Multimodal prehabilitation in lung cancer patients undergoing surgical resection

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Success is not final, failure is not fatal:

it is the courage to continue that counts

-Winston Churchill

Table of contents

Abstract

Rationale: Multimodal prehabilitation aims to prepare patients for anti-cancer treatment through exercise training, nutrition and relaxation strategies. Previous literature in oncologic surgical populations, predominantly colorectal cancer, has shown that multimodal prehabilitation can improve functional capacity and enhance functional recovery after surgery when compared to standard hospital care. In lung cancer, there has been evidence showing overall positive benefits of preoperative exercise however, the integral role that nutrition, as part of a multimodal prehabilitation program, may play in preparing lung cancer patients for surgery has not been sufficiently studied.

Objective: My doctoral work aims to investigate the effects of multimodal prehabilitation on functional capacity in lung cancer patients undergoing surgery, with a specific interest on the impact of preoperative nutrition.

Study 1 (Chapter 3): The objective of thesis study 1 was to determine whether a multimodal prehabilitation program enhances post-operative functional recovery, measured by the six-minute walk test (6MWT), eight weeks after surgery compared to multimodal rehabilitation in lung cancer patients undergoing surgery. Both interventions were entirely home-based and consisted of aerobic and resistance training, nutritional consultations with whey protein supplementation and relaxation strategies, commenced either before (prehabilitation) or after (rehabilitation) surgery. We hypothesized that prehabilitation would be superior to rehabilitation in recovering functional capacity. A total of 52 and 43 patients were randomized to the prehabilitation and rehabilitation groups, respectively. There was no difference in functional capacity at any time point during the perioperative period between the two multimodal programs. By eight weeks after surgery, both groups returned to baseline functional capacity and a similar proportion of

patients (over 75%) in both groups had recovered to their baseline. It was concluded that multimodal prehabilitation initiated four weeks prior to surgery is as effective in recovering functional capacity as multimodal rehabilitation. Among various reasons that may explain the lack of significant difference between groups, we believe that the nutritional intervention was not sufficiently optimized to complement the exercise program, therefore not providing a sufficient anabolic stimulus to promote greater improvements in functional capacity.

Study 2 (Chapter 4): To better understand the current body of literature related to preoperative nutrition in lung cancer patients undergoing surgery, a systematic review of the literature was carried out. The aim was to determine the effect of preoperative nutrition and multimodal prehabilitation on clinical and functional outcomes in surgical lung cancer patients. Only five studies were included in this systematic review, four of which were multimodal prehabilitation interventions and one was a preoperative nutrition-only intervention. This review confirmed that limited research has been performed on preoperative nutritional supplementation in lung cancer patients however, multimodal prehabilitation programs that combine nutrition and exercise may have beneficial effects on various physical function outcomes in patients with lung cancer awaiting surgery.

Study 3 (Chapter 5): Poor nutrition is a risk factor for lung cancer and malnutrition is a common condition experienced by patients that impairs physical function. The goal of this secondary analysis study was to characterize the presence of malnutrition, examine the association between malnutrition and baseline functional capacity and examine the extent to which patients benefit from preoperative multimodal prehabilitation. Data from 162 participants enrolled in multimodal prehabilitation or control before lung cancer surgery were analyzed. Malnutrition was measured using the Patient-Generated Subjective Global Assessment (PG-

SGA) according to triage levels: low nutrition risk (PG-SGA score between 0-3), moderate nutrition risk (PG-SGA score between 4-8) and high nutrition risk (PG-SGA score ≥9). A total of 83 (51.2%) patients were considered at low nutrition risk, 61 (37.7%) were at moderate nutrition risk and 18 (11.1%) were at high nutrition risk. Results confirmed that lung cancer patients awaiting surgery at high nutrition risk had significantly lower baseline functional capacity compared to patients at low nutrition risk [mean baseline 6MWT: 416 m (SD 90) vs. 484 m (SD 88)], and only the patients at high nutrition risk receiving multimodal prehabilitation experienced a significant improvement in preoperative functional capacity of 58.9 m (95% confidence interval [CI],16.7 to 101.2).

Study 4 (Chapter 6): The final study was set out to investigate, in lung cancer patients awaiting elective surgery, the feasibility of delivering a novel four-week multimodal prehabilitation intervention and its effects on preoperative functional capacity and health-related quality of life, compared to standard hospital care (control). Feasibility was assessed based on recruitment and adherence rates to the intervention and study outcome assessment. In this study, we addressed factors that may have contributed to the null findings of the first thesis study. Some changes included making the multimodal prehabilitation intervention more structured by incorporating supervised exercise training sessions and more rigorous collection of compliance data. Furthermore, the nutritional supplementation included whey protein, leucine, omega-3 fatty acids and vitamin D, to offer a stronger anabolic stimulus. Unfortunately, due to the COVID-19 pandemic, the study was stopped before recruitment was completed and follow-up post-operative data was not collected for most patients enrolled. Regardless, results showed that within a preoperative time-frame, it was feasible to deliver this novel multimodal prehabilitation intervention in lung cancer patients awaiting surgery as

recruitment rate was 58.6% and adherence to the a) prescribed intensity of the supervised exercise program was 84.1% (SD 23.1), b) home-based exercise program was 88.2 % (SD 21), c) nutritional supplement was 93.2% (SD 14.2) and d) patients' preoperative assessment was 82% and 88% in the prehabilitation and control group, respectively.

Conclusion: This thesis work contributes to gain a better understanding of the effects of multimodal prehabilitation and specifically nutrition, on functional capacity in lung cancer patients undergoing surgery. These findings lend support for launching larger trials in this clinical setting with the eventual goal of informing treatment guidelines and improving post-surgical recovery.

Résumé

Fondement: La préadaptation multimodale vise à préparer les patients au traitement anti-cancer par des exercices d'entraînement, la nutrition et la relaxation. La littérature scientifique concernant les patients en chirurgie oncologique, principalement pour le cancer colorectal, a montré que la préadaptation multimodale peut améliorer la capacité fonctionnelle et la récupération fonctionnelle après une chirurgie par rapport aux soins hospitaliers standards. Dans le cas du cancer du poumon, des avantages positifs globaux de l'exercice préopératoire ont été démontrés. Cependant, le rôle intégral que la nutrition, dans le cadre d'un programme de préadaptation multimodal, peut jouer dans la préparation préopératoire des patients atteints d'un cancer du poumon n'a pas été suffisamment étudié.

Objectif: Mon travail doctoral vise à étudier les effets de la préadaptation multimodale sur la capacité fonctionnelle des patients atteints d'un cancer du poumon qui vont subir une chirurgie, avec un intérêt particulier sur l'impact de la nutrition préopératoire.

Étude 1 (Chapitre 3): L'objectif 1 de ma thèse était de déterminer si un programme de préadaptation multimodale améliore la récupération fonctionnelle post-opératoire, mesurée par le test de marche de six minutes (6MWT), huit semaines après la chirurgie par rapport à la réadaptation multimodale chez les patients atteints d'un cancer du poumon. Les deux interventions étaient entièrement menées à domicile et consistaient en un entraînement aérobie et en résistance, des consultations nutritionnelles avec supplémentation en protéines et des stratégies de relaxation, commencées avant (préadaptation) ou après (réadaptation) la chirurgie. Nous avons émis l'hypothèse que la préadaptation serait supérieure à la réadaptation pour récupérer la capacité fonctionnelle. Un total de 52 et 43 patients ont été randomisés dans les groupes de préadaptation et de réadaptation, respectivement. Il n'y avait aucune différence de

capacité fonctionnelle à aucun moment de la période périopératoire entre les deux programmes multimodaux. Huit semaines après la chirurgie, les deux groupes sont revenus à leur capacité fonctionnelle de base et une proportion similaire de patients (plus de 75%) dans les deux groupes était revenue à sa valeur de base. Il a été conclu que la préadaptation multimodale initiée quatre semaines avant la chirurgie est aussi efficace pour récupérer la capacité fonctionnelle que la réadaptation multimodale. Parmi les différentes raisons qui peuvent expliquer l'absence de différence significative entre les groupes, nous pensons que l'intervention nutritionnelle n'a pas été suffisamment optimisée pour compléter le programme d'exercice, ne fournissant donc pas un stimulus anabolisant suffisant pour favoriser de plus grandes améliorations de la capacité fonctionnelle.

Étude 2 (Chapitre 4): Pour mieux comprendre les écrits scientifiques actuels relatifs à la nutrition préopératoire chez les patients atteints d'un cancer du poumon subissant une intervention chirurgicale, une revue systématique de la littérature a été réalisée. L'objectif était de déterminer l'effet de la nutrition préopératoire et de la préadaptation multimodale sur les résultats cliniques et fonctionnels chez les patients atteints d'un cancer du poumon. Seules cinq études ont pu être incluses dans cette revue systématique, dont quatre étaient des interventions de préadaptation multimodale et une était une intervention préopératoire uniquement nutritionnelle. Cette revue a confirmé que les recherches effectuées sur la supplémentation nutritionnelle préopératoire chez les patients atteints d'un cancer du poumon sont limitées, cependant, les programmes de préadaptation multimodale qui combinent nutrition et exercice peuvent avoir des effets bénéfiques sur divers résultats fonctionnels physiques chez les patients atteints d'un cancer du poumon en attente d'une intervention chirurgicale.

Étude 3 (Chapitre 5): Une mauvaise alimentation est un facteur de risque de cancer du poumon et la malnutrition est une condition commune qui altère la fonction physique des patients. Le but de cette analyse secondaire était de caractériser la présence de malnutrition, d'examiner l'association entre la malnutrition et la capacité fonctionnelle de base et d'examiner dans quelle mesure les patients bénéficient d'un programme de préadaptation multimodale préopératoire. Les données de 162 participants inscrits en préadaptation multimodale ou recevant des soins standards avant la chirurgie du cancer du poumon ont été analysées. La malnutrition a été mesurée à l'aide de l'évaluation globale subjective générée par le patient (PG-SGA) en fonction des niveaux de triage: risque nutritionnel faible (PG-SGA entre 0-3), risque nutritionnel modéré (4-8) et risque nutritionnel élevé (≥9). Au total, 83 (51,2%) patients ont été considérés comme risque nutritionnel faible, 61 (37,7%) étaient à risque nutritionnel modéré et 18 (11,1%) étaient à risque nutritionnel élevé. Les résultats ont confirmé que les patients à risque nutritionnel élevé en attente d'une intervention chirurgicale avaient une capacité fonctionnelle de base significativement plus faible que les patients à risque nutritionnel faible [moyenne de base 6MWT: 416 m (SD 90) vs 484 m (SD 88)], et seuls les patients à risque nutritionnel élevé recevant la préadaptation multimodale ont connu une amélioration significative de la capacité fonctionnelle préopératoire de 58,9 m (95% CI 16,7 à 101,2).

Étude 4 (Chapitre 6): L'étude finale visait à examiner, chez des patients atteints d'un cancer du poumon en attente d'une chirurgie élective, la faisabilité de fournir une nouvelle intervention de préadaptation multimodale de quatre semaines et ses effets sur la capacité fonctionnelle préopératoire et la qualité de vie liée à la santé, par rapport aux soins hospitaliers standards (contrôle). La faisabilité a été évaluée en fonction des taux de recrutement et d'adhésion à l'intervention et de l'évaluation des résultats de l'étude. Dans cette étude, nous avons abordé les facteurs qui peuvent avoir contribué aux résultats nuls de la première étude de thèse. Certains changements comprenaient la structure de l'intervention de préadaptation multimodale en incorporant des séances d'entraînement à l'exercice supervisé et une collecte plus rigoureuse des données de conformité. En outre, la supplémentation nutritionnelle comprenait des protéines, de la leucine, des acides gras oméga-3 et de la vitamine D, pour offrir un stimulus anabolique plus fort. Malheureusement, en raison de la pandémie de COVID-19, l'étude a été arrêtée avant la fin du recrutement et les données de suivi postopératoire n'ont pas été collectées pour la plupart des patients recrutés. Néanmoins, les résultats ont montré que dans un délai préopératoire, il était possible de proposer cette nouvelle intervention de préadaptation multimodale chez les patients atteints d'un cancer du poumon en attente d'une intervention chirurgicale, car le taux de recrutement était de 58,6% et l'adhésion à a) l’intensité prescrite du programme d'exercice supervisé était de 84,1%. (SD 23,1), b) le programme d'exercice à domicile était de 88,2% (SD 21), c) le supplément nutritionnel était de 93,2% (SD 14,2) et d) l'évaluation préopératoire des patients était de 82% et 88% dans le groupe préadaptation et contrôle, respectivement.

Conclusion: Grâce à ce travail de thèse, nous avons pu mieux comprendre les effets de la préadaptation multimodale et plus particulièrement de la nutrition, sur la capacité fonctionnelle des patients atteints de cancer du poumon subissant une chirurgie. Ces résultats peuvent soutenir le lancement d'essais plus importants dans ce contexte clinique, dans le but éventuel d'éclairer les directives de traitement et d'améliorer la récupération post-chirurgicale.

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Contribution to original research

This thesis was prepared according to McGill University's regulations for a manuscript-based thesis. The core thesis consists of four manuscripts, all submitted for peer-reviewed publication, now under review.

Chapter 1 includes a brief introduction to the study of prehabilitation in lung cancer patients undergoing surgery and the specifics aims and objectives of this thesis.

Chapter 2 provides a comprehensive review of literature important to the understanding of the impact of lung cancer and surgery, characteristics of lung cancer patients related to function and nutrition, the current evidence on the effects of preoperative exercise training in lung cancer patients awaiting surgery as well as preoperative nutrition and multimodal prehabilitation in general.

Chapters 3 -6 include the manuscripts for each of the 4 thesis studies. Each chapter includes title page, abstract, introduction, methods, results with tables and figures, discussion, and references specific to the manuscript. A bridging statement has been included between each manuscript chapter.

Chapter 3 consists of a manuscript entitled "Multimodal Prehabilitation for Lung Cancer Surgery: A Randomized Controlled Trial".

Originality: This was one of the first studies to truly incorporate a multimodal prehabilitation intervention consisting of exercise, nutrition and relaxation strategies in lung cancer patients undergoing surgery. Furthermore, this was the first study to compare prehabilitation with rehabilitation within the context of surgical lung cancer patients. This manuscript has been published in the Annals of Thoracic Surgery.

Chapter 4 consists of a manuscript entitled “Effects of preoperative nutrition and multimodal prehabilitation on functional capacity and postoperative complications in surgical lung cancer patients: a systematic review”.

Originality: This was the first systematic review to comprehensively review the existing literature on preoperative nutrition interventions in surgical patients with lung cancer. This manuscript has been published in Supportive Care in Cancer.

Chapter 5 consists of a manuscript entitled “Malnourished lung cancer patients have poor baseline functional capacity but show greatest improvements with multimodal prehabilitation”.

Originality: There is a paucity of research in malnutrition within the context of surgical lung cancer patients. This study is the first, to our knowledge, to show that malnourished lung cancer patients, identified by the patient-generated subjective global assessment nutritional triage levels, have poor baseline functional capacity but show the most improvement from multimodal prehabilitation during the preoperative period. This manuscript has been published in Nutrition Clinical Practice.

Chapter 6 consists of a manuscript entitled “Feasibility of a novel mixed-nutrient supplement in a multimodal prehabilitation intervention for lung cancer patients awaiting surgery: a randomized controlled pilot trial”.

Originality: Previous multimodal prehabilitation studies in surgical lung cancer patients have primarily focused on preoperative exercise interventions and, if a nutritional intervention was included, it generally consisted of providing patients with dietary advice or whey protein supplementation. This is the first study, to our knowledge, to include a specifically tailored preoperative nutritional intervention beyond dietary advice and/or whey protein supplementation, in lung cancer patients undergoing surgery. The mixed-nutrient supplement provided to patients in the intervention arm of the study consisted of whey protein, leucine, omega-3 fatty acids and vitamin D. Each of these nutrients have shown to provide muscle health benefits but had yet to be tested in the surgical lung cancer population. This manuscript is currently under review at the International Journal of Surgery.

Chapter 7 consists of a general discussion and summary of the overall thesis.

Contribution of authors

This thesis consists of four original research projects that I, Vanessa Ferreira, completed under the supervision of Dr. Celena Scheede-Bergdahl and Dr. Stéphanie Chevalier, as well as Dr. Francesco Carli at the prehabilitation unit of the Montreal General Hospital. The following describes the input and contribution to the work from the co-authors named on the title page of each manuscript.

Thesis study 1 (Chapter 3: Multimodal Prehabilitation for Lung Cancer Surgery: A Randomized Controlled Trial)

Vanessa Ferreira: Investigation, data acquisition, formal analysis, writing – original draft, publication effort.

Enrico Maria Minnella: Conceptualization, methodology, writing – review & editing.

Rashami Awasthi: Investigation; Data acquisition, project administration.

Ann Gamsa, Lorenzo Ferri, David Mulder, Christian Sirois, Jonathan Spicer and Severin Schmid: Resources, writing – review & editing.

Francesco Carli: Conceptualization, supervision, writing – review & editing.

*Celena Scheede-Bergdahl and Stéphanie Chevalier: not included in author list but contributed by supervising me.

Thesis study 2 (Chapter 4: Effects of preoperative nutrition and multimodal prehabilitation on functional capacity and postoperative complications in surgical lung cancer patients: a systematic review)

Vanessa Ferreira: Conceptualization, methodology, investigation, data curation, formal analysis, writing – original draft, publication effort.

Claire Lawson: Data curation, writing – original draft.

Taline Ekmekjian: Data curation.

Francesco Carli: Supervision, writing – review & editing.

Celena Scheede-Bergdahl: Writing – review & editing, supervision.

Stéphanie Chevalier: Conceptualization, writing – review & editing; supervision.

Thesis study 3 (Chapter 5: Malnourished lung cancer patients have poor baseline functional capacity but show greatest improvements with multimodal prehabilitation).

Vanessa Ferreira: Conceptualization, methodology, investigation, data curation, formal analysis, writing – original draft, publication effort.

Claire Lawson: Writing – original draft.

Chelsia Gillis: Writing – review & editing, formal analysis.

Celena Scheede-Bergdahl: Writing – review & editing.

Stéphanie Chevalier: Writing – review & editing.

Francesco Carli: Supervision, writing – review & editing.

Thesis study 4 (Chapter 6: Feasibility of a novel mixed-nutrient supplement in a multimodal prehabilitation intervention for lung cancer patients awaiting surgery: a randomized controlled pilot trial)

Vanessa Ferreira: Investigation, data curation, project administration, formal analysis, writing – original draft, publication effort.

Claire Lawson: Investigation, data curation, writing – review & editing.

Francesco Carli: Methodology, resources, supervision, writing – review & editing.

Celena Scheede-Bergdahl: Methodology, supervision, writing – review & editing.

Stéphanie Chevalier: Conceptualization, methodology, resources, supervision, writing – review & editing.

Chapter 1: Introduction

1.1 Thesis rationale

Multimodal prehabilitation is a growing research area that has shown to provide many benefits to cancer patients undergoing surgery such as enhanced functional recovery and better health related quality of life. However, very little research on multimodal prehabilitation has been done within the context of lung cancer surgery. The majority of preoperative interventions have focused on exercise training however the important role that nutrition may play in combination with exercise cannot be ignored. Considering that lung cancer patients undergoing surgery often present with poor nutritional and physical status, and such factors are associated with prolonged recovery, emphasis should be placed on optimizing physiological reserve through targeted therapies.

In my doctoral work, I sought to determine the effects of multimodal prehabilitation on functional recovery and discover the impact of preoperative nutritional status and supplementation in lung cancer patients undergoing surgery. I did this by 1) comparing multimodal prehabilitation to rehabilitation, 2) completing a systematic review of the current literature on preoperative nutritional and multimodal prehabilitation interventions, 3) performing a secondary analysis to determine the impact of malnutrition and 4) evaluating the feasibility of delivering a novel mixed-nutrient supplement, as part of a multimodal prehabilitation intervention, in lung cancer patients undergoing surgery.

1.2 Thesis objectives

1. Compare multimodal prehabilitation to rehabilitation in lung cancer patients undergoing surgery. Using a “standard” prehabilitation intervention that has been implemented in other

oncologic surgical specialities at our center, we will identify whether it is effective in enhancing functional capacity and superior to rehabilitation.

2. Review the literature with regards to preoperative nutritional and multimodal prehabilitation interventions by completing a systematic review, and identify gaps in knowledge.

3. Identify the prevalence, characteristics and impact of malnutrition and multimodal prehabilitation on functional capacity in lung cancer patients awaiting surgery.

4. Determine the feasibility of implementing a novel multimodal prehabilitation intervention in lung cancer patients awaiting surgery.

1.3 Research Questions

1. In lung cancer patients, does a multimodal prehabilitation program initiated four weeks prior to surgery enhance post-operative functional recovery eight weeks after surgery to a greater extent than a multimodal rehabilitation program initiated after surgery? (Chapter 3)

2. What preoperative nutritional and multimodal prehabilitation interventions for lung cancer patients awaiting surgery exist in the literature and what is their impact on clinical and functional outcomes? (Chapter 4)

3. In cancer patients undergoing lung resection: 1) what are the characteristics of those with varying degrees of malnutrition; 2) what is the association between malnutrition and baseline functional capacity; and, 3) what is the extent to which patients would benefit from a preoperative multimodal prehabilitation program that includes exercise training, nutritional supplementation and psychological support? (Chapter 5)

4. What is the feasibility of delivering a novel four-week multimodal prehabilitation intervention in lung cancer patients awaiting surgery and its effects on preoperative functional capacity and health-related quality of life, compared to standard hospital care? (Chapter 6)

1.4 Thesis implications

1. Inform our understanding of the effects of multimodal prehabilitation on functional capacity in lung cancer patients undergoing surgery.

2. A gap in the literature, with regards to preoperative nutritional and multimodal prehabilitation interventions, will be identified.

3. The importance of screening and assessing for malnutrition and demonstrating the impact of nutritional optimization on preoperative functional capacity will be determined.

4. The feasibility of a novel multimodal prehabilitation intervention will be explored and may help inform treatment guidelines for such interventions in patients with lung cancer.

Chapter 2: Literature review

Lung cancer is a serious disease that affects many Canadians and people world-wide. Increased efforts are needed to design and improve intervention strategies tailored to effectively decrease the burden of lung cancer on the patient and health care system. Integrating multimodal prehabilitation, where a patient-centric approach is taken and interdisciplinary team members work in collaboration to help prepare patients for their surgery in hopes of preventing future impairments, represents a paradigm shift away from the traditional silo-driven surgeon-centric approach in which efforts are impairment driven (reactive model of care) towards a proactive approach. The research interests of this doctoral work lie in understanding the effects of multimodal prehabilitation on functional recovery in lung cancer patients undergoing surgery, with a specific focus on the impact of nutritional optimization.

2.1 Impact of lung cancer and surgery

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer death in Canada in 2020, accounting for 1 in 4 of all cancer deaths.[1] The incidence of lung cancer increases significantly after the age of 65 years old and is more common in males than in females. The five-year net survival for lung cancer is 19% and is among the lowest of all types of cancer. The high mortality rate is largely due to the fact that half of all lung cancers are diagnosed at stage IV (metastatic).[1]

Common symptoms in lung cancer include dyspnoea, cough, fatigue, and pain, which commonly occur as a cluster of symptoms and are quite debilitating to the patient.[2-4] The majority (85-90%) of cases of lung cancer are caused by exposure to cigarette smoke and 40-70% of patients also have chronic obstructive pulmonary disease (COPD).[5]

Surgery remains the cornerstone of any potentially curative treatment plan for patients diagnosed at earlier (non-metastatic) stages. However, resection of the lung is associated with high rates of postoperative complications and results in prolonged recovery time. Even in the absence of complications, major surgery is associated with a 20-40% reduction in physiological and functional capacity in older adults over the age of 60 years.[6,7] Many may argue that a slow recovery is expected after major surgery however, similar findings have been found following minimally invasive surgery, which is aimed at enhancing recovery. Feldman et al., found that in patients undergoing laparoscopic cholecystectomy at the Montreal General Hospital, 54% had still not recovered preoperative physical activity levels, as measured by the Community Health Activities Model Program for Seniors (CHAMPS) questionnaire, one month after surgery.[8] Despite instructions that patients could return to all activities ‘‘as soon as they wanted,’’ they found that physical activity had not yet recovered because of decreased levels of moderate or greater intensity activity. When evaluating performance-based measures such as the timed-up and go and grip strength, reductions in functional capacity were still observed 6 months after surgery, when nearly 50% of patients had not recovered to preoperative levels.[6]

Recent advances in surgical technology and perioperative care have contributed to improvements in surgical outcomes however, there is evidence showing that postoperative complications are related more to patient factors than to quality of care. In fact, poor preoperative functional capacity is a well-recognized predictor of higher incidence and severity of postoperative complications and mortality after surgery.[9-11] Benzo et al.,[12] conducted a meta-analysis to examine whether preoperative exercise capacity, as measured by the gold standard method of cardiopulmonary exercise testing, differed between lung cancer patients who developed postoperative cardiopulmonary complications and those patients who did not. A total of 14 studies were included in the analysis showing that preoperative exercise capacity was significantly lower in patients who developed postoperative cardiopulmonary complications compared to those who did not.

2.2 Preoperative period – the right time to intervene

Efforts to improve the recovery process have primarily focused on intraoperative factors such as minimally invasive surgery[13] and postoperative interventions such as early nutrition and mobilization.[14] Postoperative interventions are designed to facilitate the return to functional activities however, the postoperative period may not be the most opportune time to begin intervening. After surgery, patients are often afraid to disrupt the healing process, fatigued, in pain, anxious, facing postoperative complications and weakness as a result of muscle loss and subsequent protracted disability.[15] Furthermore, considering that lung cancer patients may have poor lifestyle behaviours such as physical inactivity and poor diet, both of which are common risk factors for cancer, expecting them to participate in interventions involving major lifestyle changes may be difficult.

The preoperative period may be a better time to intervene in the factors that contribute to recovery such as physical, nutritional, emotional and medical status. The preoperative period also offers a window of opportunity when patients are usually just waiting for their treatment, therefore by involving them in their own care plan may bring important additional psychological benefits. Newly diagnosed cancer patients are often seeking ways to become immediately involved in their care that may go beyond decision making about upcoming treatments.[16] A recent study in the United Kingdom explored motivation, confidence and priority for changing health behaviours before surgery for short-term peri-operative health benefits in comparison with long-term general health benefits in patients undergoing surgery. The authors found that there was a high degree of patient motivation to change behaviour for perioperative benefits, however a comparative lack of confidence identified a need for structured support.[17] Although this period represents an opportune time to intervene, it is important to recognize that it is limited by national targets requiring lung cancer surgery to be performed within one month of diagnosis. A recent study conducted by a group of pulmonary oncologists at the Jewish General Hospital in Montreal showed that the median wait time from diagnosis to first treatment was 27 days in patients with lung cancer.[18]

2.3 Characteristics of the lung cancer patient

Poor functional status

Lung cancer patients often present with poor nutritional status and physical function adding to the major catabolic stress of surgery that negatively impacts recovery and survival.[19-22] Some of the reasons why lung cancer patients present with poor physical and nutritional status include a) high rates of physical inactivity, obesity, malnutrition and smoking, all of which are important risk factors in the development of cancer; b) following diagnosis, patients are often encouraged to rest, which can worsen their physical capacity; c) neo-adjuvant therapy (chemo/radiotherapy before surgery) can decondition patients even further; and d) the incidence of cancer is higher in older adults. Age in itself can be a negative factor contributing to poor functional status as it is known that physiologic reserve decreases with age.[23]

Low muscle mass, quality and strength

One factor that may precede poor functional status is low muscle mass. Low muscle mass may influence muscle function and lead to loss of strength, reduced pulmonary function, increased disability and poorer quality of life.[24] Muscle depleted patients (i.e. sarcopenic patients) have limited reserve to respond to the surgical stress response,[15] increasing their odds of developing complications and increasing their length of hospital stay.[25] A systematic review of 35 studies comprising mostly of lung cancer at all stages showed that low muscle mass occurs at all body mass indexes (BMI), and is associated with weight loss, poor functional status and survival.[26] Interestingly, this review also suggested that there is limited correlation between muscle mass and function, although there was very little direct evaluation of the relationship.[26] Muscle strength, on the other hand, was affected regardless of loss of muscle mass, and seemed to be the muscle outcome that was most predictive of muscle function[26] and a more relevant determinant of survival.[24] Furthermore, this systematic review demonstrated that resistance exercise training increased all parameters of muscle strength and physical performance, with no difference to muscle mass.[26] Therefore, perhaps future exercise interventions aimed at improving physical function in lung cancer patients should be specifically designed to improve muscle strength, as oppose to muscle mass. However, the relationship between muscle mass and strength cannot be ignored.

