

# Effects of A Preoperative Exercise Training Program on Postoperative Pulmonary Complications and Exercise Capacity In Patients With Abdominal Cancer: A Systematic Review Protocol of Randomized Controlled Trials

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## Protocol

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# Abstract

## Background

Abdominal cancer surgeries have a high incidence of postoperative complications. One strategy to prevent postoperative complications is preoperative exercise training. There are no systematic reviews that have compared the effects of preoperative exercise training programs of different length, frequency and duration on pre and postoperative clinical outcomes as well as on length of hospital stay (LOS) and in-hospital and late mortality in people with abdominal cancer.

## Methods

Searches for randomised controlled trials (RCTs) of preoperative exercise training for people undergoing major surgery for abdominal cancer will be conducted in Pubmed, EMBASE, PEDro (Physiotherapy Evidence Database) and the Cochrane Library. There will be no restrictions on the language or date of publication in the search. The primary outcomes of the systematic review will be incidence of postoperative pulmonary complications as well as post-intervention and postoperative exercise capacity. The risk of bias of included RCTs will be assessed using the PEDro scale. The quality of evidence will be rated using the GRADE system (Grading of Recommendations Assessment, Development and Evaluation). Subgroup analyzes will be conducted based on: intervention performed with or without supervision; types of exercises; and frequency and duration of the intervention.

## Discussion

Our hypothesis is that preoperative exercise training will reduce the incidence of postoperative pulmonary complications in people undergoing major surgery for abdominal cancer by improving their preoperative exercise capacity. We will also explore the effects of the program on LOS and mortality.

## Systematic review registration:

This systematic review protocol was registered with PROSPERO (Prospective International Register of Systematic Reviews) (number CRD42020199765).

## Background

Surgical procedures may cause both physiological and systemic changes in the patient, such as tissue trauma, immobility, psychological disorders and reduced quality of life.<sup>1</sup> In cases of major abdominal surgery, it is known that 35% of patients have postoperative complications.<sup>2</sup> Specifically, major surgery for abdominal cancer are complex procedures that have a high tax of incidence of postoperative

complications and mortality.<sup>3</sup> Of note, the preoperative exercise capacity of cancer patients, which can be often reduced, is related to both the occurrence of postoperative complications and poorer prognosis.<sup>4</sup> A reduced exercise capacity preoperatively may impair the patient's physical and mental ability to adapt to and manage the effects of both the surgical procedure and hospitalization,<sup>5</sup> increasing the likelihood of postoperative complications, potentially increasing length of hospital stay and reducing patient's quality of life.<sup>5</sup> Therefore, the implementation of strategies to improve preoperative clinical condition (e.g. exercise capacity) may play an important role on reducing the incidence of postoperative complications and the negative implications of such complications.<sup>6</sup>

A potentially useful strategy to prevent postoperative complications is preoperative exercise training.<sup>7</sup> Fitter people seem to have greater capacity to deal with the demands of major surgery.<sup>8</sup> Thus, the increased exercise capacity achieved with preoperative exercise training may improve surgical results of patients undergoing tumor resection surgeries.<sup>8</sup> The effectiveness of preoperative exercise training has already been demonstrated in several surgical specialties, such as cardiothoracic,<sup>9</sup> orthopedic,<sup>10</sup> bariatric<sup>11</sup> and also oncological.<sup>12,13</sup> Preoperative exercise training for people undergoing surgery for cancer optimises postoperative recovery and also improves tolerance to complementary treatments, such as chemotherapy.<sup>14</sup>

There are studies which investigated the effects of preoperative exercise training programs that included different types of exercises, frequency and duration in people undergoing major surgery for abdominal cancer.<sup>15-18</sup> However, no recent systematic review has compared the effects of these different exercise training protocols. Although a systematic review of preoperative rehabilitation programs in people with abdominal cancer was recently published, a meta-analysis was not carried out and new randomized controlled trials have already been published after the publication of that review.<sup>19</sup>

Therefore, the aims of this systematic review will be to, in people undergoing major surgery for abdominal cancer, evaluate the effects of preoperative exercise training on the incidence of postoperative pulmonary complications, post-intervention and postoperative exercise capacity, length of hospital stay, quality of life, hospital readmission and late complications (at least after 6 months of hospital discharge), adverse events and postoperative mortality. The review will also report on patient adherence to preoperative exercise training and undertake subgroup analyses to compare the effects of different types of preoperative exercise training programs.

## Methods

**STUDY DESIGN:** systematic review that will be conducted according to the Cochrane Handbook<sup>20</sup> and reported according to the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Additional file 1).<sup>21</sup> The protocol has been prospectively registered with the PROSPERO (Prospective International Register of Systematic Reviews) (number CRD42020199765).

