

Effect of exercise therapy on sarcopenia in pancreatic cancer: a study protocol for a randomised controlled trial

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ABSTRACT

Introduction and purpose Sarcopenia is defined as a decrease in muscle mass and muscle strength, and it has been demonstrated to be an adverse predictor in numerous types of cancers. Exercise therapy (ET) carries multiple health benefits in several diseases. Despite these clinical benefits, there are limited data available regarding patients with pancreatic cancer (PC) undergoing ET. We aim to prospectively examine the effect of ET on sarcopenia in patients with PC.

Methods and analysis All clinical stages of PC can be included. When registering study subjects, a precise evaluation of the nutritional status and the daily physical activities performed will be undertaken individually, for each participant. Study participants will be randomly allocated into two groups: (1) the ET and standard therapy group and (2) the standard therapy group. Amelioration of sarcopenia at 3 months postrandomisation will be the primary endpoint. Muscle mass will be calculated using bioimpedance analysis. Sarcopenia will be defined based on the current Asian guidelines. Participants will be instructed to perform exercises with ≥ 3 metabolic equivalents (mets; energy consumption in physical activities/resting metabolic rate) for 60 min/day and to perform exercises with ≥ 23 mets/week. In the ET group, physical activities equal to or greater than walking for 60 min/day will be strongly recommended.

Ethics and dissemination The Institutional Review Board at Hyogo College of Medicine has approved this study protocol (approval no. 2772). The final data will be publicly announced. A report releasing the study results will be submitted for publication.

Trial registration number UMIN000029271; Pre-results.

INTRODUCTION

Pancreatic cancer (PC) has been reported to be the fourth leading cause of cancer-related mortality worldwide.^{1–4} Majority of patients with PC present with locally advanced or metastatic disease at initial diagnosis and the proportion of patients with PC who can proceed with curative intent (eg, surgical resection) is <20%.^{1–4} Currently, there is no

Strengths and limitations of this study

- ▶ To the best of our knowledge, the current clinical trial is the first prospective interventional study (randomised trial) to examine the effect of exercise therapy on sarcopenia in patients with pancreatic cancer.
- ▶ Our study results will be limited to a Japanese population, and further validation studies on other ethnic backgrounds will be required.

standard programme for screening patients at a high risk of PC.^{1–4} Treatment for unresectable PC has traditionally involved use of gemcitabine with low response rates and a marginal survival benefit.^{5,6}

On the other hand, regular physical activity favourably affects the risk of disease onset and progression of several chronic diseases.^{7–12} A recent study reported that elimination of physical inactivity would increase the life expectancy of the world's population by 0.68 years.⁷ However, the clinical impact of exercise therapy (ET) on patients with PC is poorly understood.

Decrease in muscle mass and muscle strength which is related to ageing is termed as primary sarcopenia, while secondary sarcopenia is defined as a decrease in muscle mass and muscle strength that accompanies underlying diseases such as chronic inflammatory diseases, advanced malignancies and malnutrition.^{13–17} In the field of malignancies, sarcopenia has been demonstrated to be an adverse predictor in numerous types of cancers.^{18,19} Pretherapeutic sarcopenia is highly prevalent in patients with malignancies.^{18,19} In our previous investigation, we demonstrated that decreased skeletal muscle mass could be a significant predictor

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of prognosis in patients with unresectable advanced PC undergoing systemic chemotherapy, and some interventions for patients with sarcomenic PC could be beneficial for ameliorating clinical outcomes.²⁰

Again, ET brings multiple health benefits both in healthy individuals and several diseases.^{7–12 21–23} Despite these clinical benefits, there are limited data available regarding patients with PC undergoing ET. There is therefore a need to investigate this issue. In this study, we aim to prospectively examine the effect of ET on sarcopenia in patients with PC.

Patient eligibility criteria

In malnourished patients with PC, ET may be accompanied with increased health risks, as ET may accelerate further protein catabolism and muscle mass decrease.^{24–26} While registering study subjects, a precise evaluation of the nutritional status and the daily physical activities performed will be undertaken individually for each participant. For all potential participants, the researchers will explain in detail the study aims, procedure and potential benefits and risks of this study in a written informed manner. The researchers must let all potential participants know that he/she has the right to withdraw consent at any time throughout the study period. All potential participants must be given sufficient time for careful consideration prior to making a decision. All participants must sign the consent before he/she can participate in the study. Written informed consents will be kept as a part of the clinical trial documents.

Inclusion criteria

1. Both sexes.
2. Patients with PC aged ≥ 20 years. PC includes all type of pancreatic malignancies. A diagnosis of PC will be based on the current Japanese guidelines.²⁷ Clinical stage for PC will be determined based on Union for International Cancer Control classification system.²⁸
3. Patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1.

