THE FEASIBILITY OF USING CT SCANS TO DETECT CHANGES IN BODY
COMPOSITION OVER TIME IN COLON CANCER SURVIVORS ENROLLED IN A
PHYSICAL ACTIVITY INTERVENTION

by

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Abstract

Computed tomography (CT) imaging presents an accurate and readily available method to quantify changes in body composition within colon cancer patients. Unwanted changes in body composition is one pathway in which cancer outcomes, particularly survival, may be altered in this population. Sarcopenic cancer patients consistently exhibit poorer overall survival compared to non-sarcopenic cancer patients. Physical activity is associated with favourable changes in body composition, namely through promoting reductions in visceral adipose tissue and increases in muscle mass. The purpose of this feasibility study is to evaluate the practicality of using CT scans to quantify changes in body composition over time between colon cancer patients who had completed primary cancer treatment randomized to a physical activity intervention (intervention group) or usual care (control group). Eighteen participants who had completed a minimum of 12 months of the CO.21 Trial from the Vancouver CO.21 Trial center were included. Body composition outcomes were measured at baseline, 6 months and 12 months using CT scans taken as part of routine practice. Manual image analysis time took on average longer (17min:20sec) then automated analysis (57sec). Image retention rate was high (97.9%), and only a small proportion of images were deemed as having major quality issues (5.9%). All but one quantified body composition outcome had excellent measured inter- and intra-rater reliability (ICC >0.9). There were no significant time and group effect (p<0.05) across 12 months between the intervention group and control group for any of the measured body composition outcomes. CT automated analysis of body composition may be preferable and more feasible for future use in research or clinical settings compared to manual analysis. In a sub-sample of the CO.21 Trial, we found no evidence that trial participants randomized to an aerobic
physical activity intervention demonstrate favourable improvements in body composition after 12 months compared to usual care.
Lay Summary

Computer tomography (CT) scans are taken during routine care for colon cancer patients. Computer software can be used to determine in a CT scan the amount of muscle and fat within the body. Excess fat and low levels of muscle can put colon cancer survivors at higher risk of earlier death. The goal of the project was to determine if the computer software is reliable for measuring fat and muscle manually versus automatically. A secondary goal was to determine if aerobic exercise (i.e., walking) improves amounts of fat and muscle compared to patients who did not participate in the exercise program. We found no evidence of improvements between groups, but the automated method for using the software was reliable and took less time to complete than the manual approach, suggesting the automated approach may be useful to researchers to accurately and reliably measure fat and muscle in colon cancer patients.
Preface

I, Logan Meyers worked in collaboration with my supervisor (Kristin Campbell) to identify and design this thesis study. Kristin Campbell identified the participants enrolled in the CO.21 Trial at the Vancouver site as the sub-sample to use for analysis in this thesis study. I had no contribution in the design of the CO.21 Trial. I was and continue to be involved in the data collection of the CO.21 Trial as a physical activity counsellor (PAC) at the Vancouver site. I had no contribution to the CT scans conducted as a part of routine clinical care and CO.21 Trial protocol. I did fully contribute to the data analysis once appropriate approval for data sharing and transfer was made. Kendra Zadravec, a Master student in my lab who assisted with CT image analysis, was the only individual to perform data analysis other than myself. Kristin Campbell and Cameron Mitchell (thesis committee member), assisted with the data analysis planning and interpretation.

This thesis study received approval from The University of British Columbia – BC Cancer Research Ethics Board (H19-00192).
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List of Abbreviations

BIA – Bioelectrical Impedance Analysis
BMI – Body Mass Index
CON – Control Group
CO.21 – CHALLENGE Trial
CT – Computer Tomography
DXA – Dual X-ray Absorptiometry
EWG – European Working Group
HR – Heart Rate
HU – Hounsfield Unit
ICC – Inter Class Correlation
IMAT – Intramuscular Adipose Tissue
INT – Intervention Group
MA – Muscle Attenuation
MET – Metabolic Equivalent of Task
MRI – Magnetic Resonance Imaging
OS – Overall Survival
PA – Physical Activity
PAC – Physical Activity Counsellor
PPO – Peak Power Output
PYTPAQ – Past Year Total Physical Activity Questionnaire
QOL – Quality of Life
RCT – Randomized Controlled Trial
SAT – Subcutaneous Adipose Tissue
SFT – Seniors Fitness Test
SMI – Skeletal Muscle Index
TAT – Total Adipose Tissue
VAT – Visceral Adipose Tissue
6MWT – Six Minute Walking Test
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To my parents: Myles, Katherine & Ari
1 Introduction

Colorectal cancer is currently the second most common cancer in Canada, with 1 in 13 men and 1 in 16 women being diagnosed in their lifetime. Individuals with sarcopenia (i.e. low lean muscle mass) or sarcopenic obesity (i.e. loss of lean muscle mass with no change or increase in body fat) at diagnosis or those who experience these changes after diagnosis have poorer colon cancer outcomes. Across multiple observational studies, sarcopenic cancer patients consistently exhibit poorer overall survival compared to non-sarcopenic cancer patients. In a recent meta-analysis sarcopenic colorectal cancer patients were estimated to have more than double the risk of poorer overall survival (HR = 2.25, 95% CI = 1.63–3.09, p < 0.001). A potential intervention to address sarcopenia in colon cancer survivors, and thus potentially improve cancer outcomes, is physical activity. To date there is limited research examining physical activity induced changes in body composition over time in individuals with a colon cancer diagnosis. Serial Computer Tomography (CT) images are used extensively in standard of care for colon cancer from diagnosis to monitoring of treatment response. CT images can also be used to assess body composition within a single CT slice or as a proxy for body composition of the whole body.

The main purpose of this feasibility study is to evaluate the practicality of using CT scans, collected as part of routine clinical care, to examine body composition change in colon cancer survivors who are participating in a large randomized controlled trial (CO.21 Trial) to examine the efficacy of a supervised physical activity program commenced after completion of primary treatment compared to usual lifestyle. The specific study aims are as follows:
(1) To assess the feasibility of using CT scan images taken as part of the CO.21 Trial to assess body composition by collecting practicality success indicators and evaluating data reliability;

(2) To compare the change in body composition over time between colon cancer survivors in the physical activity program versus those receiving general health education materials;

(3) To examine factors that may influence change in body composition, such as age, sex, cardiorespiratory fitness and physical functioning level, and adherence to the physical activity program.
2 Background

2.1 Feasibility Study Design

Feasibility studies are often conducted with the intent of determining if an intervention is appropriate for further use and/or testing. In the context of this feasibility study, methods of CT scan image analysis are being assessed to determine if it is appropriate for the quantification of changes in body composition in colon cancer patients. Bowen et al. proposed eight general areas of focus feasibility studies may choose to address. One area of focus, practicality, focuses on the extent to which a process or measure can be successfully delivered when resources, time, commitment, or some combination thereof are constrained in some way. In the case of this feasibility study, practical will be investigated for the use of CT imaging analysis to examine changes in body composition in individuals with colon cancer, namely CT scan retention, efficiency and speed of analysis methods, and quality of CT images. An additional area of focus described by Bowen et al. is limited-efficacy testing conducted in a sample with limited statistical power. Through examining changes in body composition over time in our sample, limited conclusions can be made about the efficacy of the intervention on our body composition outcomes of interest. By evaluating the specific success indicators of practicality and efficacy testing, the feasibility of using CT images to detect changes in body composition over time in colon cancer patients may be determined.

2.2 Colon Cancer

Cancer is a disease characterized by the unchecked division and survival of abnormal cells. When this type of abnormal growth occurs in the colon or rectum, it is called colorectal cancer. Colorectal cancer may also be discussed separately as either rectum cancer or colon
cancer, depending on where the abnormal growth originates. In Canada, 26,800 individuals in 2017 were diagnosed with colorectal cancer, and it is estimated that over 100,000 Canadians are currently living with a prior diagnosis of colorectal cancer. Since the mid-1980s there has been a steady decline of colorectal cancer incidence rates in Canada for both sexes, likely attributed to the increases in screening which aims to identify and remove pre-cancerous polyps. Consequently, the 5-year net survival for those diagnosed with colorectal cancer has risen to be 64%. Even still, each year 9,400 Canadians died from colorectal cancer, which represented 12% of all cancer deaths in 2017. As seen over the past decade, continual improvements in Canadian screening rates are likely to improve incidence and survival rates for colorectal cancer. However, in 2018, no province or territory in Canada met the target of screening 60% of their population between the ages 50-74, so continued efforts to promote screening are warranted.

Treatment outcomes for colorectal cancer vary widely based on stage of cancer, tumour location, and tumour-specific molecular features, therefore treatment decisions are collaboratively made between patient and physician after considering best-options, as well as the risk and benefit of each proposed treatment option. Specifically, those with colon cancer will often undergo surgery to remove the tumour and receive subsequent adjuvant chemotherapy, while radiation therapy is not used as often to treat colon cancer. In contrast, treatment for rectal cancer often involved chemotherapy and/or radiation therapy prior to surgery. The work presented in this thesis has focused exclusively on individuals with colon cancer. The side effects that are common concurrent with colon cancer treatment include and are not limited to fatigue, temporary or permanent colostomy, cognitive impairments, neuropathy, susceptibility to infection, loss of appetite, nausea and vomiting, diarrhea, swelling and rashes. These side effects may also persistence years after termination of treatment.
There is growing evidence to suggest that cancer patients undergo a multitude of changes to their body composition that alters proportions of muscle and adipose tissue. The impacts of anti-cancer therapies on muscle loss are multi-factorial, including metabolic alterations that promote a catabolic state, physical inactivity due to fatigue or bed rest resulting in a reduction or lack of daily energy expenditure, and nutritional deficiency due to nausea. Of note, a lower muscle mass at pre-diagnosis and/or subsequent loss of muscle mass during treatment of colon cancer may put an individual at risk of becoming sarcopenic. Muscles mass also declines with the standard aging process, In addition, the incidence of colon cancer itself is also age-related, with approximately 50% of newly diagnosed colon cancer patients being over the age of 70, suggesting that a larger number of cancer survivors may have low muscle mass at diagnosis.