## ELIGIBILITY CRITERIA

- **Studies:** randomized controlled trials (RCTs) of preoperative exercise training in people with abdominal cancer awaiting tumor resection surgery will be included. This intervention can be compared to any other type of preoperative care that does not involve exercise. Clinical trials with inadequate randomization processes (alternate allocation and allocation by date of birth, for example) will be excluded from this Review.
- **Participants:** age  $\geq 18$  years with colorectal, esophageal, gastric, liver or pancreatic cancer awaiting surgical treatment for tumor resection. Patients awaiting urological, gynecological and abdominal laparoscopic surgery will be excluded from this review.
- **Interventions:** studies that delivered aerobic exercise training, resistance training, inspiratory muscle training or advice for home-based exercise training will be included. The intervention can be carried out: individually or in groups; at the patient's home, in-hospital (i.e. inpatient) or outpatient setting; supervised or unsupervised. The type of exercise, place of performance, supervision, frequency, duration, monitoring and security will be recorded and reported.
- **Main outcomes:** incidence of postoperative pulmonary complications as well as post-intervention and postoperative exercise capacity.
- **Secondary outcomes:** length of hospital stay, quality of life, hospital readmission and late complications (at least after 6 months of hospital discharge), adverse events and postoperative mortality. patient adherence to preoperative exercise training.
- **Search strategy to identify studies:** search will be conducted in Pubmed, EMBASE, PEDro and Cochrane Library. Manual searches will also be performed using the reference lists from previous systematic reviews and RCTs included in this systematic review. There will be no restrictions on the language or date of publication when searching for studies. The search strategy will consist of 3 main groups of terms related to: preoperative; exercise; abdominal cancer (Additional file 2). All existing synonyms for each search term will be used and these will be adapted for each database used.
- **Screening and selection of studies:** two researchers will independently screen the titles and abstracts for inclusion in the review. Any disagreement will be discussed with a third member of the team. Then, the same two researchers will independently read the full text of the remaining studies to determine which ones will be included in the review. In case of disagreements, the researchers will discuss inclusion until a consensus is reached. If there is no consensus, a third member of the team will be contacted.
- **Data extraction:** two researchers will extract data from included studies independently. A third researcher will be contacted in case of disagreements. Authors of included RCTs will be contacted in case of missing data or for further clarification on the methods or results of their study. A data extraction form will be used for each study. Data will be extracted of: characteristics of the study (design, methods); characteristics of the study population (age, sex, diagnosis, type of cancer, cancer treatment,

neoadjuvant chemotherapy and / or radiation therapy, previous cancer, anthropometric data, alcohol and smoking histories); characteristics of the intervention (types of exercises, intensity of exercise, frequency and duration of exercise sessions, length of preoperative exercise training program, number of supervised and unsupervised exercise sessions, location of exercise sessions, patient adherence); study outcomes (types of outcomes assessed, methods for assessing outcomes, adverse events and duration of follow-up) and results of included studies. Data extracted from the included RCTs will be entered into the Review Manager (RevMan) software by one of the researchers and checked by a second researcher.

**-Assessment of risk of bias:** risk of bias will be assessed using the PEDro scale (Physiotherapy Evidence Database), which has good validity and reliability, in addition to a strong correlation with the Cochrane risk of bias tool.<sup>22,23</sup> The PEDro scale assesses the risk of bias and the statistical description of randomized controlled clinical trials. This scale comprises 11 items: 8 items (items 2-9) related to the risk of bias (random allocation, blind allocation, baseline comparability, subject blinding, therapist blinding, evaluator blinding, adequate follow-up and analysis for intention to treat); and 2 items (10 and 11) related to statistical description (statistical comparison between groups and measures of precision and variability).<sup>23</sup> The first item on the PEDro scale (eligibility criterion) is not considered in the total score because it is related to external validity. The total score of this scale ranges between 0 and 10 points, and the higher the score, the better is the quality of the RCT.<sup>23</sup> For RCTs that have not been scored by the team at the PEDro database, two researchers will independently use the PEDro scale to assess their risk of bias, and a third researcher will decide in case of any disagreement. Studies will be classified as having a “low risk” of bias if they reach a score  $\geq 6$ . Studies with a score  $< 6$  will be classified as having a “high risk” of bias.<sup>20</sup>

**- Measures of treatment effect:** effects of treatment of continuous variables will be reported as either mean difference or standardized mean difference and their respective 95% confidence interval (CI). For dichotomous variables, the treatment effect will be reported as risk ratio and 95% CI.

