Trials

STUDY PROTOCOL

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Multimodal Prehabilitation In Pancreatic cancer Patients undergoing surgery (PIPS): study protocol for a randomized controlled trial

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Abstract

Background Pancreatic cancer surgery is challenging and associated with up to a 70% complication rate, which translates to poor postoperative recovery and patient health-related quality of life (HRQoL). Previous studies showed that preoperative low functional capacity and malnutrition have been associated with inferior postoperative outcomes. Considering the high frequency of older and frail patients, often deconditioned by long-course neoadjuvant chemotherapy, the preoperative period, including the time window after chemotherapy, is a unique opportunity to condition modifiable risk factors (e.g., functional capacity, nutritional status). This manuscript outlines the protocol for a randomized controlled trial investigating the impact of a multimodal prehabilitation program on postoperative complications and recovery following pancreatectomy.

Methods This is a single-center, randomized controlled trial evaluating a 4–6-week multimodal prehabilitation program (physical, nutritional, and psychological interventions) compared with usual perioperative care in adults scheduled for pancreatic surgery, whether upfront or following chemotherapy for pancreatic or periampullary cancer. The primary outcome will be the severity of postoperative complications, measured using the Comprehensive Complication Index (CCI®). Secondary outcomes include the level of functional capacity, time to functional recovery, length of stay, body composition parameters, and generic and disease-specific health-related quality of life (HRQoL). Follow-up assessment will be conducted at 30, 60, 90, 180, and 365 days post-surgery. A sample size of 238 patients is estimated to provide adequate power to detect a clinically meaningful difference in CCI® between groups.

Discussion A multimodal prehabilitation program may enhance functional capacity, improve nutritional status, and increase skeletal muscle mass, thereby promoting a shift from a catabolic to an anabolic state. By modulating systemic inflammation and supporting cardiovascular and immune function, this strategy could lead to fewer postoperative complications, a shorter length of stay, and a faster recovery of health-related quality of life. Positive findings from this trial would carry strong clinical significance and could be practice-changing, potentially informing future guidelines for the implementation of multimodal prehabilitation in patients undergoing pancreatic cancer surgery.

Trial registration Trial Registry NCT06069297. Registered on August 25, 2023.

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Keywords Prehabilitation, Pancreatic surgery, Functional capacity, Enhanced recovery after surgery, Comprehensive complication index, Postoperative complications, Pancreatic neoplasm

Introduction

Background and rationale {9a}

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal cancer, with a 5-year survival rate of around 10% [1]. The combination of surgical resection and chemotherapy represents the most effective therapy to improve prognosis for localized PDAC [2, 3]. Nonetheless, the complexity of surgery and its sequelae require good preoperative conditions and functional status. Patients with pancreatic cancer are generally older adults in whom frailty, sarcopenia, and malnutrition are common [4, 5]. Nowadays, patients with resectable and borderline-resectable disease increasingly undergo long-course multidrug neoadjuvant chemotherapy, which may further diminish their physical and nutritional status [6].

These features have all been associated with poor postoperative outcomes and reduced survival [7–9]. Therefore, the preoperative period and the time window after the end of chemotherapy constitute a unique opportunity to condition modifiable risk factors, improve functional capacity, nutritional status, and address deficiencies in physiologic reserves, which might enhance recovery after surgery, with a better outcome.

Prehabilitation is defined as the process from diagnosis to surgery, consisting of one or more preoperative interventions of exercise, nutrition, psychological strategies and respiratory training, that aims to enhance functional capacity and physiological reserve to allow patients to withstand surgical stressors, improve postoperative outcomes, and facilitate recovery [10]. Multimodal prehabilitation, which combines physical training, nutritional support, and psychological optimization, has emerged as an effective intervention to enhance patients' functional capacity and reduce postoperative morbidity after gastrointestinal cancer surgery [11]. A recent international multicenter randomized controlled trial (RCT), including 251 patients scheduled for colorectal cancer surgery, the PREHAB trial, found that a 4-week inhospital supervised multimodal prehabilitation program, including a high-intensity exercise program 3 times per week, a nutritional intervention, and psychological support, significantly reduced postoperative severe and medical complications [12]. Despite these promising results, evidence on the impact of prehabilitation in patients undergoing pancreatic surgery for pancreatic cancer remains limited. A systematic review examining prehabilitation in this population highlighted how all studies reported heterogeneous interventions; all of them included exercise programs, but only two included the nutritional component [13]. Additionally, Refaat et al. underlined how prehabilitation after pancreatic surgery may improve preoperative functional capacity and postoperative outcomes, specifically pulmonary complications [14]. However, evidence ranged from "moderate" to "very low" with a low proportion of RCTs, with inadequate sample sizes, high risk of bias, and inconsistency in the effect estimates [14].

The persistent need to better understand the effectiveness of multimodal prehabilitation on postoperative complications in adult patients undergoing surgery for PDAC or periampullary tumors led us to conduct a single-center, single-blinded RCT. We hypothesize that prehabilitation will enhance functional capacity, improve nutritional status, and increase skeletal muscle mass, potentially leading to fewer postoperative complications, a shorter length of stay, and a faster recovery in health-related quality of life. Additionally, we hypothesize that a higher percentage of patients receiving prehabilitation will return to preoperative health-related quality of life, functional capacity, and nutritional status compared to the usual care group at 30, 60, and 90 days after surgery.

Explanation for the choice of comparator {9b}

Usual perioperative care was selected as the comparator because it represents the current standard management for patients undergoing pancreatic surgery at our institution and in most ERAS-based pathways.

Objectives {10}

The primary objective of this RCT is to assess the extent to which a supervised 4- to 6-week multimodal prehabilitation program, compared to usual care, affects postoperative complications in patients undergoing pancreatic surgery for PDAC or periampullary tumors. Secondarily, the trial will evaluate the impact of prehabilitation on patient functional capacity, time to functional recovery, length of stay, body composition parameters, health-related quality of life (HRQoL), and circulating markers of inflammation and cancer cachexia.

Methods: patient and public involvement and trial design

Patient and public involvement {11}

Patients and the public were not involved in the design of this trial. Patients will not be involved in the conduct of the study, data analysis, or interpretation of the results. The results of the study will be disseminated to

participants upon request and through scientific publications and presentations.

Trial design {12}

The multimodal Prehabilitation In Pancreatic cancer patients undergoing Surgery (PIPS) study is a single-center, single-blind, parallel arm, randomized controlled trial of a multimodal prehabilitation program compared with usual care in adult patients scheduled for pancreatic resection, both upfront or after neoadjuvant chemotherapy. This will be a superiority trial to test the hypothesis that a 4- to 6-week hospital-based multimodal prehabilitation will result in lower postoperative complications within 90 days after surgery compared with usual care.The trial flow diagram is shown in Fig. 1. This protocol follows the Standard Protocol Items for Randomized Trials (SPIRIT) guidelines. The trial will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964), all applicable amendments established by the World Medical Assemblies, and the ICH guidelines for Good Clinical Practice. The study also complied with Italian law and the requirements of the Italian regulatory authorities. The San Raffaele Scientific Institute Clinical Trial Center (CTC) will be responsible for quality control. IRB and ethical approval for this study were granted by the Lombardy Ethics Committee under the reference number 136/INT/2022. Important protocol modifications will be addressed to the relevant parties.