Exclusion criteria

1. Patients with severe depression or psychiatric disorder.
2. Patients with far advanced PC with massive ascites or extensive metastases due to which participation in this study is anticipated to be difficult.
3. Patients with severe underlying diseases, such as severe infectious diseases, severe chronic heart failure and/or respiratory disorders.
4. Pregnant or lactating female patients.
5. Patients who may be at a risk of fall.
6. Patients considered unsuitable for the study because of the inability to participate in ET.
7. Patients considered unsuitable for the study because of other reasons.

STUDY PROTOCOL

Study design: single-centre non-double blind randomised controlled trial

Our study participants will be patients with PC. All clinical stages (stage I, II, III and IV) of PC can be included. Standard therapy for each patient with PC will be permitted. Study participants will be randomly allocated into two groups: (1) the ET and standard therapy group and (2) the standard therapy group (figure 1). Standard therapies such as surgical resection and systemic chemotherapy will be chosen based on tumour status and baseline characteristics in each patient after thorough discussion with surgeons and oncologists.^{20 27}

Exercise therapy

In the ET group, guidance for ET will be provided for each participant once a month at the outpatient nutritional guidance clinic. Participants will also be instructed to perform exercises with ≥ 3 metabolic equivalents (mets; energy consumption in physical activities/resting metabolic rate) for 60 min/day and to perform exercises > 23 mets/week.^{7–12} In the ET group, physical activities equal to or greater than walking for 60 min/day will be strongly recommended for each study participant. In both groups, standard therapies for PC will be allowed and we will ask all study participants to self-declare their daily amount of exercise. Direct monitoring of exercise will not be undertaken.

Time of starting ET

In the ET group, when the general condition of the patient is stable after initial standard therapy, and it is judged by the attending physician that ET can be performed safely, it will be started as soon as possible.

Primary endpoints

Sarcopenia improvement

Muscle mass, using bioimpedance analysis (BIA) and analysis of muscle strength (hand-grip strength) for the evaluation of sarcopenia, will be calculated once each month. Sarcopenia will be defined based on the current Asian guidelines.¹⁵ The cut-off values for hand grip strength are < 26 kg in male and < 18 kg in female patients and those for muscle mass in BIA are < 7.0 kg/m² in male and < 5.7 kg/m² in female patients.¹⁵ Patients who meet both these criteria will be defined as patients with sarcopenia. Amelioration of sarcopenia at 3 months postrandomisation will be the primary endpoint.²⁹ We will prospectively compare the amelioration of sarcopenia within the two groups.

Secondary endpoints (examination for study)

Changes over time in baseline characteristics

We will assess changes over time of the following baseline characteristics: body weight, body mass index, white blood cell count, platelet count, serum albumin level, aspartate aminotransferase, alanine aminotransferase, total cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein, fasting blood glucose, haemoglobin A1c,

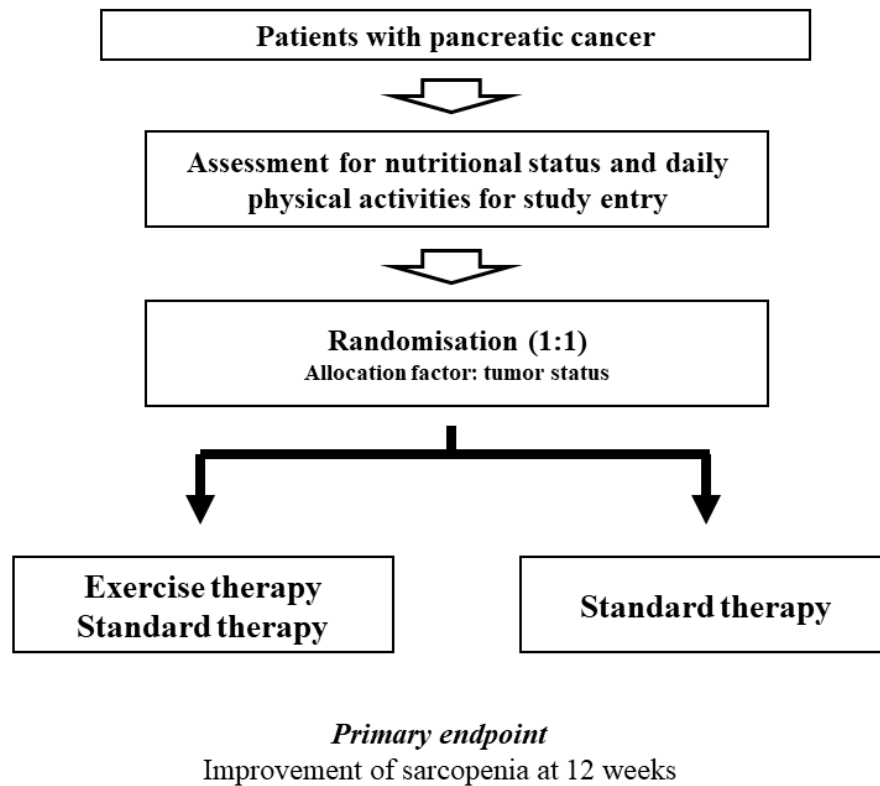


Figure 1 Study design.

