Cover Page

Title:
Physical Training for Elderly Cancer Patients with Cachexia (TEECH-01): a Prospective Clinical Trial

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Abstract

Background

Elderly cancer patients present with high comorbidities and adverse outcomes. Of note, those with cancer cachexia share an even worse result. Physical exercise improves the functional wellbeing and alleviates symptoms in patients with cancer cachexia. However, such interventions have not been explored in elderly cancer patients with cachexia.

Objectives

The proposed trial is to investigate the feasibility and efficacy of an artificial intelligence-based patient-tailored intensity-modulated physical training for cancer patients aged over 65 at risk of cancer cachexia. The primary endpoint is simplified cancer CAchexia SCOre (MiniCASCO) reduction. Secondary endpoints include geriatric assessment, physical activity and sarcopenia.

Study design and accrual

This is an open-label, single-arm, single-center phase II investigator-initiated trial. We assume a reduction of MiniCASCO by 10% after trial intervention. Under a statistical power of 80% and a probability of type I error at 0.1 (two-tailed), a minimal of 49 subjects will be enrolled.

Treatment protocol

All subjects will receive a 12-week supervised physical training and nutritional intervention. Efficacy assessments will be conducted at baseline (week 0), post-intervention (week 12) and follow-up period (week 24).

Anticipated results

An optimal patient-tailored training program is feasible and improves the symptoms and severity of elderly cancer cachexia. The results may shed light on the debilitating and burdensome condition and provide information on future clinical trials.

SYNOPSIS

Title of the study:	Physical Training for EldErly Cancer Patients with CacHexia (TEECH-01): a Prospective Clinical Trial
Intervention provider:	SeniorGym, Medical Device Innovation Center (MDIC), National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan Address: MDIC, No.1, University Road, Tainan City 701, Taiwan (R.O.C) Tel: 886-06-236-3157 E-mail: em73421@email.ncku.edu.tw
Objectives:	The objective of the study is to evaluate a patient-tailored physical training program in elderly cancer patients who have risk of cachexia. Primary outcome: at week 12 ▪ Simplified cancer CAchexia SCOre (MiniCASCO) reduction. Secondary outcome: at week 12 ▪ Geriatric assessment scales ▪ Physical activity (hand grip strength, gait speed, body mass index (BMI), sit to stand (STS), back stretch, sit reach, single leg stand (SLS), up and go (UG), 2-minute step (2MS), 6-minute walk test (6MWT) and timed up-and-go (TUG) ▪ Sarcopenia score (SARC-CALF) Exploratory outcome: Health-related quality of life (HRQoL), cancer-related survival, recurrence/progression, cancer treatment or study intervention-related adverse events, nutritional scales and Zebris gait analysis
Design:	The proposed study is an open-label, single-arm, single-country and single-center phase II investigator-initiated trial.
Sample size:	We assume the statistical power of 80% (β=0.2) and the probability of type I error by two-tailed α at 0.1, along with a reduction of MiniCASCO by 10% from baseline at week 12. A total of 49 subjects will be enrolled. The trial contains two parts: Part I: 10 subjects as a safety run-in and eligibility cohort

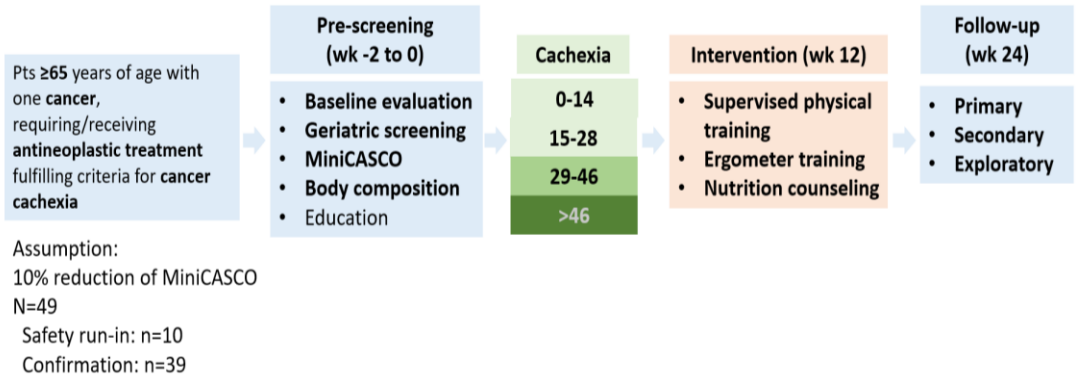
	Part II: 39 subjects as a complete cohort
Criteria for inclusion:	1. Subjects aged equivalent to or over 65 years with an existing cancer requiring antineoplastic treatments at trial enrollment, as defined by presence of a catastrophic disease certificate for malignancy in National Health Insurance (NHI)-Taiwan. 2. Subjects receive at least one systemic antineoplastic treatment within 12 weeks since trial enrollment, which includes chemotherapy, immunotherapy, hormonal, targeted and cellular therapy of whichever initial therapeutic intent (curative, palliative or salvage). 3. Subjects fulfill either cancer cachexia or pre-cachexia. 3.1. Cancer cachexia: A maximal weight loss of at least 5% from the baseline within 6 months in those whose BMI equivalent to or over 20 kg/m^2 or at least 2% in those whose BMI less than 20 kg/m^2. 3.2. Pre-cachexia: A maximal weight loss of 1% to 5% from the baseline within 6 months in patients whose BMI equivalent to or over 20 kg/m^2 or 1% to 2% in those whose BMI less than 20 kg/m^2 plus any of the following: an elevated serum C-reactive protein above upper normal limits (ULN), impaired fasting glucose or known diabetes mellitus, use of high-dose corticosteroid (over 10 mg prednisone equivalent daily), hypogonadism (disease-related or iatrogenic) or insufficient calorie intake of less than 20 kcal/kg/day 4. Subjects are in a clinical status with an expected life span exceeding 6 months and Eastern Cooperative Oncology Group (ECOG) 0 to 1 or Karnofsky Performance Scale (KPS) 80 to 100 at trial enrollment. 5. Subjects are physically and mentally capable and willing for conducting the planned physical training and agreed to comply the educational instructions and a wearable device during trial intervention. 6. Subjects are functionally and cognitively capable to be informed of the trial contents and objectives (including obtaining peripheral blood sampling for trial investigation),