Methods: participants, interventions, and outcomes

Trial setting {13}

The study will be conducted at San Raffaele Hospital (Milan, Italy).

Characteristics of the people who are needed for the trial

Characteristic	The people we would expect to see included
Age	People between 18 and 90 years
Sex	Male, female, and intersex
Gender	Man and woman
Race, ethnicity, and ancestry	Race and ethnicity will be self-reported by participants using categories routinely collected in clinical practice and reported descriptively
Socioeconomic status	Socioeconomic status will be described using education level and employment status as reported by study participants
Geographic location	Participants will be recruited in Italy at San Raffaele Hospital (Milan), an urban tertiary referral center. The study coordination site is located in Italy
Other characteristics relevant to the trial	Suspected or diagnosed resectable or borderline resectable pancreatic cancer or periampullary neoplasms

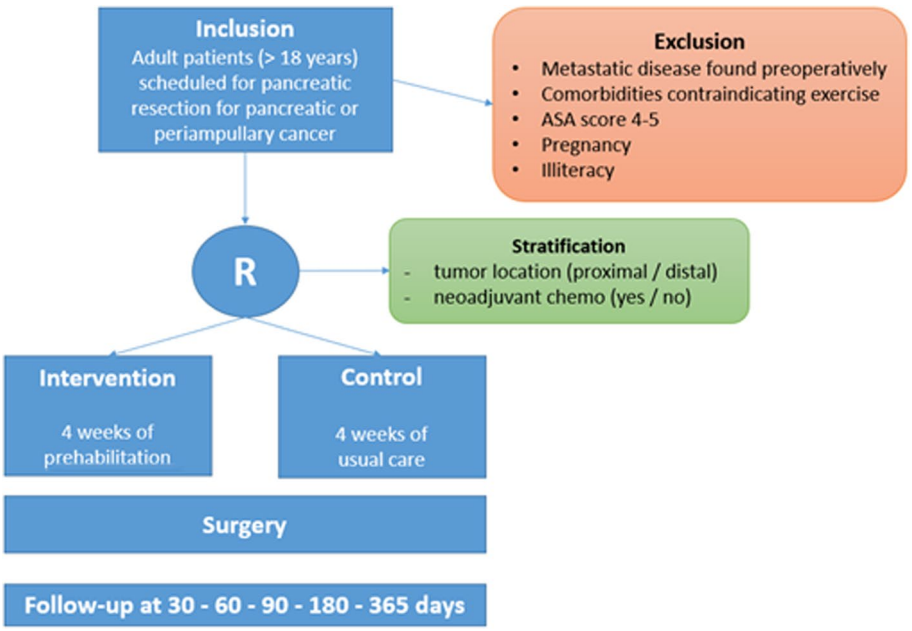

Fig. 1 Trial flow diagram

Eligibility criteria for participants {14a}

Adult patients (>17 years old) will be eligible for the PIPS trial if they have suspected or histologically confirmed PDAC or periampullary cancer (including duodenal cancer) and are scheduled for pancreatic surgery, either upfront or after neoadjuvant chemotherapy. Eligible patients should have an expected surgery date after 3 weeks from enrolment and be willing to participate in the multimodal prehabilitation program. Exclusion criteria will include patients with (1) metastatic or unresectable disease at diagnosis or preoperatively; (2) comorbidities contraindicating multimodal prehabilitation such as orthopedic, neurological, cardiac, or chronic renal failure (dialysis or creatinine > 250 mmol); (3) American Society of Anesthesiologists (ASA) score 4 or higher; (4) pregnancy; and (5) inability to read and understand the language of the country where the study will be performed.

Eligibility criteria for sites and those delivering interventions {14b}

This is a single-center trial conducted at a tertiary referral hospital. No specific eligibility criteria are defined for study sites. The intervention will be delivered by qualified healthcare professionals (physiotherapists, nutritionists, and psychologists) routinely involved in perioperative care at the study institution.

Who will take informed consent? {32a}

Patients identified at the surgical clinic or during the multidisciplinary tumor board meeting with a diagnosed or suspected PDAC or periampullary cancer, scheduled for pancreatic surgery after neoadjuvant chemotherapy or upfront, will be informed about the RCT during a preoperative surgical consultation. Those eligible and interested in participating will receive a phone call by the study coordinator with detailed explanation of the study protocol, followed by an outpatient appointment to sign the consent form and be enrolled in the trial. A subject identification code will be assigned consecutively and registered in an identification list. Surgery will be scheduled approximately 30 days after signing the consent form, also depending on the waiting list and clinical factors. This timeframe allows a minimum of four weeks of prehabilitation and ensures adequate time between the end of neoadjuvant therapy and surgery.

Additional consent provisions for collection and use of participant data and biological specimens {32b}

Participants will provide specific informed consent for the collection, storage, and future use of biological specimens and deidentified study data for ancillary research purposes related to the study objectives.

Intervention and comparator

Intervention and comparator description {15a}

The intervention consists of a supervised multimodal prehabilitation program (exercise, nutritional support, and psychosocial counseling) conducted for a minimum of four weeks prior to surgery, during the waiting time following patient enrollment. For patients who received neoadjuvant chemotherapy, the prehabilitation program will begin only after completion of treatment, during the 6-week interval typically required before surgery. For the intervention group, exercise training, nutritional therapy, and anxiety-reducing techniques will be performed under the supervision of qualified health professionals, including certified physiotherapists, nutritionists, and psychologists. A tailored intervention will be prescribed based on specific physical, nutritional, and psychological conditions recognized during the multimodal assessment. Different combinations of three domains (physical, nutritional, psychological) will be used to maximize their synergistic anabolic effect.

Exercise program

Patients will participate in a training program of two to three sessions per week. The sessions will take place at the hospital gym, supervised by a certified physiotherapist. If a participant cannot attend three sessions, the third session will be done independently at home, with a booklet of exercise instructions, a training diary, and resistance bands provided. The program includes endurance, resistance, and inspiratory muscle training, tailored to individual preferences and clinical conditions. Endurance training will consist of 30 min of either high-intensity interval training (HIIT) or moderate-intensity continuous training (MICT) using a treadmill, exercise bike, or a recumbent cross trainer. Training intensity will be adjusted based on performance during sessions and will be evaluated using the Borg scale. Resistance training will consist of three sets of 10 repetitions across six major muscle groups. The initial workload will be set at 65% of baseline one-repetition maximum (1RM), with incremental adjustments based on participant performance. In patients with chronic respiratory conditions, inspiratory muscle training will be performed using a specific portable breathing trainer with three sets of 10 breaths, performed independently at home twice daily. Intensity will be increased regularly depending on the perceived fatigue. Table 1 shows details on physical exercise prescription.