**- Unit of analysis issue:** in the case of studies with two or more follow-up data for a given outcome (post-intervention exercise capacity and post-operative exercise capacity, for example), the results from different time points will not be combined into a single meta-analysis.

**- Missing data:** the researchers will try to contact the authors of the included studies a maximum of three times. If these three attempts are unsuccessful, the researchers will limit the presentation of the outcomes of the given study to a narrative discussion.

**- Assessment of heterogeneity:** the chi-square test will be used to identify statistical heterogeneity. The significance of the heterogeneity will be confirmed by the  $I^2$  statistic (ranges from 0 to 100%).<sup>23</sup> An  $I^2 > 50\%$  indicates substantial heterogeneity, decreasing in one level the quality of the evidence due to inconsistency.<sup>20</sup> If substantial heterogeneity is detected, the researchers will investigate whether clinical or methodological heterogeneity are possible causes, through sensitivity analyses.

- **Evaluation of publication and reporting bias:** researchers will search online clinical trial registries to investigate possible publication bias as well as to assess the possibility of bias in reporting the results of studies included in the review. If more than 10 studies are included in the review, the researchers will perform analysis via a funnel plot.
- **Data synthesis:** the quality of evidence will be rated according to the GRADE system (Grading of Recommendations Assessment, Development and Evaluation),<sup>24</sup> as suggested in the Cochrane Handbook of Systematic Reviews.<sup>20</sup> The quality of evidence will be assessed for each comparison and will be classified at four levels (high, moderate, low or very low). These levels will represent the certainty in the estimated treatment effects. The choice of level is based on the result of judgements that include five factors:<sup>25</sup> methodological limitations (risk of bias);<sup>25</sup> inconsistency (significant heterogeneity);<sup>26</sup> indirect evidence;<sup>27</sup> inaccuracy<sup>27</sup> and publication bias.<sup>28</sup>
- **Subgroup analysis:** Subgroup analyses will be performed to compare: modes of intervention (supervised or not, individually or in groups, at home or in a hospital / outpatient setting); types of exercise interventions (aerobic, resistance and breathing); frequency and duration of the intervention (less than 10 days, between 10 and 30 days and more than 30 days);
- **Sensitivity analysis:** researchers will perform sensitivity analysis if substantial heterogeneity is found. Researchers will investigate the effects of blind allocation, blind evaluator or intention-to-treat analysis, or the combination of these in the results. We will also investigate the effects of RCTs with low risk of bias compared to those with high risk of bias (according to the score obtained on the PEDro scale).
- **Description of exercise interventions in pre-rehabilitation programs:** researchers will use the CERT (Consensus on Exercise Reporting Template) guideline to assess the detailed description of exercise interventions.<sup>29,30</sup> Two researchers will apply guideline to studies independently.

## Discussion

Major abdominal surgery is associated with high rates of postoperative complications.<sup>31</sup> Patients with greater preoperative exercise capacity have reduced risk of developing postoperative pulmonary complications and present with better physical and psychosocial function postoperatively.<sup>32-34</sup>

Our hypothesis is that preoperative exercise training programs reduce the incidence of postoperative pulmonary complications in patients undergoing major surgery for abdominal cancer by improving their preoperative exercise capacity. We will also explore the effects of the program on length of hospital stay and mortality. If the hypothesis is confirmed, the results will contribute to the prevention of postoperative pulmonary complications in this population and the implications these complications have on other health outcomes. Thus, our findings will inform health professionals (physiotherapists and rehabilitation professionals) who work within hospital services aimed at optimizing outcomes in people undergoing major abdominal resection for cancer. Furthermore, this systematic review may improve our

understanding of the limitations of the available literature to inform the effects of a preoperative exercise training program in patients with abdominal cancer.

The results will be presented at conference proceedings in poster or oral presentations. The final manuscript will be submitted to a peer-reviewed journal for publication. Any major changes to the protocol following publication of this protocol will be decided by consensus among the authors and included in the final manuscript.

## **Abbreviations**

CERT (Consensus on Exercise Reporting Template)

PEDro (Physiotherapy Evidence Database)

GRADE (Grading of Recommendations Assessment, Development and Evaluation)

PROSPERO (Prospective International Register of Systematic Reviews)

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)

CI (confidence interval)

## **Declarations**

### **Ethics approval and consent to participate**

Not applicable.

### **Consent for publication**

Not applicable.

### **Availability of data and materials**

Not applicable.

### **Competing interests**

The authors declare that they have no competing interests.

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## Authors' contributions

IFFG and ACL developed the research questions and methods section and wrote the first draft of the manuscript. VC contributed to the development of methods, search strategies, and writing this manuscript. All authors contributed to the drafting of the review protocol and approved the final manuscript.

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