	and agree to sign the written consent for enrollment.
Criteria for exclusion:	1. Subjects have tumor *in situ* or curatively treated malignant disease which requires no further antineoplastic treatments. 2. Subjects are anticipated to receive any surgery, radiotherapy or intervention that prevents or hinders a planned physical training within 28 weeks since trial enrollment. 3. Subjects experience a progressive body weight loss which fulfills the criteria for cancer cachexia or pre-cachexia but complicates with other confounding causes. (please refer to 5.2.3.1. to 5.2.3.4.) 4. Subjects have cachexia caused by etiologies not limited to cancer. (please refer to 5.2.4.1. to 5.2.4.3) 5. Subject's malignant disease is considered unstable and thereby unfit for a planned physical training. (please refer to 5.2.5.1. to 5.2.5.4.) 6. Subjects have an underlying medical illness causing severely impaired organ functions. (please refer to 5.2.6.1. to 5.2.6.5.) 7. Subjects have an active infection requiring hospitalized treatment or intravenous anti-pathogen therapies. 8. Subjects who receive other experimental treatments or interventions for cancer cachexia. 9. Subjects are planning to conceive or already in pregnancy. 10. Subjects are currently participating in any other observational studies concerning cancer cachexia.
Protocol intervention:	1. <u>Supervised Physical Training in SeniorGym</u> a. Aerobic exercise for 12 weeks Patient-tailored intensity-modulated ergometer training for the limbs --Target intensity: moderate --Frequency: 2 to 3 sessions per week --Duration: 8 to 25 minutes per session b. Resistance exercise for 12 weeks Patient-tailored resistance exercise by Theraband® for the limbs

	--Target resistance: moderate --Frequency: 2 to 3 sessions per week --Duration: 20 minutes per session <u>2. Nutrition intervention</u> --Dietician consultation and education at 0, 12 and 24 weeks --Nutrition intervention at 0, 12 and 24 weeks

TRIAL SCHEMA

Physical Training for Elderly Cancer Patients with Cachexia (TEECH-01): a prospective clinical trial



<u>Primary endpoint:</u> MiniCASCO reduction at week 12

TABLE OF CONTENT

1. OBJECTIVES

1.1 Objective of the study:

To investigate the feasibility and efficacy of an artificial intelligence (AI)-based patient-tailored intensity-modulated physical training program for elderly cancer patients at risk of cancer cachexia.

1.2 Primary objective:

Simplified cancer CAchexia SCOre (MiniCASCO) reduction.

1.3 Secondary objectives:

Geriatric assessment scales, physical activity (hand grip strength, gait speed, body mass index (BMI), sit to stand (STS), back stretch, sit reach, single leg stand (SLS), up and go (UG), 2-minute step (2MS), 6-minute walk test (6MWT) and timed up-and-go (TUG)), sarcopenia score (SARC-CALF), health-related quality of life (HRQoL), cancer-related survival, recurrence/progression, cancer treatment or study intervention-related adverse events, nutritional scales and Zebris gait analysis

2. BACKGROUNDS

Aging and Cancer Care

Aging has become a tremendous health-related issue worldwide in both developing and developed countries.[1] Aging and super-aging cause various consequences such as physiological alterations, impaired organ function, progressing disability, poor nutrition and comorbidities, and therefore transform the fit population into unfit ones.[2] Numerous assessment methods have emerged to cope with risk prediction and allocation in the diseased elderly, such as Geriatric 8 (G8), Groningen Frailty Indicator, Vulnerable Elders Survey 13 and abbreviated geriatric assessment (aCGA).[3] Elderly cancer patients are particularly vulnerable with an increased risk of complications and morbidities. In elderly cancer patients who would receive antineoplastic therapies, Chemotherapy Risk Assessment Scale for High-Aged Patients (CRASH) and Cancer and Aging Research Group (CARG) scale were developed to weigh the balance between treatment toxicity and benefit in those aged over 60.[4,5] However, such tools are only applied to selected fit elderly population and not robustly validated to those aged over 65. Of note, Sleeman et al. reported cancer related deaths or disability increased by 87% with an annual increment of 26

million people worldwide.[6] Aside from geriatric assessments, there are scarce interventions aimed at elderly cancer patients, in which it presents with a huge health-related burden in cancer care.

Geriatric Cancer Cachexia

Cancer cachexia, as featured by progressive body weight loss (BWL) and/or skeletal muscle mass depletion, is found in 50% to 80% of cancer patients and accounts for 20% of cancer-related deaths.[7-9] Confounded by inconsistent definitions, cancer cachexia shares undetermined characteristics in different types of cancer patients. However, growing efforts have reached an international consensus defining cancer cachexia by progressive BWL over 5% within 6 months plus several metabolic changes. The severity was also staged by pre-cachexia, cachexia and refractory cachexia, respectively.[8] Dunne et al. indicated that 80% of elderly cancer patients who had cachexia presented with prominent BWL within 6 months.[10] Poisson et al. further investigated the prevalence and severity of geriatric cancer cachexia in the French nationwide study and concluded that nearly half of the elderly cancer patients harbored cachexia, which correlated with 6-month mortality.[11]

With the discovery on its comprehensive biological and physiological impacts, Argilés et al. proposed and validated a cancer cachexia scoring system (CASCO) which contained parameters and assessments on various aspects.[12] A simplified form of CASCO (MiniCASCO) was also developed to enhance the clinical application and accessibility while maintaining a high correlation with the original version.[13] Both CASCO and MiniCASCO encompassed multifaceted parameters, such as weight loss, lean body mass, serum biochemical markers, physical performance, anorexia, and health-related quality of life (HRQoL). Interestingly, elderly patients are known especially vulnerable and suffer from cancer cachexia with progressive frailty, deconditioning and intolerability to antineoplastic treatments.[14] The phenomenon of failure to thrive in geriatric cancer patients is often multifactorial and responds poorly to conventional nutritional support or interventions.[15] However, little is known about the application of cachexic scores in elderly cancer patients. In addition, studies concerning interventional measures to improve cancer cachexia in the elderly population is extremely rare.