Nutritional program

Based on dietary habits, medical conditions, nutritional status (according to Patient-Generated Subjective Global Assessment—PG-SGA), and body composition

Table 1 Details in the prescribed exercise

	Endurance training	Resistance training	Inspiratory muscle training
Frequency	Three times per week For at least 4 weeks	Three times per week For at least 4 weeks	Twice a day, every day For at least 4 weeks
Intensity	*Moderate*: 60%–70% of RHR or Borg-RPE 12–14 *High*: 80%–90% of RHR or Borg-RPE 15–17	65% of 1 RM 1RM = weight (kg)/(1.0278–0.0278 × reps)	60% of MIP
Time and/or type	30 min (2-min warm-up and 2-min cool-down) HIIT: Alternating 3 min at moderate intensity to 2 min at high intensity MICT: 25 min maintaining moderate intensity	Six exercises targeting all major muscle groups (upper limbs, lower limbs, trunk) Three sets of 10 reps	Three sets of 10 breaths

RHR reserve heart rate, *HIIT* high-intensity interval training, *MICT* moderate-intensity continuous training, *Borg-RPE* Borg Rating of Perceived Exertion (range: 6–20), *1RM* one-repetition maximum, *reps* repetitions, *MIP* maximal inspiratory pressure

(according to bioimpedance vector analysis—BIVA), a certified nutritionist will provide a comprehensive diet management program at baseline. A food-based intervention with a balanced macronutrient composition will be prescribed to achieve the estimated daily requirements based on a caloric intake and meal pattern. Furthermore, a daily protein intake of 1.5–2.0 g/kg ideal body weight will be set, as per guidelines for surgical patients. If necessary, oral nutritional supplements, including both calorie-protein supplements and whey protein supplements, will be prescribed. This approach will be closely monitored and adjusted as necessary to enhance recovery outcomes and align with the patient's evolving health status. A follow-up visit will be scheduled in person after 2 weeks into the program.

Psychological coping

Participants will meet once with a psychologist to explore their emotional and psychological needs related to their current situation. Based on the psychologist's assessment, tailored psychological support sessions may be scheduled during the prehabilitation program.

Usual care group

Patients in the usual care control group will be treated according to usual clinical care and will be given informative material regarding a healthy lifestyle and how to best prepare for surgery.

Criteria for discontinuing or modifying allocated intervention/comparator {15b}

The allocated intervention may be discontinued or modified in the event of patient request, occurrence of adverse events or clinical conditions contraindicating continuation of the prehabilitation program, or other safety concerns as judged by the treating clinician. Participants who discontinue or modify the intervention will continue to be followed according to the study protocol and included in the intention-to-treat analysis whenever possible.

Strategies to improve adherence to intervention/comparator {15c}

Participants will receive clear, verbal instructions regarding the intervention protocol, emphasizing the importance of adhering to the prescribed regimen. To reinforce understanding, educational materials will be provided. Each participant will receive personalized written nutritional indications, including a tailored diet plan and recommendations for any necessary oral nutritional supplements. During each physical training session, the physiotherapist will maintain a training diary to monitor participants' heart rates throughout the endurance exercises, the load (expressed as a percentage of baseline one-repetition maximum), and the number of repetitions and sets completed during resistance training. Weekly, the physiotherapist will monitor the execution of inspiratory muscle training and will adjust the intensity. Frequency and exercise intensity during the training sessions will be monitored to evaluate adherence and fidelity to the exercise program. High adherence will be defined as the completion of at least 80% of the prescribed exercise sessions by the patient. Fidelity will be defined as participation to at least 12 supervised exercise sessions [15]. Adherence will be evaluated considering components of training frequency, intensity, and time [15]. Participants will also be asked to complete a 3-day nutritional diary to monitor their adherence to the nutritional indications provided. Verbal reminders will be given to encourage adherence to physical sessions and compliance with nutritional indications, particularly regarding the oral nutritional supplements.

Concomitant care permitted or prohibited during the trial {15d}

All surgeries will be carried out in a high-volume center for pancreatic surgery. The surgical approach (open or minimally invasive) will be chosen at the surgeon's discretion. Patients in both groups will be treated within a specific enhanced recovery pathway as reported in Table 2

Table 2 Enhanced recovery pathway (ERP) elements applied in both groups

ERP intervention	Definition
Preoperative	
Education	Preoperative counselling from a nurse, a surgeon, and an anesthesiologist, with a dedicated booklet including information on goals and expectations about hospital stay
No bowel preparation	No mechanical bowel preparation
Carbohydrate loading	Intake of a preoperative maltodextrin drink the night before surgery and 2 h before induction of anesthesia
No long-acting sedation	No long-acting sedating medication used before surgery
Antibiotic prophylaxis	Antibiotic prophylaxis is complete prior to surgery
Immunonutrition	Intake of oral impact 711 ml/day during the 5 days before surgery
Medical optimization	If needed, patients will receive hematological consultation for anemia, pancreatic enzyme replacement, and glycemic control optimization four weeks before surgery
Intraoperative	
Balanced intravenous fluid	Intravenous fluid infusion avoiding fluid overload. Suggested infusion rate 6 ml/kg/h
Active warming	Intraoperative active warming
PONV prophylaxis	PONV prophylaxis administration
Thromboembolic prophylaxis	Prophylactic low molecular weight heparin starting 6 h after the end of surgery
Postoperative	
Avoidance of the nasogastric tube	Nasogastric tube is removed at the end of general anesthesia
Early return to oral nutrition	Patients receive clear liquids from the night after surgery. Solid food meals start on the first day after surgery
Early mobilization out of bed	Patients are mobilized out of bed starting on the morning of the first day after surgery. Ambulation in the room and hallway is encouraged
Early urinary catheter removal	Urinary catheter is removed within the first 48 h after surgery
Early IV fluid stop	Termination of intravenous fluid infusion within postoperative day 3
Multimodal analgesia	Multimodal analgesia with oral analgesics in combination with epidural analgesia for open surgery or single-shot spinal analgesia for minimally invasive surgery

PONV Postoperative nausea and vomit

[16]. All patients will receive an informative booklet (available at https://www.hsr.it/mediaObject/ospedali/documents/HSR/documenti/Brochure-Pancreas_San-Raffaele/original/Brochure+Pancreas_San+Raffaele.pdf) regarding their surgery, anesthesia, and recovery period including daily postoperative milestones. All patients will also undergo preoperative medical optimization. This includes a hematology consultation in cases of anemia (defined as hemoglobin ≤ 13 g/dL in men and ≤ 12 g/dL in women), pancreatic enzyme replacement therapy in cases of pancreatic exocrine insufficiency (initiated at a dosage of 40,000 IU of lipase with meals and 20,000 IU with snacks), and glycemic control optimization for those with poorly regulated diabetes. For 5 days before surgery, patients will receive immunonutrition (i.e., Oral Impact®, Nestlé Health Science, 237 ml three times per day) according to ERAS Society® recommendations [16].