The pathophysiology of loss of muscle mass in patients with lung cancer is complex as it involves various molecular and metabolic factors. Low muscle mass has been associated with low albumin and high acute phase protein concentrations, reflecting the inflammatory pathways involved.[26] Abnormal protein metabolism is also implicated in the development of sarcopenia, which will be discussed further in the next section. Although it is known that the prevalence of low muscle mass is high in stage III and IV lung cancer patients,[27] it is important to recognize that it can also occur in earlier stages. A recent study found that in 90 early (stage I) lung cancer patients who underwent surgical resection, 31% of men and 58% of women were sarcopenic, and these patients had a significantly worse outcome than patients without sarcopenia (5-year-survival: 72.8% vs 85.8%, respectively, $P = 0.028$).[28] However, it is not just the quantity of muscle mass that plays a role in clinical and postoperative outcomes, but also muscle quality. Multivariable analysis of 805 colorectal cancer patients identified that low muscle mass before surgery was an independent predictor of overall survival [hazard ratio (HR) 1.70, 95% CI 1.25 to 2.31; $P < 0.001$] however, it was the presence of myosteatosis (intramuscular fat infiltration, an indicator of muscle quality), that was associated with prolonged hospital stay ($P = 0.034$). The authors also identified that obesity with low muscle mass was related to higher 30-day morbidity ($P = 0.019$) and mortality ($P < 0.001$) rates.[29] This was further confirmed in a large multi-center trial in colorectal cancer patients (n = 2100) showing that not only low muscle mass, but also visceral obesity and myosteatosis were independent predictors of length of hospital stay and rate of readmission, independently of major complications.[30]

Malnutrition

In relation to low muscle mass, strength and quality, and poor functional status, malnutrition is another culprit. Malnutrition is a common condition experienced by many patients with cancer that significantly impairs functional capacity.[31] Patients with lung cancer in particular have been associated with notably high rates of malnutrition, identified in up to 60% of patients using the Subjective Global Assessment (SGA).[32] Later stages of the disease have shown rates as high as 80% using the Patient-Generated SGA (PG-SGA), where the degree of malnutrition is estimated to be moderate in 40%, and severe in 40% of patients.[33] At present, body weight, weight loss, BMI, albumin and prealbumin are widely used in detecting malnutrition however, evidence suggests that these measurements fail to detect malnutrition among lung cancer patients when used alone as nutritional variables.[33] The SGA and PG-SGA are both subjective assessment tools that have higher sensitivity and specificity than objective anthropometric and biochemical measurements, as described above.[33]

There are several peri-operative stages at which nutritional status may potentially deteriorate. Focusing on the preoperative period alone, the onset of disease and disease treatments may introduce metabolic abnormalities, such as inflammation that alters nutritional needs, and nutrition-impact symptoms (e.g. loss of appetite).[34] Depending on the type of cancer, patients may find it difficult to meet their nutrient needs through food intake due to tumour-related issues such as obstruction and malabsorption, as in colorectal cancer for example. In addition, patient-related factors such as socio-economic status may have an impact on food intake. Higher rates of malnutrition occur in lung cancer patients as the culmination of disturbed metabolism, increased nutritional requirements and decreased nutrient intake;[34] chronic smoking may also be a contributor to malnutrition. In addition to poor nutritional status and within the context of advanced age, it is important to recognize the possible presence of anabolic resistance, which is characterized by a reduced response to anabolic stimuli including dietary protein, leading to higher protein needs compared to those of younger adults.[35] Dietary protein and/or amino acid intake strongly increase muscle protein synthesis rates and inhibit muscle protein breakdown, thereby allowing net muscle protein accretion. Relevant gains or losses of skeletal muscle mass are attributed to a persistent change in muscle protein synthesis rates, breakdown rates, or a combination of both.[35] Therefore, in states of anabolic resistance such as with age, malnutrition, and cancer, there is an imbalance between muscle protein synthesis and breakdown rates, resulting in a negative net muscle protein balance, and over time, a decline in skeletal muscle mass. Hence, it is important to note that there are several similarities between markers for malnutrition and frailty such as unintentional weight loss and low muscle mass/strength. Unfortunately, malnutrition often goes undiagnosed due to lack of screening and assessment however, additionally, it may be misinterpreted for frailty, considering that many lung cancer patients are diagnosed at older ages. In whichever context, the patient would undergo surgery in a suboptimal nutritional state, with diminished physiological reserves to respond to the demands of the surgical stress response.

Emotional distress

Furthermore, cancer patients often experience psychological stress such as anxiety and depression after diagnosis. Results of studies comparing the level of stress in patients with 14 types of cancer showed that the highest intensity of stress was among patients with lung cancer[36] and it greatly interfered with daily activities.[37] A recent study from our center showed that of 172 colorectal cancer patients awaiting surgery, 37% showed signs of moderate depression using the Hospital Anxiety and Depression Scale (HADS) questionnaire and this group of patients had significantly lower functional capacity at baseline compared to patients with no psychological symptoms and those with anxiety symptoms.[38]

2.4 Preoperative exercise training

The notion of exercise training prior to surgery has been a growing field of interest in many populations. Early studies on interventions intended to improve physical function in the preoperative period were primarily focussed on orthopaedic and cardiac patients, however the past decade has seen a drastic increase in research on preoperative exercise training in cancer patients. There are several good quality systematic reviews that have shown a positive impact of pre-operative exercise therapy on physical function, quality of life, postoperative complications and length of hospital stay.[39-44] A recent meta-analysis showed that in patients undergoing intra-abdominal surgery preoperative exercise training significantly improved preoperative fitness and reduced postoperative complications.[45] Unfortunately there are few meta-analyses, the quality of studies is often limited by significant heterogeneity of preoperative interventions, cancer type, surgical techniques and peri-operative management, and usually lack detailed information about effective doses, duration and adherence.

Preoperative aerobic and resistance training in lung cancer

In lung cancer, there has been evidence showing overall positive benefits of preoperative exercise. One of the most recent systematic reviews and meta-analyses including seven studies containing 404 lung cancer patients with and without COPD showed that preoperative exercise resulted in a lower incidence of postoperative pulmonary complications (OR 0.44, 95% CI 0.27 to 0.71) and shorter length of hospital stay (standardized mean difference −4.23 days, 95% CI −6.14 to −2.32 days).[46] Other systematic reviews and meta-analyses have shown similar results[47-50] as well as significant improvements in functional capacity and quality of life.[51]

Aerobic training is considered the best way to improve cardiopulmonary fitness and exercise performance in healthy people.[52] Jones et al., completed two uncontrolled pilot studies investigating the feasibility and preliminary efficacy of supervised aerobic training in the pre- and post-operative setting in lung cancer, and found that aerobic training was safe and feasible in lung cancer patients undergoing surgery. However, the improvements in peak oxygen consumption (VO_{2peak}) were modest (<15%), particularly in the post-operative setting (~10%) despite good exercise adherence rates (≥70% of planned sessions).[53,54] These findings may be explained by the ventilatory limitation or inadequate gas exchange commonly seen in lung cancer patients, as well as poor cardiovascular oxygen delivery and oxidative capacity, unfavorable fiber type distribution (more glycolytic fibers) and muscle atrophy/weakness, consistent with the limitations to exercise described in patients with COPD.[55] However, aerobic training has demonstrated to improve dyspnoea, as well as health-related quality of life, in patients with a variety of chronic respiratory diseases.[56,57] A recent meta-analysis showed that a significant increase in both forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC), measures of pulmonary function, can be achieved after a preoperative pulmonary rehabilitation program.[47]

As previously described, lung cancer patients often have low muscle mass/weakness and have a more glycolytic fiber type distribution. Resistance training is the most effective method to improve skeletal muscle function in human subjects[58,59] and in severely deconditioned adults, resistance training causes improvements in VO_{2peak}.[60-62] Therefore, the combination of aerobic and resistance training may be the most effective exercise intervention to optimally augment physical fitness. The complementary physiologic adaptations from the combination approach will result in higher cardiovascular oxygen delivery, skeletal muscle oxidative phosphorylation, muscle strength and optimal fiber type composition leading to higher muscle endurance and reduced fatiguability and ventilatory requirements during exercise.[55]

Limitation of exercise-only interventions

Despite the abundant evidence showing the benefits of exercise on functional capacity, unimodal prehabilitation (exercise alone) may not be best solution. One of the first studies in cancer prehabilitation was conducted at the Montreal General Hospital by Carli et al.,[63] where 112 colorectal cancer patients awaiting surgery were randomized to receive either a 4-week high-intensity training program including cycling and resistance training or a sham intervention consisting of recommendations to walk daily and do breathing exercises. The aim was to assess the extent to which the structured high-intensity preoperative exercise training intervention optimized functional recovery, measured by the 6MWT. Unexpectedly, the proportion of patients showing an improvement in walking capacity was greater in the walk/breathing group than in the bike/strengthening group at the end of the prehabilitation period (47 vs. 22%, respectively; P =

0.051) and after surgery (41 vs. 11%, respectively; $P = 0.019$). The authors reported that one of the main reasons for these surprising findings is related to poor adherence to the intense exercise regimen. Only 16% of subjects in the bike/strengthening group were fully adherent to the protocol. These results also suggest that an intervention based on exercise alone may not have been sufficient to improve functional capacity if factors such as nutrition, anxiety, and perioperative care were not taken into consideration during the program. Although physical activity undoubtedly has several advantages in restoring physiological reserve in preparation for abdominal surgery, the role played by other modalities cannot be excluded. It appears that, together, these elements may have synergistic and additive effects.

2.5 Preoperative nutrition

Protein

Nutrition is a key aspect of prehabilitation that works in synergy with the exercise intervention.[64] As previously described, malnutrition is very prevalent in pre-surgical cancer patients, often causing whole-body catabolism (body protein breakdown) and subsequently resulting in loss of muscle mass and function, primarily due to the fact that lean mass is the largest reservoir of amino acids.[34] In addition, there is the possibility that patients, especially those who are older[65] or who have advanced cancer,[66,67] demonstrate anabolic resistance, defined by a reduced ability of skeletal muscle to increase protein synthesis in response to stimuli such as amino acids such that the individual requires a larger, sufficient dose of amino acids to achieve a typical anabolic response.[65] Taken together, patients with cancer and undergoing surgery require a greater total protein intake to attenuate the net catabolism of body tissues to meet protein needs. Therefore, optimizing patients' nutrition with a protein-centered approach and evenly spreading protein across all meals for better distribution (avoiding long periods of fasting), might effectively maximize protein synthesis.[68] Recent ESPEN guidelines recommend protein intakes of at least 1.0 g and optimally, up to 1.5 g/kg/d in oncologic patients.[69] The most commonly utilized protein in interventional studies within the context of prehabilitation is whey protein, which is very rich in the branched-chain amino acid leucine. Leucine is the most potent amino acid to stimulate muscle protein synthesis from activation of the nutrient and growth factor-sensing mammalian target of rapamycin complex 1 (mTORC1).[70]

A double-blinded randomized placebo-controlled trial by Gillis et al., investigated the effects of a 4-week preoperative whey protein supplementation intervention to meet protein needs (intervention group) compared to a non-nutritive placebo (control group) on functional capacity in colon cancer patients (n=48) awaiting elective surgery. Authors reported clinically meaningful improvements in functional walking capacity before surgery of +20.8 m (SD 42.6) in the group receiving whey protein supplementation alone. Although these findings require further larger-scale investigation, they provided insight on the role that nutrition alone i.e. without exercise, plays on functional capacity before surgery. In comparison, a systematic review of eight randomized controlled trials (RCTs) showed that physical exercise alone was not found to improve clinical outcomes in the context of major surgery.[41] In fact, exercise alone, in the absence of adequate nutrition, will not lead to maximal muscle protein accretion[71] or improvements in functional capacity.[72] Instead, it is the synergistic effect of feeding- and exercise-induced stimulation of muscle protein synthesis that positively impacts protein balance, to a greater extent than either feeding or exercise could alone.[73]A recent meta-analysis of nine prospective cohort and randomized controlled studies of nutrition prehabilitation, with or without exercise, in colorectal surgery identified that nutritional prehabilitation alone or combined with an exercise program significantly reduced days spent in hospital after surgery compared with controls by 2 days (95% CI -3.5 to -0.9 days).[74]

Omega-3 fatty acids

Although protein has been the nutrient of focus in the majority of perioperative intervention studies,[74] additional nutrients such as omega-3 fatty acids and vitamin D, may also complement or augment the protein anabolic response. A study comparing omega-3 fatty acid supplementation to a placebo of corn oil for 8 weeks in healthy, older adults found that the corn oil supplement had no effect on muscle protein synthesis rate, whereas omega-3 fatty acid supplementation was found to augment muscle protein synthesis.[75] A study compared the effects of a nutritional intervention with fish oil (2.2 g/day of omega-3 fatty acids) to standard of care (no intervention) on weight, skeletal muscle, and adipose tissue in lung cancer patients undergoing chemotherapy. Findings showed that patients receiving standard of care lost considerable muscle (mean of −0.9 kg ± 0.1 kg, with some patients losing up to 5.2 kg) and concurrently gained intermuscular adipose tissue (approximate 3% increase) whereas patients supplemented with fish oil maintained or even gained muscle mass and experienced a decline in intermuscular adipose tissue.[76] This may be explained by the ability of omega-3 fatty acids to suppress lipogenesis[77] and stimulate lipid oxidation,[78] thereby reducing the deposition of lipids in muscle. Furthermore, omega-3 fatty acids may have an anabolic effect on muscle through the reduction of pro-inflammatory cytokines, improvement of insulin sensitivity,[79] stimulation of muscle protein synthesis via the mTORC1 signaling pathway[80] and diminution of mitochondrial reactive oxygen species emission.[81]

Vitamin-D

With regards to vitamin D, a meta-analysis of 13 RCTs of supplemental vitamin D in adults aged > 60 years, compared with placebo or standard treatment on muscle function, revealed that supplementation with at least 800 IU of vitamin D decreased postural sway, reduced time to complete the Timed Up and Go Test, and marginally increased lower extremity strength.[82] Among 447 patients with early-stage lung cancer, adequate vitamin D status was associated with better survival than poor vitamin D status (adjusted HR 0.64, 95% CI 0.42 to 0.98).[83] Vitamin D plays a vital role in musculoskeletal health. It is well known for its benefits on bone health however it also important for muscle health, namely by promoting muscle contractility through calcium influx, myoblast proliferation and differentiation, and improving insulin sensitivity of muscles.[84]

Therefore, among the many nutrients, high-quality protein, leucine, vitamin D, and omega-3 fatty acids are of particular interest for their demonstrated effects on skeletal muscle health. While increased protein intakes and supplements in leucine, vitamin D, and omega-3 fatty acids support potential gains in muscle mass and function when consumed individually, the combination of these nutrients may provide further benefits.[85]

2.6 Prehabilitation

Prehabilitation refers to the process of increasing functional capacity prior to medical treatment to promote an enhanced ability to withstand the stress of the procedure thereby leading to an accelerated recovery (Figure 1).

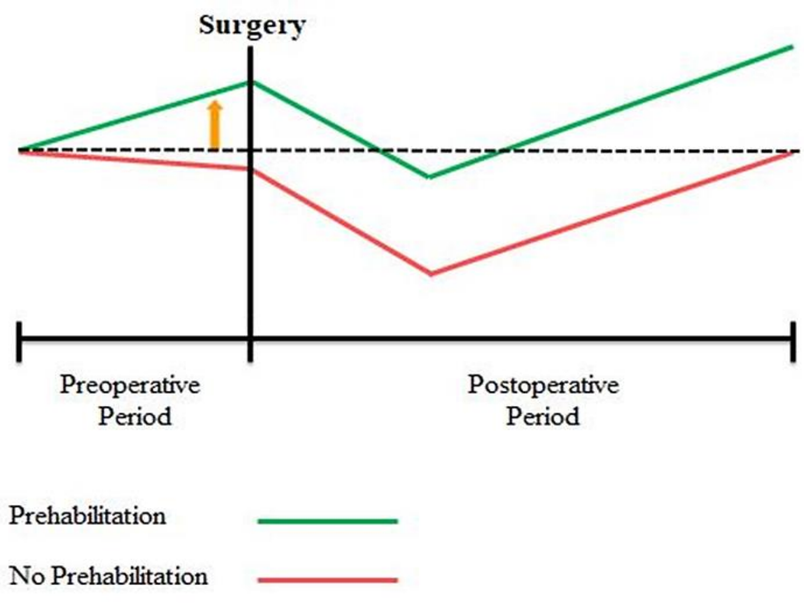

Figure 1. *Theoretical model for prehabilitation compared to standard hospital care (no prehabilitation). The x-axis represents time and the y-axis represents functional capacity. The dotted line represents baseline functional capacity. The red line represents patients who did not receive prehabilitation during the preoperative period and thus their physical condition may worsen as shown by the slight decline in functional capacity followed by the much steeper decline during the postoperative period as a result of the stress of surgery. The green line represents patients following a prehabilitation program, building their functional capacity during the preoperative period thereby minimizing the decline after surgery and thus accelerating recovery, as seen by the green line crossing the dotted line much earlier on in the postoperative continuum. Image adapted from Carli F. et al. Curr Opin Clin Nutr Metab Care. 2005; 8: 23-32.*

More specifically, multimodal prehabilitation is a multidisciplinary intervention that aims to use the preoperative period to prevent or mitigate the functional decline associated with surgery and its consequences.[86] The three main components of multimodal prehabilitation are exercise, nutrition and psychology, which work individually, synergistically and additively to increase functional reserve (Figure 2). Therefore, aside from age and other non-modifiable factors that contribute to low physiological reserve and subsequently poorer outcomes after surgery, there are various modifiable factors related to physical, nutritional and emotional health that can improve functional/physiological reserve in cancer patients prior to surgery. Physiological reserve is the set of functional abilities in an individual and includes all systems of the human body. It represents a safety margin that may be needed to meet increased demands for cardiac output, carbon dioxide excretion, protein synthesis, immune responsiveness, etc.[23]

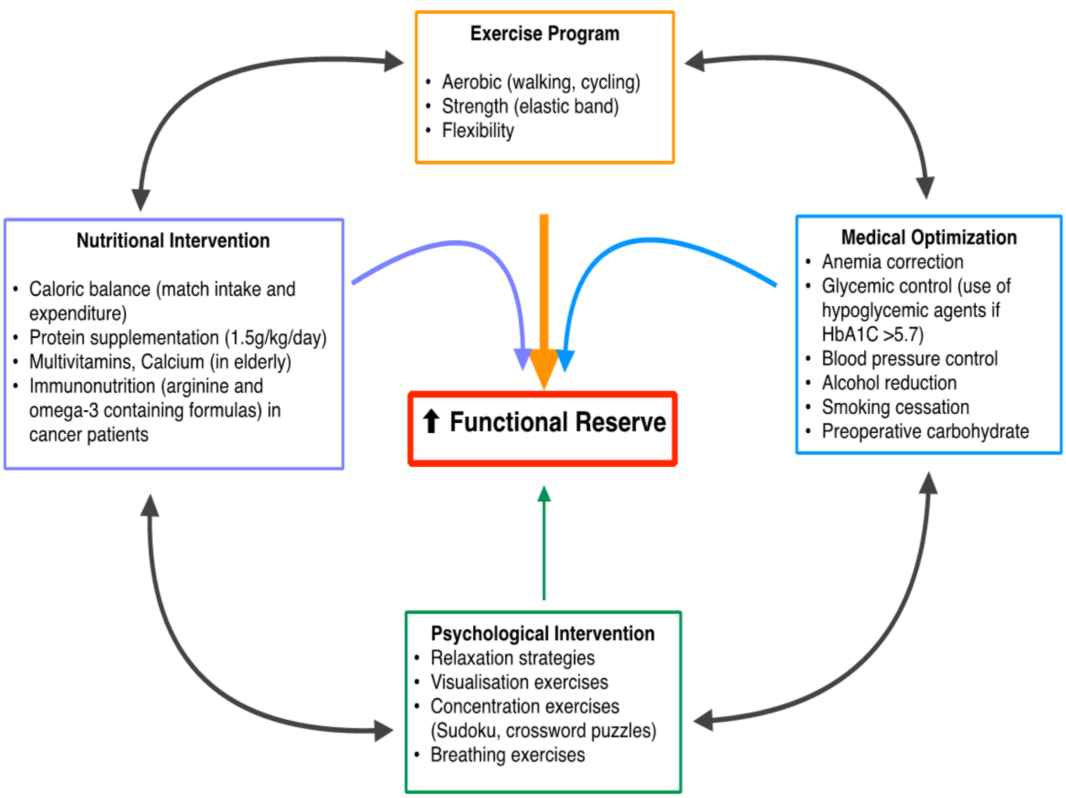

Figure 2. *The various components of a multimodal prehabilitation program that can improve functional reserve include exercise, nutrition, psychology and medical optimization. A general description of the intervention that each component offers is described. Each component can*

independently increase functional reserve as well as interact with the other components to provide synergistic and/or additive effects to improve functional reserve. Adapted from Carli F, Bousquet Dion G. Improving perioperative functional Capacity: A case for prehabilitation. Geriatric Anesthesiology. JG Reeves et al (ed) Springer, 2018, 73-84

The fundamental principle of prehabilitation is to prepare patients for treatment by promoting healthy behaviors to maximize resilience to treatment and improve long-term health. Patients are less vulnerable to the side effects of cancer treatment if they are as healthy as possible, physically and psychologically.[87] Effective prehabilitation is patient-centred, placing the patient at the core of their peri-operative journey and allowing them to regain some control over their own outcomes.[88]

Prehabilitation in cancer surgery

Scientific evidence for prehabilitation within the context of cancer surgery has been exponentially growing during the past decade. The first published article on prehabilitation actually dates back to 1946 and described men who were rejected from enlisting in the army during the Second World War on account of their poor physical and mental condition but who improved following a 2-month programme of educational, physical, and nutritional interventions such that they became standard recruits.[89] Research in prehabilitation eventually expanded to the sports medicine community in 1980 and by the turn of the century, interest shifted to using prehabilitation as a means of improving surgical outcomes in patients undergoing cardiac and orthopedic surgery.[90]

Within the oncological setting, prehabilitation has been predominantly studied in patients undergoing colorectal cancer resection. One of the early studies by our group showed that following 4 weeks of multimodal prehabilitation, colorectal cancer patients significantly improved their functional walking capacity, as measured by the 6MWT, by 40 ± 40 m (P = <0.01) during the preoperative period. Furthermore, compared to patients in the control group who did not undergo prehabilitation, patients in the prehabilitation group had better postoperative walking capacity at both 4 weeks (mean difference between groups, 51.5 ± 93 m; P = 0.01) and 8 weeks after surgery (mean difference between groups, 84.5 ± 83 m; P < 0.01). Lastly, the proportion of patients that achieved functional recovery (return to or surpass baseline 6MWT score) by 8 weeks after surgery was significantly higher in the prehabilitation group (81% of patients in the prehabilitation group vs. 40% in the control group, P < 0.01).[91] Therefore, prehabilitation has shown to be superior with regard to functional recovery when compared to standard hospital care. Similar evidence was reported one year later by our group when comparing prehabilitation to rehabilitation in colorectal cancer patients undergoing surgery. In the study by Gillis et al.,[92] a significantly greater proportion of patients in the prehabilitation group demonstrated clinically important improvements in functional walking capacity (change in 6MWT ≥20 m) during the preoperative period compared with the rehabilitation group (53 vs. 15%, adjusted P = 0.006). By 8 weeks after surgery, the prehabilitation group had a significantly higher 6MWT in relation to their baseline functional capacity compared to the rehabilitation group [mean change in 6MWT from baseline, +23.7 m (SD, 54.8) vs. −21.8 m (SD, 80.7), respectively; mean difference between groups, 45.4 m (95% CI 13.9 to 77.0)]. This also corresponded with a significantly higher proportion of patients in the prehabilitation group recovering to or above their baseline functional walking capacity by 8 weeks compared with the rehabilitation group (84 vs. 62%, adjusted P = 0.049).

Our group also conducted a secondary analysis of 179 colorectal cancer patients undergoing surgery to determine whether an improvement in preoperative functional capacity had a positive impact on surgical morbidity.[93] All historical data from patients (recruited between October 2010 and August 2015) were included, irrespective of group assignment within the original studies (prehabilitation, rehabilitation or standard of care groups) and classified into two groups depending on whether they achieved a significant improvement in functional capacity preoperatively (defined as a preoperative 6MWT change ≥19 meters) or not (6MWT change <19 meters). The findings showed that 44.7% of patients improved in the 6MWT by ≥19 m preoperatively and 55.3% did not. Patients whose functional capacity improved had significantly fewer postoperative complications within 30 days after surgery, measured by the Comprehensive Complication Index, [0 (0–8.7) vs. 8.7 (0–22.6), $P = 0.022$]. Furthermore, they were less likely to have a severe complication [adjusted odds ratio 0.28 (95% CI 0.11 to 0.74), $P = 0.010$]. Although further investigation is required to establish a causative relationship conclusively, this study indicates a strong association between enhanced preoperative physical status and lesser surgical complications in colorectal cancer patients.[93]

Several other studies have since further confirmed the effectiveness of prehabilitation in enhancing functional capacity before and after surgery[94-96] however, it has not been studied as extensively in lung cancer.

Prehabilitation in surgical lung cancer patients

In patients with lung cancer specifically, prehabilitation has primarily focused on pulmonary rehabilitation and chest physiotherapy. Incentive spirometry and inspiratory muscle training during the preoperative period has been studied and showed to improve lung function in patients with both COPD and lung cancer, however it did not include any other form of exercise.[97] In 2007, Jones et al.,[54] addressed prehabilitation studies in lung cancer by investigating the effects of preoperative exercise training on cardiorespiratory fitness in patients undergoing thoracic surgery for malignant lung lesions. Participants underwent a preoperative exercise training regimen consisting of 5 endurance cycle ergometry sessions per week at intensities varying from 60 to 100% of baseline VO_{2peak}. Results showed that mean VO_{2peak} significantly increased by 2.4 ml/kg/ min (95% CI 1.0 to 3.8; $P = 0.002$) and 6MWT distance significantly increased by 40 m (95% CI 16 to 64; $P = 0.003$) in the preoperative period. In patients who attended ≥80% of prescribed sessions, their VO_{2peak} and 6MWT significantly increased by 3.3 ml/kg/min (95% CI 1.1 to 5.4; $P = 0.006$) and 49 m (95% CI 12 to 85; $P = 0.013$), respectively. Bobbio et al.,[98] reported similar findings however their intervention incorporated both aerobic and strength training components. The prehabilitation program included cycle ergometry as well as trunk and upper limb free weight exercises, 5 days per week for 4 weeks. This prospective observational study in patients with COPD and lung cancer demonstrated a significant improvement in physical fitness measured by an improvement in peak oxygen consumption of 2.8 ml/kg/min ($P < 0.01$) during the preoperative period. Therefore, as cancer prehabilitation research began to evolve beyond preserving pulmonary function in lung cancer patients larger, randomized controlled trials began to emerge.