Physical Training for Elderly Cancer Patients

Physical activity and exercise capacity are vital components of fitness and help

reduce mortality and improve HRQoL in cancer patients.[16] Maintaining physical activity is considered a treatment discrepancy between elderly and younger patients with cancer.[17] Emerging studies have confirmed that physical training attenuated and partially reversed muscle wasting by modulating metabolic, protein degradation and inflammatory pathways.[18,19] In addition, several studies have implemented exercise-based interventions to improve the physical capacity, HRQoL and outcomes of elderly patients with cancer.[20-24] Mikkelsen et al. showed a 12-week exercise program increased lean body mass in elderly cancer patients, which provided a rationale for physical training in the patient population with potential cachexia.[25] Furthermore, the advantages of appropriate physical training are not limited to improve physical activity alone. It might extend to enhance muscle strength, nutritional absorption, cognitive function, emotional fitness and even ameliorate cancer-related symptoms.[26,27] However, considering the putatively frail and weak conditions imposed by disease activity and ongoing antineoplastic treatments, an intensity-modulated patient-tailored exercise intervention is required to increase the feasibility and tolerability in elderly cancer patients at risk of cancer cachexia.

Study Rationale and Aim of Trial

Physical training and patient-tailored exercise improve the clinical outcome of elderly cancer patients. In addition, growing evidence suggests that optimal physical training ameliorates the negative impacts on cancer cachexia in patients with cancer. However, only limited reports have focused on patient-tailored physical training in elderly cancer patients at risk of cancer cachexia. Given the paucity of studies on this issue, it prompts an investigation of potential pluripotent effects of physical training in patients with both elderly cancer and cachexia. Furthermore, an optimal model for designing an appropriate training program remains undetermined.

Therefore, the proposed clinical trial is a single-arm, prospective interventional study investigating a patient-tailored physical training program for elderly cancer patients at risk of cachexia. The aim of the proposed trial is to study the feasibility of an artificial intelligence (AI)-based patient-tailored physical training program which could be applied to elderly cancer patients at risk of developing cancer cachexia. We hypothesize that the optimal AI-modulated patient-tailored program is feasible to be implemented in the clinical practice and improves the symptoms and severity of elderly cancer cachexia post

intervention. In summary, we hope the results of the proposed trial shed light on the debilitating and burdensome condition and provide information on designing future phase III clinical trials.

3. STUDY INTERVENTION INFORMATION

3.1 Aerobic exercise:

3.1.1 Contents:

In the aerobic exercise program, an AI-based intensity-modulated supervised physical training is provided to the subjects in the SeniorGym, MDIC, National Cheng Kung University Hospital. The training module is composed of feedback assistive ergometer of lower limbs, as judged by the investigator or subject's preferences and their physical capacity. The infrastructure of training includes strengthening of limb muscles, resistance, aerobic activity and cardiopulmonary rehabilitation. An interactive program is provided during the training session, which consists of a first-person perspective video game intended to collect coins on a mountain trail. Meanwhile, automated positive feedbacks with visual or sound clues are presented to enhance the participating motives of the subject. At the end of each training session, the cumulative intensity, calorie consumption and energy expenditure are shown as a grading score to the subject. A specialized physical trainer or study nurse will act as a supervisor and accompany the subject throughout the entire training session and being responsible for monitoring the training performance and maintaining safety precautions.

3.1.2 Training target:

During each of the session, the maximal intensity is determined by a moderate intensity of aerobic exercise, reaching 80% of maximal predicted heart rate (mpHR = $208 - 0.7 \times$ age of the subject; beats per minute (bpm))[28], subjective maximal physical tolerance or discomforts, investigator or supervisor-decided adequate level of training and onset of any alarming feedbacks on the biophysical detectors, including subnormal readings on heart rate (>180 or <60 bpm), blood pressure (systolic blood pressure (SBP) >160 or <90 mmHg) or pulse oximetry (SpO2<88% with ambient air), in whichever achieves first. Each session lasts 8 to 25 minutes with a gradual increment of both resistance and duration along the training process. Two to three sessions per week will be arranged with a minimal interval of 24 hours between two consecutive sessions.

A total of 12-week training is provided to each subject when tolerated.

3.1.3 Safety information:
All sessions will be supervised and monitored by specialized physical trainers or study nurses in the trial. Emergent withdrawal or discontinuation of an ongoing training session is determined by any the following conditions: 1) onset of any abnormal readings on the biophysical detectors, including HR >200 or <45 bpm, SBP >180 or <85 mmHg or SpO2<85%; 2) subjective discomforts, failure to comply or demands for stopping upon reasonable request; 3) supervisor's professional judgment and discretion; 4) signs or symptoms suggestive of risk of physical trauma or injury. All alarming events will be recorded and presented to the principal investigator as safety monitoring references.

3.2 Resistance training:
3.2.1 Contents:
In the resistance exercise program, a trainer-assisted supervised manual physical training is provided to the subjects in the SeniorGym, MDIC, National Cheng Kung University Hospital. The training module is composed of utilizing Therabands® to conduct limb or trunk stretching under fair resistance. The size of Therabands® can be switched from light, moderate to heavy ones according to training requirement of the subject. Subjects are educated about the proper use of Therabands® and encouraged to demonstrate resistance training at home freely without a supervisor.

