PROPER—PRehabilitatiOn Plus Enhanced Recovery after surgery versus enhanced recovery after surgery in gynecologic oncology: a randomized clinical trial

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ABSTRACT

Background Prehabilitation is a process that occurs before surgery and aims to improve patient functional capacity and enhance surgical recovery. This process includes medical, nutritional, physical, and psychological interventions that may reduce the duration of hospital stay and provide postoperative physical benefits.

Primary Objective To evaluate the impact of a prehabilitation program on postoperative recovery time for patients who will undergo gynecological surgery following the Enhanced Recovery After Surgery (ERAS) guidelines.

Study Hypothesis A multidisciplinary, preoperative prehabilitation program for patients who will undergo gynecological surgery leads to a reduction in the length of hospital stay and improves patient functional capacity.

Trial Design Prospective, interventionist, and randomized controlled trial in a 1:1 ratio, open to multidisciplinary team and patients, blinded to surgeons and anesthesiologists. The control group will undergo ERAS standard preoperative care while the intervention group will have ERAS standard preoperative care plus prehabilitation.

Major Inclusion Criteria Patients scheduled to undergo gynecologic surgery performed by laparotomy with a preoperative schedule that allows prehabilitation intervention for 2 to 3 weeks.

Primary Endpoint To compare time between surgery and the day the patient is ready for discharge in patients who underwent the prehabilitation process versus those who did not. Readiness for discharge is defined as the ability to take care of one's-self, to walk alone, and to ingest at least 75% of daily recommended calorie intake.

Sample Size 194 participants

Estimated Dates for Completing Accrual and Presenting Results At present, 30 patients have been recruited. Accrual should be completed by 2023–24.

Trial Registration The study is approved by the IBCC – São Camilo Oncologia ethics committee (reference number 4.256.553) and is registered at clinicaltrials.gov (NCT04596800).

INTRODUCTION

Diagnosis of a gynecological cancer and its treatment may be a cause of significant distress and may negatively impact patients' quality of life. Patients diagnosed with gynecological cancer are more likely to suffer loss of functional capacity due to physical and psychological effects of the disease. In addition, a poor preoperative physical status at the time of surgery is associated with increased patient morbidity and mortality.[1 2] A higher number of postoperative complications, prolonged hospital admission, a greater number of readmissions, higher costs, and a negative impact on patient functional recovery may be observed in women with decreased physical functioning preoperatively.[3 4]

Given this scenario, there has been a growing interest in prehabilitation programs for patients with cancer who will undergo surgery. Such programs are multidisciplinary and address modifiable risk factors that can affect treatment outcomes.[5] Prehabilitation programs are typically based on the pillars of physical, nutritional, and psychological interventions.[3 6–8] Few studies have investigated interventions incorporating all three main pillars of prehabilitation in gynecological oncology.

We hypothesize that a multimodal program in the preoperative period for patients with gynecological cancer will lead to a reduction in complications and length of hospital stay and also will improve functional capacity.

METHODS

Trial Design

The PROPER trial (NCT04596800) is a prospective, interventional, randomized-controlled study, open-label to patients and to a multidisciplinary team (physiotherapists, nutritionists, and psychologists) but blinded to surgeons and anesthesiologists (Figure 1). It aims to test the effectiveness of a multidisciplinary prehabilitation program on patients who will undergo gynecological surgery by laparotomy.

The multidisciplinary supervised prehabilitation program consists of physical therapy, nutritional counseling, and psychological assistance. Sessions will be given to the intervention group for 2–3

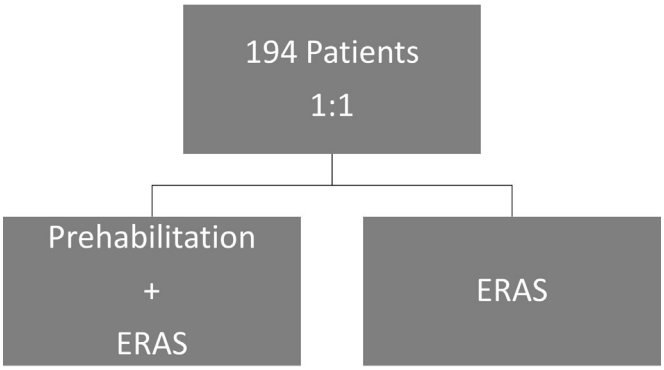

Figure 1 Study flowchart. ERAS, Enhanced Recovery After Surgery.

weeks prior to surgery. For all patients (prehabilitation and control cohorts) Enhanced Recovery After Surgery (ERAS) guidelines will be applied preoperatively, peri-operatively, and postoperatively.[9–11] Patients will be evaluated by a multidisciplinary team before prehabilitation, on the week before surgery, and on postoperative days 30 and 60. Details on patient intervention and evaluation are described in Table 1. Inclusion and exclusion criteria are detailed in Box 1.