Ancillary and posttrial care {34}

Participants will continue to receive standard perioperative and postoperative care according to institutional clinical practice. No additional ancillary or posttrial interventions are planned. Any adverse events related to study participation will be managed within the usual healthcare system, in accordance with institutional policies and applicable regulations.

Outcomes {16}

Primary outcome

Postoperative complications occurring during the index admission or in a subsequent readmission, when related to surgery, will be recorded up to 90 days after surgery and graded by severity using the Dindo-Clavien classification and the Comprehensive Complication Index (CCI®). The Dindo-Clavien system grades complications according to the therapy needed for treatment: Grade 1 are complications that require bedside management, Grade 2 are complications that require pharmacologic treatment, Grade 3 are complications that require surgical or radiologic intervention, and Grade IV are complications that require intensive care treatment. Dindo-Clavien Grade 3 or above are considered severe postoperative complications. The CCI, derived from the Dindo-Clavien system, is a validated metric summarizing the complete spectrum

of complications that occurred and their severity in a single score ranging from 0 to 100. A clinically relevant difference in this outcome is equal to 12 points [17].

Secondary outcomes

Secondary outcomes will include (1) functional capacity, (2) time to functional recovery (TFR), (3) length of stay, (4) nutritional status, (5) body composition, (6) generic health-related quality of life (HRQoL), (7) disease-specific HRQoL, (8) depression and anxiety, and (9) level of patient activation before surgery.

Functional capacity will be measured using the 6-min walking test (6MWT), Timed Up and Go Test (TUG), gait speed assessment, handgrip strength test, International Physical Activity Questionnaire (IPAQ), and Duke Activity Status Index (DASI). They will be assessed preoperative and at 30, 60, and 90 days after surgery.

- The 6MWT is a performance-based outcome measure performed along a stretch of flat corridor. Patients are instructed to walk for six minutes, aiming to cover as much distance as possible within that time at a pace that would result in fatigue. The minimal important difference (MID), defined as "the smallest change that the patient and/or physicians would find meaningful and worthwhile" has been estimated at 19 meters for between-group comparisons. A recent study found that the 6MWT is a valid measure of recovery after pancreatic surgery [18].
- TUG is used to assess functional mobility, balance, and risk of falls. Patients are instructed to stand up from a chair, walk 3 meters, turn around a cone, and return to the chair as quickly and safely as possible.
- Walking Gait Speed Test is a validated indicator of functional mobility. The patient is asked to walk at a comfortable pace along a 6-meter walkway, with time recorded over the central 4 meters.
- Handgrip Strength Test assesses muscular strength of the hand and forearm as an indicator of skeletal muscle function. The patient is asked to perform a maximal voluntary handgrip using a handheld dynamometer in a standardized seated position, with the elbow flexed at 90° and the forearm in a neutral position.
- IPAQ is a validated self-reported tool used to assess physical activity levels in adults. It records the frequency (days per week), duration (minutes per day), and intensity of physical activity over the past 7 days. Based on this information, the total energy expenditure is calculated in metabolic equivalent tf Task (MET). Individuals are classified as inactive if their total MET is less than 700, moderately active between 700 and 2519, and highly active if equal to or greater than 2520 [19].
- DASI is a brief questionnaire designed to assess physical function. Participants are asked to respond whether they are able to perform 12 listed activities of various intensity (i.e., ambulation, household tasks, and leisure activities). This measure has been validated in a variety of clinical and surgical settings [20]. A minimal important difference of 6 points implies a clinically important difference [21].

Time to functional recovery (TFR) will be defined as the postoperative day on which the participants achieve discharge criteria (tolerance of oral intake, recovery of lower gastrointestinal function, adequate pain control, ability to mobilize and self-care, and no evidence of untreated medical problems) [22].

Length of stay (LOS) will be defined as the number of days from surgery to hospital discharge.

Nutritional status will include the nutrition history (e.g., weight loss, daily intake), measurement of anthropometric parameters including body weight (kg), height (cm), and body mass index (kg/m^2), arm and calf circumferences (cm), nutritional screening questionnaires (mini nutritional assessment — MNA; scored patient-generated subjective global assessment — PG-SGA), and standard biochemical markers of malnutrition and inflammation including albumin, prealbumin, total proteins, total lymphocyte count, C-reactive protein, vitamin D, transferrin, sideremia, and ferritine.

Body composition will be assessed using bioelectrical impedance vector analysis (BIVA) at baseline, on the day before surgery, and at 30, 60, and 90 days after surgery. BIVA works by measuring tissue resistance (R) and reactance (Xc) after an alternating current passes through the body. Resistance reflects the opposition to current flow through body fluids and is primarily associated with total body water and fat-free mass. Reactance indicates the capacitive properties of cell membranes and is related to cellular integrity and body cell mass. From these values, the phase angle (PhA) is calculated as the arctangent of Xc divided by R. PhA reflects cellular mass and soft-tissue quality and quantity, serving as an indicator of cell membrane integrity and fluid distribution between intra- and extracellular compartments. In healthy individuals, PhA typically ranges between 5 and 7°, and it decreases in conditions of muscle mass loss or altered fluid balance [23]. BIVA also provides estimates of hydration and cell mass independently of body size, including extracellular (ECW) and intracellular water (as a percentage of total body water), fat mass (as a percentage of body weight), skeletal muscle mass (as a percentage of fat-free mass), and body cell mass (BCM), which represents metabolically active tissues. The body cell mass index (BCMI), obtained by normalizing BCM for

height, and the appendicular skeletal muscle mass index (ASMMI), which quantifies skeletal muscle mass in the limbs, will also be calculated.

Additionally, body composition will be assessed using computed tomography (CT) scans. As part of preoperative staging and perioperative care, patients will already have a CT scan before time of enrollment and will then perform a further CT scan at preoperative evaluation. CT scan protocol will include unenhanced, arterial, and portal venous axial scans of the abdomen before and after intravenous nonionic iodine contrast medium injection. Total abdominal muscle area (TAMA), visceral fat area (VFA), subcutaneous fat area, and intramuscular fat infiltration will be identified and quantified by predetermined HU thresholds at the level of the third lumbar vertebra (L3) using an automated deep learning-based pipeline (Data Analysis Facilitation Suite (DAFS), Voronoi Health Analytic®) that performs automated image segmentation and tissue area quantification. Areas will be quantified in cm^2 and normalized according to patient height. Hepatic steatosis will be assessed by sampling three standardized regions of interest (liver segments V, VI, and VIII) on unenhanced scans and defined as mean liver density lower than 45 HU according to previous research.

Generic health-related quality of life will be measured using Patient Reported Outcome Measure Information System (PROMIS) 29 + 2 and collected at baseline, preoperatively, and at 30, 60, 90, 180, and 365 days after surgery. PROMIS 29 + 2 Profile v2.1 is a validated questionnaire designed to measure self-reported physical, mental, and social health and well-being [24]. It contains 29 questions covering seven domains of health, including depression, anxiety, physical function, pain interference, fatigue, sleep disturbance, and ability to participate in social roles and activities. For each domain, the minimal important difference is equal to 2.7 points. PROMIS-29 will be summarized into a physical and mental health summary score, with a minimal important difference of 2.3 points [25].

