Study Protocol

The feasibility of an exercise and nutrition supportive care (palliative) intervention for advanced non-small-cell lung cancer.

Advanced Lung Cancer, Exercise, and Nutrition

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Exercise, Nutrition and Palliative care in Advanced Lung cancer (ENPAL) Study

Abstract

Background: Cancer treatments can prolong life for those with advanced non-small-cell lung cancer (NSCLC); however, it is often at the expense of a multitude of negative symptoms and side-effects that diminish quality of life (QOL). Given the complex care needs of this population, a complex intervention must be considered as part of an effective approach to supportive care. Evidence supports both exercise and nutrition as beneficial for enhancing QOL in earlier stages of lung cancer; however, there is minimal research of either type of intervention - and none with combined interventions - in advanced lung cancer patients. We hypothesize that a multimodal intervention that includes tailored nutrition and exercise components and behaviour change support, along with palliative symptom management, will optimize the potential benefits and ultimately improve patient-reported outcomes relating to symptom management and QOL.

Objectives: The primary outcome measure of this pilot study is feasibility, both quantitatively and qualitatively, including recruitment (% who participate from those eligible), attendance (weekly group class), assessment completion, safety (adverse event reporting), attrition rates, and qualitative themes generated from one-on-one participant interviews. The secondary outcome measure is the impact of the intervention on patient-reported outcomes (PROs), including QOL, fatigue and symptom burden, as well as self-reported physical activity levels and physical function assessed in-person. Data collected from this study will be used to inform the design of a future pragmatic clinical trial (PCT) for advanced NSCLC patients.

Methods: The proposed multimodal intervention will include a centre-based group exercise program with home-based exercises, as well as individualized nutrition counselling and behaviour change support and palliative symptom management, for advanced NSCLC patients classified as stage III or IV with self-reported symptom burden. Palliative symptom management will be provided by the Complex Cancer Care Management team at the Tom Baker Cancer Centre (TBCC). Eligible participants must be cleared by a clinical health care professional (HCP) to engage in mild to moderate levels of physical activity. Using a prospective, mixed-methods design (supported by the Medical Research Council guidance for the evaluation of complex interventions), the quantitative component of this pilot study will assess feasibility and exploratory outcome measures, with an embedded qualitative component to examine participant perspectives and reported outcomes about study tolerability/feasibility of the intervention. A subset of participants will be recruited for the qualitative interviews using purposive sampling in order to explore their perspectives on the engaging in the trial, with a focus on feasibility.

Relevance: The proposed work will expand the “usual” clinical cancer care approach (i.e., a focus on symptom management) and provide empirical evidence to support the positive impact of an integrated multimodal intervention on QOL and PROs. Specifically, the intervention will combine palliative symptom management via the Complex Cancer Management team, with a tailored exercise and nutrition intervention, to improve the survivorship experience for patients diagnosed with metastatic and/or nonresectable NSCLC – a growing, yet clinically underserved population. The pilot feasibility trial will utilize a mixed methods approach to gather quantitative (adherence to interventions, assessment completion rates, adverse events) and qualitative (patient perspectives on the intervention tolerability and delivery, facilitators/barriers to participation, and overall satisfaction) data that will inform the design of a future PCT for this population. The results of this work will contribute to the development of a feasible and patient-focused model of care that delivers wellness resources and supportive care with the capacity to improve the QOL and health of patients with advanced NSCLC.

Background

Lung cancer is the most commonly diagnosed cancer in Canada and is the leading cause of death from cancer.[1] Despite this, long-term survival rates for lung cancer are improving, owing largely to recent advances in treatment. The progression of symptoms of advanced lung cancer often exacerbate the emotional and psychological distress experienced by patients and families, which contributes to sedentary behaviour as well as diminished QOL.[2] In addition, the toxicities of traditional chemotherapies, such as the reduction of lean muscle mass[3,4,5], are not adequately addressed in current research or used in clinical practice. The proposed work will thus assess the feasibility and patient impact of an integrated multimodal intervention for advanced (stage III and IV) non-small-cell lung cancer (NSCLC), inclusive of tailored exercise programming, nutrition counselling, and behaviour change support, in addition to palliative symptom management.