2.3 Definitions of Sarcopenia

Sarcopenia and sarcopenic obesity are conditions that impact an individual’s muscle and adipose tissue composition. Sarcopenia is defined by the European Working Group (EWG) on Sarcopenia in Older people as, “the progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and mortality”, and is now considered a muscular disease. This group also suggests that even though sarcopenia is primarily an age-related disease the causes of sarcopenia may extend beyond aging in clinical populations. The muscular system plays an essential role in the stability, mobility, and metabolic functioning of the human body, and when a disruption to the muscle composition occurs there may be significant effects on the health of an individual. The loss of muscle mass accompanying sarcopenia and sarcopenic obesity is thought to be age-related, as 13% to 24% of older adults are living with one of these conditions. Of note, the Asian Working Group on Sarcopenia has built upon the EWG sarcopenia criteria, highlighting differences in
definitions required based on ethnicity, genetic background, and body size of Asian populations.116

A key challenge to determining the prevalence of sarcopenia within any clinical population is the lack of an established objective definition or testing procedure for sarcopenia.31

In research, there is inconsistency in the various characteristics, measurements, and assessments used to define sarcopenia in the literature. Most commonly, sarcopenia is defined using imaging techniques that can quantify muscle area and mass. Sex-specific cut-off values of muscle area normalized for stature, referred to as skeletal muscle index (SMI) are most often used to identify sarcopenia.24-27 The justification for using sex-specific cut-off values is centered on the fact that men typically exhibit larger total and regional skeletal muscle mass when compared to women.28 The integration of body mass index (BMI) as a method to categorize sex-specific cut-off values has become more common in recent literature.32,33 By doing so, obese patients (BMI ≥ 30 kg/m2) may be identified as sarcopenic obese through different sex specific cut-off values compared to the cut-off values assigned to non-obese patients (BMI < 30 kg/m2).113 The most comprehensive cut-off values currently available were defined by Caan et al.64 using a very large cohort (n = 3262) of early-stage colorectal cancer patients. Sarcopenia was defined in men with a SMI < 52.3 cm²/m² if BMI is < 30 kg/m² and < 54.3 cm²/m² if BMI is ≥ 30 kg/m² and in women with a SMI < 38.6 cm²/m² if BMI is < 30 kg/m² and < 46.6 cm²/m² if BMI is ≥ 30 kg/m².64

Another key consideration for developing a definition of sarcopenia, the EWG recommends that sarcopenia should be identified clinically with a measure of muscle strength in the absence of the imaging of muscle mass. Individuals who have low muscular strength, known as dynapenia, are then identified as having probable sarcopenia.31 Dynapenia is known to be a
separate condition compared to sarcopenia. Authors found that the correlation was strong between hand grip strength and muscle mass (Pearson coefficient = 0.53, \( P < 0.0001 \)) but that hand grip strength and loss of muscle mass had poor agreement (Kappa = 0.14 [95\% CI, 0.07-0.21]). Furthermore, linking dynapenia and sarcopenia to health outcomes was examined in a cross-sectional study performed by Neves et al. It was concluded that identifying sarcopenia in an elderly population can help prevent future self-reported physical disability, whereas identifying sarcopenia can be useful in clinical practice to screen for the early decline in mobility.

The absence of a uniform definition of sarcopenia makes it challenging to approximate the prevalence of sarcopenia, although it is estimated between 20\% to 40\% of colon cancer patients have a low muscle mass. This number is expected only to increase with the aging population, as both the prevalence of sarcopenia and colon cancer are age-related.

2.4 Measuring Body Composition and Sarcopenia

There are multiple approaches to measure and quantify body composition. Recently, improved techniques to collect body composition data have been employed by researchers, in order to better understand the evolving complexity of body composition and its potential relationship with health outcomes.

BMI, a ratio of height and weight (kg/m\(^2\)), is a commonly used approach for reporting body composition. BMI can vary depending on ethnic differences, as such the World Health Organization has created additional BMI categories to reflect Asian populations. The advantages to using BMI are that it is easy to use, inexpensive, and can be generated from self-report or measured height and weight. However, the issue with BMI is that it neglects a very
prominent bodily component, muscle. Without distinguishing between adipose and muscle tissue, patients with an identical BMI can have drastically different quantities of adipose and muscle tissues. In addition, BMI cannot indicate where these different tissues are distributed within the body (e.g., different adipose compartments). While sarcopenia is most common among those with a low BMI, the condition can be seen in those across a range of BMIs, and effects colon cancer survival independent of adiposity. Older colon cancer patients are a population that exhibit large variations of body compositions, and for this reason BMI is a poor measure of body composition. Anthropometric techniques, such as measurement of mid-upper arm circumference and skin fold thickness have also been used in the past to estimate a measure of muscle mass and body fat, respectively, but due to a high vulnerability to inter- and intra-rater error these techniques not recommended for the identification of sarcopenia in both research and clinical populations. Bioelectrical impedance analysis (BIA) is another low-cost alternative for collecting general measures of body composition. BIA accurately measures fat mass and fat-free mass (a combination of muscle, bone mineral and water mass), although measurement techniques and equations may vary depending on multiple factors such as age, sex, ethnicity, and disease status. Posture and hydration status are often reported as confounding factors when measuring body composition via BIA.

More objective measures of whole-body composition overcome many of the issues of BMI, sum fold thickness, and BIA, and provide more accurate measurement of total muscle mass and fat mass, as well as the pattern of distribution across the body. These objective approaches are frequently used to identify body composition consistent with sarcopenia in research. Objective imaging techniques used to identify sarcopenia are less frequently conducted as they take up an already overburdened clinical healthcare resources, are time consuming, costly, and
may expose patients to unwanted radiation. Assessments of sarcopenia can be further split into methods for muscle quantification and tests used for estimating muscle strength and/or function. To evaluate the former, various imaging techniques may be used, including magnetic resonance imaging (MRI), CT imaging, and dual-energy x-ray absorptiometry (DXA). CT and MRI are considered the most valid standard imaging techniques for identifying sarcopenia. Table 1 outlines the advantages and disadvantages of the commonly used body composition imaging techniques.

DXA scans are often used as a less-expensive alternative to CT and MRI. In order to detect the different regions of adipose tissue (i.e., visceral or subcutaneous), post-image measurements may be performed on DXA scans to calculate estimated values of regional adipose tissue. CT scans use x-ray attenuation measured by computer software that reconstructs slice-by-slice cross-section images represented by a 2-D map of pixels. These pixels are then given a numeric value, called a Hounsfield unit (HU), based on tissue attenuation and are coloured on a spectrum from white (most dense) to black (least dense).

As with muscle mass there are a number of tests that may be used to assess muscle strength and/or function. Handgrip strength and knee flexion/extension are commonly used as estimates of muscle strength. Dynapenia, and thus probable sarcopenia, is considered to be present when either of these measures are two standard deviations below the age-adjusted mean. Although the EWG on sarcopenia advise that these proxy measures of whole-body muscle strength may not associate with those with physical disabilities or individuals training specific muscle groups. Muscle function is commonly estimated through using tests of physical function such as usual gait speed and stair climb power test, or a battery of tests, such as the Seniors Fitness Test (SFT). The SFT is comprised of six functional tests, each test being scored
separately on different scales. The six independent tests are: the chair stand test (lower body strength), the biceps curl test (upper body strength), the six-minute walk test (aerobic endurance), the chair sit and reach test (lower body flexibility), the back scratch test (upper body flexibility), and the 2.45m up-and-go test (agility and dynamic balance). Each test of the SFT has been validated, where possible, against available gold standards. Performance standards for the SFT are based on results from 7,000 older adults from the USA, which provides normative standards for individuals ages 60-94. The SFT is appropriate for research and clinical purposes as well as similar populations outside the USA.

2.5 Using CT Imaging for Measures of Body Composition & Sarcopenia

Advancements in image-based technologies, including the gold standard CT imaging, has allowed for the increasingly accurate quantification of adipose and muscle, both metabolically important tissues. In fact, CT imaging is considered the gold standard for quantification of adipose and muscle tissue, providing a more precise indication of composition compared to other anthropometric methods outlined above. Manual segmentation and measurement of both adipose and muscle tissue using CT imaging can be performed using commercially available imaging analysis software (i.e. SliceOmatic from Tomovision, Montreal, Canada) that detects the radiodensity of specific tissues, allowing for the quantification into HU. A HU allows for the differentiation between tissues in the body. Within a cross-sectional CT image, adipose and muscle tissue have pre-determined HU ranges. These HU ranges allow adipose tissue to be further differentiated into subcutaneous (SAT, -190 to -30 HU), visceral (VAT -150 to -50 HU), and intramuscular adipose tissues (IMAT -190 to -30 HU). In addition, muscle tissue (-29 to +151 HU) can be further quantified using a muscle attenuation coefficient (MA) which is suggestive of adipose infiltration and muscle density. The tissue area (cm²) of the cross-
sectional image is then calculated by multiplying the number of pixels for a given tissue by the surface area of that individual tissue. Several parameters can be derived from these calculations including, whole body fat and muscle mass \((L3\text{ cross-sectional area (cm}^2) \times 0.3 + 6.06,\) coefficient correlation of this regression, \(r = 0.94\), SMI, various adipose to muscle ratios, and muscle density.5

The location of the abdominal cross-sectional image chosen for analysis is often an area in the lumbar vertebrae, specifically the L3 vertebrae. Previous studies have supported CT image analysis of a single abdominal cross-sectional image as an accurate measure of whole-body skeletal muscle and adipose tissue. A study performed by Shen et al. (2004) was conducted to determine which single cross-sectional region of tissue area can be extrapolated to correlate with whole-body composition. It was found that the L3 region of the vertebrae was best correlated, and as such when landmarked and identified using image analysis software, tissue differentiation using HU should be performed at L3. When assessing skeletal muscle the L3 landmark, the field of view includes the psoas, paraspinal muscles (erector spinae, quadratus lumborum), and abdominal wall muscles (transversus abdominus, external and internal obliques, rectus abdominus). Other major tissue compartments include organs and subcutaneous and visceral adipose tissue.