Disease-specific health-related quality of life will be measured using the EORTC-QLQ C30 and PAN-26 questionnaires and collected at baseline, preoperatively, and at 30, 60, 90, 180, and 365 days after surgery. EORTC QLQ C-30 is a generic core questionnaire that measures health-related quality of life in patients with any cancer. It comprises a total of 30 items on 15 quality of life scales. The minimal important difference is equal to 10 points [26]. EORTC QLQ PAN-26 is the pancreatic cancer module that supplements the EORTC QLQ-C30 [27]. The module comprises 26 questions that share the 4-level ordinal response options with QLQ-C30. The QLQ-PAN26 includes 7 multi-item scales: pancreatic pain, digestive symptoms, altered bowel habits, hepatic, body image, satisfaction with healthcare, and sexual dysfunction; the module includes 10 single-item scales: abdominal bloating, taste changes, indigestion, flatulence, weight loss, limb weakness, dry mouth, trouble from treatment side effects, worry about future health, and limits on activity planning.

Patient-reported anxiety and depression will be measured using the Hospital Anxiety and Depression Scale (HADS) questionnaire and collected at baseline, preoperatively, and at 30, 60, and 90 days after surgery. It comprises seven questions for anxiety and seven questions for depression, and the two domains are scored separately. It has been validated in many languages, countries, and settings [28].

Patient engagement and activation will be measured using the Patient Activation Measure (PAM)-13, a 13-item questionnaire measuring patients' self-reported knowledge, motivation, and skills for self-management. The Italian version of the questionnaire has been validated in a sample of chronically ill patients. The minimal important difference is 5 points [29].

Economic evaluations Hospital-related costs will be collected for all patients included in the study over a 90-day postoperative period. These costs include expenses directly associated with patient care, such as the prehabilitation program (staff time, facilities, equipment, and sessions), surgical procedures, length of hospital stay, management of complications, remissions, and follow-up visits within 90 days after surgery. Comparing hospital costs between patients receiving prehabilitation and those undergoing standard care will provide valuable insight into the economic impact of prehabilitation on healthcare resource utilization during the early postoperative period.

A cost-utility analysis will be conducted to evaluate the economic value of the prehabilitation program compared to standard care over the 90-day postoperative period. Health-related quality of life (HRQoL) will be assessed using the PROMIS-29 + 2, which provides the PROPr (Patient-Reported Outcomes Measurement Information System Preference score), a preference-based utility measure derived from PROMIS item responses. These utility values quantify the quality of health on a scale where 0 represents death and 1 represents perfect health. By combining these utility scores with the length of the follow-up period, quality-adjusted life years (QALYs) can be estimated, reflecting both the quantity and quality of life experienced by each patient during this timeframe. This approach allows for capturing the changes in patients' health status due to the intervention or standard care. Hospital costs incurred during the same 90-day

period, including all healthcare resource use such as hospital stay, procedures, complications management, and prehabilitation costs, will be integrated into the analysis. The incremental cost-effectiveness ratio (ICER) will then be calculated by dividing the difference in average costs between the two groups by the difference in average QALYs gained. The ICER represents the additional cost required to gain one additional quality-adjusted life year through prehabilitation compared to standard care, providing a summary measure of the intervention's cost-effectiveness.

Exploratory and explanatory outcomes

Exploratory and explanatory outcomes included (1) immune system response by evaluating levels of circulating pro-inflammatory cytokines, hormones, and cancer cachexia-related factors and (2) overall activity of the autonomic nervous system and heart rate variability (HRV).

- *Pro-inflammatory cytokines level*, including circulating level of tumor necrosis factor alpha (TNF-alpha), interleukin 1 (IL-1), IL-6, IL-8, IL-10, interferon gamma (IFN-gamma), and macrophage inflammatory protein alpha (MIP-1alpha), will be assessed at baseline and 1 day before surgery by multiplex immunoassays and compared between groups [30].
- *Cancer cachexia-related factors*, such as activin A, carnosine dipeptidase-1, growth differentiation factor-8 (myostatin) and -15, and zinc-alpha2-glycoprotein, will be assessed using enzyme-linked immunosorbent assay (ELISA) at baseline and 1 day before surgery [31, 32].
- The overall activity of the *autonomic nervous system and HRV* will be analyzed using the photoplethysmography (PPG) stress flow [33], which is the physiological oscillation in the time interval between heartbeats and enables the independent measurement of the parasympathetic components of the autonomic nervous system. The exam takes a few minutes and allows the study and direct monitoring of all functions of the autonomic nervous system and the related process of biofeedback. Furthermore, it enables the diagnosis of chronic inflammatory and stress-related diseases and disorders, psychological expressions and emotions analysis, and longevity and psychophysical performance [34].

Harms {17}

The multimodal prehabilitation program is considered a low-risk, non-pharmacological intervention. Potential adverse events may include transient musculoskeletal discomfort, fatigue, or minor injuries related to physical exercise. All adverse events occurring during the study period will be recorded and monitored by the study team. Exercise sessions will be supervised by qualified physiotherapists, and the intervention will be tailored and adapted according to individual clinical conditions to minimize risks. Any adverse event leading to modification or discontinuation of the intervention will be documented. Serious adverse events will be managed according to institutional clinical practice and reported to the appropriate oversight bodies as required.

Participant timeline {18}

All patients will be evaluated at baseline (T0) and the day before surgery (T1) during in-person visits at the clinic. Follow-up will be scheduled for 30 days (T2), 60 days (T3), 90 days (T4), 180 days (T5), and 365 days (T6) after surgery. The assessment plan and estimated time to complete the assessments are shown in Figs. 2 and 3.

At T0, patients will undergo a baseline evaluation, including patient medical history including comorbidities, the presence of signs or symptoms and frailty assessment using Fried's criteria, assessment of functional capacity, nutritional status, body composition, autonomic nervous system activity and heart rate variability, health-related quality of life, level of patient activation, and blood sampling (10 ml, two Vacutainers per 2.5–3.5 ml and one Vacutainer per 6 ml). A part of the blood sample for each patient will also be stored at −80 °C for future analysis. Blood samples will be stored in the biobank of the hospital.

At T1, all evaluations conducted at T0 will be repeated. At T2, T3, and T4, patients will repeat the T0/T1 assessment, excluding blood sampling and PAM-13, during in-person visits at the clinic. At T5 and T6, patients will complete only the following health-related quality-of-life questionnaires: EORTC QLQ-C30, PAN-26, PROMIS-29+2, and DASI. These assessments will be completed in person, via telephone, or by email, according to patient preference.