Six-minute walk test

The 6MWT was created to test exercise tolerance but is now used clinically and in research to assess functional capacity. It is defined as “the ability to undertake physically demanding activities of daily living” as it integrates all components of physical activity including balance, speed, muscle force and endurance.[99] The 6MWT measures the distance walked over six minutes in a 20-m corridor where participants are asked to walk at a pace that would make them tired by the end. Participants are allowed to rest, although any time spent resting is accounted for in the total distance covered in 6 minutes. The assessor administers the test following a standardized protocol and script, as per the American Thoracic Society guidelines.[100] It is the most widely used test to measure functional capacity in individuals with chronic lung disease, including those with lung cancer[101] and has been previously validated in the COPD population[102] as a measure of exercise tolerance. A change in 6MWT of 20 m is considered clinically meaningful as this is the estimated measurement error in community-dwelling elderly[103] as well as when measuring post-operative recovery in adult patients undergoing abdominal surgery.[104,105]

The 6MWT is widely used in clinical settings for its prognostic value because it strongly correlates with surgical outcomes. In older adults, the inability to walk 400 m in six minutes (a corresponding gait speed below the average of 1.1 m/s) is associated with a greater risk of mortality, cardiovascular disease, limitation in mobility, and disability.[106,107] Patients undergoing major non-cardiac surgery with a 6MWT of less than 427 m have been considered to be at high perioperative risk.[108] In lung cancer patients undergoing a lobectomy, the inability to achieve 500 m during the 6MWT is associated with an increased risk of postoperative complications and prolonged hospital stay.[109]

2.7 Conclusion

Lung cancer patients experience a high disease burden, physical and psychological impairments, and morbidity over the disease trajectory as a result of multiple processes, including the disease, the cancer treatment, and individual patient factors such as multiple co-morbidities, and a history of poor lifestyle behaviours.[110,111] The preoperative period offers a window of opportunity to begin preparing patients for surgery with a targeted multimodal prehabilitation intervention consisting of exercise, nutrition and anxiety-reducing strategies. The goal of prehabilitation is to enhance functional reserve prior to surgery so that the patient can better withstand surgical stress and, thereby, recover faster. There is growing evidence that multimodal prehabilitation is effective at improving preoperative functional capacity, promoting a faster postsurgical recovery and increasing quality of life in cancer patients undergoing surgery, especially in the colorectal cancer population. There is however, a paucity of research in this field with regards to patients with lung cancer who will undergo surgery, a population who would also greatly benefit from this type of intervention.

Perioperative intervention studies in lung cancer have predominantly focused on exercise training alone, with the majority of interventions taking place during the post-operative period (rehabilitation). Pre-operative exercise training in the context of lung cancer surgery has shown overall positive results however, the role of nutrition and emotional support have been much less studied despite evidence showing the negative impact of poor nutrition and stress on clinical outcomes. Consequently, the work of this doctoral thesis will provide important background for further discussion and research on multimodal prehabilitation in lung cancer patients undergoing surgery, and specifically, how nutrition plays an integral role in preparing patients for surgery.

It is hypothesized that the synergistic and additive effects of an exercise, nutrition and psychological intervention, as part of a multimodal prehabilitation intervention, may produce superior results compared to the highly studied rehabilitation interventions. To better understand the effects of multimodal prehabilitation on functional capacity compared to rehabilitation in lung cancer patients awaiting surgery, a RCT was carried out (Chapter 3). This is the first RCT on multimodal prehabilitation combining exercise, nutrition and relaxation-strategies in lung cancer patients undergoing surgery.

Chapter 3: Multimodal Prehabilitation for Lung Cancer Surgery: A Randomized Controlled Trial

THESIS STUDY 1

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3.1 Abstract

Objective: The study was conducted to determine whether a multimodal prehabilitation program enhances postoperative functional recovery compared with multimodal rehabilitation.

Methods: Patients scheduled for non-small cell lung cancer resection were randomized to 2 groups receiving home-based moderate-intensity exercise, nutritional counseling with whey protein supplementation, and anxiety reducing strategies for 4 weeks before the operation (PREHAB, n = 52) or 8 weeks after (REHAB, n = 43). Functional capacity (FC) was measured by the 6-minute walk test (6MWT) at baseline, immediately before the operation, and 4 and 8 weeks after the operation. All patients were treated according to enhanced recovery pathway guidelines.

Results: There was no difference in FC at any time point during the perioperative period between the 2 multimodal programs. By 8 weeks after the operation, both groups returned to baseline FC, and a similar proportion of patients (>75%) in both groups had recovered to their baseline.

Conclusions: In patients undergoing surgical resection for lung cancer within the context of an enhanced recovery pathway, multimodal prehabilitation initiated 4 weeks before the operation is as effective in recovering FC as multimodal rehabilitation.

3. 2 Introduction

Lung cancer is the leading cause of cancer death world-wide,[1] and the most effective treatment remains complete surgical resection.[2] Even in the absence of complications, lung cancer surgery is associated with significant reductions (approximately 10-18%) in functional capacity (FC).[3] Poor FC is considered a strong predictor of postoperative complications, mortality, and long-term survival in lung cancer.[4]

The process of enhancing FC by exercise of the individual to enable him or her to withstand an incoming stressor such as surgery has been termed prehabilitation. Four weeks of exercise training has been shown to significantly improve physical function before lung surgical procedures with fewer postoperative pulmonary complications, shorter length of hospital stay, and better quality of life.[5] However these studies did not account for the impact of nutrition and emotional factors. Patients with lung cancer are at nutritional risk as a result of reduced food intake and underlying metabolic derangements leading to delayed recovery and mortality.[6] Furthermore, these patients often experience psychological stress, such as anxiety and depression, after diagnosis.[7]

The present study was therefore set up to investigate the effect of a personalized and structured multimodal intervention consisting of aerobic and resistance exercise training, nutritional counselling and supplementation, and relaxation strategies initiated 4 weeks before the operation on postoperative functional recovery in the context of an enhanced recovery pathway (ERP) protocol for lung surgery. To limit potential bias of using a control group, a group receiving the same program initiated after the operation was included.

3.3 Methods

The study was approved by the McGill University Health Center Research Ethics Board (14-193-GEN), Montreal, Quebec, Canada, and registered at ClinicalTrials.gov registration (NCT02938104). Participant enrollment was initiated in November 2014 and completed in March 2017 at the Montreal General Hospital, a single tertiary hospital affiliated with McGill University located in Montréal, Québec, Canada. Consent was obtained from consecutive, eligible adult patients scheduled for non-small cell lung cancer resection. Participants were excluded if they had metastatic cancer, did not speak English or French or if they had concurrent medical conditions that contraindicated exercise. The study was conceived as a single-blind parallel-arm randomized controlled trial and compared 2 multimodal programs administered either before or after the operation.

Four weeks before the operation, participants completed a baseline assessment and were randomly assigned on a 1:1 ratio by computer-generated random numbers to receive the prehabilitation (PREHAB) or rehabilitation intervention (REHAB). Participation in this study had no effect on surgical waiting time.

Multimodal Intervention

The multimodal intervention consisted of a home-based, unsupervised exercise program, a nutritional plan and relaxation strategies, as described previously.[8] Patients assigned to PREHAB were instructed to commence immediately after the baseline assessment (approximately 4 weeks before the operation) and to continue for 8 weeks after the operation, whereas those in REHAB commenced immediately after the operation for 8 weeks.

Each participant received a personalized exercise prescription by a certified kinesiologist following the guidelines of the American College of Sports Medicine.[9] Moderate-vigorous intensity aerobic training of their preferred type was performed for 30 minutes, 3 days per week. Resistance training included 10 exercises targeting major muscle groups, 3 days per week in up to 2 sets of 8 to 12 repetitions and followed by stretching exercises. Patients were given an elastic resistance band (Theraband, Akron, OH) that was matched to their fitness level and an information booklet containing instructions and figures demonstrating all elements of the program as well as exercise progressions. The booklet also included a journal where patients recorded all activities related to the program

A registered dietitian assessed and provided individualized care to each patient based on a 3-day food diary completed at the time of enrollment. Nutritional status was evaluated using the Patient-Generated Subjective Global Assessment (PG-SGA) and the Nutritional Risk Screening tool NRS2002.[10] Daily protein intake was calculated as 1.5 g/kg ideal body weight, according to guidelines on nutrition for surgical patients,[11] and whey protein supplementation (Immunocal; Immunotec Inc., Vaudreuil, Quebec, Canada) was prescribed, if needed. Patients were instructed to ingest protein supplements within 1 hour of their exercise.

Patients met with psychology-trained personnel where techniques aimed at reducing anxiety, such as relaxation exercises based on imagery, visualization and deep breathing, were practiced. A compact disc with relaxation exercises to be used at home 2 to 3 times a week was provided.

A standardized ERP pathway for lung surgery was introduced in 2012 at the McGill University Health Center including early mobilization, feeding, and chest tube removal.[12] Smoking cessation counseling was provided if needed.

Outcomes Assessment

All primary and secondary outcomes were measured at baseline, within 1 week of the operation, and 4 and 8 weeks after the operation. The primary outcome was FC measured by the 6-minute walk test (6MWT), the most widely used test to measure FC in individuals with chronic lung disease, previously validated in the chronic obstructive pulmonary disease population as a measure of exercise tolerance.[13] The assessor, who was blinded to group assignment, used a standardized protocol and script during the test, according to American Thoracic Society guidelines.[14] A change of at least 20 m has been deemed to be the minimal clinically meaningful difference when measuring postoperative recovery in adult patients undergoing abdominal surgery.[15]

Secondary outcomes included health-related-quality-of-life (HRQoL) measured by the Functional Assessment of Cancer Therapy-Lung (FACT-L), and the 36-Item Short Form Health Survey (SF-36). The FACT-L is a validated, disease-specific instrument.[16] The SF-36 is the most widely used HRQoL measure and is validated in the surgical population.[17] It includes 8 subscales (Physical Function, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional and Mental Health) of which 2 summary scores can be derived (Physical and Mental Component Summary Scores). Higher scores on the FACT-L and SF-36 indicate better quality of life.

Total energy expenditure was measured by the Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire.[18] It is validated as a measure of recovery after elective abdominal surgery.[19]

Psychological state was assessed using the Hospital Anxiety and Depression Scale (HADS).[20] Cutoff scores suggesting moderate-high anxiety and depression are scores 7 or higher and 5 or higher, respectively.[21]

Hospital length of stay and number of 30-day emergency visits and readmissions, were also recorded. Postoperative complication rates were graded using the Dindo–Clavien classification[22] and severity using the comprehensive comorbidity index.[23]

Compliance to exercise and nutrition was assessed based on weekly telephone calls and responses in the patient booklet.

Statistical analysis

In view of missing data from previous publications using a similar design, the sample size calculation was based on 2 previous studies in colorectal cancer surgery performed at our institution. We assumed that the average 8-week 6MWT in the REHAB group would be 25 (SD 66) m lower than baseline, compared with 35 (SD 68) m above baseline in the PREHAB group.[24,25] A sample size of 60 participants completing all preoperative and postoperative assessments, 30 per group, was initially estimated to detect these differences with a power of 80%, and a 2-tailed α level of 0.05. This calculation was revised, however, and the sample increased to 124 participants to account for potential preoperative exclusions (eg, surgery not performed).

Normality of data was assessed with the Shapiro–Wilk test. Continuous variables were compared with the 2-sided Student *t* test, Mann–Whitney *U* test or 1-way analysis of variance (ANOVA), as appropriate. Categorical variables were compared using Pearson's χ^2 test or the Fisher's exact test. Changes in the primary outcome (6MWT) over time and between groups were analyzed using a factorial repeated-measures ANOVA with Bonferroni corrections. The effect of the interventions was assessed by calculating the mean difference in 6MWT compared with baseline of all subsequent measurements and the proportions of patients who increased 20 or more meters.

To minimize bias, missing data were handled with multiple imputations by fully conditional specification,[26] where missing items are estimated using the appropriate regression model from other observed data and repeated 10 times to generate 10 different imputed datasets. SEs accounted for variance both between and within imputations. The impact of missing values and higher compliance to prehabilitation (ie, >75% compliance to the exercise program) on the results was examined by performing per-protocol analyses. Statistical significance was defined as *P* value less than 0.05. All analyses were performed with SPSS Statistics for Windows 24.0 (IBM Corp, Armonk, NY).

3.4 Results

Of 230 patients scheduled for lung cancer resection were approached for consent, 106 were excluded because they either did not meet the inclusion criteria (n = 34), refused to participate (n = 49) or could not be contacted (n = 23). A total of 124 patients were randomized to either PREHAB (n = 66) or REHAB (n = 58), of which 14 and 15, respectively, were excluded due to having a benign diagnosis, metastatic disease, or not having surgery, yielding a final cohort of 95 patients (n = 52 in PREHAB and n = 43 in REHAB) (Figure 1).

Baseline demographic, clinical and operative characteristics are presented in Table 1. Median time to operation was comparable between groups at 35 days (interquartile range, 21-51 days) in PREHAB and 27 days (interquartile range, 15-48 days) in REHAB (*P* = .17. The rate of missing data before multiple imputation at the preoperative and 4- and 8-week postoperative visit was 35%, 43%, and 48%, respectively.

Mean change in 6MWT between PREHAB and REHAB was 14.9 m (SD 44.4) vs. 8.2 m (SD 39.3) preoperatively, -12.1 m (SD 76) vs. -16.7 m (SD 56) at 4 weeks postoperatively and 5.4 m (SD 39.7) vs. 8.7 m (SD 39.1) at 8 weeks postoperatively, respectively. There was no significant difference between groups in the mean change in 6MWT at any time point and in the proportion of patients that recovered to or surpassed their baseline FC (Table 2 and Figure 2).

A factorial repeated-measures ANOVA showed a significant effect of time on FC ($F_{2, 185}$ = 7.3, *P* = .001), but a nonsignificant main effect of group ($F_{1, 93}$ = 1.1, *P* = .3), and nonsignificant interaction between group and time ($F_{2, 185}$ = 0.29, *P* = .75). Bonferroni corrected post hoc tests showed a significant difference in FC at all time points in the PREHAB group (*P* = .013 in preoperative period, *P* = .013 between preoperative and 4-week postoperative visit, and *P* = .024 between 4- and 8-week postoperative visit). The REHAB group showed a significant difference in FC only in the postoperative period (*P* = .036 between the preoperative and 4-week postoperative visit and *P* = .003 between the 4-week and 8-week postoperative visit). Both groups returned to baseline FC by 8 weeks after operation (*P* = .33 in PREHAB and *P* = .15 in REHAB, compared with baseline).

By 8 weeks after the operation, both groups returned to baseline FC, and a similar proportion of patients demonstrated functional recovery (ie, returned to or surpassed baseline 6MWT values). The per-protocol analysis (n = 28 in PREHAB and n = 19 in REHAB) found no significant differences in mean change 6MWT between groups before and after the operation. Similar results were seen when the compliers (75%) in the 2 groups were compared.

A sub-analysis comparing unfit (baseline 6WMT ≤400 m) and fit (>400 m) patients between interventions groups over time showed a significant mean improvement in FC of 34.6 m (SE 10.7), *P* = .01, in unfit patients receiving PREHAB during the preoperative period. Fit patients receiving REHAB significantly improved by 28 m (SE 9.1), *P* = .016 from 4 to 8 weeks postoperatively. All groups returned to or surpassed baseline FC by 8 weeks postoperatively.

The PREHAB group reported significantly higher total, Mental and Physical Summary Scores compared with the REHAB group at 4 weeks (Table 3). We analyzed the 8 individual subscales of the SF-36 and found that at 4 weeks after the operation, the PREHAB group had significantly greater scores in General Health (80.1 [SD 14.7] vs. 64.9 [SD 21], *P* = .007) and Mental Health (79 [SD 15.2] vs. 69 [SD 17.2], *P* = .044) and, clinically important improvements in Physical Function (71 [SD 18.5] vs. 59.3 [SD 23.2], *P* = .065) and Social Function (73.5 [SD 27.6] vs. 60 [SD 23.9], *P* = .091) compared to the REHAB group. There were no differences in the interpretation of the results of the multiply imputed or complete case analyses for outcomes presented in Table 3.

Median length of hospital stay was similar between groups, but significantly more patients in the PREHAB group were discharged by postoperative day 2 (42% vs 16%). The number of 30-day emergency visits or readmissions, deaths after the operation, Clavien grade, and the Comprehensive Comorbidity Index were similar in both groups (Table 4). A list of postoperative complications between groups is detailed in Supplemental Table 1.

3. 5 Discussion

The present study, conducted within the context of an ERP, showed no difference in FC at any time point during the perioperative period between the 2 multimodal programs. Hence, preparing patients for surgical resection of lung cancer with a preoperative multimodal prehabilitation program is as effective in recovering FC at 8 weeks after the operation as starting the same multimodal program postoperatively.

The trajectory of FC after the operation was similar between groups, and a similar proportion of patients in both groups recovered to or surpassed their baseline FC by 4 and 8 weeks after the operation. Compared with other studies reporting delayed recovery,[27,28] 65% and 51% of patients, respectively, in the present study recovered FC as early as 4 weeks after the operation. The impact of a standardized ERP protocol that favoured earlier oral feeding and mobilization cannot be excluded.[12] The finding that patients with a lower baseline FC improved the most with prehabilitation during the preoperative period is consistent with previous work in colorectal cancer patients awaiting surgery.[29]

The small difference in 6MWT between groups before the operation might be explained by the behavioural nature of the study design, where patients in the REHAB group might have been prompted to become active before the operation, as confirmed by the increase in energy expenditure, thus underestimating the comparative benefit of prehabilitation. Perhaps integrating supervised exercise sessions may help further engage PREHAB patients in greater participation, thus enhancing functional recovery as shown in a previous study from our institution.[30]

Patients in the PREHAB group had scored significantly better in General Health, Mental Health and nearly significantly better in Physical Function and Social Function compared with the REHAB group 4 weeks after the operation, although this was not reflected in the change in FC. This might be explained by the difference between the 2 outcome measures. The 6MWT is a measure of FC at a specific moment, whereas HRQoL is a self-reported measure reflecting the overall quality of life of the previous 4 weeks.

While physical activity was of primary importance in the present study, the additional role of nutritional optimization cannot be ruled out as a contributor to the recovery of FC after the operation in both groups. The primary goal of the nutritional intervention was provision of proteins and energy to guarantee an available substrate for the anabolic effect of exercise and to attenuate the catabolism commonly seen in cancer and surgery.[6] Similarly, the interaction with the psychologist was aimed not only to teach patients how to manage stressful situations throughout the treatment, but also to encourage participation in the program.

Although there was no significant difference between groups in mean length of hospital stay and postoperative complication rates, more than 40% of patients in the PREHAB group were discharged by postoperative day 2. Whether prehabilitation had an impact is not clear because the study was not powered for postoperative outcome.

An important limitation was the loss to follow-up, which raises concerns about the generalizability of the study. To minimize this, we used an elaborate statistical approach accounting for missing data and potential imbalances between groups by using multiple imputations instead of excluding observations with missing data, which decreases statistical power and may result in biased estimates of effect.[26]

3.6 Conclusion

This study demonstrated that preparing patients for surgical resection of lung cancer with a home-based multimodal prehabilitation program comprised of moderate aerobic and resistance exercises, nutritional counselling with whey protein supplementation, and anxiety-reduction strategies was as effective in recovering FC as the same multimodal intervention initiated after the operation.

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Conflict of interest statement

None declared.

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Table 1. Baseline demographic, clinical and operative characteristics

Variable	Prehab	Rehab	P-Value
	N=52	N=43	
Age, y	67.4 (10)	66.5 (8.6)	.62
≥ 65y	29 (56%)	24 (56%)	>.99
Sex-male, n (%)	26 (50%)	25 (58%)	.43
Current smoker, n (%)	10 (19%)	11 (26%)	.46
Weight, kg	75.4 [64.7-95.9]	70.2 [60.8-82.4]	.15
Body mass index, kg/m^2	27.9 [25.9-32.8]	26.9 [22.9-30.2]	.17
ASA, n (%)			
1	1 (2%)	1 (2%)	
2	33 (64%)	23 (54%)	
3+	18 (35%)	19 (44%)	.56
Comorbidities, n (%)			
Diabetes	7 (14%)	7 (16%)	.7
Hypertension	25 (48%)	11 (26%)	.029*
Cardiovascular disease	5 (10%)	7 (16%)	.33
COPD	5 (10%)	7 (16%)	.33
Neoadjuvant therapy, n (%)	7 (14%)	3 (7%)	.31
Tumor Stage[1], n (%)			
0	10 (19%)	6 (14%)	
IA1	2 (4%)	2 (5%)	
IA2	10 (19%)	10 (23%)	
IA3	11 (21%)	6 (14%)	
IB	3 (6%)	6 (14%)	
IIA	2 (4%)	0 (0%)	
IIB	7 (13%)	2 (5%)	
IIIA	5 (10%)	10 (23%)	
IV	2 (4%)	1 (2%)	.44
Surgical approach, n (%)			
VATS	30 (58%)	23 (53%)	
Open	22 (42%)	20 (47%)	.52
Main Procedure, n (%)			
Lobectomy	28 (54%)	26 (60%)	
Segmentectomy	3 (6%)	5 (12%)	
Wedge	7 (14%)	6 (14%)	
Extended Lobectomy	10 (19%)	6 (14%)	
Other	4 (8%)	0 (0%)	.68
6-minute walking distance, meters			
Actual	458.5 [396-512.3]	478 [433-509]	.3
Percent predicted	72.2 [62.2-79.6]	75.4 [69-79.4]	.23
<400 meters, number of patients, n (%)	14 (27%)	6 (14%)	.12
Total energy expenditure, kcal/kg/week	54.8 [29.4-102.1]	61.5 [23-83]	.57
FEV_1, L	2.3 (0.7)	2.2 (0.4)	.44

FEV_1/FVC, %	68.3 (113.9)	69.8 (68)	.54
D_{LCO}, %	78.6 (24.1)	73.7 (14.2)	.368
Fat-free mass, kg	50.3 (13.2)	46.4 (10.5)	.12
Body fat, % weight	33.7 (8.9)	33.9 (9.1)	.93
PG-SGA, n (%)			
A (well nourished)	38 (73%)	30 (70%)	
B (moderately malnourished)	9 (17%)	5 (12%)	
Missing	5 (10%)	8 (19%)	.56
Albumin, g/l	42 [41-46]	43 [41-45]	.936

*Statistically significant (*P* < .05).

Data are presented as mean (SD), median [IQR] or as otherwise noted.

[1]Pathological tumor staging according to 8th edition classification system.

ASA = American Society of Anesthesiologist; COPD = Chronic Obstructive Pulmonary Disorder; D_{LCO} = Diffusing capacity for carbon monoxide; FEV_1 = Forced expiratory volume in 1 second; FVC = Forced vital capacity; PG-SGA = Patient Generated Subjective Global Assessment; VATS = Video-Assisted Thoracoscopic Surgery. “Other” in main procedure includes lobectomy + segmentectomy, wedge + segmentectomy, and pneumonectomy.

Table 2. Changes in 6-minute walk test compared with baseline, before and after operation

	Prehabilitation (N=52)	Rehabilitation (N=43)	P-Values
Pre-operation			
Mean change during this period (SD)	14.9 (44.4)	8.2 (39.3)	0.44
Decreased	9 (17%)	7 (16%)	0.92
No Change	22 (42%)	20 (47%)	
Improved	21 (40%)	16 (37%)	
4 weeks after operation			
Mean change during this period (SD)	-12.1 (76)	-16.7 (56)	0.74
Decreased	18 (35%)	21 (49%)	0.31
No Change	14 (27%)	11 (26%)	
Improved	20 (39%)	11 (26%)	
8 weeks after operation			
Mean change during this period (SD)	5.4 (39.7)	8.7 (39.1)	0.68
Decreased	12 (23%)	9 (21%)	0.6
No Change	21 (40%)	14 (33%)	
Improved	19 (37%)	20 (47%)	

*Statistically significant ($P < .05$).
Data presented as mean n (%) or as indicated otherwise.
6MWT = six-minute walk test; Decreased = >20 m decrease compared with baseline; No change = within 20 m of baseline; Improved = >20 m increase compared with baseline.

Table 3. Patient-reported outcomes

	Prehabilitation (n=52)	Rehabilitation (n=43)	P-Value
Total energy expenditure, kcal/kg/week			
Baseline	83.8 (88.6)	58.5 (43)	.11
Pre-operation	112.6 (97.2)	74 (95.9)	.07
4 weeks after operation	64.3 (81.4)	66.1 (53.5)	.9
8 weeks after operation	87.9 (123.6)	92.6 (84.1)	.84
Compliance Exercise, %			
Pre-operation	84.9 (25.3)	N/A	N/A
4 weeks after operation	64.5 (33.1)	58.6 (37.9)	.5
8 weeks after operation	67.8 (35.7)	61.7 (34.7)	.49
Compliance Nutrition, %			
Pre-operation	89.5 (23.5)	N/A	N/A
4 weeks after operation	75.7 (35.1)	71.4 (39.7)	.64
8 weeks after operation	77.8 (34.8)	59.9 (44.9)	.07
SF-36 Mental Summary			
Baseline	72.7 (17.6)	66.8 (22.8)	.18
Pre-operation	74.8 (16.4)	68.8 (21.3)	.15
4 weeks after operation	66.9 (15.2)	60.5 (14.5)	.052
8 weeks after operation	71.3 (16.9)	70.1 (18.1)	.76
SF-36 Physical Summary			
Baseline	70.3 (16.3)	67.2 (21)	.44
Pre-operation	73.7 (17.5)	69.6 (19.8)	.3
4 weeks after operation	56.6 (13.7)	48.1 (14.3)	.006*
8 weeks after operation	69.3 (15.4)	61.9 (16.3)	.034*
SF-36 Total			
Baseline	73 (16.6)	68.1 (22.4)	.26
Pre-operation	75.5 (16.6)	70.3 (21.1)	.2
4 weeks after operation	60.9 (14.5)	53.7 (13.8)	.022*
8 weeks after operation	70.4 (16.4)	66.3 (15.2)	.24
FACT-L Total			
Baseline	104.8 (17.2)	103.6 (19.6)	.77
Pre-operation	109 (14.3)	107 (16.8)	.54
4 weeks after operation	105.6 (12.3)	101.3 (16.3)	.17
8 weeks after operation	104.9 (26.6)	109.6 (12.9)	.32
FACT-L Lung Cancer Subscale			
Baseline	21.1 (4.4)	21.7 (4.1)	.5
Pre-operation	22.6 (3.6)	22.8 (3.3)	.77
4 weeks after operation	21 (3.9)	20.2 (4.5)	.35
8 weeks after operation	21.6 (4.4)	22.1 (3.7)	.58
HADS-Anxiety			
Baseline	6.2 (4.5)	6.7 (4.7)	.6
Pre-operation	4.7 (4.3)	6.2 (4.8)	.11
4 weeks after operation	3.9 (3.1)	4.9 (4.3)	.19
8 weeks after operation	4 (3.8)	4.3 (3.7)	.74

HADS-Depression			
Baseline	3.5 (4.1)	3.7 (4.5)	.78
Pre-operation	2.7 (3.2)	4 (4.7)	.15
4 weeks after operation	2.6 (2.7)	3.6 (4.3)	.16
8 weeks after operation	2.4 (2.5)	3.1 (3.3)	.25

*Statistically significant ($P < .05$).
Data presented as mean (SD).
FACT-L = Functional Assessment of Cancer Therapy-Lung; HADS = Hospital Anxiety and Depression Scale; SF-36 = 36-Item Short Form Health Survey.

Table 4. Postoperative clinical outcomes

	Prehabilitation (N=52)	Rehabilitation (N=43)	P-Value
Length of hospital stay, d	4 [2-5.75]	4 [3-5]	.27
Discharge day			
Postoperative day 1-2	22 (42%)	7 (16%)	.007*
Postoperative day 3-4	12 (40%)	22 (61%)	.005*
Postoperative day ≥5	18 (100%)	14 (100%)	.84
Emergency Visits in 30 d	7 (14%)	9 (21%)	.33
No. of Readmissions in 30 d	4 (8%)	6 (14%)	.32
Death	2 (4%)	0 (0%)	.19
Clavien Grade			
0	25 (48%)	17 (40%)	
I	13 (25%)	12 (28%)	
II	9 (17%)	9 (21%)	
IIIa	2 (4%)	3 (7%)	
IIIb	1 (2%)	2 (5%)	
V	2 (4%)	0 (0)	.66
Comprehensive Comorbidity Index	8.7 [0-20.9]	8.7 [0-20.9]	.39

*Statistically significant ($P < .05$).
Data presented as median [IQR] or n (%).