homeostasis model assessment of insulin resistance and tumour markers

Follow-up and standard of care

During the observation period and after completion of the study, all study subjects will be seen in our clinic every 4 weeks to address complications of PC and other comorbidities. In both groups, standard therapies for PC will be continued. Regular laboratory tests (haematology, biochemistry and coagulation) will be requisite at study entry and at completion of the study and on an as-required basis.

Case registration period

From October 2017 to March 2021.

Data collection

A study assistant will gather data elements from the patient medical records, including the following:

Baseline data:

- a. Sex and age
- b. Height and body weight
- c. Vital signs and ECOG-PS
- d. History of alcohol consumption and history of smoking
- e. Clinical stage of PC
- f. Previous treatment and medication
- g. Comorbid conditions
- h. Baseline laboratory tests
- i. Presence or absence of ascites on radiological findings

Statistical methods

Descriptive statistics

Data will be entered using JMP software (SAS Institute), and all data will be checked to confirm consistency. Data at each time point will be compared. Quantitative parameters will be compared using a paired or an unpaired *t*-test. Categorical parameters will be compared using Pearson χ^2 test or Fisher exact test, as applicable. Statistical analyses will be undertaken on an intention-to-treat basis, and all patients will be analysed in the group to which they are assigned.

Sample size estimation

According to our previous BIA results, considering that the α error (type 1 error) is 0.05, the detection power (β) is 0.8, the difference in the two groups to be detected and measured using BIA is 10, and the SD of outcome is 10, the number of required participants in each group will be 17 (total of 34 participants) in order to randomly allocate one to one.^{30 31} Randomisation will be performed using a dedicated computer and using the clinical stage of PC as an allocation factor for matching baseline characteristics between the two groups. We anticipate that a few of the participants may drop out of the study; therefore, a total of 40 participants will be required to confirm our hypothesis.

DISCUSSION

The population of Japan has the longest life expectancy in the world.¹¹ Japan is an ageing country, and the clinical



importance of ET has recently gained considerable attention due to its multiple health benefits.^{7–12,21–23} Sarcopenia is closely associated with ageing and underlying disease and ET has been shown to impact epigenetic modulation, reducing the risk and mortality in patients with malignancies.^{30–32,33} In addition, ET may have a potential favourable impact on tumour outcome by reducing insulin resistance and insulin-like growth factor-I secretion.³⁴ Based on this background, we conducted the current randomised controlled trial (RCT). To the best of our knowledge, this is the first prospective interventional clinical trial that will objectively assess the effect of ET on sarcopenia in patients with PC. From a clinical practice perspective, we highlight the potential safety risks of ET in malnourished patients with PC, because ET may risk promoting further protein catabolism and muscle mass loss. An appropriate nutritional assessment will be needed prior to starting ET and this study will be performed with sufficient care.

One of the major strengths of our study is that this will be an RCT. We acknowledge several limitations of this study design. First, this study will be based solely on a Japanese population. Additional research in different ethnic populations will be required to further verify the efficacy of ET in sarcopenia and to extrapolate our results to other ethnicities. Second, direct monitoring of ET will not be undertaken. Third, short duration of ET alone cannot assess the clinical outcome in patients with PC. However, if the clinical efficacy of ET for sarcopenia in patients with PC is confirmed in this RCT, the information provided may be beneficial to clinicians.

Ethics and dissemination

Research ethics approval

The study protocol, informed consent form and other submitted documents were reviewed and approved. Throughout the study period, Declaration of Helsinki will be strictly followed in order to guarantee the rights of the study subjects. No patient is registered at the time of submission of our manuscript.

Confidentiality

Personal information of all study subjects will be kept confidential. All relevant documents will be kept locked and preserved at the department of Hepatobiliary and Pancreatic Disease, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan, in accordance with data protection procedures. For each study subject, all data collected during the study period will be identified by a serial number and a name acronym in the case report forms.

Dissemination policy

Final data will be publicly disseminated irrespective of the study results. Results will be presented at relevant conferences and submitted to an appropriate journal following trial closure and analysis.

Contributors KY: designed the study and will write the initial draft of the manuscript. HN and HE: will do analysis and interpretation of the data, and assist in preparation of the manuscript. All other authors: will do data collection and interpretation, and will critically review the manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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