Evidence shows that physical function and physical independence are among the most important determinants of QOL for cancer patients with palliative care needs.[6] There is strong empirical evidence to demonstrate the positive impact of each individual modality included in the proposed intervention – symptom management, nutrition, and exercise – on QOL in advanced cancer populations, including patients with metastatic NSCLC.[7,8] Nutritional status has been shown to be predictive of QOL in patients with cancer, including in those diagnosed with inoperable NSCLC.[9] Exercise is also supported as beneficial for overall QOL in advanced cancer populations, with particularly strong effects on physical and mental well-being.[10] Exercise promotes the retention and utilization of nutrients and anabolism, while palliative symptom measures can help improve oral intake by ameliorating symptoms such as nausea, mucositis, thrush or constipation.[11] Palliative symptom measures may also help reduce obstacles to exercise, such as pain or dyspnea, that are commonly experienced by patients with advanced lung cancer. Despite the promising evidence, few studies have examined the effect of combining a nutrition and exercise intervention within palliative care, yet preliminary data suggests synergistic effects. Results from a recent randomized control trial suggest that an intervention combining nutrition and exercise components may be feasible in advanced cancer care (including stage IV NSCLC care), with an attrition rate of only 86% during the 3-month trial period. [12] While this is promising, there is still limited data on the feasibility of these interventions, and there have been no RCTs to date that have combined palliative care with nutrition and exercise interventions (Hall CC, Cook J, Maddocks M et al. Combined exercise and nutritional rehabilitation in outpatients with incurable cancer: a systematic review. *Support Care Cancer* 2019; 27:2371–2384) .[13,14]

Given the growing number of NSCLC patients entering long-term survivorship, this work is critical for ensuring that the healthcare system is addressing their unique supportive and palliative care needs. Our project is relevant to the present funding opportunity because of its focus on **patient reported outcomes** (PROs). We will utilize PROs that are used in AHS ("Putting Patients First") and in the cancer population (FACT-G, FACT-lung, and FACIT-F), and will collect patient feedback (qualitative interviews) on the intervention recruitment and delivery. This work will also help connect existing palliative resources at the Tom Baker Cancer Centre (Complex Cancer Care team, physiatry, and nutrition), along with ongoing work on the University of Calgary's Alberta Cancer Exercise (ACE) program.[15] The preliminary outcome and feasibility data will inform the sample size and characteristics for a future PCT. By showing proof of concept in advanced lung cancer, a disease with high patient burden, we hope results from this work will facilitate further adaptation of the proposed multimodal intervention to support the palliative care needs of other tumour groups.

Research Objectives

a) **Objectives and Deliverables:** This pilot study will examine a multimodal intervention, including exercise and nutrition in conjunction with palliative symptom management, on the

QOL of advanced NSCLC patients. The impact of symptom burden on the QOL in NSCLC patients is significant and under-recognized. Due to improvements in therapies, there is an opportunity to address QOL in this population, whose members are now, on average, living longer and potentially more able to engage in rehabilitation interventions. This work will address a gap in research and clinical practice by providing initial data that to examine delivery of supportive and palliative cancer care to the advanced NSCLC population and provide a starting point for tailoring interventions in other tumour groups. Given the novel nature of this research, both in terms of the multimodal intervention as well as the focus on an underserved population, the ***primary objective is to assess the feasibility of the intervention.*** Secondary objectives are to obtain preliminary data on patient-reported outcomes (PROs) of QOL (FACT-G and FACT-lung), and patient functioning measures (symptom measurement, Putting Patients First assessment tool, exercise levels, and fitness outcomes).

b) Methodology: Design: This pilot study will involve a prospective, mixed-methods design. The quantitative component includes measures of study feasibility and exploratory outcome measures, as described below. The embedded qualitative component will use semi-structured one-on-one interviews to explore participant perspectives about intervention tolerability/feasibility, with a focus on barriers and facilitators to participation, perspectives on recruitment, the type and combination of intervention modalities (exercise type, role of instructor, and content within the palliative symptom and nutrition intervention), delivery locations, duration of the intervention and satisfaction with the outcome measures used. The rationale for this study design follows the Medical Research Council guidelines for the evaluation of complex interventions[16,17] which supports the use of qualitative methods nested within a larger trial to understand the "active ingredients" and contextual factors that result in certain outcomes in a complex intervention study. This has been used as a framework for previously published complex intervention trials in palliative care.[18, 19]