2.6 Using CT Imaging for Measures of Body Composition & Sarcopenia for Individuals with Colon Cancer

CT images taken from clinical centers are stored in health records and are often readily available for research use. CT imaging used for body composition assessment outside of a cancer population is rare, as it is deemed unethical to expose healthy individuals to high radiation doses that accompany obtaining CT images. This risk is acceptable for cancer patients, specifically
colon cancer patients, as these scans are taken as a part of routine clinical care for diagnostic, treatment, and follow-up purposes. The regularity of these scans may vary slightly, although in most clinical settings colon cancer patients undergo CT imaging at least 2-3 times a year. Tumour progression and response to therapy are tracked through these CT scans. Despite this, the amount of information from these CT images far exceeds their current clinical purpose. In fact, it is only quite recently that both cancer care specialists and researchers are discovering the unmatched availability and ability of CT images to evaluate cancer patients’ body composition.

Mourtzakis et al. compared methods to achieve practical and precise measures of body composition in cancer patients. BIA over and under-estimated muscle mass compared to DXA and manual CT analysis, respectively. Also, DXA could not provide details on organs, specific muscles and adipose tissue when compared to CT images. The study concluded that that CT presented the greatest practical significance, as well as being highly precise. For these reasons, we believe that utilizing existing CT images for the evaluation of body composition over time in colon cancer survivors may produce original findings that have yet to be established in similar previous research. There are no specific CT image acquisition parameters that are required for the purpose of cross-sectional body composition analysis. For patients undergoing routine CT scans the following standard parameters are acceptable: 120kV, variable mA with dose modulation, soft tissue reconstruction algorithm, matrix of 512 x 512, field of view of 30-35 cm and reconstructed thickness of 5 mm.

2.7 Body Composition and Cancer Outcomes

Sarcopenia is consistently associated with a decrease in overall survival, disease-free survival, and cancer-specific survival in non-metastatic colon cancer survivors. In a systematic review and meta-analysis published in 2018, Sun et al. reported in their pooled-
analysis that the sarcopenic colorectal cancer group showed a significant decreased overall survival (HR = 1.73, 95% CI = 1.28–2.35, P < 0.01), disease-free survival (HR = 1.95, 95% CI = 1.36–2.80, P < 0.01), and cancer-specific survival (HR = 1.62, 95% CI = 1.16–2.27, P < 0.01) in comparison with the non-sarcopenia colorectal cancer group.

In 2016, Shachar et al.\textsuperscript{36} conducted a systematic review and subsequent meta-analysis to quantify the prognostic value of SMI on clinical outcomes in solid tumours. Including all solid tumour types, the effect of SMI lower than the cut-off value indicated poor overall survival (OS) (HR = 1.44, 95% CI = 1.32–1.56, p < 0.001). Three colorectal cancer studies were included in the meta-analysis, totaling 493 patients, and were found to have the largest hazard ratio across all tumour types for OS (HR = 2.25, 95% CI = 1.63–3.09, p <0.001). The findings of this study suggested that low SMI (a marker of sarcopenia), is associated with poorer survival in cancer patients across all solid tumour types.

In 2018, Cespedes Feliciano et al.\textsuperscript{33} conducted a similar meta-analysis in order to update the results found by Shachar et al.\textsuperscript{36}. The meta-analysis evaluated an additional 10 colorectal cancer studies and found that the majority produced significant results to support sarcopenia being associated with a higher risk of mortality. Furthermore, no study across all tumour types, or specifically colorectal cancer, reported a significant protective association of sarcopenia on mortality.\textsuperscript{33}

2.8 Proposed Mechanisms Linking Sarcopenia to Poorer Cancer Outcomes

2.8.1 Skeletal Muscle

A reduced muscle mass can be the consequence of one or a combination of the following factors: aging, behaviours (such as physical inactivity), malnutrition, or induced by the body’s
response to a disease, such as cancer. Each pathway involves varying mechanisms in which low muscle mass is the result. Muscle loss due to aging is characterized by a number of mechanisms, the first is driven by continued cellular death of spinal motor neurons. The corresponding denervated muscle fibers are re-innervated through adjacent motor axons or end plates, leading to enlarged motor units which result in a decline in total muscle fiber number and size. Muscle performance is therefore impaired through this pathway which also translates into a compromised functional capacity to perform everyday tasks. Chronic systemic inflammation caused by increased levels of pro-inflammatory cytokines is thought to be a second underlying mechanism of muscle mass and muscle strength loss associated with the aging process. Systemic inflammation is suggested to be induced and sustained through fluctuating levels of hormonal factors, reduced growth factor signaling and protein uptake, and increased oxidative stress, all which may be exacerbated with malnutrition and reductions in physical activity that decrease energy expenditure. There is strong evidence to suggest the existence of cross-talk between systemic inflammation and losses in muscle mass, meaning chronic inflammation may contribute to muscle catabolism, which then prompts an enhanced pro-inflammatory response. In a cohort study of individuals with colon cancer He et al. reported a strong association between low muscle mass (i.e., SMI) and high systemic inflammatory response, characterized by high interferon γ-induced protein 10 levels (r = -0.276, p = 0.002). Furthermore, 3-year disease-free survival rates were significantly lower for those who exhibited poor muscle mass (HR = 2.036; p = 0.034).

Muscle mass loss occurs in muscles which experience denervation, malnutrition or inactivity, but is also a response to tumour growth and aggressive anti-cancer therapies used during colon cancer treatment. There are numerous features of a colon cancer diagnosis that
have the potential to contribute to a catabolic muscle state, which ultimately results in the loss of muscle mass. For example, alterations in protein synthesis and degradation can occur because of tumour induced pro-inflammatory mediators that interfere with the typical metabolic functioning of the muscle. In a perspective observational study conducted by Cespedes Feliciano et al. in 2017, the authors reported that pre-diagnosis inflammation was associated with sarcopenia at-diagnosis. Additionally, those with sarcopenia combined with inflammation had approximately double the risk of overall death (HR, 2.12; 95% CI, 1.70-2.65) and colorectal cancer-related death (HR, 2.43; 95% CI, 1.79-3.29) compared to patients who had neither condition. In addition, changes in nutrition due to chemotherapy-induced nausea, and physical inactivity due to bed rest, may further contribute to the loss of muscle mass following a colon cancer diagnosis.

Beyond survival, low muscle mass at the time of a colon cancer diagnosis may indicate a reduced functional capacity in patients (i.e. the ability to perform activities of daily living) and therefore by association, patient perceived QOL. This has led to a recent narrative review by Hubbard et al. which suggests the use of imaging to identify sarcopenia, as a potentially valuable clinical biomarker of frailty. Frailty may predispose patients to complications from cancer treatments, including increased toxicity, functional decline, decreased QOL, and poorer survival, and therefore may be an important consideration in treatment planning decisions. Indeed, low muscle mass at time of diagnosis and during treatment can pre-dispose patients to a higher risk of chemotherapy intolerance, postoperative complications and mortality.

2.8.2 Interaction between Adipose Tissue & Skeletal Muscle

Excess adipose tissue is thought to promote cancer development and progression through a number of different mechanisms. In particular, the biological factors consistent with higher
visceral adipose tissue (VAT) are associated with worsen cancer outcomes such as, survival, physical function, and consequently QOL through mechanisms that impact the promotion of systemic inflammation and increases in insulin resistance.33

There is no defined normal range for VAT, as it varies with age, sex, ethnicity, and other comorbid conditions.41 VAT is characterized by its large number of metabolically active adipocytes, increased amount of glucocorticoid and androgen receptors, as well as its significant production of free fatty acids.40 Adipocytes actively contribute to a systemic inflammatory state, as they are capable of synthesizing pro-inflammatory and anti-inflammatory proteins. Furthermore, the production of free fatty acids within VAT can induce lowered insulin sensitivity and sometimes insulin resistance. The excessive accumulation of VAT within the abdominal cavity is often referred to as visceral obesity.5

Although visceral obesity is a major health concern because of the aforementioned reasons, it is in fact the infiltration of adipose tissue into skeletal muscle tissue that may induce the most harmful consequences on the body. This “fatty infiltration” of muscle is often associated with additional lowered insulin sensitivity and influence on endocrine hormone secretion.42 More recently, the consequences of fatty infiltration are beginning to be linked to cancer progression and survival.43, 44 Free fatty acids produced by adipose tissue are behind the mechanism that drives fatty infiltration of muscle. These free fatty acids can be redirected to peripheral tissues, such as skeletal muscle for storage when the capacity of adipose tissue to store lipids is exceeded. Once stored, reductions in muscle lipid oxidation can occur, thereby promoting fatty acid accumulation within the muscle which in-turn drives the presence of macrophages into the muscle tissue.42 Ultimately, the consequence of this infiltration and accumulation of fatty acids results in lipotoxicity in the muscle. Lipotoxicity is hypothesized to
substantially contribute to a state of pro-inflammation that decreases insulin sensitivity and promotes muscle loss.\textsuperscript{45} It is important to note that adipose tissue induced inflammation can occur in patients with a normal calculated BMI, and therefore the risk of lipotoxicity is not limited to individuals with a high calculated BMI. Relevant to colon cancer survivors is not only the potential for muscle loss but the introduction of insulin sensitivity caused via adipose tissue inflammation can trigger synthesis of insulin like growth factor-1 that has mitogenic effects on tumour cells.\textsuperscript{45}

