the study and 67 have completed the 3-month program, including 17 cachectic patients. We plan to continue recruitment until the end of 2025 to reach the targeted number of subjects required.

Intervention

Exercise intervention

The exercise intervention will consist of a personalized and supervised program lasting 12 weeks with two sessions per week, held on Tuesdays and Thursdays at the Sports and Medicine Center SPORMED in Rennes, France. Patients will have the flexibility to choose their session time between 11:30 a.m. and 4 p.m and each session will last 1 h under the supervision of physiotherapists. The program will include both aerobic and resistance exercises. The program will adhere to the principle of "autoregulation," allowing for a reduction in exercise intensity and/or duration when treatment-related side effects will be heightened. Patients will be encouraged to maintain the prescribed exercise intensity and duration if treatment-related side effects will be manageable.

Each session will combine endurance and resistance training, commencing with a 6-minute cardiovascular warm-up on ergometers (cycling ergometer or treadmill). This will be followed by 20 min at moderate intensity (60–70% of Heart Rate Reserve (HRR)), concluding with a 2-minute recovery period at light intensity. Heart rate will be monitored using a pulse oximeter. Participants will report their rate of perceived exertion during endurance training using a 5-point scale ("very easy," "easy," "moderate," "difficult," "very difficult"). Session intensity will be determined based on the HRR, which will be calculated with the theoretical maximal heart rate (HR maximal) and resting heart rate (HR rest) of the patient, with adjustments made according to the patient's feedback and treatment-related side effects.

Subsequently, resistance training will begin with a mobility warm-up, followed by exercises involving body weight, free weight, elastics, swissball, etc. The protocol for resistance training is described in the Supplemental Material. Patients will perform 2 to 4 sets per exercise and 8 to 14 repetitions.

Study outcome measures

Outcomes will be assessed at baseline (at the initiation of the program), post-intervention (at the end of the program), and at 3, 6, and 12 months of follow-up. All assessments will be conducted by an exercise physiologist. Socio-demographic (sex, age, profession, marital status, distance from practice) and medical characteristics will be collected at baseline during a short interview. Medical characteristics will include cancer type, stage, treatment type and temporality but also comorbidities. The trial timeline, from enrollment to completion, is presented in Table 1.

Feasibility, compliance, fidelity and safety

Feasibility Feasibility will be evaluated through completion and attrition rates, overall program compliance, and fidelity to the program.

Overall program compliance The overall compliance rate will be calculated as the number of completed exercise sessions/total prescribed sessions. Reasons for missed sessions will be collected from the participant by phone or at their next session. Reasons will be categorized into medical reasons, personal reasons, environmental reasons, and professional reasons. The timing of absences will also be recorded and studied.

Fidelity Fidelity rates will be determined by comparing the prescribed versus actual exercise sessions, including duration (minutes) and intensity (HRR and self-perception of effort) completed. The occurrence and reasons for adjustments in aerobic exercise intensity will be recorded by a physiotherapist. Resistance training will be proposed and adapted of daily limitations of the patients, limiting the potential measure of fidelity.

Safety Safety will be assessed by monitoring for adverse events and serious adverse events and program interruptions due to exercise complications. Adverse events will be observed by physiotherapists and reported by patients during aerobic and resistance training. Adverse events will be classified and assessed in terms of severity using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (2017). This classification lists the severity of adverse events in 5 categories. Collecting and analyzing adverse events will help to define the potential harms of exercise and determine whether the intervention is acceptable or not [24].

Cachexia-Specific Symptoms

Clinical parameters

Anthropometrics and Nutritional Assessments Cancer cachexia involves muscle and adipose tissue wasting, involuntary weight loss, and reduced appetite and food intake. The effects of exercise on these specific components will be assessed.