Research Team: Co-Principal Investigators (Culos-Reed and Abdul-Razzak) will share responsibility for the research project. Dr. Culos-Reed will coordinate the overall project, as well as oversee the exercise component of the intervention. She has 20 years of experience working in cancer and exercise research and brings a strong background in knowledge translation to the proposed work. Dr. Culos-Reed will also provide in-kind support through use of her research facility (Health and Wellness Lab) at the University of Calgary, as well as support from current graduate students and staff (CEP, CPTs and research coordinators) affiliated with her lab. Dr. Abdul-Razzak will oversee the clinical implementation of the project at the TBCC, including support of participant recruitment and delivery of the care by the intervention teams. She has extensive training in qualitative methodology and in clinical trials research in the palliative population. Several co-applicants and collaborators have been instrumental in the conceptualization of this project, and bring extensive clinical expertise in oncology (Bebb), cancer physiatry and rehabilitation (Francis, Capozzi) and nutrition therapy for patients with advanced cancer (Dexter, Gillis, Walker, Black). This multidisciplinary team will continue to be involved in the pilot study design and delivery, as well as subsequent work on the PCT.

Study Participants: Advanced NSCLCA patients, classified as stage III or IV, with self-reported symptom burden, and cleared by the health care professionals (HCP) to engage in mild to moderate levels of physical activity (PA). Further selection criteria are listed below:

Inclusion Criteria:

-Age ≥18 years old

-Outpatient at the Tom Baker Cancer Centre (or Holy Cross Centre)
-Non-small cell lung cancer stages III-IV
-Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
-Edmonton Symptom Assessment System (ESAS) score ≥3/10 on any item
-Hemoglobin level of ≥80g/L as measured within 30 days of enrollment
-Life expectancy >6 months (as judged by most responsible physician)
-Screening using the Physical Activity Readiness Questionnaire + (PAR-Q+) for engaging in the exercise program
-May or may not be receiving any form of active cancer treatment (i.e. chemotherapy, radiation therapy, immunotherapy or targeted therapy)

Exclusion Criteria:

- Active infections at the time of enrollment
- Enteral tube feeding/parenteral nutrition
- Mechanical or functional bowel obstruction due to any cause
- Cognitive impairment
- Non-English speaking
- Neuromusculoskeletal issues that impede participation

We will recruit n=10-15, and based on current patient numbers, this is a conservative expectation for the 6 month recruitment period. This is based on current numbers of advanced cancer patients seen at the TBCC (approximately 1900 patients die of advanced cancer annually; Personal communication: Dr. Ayn Sinnarajah, Medical Director, Palliative /End-of-Life Care, Calgary Zone.). As this is a pilot study focused on feasibility, there is no *a priori* sample size calculation. A research assistant (RA) will receive electronic alerts of patients who score ≥3/10 on any one of the Edmonton Symptom Assessment System (ESAS) "tiredness/ pain/well-being" items done routinely on all outpatient cancer clinic visits) and contact these patients and their oncologists to assess eligibility. After referral from the HCP, potential participants will be screened by the Certified Exercise Physiologist (CEP) using the PAR-Q+ to ensure that participation is feasible. Patients demonstrating an inability to participate secondary to neuromusculoskeletal issues are ineligible and will be referred to a Cancer Physiatrist (i.e., Dr. George Francis) for evaluation and treatment.

A subset of participants will be invited to participate in one-on-one qualitative interviews with the aim of understanding their perspectives on engaging in the study, including barriers and facilitators to participation and the impact of the interventions of quality of life and symptom control. A thematic analysis approach will be utilized, and although an exact *a priori* sample size cannot be calculated, we estimate that 5-10 interviews may be required in order to achieve an adequate understanding of patient perspectives (i.e., data saturation). We will use a maximum variation sampling strategy based on age, gender, functional status and cancer treatments. Interviews will occur within 2 weeks of the program start, the mid-point (6 weeks) and at the end of the intervention (12 weeks) in an attempt to capture the voices of participants who could complete the program as well as those who subsequently dropped out before the end of the program. All participants will be offered interviews, if they consented to be contacted, and sampling will occur until adequate understanding at each timepoint is achieved via the patient perspective.