This study has no funding and was designed to be developed in a single institution, the Instituto Brasileiro de Controle do Cancer (IBCC) – São Camilo Oncologia, a philanthropic cancer hospital located in the city of São Paulo, Brazil.

Primary Endpoint

The primary endpoint is to compare postoperative recovery time between patients who participated in a prehabilitation program and those who did not. Final day of recovery is defined as the day of discharge when patients have the ability to walk alone, to ingest at least 75% of the daily caloric needs, and have the capacity for self care.

Secondary endpoints include evaluation of compliance to the ERAS guidelines and analysis of postoperative complication rates, rates of intensive care unit admissions, and health-related quality of life, and changes in functional capacity, muscle strength, body mass index, and patient anxiety and depression.

Box 1 Inclusion and exclusion criteria

Inclusion criteria

- Gynecological surgery by laparotomy
- Preoperative schedule that allows at least 2–3 weeks for the prehabilitation intervention
- Eastern Cooperative Oncology Group Performance Status of at least 2 (ECOG ≤2)

Exclusion criteria

- Significant comorbidities or limitation of locomotion that prohibit the patient to perform physical exercise
- Emergency surgeries
- Surgeries by minimally invasive approach (laparoscopy or robotics)
- Vulvectomies or minor surgeries like conizations without abdominal approach
- Surgeries performed together with other medical specialties, in which the gynecology team is not primarily responsible for postoperative care
- Surgeries performed after 21 days of the prehabilitation program

Sample Size

A pilot study was performed between 2019 and 2020. Sample size for the PROPER study was determined by the greatest variation in recovery time between the groups of the patients in the pilot study, which was 2.27 days (SD 2.27 days). For a 95% confidence interval and an 80% power analysis, the sample needed to find a 1 day difference between groups is 81 patients in each group. Considering a 20% sample loss, 97 patients would be needed in each arm of the study, for a total of 194 recruited patients. To ensure patient safety and integrity, a data monitoring committee was established.

Randomization and Blinding

Elegible patients will be randomized to one of the two arms of the study, in a 1:1 ratio. The control group will undergo ERAS standard preoperative care while the intervention group will have ERAS standard preoperative care plus prehabilitation. Randomization will be performed through the website www.randomization.com.

Study randomization will be blinded to surgeons and anesthesiologists. Patients will be instructed not to reveal the group to which they are allocated. If the medical team, for any reason, becomes aware of

Table 1 Multidisciplinary prehabilitation program with duration of 2 to 3 weeks

Multidisciplinary team	Frequency	Intervention	Evaluation
Physiotherapy	6–9 sessions	▶ Aerobic, inspiratory and stretching exercises ▶ Muscle strengthening ▶ 135 min per week in 3 sessions	▶ 6-minute walk test ▶ Blood pressure, heart rate, and oxygen saturation during the test
Nutrition	Patient food diary	▶ Hypercaloric and hyperprotein nutritional supplement, or whey protein 1 or 2x/day if indicated ▶ Nutritional counseling	▶ Handgrip strength test ▶ Body mass index ▶ Bioelectric impedance analysis ▶ Muscle quality and thickness by ultrasound imaging
Psychology	2–6 sessions	▶ Psychological counseling ▶ Image-based exercises and visualization for relaxation ▶ Breathing exercises	▶ EORTC QLQ-C30 ▶ Hospital Anxiety and Depression Scale

*EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer: Quality of Life Questionnaire Core 30.

the arm in which a patient was allocated, this event will be reported. However, the patient in question will not be excluded from the study.

Statistical Methods

All investigations will be performed on an intention- to-treat and per-protocol analysis. Qualitative characteristics will be described using absolute and relative frequencies and associates with the use of χ^2 tests or exact tests. Quantitative characteristics will be described using mean, SD, median, minimum, and maximum and compared between groups using Student's t-test or Mann-Whitney test. Analyses will be followed by multiple Bonferroni comparisons when necessary.

Analyses will be performed using Statistical Package for the Social Sciences (SPSS) for Windows version 22.0 software, and tests will be performed with a significance level of 5% ($p<0.05$).

DISCUSSION

This trial was designed to evaluate the impact of prehabilitation in patients with gynecological cancer who will undergo surgery by laparotomy. Loss of muscular mass, malnutrition, psychological distress, and frailty are major concerns in patients with cancer and are associated with longer hospital stay, readmissions, complications, and prolonged recovery.[3] We expect that a prehabilitation program will enhance postoperative recovery, provide better quality of life, and reduce postoperative complications, benefiting a significant number of patients.[12]

Prehabilitation programs are consistent with the principles of ERAS and may represent an extension of existing guidelines for the recovery of functional capacity in the postoperative period.[3 6] Even though compliance with ERAS, data collection, and extra work for the multidisciplinary team are possibly major challenges,[13 14] we presume that implementing both ERAS and the prehabilitation program may reduce hospital stay, reduce costs, and spread the culture of an evidence-based protocol in Latin America and around the world.

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