Body stature and composition

Body weight, body mass index (BMI), fat free mass, muscle mass, and fat mass (expressed in kg and as a percentage of total body weight) will be determined by bioelectrical impedance analysis (BIA) (Tanita, DC-360 S). The Tanita Body Composition Analyzer will measure body composition using a constant current source with a high frequency current (50 kHz). The four electrodes will be positioned on the tips of the toes of both feet, and voltage is measured on the heel of both feet. From the electrical resistance quotient, an equation will determine the total body water. From this TBW value, the fat free mass is estimated by the equation FFM = 0.73*TBW. This equation was defined for healthy people, and we are aware of its limitations for people in pathological situations, but there are hardly any specific equations for people with cancer [25]. However, as we wish to monitor the parameters longitudinally, it seems appropriate to use this estimate [26]. In oncology, changes in body composition are predictive of increased treatment toxicity and reduced quality of life and survival [26].BIA is a valid and relevant tool for detecting variations in body composition through muscle mass and fat mass evolutions in routine clinical practice by malnourished and cachectic patients [27] and sometimes predicting health complications [26]. The measurement conditions will be standardized in terms of position of the body, hydration level, nutrition, clothing and PA level to improve reproducibility [28]. Despite this, BIA may have some limitations in that its effectiveness may be altered by nutritional status (very high BMI (≥ 35 kg/m2) or very low BMI (≤ 16 kg/m2)), oedema, lymphoedema or ascites accumulation [26]. The measurement of total body water does not distinguish ascites from other fluids, which could lead to a bias.

Food intake

Food intake will be assessed using a visual analog scale (VAS). The SEFI (Simple Evaluation of Food Intake) is a scale that evaluates the quantity of ingesta from 1 to 10. A score of 7 or less indicates anorexia [29, 30].

Physical Outcomes

Physical performance A battery of four tests will be employed to assess the physical performance of the patients.

Aerobic fitness: Participants will undergo a six-minute walk test on a flat, indoor, 20-meter walkway. This test is a valid and reliable assessment of aerobic fitness in clinical populations [31]. Patients will be instructed to walk the greatest distance in 6 min, with standardized encouragement provided every minute. Heart Rate (HR) and saturation (Sat) will be recorded every minute.

- *"That's good, you've got another 5'.*
- *That's good, keep going, you've got another 4'.*
- *Good, you're halfway there.*
- *That's good, keep going, you've got 2' left.*
- *Good, you've got 1' left.*
- *And now, stop (at 6 minutes)."*.

Muscular function of the lower limbs: Muscular function of the lower limbs will be assessed using the sit-to-stand test. Patients will be instructed to rise from a seated

position to a standing position and return to seating, without assistance and without using their arms, as many times as possible within 30 s. The 30-second sit-to-stand test (30STS) is a valid and reliable measure muscle function of the lower limbs [32].

Muscle strength of the upper limbs: The muscular strength of the upper limbs will be assessed through a handgrip test using a hand dynamometer (Takei 5401 Hand Grip Dynamometer (digital)). Handgrip strength measures upper limb muscle strength and has been validated in digestive cancer patients [33], is frequently affected by cachexia, and is a reliable tool for screening for sarcopenia and malnutrition [34].

The test will be performed with patients in a sitting position, with both feet touching the ground, the hand holding the dynamometer, the elbow flexed at 90° and the shoulder adducted. The participant will be instructed to squeeze the handle with maximum force for 3 s. The test will be repeated three times, with sufficient rest between each effort. The highest value of the three repetitions will be retained in kilograms for each hand (in kg) [35].

Static balance ability: Static balance ability will be assessed using a one-leg stand test. Patients will be instructed to stand as long as possible on one leg with their eyes open. The time will be recorded (a maximum of 30 s).

Patient-reported outcomes

Patient-reported outcomes will offer a comprehensive and personalized perspective on intervention effects, assessed through questionnaires. The completion rates of the questionnaires will provide insights into the feasibility of these measures.