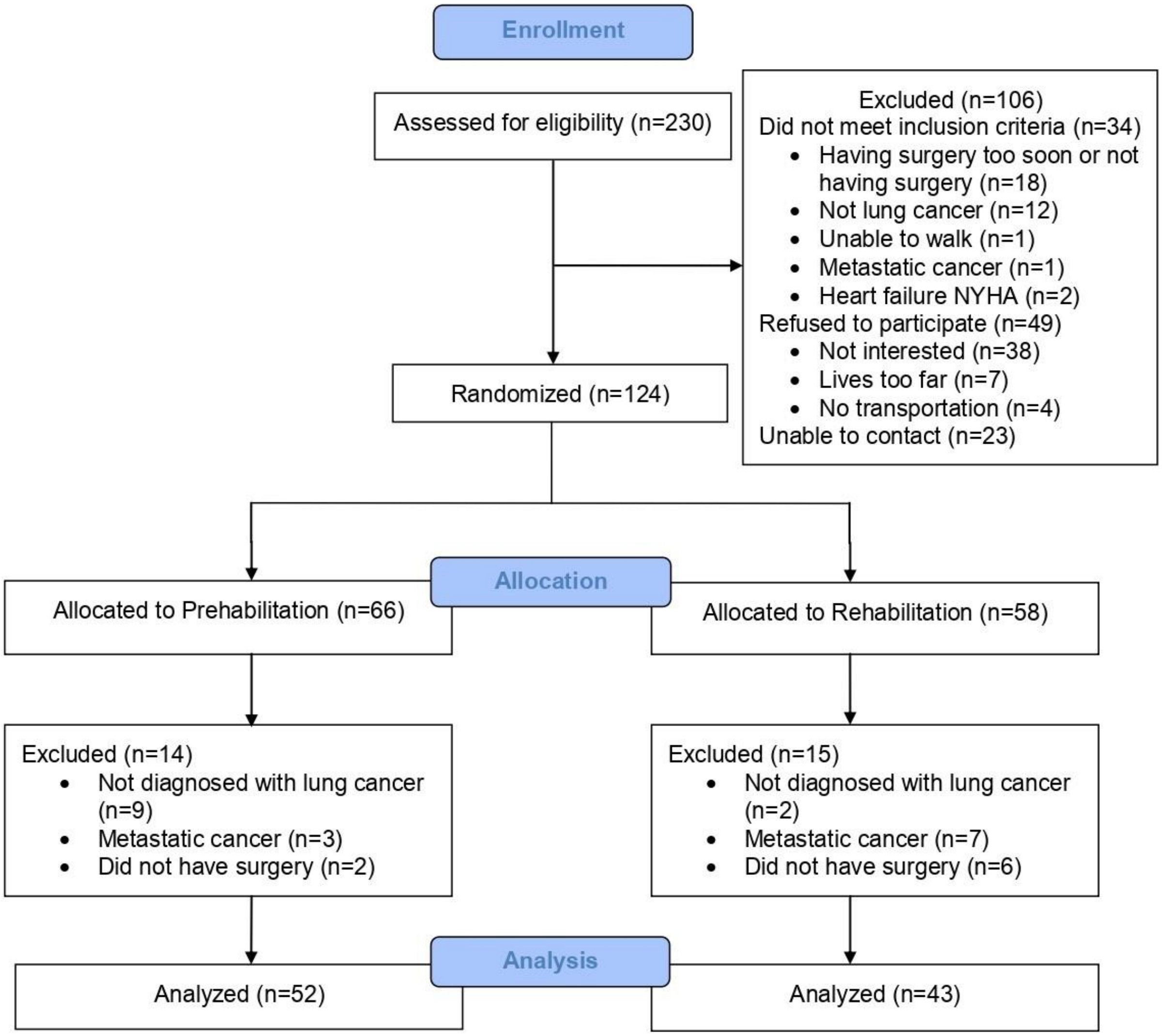

Figure 1. CONSORT diagram

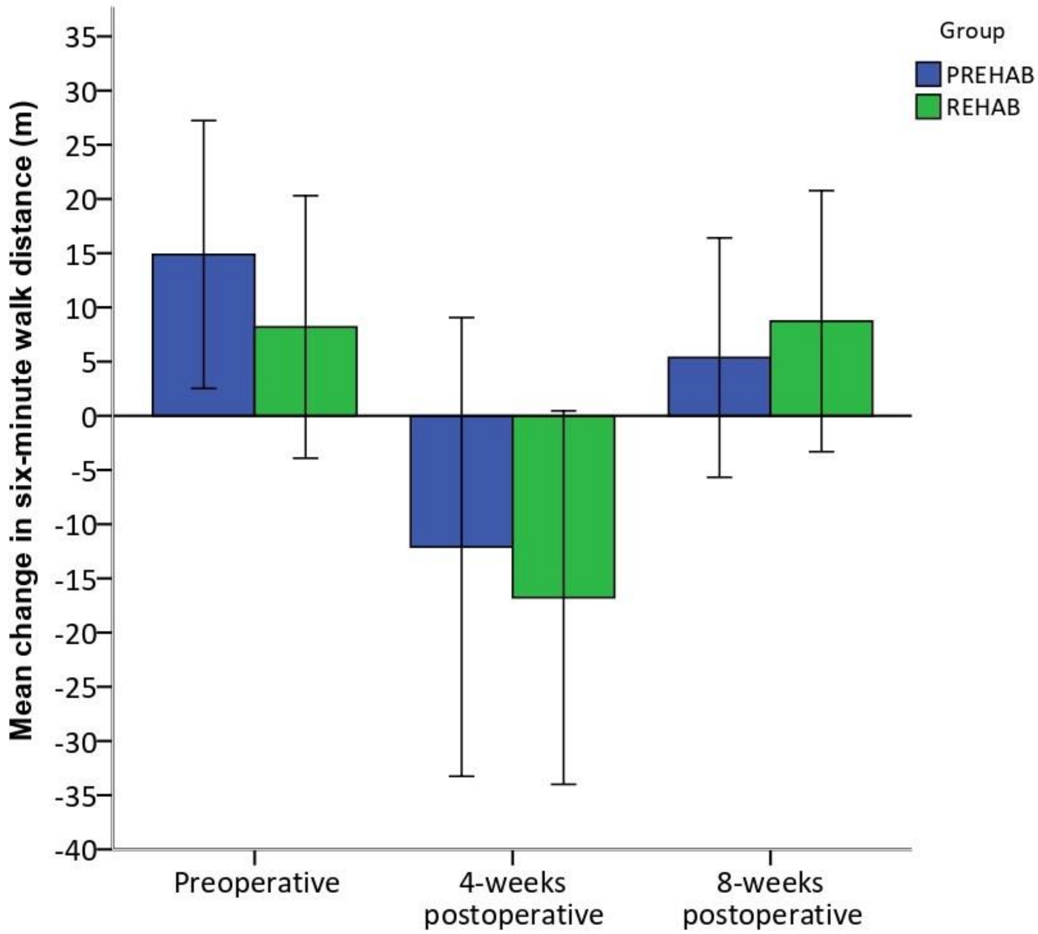

Figure 2. Mean change in 6-minute walk test between the prehabilitation (PREHAB) and rehabilitation (REHAB) groups during the perioperative period. The whiskers represent 95% confidence intervals.

Supplemental Table 1. A detailed list of postoperative complications between groups.

Complications	Prehab N=52	Rehab N=43	P-value
Cardiovascular complications			
Atrial arrhythmia	2 (3.8)	0	.194
Hypotension	4 (7.7)	2 (4.7)	.547
Hypertension	0	2 (4.7)	.115
Myocardial infarction	1 (1.9)	0	.362
Pulmonary embolism	0	1 (2.3)	.268
Pulmonary complications			
Atelectasis	0	1 (2.3)	.268
Pneumonia	1 (1.9)	0	.362
Effusion	1 (1.9)	1 (2.3)	.889
Empyema	1 (1.9)	3 (7)	.22
Hemothorax	1 (1.9)	0	.362
Pneumothorax	1 (1.9)	3 (7)	.22
Air leak	7 (13.5)	8 (18.6)	.514
Prolonged alveolar air leak	2 (3.8)	0	.194
Sub-Q emphysema	6 (11.5)	5 (11.6)	.983
Gastrointestinal bleeding	1 (1.9)	0	.362
Renal complications			
Urinary retention	3 (5.8)	6 (14)	.173
Urinary tract infection	0	1 (2.3)	.268
Hematoma	0	1 (2.3)	.262
Confusion/Delirium	1 (1.9)	1 (2.3)	.876
Infection	0	1 (2.3)	.268

Data are presented as n (%).

Bridging statement 1: Chapter 4

From my first study, I found that multimodal prehabilitation initiated four weeks prior to surgery was as effective in recovering functional capacity as multimodal rehabilitation, in lung cancer patients undergoing surgery. I believe that the original hypothesis that multimodal prehabilitation would be superior to rehabilitation with regard to enhancing functional recovery was not confirmed for various reasons: 1) the multimodal prehabilitation intervention was entirely home-based, which provides less structure and perhaps a lesser intensity than if it had been supervised, 2) the prehabilitation intervention was compared to a rehabilitation intervention, as opposed to standard of care (no prehabilitation or rehabilitation), therefore minimizing the comparative benefit of prehabilitation, 3) although this multimodal prehabilitation intervention included 3 components (exercise, nutrition and relaxation strategies), the main focus was the exercise program. I believe that the nutritional intervention was not optimized enough to complement the exercise program therefore not providing a sufficient anabolic stimulus to promote greater improvements in functional capacity.

The points I have raised will be addressed in the following chapters of this dissertation. To better understand the current body of literature related to preoperative nutrition in lung cancer patients undergoing surgery, a systematic review of the literature was carried out (Chapter 4). This was the first paper to comprehensively review the existing literature on preoperative nutrition interventions in surgical patients with lung cancer, with results specific to lobectomy thereby minimizing heterogeneity from other types of surgery.

Chapter 4: Effects of preoperative nutrition and multimodal prehabilitation on functional capacity and postoperative complications in surgical lung cancer patients: a systematic review

THESIS STUDY 2

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4.1 Abstract

Objective: To determine the effect of preoperative nutrition and multimodal prehabilitation on clinical and functional outcomes in surgical lung cancer patients. **Methods:** We searched MEDLINE, Cochrane Library and CENTRAL, EMBASE, Scopus and clinical trial registries (clinicaltrials.gov, International Clinical Trials Registry Platform and Google Scholar) to identify studies involving a preoperative nutrition-based intervention or multimodal prehabilitation (nutrition with exercise) of at least 7 days, in lung cancer patients awaiting surgery. Studies must have reported results on at least one of the following outcomes: functional capacity, pulmonary function, postoperative complications and length of hospital stay. The quality of included studies was assessed using the Cochrane Risk of Bias assessment tool for randomized trials and the Modified Newcastle–Ottawa scale for non-controlled trials. **Results:** Five studies were included (1 nutrition-only and 4 multimodal prehabilitation studies). Due to substantial heterogeneity in the interventions across studies, a meta-analysis was not conducted. Findings suggest that multimodal prehabilitation, compared with standard hospital care, is associated with improvements in both functional walking capacity and pulmonary function during the preoperative period however it does not appear to have an effect on postoperative outcomes. Rather, the finding of significantly lower rates of postoperative complications in the intervention group was unique to the nutrition-only study. **Conclusion:** Multimodal prehabilitation programs that combine nutrition and exercise may have beneficial effects on various physical function outcomes in patients with lung cancer awaiting surgery. Optimizing preoperative nutrition may have postoperative benefits which remains to be confirmed.

Keywords: nutritional prehabilitation; prehab; surgery preparation; nutrition and exercise; thoracic surgery

4.2 Introduction

Lung cancer is the leading cause of cancer-related death worldwide [1]. For early stages of the disease (stage I and II), the most effective treatment remains complete surgical resection with curative intent [2]. However, patients often present with poor nutritional and physical status at diagnosis, which can increase the risk for postoperative complications and mortality [3].

Prehabilitation is the process of care, initiated before surgery, whereby patients' physical, nutritional, medical and mental conditions are optimized to promote an accelerated postoperative recovery [4] however, defining an optimal approach is still a research gap identified by experts [5]. While physical exercise is a recognized strategy [6], nutrition is often limited to protein-energy supplements, with varying results. The higher nutritional requirements of cancer patients due to underlying metabolic derangements and poor appetite pose challenges for reaching adequate nutrient intakes. Malnutrition can significantly impair muscle strength and physical function [7], and may lead to poor treatment outcomes and tolerance, and delays in treatment [8]. Malnutrition has been reported in 39% of lung cancer patients awaiting surgery, and can predict postoperative complications and 90-day mortality [3]. Despite this, evidence on the impact of preoperative nutrition alone or multimodal prehabilitation (nutrition with exercise) in lung cancer patients is lacking and inconsistent.

To date, available systematic reviews and meta-analyses on preoperative interventions in lung cancer patients have focused on exercise only [6,9,10]. Nutrition is a key aspect of prehabilitation that may work in synergy with exercise interventions to promote a faster postoperative recovery, and thus merits further investigation. This notion has recently been supported in the context of colorectal surgery [11].

The aim of this systematic review was to determine the effect of preoperative nutrition and multimodal prehabilitation (nutrition with exercise) on clinical and functional outcomes in adult lung cancer patients scheduled to undergo surgery. Our review focused on short-term measures of recovery from surgery, including length of primary hospital stay, readmissions and postoperative complications, and longer-term patient-oriented measures of recovery; namely functional capacity, pulmonary function and nutrition-related outcomes.

4.3 Methods

We performed a systematic literature search according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations [12]. The protocol was registered with PROSPERO (CRD42019116043).

Search strategy

The last update of the search was performed on July 31, 2019 and included the following databases: MEDLINE, The Cochrane Library and CENTRAL, Embase, and Scopus. The search strategies designed by a librarian used text words and relevant indexing to identify studies about preoperative nutrition-based interventions for lung cancer. The MEDLINE strategy was applied to all databases, with modifications to search terms as necessary. No language limits were applied. Search strategies were peer-reviewed by a second librarian. In addition, we searched clinical trials registries and citation searches for the reference lists of included studies.

Inclusion and Exclusion Criteria

One reviewer (VF) conducted the first screening of potentially relevant records based on titles and abstracts. Full-text analysis was conducted by two independent reviewers (VF and CL) if articles met the inclusion criteria: randomized controlled trials or prospective cohort studies including a preoperative nutrition-based intervention or multimodal prehabilitation (nutrition with exercise), defined as any oral nutritional intervention including supplementation, with or without dietary counseling, in adults at least 18 years old awaiting lung cancer surgery. Studies including specialized immunonutrition products (nutritional supplements enriched with pharmaco-nutrients such as arginine, glutamine, vitamins, omega-3 fatty acids, nucleotides, and antioxidants) for a minimum of 7 days before surgery were included. Intervention duration of at least 7 days was considered minimally adequate based on current surgical care guidelines which recommend a minimum of 7 days of preoperative nutritional support if malnutrition is present [21]. Studies were excluded if they included invasive preoperative nutritional support requiring hospitalization such as parenteral and/or enteral nutrition, or carbohydrate loading-only. Consensus between the two reviewers resolved disagreement.

Data extraction

Study characteristics were independently extracted by VF, including study design, location of the study, sample size, study groups and whether the study was conducted under Enhanced Recovery Pathways [13] or traditional surgical care. Type of surgical care (Enhanced Recovery Pathways vs. traditional care) was extracted because it may have an impact on post-operative outcomes. Enhanced Recovery Pathways include fast-track protocols that have shown to be associated with decreased length of hospital stay (LOS) and complications compared to traditional care [14], such that there might be little space for further clinical improvements. Baseline characteristics were recorded if the data were available: patient age, patient sex, number of patients with malnutrition, cancer stage, type of surgery performed, and baseline physical condition of the patients. Intervention characteristics were collected, including nutrition and/or exercise prescription, type of oral nutritional supplement, duration of intervention, intervention compliance, and estimated supplemental energy and protein intakes. The following results were collected: pre- and postoperative changes in physical parameters such as functional walking capacity measured by the six-minute walk test (6MWT), pulmonary function test variables such as forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1), nutritional parameters, post-operative complications (defined as any deviation from the normal postoperative course), readmissions and LOS. We attempted to contact authors of the included studies to provide any missing data.

Data synthesis and quality assessment

Data from included studies was synthesized narratively. Quality of included studies was assessed by two review authors independently (VF and CL) using the Cochrane Risk of Bias assessment tool for randomized trials [15]. Each domain of the risk of bias tool was classified as low, high or unclear risk of bias. The quality of non-controlled trials was assessed using the Modified Newcastle–Ottawa scale. The scoring scale ranged from 0 to 9, and studies with a score of 6 or greater were considered to be of high quality [16]. Disagreements were resolved by discussion and consensus.

4.4 Results

Study selection

The primary literature search produced 778 results, including 250 duplicates. An additional 61 were identified through other sources, yielding 578 articles. After screening titles and abstracts, 8 studies were found possibly relevant and underwent full review, resulting in 5 exclusions. Reasons for exclusion included conference abstracts (n = 3) [17-19], non-accessible full-article (n = 1) [20], non-nutritive supplement (n = 1) [21]. Three studies satisfied the inclusion criteria and were included in this review [22-24]. The search was repeated later on during which two additional studies were included [25], one of which is from our group [26].

Figure 1 summarizes the search results. Due to heterogeneity in interventions and lack of systematic reporting of outcome measures, a meta-analysis was not conducted.

Study Characteristics

Study characteristics are presented in Table 1. Two of the five studies were prospective cohort studies, published in 2013, included a multimodal intervention and were completed under traditional care hospital settings [23,22]. The third study was a prospective randomized study, published in 2016, included a nutrition-only prehabilitation intervention and did not specify the type of surgical care [24]. The fourth study published in 2019 [25] and fifth study [26] published in 2020, were single-blind prospective randomized controlled trials that assessed a multimodal intervention compared to either traditional hospital care [25] or to the same intervention administered after surgery (rehabilitation) [26]. In total, the five studies consisted of 639 lung cancer patients undergoing surgery (intervention groups, n = 199; control groups, n = 440).

The mean age of participants ranged from 56.2 to 73.7 years (Table 2). All five studies enrolled lung cancer patients undergoing a lobectomy. Four out of five studies specified cancer stage, ranging from stage IA to stage IV [23-26]. Malnutrition was assessed in three of the five studies. The first used weight loss of 10% or more in the last three months and a body mass index (BMI) of <20 kg/m^2 as criteria, and diagnosed 16% of patients as malnourished although none had a BMI of <20 kg/m^2 [22]. The second study excluded patients with a BMI <18.5 kg/m^2 [24]. The third study assessed nutritional status using the Nutritional Risk Screening tool NRS2002 and the Patient Generated Subjective Global Assessment where 73.1% and 69.8% were well-nourished while 17.3% and 11.6% were moderately malnourished in the prehabilitation and rehabilitation groups, respectively[26].

Intervention Characteristics

The length of the interventions in the four multimodal prehabilitation studies ranged from two to four weeks [22,23,25,26]; one study did not report the specific duration of the intervention (Table 3) [22]. In the study by Bradley et al. [22], the nutritional intervention was two to four weeks in duration, included dietary advice and if patients met the criteria for malnutrition they also received an unspecified nutritional supplement drink. The nutrition intervention was combined with supervised, moderate intensity endurance, resistance and inspiratory muscle training performed twice per week for an hour. The control group received standard care. This study was conducted within the context of Enhanced Recovery After Surgery (ERAS) pathway [27].

In the study by Harada et al. [23], the intervention group received one of two packs of branched-chain amino acid (BCAA) supplementation including 6.2 grams of amino acids daily based on dietary intake since the amount of calories in each pack was different, as well as herbal medicine composed of 10 "nature remedies" for a duration of 29.1±8.9 days. The nutrition intervention was combined with exercise consisting of inspiratory muscle training and supervised, moderate intensity endurance cycling at least twice per week. The control group received physical training focused on exercises for improving activities of daily life at least once a week for a duration of 27.9±7.8 days. The authors stated there were no apparent differences in the physical training interventions between groups except for the minimal required times of hospital visits.

The study by Kaya et al. was the sole nutrition-only study [24]. Intervention duration was 10 days and the nutritional supplement was an immune modulating formula enriched with arginine, omega-3 fatty acids and nucleotides, however the prescribed dose was not provided. The control group maintained their normal diet.

In the study by Liu et al. [25], the median length of intervention was 15 days, during which the intervention group received daily whey protein supplementation to reach a protein intake of 1.5 g/kg/day, ingested within 1 hour post-exercise. Exercise consisted of a home-based program whereby individuals completed 30 minutes of aerobic training at least three days per week and resistance training twice per week. The intervention group also performed respiratory training for 10 minutes at least twice per day and were encouraged to practice basic relaxation skills they had been taught. The control group received standard of care.

The study by Ferreira et al., [26] reported a median time to surgery of 35 days (IQR 21-51) in the prehabilitation and 27 days (IQR 15–48) in the rehabilitation groups. Patients in the multimodal intervention received a nutritional plan to reach a daily protein intake of 1.5 g/kg ideal body weight, and whey protein supplementation (Immunocal®) if needed. Additionally, a home-based exercise program was prescribed of moderate to vigorous intensity aerobic training of their preferred type for 30 minutes, three days per week, and resistance training of ten exercises targeting major muscle groups, three days per week in two sets of 8–12 repetitions followed by stretching. Lastly, techniques aimed at reducing anxiety were practiced. Patients in the rehabilitation group received the same multimodal program at their preoperative visit and were instructed to commence immediately after surgery. This study was conducted within the context of Enhanced Recovery Pathways, a standardized pathway for lung surgery [14].

None of the studies provided information on preoperative supplement energy content, protein content or compliance, except for two. The study by Harada et al. described the supplement as containing 6.2 grams of BCAAs [23] and the supplement in the study by Ferreira et al., [26] contained 10 grams of whey protein, with self-reported compliance to the nutritional program assessed peri-operatively using weekly telephone calls and patient responses.

Risk of bias within studies

Risk of bias in all five studies was deemed to be low, as determined by the Cochrane Risk of Bias Tool [15] (Table 4) and Modified Newcastle-Ottawa Quality Assessment Scale (Table 5) [16]. As expected with nutrition and exercise interventions, the use of blinding of dietary changes when providing dietary counselling was not possible in the randomized controlled trials, proving this to be the greatest weakness of these studies [24,25], however Ferreira et al. [26] reported blinding the outcome assessors. All five studies included a control (or rehabilitation) group thereby improving the methodological quality of the study designs however, only Liu et al. [25] and Ferreira et al. [26] applied appropriate statistical comparisons of the mean change in 6MWT between groups. The overall methodology and outcome assessment performed in all five studies was considered to be of high quality.

Outcomes

A description of the following outcomes is shown in Table 6.

Pre- and postoperative changes in functional outcomes

In the study by Bradley et al., the intervention group experienced a significant improvement in preoperative 6MWT by 20 m (n=30, range −73 to 195 m, p=0.001), followed by a significant decrease in 6MWT by – 41 m (n=15, range −240 to 58 m, p=0.005) postoperatively [22]. There was no report on physical changes in the control or between-group comparisons.

In the study by Liu et al., both groups experienced an improvement in 6MWT; by 45.1 m in the intervention group and 3.8 m in the control (no SD, CI or p-values reported). Thirty days post-operatively, 6MWT was 21.5 m above baseline in the intervention group compared to -36.1 m in the control. By 30 days post-surgery, 33 (89%) patients in the intervention group either recovered to or above their baseline 6MWT compared to 13 (36%) patients in the control. Overall, there was a significant mean difference throughout the perioperative period between the intervention and control in 6MWT of 60.9 m (95% CI, 32.4–89.5; p<0.001) and also in FVC (L) of 0.35 (95% CI, 0.05–0.66; p=0.021) [25].

In the study by Ferreira et al., [26], mean change in 6MWT between the prehabilitation and rehabilitation group was 14.9 m (SD 44.4) vs. 8.2 m (SD 39.3) during the preoperative period, -12.1 m (SD 76) vs. -16.7 m (SD 56) during the 4-week postoperative period and 5.4 m (SD 39.7) vs. 8.7 m (SD 39.1) during the 8-week postoperative period, respectively. There were no significant differences in mean change in 6MWT between groups at any time or in the proportion of patients who recovered to or surpassed their baseline 6MWT. However, there was a significant change in 6MWT at all time points within the prehabilitation group (p=0.013 in pre-operative period, p=0.013 between pre- and 4-week postoperative visit, and p=0.024 between 4 and 8-week postoperative visit), whereas the rehabilitation group showed a significant change in 6MWT only in the postoperative period (p=0.036 between pre- and 4-week postoperative visit and p=0.003 between 4 and 8-week post-operative visit). Both groups returned to baseline 6MWT by eight weeks after surgery compared to baseline (p=0.328 and p=0.150 in prehabilitation and rehabilitation group, respectively).

The studies by Harada et al., [23] and Kaya et al., [24] did not report any pre- or postoperative changes in functional walking capacity.

Changes in preoperative pulmonary function were reported in two studies. Bradley et al., showed a significant improvement in FEV_1 by 0.66 L (n=43, range −1.85 to 1.11 L, p=0.009) in the intervention group [28]. Harada et al., showed a significant improvement in vital capacity and FEV_1 in the intervention group (p=0.0043 and p=0.0012, respectively) and no statistically significant change in the control [29].

Nutritional outcomes

Four out of five studies [22,23,25,26] did not report any nutritional outcomes, one of which stated that there were too little data to comment on the efficacy of the nutritional supplementation [22]. The study by Kaya et al., was the only study to report a nutritional (and inflammatory) outcome showing that mean albumin levels decreased by 14.7% from baseline to third postoperative day compared to 25.7% in the control group, and that the difference in reduction rates was statistically significant (p<0.001) [24].

Postoperative complications, readmissions and length of hospital stay

All five studies reported postoperative complications. Only the study by Kaya et al., found a significant difference between groups whereby 44.4 % of patients in the control group had a postoperative complication compared to 19.4% in the intervention (p=0.049) [24].

The study by Bradley et al., reported fewer postoperative pulmonary complications and readmission rates in the intervention group compared to the control. These were not statistically significant (postoperative pulmonary complication rates: 9% vs. 16%, respectively, p=0.2;

readmission rates: 5% vs. 14%, respectively, p=0.12). LOS was similar between groups, 5 [3-24] days in the intervention group and 5 [1-52] days in the control [22]. The study by Harada et al., reported 28.6% vs. 48.3% (p=0.243) postoperative complications in the intervention and control groups, respectively [23]. Furthermore, Liu et al. found no significant differences in incidence or severity of 30-day postoperative complications using the Clavien–Dindo classification, mortality and median LOS (p=0.973) [25]. Ferreira et al., [26] reported a similar median LOS between the prehabilitation and rehabilitation group of 4 days [2-5.75] and 4 days [3-5]. Significantly more patients in the prehabilitation group were discharged earlier (by postoperative day 2) compared to the rehabilitation group (42% vs. 16%, p=0.0069). The number of 30-day readmissions, deaths, Clavien grade and the Comprehensive Comorbidity Index were similar.

4.5 Discussion

This systematic review highlights the current evidence on the effects of preoperative nutritional and multimodal prehabilitation in patients with lung cancer scheduled for surgery. The results illustrate the infancy of the field because despite an extensive search strategy, only five studies met the inclusion criteria for this review. Four of these studies consisted of multimodal prehabilitation (nutrition and exercise intervention) and one comprised of preoperative nutrition-only; indicating a lack of consensus around the design of these interventions. However, the reported outcomes and methodology used to measure some outcomes were found to be fairly consistent across the studies whereby 6MWT was the most commonly used measure of physical function. Quality assessment revealed an overall high methodological quality of study design mainly due to the fact that all studies included a control (standard care or rehabilitation) group. However, quality could be downgraded to moderate as none used a placebo when nutritional supplements were tested, increasing the risk of bias, and only Liu et al., [25] and Ferreira et al. [26] used appropriate statistical approaches to compare changes between groups.

The four multimodal prehabilitation studies described improvements in physical outcomes pre- and post-surgery. Specifically, three reported changes in functional capacity assessed using the 6MWT [22,25,26] and two reported results of pulmonary function tests [22,23]. Findings from this review suggest that multimodal prehabilitation interventions including nutrition, compared with standard hospital care, are associated with improvements in both functional walking capacity and pulmonary function, however the magnitude of improvement varied. Possible sources of heterogeneity were the different durations, and variability of the multimodal interventions. Improvements in walking capacity as a result of multimodal prehabilitation have been previously reported in other oncologic surgical populations, particularly colorectal cancer [30]. This finding is relevant because lean tissue anabolism requires sufficiency in both dietary intake and contractile activity [31], thus supporting the combination of nutrition and exercise. Improvements in pulmonary function may be due to increased respiratory muscle strength and increased thoracic compliance as a result of exercise training performed in multimodal prehabilitation [32].