In 2018, van Baar et al.\textsuperscript{43} conducted a prospective cohort study of 1681 early stage colorectal patients and found that low muscle density (reflective of adipose tissue infiltration) was associated with higher overall mortality (HR = 1.91, 95\% CI 1.53–2.38) and worse disease-free survival (HR = 1.68, 95\% CI 1.14–2.47). Interestingly, the same study reported 39\% of their colorectal study sample had low muscle density, suggesting that this condition may be common in this cancer population. In addition, an observational study conducted by Moon et al. evaluated the prognostic significance of VAT, as measured by CT scan images, compared to BMI in 161 colorectal cancer patients. Findings from the study suggested that VAT was a significant predictor of disease-free survival (p =<0.01), whereas BMI was not.\textsuperscript{46} In summary, for colon cancer survivors excess adipose tissue is harmful to long-term health, and when compounded with its damaging effects on skeletal muscle, causing inflammation and lowered insulin sensitivity. Both excess adipose tissue accumulation in normal fat depots and adipose tissue infiltration into skeletal muscles, along with low muscle mass may be strong predictors of survival.
2.9 Potential of Physical Activity to Address Sarcopenia and Excess Adipose Tissue

Observational evidence suggests that colon cancer survivors who are physically inactive have a higher risk of cancer-specific and all-cause mortality. A meta-analysis conducted by Je et al.56 concluded both pre and post diagnosis physical activity are associated with reduced colorectal cancer-specific and all-cause mortality. Specifically, the relative risk of cancer-specific mortality for patients who participated in any physical activity after diagnosis compared to those who did not participate in any physical activity was 0.74 (95% CI: 0.58-0.95, p = 0.02). Physical activity interventions have the potential to counter-act the development of sarcopenia and excess adipose tissue, and the resulting detrimental physiology effects. The biological pathways in which physical activity favourably alters disease outcomes among colon cancer survivors is largely unknown. It has been postulated that changes in body composition, mainly increases in muscle and reductions in adipose tissue, induced through participation in physical activity may be a plausible mechanism, thus reducing exposure to systemic inflammation, metabolic dysregulation, adipokines, and sex hormones.33,78 Specific to the physiological effect of physical activity outside of changes to body composition, a recent meta-analysis concluded that higher cardiorespiratory fitness is correlated with a 45% reduction in cancer-specific mortality when compared to low cardiorespiratory fitness.60 These relationships demonstrate the importance of maintaining and/or improving cardiorespiratory fitness through involvement in physical activity in cancer survivors. In addition, physical activity is hypothesized to have direct beneficial effects on basic mechanisms causing sarcopenia, including but not limited to a reduction of inflammation and reduced fat infiltration.79

Historically, aerobic physical activity has been one the most effective intervention strategies to improve metabolic function of skeletal muscle and limit accumulation of VAT.
Aerobic physical activity promotes mitochondrial bioenergetics and contractile protein remodeling, influencing protein synthesis, decreased inflammation, and antioxidant capacity improvement in skeletal muscle.\textsuperscript{61} Aerobic physical activity is also well-established as being able to reduce excess VAT in individuals. In a randomized control trial in 52 healthy, obese men, randomized to a 12-week aerobic exercise intervention, compared to diet-induced weight loss controls, Ross et al.\textsuperscript{63} reported a decrease in VAT of 52 cm\(^2\) (cross—sectional area of a CT image) in the exercise only study arm, which corresponds to a decrease of 6.9 cm\(^2\) of VAT per kilogram of weight loss. Furthermore, the same study reported reductions in insulin resistance in participants who lost significant amounts of VAT. Additionally, a systematic review and meta-analysis conducted by Vissers et al.\textsuperscript{80} in 2013 reported that moderate to vigorous 12-week exercise programming, without hypocaloric dieting, represented a pooled effect size of reducing VAT >30 cm\(^2\) in women and >40 cm\(^2\) in men. The powerful effect of aerobic physical activity seems to mitigate the harmful consequences of a poor body composition phenotype.

There is strong evidence to suggest that skeletal muscle function deficits, such as sarcopenia, are treatable with physical activity interventions, specifically resistance training programs.\textsuperscript{81} A recent systematic review conducted by Papa et al.\textsuperscript{82} in 2017 examined the evidence that exists regarding resistance training in older adults with skeletal muscle function deficits. This review found that resistance training can attenuate age-related changes in functional mobility and is associated with improvements in gait speed, static and dynamic balance, and fall risk reduction.\textsuperscript{82} Furthermore, the benefit of resistance training has been shown to be correlated with improvements in muscle mass. In a controlled clinical trial, Leenders et al.\textsuperscript{83} reported significant changes in lean body mass measured via DXA in both men (1.2 ± 0.3 kg, \(p < 0.01\)) and women (1.2 ± 0.2 kg, \(p < 0.01\)) after a 24-week resistance training intervention. A
systematic review performed by Stene et al.85 in 2013 reported that both aerobic and resistance training interventions improve upper and lower body muscle strength in cancer patients compared to usual care. The same review acknowledged that there are few studies that examine the relationship between aerobic activity and muscle mass in cancer patients. Specific to colon cancer, to our knowledge, only three RCTs of aerobic physical activity have been conducted that report on body composition changes with the intervention (Table 2). None of these studies used CT images for quantification of adipose and muscle tissue, but rather DXA scans15,16 and anthropometric measures.49

First, a study conducted by Courneya et al.49 in 2003 randomized colorectal cancer survivors, who had completed surgery for colorectal cancer within the past 3-months, to a 16-week aerobic exercise intervention group (n=69) or usual care (n=33). Sum of skin folds was used as the method to measure body composition in participants, and no statistically significant change was found between groups (p = 0.61). No change in cardiorespiratory fitness, as measured by treadmill time, or resting heart rate was reported between groups (p = 0.33, p = 0.36, respectively). However, increases in cardiorespiratory fitness were associated with self-reported increases in QOL (p = 0.04) in an ancillary analysis. In the context of the study, this means that individuals who had an increase in fitness over the course of the intervention showed significant improvements in the self-reported measures of QOL compared to those who had a decrease in fitness. It was reported that the study experienced a major problem with exercise contamination in the control group, meaning the control group engaged in a similar amount of exercise to the intervention group.

A second RCT study conducted by Devin et al.16 in 2016 randomized colorectal cancer survivors to either moderate-intensity exercise (n=17) or high-intensity exercise (n=30) training
for 4 weeks. Using DXA scans, the study reported that the high-intensity exercise intervention led to statistically significant increases in total muscle mass (0.72±0.80 kg; p<0.01) and reductions in total fat mass (−0.74±0.65 kg; p<0.001) and body fat percentage (−1.0±1.0 %; p<0.001), whereas no significant changes were observed in the moderate-intensity exercise group. Cardiorespiratory outcomes were measured as relative VO2max (ml/kg/min) and peak power output (W/kg). The high-intensity group showed statistically significant changes from baseline in both fitness measures (p < 0.001), whereas the moderate-intensity group showed a statistically significant change only in relative peak power output (p <0.030).

Lastly, a RCT study by Brown et al. conducted in 2017 randomized colon cancer survivors, who had finished surgical resection and adjuvant chemotherapy within 36-months into a 3-arm study; usual lifestyle control (n=13) or low-dose (n=14) or high-dose exercise (n=12) interventions. Using DXA, exercise reduced VAT in a dose-response fashion over the 6-month intervention. Compared with the control group, the low- and high-dose exercise groups lost 9.5 cm² (95% CI: −22.4, 3.5) and 13.6 cm² (95% CI: −27.0, −0.1) in VAT, respectively, measured via DXA scans. In addition, each 60 minutes/week increase in exercise predicted a 2.7 cm² (95% CI: -5.4, -0.1) reduction in VAT. No significant differences in lean mass was reported (p = 0.45). This study reported differences in MET hours per week between the low dose group (13.7 MET hours/week) and the high dose exercise group (23.9 MET hours/week). Compared with the control group, over 6 months, the distance walked in 6 minutes increased by 11.4 m in the low-dose group, and 40.9 m in the high-dose group, respectively (P<0.01). By accelerometer-quantified moderate to vigorous intensity physical activity increased by 22.3 minutes per day in the low-dose group, and 28.8 minutes per day in the high-dose group, respectively (P<
The authors concluded that VAT may be a mechanism through which exercise reduces the risk of disease recurrence among colon cancer survivors.

No randomized controlled trial to date has examined the impact of *resistance* training alone on body composition measures in colon cancer survivors. A 2018 single-arm intervention feasibility study by Singh et al. investigated the efficacy of a 10-week combined resistance and aerobic exercise intervention with rectal cancer patients currently undergoing neoadjuvant chemoradiation. DXA scans were analysed for measures of body composition. The intervention resulted in a significant increase in lower limb muscle strength (32.9 kg, 95% CI: 3.9 to 61.9, p = 0.03) and muscle endurance (9.2 reps, 95% CI: 3.2 to 15.3, p = 0.007), as well as a decrease in lower limb muscle mass (-0.9 kg, 95% CI: -1.5 to -0.3, p = 0.007) and skeletal muscle mass (-1.1 kg, 95% CI: -1.9 to -0.3, p = 0.012). A significant reduction in total body fat mass (-0.8 kg, 95% CI: -1.6 to -0.1, p = 0.03) was also found. Intervention studies examining change in muscle mass and function during cancer treatment, such as this one, typically aim to preserve muscle mass and strength, while mitigating the commonly observed decline in both measures with neoadjuvant treatment. The intervention effect reported by Singh et al. is consistent with this; demonstrating the potential of resistance exercise to have a positive, but small, impact on body composition in rectal cancer demonstrating the potential of physical activity to improve body composition in colon cancer survivors.