Health-Related Quality of Life: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) version 3.0 will be used to assess changes in levels of health-related Quality of Life (QOL). The EORTC QLQ-C30 is an internationally validated, concise, self-reporting cancer-specific measure of health-related QOL [36]. This scale comprises 30 items, including one global health status/QOL scale and five multi-item functional scales evaluating physical, role, emotional, cognitive, and social function. Additionally, three multi-item symptom scales assess fatigue, pain, and nausea/vomiting, and six single items assess symptoms such as dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. A high score for the global health status and QoL and for the functional scales represents a high level of QoL and functioning. Nevertheless, a high score for a symptom scale / item represents a high level of symptomatology. Threshold differences are defined to interpret QOL changes [37]. The QoL is defined as unchanged if the difference of score is between 0 and 5 points between two measurement, a slightly better or a slightly worse (a difference of 5 to 10 points), a situation with moderate change (10 to 20 points) or a large change (20 points or more) [37].

Fatigue: Fatigue will be measured using the Multidimensional Fatigue Inventory (MFI-20). The questionnaire consists of 20 statements in which the patient rate themselves on a Likert scale ranging from 1 (“strongly disagree”) to 5 (“strongly agree”) [38]. Responses reflect perceived fatigue across five dimensions: general fatigue, physical and mental fatigue, reduced motivation, and reduced activity. Each subscale contains four items, scored from 4 to 20, with a higher score indicating greater fatigue.

Physical Activity and Sedentary Levels: Participants will recall and self-report their physical activity levels (frequency and duration of vigorous intensity, moderate intensity, walking, and sitting) during the previous 7 days, using the International Physical Activity Questionnaire Short Form (IPAQ-SF) [39]. The IPAQ-SF allows the estimation of total physical activity in MET-min/week and time spent sitting. Although the IPAQ-SF tends to overestimate reported physical activity compared to objective devices, it is chosen for its reliability and validation for longitudinal individual comparisons and its fast filing [40].

Stages of change for exercise: The stages of change for exercise will be evaluated by a scale derived from the transtheoretical model of behavior change [41]. Our questionnaire is inspired and translated from the Marcus study [42] and called “Échelle des stades de changement vis-à-vis de la pratique d’une activité physique”. The questionnaire contains a single item presented in multiple-choice format. It will assess the stage from a self-reported discrete categorical measure.

Exercise beliefs: Exercise beliefs will be assessed through the Cancer Exercise Stereotypes Scale (CESS). The questionnaire consists of 19 statements in which the patients rate themselves on a Likert scale ranging from 1 (“strongly disagree”) to 6 (”strongly agree”). This 19-item questionnaire is validated to measure cancer exercise stereotype through 5 dimensions [43]. The dimensions are (1) stereotypes related to the lack of interest, (2) stereotypes related to the lack of physical abilities, (3) stereotypes related to the side effects of treatment, (4) stereotypes related to the risks of exercise, and (5) stereotypes related to the benefits of exercise.

Data collection, management, and analysis

Data Collection Methods

Data will be collected using a paper survey specifically designed for the study, and subsequently, this information will be digitally transferred to a password-protected data file stored on a secure server and an external hard

drive. Manuscript data will be kept in a secure cabinet. Handwritten documents will be used to minimize errors, decrease the potential alteration of patient interactions, and ensure accessibility during exercise sessions. To enhance data quality, assessments will be consistently conducted by the same person, and standardized instructions and measurements will be maintained across patients and assessment time points.

Data Completion and Participant Retention

The questionnaires will be analyzed upon return, allowing for completion if any answers are missing. Telephone follow-ups will be implemented for consecutive absences to collect reasons and motivate return. Post-intervention assessments will coincide with exercise sessions. Follow-up assessments at 3, 6, and 12 months will be facilitated through telephone reminders and the use of booklets. Reasons for discontinuation will be collected by phone.

Data Management

The data will be recorded in Excel sheets, and range checks will be implemented to identify and correct outliers. To minimize errors, data will be entered into two separate files.

Statistical Methods

Primary analysis

Descriptive statistics (mean, standard deviation, number, percentages) will be employed for both quantitative and qualitative variables. Univariate analysis using the Wilcoxon test, Chi-square test, or Fisher exact test will compare intervention completers with dropouts. Paired t-tests or non-parametric tests will assess changes in various outcomes between baseline, at the end of the program, and at follow-ups. Independent t-tests or non-parametric tests will assess differences in evolution between the cachectic and non-cachectic groups. Bootstrap resampling will be utilized to enhance robustness in the analysis of small sample sizes. Statistical significance will be considered at $p < 0.05$, and the analysis will be conducted using R software.