From this review, it is unknown whether a preoperative nutrition-only intervention in lung cancer patients affects physical function. Positive results have been shown in a study by Gillis et al., which provided nutrition supplementation to colorectal cancer patients awaiting surgery. The study reported that four weeks of nutrition counseling with whey protein supplementation resulted in a clinically meaningful improvement in functional walking capacity of 20.8 m (SD 42.6), measured by the 6MWT, compared to 1.2 m (SD 65.5) in the placebo group ($p=0.27$) [33]. Although practical inferences cannot be made from the aforementioned study because of the small sample size, variability and pilot nature of the project, these results are promising and suggest that nutrition alone can play an integral role in improving functional capacity.

All five studies reported postoperative clinical outcomes however, the only study that found significant differences in postoperative complication rates between groups was the preoperative nutrition-only study [24]. This study did not include any measure of physical function however it was also the only to measure nutritional outcomes. Findings showed that by mitigating surgery-induced reduction in mean albumin levels by supplementing patients with a protein-rich immune modulating formula pre-operatively, patients had significantly fewer postoperative complications. Unfortunately, these findings would be hard to replicate since the dose, contents and compliance to the formula were not reported. These findings are similar to those from a recent systematic review in colorectal cancer patients undergoing surgery showing that when compared to multimodal prehabilitation (nutrition with exercise), preoperative nutrition-only interventions significantly reduced LOS [11].

The main findings from this review suggest that multimodal prehabilitation including nutrition, compared with standard hospital care, is associated with improvements in functional walking capacity and pulmonary function pre-operatively, however it does not appear to have an effect on postoperative outcomes. Interestingly, the only study that reported significantly lower rates of postoperative complications in the intervention was the nutrition-only study [24]. It is difficult to distinguish the contribution or impact of exercise and nutrition individually which should be investigated further however, it is generally accepted that exercise provides the main anabolic stimulus and nutrition potentiates the muscle protein response [34]. Prehabilitation interventions should be designed to focus on enhancing this additive or synergistic effect of nutrition and exercise together.

A strength of this systematic review is the methodology followed to limit reporting bias. Two independent reviewers (VF and CL) analyzed the research and extracted data, reducing the likelihood of bias and error. To minimize selection bias associated with including the first author's own study, the second reviewer was selected to be someone who was not in involved with the study conduct or manuscript preparation (which was submitted for publication at the time of the systematic review). Furthermore, the criteria for study inclusion was set a priori using a protocol published in PROSPERO, which improved transparency and helped reduce bias. This paper is also the first of our knowledge to comprehensively review the existing literature on preoperative nutrition interventions in surgical patients with lung cancer, with results specific to lobectomy thereby minimizing heterogeneity. Another strength is the focus on both clinical and functional outcomes. This is an important consideration for surgical patients, as most consider recovery to be the return to normal functioning, and are less concerned with clinical outcomes [35]. Additionally, having extracted data on type of surgical care (Enhanced Recovery Pathways vs. traditional care) allows readers to interpret the results of this systematic review in light of the potential impact that it may have on post-operative outcomes.

This review has numerous limitations, the first being its size. Literature in preoperative nutrition is scarce such that this review contains a very small number of studies (n=5). Four of the five studies also utilized nutrition supplementation as one component of multimodal prehabilitation [22,23,25,26]. These factors make it difficult to draw conclusions on the benefits of a preoperative nutrition intervention for lung cancer patients and impossible to conduct a meta-analysis. Secondly, there is substantial heterogeneity between the eligible studies in this review, making comparison difficult. The length of interventions ranged from 10 [24] to 35 days [26] with a variety of supplements including an immune modulating formula, BCAAs, herbal remedies, and whey protein. Lastly, all studies provided limited disclosure regarding information about nutritional content of the supplements, quantity, timing of ingestion and nutrition-related outcomes. No studies reported energy content of the supplements, only one reported the protein content [23], and two reported adherence to the nutrition intervention, one of which stated that participants would be excluded if compliance was <70% and none were excluded [25]. None reported dietary intake from foods in addition to supplements. This lack of nutrition-specific reporting presents significant challenge for focusing future research directions.

Based on this systematic review, we have identified several practical suggestions for future prehabilitation investigators. Future research on preoperative nutrition for surgical cancer patients should be designed such that one arm receives nutrition alone compared to another receiving multimodal prehabilitation, and collect nutrition-related outcomes, for instance, from a comprehensive dietary assessment conducted by a registered dietician based on patient-reported food diaries, anthropometric measurements, presence of nutrition-impact symptoms using tools such as the Patient-Generated Subjective Global Assessment (PG-SGA), biochemical data (anemia, C-reactive protein, albumin and glycated hemoglobin), and a nutrition-focused physical exam. This approach would allow researchers to truly investigate the effects of nutrition on clinical, functional and peri-operative outcomes. Secondly, in order to perform high quality research, thorough reporting of dietary and supplement nutrient content is needed. Without this information, recommendations on pre-operative nutrition in surgical cancer patients cannot be improved. Lastly, investigators could identify and stratify findings by nutritional status and report compliance data, as well as apply appropriate statistical approaches for between-group comparisons. Self-reported data is the main method to assess compliance to nutritional plans and supplements in clinical studies, and should be collected, however there are also many reliable nutritional biomarkers that can be assessed to measure compliance depending on what nutritional supplements are utilized. For example, studies utilizing an omega-3 fatty acid and vitamin D supplement could incorporate blood biomarkers such as serum vitamin D or plasma phospholipid fatty acid profiles to assess adherence. Unfortunately, there is no simple biomarker to assess compliance to protein supplements. Although urinary nitrogen excretion analysis could be performed, a 24-hour urine collection would not likely be feasible in pre-surgical cancer populations.

4.6 Conclusion

In conclusion, limited research has been performed on preoperative nutritional supplementation in lung cancer patients, and more research is warranted on nutrition-only preoperative interventions. Knowledge of effective preoperative nutrition programs on pre- and postoperative outcomes will allow clinicians to better provide guidance to patients undergoing oncological surgery and inform policymakers.

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Consent to participate: N/A

Consent to publication: N/A

Availability of data and material: N/A

Code availability: N/A

Author Contributions:

Vanessa Ferreira: Conceptualization; methodology; data curation; formal analysis; writing – original draft.

Claire Lawson: Data curation; writing – original draft.

Taline Ekmekjian: Data curation.

Francesco Carli: Writing – review & editing.

Celena Scheede-Bergdahl: Writing – review & editing, supervision.

Stéphanie Chevalier: Conceptualization, writing – review & editing; supervision.

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Table 1. Study characteristics

Study	Location	Study design	Study groups	Surgical care	Sample size
Bradley et al., 2013 [22] *multimodal prehabilitation	United Kingdom	Prospective cohort study, multicenter	Intervention: pre- and post-surgery pulmonary rehabilitation program including patient education, smoking cessation, nutrition and supervised exercise aerobic and resistance training Control: standard hospital care	Enhanced recovery pathway	Intervention: n=58 Control: n=305
Harada et al., 2013 [23] *multimodal prehabilitation	Japan	Prospective cohort study, single center	Intervention: comprehensive pulmonary rehabilitation (CHPR) including incentive respiratory training, exercise training and nutrition Control: conventional preoperative pulmonary rehabilitation (CVPR) consisting only of conventional physical training for improving the activity of daily living	Traditional care	Intervention: n=21 Control: n=29
Kaya et al., 2016 [24] *preoperative nutrition	Turkey	Prospective randomized study, single center	Intervention: immune modulating formula Control: normal diet without any additional nutritional products	N/A	Intervention: n=31 Control: n=27
Liu et al., 2019 [25] *multimodal	China	Prospective, single-blind randomized study, single	Intervention: pre-surgery multimodal prehabilitation program including exercise training, respiratory training,	Traditional care	Intervention: n=37 Control: n=36

prehabilitation		center	nutritional supplementation and psychological counseling Control: standard hospital care		
Ferreira et al., 2020 [26] *multimodal prehabilitation	Canada	Prospective, single-blind randomized study, single center	Intervention: multimodal prehabilitation program including home-based exercise training, respiratory training, nutritional counselling and supplementation and psychological counseling with relaxation techniques. Control: program identical to intervention group but commenced immediately post-surgery.	Enhanced recovery pathway	Intervention: n=52 Control: n=43

N/A: not available.

Table 2. Baseline sample characteristics

Study	Age, (y)	Men, n (%)	Type of surgery	Cancer stage, n (%)	Malnutrition, n (%)	Baseline physical condition
Bradley et al., 2013 [22]	Median [range] I: 69 [41-85] C: 67 [21-88]	I: 31 (53) C: 182 (60)	Majority underwent a lobectomy.	N/A	9 (16) patients were identified as being at risk of malnourishment due to self-reported recent weight loss, although none had a BMI of <20 kg/m^2.	ECOG performance status, n (%): Score 0: 29 (50) in I, 147 (48) in C. Score 1: 20 (34) in I, 111 (36) in C. Score 2: 8 (14) in I, 42 (14) in C. Score 3: 1 (2) in I, 5 (2) in C. FEV_1 (L), median [range]: 1.9 [1.0-3.8] in I, 2.1 [0.8-4.9] in C.
Harada et al., 2013 [23]	I: 73.7±7.1 C: 72.2±8.1	I: 11 (52.4) C: 18 (62)	Lobectomy.	I: 8 (38.1) stage IA, 10 (47.6) stage IB, 4 (19.0) stage IIA, 7 (33.3) stage IIIA, 0 stage IV. C: 7 (24.1) stage IA, 9 (31) stage IB, 1 (3.4) stage IIA, 3 (10.3) stage IIIA, 1 (3.4) stage IV.	N/A	FEV_1 (L): 1.96±0.57 in I, 1.93±0.55 in C. Vital capacity (L): 2.77±0.73 in I, 2.82±0.74 in C.

Kaya et al., 2016 [24]	I: 57.8±9.7 C: 59.04±7.61	I: 29 (93.5) C: 25 (92.6)	Lobectomy.	I: 11 (35.5) stage IA, 3 (9.7) stage IIB, 7 (22.6) stage IIA, 6 (19.4) stage IIB; 4 (12.9) stage IIIA. C: 7 (25.9) stage IA, 6 (22.2) stage IB, 8 (29.6) stage IIA, 3 (11.1) stage IIB, 3 (11.1) stage IIIA.	Patients who were malnourished (BMI less than 18.5 kg/m^2) were excluded from the study.	FEV_1 (%): 71.55±15.52 in I, 74.50±15.01 in C.
Liu et al., 2019 [25]	I: 56.2±10.3 C: 56.2±8.7	I: 12 (32) C: 11 (31)	Lobectomy.	I: 33 (89) stage I-II, 4 (11) stage III. C: 32 (89) stage I-II, 4 (11) stage III.	N/A	FEV_1 (L): 2.4±0.6 in I, 2.39±0.53 in C. FVC (L): 3.2±0.78 in I, 3.01±0.68 in C.
Ferreira et al., 2020 [26]	I: 67.4±10 C: 66.5±8.6	I: 26 (50) C: 25 (58.1)	Lobectomy. Majority underwent a video-assisted thoracoscopic surgery.	I: 12 (23.1) stage 0, 29 (55.8) stage I, 9 (17.3) stage II, 2 (3.8) stage III. C: 6 (14) stage 0, 23 (53.5) stage I, 6 (14) stage II, 8 (18.6) stage III.	I: 9 (17.3) C: 5 (11.6) identified as being moderately malnourished according to the Patient Generate Subjective Global Assessment.	Median [range] 6MWT (m): 458.5 [396-512.3] in I, 478 [433-509] in C. Physical activity energy expenditure measured by CHAMPS questionnaire (kcal/kg/week): 54.8 [29.4-102.1] in I vs. 61.5 [23-83] in C.

Data presented as mean ± standard deviation, unless otherwise stated. I: intervention; C: control; BMI: body mass index; 6MWT: six-minute walk test; FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second of the forceful exhalation; ECOG: Eastern Cooperative Oncology Group; CHAMPS: Community Healthy Activities Model Program for Seniors questionnaire; N/A: not available.

Table 3. Description of intervention

Study	Type of oral nutritional supplement	Prescription	Duration of preoperative intervention	Preoperative supplement energy content (kcal)	Preoperative supplement protein content (g)	Compliance to preoperative intervention (%)
Bradley et al., 2013 [22]	N/A	Nutrition: all patients had dietary advice by a lung cancer nurse and a nutritional assessment. If patients met the criteria for dietary intervention (BMI <20 kg/m^2, or 10% weight loss in the last 3 months), the patients were referred to a Macmillan dietician and received a preoperative nutritional drink supplement, which continued for up to 3 months postoperatively based on following nutritional assessment. Exercise: supervised endurance + resistance + inspiratory muscle training, twice per week for one hour. Intensity at 60% of max capacity measured by Borg scale.	2-4 weeks. "flexible to fit the 'referral-to-treatment' target timeframe". Preoperatively "patients attended four rehabilitation classes (range 1–15) and seven education sessions (range 2–13)".	N/A	N/A	N/A
Harada et al., 2013 [23]	BCAAs, consisting of two packs of supplement (Hepas second^{TM}; Clinico Co., Tokyo, Japan or AminofeelTM; Terumo Co., Tokyo, Japan)	Intervention group: *Nutrition:* BCAA supplementation taken daily. Registered dieticians chose one of the two packs of BCAA supplements mainly on the basis of the status of dietary intake, because the total calories in each of them was different. *Exercise:* inspiratory muscle training + supervised endurance training (cycling) at least twice per week at moderate intensity	I: 29.1±8.9 days C: 27.9±7.8 days	N/A	6.2 grams	N/A

	and Hochuekkito™, a herbal medicine composed of 10 nature remedies	(13 on Borg scale) for 2-5 weeks. Control group: *Exercise*: physical training at least once a week, mainly focused on muscle training exercises for improving activities of daily life.* *There were no apparent differences in the physical therapy programs between groups, except for the minimal required times of hospital appointments.				
Kaya et al., 2016 [24]	Protein-rich immune modulating formulae enriched with arginine, omega-3 fatty acids and nucleotides	N/A	10 days	N/A	N/A	N/A
Liu et al., 2019 [25]	Whey protein powder (Inerish; Sino-American Medical Institute Inc, San Diego, CA)	Nutrition: whey protein supplementation ingested within 1-hour post-exercise to reach protein intake of 1.5 g/kg/day. Exercise: home-based program involving 30 minutes of aerobic exercise at least 3 days per week at moderate-to-high intensity (13-16 on Borg scale) + resistance training twice per week (10-12 reps for 3 sets of strengthening exercises with an elastic resistance band) + respiratory training for 10 minutes at least twice daily.	Median 15 days	N/A	N/A	>70%

		The patients were taught basic mental relaxation skills, such as imagery and visualization with relaxing music (patients were provided with a music player) and advised to perform these activities and listen to the music every day before sleeping.				
Ferreira et al., 2020 [26]	Whey protein supplementation (Immunocal®; Immunotec Inc., Vaudreuil, Quebec, Canada)	Nutrition: whey protein supplementation ingested within 1-hour post-exercise to reach protein intake of 1.5 g/kg/day. Exercise: home-based moderate to vigorous intensity aerobic training for 30 minutes, 3 days per week + resistance training (10 exercises targeting major muscle groups, 3 days per week in up to 2 sets of 8 – 12 reps with an elastic resistance band) followed by stretching exercises + pedometer to track daily steps. All patients were taught techniques aimed at reducing anxiety, such as relaxation exercises based on imagery, visualization and deep breathing were practiced. Patients were provided with a compact disc containing relaxation exercises to be performed at home two to three times per week.	Median [range] I: 35 days [21-51] C: 27 days [15–48]	40 kcal per pouch	10 grams per pouch	I: 89.5% to pre-operative nutrition and 84.9% to pre-operative exercise

Data presented as mean ± standard deviation, unless otherwise stated. I: intervention; C: control; BMI: body mass index; BCAA: branched-chain amino acid; N/A: not available.

Table 4. Evaluation of randomized controlled study quality using the Cochrane Risk of Bias Tool.

Study	Random sequence generation	Allocation concealment	Selective reporting	Other bias	Blinding participants	Blinding outcome	Attrition description
Kaya et al., 2016 [24]	Low	Low	Unclear	Low	High	Low	Low
Liu et al., 2019 [25]	Low	Low	Unclear	Low	High	Low	Low
Ferreira et al., 2020 [26]	Low	Low	Low	Low	High	Low	Low

Table 5. Evaluation of cohort study quality using the Modified Newcastle-Ottawa Scale.

Study	Selection (0-4)	Comparability (0-2)	Outcome (0-3)	Total score
Bradley et al., 2013 [22]	3	2	3	8
Harada et al., 2013 [23]	4	1	2	7

Table 6. Description of results

Study	**Preoperative physical changes**	**Post-operative physical changes**	**Nutrition results**	**Postop complications, readmissions and LOS**
Bradley et al., 2013 [22]	Significant improvement in 6MWT of 20 m (*n* = 30, range −73 to 195 m, p = 0.001) and FEV_1 of 0.66 L (*n* = 43, range −1.85 to 1.11, p = 0.009) in I. Control group: N/A Diff. in mean change between groups: N/A	Significant decrease in 6MWT of 41 m (*n* = 15, range −240 to 58 m, p = 0.005) compared with preoperative (post-rehabilitation) in I. Control group: N/A Diff. in mean change between groups: N/A	There were too little data to comment on the efficacy of the nutritional supplementation.	No significant difference in postoperative pulmonary complication rates (9% in I and 16% in C, p= 0.21), readmission rate (5% in I and 14% in C, p= 0.12) and LOS 5 [3-24] days in I and 5 [1-52] days in C.
Harada et al., 2013 [23]	Significant improvement in vital capacity in I from 2.63±0.65 L to 2.75±0.63 L (p = 0.0043); no statistically significant change in C (p = 0.682). Significant improvement in FEV_1 in I from 1.73±0.46 L to 1.87±0.46 L (p = 0.0012); no statistically significant change in C (p = 0.642). Diff. in mean change between groups: N/A	N/A1	N/A	No significant difference in postoperative complication rate: 6/21 (28.6%) in I and 14/29 (48.3%) in C (p=0.243). I: n=5 had pulmonary complications of grade 2-3 and n=1 had cardiovascular complications of grade 2-3. C: n=10 had pulmonary complications of grade 2-3 and n=2 of grade 4-5, and n=2 had other complications of grade 2-3.

Kaya et al., 2016 [24]	N/A	N/A	I: mean albumin levels decreased by 14.7% (4.2±0.3 mg/dl at baseline to 3.5±0.4 mg/dl on the third postoperative day). C: mean albumin levels decreased by 25.71% (4.20±0.43 mg/dl at baseline to 3.12±0.35 mg/dl on the third postoperative day). The difference of the reduction rates was statistically significant (p <0.001).	Statistically significant difference in post-operative complications: 12/31 patients (44.4 %) in C compared to 6/27 patients (19.4%) in I (p=0.049). I: n=4 (66.67 %) had prolonged air leak, n=1 (16.67 %) had atelectasis requiring bronchoscopy and n=1 (16.67 %) had pneumonia. C: n=7 (58.33 %) had prolonged air leak, n=3 (25.0 %) had atelectasis requiring bronchoscopy, n=1 (8.33 %) had pneumonia and n=1 (8.33 %) had cardiac arrhythmia.

Liu et al., 2019 [25]	Improvement in 6MWT by 45.1 m in I and 3.8 m in C.* *No SD, CI or p-value reported.	6MWT at 30 days after surgery was 21.5 m above baseline in I compared to -36.1 m in C. At 30 days after surgery, 33 patients (89%) in I either recovered to or above baseline 6MWT values compared to only 13 patients (36%) in C. Significant mean difference throughout the perioperative period between I and C in 6MWT of 60.9 m (95% CI, 32.4–89.5; p<0.001) and in FVC (L) of 0.35 (95% CI, 0.05–0.66; p = 0.021).	N/A	No significant differences in incidence and severity of 30-day post-operative complications (pneumonia, p=0.307; atelectasis, p=0.307; cardiac complications, p=0.666), mortality, median LOS (p=0.973) or chest tube duration (p=0.762).
Ferreira et al., 2020 [26]	Mean change in 6MWT was 14.9±44.4 m in I vs. 8.2±39.3 m in C (p=0.444). No significant difference between groups in the proportion of patients who increased, decreased or maintained 6MWT compared to baseline (p=0.919) Significant difference in 6MWT	Mean change in 6MWT was -12.1±76 m in I vs. -16.7±56 m in C by 4 weeks postop (p=0.738). Mean change in 6MWT was 5.4±39.7 m in I vs. 8.7±39.1 m in C by 8 weeks postop (p=0.680). No significant difference between groups in the proportion	N/A	Significant difference in proportion of patients discharged by postoperative days 1-2 [22/52 (42%) patients in I vs. 7/43 (16%) in C, p=0.007] and postoperative days 3-4 12/30 (40%) in I vs. 22/36 (61%) in C, p=0.005]. No significant difference in proportion of patients discharged by postoperative days 5+ (18 patients in I vs. 14 patients in C,

	within I (p=0.013) compared to baseline.	of patients who increased, decreased or maintained 6MWT compared to baseline at 4 (p=0.306) and 8 weeks (0.604) postop. Significant change in 6MWT within I between pre- and 4-week postoperative visit (p=0.013) and between 4- and 8-week (p=0.024) postoperative visit. Significant change in 6MWT within C between pre- and 4-week postoperative visit (p=0.036) and between 4 and 8-week postoperative visit (p=0.003). Both I and C returned to baseline 6MWT by 8 weeks postoperative (p=0.328 and p=0.150, respectively). No significant difference in change between I and C		p=0.841). No significant differences in LOS (4 [2-5.75] days in I vs. 4 [3-5] days in C, p=0.272), postoperative complication rate (p=0.658) or severity (p=0.393), and rate of readmissions (p=0.322).

Data presented as mean ± standard deviation, unless otherwise stated. I: intervention; C: control; 6MWT: six-minute walk test; VC: vital capacity; FEV_1: forced expiratory volume in the first second of the forceful exhalation; LOS: length of stay; N/A: not available

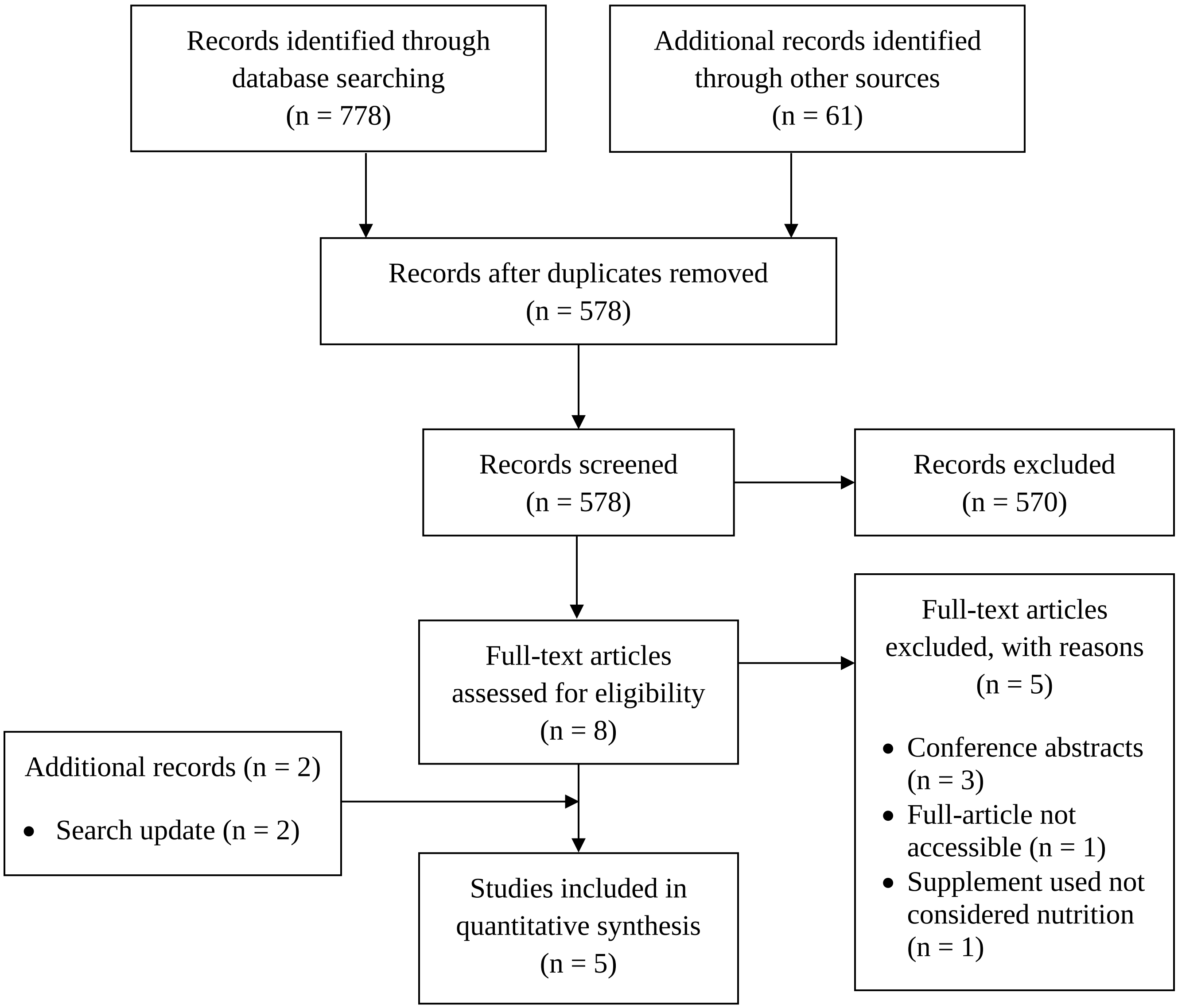

Figure 1. PRISMA flow diagram

Bridging statement 2: Chapter 5

From my systematic review, I learned that very limited research has been performed on preoperative nutritional interventions in lung cancer patients. Initially I had set out to investigate the effect of preoperative nutrition alone on clinical and functional outcomes in surgical lung cancer patients. However, following the results of the first search, I quickly realized that the literature on preoperative nutritional interventions was far too scarce in the lung cancer population. Hence, I expanded my search to include preoperative nutrition interventions with or without exercise interventions. As reported, the majority of studies included in my systematic review consisted of nutrition combined with exercise.

The results of my systematic review led me to question if the lack of preoperative nutritional interventions in the surgical lung cancer population was due to a lack of necessity. Perhaps the prevalence of malnutrition was low in lung cancer or the impact of poor nutritional status on clinical outcomes was minimal? The literature in other cancer types, such as colorectal cancer, has shown that malnutrition is indeed prevalent and is associated with deleterious effects on recovery after surgery. Therefore, to address these questions, I conducted a secondary analysis of data from prior, completed studies in surgical lung cancer participants in our center (Chapter 5). The goal of this study was to characterize the presence of malnutrition, examine the association between malnutrition and baseline functional capacity and examine the extent to which patients benefit from preoperative multimodal prehabilitation.

Chapter 5: Malnourished lung cancer patients have poor baseline functional capacity but show greatest improvements with multimodal prehabilitation

THESIS STUDY 3

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5.1 Abstract

Objective: The objective is to characterize the presence of malnutrition, examine the association between malnutrition and baseline functional capacity (FC), and examine the extent to which patients benefit from preoperative multimodal prehabilitation in patients undergoing lung resection for cancer.

Methods: Data from 162 participants enrolled in multimodal prehabilitation or control before lung cancer surgery were analyzed. Malnutrition was measured using the Patient-Generated Subjective Global Assessment (PG-SGA) according to triage levels: low nutrition risk (PG-SGA 0-3), moderate nutrition risk (4-8) and high nutrition risk (≥9). Baseline differences in FC, measured by the 6-minute walk test (6MWT), were compared. Factorial analysis of covariance (ANCOVA) was conducted to examine the effect of nutrition status and intervention on mean change in 6MWT preoperatively.

Results: 51.2% patients were considered low nutrition risk, 37.7% moderate nutrition risk and 11.1% high nutrition risk. Low nutrition risk patients had significantly higher 6MWT scores at baseline (mean of 484 m [standard deviation (SD) = 88)]) compared with moderate nutrition risk (432 m [SD = 107], *P* = .005) and high nutrition risk groups (416 m [SD 90], *P* = .022). The adjusted mean change in 6MWT between prehabilitation vs. control was 18.1 (95% confidence interval, 3.8-32.3) vs. 5.6 m (-14.1 to 25.4) in low nutrition group (*P* = .309), 28.5 (11-46) vs. -4 m (-31.3 to 23.4) in the moderate nutrition risk group (*P* = .053), and 58.9 (16.7-101.2) vs. -39.7 m (-80.2 to 0.826) in the high nutrition risk group (*P* = .001).