Intervention Components:

1) Exercise: The proposed exercise intervention (under the direction of Drs. Capozzi, Culos-Reed and Francis) will include a centre-based group exercise program plus home-based exercises, along with behaviour change support. The interventionist will be a CEP who will receive prior training on the health behaviour change support, similar to that currently used within the ACE program.[15] The 12-week group-based exercise program, consisting of 1 weekly 75 minute session, of which 45 minutes are exercise and 15 minutes of yoga, and the other 15 minutes includes education and facilitating the group social support, will be

delivered in dedicated fitness facilities located at the Holy Cross Hospital in Calgary and at the University of Calgary. Forty-five minute exercise circuits will include 6 exercise stations, with modifications made according to the baseline physical function of each participant. The exercise circuit will be followed by a 15-minute therapeutic yoga class, based on Dr. Culos-Reed's Yoga Thrive program.[20-22] Overall, the 60 minute session will include a light warm up (5-10 minutes), and 6 exercise stations with a range of functional exercises designed to target both aerobic and strength components of fitness (35-40 minutes), with modifications made according to physical function at the start of the program. The main focus of the circuit will be on muscle strength, balance, flexibility and aerobic capacity as associated with beneficial daily physical function (i.e., for activities of daily living). Most group sessions will involve a series of circuit-style classes, that allow for adequate group supervision as well as the ability for individuals to work at their own pace. In addition to the weekly group-based class, a home-based exercise prescription for an additional 1-2 sessions per week, facilitated by provision of basic home-based fitness equipment and the Yoga Thrive class videos, will be provided. A FitBit will also be provided for the duration of the study to support physical activity behavior change and enhance safety, and returned upon completion of the exercise program. To reduce burden, participants will not be required to report objective physical activity from the device.

2) Palliative Symptom Management: Palliative symptom management (under the direction of Drs. Abdul-Razzak and Bebb, and Dr. Lyle Galloway) will focus on symptoms that contribute to reduced QOL (e.g. pain, fatigue, nausea), limit one's ability to engage in exercise, or present barriers to oral intake (e.g., pain management, nausea, mucositis, thrush). These will be delivered by the Complex Cancer Care Management team at the TBCC, which includes a team of physicians, a nurse practitioner, advanced practice pharmacists and a nurse coordinator. Clinicians will deliver pharmacologic and non-pharmacologic therapies based on their clinical judgement. Participant assessments will occur in conjunction with scheduled lung cancer clinic visits, cancer therapy treatment visits, or as separate dedicated research visits when necessary. The initial assessment will occur within two weeks of the exercise program initiation. After the initial assessment, follow-up consultations can occur at the discretion of the palliative care clinicians and participants and may occur either in person or by phone. Clinical case report forms will be used to track the type of treatments provided during these visits for descriptive purposes.

3) Nutrition: The nutrition component of the intervention is designed to meet individual nutrient needs and lifestyle of participants, as well as work synergistically with the previously described exercise component. The study coordinator will ask participants to complete a self-administered online 24-hr dietary food recall. Participants will be asked to record one weekday and one weekend day. The Automated Self-Administered 24-hour (ASA24®) dietary assessment tool was created by the National Cancer Institute (NCI), and is a free web-based tool that enables multiple, automatically coded, self-administered 24-hour recalls (http://asa24.ca/). Participants will be provided with instructions on how to use this technology. Chelsia Gillis (PhD Candidate, RD on the research team) will consult with the TBCC Registered Dietitian (RD) team to develop a relevant feedback form and tailored nutrition advice based on a pre-study food recall evaluation ("what do you typically eat in a day?").This evaluation will assess micro- and macronutrient intake, as well as individual client needs. Data from this evaluation will be analyzed and managed under the leadership of Gillis, who will also direct TBCC staff nutritionist on the nutrition intervention delivery within 2 weeks of study enrollment. RDs involved in the study will also have the ability to recommend interventions based on the nutrition assessment feedback form, such as oral nutritional

supplementation or target daily protein and caloric intake. The number of follow-up dietitian visits will be determined based on individual need for each participant, and post-study food recall evaluation data will be collected and analyzed by Gillis (with support from appropriate members of the research team) to assess changes in food intake behaviours, and possible correlations to levels of exercise participation and patient-reported outcomes.

Data Collection: We will collect demographic data and details of tumour type (e.g., histology, biomarkers) and treatments received prior to and during the trial (e.g., chemotherapy, targeted therapy, radiation therapy). Primary outcome measures will assess study feasibility both quantitatively and qualitatively, including recruitment (% who participate from those eligible), attendance (weekly group class), assessment completion, safety (adverse event reporting), attrition rates, and qualitative themes generated from one-on-one participant interviews (conducted at the end of the intervention). We will recruit a subset of participants for the interviews, using purposive sampling to achieve maximum variation based on factors that may lead to different viewpoints (e.g., age, gender, lifestyle factors, cancer stage, treatment). It is hypothesized that a weekly group-based PA intervention will be feasible for advanced NSCLC patients, (predicted as 30% recruitment of patients approached for participation and 60% attendance at weekly group class and 70% assessment completion), and safe (zero reported adverse events related to the exercise intervention).