At T1, patient satisfaction will be measured using a 5-point Likert scale. In addition, patient adherence to the program will be evaluated. Adherence will be defined as completing at least 80% of the scheduled sessions. For patients who do not meet this adherence threshold, barriers to adherence will be identified and analyzed and then categorized according to the COM-B model, which considers Capability, Opportunity, and Motivation factors [35].

Sample size {19}

The sample size is calculated considering the primary aim of the study: the reduction of postoperative

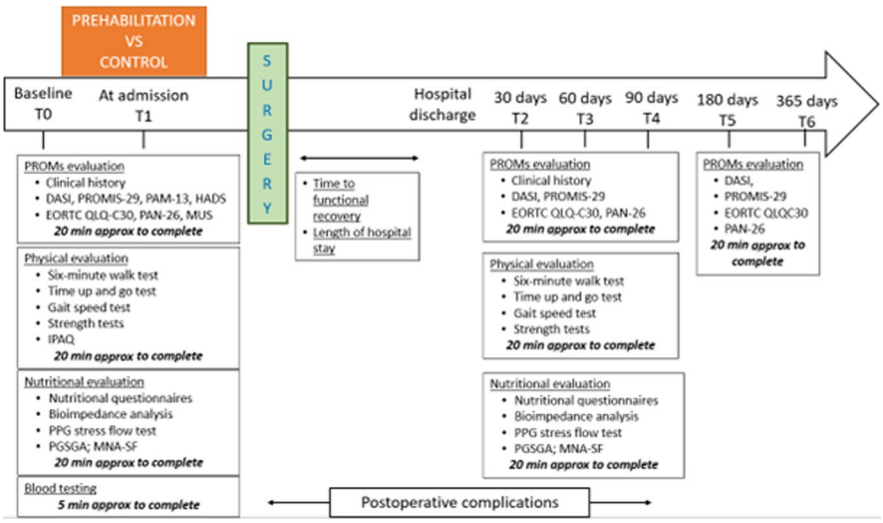

Fig. 2 Assessment plan and time

		STUDY PERIOD							
	Enrolment	Allocation	Post-allocation						Close-out
TIMEPOINT**	$-t_1$	0	t_1	t_2	t_3 (30 day)	t_4 (60 day)	t_5 (90 day)	t_6 (180 day)	t_7 (360 day)
ENROLMENT:									
Eligibility screen	X								
Informed consent	X								
Allocation		X							
INTERVENTIONS:									
Prehabilitation			←	—	→				
Surgery				←	→				
ASSESSMENTS:									
Baseline variables	X	X	X						
Preoperative variables				X					
Primary Outcome						X			
Physical Evaluation			X	X	X	X	X		
Nutritional Evaluation			X	X	X	X	X		
Patient-reported outcome measures			X	X	X	X	X	X	X
Blood Testing	X	X	X	X					

*Recommended content can be displayed using various schematic formats. See SPIRIT 2013 Explanation and Elaboration for examples from protocols.
**List specific timepoints in this row.

Fig. 3 Schedule of enrollment, interventions, and assessments. *Recommended content can be displayed using various schematic formats. See SPIRIT 2013 Explanation and Elaboration for examples from protocols. **List specific timepoints in this row

complications as determined with the CCI® score at 90 days after surgery. In our preliminary data on the PDAC surgical population, the CCI® has a mean ± SD equal to 21 ± 16, and a target reduction is 30%. We consider a critical value alpha equal to 0.05 and a statistical power of 80% for a two-sided test. Accounting for a 15% dropout rate, the required sample size was 238 patients, 119 for each arm over a 90-day postoperative period.

Recruitment {20}

Eligible patients will be identified during outpatient surgical clinics and multidisciplinary tumor board meetings at the study center. Consecutive eligible patients scheduled for pancreatic surgery, either upfront or after neoadjuvant chemotherapy, will be screened for inclusion. Recruitment will be supported by close collaboration among surgeons, oncologists, anesthesiologists, and the prehabilitation team. Regular monitoring of recruitment rates will be performed, and enrollment strategies will be adjusted as needed to ensure achievement of the target sample size.

Assignment of interventions: randomization

Sequence generation: who will generate the sequence {21a}

The random allocation sequence will be generated by an independent researcher not involved in participant recruitment, intervention delivery, or outcome assessment, using the RandomizeR package in R.

Sequence generation: type of randomization {21b}

Participants will be randomized in a 1:1 ratio using restricted randomization with permuted blocks of random sizes generated in RandomizeR (R). Randomization will be stratified by neoadjuvant chemotherapy (yes vs no) and tumor location (proximal vs distal), where proximal includes periampullary or pancreatic head–neck tumors.

Allocation concealment mechanism {22}

Allocation concealment will be ensured using opaque, sequentially numbered, sealed envelopes prepared in advance by an independent researcher. The randomization code will not be released until the participant has been recruited, after completion of baseline assessments and signed informed consent.

Implementation {23}

Participants will be enrolled by the study team. The allocation sequence will be generated and safeguarded by an independent researcher; personnel involved in recruitment and intervention assignment will not have access to the randomization list. Group assignment will be revealed only after consent and baseline measures, by opening the next sequential sealed envelope.

Assignment of interventions: blinding

Who will be blinded {24a}

Due to the nature of the intervention, participants and care providers will not be blinded. Outcome assessors and the statistician will be blinded to group allocation.

How will be blinding be achieved {24b}

Blinding will be maintained by ensuring that outcome assessments and data analysis are performed by personnel unaware of treatment allocation. To minimize performance and expectation bias, participants will be informed that the study compares two strategies (prehabilitation and usual care), both intended to optimize preoperative condition, and neither will be presented as superior. Participants in the control arm will receive general physical activity and nutritional recommendations.

Procedure for unblinding if needed {24c}

Unblinding of outcome assessors or the statistician is not anticipated. If unblinding becomes necessary for safety or clinical reasons, it will be documented and limited to the minimum information required, following authorization by the principal investigator.

Data collection and management

Plans for assessment and collection of outcomes {25a}

Outcome data will be collected using standardized procedures and validated instruments according to the predefined assessment schedule. Postoperative complications will be assessed by trained clinicians and graded using the Clavien–Dindo classification and the Comprehensive Complication Index. Functional capacity will be evaluated using performance-based tests administered by trained assessors, while nutritional status, body composition, and laboratory outcomes will be measured using standardized clinical and imaging protocols. Patient-reported outcomes will be collected in paper form using validated questionnaires administered in accordance with developers' guidelines. Study personnel involved in outcome assessment will be trained prior to study initiation, and standardized operating procedures will be used to promote consistency and data quality. Data will be recorded on structured case report forms included in the study protocol.

Plans to promote participant retention and complete follow-up {25b}

Participant retention will be promoted through clear communication regarding study procedures, scheduled

follow-up visits aligned with routine clinical care, and flexible options for questionnaire completion (in-person, telephone, or electronic formats). Reminder contacts will be used to encourage attendance at follow-up assessments. Participants who discontinue or deviate from the intervention will be encouraged to complete follow-up assessments whenever possible, and outcome data routinely collected as part of standard clinical care will be recorded for these participants.