In summary, these initial studies produced preliminary evidence that engaging in aerobic physical activity is associated with favourable changes in body composition, specifically reductions in fat mass, body fat percentage and VAT in colon cancer survivors. The impact of aerobic physical activity on muscle outcomes (i.e., muscle mass, muscle attenuation, muscle strength) in colon cancer survivors is less clear. To date, there are limitations in measurement
approaches used to measure body composition, including sum of skins folds that is a dated technique with poor reliability, and DXA is unable to detect measures of muscle attenuation, which may be extremely important to the muscle wasting associated with sarcopenia. Specific to measures of muscle strength and function were not included. Lastly, physical activity interventions ranged in duration from 4-24 weeks. Interventions exceeding 6-months in duration may be critical in order to see larger differences and improvements in key body composition components (muscle mass, muscle attenuation, and VAT) and associated cardiorespiratory fitness.
3 Study Aims and Hypothesis

The specific aims of the feasibility study are as follows:

(1) To assess the practicality of obtaining and using CT scan images taken as part of the CO.21 Trial to assess body composition by way of collecting practicality success indicators and evaluating data reliability; specifically, these indicators are:

a) Image retention rate
b) Image analysis duration
c) Image analysis intra- and inter-rater reliability
d) Image quality score

(2) To compare the change in body composition over 12-months between colon cancer survivors in the physical activity intervention group versus those receiving general health education materials;

(3) To examine factors that may influence change in body composition, such as age, sex, cardiorespiratory fitness level, and adherence to the physical activity program.

The hypotheses are that:

1) It will be feasible and reliable to use existing clinical CT scan images for the assessment of body composition measures (aim 1). Specifically, an image retention rate of >80% is hypothesized to be achieved, image analysis duration for individual slices will be less than 30 minutes, and that excellent (ICCs >0.9) intra- and inter-rater reliability, and image quality exist for L3 slice image analysis.

2) Relative to the general health education materials group, a structured aerobic physical activity program after treatment for colon cancer patients will improve important prognostic measures of body composition (aim 2)
3) Individual participant characteristics will influence the changes in body composition detected over time (aim 3).
4 Methods

4.1 Study Participants

The CO.21 (CHALLENGE) trial enrolled individuals previously treated for high risk stage II-III colon cancer, who were then randomized to either a physical activity intervention group or a general health education group. This study included participants in the CO.21 trial at the Vancouver, British Columbia research site that had completed a minimum of 12-months of the CO.21 trial with baseline (prior to randomization), 6-months, and 12-months CT images available as of December 2018.

CT images were analyzed by a trained graduate student who was blinded to group assignment. See figure 1 for further study sample and CT scan collection details.

4.2 Study Design

The CO.21 trial is a multi-national, multi-centre, randomized phase III study comparing patients allocated to a physical activity intervention (designed to induce increased physical activity participation) plus general health education materials arm to patients allocated to a general health education material only arm (standard of care group) for patients with high risk stage II/III colon cancer. Patients were stratified by disease stage (high risk II vs. III), center, BMI (≤ 27.5 vs. > 27.5), and ECOG performance status (0 vs. 1). All eligible patients underwent baseline testing consisting of medical and anthropometric measurement, a sub-maximal exercise test, the seniors fitness testing battery, and a six-minute walking test (6MWT) prior to randomization.
4.3 CO.21 Trial Interventions

4.3.1 General Health Education Group

Participants randomized to this group received general health education materials, which was designed to serve as standard of care control group (CON). The standard of care for provision of education materials following cancer treatment is different between countries involved in the study and for the Canadian study sites, all patients were provided with the most up-to-date Canada Food Guide for recommendations related to nutrition and the most up-to-date Canada’s Tips to Get Active (for adults aged 18-64) and older adults (over 65) for recommendations related to physical activity.

4.3.2 Physical Activity Intervention Group

Participants randomized to this group also receive the same education materials as the general health education group, in addition to the physical activity intervention (INT). In addition, the physical activity intervention consisted of two components. The first being behavioural support sessions with a physical activity consultant. The second was supervised physical activity sessions with a physical activity consultant. The goal of the physical activity intervention was to increase recreational physical activity from baseline (by at least 10 MET hours/week to a maximum of 27 MET hours/week. Baseline physical activity level was calculated using the month prior only of the recreational activity module of the Past Year Total Physical Activity Questionnaire (PYTPAQ). Behavioural support sessions included a personalized physical activity prescription that took into account the baseline fitness test results, physical activity history, performance status and patient’s personal physical activity preferences and any barriers to activity. Supervised physical activity sessions were completed in combination...
with behavioural support sessions when feasible or occurred independently. The focus of these sessions was to teach proper physical activity technique and monitoring. During exercise sessions aerobic physical activity type, intensity and duration was self-selected to align with the patient fitness goals.

The CO.21 trial consists of 3 phases, spanning over 36 total months. During phase 1, patients in the physical activity program completed 12 mandatory face-to-face bi-weekly behavioural support and physical activity sessions over a 6-month time period. Phase 2 began after 6-month fitness testing and consisted of 12 mandatory face-to-face or by telephone bi-weekly behavioural support sessions. Physical activity sessions were also held bi-weekly and were recommended but not mandatory for patients in phase 2. Fitness testing was performed at 12-months which marked the completion of phase 2. Mandatory monthly behavioural support sessions and recommended monthly exercise sessions were conducted for patients in phase 3. The final fitness testing were conducted at 36-months, which marked the end of the structured physical activity intervention. Additional support was provided by physical activity consultants during any phase if they determined the patient was having difficulty with physical activity compliance.

**4.4 Ethics and Informed Consent**

This feasibility study has received ethical approval through the BC Cancer Research Ethics Board. As per the CO.21 trial consent and confidentiality agreement, study participants were not required to sign an alternate informed consent for the use of their CT images in this study. Acquired patient data will be kept anonymous, as new participant codes will be assigned upon CT image collection. Participants were not remunerated for the use of their CT images or require reimbursement for expenses related to study participation.
4.5 Outcome Measures

The trial duration is 36 months. Outcome measures are collected at 5 timepoints: 1) Baseline (prior to randomization; patients are 60-180 days post colon cancer treatment); 2) 6-months after date of patient randomization, 3) 12-months after date of patient randomization, 24-months after date of patient randomization, and 36-months after date of patient randomization. For the purposes of our study, previously collected CO.21 Trial outcomes, including patient CT images, were from the first 12 months in the CO.21 Trial.

4.5.1 Demographic factors

Age and sex were extracted from medical records by the CO.21 Trial study coordinator.

4.5.2 Feasibility

Practicality of obtaining and examining CT images was tested (Aim 1), as

a) **Image retention rate:** Defined as the proportion of participant CT scans available from 2009 to 2018 divided by the proportion of participant CT scans taken from 2009 to 2018, multiplied by 100. Success was defined a priori as >80% of CT images retained.

b) **Image analysis duration:** For manual segmentation analysis duration was measured as the time spent quantifying components of body composition for each CT image and reported as mean time. Manual image analysis start, and end time were defined when L3 landmarking begins and when manual segmentation ended, respectively. For automated image analysis, duration was measured as the time for the Voronoi Health Analytics ABACS L3 Module quantify components of body composition for each CT image. Start time was defined when the L3 slice was loaded into the module, thus does not account for the time required for L3 landmarking. Automated
analysis end time was defined when the module had completed quantifying each specific tissue region.

c) **Image analysis intra- and inter-rater reliability:** The intra and inter-rater reliably of manual body composition analysis using the SliceOmatic software and CT scans collected as part of the CO.21 Trial was examined (Aim 2) by reporting:

i. **Intra-rater reliability:** A random sample of 25 CT L3 images were manually segmented and quantified by the same individual for a second time 1 month after the original analysis. The intra-class correlation (ICC) was then calculated for SMI, VAT, SAT, and MA determined by analysis 1 and analysis 2 (1-month post). The ICC was reported as a measure of the agreement between repeated the manual analysis rater.

ii. **Inter-rater reliability:** The same random of CT L3 images underwent a separate analysis conducted by another individual who is less familiar with the software. The ICC was then calculated for SMI, VAT, SAT, and MA between analyst 1 and analyst 2. The resulting ICC was reported on as a measure of manual CT image segmentation agreement between raters.

iii. **Reliability of Manual versus Automated Measurement:** All scans were analyzed using the manual technique by one trained rater and compared to the automated measurements completed by the SliceOmatic program. The ICC was then calculated for TAT, VAT, SAT, and MA.

d) **Image quality score:** CT images may be excluded from analysis due to noise, an unwanted change in pixel values creating a grainy or blurred cross sectional image or image distortion caused from excessive patient motion during CT imaging. Additionally, the exclusion of subcutaneous adipose tissue in the CT image field of view due to patient tissue touching or being
outside the bore of the CT scanner may produce an inappropriate CT image for our analysis. Table 9 provides further details regarding the L3 slice image quality scoring.