Secondary analysis

The secondary analysis will explore the influence of adherence parameters and physical activity level on outcomes. Moreover, we will analyze the maintenance of physical exercise and whether any parameters predict the individual's trajectory. Additional analyses may include subgroup analysis and adjusted analyses to estimate the impact of medical characteristics on outcomes. Analysis will be based on multivariate models that provide information on the effect of a factor, independently of the other co-variates entered in the model. We will also carry out a clustering analysis of patients using centroid methods in order to identify potential characteristics of the most compliant and responsive patients and the least compliant and responsive patients.

Handling missing data

The questionnaire scores will respect to author recommendations. An analysis of missing data profiles will be conducted to distinguish between responder and non-responder profiles. If necessary specific measures will be implemented to encourage responses and multiple imputation methods will be used. Patients with missing baseline or post-intervention data will be excluded from the primary analysis.

Results

Discussion

The 2CAPA study aims to assess the efficacy of an exercise intervention to improve cachexia-related symptoms in cancer patients. Despite the prevalence of this syndrome, few studies have been conducted and more evidence is needed to establish recommendations [15]. Additionally, compliance with the exercise program, barriers to regular exercise and the impact of compliance on physical and psychological effects will be assessed. Furthermore, the study aims to determine the maintenance of physical activity levels and the effects post-program over a one year follow-up on cachexia-related symptoms.

The 2CAPA study consists of concurrent endurance and resistance training. Resistance training is known to improve physical function and increase muscle mass and strength in cancer patients [8]. Indeed, muscle wasting is inversely correlated with lifespan and increased treatment failure risk and susceptibility to treatment side effects [44]. Therefore, offering resistance training to cachectic patients is fundamental to preserving muscle mass. In studies of cachectic patients, resistance training alone has been shown to be more beneficial for muscle strength and mass than combined training [15]. Nevertheless, muscle mass alone is not a sufficient outcome in oncology [16]; interventions aim to improve overall well-being. In this context, aerobic exercise is known to reduce anxiety and depression, as well as improve sleep quality in cancer patients [8]. Additionally, the endurance component could be beneficial for cachectic patients because cachexia induces mitochondrial disorders [7] while aerobic exercise could restore mitochondrial function. Nevertheless, due to cachexia perturbations that affect energy expenditure and muscular function (mitochondrial dysfunction, disruption of the balance between protein synthesis and degradation), it is fundamental to define which quantity of exercise (duration, intensity) could be beneficial or detrimental [10]. Endurance exercise could be detrimental if energy expenditure exceeds what the patients can sustain, leading to exacerbated weight loss

[10, 21]. Therefore, our study is the first to investigate the effects of an endurance and resistance training in cancer patients with cachexia. We will try to determine how exercise dose (i.e. number of sessions, intensity, duration) influences cachexia specific symptoms (body stature and composition and food intake), physical outcomes (aerobic fitness, muscular strength, static balance ability), and patient-reported outcomes (HRQoL, fatigue, PA and sedentary levels and stages of change). The effects of the same program will be compared between cachectic and non-cachectic patients to identify potential specificities associated with cachexia. Our results could help to refine guidelines for cachectic cancer patients.

Regarding barriers to exercise, our study will identify which barriers might limit exercise participation and fidelity to exercise prescription in cachectic patients. We will investigate when these barriers arise. These results will help to propose programs that encourage a high level of compliance, to maximize the benefits of exercise. Previous studies demonstrated that exercise intervention can be applied in patients with cancer cachexia. Patients recruited in hospitals had completion rates ranging from 74 to 83% and compliance rates ranging from 64 to 85%. Nevertheless, it seems essential to study the effects of and barriers to this practice in real-life conditions, outside clinical trial conditions [23].