Data management {26}

Study data will be entered into a secure, password-protected electronic database accessible only to authorized study personnel. Data entry will follow predefined coding rules, with built-in range and consistency checks to minimize errors. Regular data monitoring and quality control procedures will be performed, including verification of source data and resolution of discrepancies. All data will be stored in accordance with institutional policies and applicable data protection regulations.

Confidentiality {33}

Personal information of potential and enrolled participants will be collected and managed in accordance with institutional policies and applicable data protection regulations. Each participant will be assigned a unique study identification code, and identifiable information will be stored separately from study data. Access to identifiable data will be restricted to authorized study personnel only. De-identified data may be used for analysis, reporting, and data sharing as specified in the protocol, ensuring participant confidentiality before, during, and after the trial.

Statistical methods

Statistical methods for primary and secondary outcomes {27a}

Continuous variables will be summarized using either median and interquartile range (IQR) or mean ± standard deviation (SD), depending on data distribution. Categorical variables will be reported as frequencies and percentages. The between-group difference in the primary outcome will be assessed using a linear regression model after applying a log(+1) transformation to the 90-day Comprehensive Complication Index (CCI®), adjusting for relevant confounders. Continuous secondary outcomes will be analyzed using appropriate generalized linear models, while binary outcomes will be evaluated using logistic regression to estimate odds ratios (ORs) with 95% confidence intervals (CIs). To account for the repeated measures design, linear mixed-effects models will be employed, incorporating treatment group and time as fixed effects and patient ID as a random effect. This model will estimate the mean differences in outcomes over time between groups. The effect of the intervention will be reported as adjusted least-square mean differences along with corresponding 95% CIs. Patient satisfaction will be described using means and SDs for continuous variables (or medians and IQRs for skewed distributions) and frequencies and percentages for categorical data. Barriers to adherence among participants who did not meet the 80% session completion threshold will be transcribed and categorized according to the COM-B model (Capability, Opportunity, Motivation). Statistical significance will be set at a p-value < 0.05. All analyses will be conducted using STATA® version 18 (StataCorp, College Station, TX, USA).

Who will be included in each analysis {27b}

All analyses will follow the intention-to-treat principle. A sensitivity analysis will be conducted to assess the impact of missing data on the primary outcome. A per-protocol analysis will also be performed, including only patients who completed at least 80% of the prehabilitation sessions and excluding those lost to follow-up or who withdrew.

How missing data will be handled in the analysis {27c}

To minimize attrition bias, missing data will be handled using multiple imputation with chained equations and predictive mean matching. A sensitivity analysis will be conducted to assess the impact of missing data on the primary outcome.

Methods for additional analyses (e.g., subgroup analyses) {27d}

A pre-specified subgroup analysis will explore whether the effect of prehabilitation versus standard care on the primary outcome and functional capacity differs across the following patient subgroups:

1. Frail versus non-frail, defined by Fried Frailty Score Index (FFSI ≥ 2 vs < 2)
2. Neoadjuvant therapy versus upfront surgery
3. Proximal versus distal pancreatectomy
4. Elderly versus younger patients, defined as > 75 years vs ≤ 75 years
5. Low versus high baseline functional capacity, based on 6-min walk distance (6MWD < 400 m vs ≥ 400 m) or Duke Activity Status Index (DASI < 34 vs ≥ 34)
6. High versus low psychological distress, defined by HADS subscale scores (≥ 8 vs < 8)

7. Nutritional status, defined by PG-SGA scores (< 4 well-nourished, 4–8 moderately malnourished, > 8 severely malnourished)
8. Sarcopenic versus non-sarcopenic, defined by BIVA-derived ASMMI values (< 7.0 kg/m^2 in men and < 5.7 kg/m^2 in women) and CT scan-derived skeletal muscle areas
9. Overweight versus non-overweight patients, defined by BMI values (> 24.99 kg/m^2)
10. High risk of postoperative pancreatic fistula versus low risk, as defined by preoperative CT scan imaging

Interim analyses {28b}

No formal interim analyses are planned for this trial.

Protocol and statistical analysis plan {5}

The statistical analysis plan is fully integrated within the Statistical Methods section of the protocol and describes all planned primary and secondary analyses, including handling of missing data and subgroup analyses. No separate standalone statistical analysis plan is planned; any substantial modifications will be documented and reported prior to database lock.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {3d}

The trial will be coordinated by the study center, which will be responsible for day-to-day trial management, including participant recruitment, intervention delivery, data collection, and regulatory compliance. A trial steering committee composed of senior clinicians and investigators involved in the study design will provide overall scientific oversight. The coordinating team will meet regularly to monitor recruitment, protocol adherence, and operational issues, while the steering committee will meet periodically to review trial progress and address any major issues arising during the study. of staff.

Composition of the data monitoring committee and its role and reporting structure {28a}

Given the low-risk, non-pharmacological nature of the intervention, no independent data monitoring committee has been established. Trial oversight with respect to safety and data quality will be performed by IRCCS Ospedale San Raffaele Institutional Clinical Trial Center, the principal investigator, and the study team. The sponsor and funder will have no role in data monitoring and data analysis.

Frequency and plans for auditing trial conduct {29}

Trial conduct will be monitored through regular internal review by the coordinating center (IRCCS Ospedale San Raffaele Clinical Trial Center) in accordance with institutional policies. Data completeness, protocol adherence, and safety reporting will be periodically reviewed. Formal external auditing is not planned; however, an interim report regarding trial recruitment rates will be sent to the Ministry of Health (support received from competitive grant funding).

Protocol amendments {31}

Any substantial protocol modifications will be communicated to the relevant ethics committees, trial registries, and institutional bodies in accordance with regulatory requirements. Amendments will be implemented only after approval and will be documented and reported transparently.

Dissemination policy {8}

The results of the trial will be disseminated through publication in peer-reviewed scientific journals and presentation at national and international conferences. Trial results will also be reported in the relevant clinical trial registry. Participants will be informed of the study results upon request. Dissemination will adhere to established authorship and reporting guidelines.

Discussion

Patients with pancreatic cancer represent a high-risk population for postoperative complications and prolonged hospital stay following pancreatectomy. They can present with a reduced preoperative functional capacity due to sarcopenia, malnutrition, and cachexia, reflecting a tumor-induced catabolic state and pancreatic insufficiency, which leads to malabsorption and weight loss [4, 7]. These factors leave patients inadequately prepared to withstand the surgical stress of a major surgical procedure such as pancreatectomy, ultimately contributing to poor surgical outcomes [36, 37]. Interventions able to enhance surgical outcomes in this high-risk population are needed. This randomized clinical trial will address knowledge gaps about the effect of multimodal prehabilitation on postoperative morbidity in patients with pancreatic cancer who will undergo pancreatectomy.