4.5.3 Body composition

Body composition parameters were measured using sliceOmatic V5.0 (Tomovision, Montreal, Canada) to conduct manual tissue segmentation at baseline, 6 and 12 months. The same parameters were then measured using Voronoi Health Analytics ABACS L3 Module to conduct automated tissue segmentation. SliceOmatic software used to conduct manual segmentation has been used extensively for body composition analysis research and has been deemed a reliable and valid measure of muscle and adipose tissue. Using previously published methods, a single slice abdominal region image at the third lumbar vertebra (L3) will be selected as the landmark to quantify skeletal muscle, SAT, VAT, total adipose tissue (TAT) surface area and MA coefficient. A single slice cross-sectional area at L3 is chosen as tissue area (cm²) at this landmark has been shown to be strongly correlated with whole-body muscle and adipose tissue masses. A skeletal muscle index (SMI; total skeletal muscle area (cm²)/height (m²)) will be created for muscle comparison between patients normalized for stature. MA was assessed via skeletal muscle radiodensity HU, which is a radiologic measure of the lipid content contained within the muscle. Height and body mass was used to calculate the BMI (kg/m²) of patients.

To define sarcopenia, established sex, BMI and cancer-specific SMI cut points defined by Caan et al. were used to create a dichotomous variable (yes/no) of those who are sarcopenic and those who are non-sarcopenic. Probable sarcopenia was identified in our study sample using the SFT chair sit-to-stand assessment normative scores as cut points. Both age and sex of patients are considered when identifying probable sarcopenia.
4.5.4 Physical Performance

i. **Cardiorespiratory Fitness:** This was measured by administration of submaximal treadmill testing during the CO.21 trial. The exercise test was completed when the patient had reached 85% of their maximum predicted heart rate. Patient VO\(_2\)max can then be estimated from this data using the American College of Sports Medicine formula (VO\(_2\)max = SM2 + b (HR\(_{\text{max}}\) – HR2)).117

ii. **Physical Function:** This was assessed using the Seniors Fitness Test (SFT) battery, which purpose is to measure basic physical fitness parameters associated with functional tasks and activities that are significant in the everyday living of older adults. The SFT is comprised of six measures, 8-foot up-and-go, 30-second chair stand, arm curl, 6-minute walk, chair sit-and-reach, and the back scratch. The SFT has been validated in community-living older adults.69

iii. **Usual Physical Activity:** The Past Year Total Physical Activity Questionnaire (PYTPAQ) was used to assess self-reported usual physical activity. The PYTPAQ has been shown to have acceptable reliability and validity for measurement of past-year physical activity70 and was slightly modified to refer to the month prior to its administration for the CO.21 trial. This PYTPAQ has an open table format, rather than specific questions, and is separated into three sections to assess occupational (including transportation to and from work), household and recreational activity during that reporting period. It includes a description of the activity type as well as the frequency (months per year, days per week), duration (hours per day) and perceived intensity of the activity. Definitions of each level of intensity (1=sedentary, 2=light, 3=moderate and 4=heavy) are provided with examples in the questionnaire. Respondents are required to
report household activities that involve at least standing and all types of recreational and occupational activities. A list of possible recreational activities is also given at the end of the questionnaire as a prompt for completion of this section. The metabolic equivalent of task (MET) hours per week have been extracted from the PYTPAQ and was used as a measure of weekly physical activity level.

4.6 Data Analysis

Baseline characteristics of the two groups were compared using descriptive statistics. Normality of data was assessed using histograms, Q-Q plots and the Shapiro-Wilk test. Parametric tests were used namely the Independent t test for continuous variables presented as the mean ± standard deviation (age, BMI, treatment completion, treatment exposure, days since treatment, estimated VO$_{2\text{max}}$, treadmill time, 6MWT, self-reported PA, SMI, muscle area, TAT area, VAT area, SAT area, MA) and Fisher’s Exact test for dichotomous variables presented as counts and proportions (sex, treatment type, probable sarcopenia and sarcopenia). Statistical significance of each test was set at an alpha value of p < 0.05 SPSS (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp) will be used for data analysis.

Aim 1: Retention rate of images was summarized as a percentage of total patient CT scans deemed appropriate for image analysis (retained) divided by the total number of CT scans received multiplied by 100. In addition, mean and standard deviation of the time required to complete CT image analysis, and an image quality score was assigned to each L3 slice. An inter- and intra-correlation coefficient were reported as a measure of CT image analysis manual and automated reliability. ICC estimates and their 95% confident intervals were based on a single rater, absolute-agreement, two-way mixed-effects model. Adhoc analysis using Bland-Altman plots was conducted to determine the level of agreement between manual and automated...
segmented body composition outcomes, using with two standard deviations of the mean
difference as the limits of agreement.

**Aim 2:** Secondary outcomes, namely change in body composition (SMI, muscle area, VAT area,
SAT area, and MA), were summarized as means ± standard deviations between baseline and 12-
month CT scan timepoints and sarcopenia and probable sarcopenia status (Y/N) was reported as
a proportion. A linear mixed model was used to test group and time interactions within and
between groups at and across baseline and 12 months. The linear mixed model was based on a
AR(1): Heterogeneous repeated covariance, using fixed factors. Pairwise group and time
comparisons were made based on estimated marginal means that were adjusted using SIDAK.
Change in sarcopenia and probable sarcopenia status (Y/N) was analyzed using a Fisher’s Exact
test of significance

**Aim 3:** A linear mixed model based on a AR(1): Heterogeneous repeated covariance, using fixed
factors was used to compare exploratory variables within and between groups at and across
baseline, 6 months, and 12 months. Pairwise group and time comparisons were made based on
estimated marginal means that were adjusted using SIDAK. A bivariate correlation matrix was
created to report the Pearson’s correlations between body composition measures and exploratory
measures.
5 Results

Between October 2009 and October 2018, 33 post-treatment colon cancer participants enrolled in the CO.21 Trial at the Vancouver BC, Canada site. The 18 participants who had completed at least 12 months in the trial as of December 1, 2018 and had CT scans were included in the feasibility study (Figure 1). The study sample was 8 participants in CON and 10 participants in INT.

The baseline characteristics of participants are presented in Table 3. The majority of participants were male (56%). The mean age was 59.1 years of age and mean body mass index was 26.9 kg/m². Participants were also a mean 144 days since end of cancer treatment or approximately 4.8 months. Expected number of chemotherapy treatment cycles was determined by an oncologist and varied by participant. In total, 16 participants (88.9%) completed all of their expected treatment cycles, with all participants in the CON group meeting this level (100%) and it was 80% for the INT group, with 2 participants missing 2 cycles and 1 cycle, respectively. Treatment exposure of at least 90% of expected treatment exposure was 87.5% in the CON group and 50% in the INT group. Adherence to the INT was high. All participants in the INT group completed >90% of the combined mandatory exercise and PA behavioural support sessions. The primary reasons for missing a session was due to scheduling conflicts (n=2) or being too busy (n=1). Overall, groups did not differ on any of the baseline demographic or medical characteristics.

Feasibility measures for the CT L3 Scan slice analysis are displayed in Table 4. The mean time to complete manual analysis was measured to be 15min:20sec ± 3min:30sec. The mean time to complete automated analysis using Voronoi Health Analytics ABACS L3 Module was measured to be 0min:57sec ± 0min:10sec. Time to complete analysis for the first five and
last five L3 CT slices are displayed in Figure 2. The image quality of the CT scan L3 slice was ‘high quality’ for 18 images (33.3%), having ‘minor issues’ (i.e. spinous process not fully intake in the image, partial floating rib captured in the image) 25 images (46.3%) and ‘major quality issues’ (i.e. image had high level of blur which impacted the software’s ability to quantify tissue) for 3 images (5.6%). Only 1 image (1.9%) was unavailable for analysis because the particular L3 landmark was not captured in the participants CT scan.

Data on the reliability of the CT scan L3 slice analysis is presented in Table 5. Intra-class correlations comparing values between analyst 1 at two different scan reads were statistically significant for all body composition measures (muscle = 1.000, IMAT = 0.971, VAT = 1.00, SAT = 0.999, MA = 1.000). Inter-class correlations comparing values between analyst 1 and analyst 2 were statistically significant for all body composition measures (muscle = 0.999, IMAT = 0.928, VAT = 1.000, SAT = 0.999, MA = 0.999). Inter-class correlations comparing values between analyst 1 and the Voronoi Health Analytics ABACS L3 Module were statistically significant for all body composition measures (muscle = 0.981, IMAT = 0.710, VAT = 0.997, SAT = 0.992, MA = 0.992). Bland-Altman plots (Figures 15-19) display agreement between body composition outcomes measured manually and using automated segmentation can be found in the Appendix. Agreement between manual and automated segmented measures of muscle, VAT, and SAT surface area were strong, as only one or two outliers fell beyond the 95% limits of agreement for each plot. No bias or trends were observed between the measures of muscle, SAT, and VAT surface area, as indicated by consistent variability around zero difference values as the mean values increase. Agreement between manual and automated segmented measures of IMAT surface area were strong as well, with only a single outlier present beyond the limits of agreement. Although, it is clear that a trend does exist which may indicate bias between
measures. At relatively lower mean values, the difference in IMAT values is quite small and is grouped around zero. This indicates that there is little difference between IMAT values measured manually and with automated segmentation when the surface area of IMAT is relatively small. Consequently, at higher mean values of measured IMAT, the difference is quite large which indicates weaker agreement as the surface area of IMAT increases. This difference in agreement is observed at a mean IMAT surface area of approximately 10cm². Agreement between manual and automated segmented measures of MA were relatively strong as well, with three outliers present beyond the limits of agreement. The bias observed in measures of MA is similar to that seen in IMAT, meaning as the mean values increase the difference in MA measured manually and with automated segmentation increases.