Concerning the parameters measured in our study; our strength will be to assess body composition through impedance analysis. Most of the studies assess body stature through weight and BMI [15]. Nonetheless, weight variations do not reflect changes in fat and lean mass. However, each of these tissues is involved in specific functions [45, 46]. Distinct cachexia phenotypes exist (i.e., muscle and fat wasting, fat-only wasting, muscle-only wasting) and survival prognoses are phenotype-specific [47, 48]. Therefore, it seems fundamental to determine the effects of exercise on each category of tissue. Our study will investigate the effects of exercise on weight and BMI but also on the parameters estimated through impedance analysis (i.e. lean mass, muscle mass and fat mass).

A strength of our study will be the assessments of physical parameters and patient reported outcomes. Oncological studies could focus on lean mass because its improvement is associated with mortality reduction [49]. In cachectic patients, maintaining lean mass could be considered as positive as it prevents cachexia development. Nevertheless, recent study explains that studying solely lean mass may result in effective interventions not being considered as such in clinical practice (one criterion could not reflect the other improvements). As a result, it is recommended to adopt a composite endpoint including quality of life in studies focusing on sarcopenia and cachexia [21]. In brief, 2CAPA will combine physical assessments and patient-reported outcomes, and study possible correlations between them.

Additionally, an innovative aspect of the study will be the long-term follow-up, aiming to comprehend the enduring effects of exercise on physical, psychological, and behavioral variables in cachectic patients [7]. This extended observation period will shed light on whether a 12-week supervised exercise program could instigate a sustained positive trajectory in patients' autonomous exercise practices or whether individuals will tend to disengage after the program. Assessments at 3-, 6-, and 12-months post-intervention will provide valuable insights into this aspect. In addition, assessing the stage of change for exercise of the transtheoretical model may enable us to identify dropout profiles and propose specific interventions, using behavior change techniques, to promote an active lifestyle (i.e. action and maintenance stage) [50].

Conclusion

In conclusion, the 2CAPA study is a prospective, monocenter, real-life investigation designed to evaluate the effects of a supervised 12-week exercise program on various outcomes related to cancer cachexia (body composition, food intake, endurance, strength, physical activity and sedentary levels, HRQoL and fatigue). Exercise may pose challenges in these patients due to multiple and exacerbated cancer-related symptoms, particularly muscle wasting and dysregulation of energy expenditure. Nevertheless, we hypothesize that exercise could be beneficial for these patients by improving their HRQoL, reducing cachexia development and potentially enabling muscle mass gain. The results of our study will contribute to confirm the effects of exercise in this specific population. Moreover, our results will help to refine exercise recommendations to reduce practice-related barriers and propose optimal exercise interventions to manage cancer cachexia. Finally, we will be able to determine the repercussions of the 12-week exercise intervention during a one-year follow-up in terms of behavioral, psychological, physical and medical effects for cachectic patients.

Abbreviations

30STS	30-second sit-to-stand test
6MWT	A six-minute walk test
BMI	Body Mass Index
CESS	Cancer Exercise Stereotypes Scale
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
HR	Heart Rate
HRQoL	Health-Related Quality of Life
HRR	Heart Rate Reserve
HRr	Heart Rate Rest
IPAQ-SF	International Physical Activity Questionnaire Short Form
Kg	Kilogram
MET	Metabolic Equivalent Task
MFI-20	Multidimensional Fatigue Inventory
MID	Minimally Important Differences

Sat	Oxygen Saturation
SEFI	Simple Evaluation of Food Intake

Supplementary Information

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Supplementary Material 1: Resistance training sessions

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Author contributions
RP (PhD), CR (PhD) and AR (Full Professor) designed research; RP (PhD) will conduct research; CR will conduct exercise sessions; RP will analyze data; and RP and AR wrote the paper. NA (Professor) provided psychological questionnaires and guidance on the concept of compliance and adhesion. BG guided plan for statistical analysis. NA and BG corrected the article. AL (Full Professor and Physician) and KC (Physician) will orient patients to PA program and provide essential structures. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Ethics approval by the Ethics Committee of Rennes. Consent to participate. Patients will be asked for permission to participate in the trial, to collect and use their data through a signed informed consent before inclusion in the study.

Competing interests
The authors declare no competing interests.

Consent for publication
Not applicable.

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