Conclusions: Lung cancer patients at high nutrition risk awaiting surgery had significantly lower baseline FC compared with low nutrition risk patients but experienced significant improvements in preoperative FC upon receiving multimodal prehabilitation.

5.2 Introduction

Malnutrition is a common condition experienced by patients with cancer.[1] Patients with lung cancer in particular have been found to have notably high rates of malnutrition (up to 60% and even 80% in late stages of the disease).[2,3] Possible reasons are disturbed metabolism, increased nutritional requirements and decreased nutrient intake.[4]

Malnutrition can impair physical function, performance status and muscle strength, all of which lead to a significant decline in functional capacity (FC).[5,6] Malnutrition often goes unrecognized and can lead to serious consequences when patients begin cancer treatments as it can accelerate further weight loss and worsen appetite-reducing symptoms.[7] It may also lead to poor tolerance and delays in treatment.[8] The primary form of treatment for lung cancer is complete surgical resection; malnourished patients who undergo surgery often spend a longer time in hospital and experience more postoperative complications compared to adequately-nourished patients.[9,10]

Malnutrition can be a modifiable risk factor for surgery.[4] Early identification and treatment of nutrition deficiencies might improve FC and rates of long-term survival in patients with lung cancer.[11] Nutrition assessment tools such as the Subjective Global Assessment (SGA) and Patient-Generated SGA (PG-SGA) can quickly identify and classify patients with malnutrition.[7] Comprehensive preoperative nutrition assessment and intervention to replenish nutritional reserves should be initiated before surgery to prepare patients for the catabolic demands of surgery and aid with maintaining and quickly regaining their FC following treatment. We studied cancer patients undergoing lung resection with the aims to (1) characterize those with varying degrees of malnutrition, (2) examine the association between malnutrition and baseline FC, and (3) examine the extent to which patients would benefit from a preoperative multimodal prehabilitation program that includes exercise training, nutrition supplementation and psychological support.

5.3 Methods

Participants

This study is a secondary analysis of data from 162 lung cancer participants from 1 randomized controlled trial (RCT) (ethics approval code 14-193-GEN), 1 cohort study (REB 2021-6788) and 1 pilot RCT (REB 2020-5633). All participants were adults scheduled for elective lung cancer resection from November 2014 to February 2020. Patients with insufficient comprehension of English or French, premorbid conditions that contraindicated exercise (severe cardiovascular and neuromuscular diseases) and metastatic cancer were excluded. All trials were approved by the Research Ethics Board.

Study design

Approximately 4 weeks before their scheduled operation, each eligible participant met with a registered dietitian and nutrition status was evaluated using the PG-SGA as previously described.[12] The evaluation is based on features of medical and diet history (weight change, dietary intake change, gastrointestinal and other symptoms that have persisted for >2 weeks, and changes in FC) and physical examination (loss of subcutaneous fat, muscle wasting, ankle/sacral edema, and ascites). The evaluation was adapted from the SGA, specifically developed for and validated in patients with cancer,[13,14] and has been accepted as the standard for nutrition assessment for patients with cancer by the Oncology Nutrition Dietetic Practice Group of the American Dietetic Association.[15] Unlike the SGA which is categorical in nature, the PG-SGA measures nutrition status on a continuous scale on which the higher the score, the greater the risk of malnutrition. The scoring system allows for the detection of subtle changes in nutritional status over a short period of time and allows patients at risk for malnutrition to be identified and triaged for nutrition intervention. The nutrition triage levels are defined as PG-SGA score of 0-3 (an intervention by a dietitian is unnecessary), 4-8 (necessitating an intervention by a dietitian) and ≥9 (in critical need for nutrition intervention). For simplicity of reporting and ease of language, the nutrition triage levels will be herein referred to as low nutrition risk (PG-SGA scores 0-3), moderate nutrition risk (PG-SGA scores 4-8) and high nutrition risk (PG-SGA scores ≥9).

Following baseline assessment, patients received either a multimodal prehabilitation intervention as per the original studies, or standard hospital care (control).

Prehabilitation program

Patients in the prehabilitation intervention underwent a similar program as previously described [16] for 4 weeks prior to surgery. Briefly, a certified kinesiologist assessed, trained and prescribed a personalized exercise program for each participant following the guidelines of the American College of Sports Medicine and derived from baseline assessment.[17] The home-based training included moderate intensity aerobic training (eg, bicycling, walking, swimming) 5 days per week for 30 minutes, resistance exercises targeting major muscle groups performed using elastic bands, and flexibility exercises. Patients were provided an information booklet containing instructions and figures demonstrating all elements of the program, as well as exercise progressions. The booklet also included a journal in which patients recorded all activities related to the program.

A registered dietitian conducted a comprehensive dietary assessment based on a 3-day food diary, anthropometric measurements, presence of nutrition-impact symptoms, biochemical data (anemia, C-reactive protein [CRP], serum albumin level, and glycated hemoglobin [A1C]), and a nutrition-focused physical exam completed at baseline. Based on the nutrition assessment, an individualized care plan was devised to meet each patient's need. Additionally, standard instructions included how to optimize a diet by eating well-balanced meals with a focus on meeting an adequate dietary protein intake. Whey protein supplementation was prescribed as needed to achieve a total protein intake of 1.2-1.5 g/kg/d as per recommendations of the European Society for Clinical Nutrition and Metabolism (ESPEN).[18]

Patients met with psychology-trained personnel (nurses with psycho-social specialization) once at baseline for individual sessions and were provided with techniques aimed at reducing anxiety, such as relaxation exercises based on imagery, visualization and deep breathing exercises. Patients were also provided with a compact disc with relaxation exercises to be used at home 2-3 times a week. Additional sessions were provided as needed.

Control group

Two of the 3 pooled studies contained a control group. The control groups did not receive a preoperative intervention.

Perioperative standard of care

All patients followed a standardized enhanced recovery pathway for lung surgery including preoperative patient education, early feeding, and mobilization after surgery.[19]

Outcome measures

The primary outcome was FC as measured by the 6-minute walk test (6MWT). It is the most widely used test to measure FC in individuals with chronic lung diseases and has been previously validated in cancer populations[20] and the chronic obstructive pulmonary disease (COPD) population as a measure of exercise tolerance.[21] Participants were instructed to walk back and forth along a 15-meter stretch of hallway for 6 minutes at a pace that would make them tired by the end of the walk. The total distance covered in 6 minutes was recorded in meters. If needed, participants were allowed to rest during the test, although the timer was not stopped. The standardized protocol and script, as per American Thoracic Society guidelines, was used.[29] The 6MWT was measured at baseline and repeated within one week of surgery.

Other outcomes measures included physical outcomes such as the timed-up and go (TUG)[22] and grip strength test,[23] anthropometrics such as weight and body composition measured by body impedance analysis, waist circumference; and blood biochemistry measures such as serum albumin level, CRP, hemoglobin concentrations and A1C (%). Total physical activity energy expenditure was estimated by the Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire. Participants estimated the number of total hours spent performing 41 listed activities of various intensities during the previous week and an estimate of weekly energy expenditure (kcal/kg per week) was determined.[24]

Statistical analysis

Normality of the data distribution was assessed with the Shapiro–Wilk test. A 1-way analysis of variance (ANOVA) with post-hoc Bonferroni corrections to adjust for multiple comparisons was conducted to examine differences in baseline FC across PG-SGA nutrition triage levels, which were defined as PG-SGA scores 0-3 (low nutrition risk), PG-SGA scores 4-8 (moderate nutrition risk) and PG-SGA scores ≥ 9 (high nutrition risk). To further characterize patients with poor nutritional status, baseline characteristics were compared with 1-way ANOVA or the Kruskal-Wallis *H*-test, as appropriate, for continuous variables and $\chi 2$ test for categorical variables. Per protocol, a secondary analysis using a factorial analysis of covariance (ANCOVA) with Bonferroni corrections while adjusting for COPD, anemia and smoking status was carried out to examine the effect of prehabilitation vs. control (2 levels) and degree of malnutrition (3 levels) on the mean change in 6MWT over the preoperative period. Statistical significance was defined as a P value less than 0.05. All analyses were performed with IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp, Armonk, NY).

5.4 Results

Of the 162 patients analyzed, 83 (51.2%) had a PG-SGA score between 0-3 (low nutrition risk group), 61 (37.7%) had a PG-SGA score of 4-8 (moderate nutrition risk group) and 18 (11.1%) had a PG-SGA score of ≥9 (high nutrition risk group). Thus, the prevalence of nutrition vulnerability in the current study, as determined by the PG-SGA nutrition triage levels, was 48.8%. Baseline demographic and clinical characteristics are described in Table 1. Compared to the low nutrition risk group, high nutrition risk patients had significantly higher rates of COPD and anemia, and the majority of said patients were current smokers. Furthermore, patients in the moderate nutrition risk and high nutrition risk groups scored significantly worse in all physical function outcomes (6MWT, TUG, absolute grip strength and total energy expenditure) compared to the low nutrition risk group. Lastly, the high nutrition risk group had significantly lower serum albumin (mean still within reference range) and hemoglobin levels and significantly higher A1C concentrations compared with the other groups. Tumor stage, length of hospital stay, age, weight, body composition and other clinical characteristics were not different across all groups.

Participants' baseline mean 6MWT distance is shown in Figure 1. A 1-way ANOVA showed a statistically significant difference in baseline 6MWT among groups, $F_{2,161} = 6.915$, $P = .001$. Bonferroni corrected post-hoc tests showed that patients in the low nutrition risk group had significantly higher 6MWT distance with a mean of 484 m (standard deviation [SD] = 88) compared to the moderate nutrition risk (mean of 432 m [SD 107], $P = .005$) and high nutrition risk groups (416 m [SD = 90], $P = .022$).

Thirty percent of missing data were for the 6MWT measurement at the preoperative visit because of a failure to follow-up. Patient characteristics and outcomes for the missing sample were similar to the characteristics of the entire cohort, suggesting the data were missing completely at random (Table S1).

A factorial ANCOVA was conducted to examine the effect of nutrition status (PG-SGA) and effect of intervention (prehabilitation n = 76 vs. control n = 37) on mean change in 6MWT during the preoperative period while adjusting for COPD, anemia and smoking status. There was a non-significant main effect of PG-SGA group, $F_{2, 104} = .013$, $P = .987$, partial $\eta^2 = <.001$, a significant main effect of intervention allocation, $F_{1, 104} = 15.34$, $P < .001$, partial $\eta^2 = .129$, and a significant interaction between PG-SGA group and intervention allocation, $F_{2, 104} = 3.65$, $P = .029$, partial $\eta^2 = .066$.

The adjusted mean change in 6MWT during the preoperative period between patients receiving prehabilitation (n = 76) compared to the control intervention (n = 37) was 35.2 m (95% confidence interval [CI] 19.2-51.2) vs. -12.7 m (-30.4 to 5), respectively. Stratification by PG-SGA groups resulted in an adjusted mean change in 6MWT between the prehabilitation and control intervention of 18.1 m (3.8-32.3) vs. 5.6 m (-14.1 to 25.4) in the low nutrition risk group (n = 63), 28.5 m (11-46) vs. -4 m (-31.3 to 23.4) in the moderate nutrition risk group (n = 40), and 58.9 m (16.7-101.2) vs. -39.7 m (-80.2 to 0.826) in the high nutrition risk group (n = 10), respectively (Figure 2). The mean difference in change in 6MWT between prehabilitation and control within each PG-SGA group was 12.5 m (-11.7 to 36.6) in the low nutrition risk group, 32.5 m (-0.475 to 65.5) in the moderate nutrition risk group and 98.7m (40.1-157.2) in the high nutrition risk group. Simple main effects analysis showed no statistically significant differences between intervention allocation in the low nutrition risk group ($P = .309$), however there was a nearly significant (*P* = .053) and statistically significant (*P* = .001) difference between intervention allocation in the moderate nutrition risk and high nutrition risk groups.

To try to explain these findings, the changes over the preoperative period in various outcomes were compared across PG-SGA groups. There were no significant differences in change in total physical activity energy expenditure (*P* = .878), grip strength of the right (*P* = .464) and left (*P* = .539) hand, weight (*P* = .215) and fat-free mass (*P* = .150) between PG-SGA groups.

5.5 Discussion

The findings of the present study suggest that patients classified with moderate nutrition risk and high nutrition risk (according to the PG-SGA) exhibit significantly lower physical performance at baseline, including FC, TUG, absolute grip strength and self-reported physical activity levels, compared with low nutrition risk patients. The greater proportion of patients with COPD and anemia, along with the mean elevated A1c and lower serum albumin concentration, in the high nutrition risk compared with the low nutrition risk group, suggests that disease burden significantly contributed to these malnourished states. High nutrition risk patients receiving multimodal prehabilitation had significantly greater improvements in FC over the preoperative period compared to the control group receiving standard of care.

These findings highlight the significant impact that balanced nutrition has on physical status and suggests that high nutrition risk patients have the most to gain (functionally) from multimodal prehabilitation compared with low nutrition risk patients. The finding that patients with a lower baseline functional reserve improved the most is consistent with previous work in colorectal cancer patients awaiting surgery.[17] These findings may have important clinical and practical implications, as multimodal prehabilitation is resource intensive; thus, targeting at-risk populations would be an attractive strategy to increase its effectiveness.

We identified that high nutrition risk patients suffered from low FC before surgery. Poor FC is considered a strong predictor of postoperative complications and mortality in lung cancer.[9,25,26] A 6MWT performance of <409 m is predictive of a peak oxygen uptake (peak VO_2) <15 ml/kg/min measured with cardiopulmonary exercise testing, the criterion standard reference for the evaluation of physical fitness.[27] A peak VO_2 less than this threshold is a well-validated, independent predictor of both postoperative morbidity and decreased mid-term survival after major elective surgery.[28,29] In older adults, the inability to walk 400 m in 6 minutes (a corresponding gait speed below the average of 1.1 m/s) is associated with a greater risk of mortality, cardiovascular disease, limitation in mobility, and disability.[30,31] Furthermore, patients undergoing major noncardiac surgery with a 6MWT of <427 m have been considered to be at high perioperative risk.[27] Based on this, our study patients in the moderate nutrition risk and high nutrition risk groups with baseline 6MWT of 432 m (SD = 107) and 416 m (SD = 90) are considered at high risk; however, these very patients experienced the largest improvements in FC following multimodal prehabilitation. The ability for individuals to improve their FC after a prehabilitation intervention, as seen in the current study, can have significant positive consequences on surgical outcomes and recovery.[17] Unfortunately, the present study was not powered to examine rates of postoperative complications.

It is worth highlighting that according to the PG-SGA triage classification, nearly 50% of patients in the present study were found to be in need of a nutrition intervention (of varying intensities) using the PG-SGA classification. Despite published evidence, support from surgeons and demonstrated cost-effectiveness, only 1 in 5 patients receive any preoperative dietary intervention, and only 1 in 5 hospitals have screening processes for nutritional risk.[32-34] Additionally, many screening processes rely on serum albumin levels, which can be an unreliable marker of nutrition status, especially in patients with an ongoing inflammatory response (only 4.4% of patients in the present study had a serum albumin <35 g/L).[35] Furthermore, although a BMI of <18.5 kg/m^2 is often used as a criteria to identify malnutrition, it is not reflective of body composition, and sarcopenia (reduced muscle mass and strength) is associated with worse outcomes (only 3.1% of patients in the present study had a BMI <18.5 kg/m^2).[36] Other screening tools based on prior weight loss and decreased appetite such as the Canadian Nutrition Screening Tool may be more appropriate to identify patients at risk of malnutrition, requiring further nutritional assessment.[37]

There is no consensus regarding a single malnutrition assessment tool for use in oncology settings;[38] however, the current guidelines of the ESPEN recommend the use of the PG-SGA as an assessment tool to identify malnutrition.[39] The PG-SGA has been validated for use in cancer populations.[14] In fact, in comparison to the SGA (widely accepted as the "criterion standard" for assessment of malnutrition), the PG-SGA score has a sensitivity of 98% and a specificity of 82% at predicting malnutrition classification. Additionally, PG-SGA-diagnosed malnutrition is predictive of prolonged hospitalization for oncology patients.[14] Standardizing the use of nutrition assessments, such as PG-SGA or SGA, would allow for timely identification and treatment of perioperative malnutrition..

This study had several limitations. First, nutrition assessment using the PG-SGA was not repeated at follow-up visits. This information may have allowed us to measure the change in PG-SGA score to evaluate the change in nutrition status over the preoperative period and to specifically identify which of the PG-SGA categories were most affected by multimodal prehabilitation such that future programs can incorporate more targeted interventions. Second, because of the exploratory nature of the study, nutrition records (ie. patient food diaries, nutrition care plan, and compliance) were not systematically recorded, and therefore, we do not have data on the success of the implementation. Future studies should be more precise in the recording of comprehensive, detailed nutritional outcomes. Third, because of the well-known interaction between exercise and nutrition on physical function, it is not possible to determine which of these prehabilitation components had the greatest impact on FC. Fourth, the small sample size and wide CI in the high nutrition risk group suggest imprecise estimates, and the unequal sample sizes across each PG-SGA group violated the assumption of homogeneity of variances, however a factorial ANCOVA is robust enough to control for type 1 error. Fifth, we conducted a per protocol analysis and there was a high proportion of missing data (30%) for the 6MWT measurement at the preoperative visit due to loss to follow-up, which might have overestimated our findings; however, because baseline characteristics such as age, weight and baseline 6MWT were not statistically different in the missing compared to non-missing groups except for sex (Table S1), the data is likely missing completely at random.

5.6 Conclusion

In conclusion, this study demonstrated that high nutrition risk lung cancer patients awaiting surgery have significantly lower baseline FC compared with low nutrition risk patients. Moreover, only the high nutrition risk patients receiving multimodal prehabilitation experienced a significant improvement in FC over the preoperative period. Therefore, screening and assessment of malnutrition in surgical cancer patients should be considered and followed by personalized therapeutic interventions.

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Conflict of interest

None declared.

Author Contributions

Vanessa Ferreira and Francesco Carli equally contributed to the conception and design of the research; Vanessa Ferreira and Francesco Carli contributed to the design of the research; Vanessa Ferreira, Claire Lawson, and Chelsia Gillis contributed to the acquisition and analysis of the data; Vanessa Ferreira, Claire Lawson, and Chelsia Gillis contributed to the interpretation of the data; Vanessa Ferreira, Claire Lawson, Celena Scheede-Bergdahl, and Stéphanie Chevalier drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Table 1. Baseline demographic and clinical characteristics

Variable	Low nutrition risk	Moderate nutrition risk	High nutrition risk	P-value
	N=83	**N=61**	**N=18**	
Age, y	68.1 (9.3)	67.1 (10.4)	70.7 (8.9)	.369
>75y	38 (45.8%)	24 (39.3%)	9 (50%)	.636
Sex-male, n (%)	45 (54.2%)	23 (37.7%)	7 (38.9%)	.116
Weight, kg	73.9 (62-87.3)	71.2 (60.3-85.8)	63.5 (56.1-77)	.178
BMI, kg/m^2	26.9 (22.8-30)	27.5 (22.9-32.7)	23 (20-28.6)	.134
Body fat, % weight	32.8 (9.7)	36.2 (12.4)	31.2 (12.3)	.112
Fat-free mass, kg	48.8 (10.6)	46.2 (11)	45.1 (9.8)	.22
Waist circumference, cm	97.9 (14.2)	98.9 (15.5)	89.8 (15.3)	.09
Comorbidities, n (%)				
Diabetes	8 (9.6%)	11 (18%)	5 (27.8%)	.097
Hypertension	32 (38.6%)	24 (39.3%)	6 (33.3%)	.897
Cardiovascular disease	8 (9.6%)	12 (19.7%)	5 (27.8%)	.079
COPD	11 (13.3%)	16 (26.2%)*	8 (44.4%)*	.008
Anemia	2 (2.4%)	3 (4.9%)	3 (16.7%)*	.041
Hypothyroidism	14 (17.1%)	12 (19.7%)	3 (16.7%)	.912
Hypercholesterolemia	31 (37.3%)	23 (37.7%)	4 (22.2%)	.443
Neoadjuvant therapy, n (%)	7 (8.4%)	5 (8.2%)	4 (22.2%)	.176
Tumor Stage[a]**,** n (%)[b]				
0	18 (23.1%)	9 (17%)	1 (6.7%)	
1	43 (53.1%)	30 (56.6%)	8 (9.9%)	
2	9 (11.5%)	8 (15.1%)	4 (26.7%)	
3	8 (10.3%)	6 (11.3%)	2 (13.3%)	.656
Length of hospital stay, d	3 (2-4.3)	3 (2-5.5)	3 (1.8-4.8)	.378
Smoking status, n (%)				

Current smoker	14 (16.9%)	17 (27.9%)	7 (38.9%)*	
Ex-smoker	17 (20.5%)	20 (32.8%)	5 (27.8%)	
Non-smoker	52 (62.7%)	24 (39.3%)*	6 (33.3%)*	.027
Six-minute walking distance, m				
Actual	483.8 (88.2)	432.3 (107.1)*	415.8 (89.9)*	.001
Percent predicted	76.3 (69.6-84.7)	71.6 (62.6-79.9)*	70.2 (58.9-77.2)*	.016
<400 meters, number of patients, n (%)	13 (15.7%)	20 (32.8%)	4 (22.2%)	.054
Timed-up and go, s	6.2 (5.4-7.3)	7 (6.3-7.7)*	7.4 (6.1-9)*	.001
Grip strength				
Right hand, kg	28 (22-32.7)	24 (18-30)*	23.6 (19.8-29)	.042
Right hand *z*-score	-0.8 (1.3)	-1 (1.1)	-1 (0.8)	.544
Left hand, kg	27 (10.3)	23.2 (8.3)*	22.4 (7.2)	.026
Left hand *z*-score	-1 (1.3)	-1.3 (1.1)	-1.4 (0.8)	.190
Total physical activity energy expenditure, kcal/kg/week	65.6 (27.6-97.9)	48 (19-74.8)*	15.8 (10.4-32.5)*,**	<.001
Blood biochemistry				
C-reactive protein, mg/l	2 (.9-5.4)	2.8 (1.2-5.7)	6.3 (1.6-106.3)	.112
Serum albumin level, g/l	43.1 (2.8)	42 (5.3)	38.1 (4.5)*,**	<.001
A1C, %	5.7 (5.4-6.1)	6 (5.4-6.4)*	6.2 (5.7-7.3)*	.021
Hemoglobin, g/l	140.8 (13)	136.1 (14.2)	126.3 (20.3)*	.001

Data are presented as mean (standard deviation) analyzed by 1-way analysis of variance and post hoc Bonferroni, medians (interquartile range are analyzed by Kruskal-Wallis, and frequencies (percentages) are analyzed by $\chi 2$. Total physical activity energy expenditure assessed by the Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire. Normal ranges for blood biochemistry markers are as follows: C-reactive protein = 0–5 mg/L; serum albumin levels = 38–52 g/L; A1C < 6%; hemoglobin = 135–175 g/L.

Abbreviations: A1C, glycated hemoglobin; BMI, body mass index; COPD, chronic obstructive pulmonary disorder.

a Pathological tumor staging according to eighth edition classification system.

b Tumor stage: 16 (9.9%) patients are missing data as they are still awaiting surgery or the staging report is not available.

*Significant difference ($P < .05$) compared with the low-nutrition-risk group.

**Significant difference ($P < .05$) compared with moderate-nutrition-risk group.

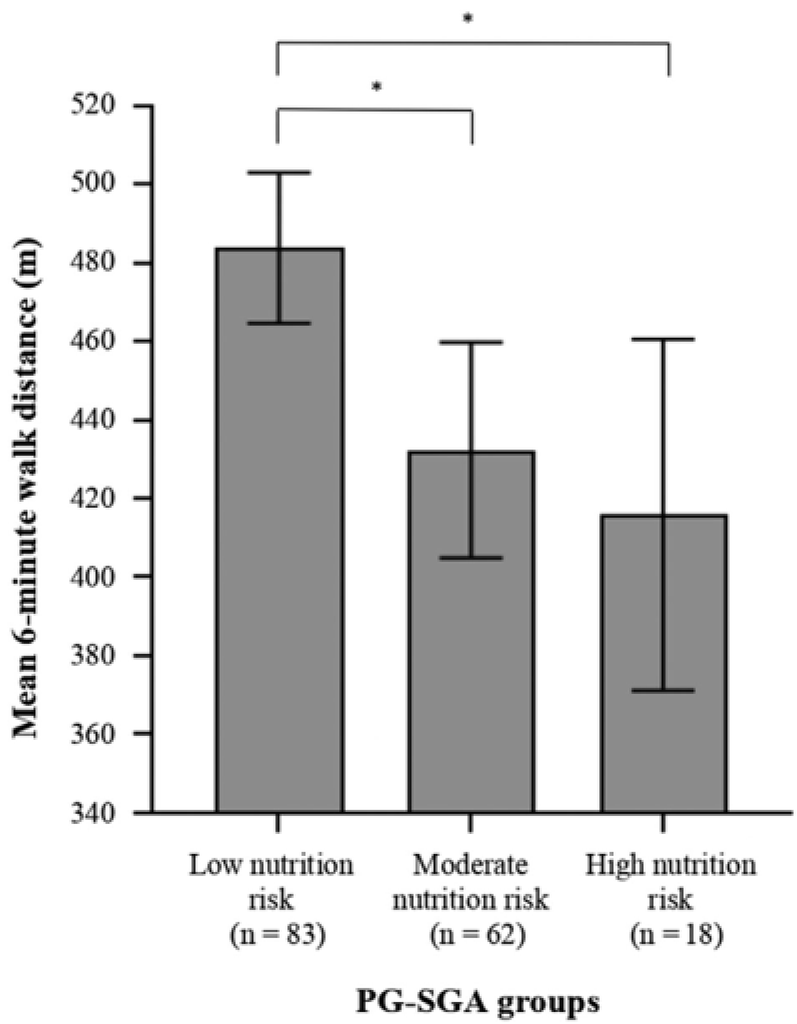

FIGURE 1. Mean 6-minute walk test distance at baseline between PG-SGA triage groups shown as a bar graph. The whiskers represent 95% confidence intervals. *P < .05. PG-SGA, Patient-Generated Subjective Global Assessment

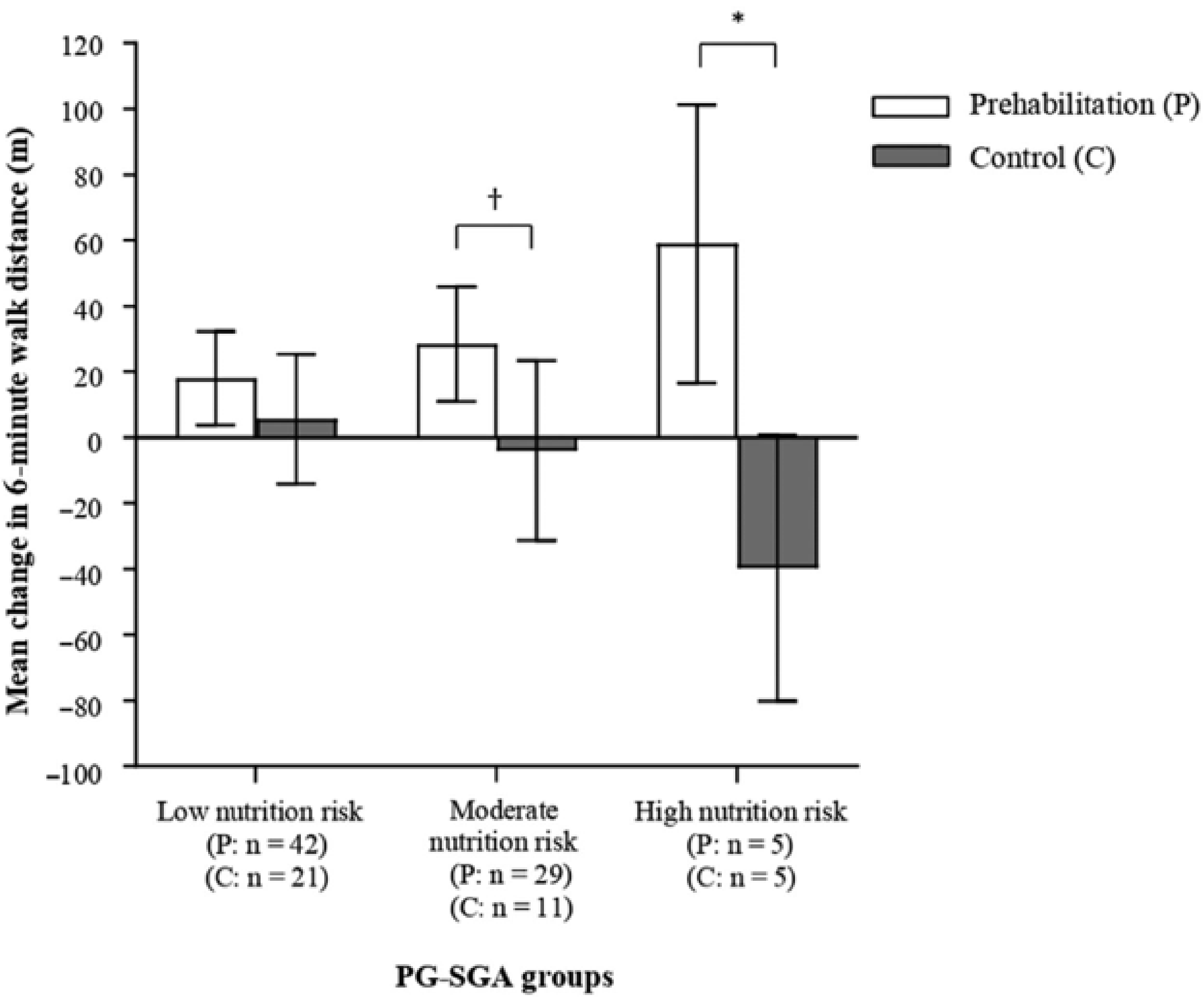

FIGURE 2. Adjusted mean change in 6-minute walk test between PG-SGA groups and allocation to the prehabilitation and control interventions during the preoperative period shown as a bar graph. The whiskers represent 95% confidence intervals. †P = .053, *P < .05. C, control; P, prehabilitation; PG-SGA, Patient-Generated Subjective Global Assessment

Supplemental Table 1. Baseline characteristics between patients with missing data compared to patients with no missing data.