Body composition outcomes using CT scan imaging are shown in Table 6. There was no statistically significant change in body composition between groups at 12-months. The CON group gained an average of 2.1cm² of muscle surface area between baseline and 12 months, compared to the INT group who lost an average of 2.6cm² of muscle surface area (p = 0.79). Consequently, SMI was found to have decreased by 0.7cm²/m² on average within the INT group, compared to an average increase of 0.6cm²/m² in the CON group (p = 0.91). The CON group showed a larger average increase in IMAT surface area (1.3cm²) across 12 months, compared to an average increase of 0.5cm² in the INT group (p = 0.12). Compared to the CON group (6.1cm²), there was on average a larger gain in VAT surface area (12.9cm²) during the 12 month PA intervention timeframe (p = 0.55). Gains in SAT surface area within the INT group (12.5cm²) was on average larger when compared to the average change of 6.8cm² in the CON group (p = 0.83). TAT was therefore, on average, greater among those in the INT (25.9cm²) compared to the CON group (14.2cm²) after 12 months (p = 0.74). MA, an indicator of muscle density, was on
average decreased in both the CON (-1.0 mean HU) and INT group (-1.4 mean HU) during 12 months (p = 0.77). Individual participant changes from baseline to 12 months for various body composition measures are displayed in Figures 3-9.

At baseline, the criteria for probable sarcopenia was met by 39% of participants overall (25% or 2 participants in CON group and 50% or 5 participants in the INT group) and the criteria for sarcopenia was met by 22% participants overall (12.5% or 1 participant in CON group and 30% or 3 participants in the INT group). After 12 months, the criteria for probable sarcopenia was met by 22% of participants overall (12.5% or 1 participant in CON group and 20% or 2 participants in the INT group) and the criteria for sarcopenia was met by 33% participants overall (none in CON group and 50% or 5 participants in the INT group). There was no difference in number of participants who fit the criteria for probable sarcopenia over time (p=0.75). Individual change in 30 second chair stand from baseline to 12 months is presented in Figure 10. Within the INT group, at 12 months, 3 participants improved their 30 second chair sit to stand scores beyond the probable sarcopenia threshold, whereas 2 participants remained categorized as having probable sarcopenia, as improvement in their scores were not large enough. Within the CON group, at 12 months, 1 participant improved their 30 second chair sit to stand score beyond the probable sarcopenia threshold, whereas 1 participant remained categorized as having probable sarcopenia, as improvement in their score was not large enough. A higher number of individuals met the criteria for sarcopenia in the INT group at 12-month compared to CON (0 vs. 2, p=0.01). Individual participant changes from baseline to 12 months in sarcopenia categories is presented in Figure 4. In the INT group, 3 participants remained sarcopenic, while another one participant was identified as sarcopenic after 12 months. In the
CON group, the one participant identified as sarcopenic at baseline was categorized as non-sarcopenic at 12 months.

Change in performance outcomes and body mass index is shown in Table 7. From baseline to 12 months body mass index changed on average -0.3kg/m² and -0.2kg/m², in the CON and INT groups, respectively, with a significant group effect only (p = 0.03), but no group by time effect (p = 0.23). From baseline to 12 months there was a trend towards less of a decline in estimated VO₂max in the INT group (-1.2 ml/kg/min) compared to the CON group (-6.2 ml/kg/min) and improvement in time on treadmill in the INT group (+3min:30 sec) compared to CON (0min:40sec), but neither was statistically significant for time x group effect (p=0.21 and p=0.87, respectively). There was a significant time effect (p=0.03) and time x group effect (p=0.02) for the 6MWT, with the INT increasing their average distance by 66.7m compared to 43.3m seen in the CON group. The absolute change between groups from baseline to 12 months is displayed in Figures 11-14.

Correlations between the change in body composition measures and change in exploratory measures are presented in Table 8. Most notably in the INT group were the significant positive correlations observed between the change in BMI and change in adipose tissue measures, such as VAT (r = 0.90, p < 0.01), SAT (r = 0.94, p < 0.01) and TAT (r = 0.95, p < 0.01). Significant positive correlations in the CON group between change in muscle and change in BMI (r = 0.76, p < 0.05) and change in SMI and change in BMI (r = 0.79, p < 0.05) was observed.
6 Discussion

The findings from this feasibility study support the perception that CT scan images taken as a part of routine clinical care may be collected and analyzed to produce reliable data in a post-treatment colon cancer population. The feasibility of CT scan availability and collection, as well as the image quality and time to analyze were all assessed as part of our study. The analysis of clinical CT scans collected from a cohort of post-treatment colon cancer patients was found to be feasible and reliable for assessing multiple measures of body composition.

6.1 CT Image Analysis Feasibility

The current recommended follow up for colon cancer patients being seen at BC Cancer is at least two CT scans during a three-year follow-up period, depending on their risk of reoccurrence. In our study, a minimum of two (baseline and 12 month) CT scans were available for all but one of the patients in our study, demonstrating that there is very high availability of these scans for collection. In addition to the high accessibility, our study showed that the large majority of images (87.8%) available for analysis were of high quality or had minor quality issues (36.7%) visible to the analyst. Of note, those images that were rated as having minor issues did not present difficulty quantifying particular tissues using the SliceOmatic software. On the other hand, images identified as having major quality issues (6.1%), had seemingly large amounts of noise compared to other images. It is unknown what threshold of noise in a CT image impacts accuracy of tissue surface area quantification made by the SliceOmatic software. Therefore, images in our study that had visible noise were thought to have major quality issues, as tissue quantification may have been altered because of low contrast between tissues. Tube current modulation is used to adjust the CT x-ray current in order to
deliver a similar dose to the detector at all angles and commonly abbreviated as mA. mA has been suggested as a method to reduce noise in CT images, but to our knowledge the CT scans operation parameters, including mA, did not differ between patients in our study.

In addition, the ability for a newly trained analyst to become efficient and reliable was rapid. It only required the first five CT images to reach the same average manual segmentation analysis time as the last five CT images analyzed. This highlights that once trained, CT image analysts can be swift learners, becoming more time-efficient within a small sample of CT images. Despite the manual segmentation analysis having this rapid learning curve, the automated segmentation (Voronoi Health Analytics ABACS L3 Module) proved to take considerably less time to complete the analysis (15min:20sec – manual segmentation vs. 57sec – automated segmentation) and demonstrated good reliability compared to manual segmentation analysis. The body composition outcomes measured with SliceOmatic software were showed to be reliable when used by a single analyst across time, between multiple analysts and between a manual analyst and the automated Voronoi Health Analytics ABACS L3 Module. In terms of manual segmentation of tissue compartments, the findings of this study support that a single trained analyst is sufficient to produce reliable measures of muscle, IMAT, VAT and SAT surface area, as well as MA coefficients.

Recently, there has been an attempt to shift towards automated analysis and interpretation of CT imaging. Both clinical and research settings are looking to expand into this new method of CT image analysis for similar reasons. The time-consuming process of manual segmentation is a burden for radiologists and researchers alike. Automation is thought to directly address this time efficiency issue, as well as contribute to possibly more accurate measures free from human error. A 2016 paper by Popuri et al. introduced a novel fully automatic framework for CT
image segmentation of muscle and fat tissue. The newly developed framework was compared to SliceOmatic manual segmentation using Jaccard scores, a measure of similarity between two images, and found that abdominal images achieved very high (>95%) Jaccard scores. This fully automated framework was deemed to be fast and accurate but does not distinguish between adipose tissue compartments. In a 2018 validity and reliability study conducted by Cedes-Feliciano et al. the authors assessed a digital ruler, a clinical friendly tool used to quantify low skeletal muscle on CT images among cancer patients. Linear area measured by the digital ruler was highly correlated (r = 0.92) with standard methods to assess muscle cross-sectional area. Inter and intra-rater reliability were high (ICCs = 0.98), as well as sensitivity (0.75) and specificity (0.78) for detecting low skeletal muscle relative to total cross-sectional area methods. Though the authors suggest that this tool is a clinically friendly alternative to standard manual methods, other tissue compartments were not assessed. Although other feasibility studies have been conducted, to our knowledge this is the first time that feasibility and reliability comparisons have been made between manual segmentation and automatic segmentation of tissue compartments using the Voronoi Health Analytics ABACS L3 Module in a colon cancer population. In the current study, inter-class correlations for analysis by a single analyst and the automated module were excellent for muscle, VAT, SAT and MA. IMAT had a lower inter-class correlation of only 0.71, which indicates moderate reliability suggesting that this measure displays the most disagreement between the automated module protocol and the manual interpretation of what characterizes IMAT on these CT images. A validation study conducted by Takahashi et al. reported similar reliability results between manual SliceOmatic analysis and BodyCompSlicer, a semi-automated analysis software. Calculated ICCs between manual and semi-automated analysis were reported as 0.997 for muscle, and 1.000 for both VAT
and SAT. Unfortunately, this study did not include a measure of muscle density (either IMAT or MA). The precision of IMAT, a surrogate measure of muscle density, is important as many publications have suggested a relationship between IMAT and muscular strength, as well as mortality. Despite this established relationship, specific quantitative thresholds have not been established between IMAT and clinical outcomes. In our study, the average surface area of IMAT measured by manual segmentation was $11.31 \text{cm}^2 \pm 6.33$, compared to $7.26 \text{cm}^2 \pm 3.00$ as measured by the automated software. Since IMAT thresholds have yet to be established, it is difficult to comment on what clinical implications this difference in IMAT measured manual versus automatically might have.