3.2.2 Training target:
Each session lasts 20 minutes with a gradual increment on resistance along the training process. Two sessions per week will be arranged with a minimal interval of 24 hours between two consecutive sessions. A total of 12-week training is provided to each subject when tolerated.

3.2.3 Safety information:
All sessions will be supervised and monitored by specialized physical trainers or study nurses in the trial. Emergent withdrawal or discontinuation of an ongoing training session is determined by any the following conditions: 1) onset of any abnormal readings on the biophysical detectors, including HR >200 or <45 bpm, SBP >180 or <85 mmHg or SpO2<85%; 2) subjective discomforts, failure to comply or demands for stopping upon reasonable request; 3)

supervisor's professional judgment and discretion; 4) signs or symptoms suggestive of risk of physical trauma or injury. All alarming events will be recorded and presented to the principal investigator as safety monitoring references.

3.3 Nutrition assessment and intervention:

3.3.1 Contents:

In the nutrition assessment and intervention program, a specialized dietician will be responsible for calculating and analyzing the daily calorie requirement and food composition of the subject in the specialized dietary outpatient clinic. A professional diet consultation and nutritional recommendations will be provided upon willingness of the subject. Dietary prescriptions will be adjusted according to subject's food preferences, underlying illness, food allergy and cost-effectiveness. In addition, subjects are educated and encouraged to record all the ingested food as a dietary diary and presented to the dietician when visited.

3.3.2 Intervention target:

During dietary and nutrition consultation, the calorie intake is adjusted to a target of 25 to 30 kcal/kg/day. Forty to fifty percent of the daily calorie is expected to derive from carbohydrate source. Protein ingestion, as either from animal or vegetarian sources, is aimed at 1.2 g/kg/day at least. Given that subjects may fail to achieve the target calorie dose, the actual maximal calorie intakes are recorded and compared with the prespecified targets.

3.2.3 Safety information:

Since the nutrition assessment and intervention are advisory and educational, there are no safety warnings of the session.

4. DISEASE SEVERITY CRITERIA AND TOOLS

Cancer cachexia or pre-cachexia of the elderly in the trial is defined according to Fearon et al. and analyzed collectively.[8] The disease severity is defined by MiniCASCO from 0 to 100 points. The grading of cancer cachexia is followed by minimal (0 to 14), mild (15 to 28), moderate (29 to 46) and severe cachexia (47 to 100), respectively.[17]

5. PATIENT SELECTION

5.1 Inclusion criteria

5.1.1. Subjects aged equivalent to or over 65 years with an existing cancer requiring antineoplastic treatments at trial enrollment, as defined by presence of a catastrophic disease certificate for malignancy in National Health Insurance (NHI)-Taiwan.

5.1.2. Subjects receive at least one systemic antineoplastic treatment within 12 weeks since trial enrollment, which includes chemotherapy, immunotherapy, hormonal, targeted and cellular therapy of whichever initial therapeutic intent (curative, palliative or salvage).

5.1.3. Subjects fulfill either cancer cachexia or pre-cachexia.

5.1.3.1. Cancer cachexia:

A maximal weight loss of at least 5% from the baseline within 6 months in those whose BMI equivalent to or over 20 kg/m^2 or at least 2% in those whose BMI less than 20 kg/m^2.

5.1.3.2. Pre-cachexia:

A maximal weight loss of 1% to 5% from the baseline within 6 months in patients whose BMI equivalent to or over 20 kg/m^2 or 1% to 2% in those whose BMI less than 20 kg/m^2 plus any of the following: an elevated serum C-reactive protein above upper normal limits (ULN), impaired fasting glucose or known diabetes mellitus, use of high-dose corticosteroid (over 10 mg prednisone equivalent daily), hypogonadism (disease-related or iatrogenic) or insufficient calorie intake of less than 20 kcal/kg/day

5.1.4. Subjects are in a clinical status with an expected life span exceeding 6 months and Eastern Cooperative Oncology Group (ECOG) 0 to 1 or Karnofsky Performance Scale (KPS) 80 to 100 at trial enrollment.

5.1.5. Subjects are physically and mentally capable and willing for conducting the planned physical training and agreed to comply the educational instructions and wearable devices during trial intervention.

5.1.6. Subjects are functionally and cognitively capable to be informed of the trial contents and objectives (including obtaining peripheral blood sampling for trial investigation), and agree to sign the written consent for enrollment.

5.2 Exclusion criteria

5.2.1. Subjects have tumor *in situ* or curatively treated malignant disease which requires no further antineoplastic treatments.

5.2.2. Subjects are anticipated to receive any surgery, radiotherapy or intervention that prevents or hinders a planned physical training within 28 weeks since trial enrollment.

5.2.3. Subjects experience a progressive BWL which fulfills the criteria for cancer cachexia or pre-cachexia but complicates with the following causes:

5.2.3.1. Severe oral or dental disorders that prevent reasonable intake of food per oral.

5.2.3.2. Known functional or mechanical gastrointestinal disorders that prevent reasonable nutritional absorptions.

5.2.3.3. Intentional body weight reduction by any measures.

5.2.3.4. Known hormonal disorders that cause unintentional or pathogenic BWL.

5.2.4. Subjects have cachexia caused by etiologies not limited to cancer as the following:

5.2.4.1. Pulmonary cachexia which caused by chronic respiratory failure or chronic obstructive pulmonary disease.

5.2.4.2. Cardiac cachexia which caused by chronic and persistent congestive heart failure.

5.2.4.3. Cachexia related to acquired immunodeficiency syndrome.

5.2.5. Subject's malignant disease is considered unstable and thereby unfit for a planned physical training as the following:

5.2.5.1. Uncontrolled or untreated symptomatic brain metastasis.

5.2.5.2. Unstable or deteriorating organ dysfunction.

5.2.5.3. Unstable or symptomatic bone metastasis.

5.2.5.4. Cancer or treatment related physical disability.

5.2.6. Subjects have an underlying medical illness causing severely impaired organ functions as the following:

5.2.6.1. Any liver disease or cirrhosis above Child-Turcott-Pugh score B

5.2.6.2. Any renal disease or insufficiency requiring regular dialysis or eGFR

≤30 mL/min/1.73 m^2 as calculated by Modification of Diet in Renal Disease (MDRD) formula.