Variable	Non-missing (n=113)	Missing (n=49)	P-value
Age, years	68 (9.7)	68 (9.8)	0.885
Sex-male, n (%)	44 (58.7)	31 (41.3)	0.004
Weight, kg	74 (18.7)	73.5 (16.4)	0.869
BMI, kg/m^2	27.7 (6)	26.7 (5.7)	0.33
Baseline six-minute walking distance, meters	455 (93.1)	461 (113.5)	0.237
Timed-up and go, seconds	7.1 (2)	7.4 (3.4)	0.483
Total physical activity energy expenditure, kcal/kg/week	70.1 (72.2)	55.8 (42.5)	0.267

Data are presented as mean (SD) or n(%).

Bridging statement 3: Chapter 6

The secondary analysis revealed that malnutrition was indeed prevalent in lung cancer patients awaiting surgery with nearly 50% either at moderate or high nutrition risk according to the PG-SGA. We also found that these patients with poor preoperative nutritional status also had poor preoperative physical function. However, importantly, the lung cancer patients at high nutrition risk receiving multimodal prehabilitation experienced significant improvements in preoperative functional capacity. Together these findings highlight the importance of identifying malnutrition and optimizing nutritional status prior to surgery with targeted interventions.

Consequently, for my final thesis study (Chapter 6) I conducted a randomized controlled pilot trial to assess the feasibility of delivering a novel multimodal prehabilitation intervention that includes a mixed-nutrient supplement containing whey protein, leucine, omega-3 fatty acids and vitamin D. Furthermore, as I learned from my first thesis study regarding the prehabilitation intervention being home-based and the comparative group receiving rehabilitation, my final study included a prehabilitation group that received supervised exercise training and a control group that received standard hospital care. I believe that these additions and changes to the first multimodal prehabilitation intervention will provide superior results with regard to functional recovery after lung cancer surgery.

Chapter 6: Feasibility of a novel mixed-nutrient supplement in a multimodal prehabilitation intervention for lung cancer patients awaiting surgery: a randomized controlled pilot trial

THESIS STUDY 4

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6.1 Abstract

Objective: To investigate, in lung cancer patients awaiting elective surgery, the feasibility of delivering a novel four-week multimodal prehabilitation intervention and its effects on preoperative functional capacity and health-related quality of life (HRQoL), compared to standard hospital care.

Methods: This was an open-label, randomized controlled trial of two parallel arms: multimodal prehabilitation combining a mixed-nutrient supplement with structured supervised and home-based exercise training, and relaxation-strategies (Prehab) or standard hospital care (Control). Feasibility was assessed based on recruitment and adherence rates to the intervention and study outcome assessment. Functional capacity, measured by the six-minute walk test (6MWT), and HRQoL were measured at baseline and after four weeks (prior to surgery).

Results: Within 5 months, 34 patients were enrolled and randomized (2:1) to Prehab (n=24; median age=67 years) or Control (n=10; median age=69 years); recruitment rate of 58.6%. The study was interrupted by the COVID-19 pandemic. Adherence to the prescribed intensity of the supervised exercise program was 84.1% (SD 23.1). Self-reported adherence to the home-based exercise program was 88.2 % (SD 21) and to the nutritional supplement, 93.2% (SD 14.2). Adherence to patients' preoperative assessment was 82% and 88% in Prehab and Control, respectively. The mean change in 6MWT in Prehab was 21 m (95% CI -2.7 to 44.6, p=0.08) compared to -17 m (-53 to 18.8, p=0.338) in Control; no difference between groups (interaction p= 0.08). No improvements in HRQoL.

Conclusion: Within a preoperative time-frame, it was feasible to deliver this novel multimodal prehabilitation intervention in lung cancer patients awaiting surgery.

6.2 Introduction

Reduced functional capacity and low muscle mass are common in patients with lung cancer as a result of impaired pulmonary function, smoking, sedentary behaviour and poor nutrition, and further accentuated by aging and cancer itself [1, 2]. Poor functional capacity is considered a strong predictor of postoperative complications, mortality and long-term survival in lung cancer [3].

Multimodal prehabilitation, including exercise, nutrition and anxiety-reducing strategies, aims to enhance functional capacity in anticipation of the predictable detrimental effects of surgery [4, 5] and facilitate postoperative recovery of functional capacity [6]. In lung cancer, evidence on the benefits of preoperative exercise is abundant however there is a paucity of research on the role of nutrition in prehabilitation.

Malnutrition is common in cancer patients [7] due to a combination of increased nutritional requirements, reduced food intake and disturbed metabolism [8]. Protein has been the nutrient of focus in the majority of perioperative intervention studies with whey as the choice protein [9]. However, there is emerging evidence on the beneficial roles of leucine, vitamin D and omega-3 fatty acids on muscle health and the prevention of functional decline [10].

The aim of this pilot trial was to assess the feasibility of delivering a novel four-week multimodal prehabilitation intervention combining a mixed-nutrient supplement with structured exercise training and relaxation-strategies for patients with lung cancer awaiting surgical resection. We tested the two-fold hypothesis that during the preoperative period 1) the novel multimodal prehabilitation intervention is feasible and that 2) such an intervention will improve preoperative functional capacity compared to standard hospital care. The impact of multimodal prehabilitation on preoperative health-related quality of life (HRQOL) was also assessed. Results will inform the design of a larger trial.

6.3 Methods

Participants

The study was approved by the McGill University Health Centre (MUHC) Research Ethics Board (REB 2020-5633) and registered (ClinicalTrials.gov registration: NCT04610606). Consecutive adult patients scheduled for elective video-assisted thoracic surgery or open thoracotomy surgery of lung cancer stages I, II or IIIa, were approached following their first appointment with their surgeon at the MUHC-Montreal General Hospital, a single tertiary hospital located in Montréal, Québec, Canada. Written informed consent was obtained in eligible patients. Exclusion criteria included prior recent (<3 months) chemotherapy, comorbidities contraindicating exercise, walking aids other than a cane, glomerular filtration rate <30 mL/min/m^2, allergy to milk or seafoods, chronic use of anti-coagulants, hypercalcemia, hypervitaminosis D, insufficient understanding of English or French language to provide informed consent.

Study design

This was an open-label, randomized controlled trial of two parallel arms: multimodal prehabilitation (Prehab) and standard of care (Control). Following baseline assessment, patients were randomized to either group, in a 2:1 Prehab:Control ratio using a computer-generated randomization scheme by block of three, with stratification by sex and functional capacity (< or ≥ 400 m on the 6MWT), a better predictor than age per se, to balance groups since those with less functional capacity may have more potential to improve [11].

This study was initially intended to follow patients for four weeks preoperatively and 8 weeks postoperatively with a total of 4 assessments: baseline, preoperatively, 4 and 8 weeks postoperatively. Unfortunately, due to the COVID-19 pandemic and ensuing cancellations of surgeries and closure of the clinic, the study was stopped in March 2020 resulting in a high proportion of missing data for the postoperative 6MWT measurements. Thus, for the purpose of this study, results from the preoperative period are presented.

Intervention

The multimodal prehabilitation intervention lasted for 4 weeks pre-surgery and included a personalized exercise, nutrition and relaxation program. The exercise program consisted of aerobic and resistance training, supervised by a certified kinesiologist once per week combined with unsupervised sessions at home. The exercise intensity for the supervised aerobic training program corresponded to 90% of the workload achieved at the anaerobic threshold during the cardiopulmonary exercise test performed at baseline. For the unsupervised sessions at home, participants were asked to 1) accumulate 30 min/day of aerobic training of their preferred type of modality, at a moderate intensity corresponding to 12-15 on a Borg scale of 6 to 20,[12] including a 5-min warm up and cool down at an intensity of 10-11 and 2) perform 10 resistance exercises targeting major muscle groups with either the use of a Theraband®, body weight or free weights, every second day in 1-2 sets of 8-15 repetitions, followed by stretching exercises. Exercise progressions were provided to ensure a continuous stimulus when adaptations occurred. The exercise program was individualized based upon initial assessments and in line with the American College of Sport Medicine (ACSM) standards [13].

Participants received an individualized comprehensive dietary assessment from a registered dietitian on how to optimize their diet with a focus on protein-rich foods to meet protein intake of >1.2 g/kg/d and energy of 25-30 kcal/kg/d [7]. The nutritional assessment was based on a 3-day food diary, anthropometric measurements, presence of nutrition-impact symptoms, biochemical data such as anemia, C-reactive protein, albumin and glycated hemoglobin (HbA1c), and a nutrition-focused physical exam completed at baseline. The supplement consisted of whey protein isolate (NZ All Natural Whey Protein Isolate, ProteinCo., Quebec, Canada) consumed in 2 daily doses, one before breakfast and one at bedtime. Pre-weighted doses of 10 or 20 g were given depending on usual protein intake from foods with the goal of reaching ≥1.5 g/kg/d, providing ≥25 g/meal. To each protein dose, 3 g of leucine (Leucine, ProteinCo., Quebec, Canada) were added for a total of 6 g/d. Participants received whey protein + leucine doses pre-mixed in powder form, in unlabeled containers to dilute in 125 mL water. In addition, participants were asked to ingest a daily dose of fruit-flavored fish oil containing vitamin D (NutraSea+D™ Omega-3, NutraSea®, Ascenta, Dartmouth NS, Canada) provided as a liquid oil, in an unlabeled brown bottle. They received a dosing cup, pre-marked to 10 mL, providing 1500 mg EPA, 1000 mg DHA and 2000 IU vitamin D3.

Additionally, patients received private consultations with psychology-trained personnel whereby techniques aimed at reducing anxiety such as relaxation exercises based on imagery, visualization and deep breathing were practiced. Patients were also provided with a compact disc with relaxation exercises to be performed at home 2-3 times per week.

Patients were given an information booklet containing instructions and figures demonstrating all elements of the program and included a journal where patients recorded all activities related to the program. Adherence to the intervention was assessed based on responses in the patient information booklet, the number of empty supplement containers/bottles returned and asking a set of standardized questions over the telephone or directly in-person, on a weekly basis.

Patients in the control group received standardized hospital care and were provided with education on the benefits of a healthy diet and physical activity but without specific information. All patients were treated within the context of the enhanced recovery after surgery (ERAS) protocol [14]. Additionally, patients received smoking cessation counseling if needed.

Outcomes

Feasibility of delivering the intervention was assessed based on recruitment and adherence rates to the prescribed intervention and study outcome assessments (completing full battery of tests), measured as a percentage. Specifically, adherence to the prescribed exercise and nutrition intervention was calculated individually per subject on a weekly basis and averaged over 4 weeks.

Secondary outcomes were measured at baseline and preoperative visit, and include functional capacity measured by the six-minute walk test (6MWT), which measures the distance walked over six minutes in a 15-m corridor. It is the most widely used test to measure functional capacity in individuals with chronic lung disease, including those with lung cancer and has been previously validated in the chronic obstructive pulmonary disease (COPD) population as a measure of exercise tolerance [15]. The assessor followed a standardized protocol and script, as per American Thoracic Society guidelines [16].

Health-related-quality-of-life (HRQoL) was measured by the Functional Assessment of Cancer Therapy-Lung (FACT-L) and the 36-Item Short Form Health Survey (SF-36). The FACT-L is a validated, disease-specific instrument [17]. The SF-36 is the most widely used HRQoL measure and is validated in the surgical population [18]. Higher scores on the FACT-L and SF-36 indicate better quality of life. Emotional state was assessed using the Hospital Anxiety and Depression Scale (HADS) [19] where the cut-off suggesting moderate-high anxiety and depression are scores ≥7 and ≥5, respectively [20]. Physical activity energy expenditure from light and moderate-vigorous intensity activities was measured by the Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire [21]. Nutritional status was assessed using the Patient-Generated Subjective Global Assessment (PG-SGA), a tool specifically developed for and validated in patients with cancer [22]. Higher scores indicated greater risk of malnutrition.

Other outcomes included body composition (lean and fat mass) [23] and physical function tests such as the timed-up and go (TUG), 30-second sit-to-stand, 30-second arm-curl and grip strength of the dominant and non-dominant hand, as previously described [24]. CPET for the measurements of oxygen consumption, power and heart rate at the anaerobic threshold (VO2 AT) and peak exercise (VO2 peak) were also assessed [25].

All outcomes that required in-person assessments such as body composition and physical function tests were collected pre-pandemic. Only data from questionnaires was collected virtually during the first month of the pandemic (mid-March to mid-April 2020).

Statistical analysis

As a pilot study designed to generate data on feasibility and adherence to the intervention and study tests, no power calculation was performed to identify statistical differences in 6MWT, HRQoL or other secondary outcomes. A sample size of 36 participants was deemed feasible and adequate to provide sufficient information to determine sample size for a definitive study [26].

Normality of data was assessed with the Shapiro–Wilk test. To compare baseline characteristics of continuous variables, a one-way analysis of variance (ANOVA) was conducted when the assumption of homogeneity of variances was met, otherwise a one-way Welch ANOVA was conducted. The Kruskal-Wallis test was conducted when the assumption of normality was not met. Categorical variables were compared using Pearson's Chi-Square test.

Due to the COVID-19 pandemic, in-person assessments were not possible resulting in a higher proportion of missing data than expected for the preoperative 6MWT measurement (n=9). To minimize bias, missing data for the 6MWT were handled with multiple imputations by fully conditional specification generating 10 different imputed datasets [27]. Standard errors accounted for variance both between and within imputations. The 6MWT was the only multiply imputed variable because it was the main secondary outcome of the present study and likely to be the primary outcome of a larger trial. Changes in the 6MWT over time (baseline to pre-surgery) and between groups (Prehab vs. Control) were analyzed using a mixed factorial ANCOVA while controlling for frailty score based on the Fried criteria [28] measured at baseline. Frailty score (continuous variable) was selected as it encompasses covariates that should be controlled for but not included in the model to avoid overfitting. A complete case analysis without imputation of missing values was conducted on all other secondary outcomes using a mixed factorial ANOVA. Statistical significance was defined as P value less than 0.05. All analyses were performed using IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.

6.4 Results

Recruitment

From October 2019 to March 2020, a total of 85 lung cancer patients scheduled for elective surgical resection were assessed for eligibility, of which 27 were ineligible (Figure 1). Out of the 58 patients approached, 24 were not recruited due to the following reasons: live too far (n = 9), not interested (n = 9), insufficient time (<2 weeks) until surgery (n = 3), too busy/overwhelmed (n = 2) and unable to contact (n = 1). Thirty-four patients consented and were randomized to Prehab (n = 24) and Control (n = 10), equalling a recruitment rate of 58.6%. Due to the COVID-19 pandemic, the study was stopped in March before all 36 patients were enrolled.

Adherence to intervention

The median number of supervised exercise sessions attended was 4 [IQR 3-4] in the Prehab group, corresponding to 1 supervised exercise session per week during the 4-week preoperative period. Adherence to the supervised exercise program, with regard to ability to complete all exercises at the prescribed intensity, was 84.1% (SD 23.1). Self-reported compliance to the unsupervised (home-based) exercise program was 88.2 % (SD 21) and to the nutritional supplement was 93.2% (SD 14.2), specifically 95% to the powder and 91.3% to the oil. Reported reasons for skipping, missing or stopping the supplements are as follows: complaints of indigestion due to the oil (n = 1, patient stopped taking it), heartburn (n = 2; one patient reported it from the powder and stopped taking it, the other patient reported it from the oil and stopped taking it halfway through the intervention however it was likely due to the patient's Barrett's esophagus condition) and regularly forgot to take the powder (n = 1). In all cases, these complaints happened with either the powder or the oil part of the supplement therefore, patients continued taking the other parts of the supplement. No adverse events related to any part of the intervention were reported.

Adherence to study outcome assessments

Thirteen patients (n = 10 in Prehab and n = 3 in Control; total of 38.2%) did not complete their preoperative assessment, the main reason being due to the COVID-19 pandemic (n = 9; Figure 1). On-line study questionnaires were provided to patients whose preoperative assessment was affected by the pandemic; 5 patients out of 9 completed them successfully. Excluding patients whose preoperative assessment was affected by the pandemic, 3 patients in the Prehab group did not complete their preoperative assessment out of 17 patients, equalling to 82% adherence rate. In the Control group, 1 patient refused their preoperative assessment out of 8, equalling to 88% adherence rate.

Patient characteristics and outcomes for the missing sample were similar to the characteristics of the entire cohort, suggesting the data were missing at random (supplemental Table 1).

Six-minute walk test

A mixed factorial ANCOVA adjusted for frailty status on the multiply imputed dataset showed no significant main effects of time ($F_{1,31}$ = 0.046, P = 0.856) or group ($F_{1,31}$ = 0.048, P = 0.829) and a nearly significant interaction effect of time x group ($F_{1,31}$ = 3.27, P = 0.08), over the preoperative period. Simple effects analysis showed a nearly significant mean change over time of 21 m (95% CI -2.7 to 44.6, P = 0.08) in the Prehab group and a mean change of -17 m (-53 to 18.8, P = 0.338) in the Control group with no significant difference in 6MWT between groups at the preoperative visit (P = 0.477).

Health-related quality of life

As reported in Figure 1, a total of 5 patients (n=4 in Prehab and n=1 in Control) completed their preoperative questionnaires virtually within the first month of the pandemic (mid-March to mid-April 2020). Per protocol analysis on outcomes for the SF-36, FACT-L, PG-SGA, HADS and CHAMPS questionnaires are presented in Table 2. The Control group reported a significant decrease in role limitation due to emotional problems (SF-36) and general health (SF-36), a nearly significant decrease in the mental component summary score (SF-36) and a nearly significant increase in emotional well-being (FACT-L). The Prehab group reported a significant decrease in physical functioning (SF-36). Both groups significantly improved in self-reported moderate-vigorous intensity physical activity.

Body composition and functional outcomes

Per protocol analysis (n = 14 Prehab and n = 7 control) showed no significant differences within or between groups for all body composition and functional outcomes except for the sit-to-stand test where there was a significant main effect of time (P = 0.002; supplemental table 2).

6.5 Discussion

This pilot study confirmed the feasibility of a novel four-week multimodal prehabilitation intervention in lung cancer patients awaiting surgery. Feasibility was based on an adequate recruitment rate and the high adherence rate to the intervention (supervised and home-based exercise program and nutritional supplements) and to the comprehensive set of assessments. Furthermore, there were no reported adverse events related to the intervention aside from one complaint of indigestion from taking the oil supplement and two complaints of heartburn from taking the oil or powder supplement.

The rate of recruitment of the present study (58.6%) was comparable to the 63% rate of a previous trial by our group comparing prehabilitation to rehabilitation in lung cancer patients and reported in colorectal cancer patients [29, 30]. The rate is deemed adequate for a larger trial if extrapolated over one year considering that recruitment was slowed during the Holiday period.

The acceptability of the mixed-nutrient supplement was high considering it consisted of both a powder to be taken twice daily and a liquid oil. This supplement was designed specifically to provide a nutrient-dense, palatable supplement in a small volume to avoid interference with usual food intake of patients who may experience low appetite. Similar high adherence rates to the same supplement provided to frail older adults was found previously, which was confirmed objectively from increased plasma phospholipid omega-3 fatty acids [31]. In the present study, very few patients reported complaints, and amongst those who did, the majority continued ingesting the supplement or at least the other half of the supplement.

No differences in functional or body composition outcomes were found between groups. Although this pilot study was not powered to determine the impact of prehabilitation on such outcomes, the change in the 6MWT of 21 m (95% CI -2.7 to 44.6) was trending towards improvement in the Prehab group. This is consistent with recent findings showing an improvement in the 6MWT of 28.6 ± 18.2 m in 30 lung cancer patients awaiting surgery following a preoperative exercise intervention [32]. Our findings may be meaningful since changes of 20 m and 14 m have been deemed clinically relevant in healthy older adults [33] and in patients undergoing abdominal surgery [34]. However, prehabilitation did not improve quality of life during the preoperative period which is similar to findings reported in earlier prehabilitation trials in colorectal cancer patients [35, 36] and a systematic review [37]. This may be explained by the fact that HRQoL questionnaires reflect overall quality of life of the previous 4 weeks, a time frame that includes receiving a cancer diagnosis, facing new challenges and learning new lifestyle behaviours, as in the case of prehabilitation. It is also important to note that a small portion of patients completed the questionnaires during the first month of the COVID-19 pandemic, which may have had an effect on their HRQoL and stress. The preliminary results of the current study are intended to serve as proof of concept and need to be confirmed in a large randomized study.

Preoperative exercise in lung cancer patients has shown overall positive results over the past two decades however, very few studies incorporate supervised training [38]. Our decision to include a weekly supervised exercise session followed recent evidence showing that it led to superior outcomes in functional capacity compared to non-supervised exercise training in colorectal cancer patients [39]. In addition, our exercise intervention was personalized to the patients' baseline fitness level. By setting the exercise intensity relative to the patient's capacity, as opposed to a standardized value, over-exertion and the associated risks were avoided.

To date, there are only four published studies that combine preoperative exercise and nutrition in lung cancer patients undergoing surgery [29, 40-42]. Even amongst other cancer types, preoperative nutrition interventions are often limited to dietary advice or whey protein supplementation [9]. The rationale for providing a mixed-nutrient supplement containing whey protein, leucine, omega-3 fatty acids and vitamin D is that these are the main nutrients involved in muscle health, which directly impacts functional capacity [10]. Through different mechanistic pathways such as stimulation of muscle protein synthesis and reduction of intramuscular fat infiltration and inflammation, these nutrients may potentiate the anabolic response stimulated by exercise [10, 43]. As well, the anxiety-reducing strategies aimed to help patients cope with stressful occasions throughout their treatment, promote emotional well-being and enhance participation in the program. Although it is not possible to disentangle the contribution of each component of the intervention, they are expected to complement one another.

The present study has several strengths. This is the first study, to our knowledge, to include a specifically tailored preoperative nutritional intervention beyond dietary advice and/or whey protein supplementation, in lung cancer patients undergoing surgery. Second, the trial was performed in a pragmatic, real-world peri-operative setting where patients underwent regular preoperative activities. Perioperative care proceeded as per usual hospital standards, without additional intervention aside from prehabilitation thus, results are highly generalizable to the surgical setting.

An open-label study design is a limitation for the associated risks of bias, including a possible placebo effect in the Prehab group and self-supplementation in the Control group. This design was chosen, as opposed to a blinded experiment, to encourage adherence to the nutritional intervention, given the aim to assess feasibility. Second, due to the behavioural nature of the intervention, Control patients may have sought out similar exercises on their own, as evidenced by the significant increase in self-reported moderate-vigorous intensity physical activity. This may have underestimated the comparative benefit of prehabilitation. Third, the unexpected high proportion of missing data at the preoperative visit, due to the COVID-19 pandemic is another limitation. Since these data were missing at random (supplemental Table 1), the preoperative 6MWT variable was handled with multiple imputations [27].

6.6 Conclusion

In conclusion, this pilot trial demonstrated that a four-week preoperative intervention combining a mixed-nutrient supplement with structured exercise training and relaxation strategies is feasible in lung cancer patients awaiting surgery. Findings lend support for launching larger trials in this clinical setting with the eventual goal of improving post-surgical recovery.

Declarations

Funding: The authors did not receive support from any organization for the submitted work.

Conflicts of interest/Competing interests: The authors have no relevant financial or non-financial interests to disclose.

Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the McGill University Health Centre (REB 2020-5633) and registered (ClinicalTrials.gov registration: NCT04610606).

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent for publication: The authors affirm that human research participants provided informed consent for publication of the article.

Availability of data and material: N/A

Code availability: N/A

Authors' contributions:

Vanessa Ferreira: Investigation; Data curation; Project administration; Formal analysis; Writing – original draft

Claire Lawson : Investigation; Data curation; Writing – review & editing

Francesco Carli : Methodology; Resources; Supervision; Writing – review & editing

Celena Scheede-Bergdahl : Methodology; Supervision; Writing – review & editing

Stéphanie Chevalier : Conceptualization; Methodology; Resources; Supervision; Writing – review & editing

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Table 1. Baseline demographic and clinical characteristics.

Variable	Control (n=10)	Prehab (n=24)	P-value
Age, years	69 [66.8-73.3]	67 [63.3-72]	0.507
≥75 y	2 (20%)	5 (21%)	0.956
Sex-male	5 (50%)	13 (54%)	0.824
Weight, kg	77.8 [65.4-82.6]	74.3 [61.3-91.4]	0.762
Body mass index, kg/m^2	28.3 [23.6-31.2]	26.6 [23-32.6]	0.705
Body fat, % of weight	34.5 (11.5)	34.3 (10.5)	0.955
Fat free mass, kg	50.5 (10.8)	49.6 (11)	0.832
Muscle mass, kg	23.1 (6.1)	22.7 (6.1)	0.875
Smoking status			0.95
Never smoked	2 (20%)	6 (25%)	
Current smoker	3 (30%)	7 (29%)	
Ex-smoker	5 (50%)	11 (46%)	
Pack-year	36.6 (21.2)	43.3 (29.2)	0.569
Comorbidities			
Diabetes	3 (30%)	3 (12.5%)	0.223
Hypertension	4 (40%)	10 (42%)	0.928
Cardiovascular disease	4 (40%)	4 (16.7%)	0.144
Sleep apnea	1 (10%)	5 (21%)	0.45
COPD	3 (30%)	6 (25%)	0.763
Hypercholesterolemia	4 (40%)	10 (42%)	0.928
Hyper/Hypo-thyroism	0 (0%)	8 (33%)	0.037
Anemia	1 (10%)	1 (4%)	0.51
Depression	0 (0%)	2 (8%)	0.347
Previous cancer	2 (20%)	8 (33%)	0.437
Six-minute walking distance, meters			
Actual	489.6 (87.4)	481.1 (78.5)	0.689
Percent predicted	77.6 (8.3)	74.4 (12.5)	0.470
<400 meters, # of patients	1 (10%)	4 (17%)	0.586
Pulmonary function test			
FEV1 %pred	89.9 (18.1)	80.5 (17.5)	0.169
FVC % pred	95.4 (13.1)	89.8 (14.6)	0.307
FEV1/FVC, %	72 (4.9)	69.5 (12.1)	0.532
PG-SGA global score	5.5 [2-8.5]	3 [2-4]	0.103
PG-SGA nutritional triage levels			
0-3	4 (40%)	16 (70%)	0.169
4 to 8	4 (40%)	6 (26%)	
≥9	2 (20%)	1 (4%)	
Blood biochemistry			
Creatinine, μmol/l	86.5 [70.5-108.8]	80 [67-94]	0.378
C-reactive protein, mg/l	1.9 [1.6-4.8]	1.8 [1.2-4.2]	0.814

Albumin, g/l	42.5 [39.8-44]	41 [40-43]	0.591
Prealbumin, mg/l	274.5 [258.8-296.8]	268 [208-288]	0.468
HbA1c, %	5.95 [5.75-6.28]	5.85 [5.55-6.55]	0.581
Hemoglobin, g/l	138.2 (12.7)	146.7 (11.4)	0.066

Data presented as mean (SD), median [IQR] or n (%).Significant P-value (<0.05) in bold. COPD = Chronic Obstructive Pulmonary Disorder; HbA1c = Glycated hemoglobin; PG-SGA = Patient Generated Subjective Global Assessment; PG-SGA nutritional triage level score of 0-3 = an intervention by a dietitian is unnecessary, 4-8 = necessitating an intervention by a dietitian and ≥9 = in critical need for nutrition intervention; Pulmonary function test: FEF 25-75% = forced expiratory flow at 25-75% of pulmonary volume, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity.