Secondary outcomes include exploratory analysis of the intervention's impact on PROs, including QOL, including fatigue and symptom burden. QOL will be measured with the FACT-general and FACT-lung, and fatigue will be measured with the FACIT-fatigue. The symptom burden inventory (ESAS) that is part of the Putting Patients First (PPF) assessment is collected for all patients at TBCC and will be collected from chart review. It will also be collected before and after each exercise session. Nutrition will be assessed from the food recall evaluation data collected pre and post intervention. Physical performance (modified senior's fitness test: resting heart rate, resting blood pressure, height, weight, waist/hip circumference, sit-and-reach, shoulder range of motion, 30-second sit to stand, handgrip strength, 6-minute walk test, single-leg balance), activity levels (self-reported, Godin Leisure Time Exercise Questionnaire) and opioid/other drug use (chart review) will be assessed at baseline (pre-intervention) and post-intervention. To reduce burden in this feasibility study, participants will not be required to report objective physical activity from the device.

PRO measures will be collected through questionnaires administered at baseline (pre-intervention) and post-intervention and completed either online (survey monkey) or in person during the clinic or exercise assessment using a hard copy of the online survey. Exercise assessments will be completed at the Health and Wellness Lab (Culos-Reed) by a CEP not involved in the delivery of the exercise intervention. Relevant medical or symptom management information will be obtained from chart review and from the case report forms collected over the duration of the 12-week intervention, and stored in a secure offline database.

A**nalysis**: Quantitative analysis will include descriptive statistics (means/medians, standard deviations) and dependent t-tests to measure change over time within the participants. The qualitative analysis of the interviews will include verbatim transcription and input into NVivo for thematic analysis. Results of both data sources analyses will be examined to provide a richer understanding of the feasibility and tolerability of the described multimodal intervention in the advanced NSCLC population.

Funding

The proposed work will inform the feasibility of providing a multimodal complex care intervention to promote QOL in advanced NSCLC patients. Specifically, by evaluating feasibility of this intervention, we aim to develop a larger trial (PCT) aimed at measuring the impact of a multimodal cancer rehabilitation service on QOL in numerous advanced tumour group populations. Along with ongoing pilot data collection in the advanced multiple myeloma population[23] and the delivery of exercise to all tumour groups within the ACE program, the current data will enhance our understanding of how our standard cancer and exercise program (ACE) needs to be tailored, and possibly complemented by nutrition and palliative symptom management, to address unique needs of NSCLC patients, and eventually other tumour groups in need of palliative care. In addition, utilizing resources available within nutrition services and from the Complex Cancer Management team, we aim to deliver a feasible clinic-based supportive care program advanced cancer care. Specifically, this pilot work will inform advanced cancer care exercise programming within ACE, as well as the logistics of multimodal interventions delivered in the cancer care setting, utilizing nutrition counselling and palliative symptom management services.

The compilation of data from these three projects will be used to inform submissions for CCSRI Impact and Quality of Life grants (2020), and a CIHR project team grant (September 2020). Given the increased focus in cancer survivorship and recognition that tailored interventions must consider the unique needs of differing cancer populations, we believe this preliminary work will support our team's capacity to be successful for larger grants, and deliver successful implementation effective palliative programming in clinic-based settings.

Outside of the research impact of this work, the proposed study could have direct impact on how we use "putting patients first" symptom burden information to deliver wellness resources that positively impact QOL for NSCLC patients. Specifically, this pilot study will provide (a) an understanding of appropriate referral and screening procedures prior to intervention delivery, (b) the needs of the clinic HCPs to support referral and address their patient needs, and (c) based on PROs and the interviews with patient, an assessment of the intervention feasibility and potential benefits. Utilizing a patient-perspective and delivering the intervention using existing resources will help to inform future clinical practice and guidelines for more responsive advanced cancer care. Despite overwhelming evidence as to potential benefits, wellness interventions such as exercise and nutrition are generally lacking across the cancer care pathway. The current work will increase the efficacy of the cancer care pathway by collating and contributing evidence to a feasible intervention for advanced NSCLC patients. Longer term, we hope to translate the findings from this pilot to other tumour groups, working on tailoring referral and screening and best addressing the unique symptom burdens for each group by tailoring the interventions to address specific needs.

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