5.2.6.3. Any heart failure with New York Heart Association functional class III-IV.

5.2.6.4. Any pulmonary disease requiring daily oxygen support.

5.2.6.5. Any bone, joint or soft tissue illness with range of motion limitations which prevents physical training of the limbs.

5.2.7. Subjects have an active infection requiring hospitalized treatment or intravenous anti-pathogen therapies.

5.2.8. Subjects who receive other experimental treatments or interventions for cancer cachexia.

5.2.9. Subjects are planning to conceive or already in pregnancy.

5.2.10. Subjects are currently participating in any other observational studies concerning cancer cachexia.

6. STUDY DESIGN AND INTERVENTION PLANS

The proposed study is an open-label, single-arm and single-center phase II investigator-initiated trial consisting of two parts. The first part is a feasibility testing and safety run-in cohort and followed by a hypothesis testing cohort as the second part. The primary objective is to investigate the feasibility and efficacy of a supervised intensity-modulated physical training program for elderly cancer patients with risk of cachexia. The primary endpoint is MiniCASCO reduction at week 12 and 24. The secondary endpoints are geriatric assessment, physical activity and sarcopenia. Exploratory objectives include HRQoL, cancer-related survival, recurrence/progression, cancer treatment or study intervention-related adverse events, nutritional scales and gait analysis. Enrolled subjects will receive physical training program per protocol until its completion, intolerability, death at any causes, subject's refusal, investigator's discretion or trial termination according to the principal investigator. A pre-planned study schedule is due at week 24 with the following time points, week -4 to -2 (pre-screening), week -2 to 0 (screening and preparation or baseline), week 0 (intervention initiation), week 6 (intervention midway), week 12 (completion) and week 24 (post-intervention follow-up).

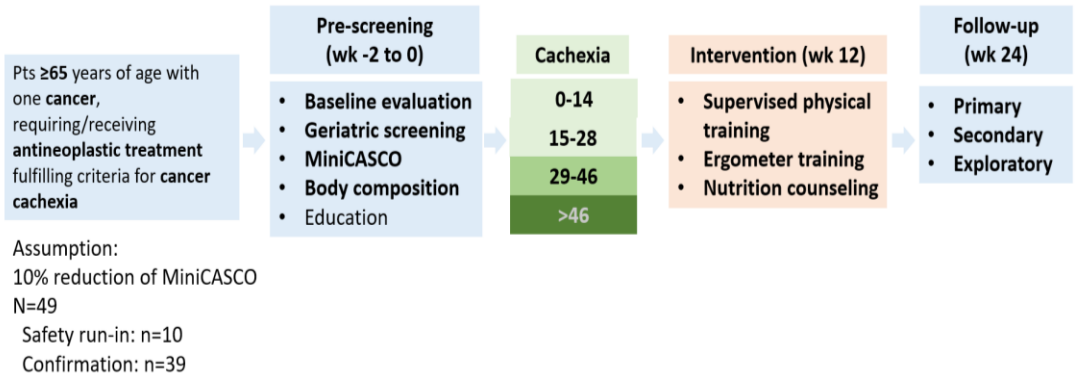


Figure 1. Trial schema

6.1 Overall protocol

6.1.1. Aerobic exercise

Intensity-modulated ergometer training will be provided in the SeniorGym, MDIC, National Cheng Kung University Hospital. Each session lasts 8 to 25 minutes with a gradual increment of both resistance and duration along the training process. Two to three sessions per week will be arranged with a minimal interval of 24 hours between two consecutive sessions. Training targets are determined at a moderate intensity of aerobic exercise or reaching 80% of mpHR. A total of 12-week training is provided to each subject when tolerated (week 0 to 12).

6.1.2. Resistance exercise

Trainer-assisted supervised manual physical training will be provided to the subjects in the SeniorGym, MDIC, National Cheng Kung University Hospital. The training module is composed of utilizing Therabands® to conduct limb or trunk stretching under reasonable resistance. Each session lasts 20 minutes with a gradual increment on resistance along the training process. Two sessions per week will be arranged with a minimal interval of 24 hours between two consecutive sessions. Training targets are determined at a moderate intensity of resistance exercise or reaching 80% of mpHR. A total of 12-week training is provided to each subject when tolerated (week 0 to 12).

6.1.3. Nutrition assessment and intervention

Nutrition assessment and intervention will be conducted by dieticians in specialized nutrition outpatient clinics. A professional diet consultation and nutritional recommendations will be provided upon willingness of the subject.

Dietary prescriptions will be determined and adjusted to a target daily calorie intake of 25 to 30 kcal/kg/day. Forty to fifty percent of the daily calorie is expected to derive from carbohydrate source. Protein ingestion is aimed at 1.2 g/kg/day at least. Subjects will be visited at week 0, 12 and 24 for nutrition assessment, calorie calculation and dietary target adjustments.

6.2 Screening and preparation

6.2.1 Screening and pre-intervention assessment

During the pre-screening period (week -4 to -2), study nurse will confirm the eligibility for enrollment, record the baseline demographics and clinical characteristics of the subject and prepare him/her for pre-intervention preparation. In addition, a written informed consent of the subject will be obtained under reasonable request to initiate the trial assessment and intervention.