Table 2. Self-reported outcomes for SF-36, FACT-L, PG-SGA, HADS and CHAMPS questionnaire between groups at baseline and preoperative visit.

Variable	Control (n=8)			Prehab (n=18)			P-value between
	Baseline	Preop	P-value	Baseline	Preop	P-value	
SF-36							
Physical Functioning	67.5 (25.6)	69.4 (26)	0.644	65.6 (25.6)	59.4 (26.5)	**0.031**	0.586
Role limitation due to physical health	53.1 (47.1)	53.1 (47.1)	1	68.1 (44.4)	70.8 (39.5)	0.608	0.37
Role limitation due to emotional problems	91.1 (16.6)	58.3 (46.3)	**0.028**	72.2 (43.2)	68.5 (43.5)	0.695	0.779
Social Functioning	75 (25)	76.6 (18.2)	0.84	78.5 (27.7)	77.8 (28.6)	0.893	0.822
Bodily pain	80.8 (24.9)	71.1 (22.4)	0.182	72.1 (25.4)	77. 9 (23.8)	0.222	0.919
Vitality	49 (20.2)	55 (12)	0.29	62.2 (21.2)	63.1 (19)	0.823	0.164
Mental health	64 (9.3)	69 (17.3)	0.362	74.4 (18)	70.4 (18.9)	0.276	0.374
General health	72.9 (11.6)	60.4 (18.5)	**0.019**	65.6 (24.4)	63.6 (22.5)	0.54	0.815
Physical component summary score	63.5 (21.4)	61.8 (21.2)	0.535	66.7 (23.2)	67 (20.1)	0.884	0.646
Mental component summary score	71.3 (12.6)	63.9 (19.1)	0.057	70.6 (22.2)	68.7 (22.1)	0.448	0.812
Total	69.2 (17)	64.1 (21.7)	0.121	69.8 (22.5)	69 (21.9)	0.677	0.761
FACT-L							
Physical well-being	24.9 (2.2)	24.1 (2.5)	0.395	23.1 (4.8)	23.7 (5.6)	0.3	0.55
Social/family well-being	20.6 (4.7)	20 (5.2)	0.681	20.6 (5.6)	21.2 (3.8)	0.585	0.78

Emotional well-being	15.5 (3)	18.6 (3.8)	0.057	15.9 (5)	17.7 (5.4)	0.101	0.899
Functional well-being	17.6 (3.6)	18.8 (6.3)	0.431	19.4 (6.2)	19.3 (6.6)	0.907	0.642
Lung cancer subscale	22.4 (3.5)	23.8 (2.3)	0.201	21.3 (3.8)	21.2 (4.9)	0.875	0.258
Total	101 (13)	105.3 (17.5)	0.366	100.2 (19.2)	102.9 (22.1)	0.384	0.843
PG-SGA total	6.4 (4.3)	5 (3.1)	0.272	4.1 (4.1)	2.4 (1.2)	0.101	0.087
HADS-anxiety	7.75 (3.9)	6.9 (2.9)	0.444	5.1 (4.6)	5.7 (3.7)	0.423	0.221
HADS-depression	4.7 (3)	4.9 (3.4)	0.891	4.1 (3.1)	3.7 (2.7)	0.609	0.455
Physical activity energy expenditure (CHAMPS), kcal/kg/week							
Light intensity	32.9 (32.5)	31.9 (45.7)	0.957	39.4 (41.7)	40.1 (27.5)	0.952	0.508
Moderate-vigorous intensity	9.6 (11.8)	41.8 (57.6)	**0.03**	16.8 (26.8)	45.2 (32.5)	**0.005**	0.651
Total	42.4 (27.9)	64.3 (78.7)	0.358	56.2 (47)	85.3 (47.8)	0.073	0.304

Data presented as mean (SD). Significant P-value (<0.05) in bold.
CHAMPS = Community Healthy Activities Model Program for Seniors; FACT-L = Functional Assessment of Cancer Therapy-Lung; HADS = Hospital Anxiety and Depression Scale; PG-SGA = Patient-Generated Subjective Global Assessment; Preop = Preoperative visit; SF-36 = 36-Item Short Form Health Survey.

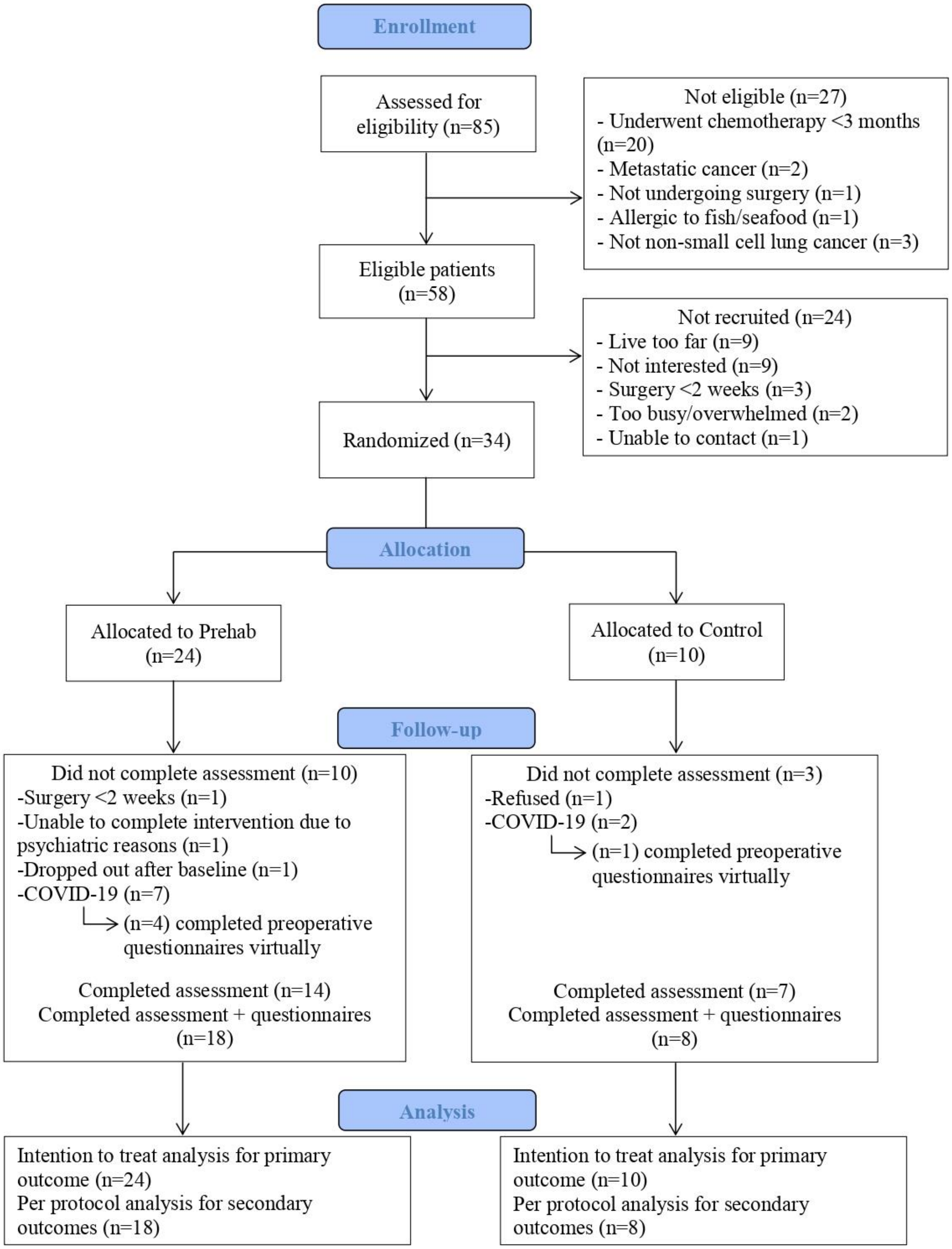

Figure 1. Consort diagram

Supplemental Table 1. Baseline characteristics between patients with missing data compared to patients with no missing data.

Variable	Non-missing (n=21)	Missing (n=13)	P-value
Age, years	67 [64-72]	69 [62.5-73.5]	0.873
Sex-male, n (%)	10 (47.6)	8 (61.5)	0.429
Weight, kg	72.5 [62.9-86.5]	75.2 [64.5-88.5]	0.684
Body mass index, kg/m^2	28 (7)	27.8 (4.8)	0.950
Baseline six-minute walking distance, meters	462.7 (79.8)	513.3 (67.8)	0.074
Cardiopulmonary exercise test			
VO_2 AT, ml/kg/min	11.9 (2.5)	12.1 (2.2)	0.830
VO_2 peak, ml/kg/min	15.9 [13.1-18.6]	17.2 [15.2-22.1]	0.213

Data are presented as mean (SD) or median [IQR] or n(%). Analyses performed included one-way ANOVA for normally distributed data or Kruskal-Wallis for non-normally distributed data. Cardiopulmonary exercise test: VO_2 = oxygen consumption, AT = anaerobic threshold.

Supplemental table 2. Per protocol analysis comparing body composition and functional outcomes between groups and over time.

Variable	Control (n=7)		Prehab (n=14)		P-value		
	Baseline	Preop	Baseline	Preop	Time	Interaction	Group
Body composition							
Body fat, % of weight	36.5 (11.5)	36.3 (11.6)	35.8 (10.8)	34.8 (9.6)	0.509	0.715	0.828
Fat free mass, kg	45.4 (7.3)	45.9 (7.2)	50 (11.8)	50.5 (11.7)	0.127	0.988	0.384
Muscle mass, kg	20.3 (4.4)	20.8 (4.5)	23 (6.6)	23.1 (6.6)	0.110	0.328	0.405
Grip strength dominant hand, kg	22.9 (4)	22.9 (4.1)	25.7 (13.6)	25.9 (11.2)	0.921	0.921	0.551
Grip strength non-dominant hand, kg	21.4 (5)	20 (5.3)	24.7 (10.5)	26.1 (10)	1.0	0.078	0.261
Bicep curls – right arm, # in 30 sec.	21.7 (1.2)	21.3 (2.1)	20.4 (4.2)	22.6 (5.5)	0.194	0.085	1.0
Bicep curls – left arm, # in 30 sec.	20 (1.7)	20 (3.3)	20.2 (3.2)	21.9 (4.8)	0.152	0.152	0.515
Sit-to-stand, # in 30 sec.	12.4 (3)	14.3 (3.9)	13.4 (4.9)	15.1 (4.7)	**0.002**	0.945	0.629
Timed-up and go, seconds	6.6 (1)	6.5 (0.8)	6.6 (1.5)	6.5 (1.4)	0.627	0.821	0.972
Cardiopulmonary exercise test							
VO_2 AT, ml/kg/min	12.4 (1.9)	12.9 (2.3)	11.7 (2.8)	12 (3.5)	0.357	0.803	0.629
Heart rate AT, bpm	98.3 (10.5)	101.5 (7.6)	99.8 (15.5)	102.3 (13.3)	0.285	0.887	0.872
Power AT, watts	57.3 (10.1)	64.8 (14.3)	54.8 (12.7)	57.3 (24.3)	0.241	0.550	0.618
VO_2 peak, ml/kg/min	17.3 (6.1)	16.6 (5.3)	16.5 (4.7)	17.4 (5.9)	0.855	0.098	0.997
Heart rate peak, bpm	125.5 (12.1)	125.2 (12.4)	124.1 (21.6)	124.2 (19.5)	0.979	0.947	0.888
Power peak, watts	96.8 (35.2)	95 (33.8)	94.4 (30.3)	99.6 (35.9)	0.479	0.145	0.948

Data presented as mean (SD). Significant P-value (<0.05) in bold.
Cardiopulmonary exercise test: VO_2 = oxygen consumption, AT = anaerobic threshold.

Chapter 7: General discussion

7.1 Summary of findings

This doctoral thesis set out to further our understanding on the effects of multimodal prehabilitation, with a focus on nutritional optimization, on functional capacity in lung cancer patients undergoing surgery. This was achieved by first conducting a RCT comparing multimodal prehabilitation to rehabilitation from which we found no difference in functional capacity at any time point during the perioperative period between the two multimodal programs. Hence, it was concluded that preparing patients for surgical resection of lung cancer with a pre-operative multimodal prehabilitation program is as effective in recovering functional capacity at 8 weeks after surgery as starting the same multimodal program post-operatively. Although this first study failed to show that prehabilitation was superior to rehabilitation in recovering functional capacity after lung cancer surgery, as we had hypothesized, it provided important insight on potential aspects of the intervention that can be ameliorated. For instance, the prehabilitation intervention of this first study could be considered a "standard" prehabilitation program, where the exercise program was entirely home-based and the nutritional program included mainly just whey protein supplementation. Although prehabilitation is certainly not standard of care, this particular intervention was similar to prior prehabilitation interventions undertaken at our center in colorectal cancer patients awaiting surgery and showed to provide meaningful changes in postoperative functional exercise capacity.[92] A potential reason why this "standard" prehabilitation program was effective in improving functional capacity in colorectal cancer but not in lung cancer patients may be because lung cancer is associated with significant disease burden and high symptom levels (cancer-related symptoms as well as smoking-related comorbidity such as

COPD),[3,112] which can greatly impair physical function and impede the patients' ability to fully participate and respond to prehabilitation interventions. Despite this, it was still a very important trial to conduct since prehabilitation had not yet been studied in the context of lung cancer surgery. In other words, it was a good first step in developing targeted multimodal prehabilitation programs for this cancer population and a great learning experience that inspired the other studies in this doctoral thesis.

As described earlier, despite having included a nutritional program in the multimodal prehabilitation intervention of the first study, it was certainly not as developed or targeted as the exercise intervention which may, in part, explain the null findings. Therefore, I performed a systematic review of all relevant literature pertaining to preoperative nutritional interventions in lung cancer patients undergoing surgery and investigate the effects on clinical and functional outcomes. Due to the lack of research in this area, I had to expand the search to include preoperative nutrition interventions alone or in combination with exercise. Even upon expanding the search, only 5 relevant studies were found, including my first thesis study. The interventions and results were too heterogeneous to perform a meta-analysis and provide strong conclusions however we did find that multimodal prehabilitation programs that combine nutrition and exercise may have beneficial effects on various physical function outcomes in patients with lung cancer awaiting surgery. Furthermore, optimizing preoperative nutrition may have postoperative benefits as found in the one nutrition-only study which reported significantly lower rates of postoperative complications in the intervention group. Interestingly, a recent systematic review and meta-analysis on preoperative nutrition with or without exercise in colorectal cancer patients undergoing surgery identified 9 relevant studies and found that nutritional prehabilitation alone or combined with an exercise program significantly decreased length of hospital stay by 2 days.[74] It also reported that multimodal prehabilitation significantly improved results of the 6MWT at 4 and 8 weeks after surgery compared with standard care. Therefore, compared to lung cancer surgery, the surgical colorectal cancer population had nearly twice as many research studies on preoperative nutrition and findings were sufficiently homogenous to conduct a meta-analysis. This highlights a gap in knowledge in the surgical lung cancer literature with regard to preoperative nutrition. Thus, I set out to determine whether nutritional optimization was even necessary in the lung cancer population by exploring malnutrition and its effects on functional capacity.

My third thesis study was a secondary analysis of data from lung cancer participants in prehabilitation studies from our center. The aim was to characterize the presence of malnutrition, examine the association between malnutrition and baseline functional capacity, and examine the extent to which patients benefit from preoperative multimodal prehabilitation. This study revealed that nearly 50% of lung cancer patients awaiting surgery have some degree of malnutrition and poor baseline functional capacity. However, upon receiving prehabilitation, the patients at high nutrition risk significantly improved their functional walking capacity during the preoperative period. This finding highlighted the importance of assessing malnutrition and providing a personalized nutritional intervention to lung cancer patients undergoing surgery. In fact, a recent study in colorectal cancer patients undergoing surgical resection identified that approximately one-third of the studied patients were found to be at nutritional risk by using the PG-SGA nutritional assessment tool and approximately 60% of patients scored a 3 to 4 when screened with the Nutrition Risk Screening-2002 tool, indicating the need for further nutritional assessment and possible intervention.[113] Interestingly, when these patients received nutrition counseling with whey protein supplementation, a clinically relevant mean improvement of +20.8

(SD 42.6) m in functional walking distance was observed before surgery. Recent consensus recommendations from the North American Surgical Nutrition Summit suggest a shift from focusing on postoperative nutrition to preventive preoperative nutrition therapy. The consensus emphasized the concept of preoperative “metabolic preparation” in all patients deemed to be at nutritional risk.[114]

Therefore, for my final thesis study, we decided to support patients’ nutritional needs by providing more than just whey protein supplementation, as was done previously, but rather also provide other nutritional supplements such as leucine, omega-3 fatty acids and vitamin D to maximally promote muscle health and anabolism. Initially we had aimed to conduct a pilot RCT to assess the effects of this mixed-nutrient supplement on functional walking capacity. Unfortunately, due to the COVID-19 pandemic, this study was stopped before all participants could be recruited and follow-up assessments for the collection of data were no longer possible. Therefore, our sample size was slightly smaller than anticipated and the rate of missing data was very high, especially in the postoperative period. In order to adapt to this situation, we focused on assessing the feasibility of delivering our novel, mixed-nutrient supplement as part of the multimodal prehabilitation program, during the preoperative in lung cancer patients awaiting surgery. Our findings revealed that within a preoperative time-frame, it was feasible to deliver this novel multimodal prehabilitation intervention seeing as the recruitment rate was comparable to previous trials and adherence to all parts of the intervention and to the study outcome assessments was very high. These findings will inform the design of larger trials in this clinical setting with the eventual goal of improving post-surgical recovery.

7.2 General strengths and limitations

The strengths and limitations for each individual thesis study have been previously described in each chapter, however there are some general strengths and limitations to the work of this doctoral thesis. A major strength was that the RCTs (Chapter 3 and 6) were both conducted in a real-life perioperative setting. The study outcome assessments and intervention were delivered in a hospital-setting and included patients awaiting surgery. Although this brought up some challenges with regards to time restraints where patients often had multiple other medical appointments, and surgery dates were sometimes changed, these studies provided results that are generalizable to the surgical cancer population. Another strength was that each of my thesis studies were the first, to my knowledge, to investigate their respective aims. As highlighted throughout this dissertation, there is a paucity of research in the surgical lung cancer population with regards to multimodal prehabilitation and preoperative nutritional interventions, especially compared to other cancer types such as colorectal cancer. The research in each thesis study provides novel findings in the field of prehabilitation for lung cancer surgery and may lend support for launching larger trials in this clinical setting.

A limitation to this doctoral work may be the outcome measure of exercise capacity. For the most part, I used the 6MWT to assess functional capacity however the gold standard method of measuring exercise capacity is cardiopulmonary exercise testing (CPET). There are various physiological variables recorded during CPET such as ventilatory parameters, inspiratory and expiratory gases, blood pressure and electrocardiogram therefore, CPET provides an objective, dynamic, and integrative assessment of cardiorespiratory fitness. During CPET, participants are exposed to incremental exercise up to their maximally tolerated level which provides the assessor the ability to determine the participant’s physiological capacity to cope with stress; in the perioperative context this would refer to the ability to cope with the metabolic demands created by the trauma of major surgery.[115] CPET derived variables such as oxygen consumption at anaerobic threshold and VO_{2peak} are known to predict postoperative outcome.[116] Therefore, CPET is often used in risk prediction before major surgery and, in the context of prehabilitation, provides a higher clinical standard for exercise prescription.[115] However, some of the most important limitations of conducting a CPET are that it is very costly, it requires qualified personnel to perform and interpret the test, and requires maximal exertion from the participant which may cause a high degree of discomfort and exhaustion.[117]

On the other hand, the 6MWT is simple to administer, cost-efficient, does not require a lot of time, expensive equipment or specialized training of personnel, and has been validated as a measure of functional recovery after abdominal surgery[104] and in the cancer population.[101] Furthermore, considering that activities of daily living are mostly pursued at a sub-maximal level of intensity, the 6MWT is a direct measure of functional capacity as it better reflects such activities compared to maximal exercise testing such as CPET. Additionally, evidence shows that in patients following curative intent treatment for lung cancer, the 6MWT elicited a lower peak hear rate response and less symptoms of dyspnoea and leg fatigue compared with CPET.[118] The 6MWT may also be a more relevant outcome to patients, i.e. a better index of patient's ability to perform daily activities, than CPET derived variables. For instance, there is evidence showing that in patients with chronic lung disease, the 6MWT correlates better with formal measures of quality of life.[119] This is important because one of the key aspects when selecting the primary outcome of RCTs is that it should give the most patient-important outcome. Despite the differences between the 6MWT and CPET, significant positive correlations between them have been reported in patients with COPD[120] and in patients awaiting scheduled major non-cardiac surgery.[108] Therefore, given the benefits of the 6MWT listed above that make it a more feasible test to perform in the perioperative setting, combined with it being a more pleasant test for participants to perform (fewer symptoms of discomfort), is more reflective of activities of daily living, is considered to be a more patient-important outcome and, is validated in the population selected for this doctoral work, we considered that it would be the most appropriate measurement of functional capacity to include as the primary outcome of our studies.

In light of this, it is important to note that the 6MWT has several limitations. It requires a lot of space to administer, i.e. a long corridor of at least 20 meters, and the test must be performed in an environment that is uninhibited by human traffic, which may be particularly difficult when administered in a clinical or hospital setting. Furthermore, as compared to the CPET, the 6MWT does not provide a global assessment of the exercise response or determination of the factors limiting/impairing exercise capacity such as underlying pathophysiological mechanisms of the different organ systems involved in exercise.[100]

An unexpected limitation was the COVID-19 pandemic which primarily affected the final study of my thesis (Chapter 6). Unfortunately, we were unable to continue collecting data and complete the trial since study visits were prohibited and elective surgeries were cancelled. Luckily, we had collected sufficient data in the preoperative period to assess feasibility of the intervention therefore, we limited the aims of the pilot trial from investigating the effects of a mixed-nutrient supplement on functional capacity and other secondary outcomes such as health-related quality of life, to assessing the feasibility of this intervention.

7.3 Clinical relevance and future work

From this thesis work I have been able to contribute to our understanding of the effects of multimodal prehabilitation, with a stronger focus on nutritional optimization, on functional capacity in lung cancer patients undergoing surgery. As evidenced by the lack of research on prehabilitation in lung cancer surgery, my research has provided the ground work for future trials and may contribute to the development of more targeted and personalized therapies. It will inform treatment guidelines for implementing the multimodal intervention in patients with lung cancer which could be further tested in other cancers. Specifically, this dissertation has highlighted the need for further investigation on preoperative nutritional interventions, as part of a multimodal prehabilitation program, in surgical cancer patients. The nutritional component of prehabilitation functions to complement the exercise regimen, but can also stand alone to promote optimal patient outcomes.[74] However, nutrition in perioperative research has been greatly understudied, despite being recognized as an important factor for recovery. Furthermore, considering the abundant research on preoperative exercise and the well-known beneficial interaction between exercise and nutrition, there is a need to further our understanding on the effects of preoperative nutrition on functional and clinical outcomes.

Current standard of care does not include prehabilitation therefore, the research in this dissertation can eventually play a significant role in changing the medical norms for the betterment of the patients once supported by data from larger trials. The ability to effectively utilize exercise and nutrition to preserve lean muscle mass and improve functional recovery in patients with lung cancer undergoing surgery may provide a cost effective means of minimizing hospitalization time, accelerating recovery, saving health care dollars and improving overall patient quality of life.

The importance of screening for nutritional risk as early as possible has been highlighted in the literature yet it is not routinely performed.[121] Considering that there are various tools available to screen for nutritional risk and to complete a comprehensive nutritional assessment, future research should focus on "stream lining" or in other words developing a nutritional clinical pathway. For instance, a clinical pathway can include a screening process followed by an assessment and finally an intervention, where if patients meet certain criteria when screened, they must receive a comprehensive nutritional assessment which will determine the course of the nutritional intervention. Just as how patients would be flagged for medical optimization such as anemia correction when their hemoglobin concentration is below a certain threshold or glycemic control when their glycated hemoglobin concentration is above a certain cut-off, patients should be flagged for nutritional optimization when they meet certain criteria, hence the need to investigate and develop a standardized clinical pathway.

In order to better understand the impact of optimizing nutrition or integrating a clinical pathway, as previously suggested, on functional recovery, future work can investigate the effects of a nutrition-only prehabilitation intervention or even include a nutrition-only arm in a larger prehabilitation trial comparing multimodal prehabilitation arm to standard of care. Doing so may aid in teasing out the individual contribution of nutrition on functional capacity and enhance our understanding of its impact when integrated into a multimodal prehabilitation intervention. It would also be of interest to explore the effects of different combinations of nutrients, as part of a nutritional supplement, on functional recovery in order to better tailor and personalize nutritional interventions according to patients' needs. Furthermore, investigators can study the potential mechanisms of action of nutritional supplementation on muscle health and function since the main nutritional problem in cancer is wasting of muscle mass, acknowledged to be a predictor of lower quality of life, impaired functionality, surgical complications and shortened survival.[21,122,123]

7.4 Overall conclusions

This thesis dissertation contains some of the first work on multimodal prehabilitation and preoperative nutritional optimization in lung cancer patients undergoing surgery. A RCT comparing prehabilitation to rehabilitation showed no difference in functional capacity at any time point during the perioperative period between the two multimodal programs, therefore prehabilitation was deemed as effective as rehabilitation in recovering functional capacity 8 weeks after surgery. This null finding prompted an investigation into the current body of literature on preoperative nutritional and multimodal prehabilitation interventions in lung cancer patients undergoing surgery. A systematic review was carried out where only five studies were included (four multimodal prehabilitation interventions and one preoperative nutrition-only intervention) and findings suggested that multimodal prehabilitation programs that combine nutrition and exercise may have beneficial effects on various physical function outcomes. Having postulated that the nutritional intervention was not sufficiently optimized in my first thesis study and having identified a gap in the literature with regard to preoperative nutritional interventions in my second thesis study, I conducted a secondary analysis on lung cancer patients enrolled in multimodal prehabilitation or control interventions at our center. From this thesis study we identified the prevalence of malnutrition in lung cancer patients awaiting surgery at our center, we found that patients with high nutrition risk awaiting surgery had significantly lower baseline functional capacity compared to patients with low nutrition risk and that only the patients at high nutrition risk receiving multimodal prehabilitation experienced a significant improvement in preoperative functional capacity. Therefore, for my final thesis study, I conducted a pilot RCT to investigate the feasibility of delivering a novel, mixed-nutrient supplement, as part of a multimodal prehabilitation intervention, and its effects on preoperative functional capacity and health-related quality of life, compared to standard hospital care. Although this final study was interrupted by the COVID-19 pandemic, results showed that within a preoperative time-frame, it was feasible to deliver this novel multimodal prehabilitation intervention in lung cancer patients awaiting surgery as recruitment rate and adherence to the prescribed intensity of the supervised exercise program, home-based exercise program, nutritional supplement and patients' preoperative assessment was high.

This doctoral work provides a foundation for future trials on prehabilitation in lung cancer surgery. As we better understand the impact and important role that each element of a multimodal prehabilitation program has on functional recovery, we can better develop treatment guidelines and targeted interventions to improve the lives of patients.

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