Multimodal prehabilitation has been shown to be effective in improving preoperative functional capacity, with a reduced incidence of postoperative surgical complications in patients undergoing colorectal surgery [12]. This intervention relies on a multidisciplinary team of experts

who can tailor the program to the patient's needs for at least 4 weeks before surgery. It should include a personalized and balanced approach that combines optimal nutritional support (caloric and protein intake) with both aerobic and resistance training [38]. This strategy aims to shift the patient's metabolic state from catabolic to anabolic and enhance overall functional capacity [39]. Prehabilitation may also modulate systemic inflammation by reducing the production of proinflammatory cytokines, such as interleukins, TNF-alpha, and interferon-gamma, thereby potentially decreasing the risk of sepsis and mortality. Additionally, it may promote favorable organ remodeling, attenuate skeletal muscle loss, and improve cardiovascular and immune function [40].

Despite promising data from other surgical populations, limited and underpowered studies have assessed the impact of multimodal prehabilitation in patients undergoing pancreatectomy [13, 14]. Moreover, existing studies often suffer from methodological limitations and bias. This trial is adequately powered to detect meaningful changes in postoperative outcomes, specifically the 90-day CCI, and incorporates rigorous methods for randomization and outcome collection. Furthermore, prehabilitation could extend its role beyond the preoperative period, potentially offering benefits during neoadjuvant or adjuvant chemotherapy. This phase often adds to the physiological burden through reduced nutritional intake, impaired mobility, immunosuppression, and systemic inflammation. Implementing prehabilitation during chemotherapy could help preserve functional capacity, enabling patients to reach better treatment outcomes.

Limitations

Blinding of participants is not feasible in this trial, increasing the risk of selection bias. To assess and minimize this risk, baseline demographic and clinical characteristics will be compared between study arms to ensure balance. Similarly, blinding of inhospital caregivers is not possible, which may introduce performance bias through differences in postoperative care. However, this risk is mitigated by the application of a standardized postoperative management protocol aligned with ERAS Society guidelines, which is uniformly applied across both study groups. Additionally, this trial is expected to have a low recruitment rate with around 30% of acceptance rate, primarily because a large proportion of eligible patients (60%) reside outside the region and are therefore less likely to participate in the supervised inhospital prehabilitation program. This limitation introduces a potential risk of selection bias. To mitigate this concern, we are prospectively collecting preoperative clinical, nutritional, and functional data from all patients who meet the inclusion criteria but decline participation. This will allow for a descriptive comparison between enrolled and non-enrolled patients, helping to assess the representativeness of the study population.

Outcome assessors were also not blinded, raising the potential for detection bias. Nonetheless, this risk is considered minimal given the nature of the primary outcome. The CCI® is an objective measure derived from prospectively collected clinical data, based on the number and severity of all complications occurring within 90 days after surgery.

Deviations from the intended intervention may occur, particularly due to potential low adherence to the prehabilitation program. To address this, regular compliance support will be provided to participants in the intervention group. A per-protocol analysis will complement the intention-to-treat analysis to explore the efficacy of the intervention among patients with high adherence.

There is also a risk that some randomized participants may become ineligible for surgery following completion of the prehabilitation phase, either due to the discovery of unresectable disease or intraoperative findings of metastases. These scenarios could impact the interpretation of treatment effects. Nevertheless, they reflect real-world clinical practice and will be documented and reported transparently to support robust interpretation of study outcomes.

Missing data are expected to be minimal due to the objective nature of the primary outcome. However, any missing outcome data may still contribute to attrition bias. To address this, multiple imputation using chained equations will be applied, and a sensitivity analysis will be conducted to assess the robustness of the primary findings.

Trial status

- *Protocol version number and date*: Protocol 1.2, 03/05/2024
- *Protocol ID*: GR-2021-12374985
- *Overall recruitment status*: Recruiting
- *Study start date*: July 14, 2023, actual
- *Primary completion date*: December 31, 2026, anticipated
- *Study completion date*: December 31, 2027, anticipated

Abbreviations

ASA	American Society of Anesthesiologists
ASMMI	Appendicular Skeletal Muscle Mass Index
BCM	Body cell mass
BCMI	Body Cell Mass Index
BIV	Bioimpedance vector analysis
CCI	Comprehensive Complication Index
CT	Computed tomography

DASI	Duke Activity Status Index
ECW	Extracellular water
ERAS	Enhanced Recovery After Surgery
FFSI	Fried Frailty Score Index
HADS	Hospital Anxiety and Depression Scale
HIIT	High-intensity interval training
HRQoL	Health-related quality of life
HRV	Heart rate variability
ICER	Incremental cost-effectiveness ratio
IPAQ	International Physical Activity Questionnaire
LOS	Length of stay
MET	Metabolic equivalent of task
MICT	Moderate-intensity continuous training
MNA	Mini nutritional assessment
PAM	Patient activation measure
PDAC	Pancreatic ductal adenocarcinoma
PhA	Phase angle
PGSGA	Patient-Generated Subjective Global Assessment
PPG	Photoplethysmography
PROMIS	Patient-Reported Outcome Measure Information System
PROPr	Patient-Reported Outcomes Measurement Information System Preference Score
QALYs	Quality-adjusted life years
RCT	Randomized controlled trial
TAMA	Total abdominal muscle area
TFR	Time to functional recovery
TUG	Timed Up and Go Test
VFA	Visceral fat area
6MWT	Six-minute walking test

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-026-09467-z.

Additional file 1. SPIRIT 2025 checklist of items to address in a randomized trial protocol.

Authors' contributions {3a}

NP is the principal investigator; he conceived the study and led the development of the proposal and study protocol. FF contributed to the study design and proposal preparation, and will be responsible for statistical analysis and future manuscript development. MA, BB, LF, GC, GG, MM, SG, VDM, and AT were involved in patient selection, enrollment, and randomization. They are actively engaged in delivering the intervention, serving as nutritionists, physiotherapists, or psychologists. GG also supervised the clinical aspects of the intervention. AD, DP, and FDC will contribute to data collection by reviewing CT scans and assessing radiological measures of body composition. MF provided overall project supervision. All authors will contribute to the dissemination of trial findings.

Funding {7a}

The work was supported by Ricerca Finalizzata Ministero della Salute — Giovani Ricercatori "Change-promoting"/GR-2021-12374985 (principal investigator: N. P.).

Data availability {6}

All trial investigators will have access to the final trial dataset. In accordance with data protection regulations, individual de-identified individual participant data will be shared with other researchers upon reasonable and justified request.

Declarations

Ethics approval and consent to participate {30}

Ethical approval has been obtained on December 14, 2022, from our institutional ethics review board (136/INT/2022). Institutional authorization for clinical trial initiation was granted on February 9, 2023. Each participant will sign an informed consent form, with the opportunity to read and ask questions about the PIPS trial. Any modifications to the protocol will require formal amendment and approval from the hospital's CTC and regional ethics committee. Each participant will have the right to withdraw from the study at any time. Trial auditing will be conducted every 6 months.

Consent for publication

Not applicable. No details, images, or videos relating to an individual person are published.

Competing interests {7b}

The authors declare that they have no competing interests.

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