6.2.2 Preparation of exercise intervention

A detailed introduction and education will be delivered at week -2 to week 0 and the exercise intervention will be initiated at week 0. In addition, study nurses will complete pre-intervention assessment at week -2 to week 0 (preparation). During week 0 (baseline), 6 (midway), 12 (completion) and 24 (follow-up), all subjects will be reviewed and evaluated of the eligibility for continuation of exercise training or mid-, and post-intervention assessments. Subjects will be followed at a specialized outpatient clinic at week 0, 6, 12 and 24, respectively.

6.3 Modifications of intervention

6.3.1 Exercise requirement:

Subjects are required to be in generally well-being condition on each of the training session and assessment. Subjects will be asked for self-reported health or physical status on whether he or she feels suitable or comfortable to engage in each of the training session independently. In addition, subjects with any of the following subnormal vital biophysical readings, including HR (>180 or <60 bpm), SBP (>160 or <90 mmHg) or pulse oximetry (SpO2<88% with ambient air) before each training session will be subjected to postpone or cancel the intervention under investigator's discretion.

6.3.2 Postponing exercise:

If subjects fail to meet the aforementioned requirements to initiate or continue

a training session or assessment, a postponement is required. Each delay is set at a minimum of 2 consecutive days to a maximum of 28 consecutive days. Given the presence of delays in the intervention period, the pre-scheduled intervention midway (week 6), completion (week 12) and follow-up (week 24) time points are thereby postponed accordingly.

6.3.3 Specific considerations:
If the investigator or study nurse observes any signs or symptoms suggestive of physical or bodily injury or trauma related to the exercise training, given a permission from the subject, a delay is required until all harmful conditions are alleviated to baseline. The principle of delay will follow the guidance as described in 6.3.2.

6.4 Off-study criteria

Subjects who meet any one of the following conditions will be withdrawn from the study,

- Clinical evidence of progression or recurrence of the malignant disease which prevents or hinders further physical training.
- Delayed recovery of intervention-related injuries or comorbidities, which prohibits the protocol intervention beyond 28 consecutive days since the inciting physical exercise.
- Unacceptable or unanticipated toxicity or adverse events
- Subject's death.
- Subject's refusal.
- Investigator's discretion to stop the protocol intervention.
- Available and potentially better alternative treatments at the discretion of the investigator.
- Confirmed futility or potential harms of the study intervention to the subjects, as determined by the chief principal investigator.

7. STUDY SCHEDULE

7.1 Assessment timeline

The following assessments, including primary endpoint (MiniCASCO), geriatric assessment, physical activity, sarcopenia, HRQoL, nutrition assessment and gait analysis, are performed at the pre-scheduled timeline, respectively. In addition, cancer-related events, recurrence/progression of cancer, cancer

treatment or study intervention-related adverse events are recorded at whenever time points if present. We will implement a wearable device to record the motility of subjects during the intervention. The details and timetable for assessments of the trial are shown in 7.5 (Figure 2).

7.1.1 Primary endpoint: MiniCASCO
The endpoint is assessed and recorded at baseline (week -2 to 0), completion (week 12) and post-intervention follow-up (week 24). The evaluation tools and gradings are followed by MiniCASCO as reported by Argilés et al.[13] Please refer to the descriptions in 8.1.

7.1.2 Geriatric assessment: Integrated Care for Older People (ICOPE)
The endpoint is assessed and recorded at baseline (week -2 to 0), completion (week 12) and post-intervention follow-up (week 24). Please refer to the descriptions in 8.2.1.

7.1.3 Physical activity: hand grip strength, gait speed, body mass index (BMI), sit to stand (STS), back stretch, sit reach, single leg stand (SLS), up and go (UG), 2-minute step (2MS), 6-minute walk test (6MWT) and timed up-and-go (TUG)
The endpoint is assessed and recorded at baseline (week -2 to 0), midway (week 6), completion (week 12) and post-intervention follow-up (week 24). Please refer to the descriptions in 8.2.2.

7.1.4 Sarcopenia: sarcopenia-calf circumference (SARC-Calf)
The endpoint is assessed and recorded at baseline (week -2 to 0), completion (week 12) and post-intervention follow-up (week 24). Please refer to the descriptions in 8.2.3.

7.1.5 HRQoL: European Organisation for Research and Treatment of Cancer-Quality of Life Cancer C30 (EORTC-QLQ C30; 10 questions)[29]
The endpoint is assessed and recorded at baseline (week -2 to 0), completion (week 12) and post-intervention follow-up (week 24). Only 10 questions are included and appended in the MiniCASCO. Please refer to the descriptions in 8.1.5.

7.1.6 Nutrition: Mini Nutritional Assessment Short-Form (MNA-SF)
The endpoint is assessed and recorded at baseline (week -2 to 0), completion (week 12) and post-intervention follow-up (week 24). Please refer to the

descriptions in 8.2.4.

7.1.7 Gait analysis: Zebris gait
The endpoint is assessed and recorded at baseline (week -2 to 0), completion (week 12) and post-intervention follow-up (week 24). Please refer to the descriptions in 8.2.5.

7.2 Peripheral blood sampling

Peripheral blood sampling by venous puncture will be performed at baseline (week -2 to 0), completion (week 12) and post-intervention follow-up (week 24).

7.4 Wearable device

Wearable non-invasive watches are applied to the subjects. Subjects are required to wear the watch over one of the limbs for 14 randomly selected consecutive days during baseline (week -2 to 0), midway (week 6) and completion (week 12). The watch will detect acceleration and sunlight exposure of the subject, in which that a post hoc algorithmic analysis would be applied to transform the digital data into daily activity. The information will be saved to a central hub periodically via portable memory devices. Analysis and calculation of the stored digital information will be de-identified and then reviewed by a blinded independent investigator.

7.5 Timetable for assessments

Dimension	Parameter	Pre-screening (Week -4 to -2)	Baseline (Week -2 to 0)	Midway (Week 6)	Completion (Week 12)	Follow-up (Week 24)
	Pre-screening and preparation	X				
Primary endpoint						
Cancer cachexia	MiniCASCO		X		X	X
Secondary endpoint						
Geriatric	Geriatric assessment ICOPE		X		X	X
Physical activity	hand grip strength, gait speed, STS, back stretch, sit reach, SLS, UG, 2MS, 6MWT, TUG		X	X	X	X
Sarcopenia	SARC-CalF		X		X	X

Dimension	Parameter	Pre-screening (Week -4 to -2)	Baseline (Week -2 to 0)	Midway (Week 6)	Completion (Week 12)	Follow-up (Week 24)
Exploratory outcome						
HRQoL	EORTC-QLQ C30[a]		X		X	X
HRQoL	WHO_QOL_Aged		X			X
Nutrition	MNA-SF		X		X	X
Gait	Zebris gait analysis		X		X	X
Oncology	Recurrence/progression of cancer			Any time		
Oncology	Intervention-related adverse events[b]			Any time		
Oncology	Cancer treatment-related adverse events[b]			Any time		
Wearable device	Motion, activity		X	X	X	

Figure 2. Timetable for assessments in the trial

a. Only 10 questions are included and as a part of MiniCASCO.

b. According to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

8. EVALUATION OF INTERVENTION EFFICACY

8.1 MiniCASCO

8.1.1 Specification of assessment metrics:

Assessment metrics according to MiniCASCO are implemented to each subject at baseline (week -2 to 0), intervention completion (week 12), and post-intervention follow-up (week 24). Five dimensions of MiniCASCO are assessed independently, summed up as a total score ranging from 0 to 100 points and graded as minimal (0 to 14), mild (15 to 28), moderate (29 to 46) or severe cachexia (47 to 100).

8.1.2 Weight (40%)

In the dimension “Weight”, BWL and lean body mass (LBM) loss are accounted as two categories. BWL of 1 to 5%, 5 to 10%, 10 to 15%, 15 to 20% or >20% are given 6, 12, 18, 24 or 32 points, respectively. LBM loss >10% is given 8 points if presents. The dimension “Weight” constitutes a total of 40% in the MiniCASCO.

8.1.2 Blood parameters (20%)

In the dimension “Blood parameters”, metabolic, inflammation and immunosuppression associated parameters are accounted as three categories. In the metabolic category, serum albumin <3.2 mg/dL is given 4 points and

anemia with hemoglobin <12.0 g/dL is given another 4 points. Serum C-reactive protein (inflammation) with 10.0 to 20.0 or >20.0 mg/L is given 4 or 8 points. Absolute lymphocyte count (immunosuppression) with ≤500 $x10^4$/mL is given 4 points. The dimension "Blood parameters" constitutes a total of 20% in the MiniCASCO.

8.1.3 Physical performance (15%)

In the dimension "Physical performance", stair climbing and 500-meter walk are accounted. The questions *"Did you have to put more effort on climbing stairs?"* and *"Have you felt tired after walking approximately half a kilometer?"* are asked to the subject and replied by none, mild, moderate, or strong, as each is given 0, 2.5, 5.0 or 7.5 points, respectively. The dimension "Physical performance" constitutes a total of 15% in the MiniCASCO.

8.1.4 Anorexia (15%)

In the dimension "Anorexia", appetite and food intake are accounted. Subjects are required to answer by *"My appetite is (very good, good, average, poor or very poor)*" and is given 0, 1.9, 3.8, 5.7, or 7.5 points in the appetite category. In the food intake category, subjects are asked to describe *"When I eat (I hardly ever feel full, I feel full after eating most of the meal, I feel full after eating over half a meal, I feel full after eating about a third of a meal or I feel full after eating only a few mouthfuls"* and is given 0, 1.9, 3.8, 5.7, or 7.5 points, respectively. The dimension "Anorexia" constitutes a total of 15% in the MiniCASCO.

8.1.5 HRQoL (10%)

In the dimension "HRQoL", 10 standardized questions from EORTC-QLQ C30 are asked to the subjects as the following: *"Do you need to stay in bed or a chair during the day?"; "Were you limited in doing either your work or other daily activities?"; "Were you limited in pursuing your hobbies or other leisure time activities?"; "Have you had pain?"; "Did you need to rest?"; "Have you felt weak?"; "Did pain interfere with your daily activities?"; "Have you had difficulty in concentrating on things, like reading a newspaper or watching television?"; "Has your physical condition or medical treatment interfered with your family life?"; How would you rate your overall health during the past week?"*. The answers are graded as none/not at all, a little/slightly, average/moderately, or a lot/considerably and each question is given 0, 0.25, 0.75 or 1.0 point, respectively. The dimension "HRQoL" constitutes a total of

10% in the MiniCASCO.

8.2 Other assessments

8.2.1 ICOPE

The World Health Organization (WHO) published *Integrated Care for Older People Guidelines* (ICOPE) to provide comprehensive assessment and person-centered service to older populations to ensure healthy ageing 2017.[30,31] ICOPE focuses on six domains of individual's physical and mental capacities, which includes (1) cognitive, (2) mobility, (3) nutrition, (4) visual, (5) hearing, (6) depressive symptoms. The Taiwan Health Promotion Administration subsequently added two domains, (7) medication and (8) life goals, to meet older people's health and social care needs in Taiwan's socioeconomic context. People reporting declines in any domain of the ICOPE screening tool should continue for further evaluation using scales such as BHT, SPPB, MNA-SF, Simplified Visual Acuity Chart, and GDS-15 for a more in-depth assessment. With the ICOPE assessment, conditions in older people associated with functional decline can be identified.

8.2.2 Physical activity

The participants undergo physical examinations at baseline (week 0), midway (week 6), completion (week 12), and post-intervention follow-up (week 24). The Body Mass Index (BMI) is calculated as personal weight (in kilograms) divided by the square of height (in meters).

8.2.2.1. 30-second sit-to-stand (STS) test:

Participants are instructed to rise as fast as possible from a seat in 30 seconds with arms folded across the chest. The number of full stands in 30 seconds is recorded.

8.2.2.2. Back stretch:

Participants are asked to reach over the shoulder with one hand and extend the other one up the middle of the back. The distance (cm) between the extended middle fingers between both hands is then recorded.

8.2.2.3. Sit reach:

Participants sit on the edge of a chair, stretch out one leg, hands overlapped, and reach towards the toes. The distance between fingers and feet is recorded.

8.2.2.4. Single leg stand (SLS):

Assessed with a test that involves standing on one leg with eyes open. The subjects are asked to stand on one foot and maintain balance. The total time is

recorded, with more than 30 seconds counted as 30 seconds.

8.2.2.5. Up and go (UG):

Participants are instructed to get up from a seat, walk 8 feet, turn, and return to the seated position. The total time is recorded.

8.2.2.6. 2-minute step (2MS):

Participants are instructed to raise each knee to a point midway between the patella and iliac crest in 2 minutes. The score is the number of repetitions required for the right knee to reach the target height.

8.2.2.7. 6-minute walk test (6MWT):

Participants are asked to walk for 6 minutes in a 30-meter-long quiet corridor. The total distance that the participants walk during the period is recorded.

8.2.2.8. Timed up-and-go (TUG):

Uses the time that a person takes to rise from a chair, walk 3 meters, turn around 180 degrees, walk back to the chair, and sit down while turning 180 degrees. Participants can use a walking aid if needed.

8.2.3 SARC-Calf

SARC-CalF is a questionnaire that rapidly screens sarcopenia. In accordance with the 2019 Asian Working Group for Sarcopenia (AWGS) criteria, the SARC-CalF scale contains six objects: (1) strength, (2) walking assistance, (3) rising from a chair, (4) climbing stairs, and (5) falls, and (6) is calf circumference (CC). CC thresholds are 34 and 33 cm for men and women, respectively. If the score is above the cut-off value, CC is scored as 0; if it is below the cut-off value, the score is 10. The maximal score of the SARC-CalF is 20 points. A total score of ≥11 points indicate the risk of sarcopenia.

8.2.4 MNA-SF

The MNA-SF is a validated nutrition screening and assessment tool that can identify geriatric patients aged 65 or above who are malnourished or at risk of malnutrition. It is a screening tool consisting of six questions on food intake, weight loss, mobility, psychological stress, or acute disease, the presence of dementia or depression, and body mass index (BMI). The maximum score for this part is equal to 14. A score equal to or higher than 12 indicates that the subject under study has an acceptable nutritional status thus excluding malnutrition and/or malnutrition risk, meanwhile, a score ≤ 11 implicates to proceed with the complete version of the MNA (MNA-LF).

8.2.5 Zebris gait

The Zebris gait analysis system is used to obtain numerical data for kinetic and kinematic gait parameters (Zebris Medical GmbH, Isny im Allgau, Germany). The pressure platform has a sensing area of 149 x 54.2 cm and the sensor unit has 11,264 pressure/force sensors. The foot is mapped at high resolution to facilitate the detection of even the subtlest changes in force distribution, including center of pressure (COP) trajectories during static stance and gait. The gait pattern is collected and analyzed to investigate the effect of intervention.

9. STATISTICAL CONSIDERATION

In the proposed study, a two-staged design is utilized as an optimal arrangement of the subjects. We assume a statistical power of 80% (β=0.2) and the probability of type I error by two-tailed α at 0.1. According to our preliminary results, we found the MiniCASCO (n=11, mean ±SD=22 ±5) of the identical study target population. We hypothesize a 10% of reduction of MiniCASCO in elderly cancer patients with risk of cachexia post intervention. A minimum of 49 subjects are required under the optimal assumption. We presume the part I as a safety run-in period enrolling 10 subjects to assess the feasibility and safety of the protocol. After the confirmation by the principal investigator, the remaining 39 subjects will be enrolled as part II. In summary, a total of 49 subjects will be enrolled to meet the prespecified statistical threshold.

10. REPORTING OF SEVERE ADVERSE EVENTS TO INSTITUTIONAL REVIEW BOARD (IRB) OF ETHICS

10.1 Reporting events to IRB

All investigators must receive adequate professional training according to the Good Clinical Practice (GCP) guideline, be approved by the IRB, abide to the related obligations and be accredited for clinical trial investigations. Serious adverse events/Suspected unexpected serious adverse reactions/Unanticipated problems (SAE/SUSAR/UP) must be reported in written form to the PI immediately. The PI will then report to IRB within 72 hours. The events are defined as any of those described in sections 10.1.1. to 10.1.6. below. However, serious events occurring after the subject is withdrawn from the study do to warrant mandatory reporting under the investigator's discretion. Events which are anticipated morbidities associated with malignancy and chemotherapy are

waived from the reporting.

10.1.1 Causes death
Study-specific clinical outcomes of death because of cancer progression are excluded from the reporting unless the investigator deems the death related to the study intervention.

10.1.2 Are life-threatening.

10.1.3 Causes severe or permanent disability.

10.1.4 Causes prolonged inpatient hospitalization.

10.1.5 Causes congenital anomaly.

10.1.6 Is significant for any other reasons.

11. OTHERS

11.1 All patients must have a signed Informed Consent form and an on-study (confirmation of eligibility) form filled out and signed by a responsible investigator before entry.

11.2 The responsible study investigators and research nurses must approach each patient prior to study drug administration. All required pre-intervention and interim information should be available and the investigators must decide if a re-evaluation is needed and the grade of intervention-related toxicity or adverse events if present.

11.3 Data must be recorded before a course of intervention can be given. A brief explanation for required but missing data should be recorded as a comment.

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