The present study did not use any manual correction on the automated image analysis. Manual correction is a method that can be performed to adjust automated analysis based off the discretion of the analyst. Automated segmentation is often not perfectly accurate due to individual biological variability, and thus manual correction is frequently used in tandem with automated software. Manual correction, depending on the image and variable, may increase the amount of additional time spent on image analysis. Another method of adjusting automated analysis is to modify the HU ranges for each measure, although the risk of the automated software including false or missing tissue regions may increase. Our findings suggest that muscle, VAT, SAT and MA measures taken via Voronoi Health Analytics ABACS L3 Module exhibited excellent reliability for CT scan L3 images taken from a clinic site. Results from the Bland Altman analysis suggest that strong agreement exists between manual and automated measures of muscle, VAT and SAT. Therefore, after considering the ICC and Bland Altman analyses our quantification of skeletal muscle quantity (i.e. muscle surface area and SMI) was shown to be reliable when the analysis was performed with the automated Voronoi Health
Analytics ABACS L3 Module. Alternatively, measures of skeletal muscle quality (i.e. IMAT and MA) showed larger reliability differences between the manual and automated analyses. Manual correction should be considered when measuring IMAT values above 10cm² with automated segmentation, as our results show that bias may be present when measuring the surface area of this tissue. To our knowledge no study has investigated the reliability of IMAT measured via manual or automated segmentation. This may be an area of interest for future research as the importance of muscle quality and its relationship to clinical outcomes evolves. When comparing the reliability results of automated measured MA to automated measured IMAT in our study, it was observed that MA demonstrated a superior ICC and an observably smaller agreement bias for large mean values. Measured MA has previously been linked to muscle density, whereas IMAT does not have this established connection. It is for these reasons that we suggest automated measures of MA be used as markers of muscle quality, as opposed to automated measures of IMAT.

6.2 Changes in Muscle and Sarcopenia

At baseline 22.2% of participants in the study were identified as having sarcopenia based off pre-established sex and BMI-specific SMI cut off values. This proportion is in line with the estimated range of 20%-40% of colon cancer patients having sarcopenia. It has previously been established in a meta-analysis that sarcopenic colorectal cancer patients have over double the risk of all-cause death. Courneya et al, Devin et al, and Brown et al have all established that a PA intervention can favourably change some elements of body composition over time in colon cancer patients. These studies did not characterize sarcopenia in their samples, nor did they establish if favourable changes in body composition can be attained in sarcopenic patients. Over the course of 12 months, the number of study participants identified as sarcopenic was reduced
from one to none in the CON group and increased from three to five in the INT group. This increase observed in the INT group is likely in part due to a mean loss of SMI and muscle surface area in this group. The established cut-offs for sarcopenia are based on individual BMI and SMI values and thus increased BMI values are associated with larger SMI values to take into account those individuals who are sarcopenic obese. The majority of participants in the INT group did not increase BMI over the 12-month study and did not gain sufficient muscle to increase their SMI values and in turn alter their classification from sarcopenic to non-sarcopenic. One participant became obese (BMI $\geq 30\text{kg/m}^2$) and therefore would have needed to experience a sufficiently large increase in muscle to be considered non-sarcopenic based off the pre-established cut off values. Accordingly, this individual had a change in status from non-sarcopenic at baseline to being defined sarcopenic obesity at 12-months. Similarly, in the control group one participant who was sarcopenic at baseline had an increase in BMI that resulted in being defined as obese at 12 months. However, that individual was able to gain sufficient muscle at 12 months such that the definition of sarcopenic or sarcopenic obese was not met accordingly to the pre-established cut off values.

Identification of those who are experiencing sarcopenia and/or sarcopenic obesity may have clinical importance. The EWG on Sarcopenia in Older People suggest that being sarcopenic and/or sarcopenic obesity is associated with an increased risk of falls and fractures, cardiac disease, respiratory disease, cognitive impairment, and mobility disorders, which in turn may contribute to impaired activities of daily living and reduced quality of life. Establishing a diagnosis of sarcopenia may be difficult without the availability of imaging techniques like CT, MRI and DXA. In the absence of imaging, measures of muscular strength are recommended to identify probable sarcopenia. However, there have been conflicting research results on whether
these measures are in fact accurate and helpful when attempting to detect probable sarcopenia in an older population. A cross sectional survey was conducted by Paloma et al.\textsuperscript{98} in 306 community dwelling elderly women, findings concluded that performance on the chair stand test was predictive of sarcopenia in this population. Alternatively, a cross sectional study performed by Looijaard et al.\textsuperscript{99} in 140 community dwelling elderly found that no single performance measure of muscular strength could identify those with sarcopenia, when a battery of balance tests, four-meter walk test, timed up and go, chair sit to stand, and handgrip strength were tested. Thus, there is inconsistency when using the chair sit to stand test for identifying probable sarcopenia. The SARC-F questionnaire is an alternative option to identifying probable sarcopenia and has been reported as being a consistent and valid measure.\textsuperscript{100} This clinician administered, self-reported questionnaire aims to identify those at risk of adverse outcomes from sarcopenia, by asking about strength, assistance walking, rising from a chair, climbing stairs and falls. Although this is a rapid method to potentially detect probable sarcopenia, it lacks a measure of muscular strength or quantity and therefore is very difficult to assess the severity and progress of the disease.

Muscle density, an indication of muscle quality was measured at baseline and 12 months by assessing MA, an average measure of radiodensity of the small stores of lipids within muscle fibers. IMAT was also assessed and reflects the infiltration of lipid content within and between muscle and is measured in terms of lipid surface area. Both groups displayed an average increase in IMAT and loss of MA over 12 months, indicating increased lipid infiltration of muscle. This reduction in muscle quality was generally not reflected in the performance outcomes of these participants, as both groups showed mean increases in both treadmill time and the 6MWT.

\textbf{6.3 Changes in Adipose Tissue}
At 12 months, all three measures of adipose tissue, mean VAT, SAT and TAT, were increased from baseline in both groups, with the INT group displaying larger gains. The increase in adipose tissue observed in the INT group were strongly correlated with increases in BMI, suggesting that the majority of the weight gained by those in the INT group was adipose tissue. This was different in the CON group, as change in muscle was correlated to increases in BMI, suggesting that those who gained weight in the CON group were increasing both muscle and fat. Furthermore, changes in adipose tissue within the INT group were negatively correlated with a reduction in total treadmill time. These trends are concerning due in part to epidemiological research suggesting that excess VAT puts colon cancer patients at an increased risk of disease reoccurrence and mortality.101 Favourable changes in body composition have been hypothesized as one of the pathways in which exercise may improve disease outcomes for colon cancer patients, which includes controlling and limiting excess adipose tissue. This is because adipose tissue is a metabolically active tissue that secretes adipokines, cytokines, hormone-like factors and metabolites.102 Excess VAT can activate biological pathways associated with the growth and progression of colon cancer metastases103, and by reducing excess VAT unwanted cell growth may be inhibited and commencement of apoptosis of cancer cells can occur.104

6.4 Performance Outcomes

Comparisons made between groups showed non-significant differences in the change in estimated VO\(_2\)\text{max} and treadmill time, whereas significant changes over time were observed in the 6MWT. In 2016, Courneya et al.105 published the one-year feasibility results for the first 273 participants from the Canadian and Australian CO.21 Trial site centers. Results showed that relative to the control group, the PA intervention group showed a trend toward increases in estimated VO\(_2\)\text{max} and a statistically significant increase in 6MWT distance.105 This is consistent
with the findings of the current study, which was a sub-set of individuals in the CO.21 Trial, as
the INT group had statistically significant improvement in 6MWT compared to CON group at 12
months. However, there was no change in estimated VO$_{2\text{max}}$. In the larger sample, Courneya et
al.\textsuperscript{105} reported the increase for the control group was 31m, which is similar to the improvement of
43.3m observed in our smaller sample. For the intervention group change, the increase was 59m
in the larger sample and 66.7m in our smaller study. This suggests that the small number of
individuals included in our sample resulted in a lack of statistical power to observe a statically
significant change over time. A change in the 6MWT between 43–54 meters is representative of
the minimal clinically important difference in a variety of patient populations, therefore the
difference of 23.4m observed between groups at 12 months in our small sample is not considered
a clinically significant increase in 6MWT distance.\textsuperscript{106} In both studies relative to the control,
estimated VO$_{2\text{max}}$ was higher at 12 months in the intervention, but not statistically significant. Of
note, for the INT group in the current study, a modest decrease of 1.2 ml/kg/min in mean change
in estimated VO$_{2\text{max}}$ was observed compared to an increase of 1.6ml/kg/min that was reported in
the larger study by Courneya et al.\textsuperscript{105}. The interpretation by Courneya et al.\textsuperscript{105} was that the
intervention improved on the fitness parameters consistent with the program design of promoting
aerobic exercise rather than resistance training or weight loss.

\textbf{6.5 Limitations}

This feasibility study had a number of limitations associated with it. First, we only had
access to scans that were available from the BC Cancer site of the CO.21 trial during the
timeframe of study inception (2010) to December 1, 2018, to examine change over time between
the physical activity intervention and general health education materials groups. Thus, our data
analysis cannot be generalized to the other participants within the CO.21 Trial. In addition,
participants randomized to the control group were not prohibited from exercising on their own during the duration of the CO.21 trial, and therefore we are unable to detect if involvement in PA may have caused changes in outcomes observed in this group. The type of physical activity intervention for the CO.21 Trial is focused on aerobic exercise (i.e., walking, cycling and swimming). The impact of this type of activity on body composition is most often reflected on improvements in cardio respiratory fitness\textsuperscript{110}, whereas greater improvements in muscle mass are often attributed to resistance training activities\textsuperscript{111}. Resistance training which is specifically targeted at improving muscle mass and strength, and weight loss is not part of the CO.21 Trial intervention. Therefore, there may be an issue with specificity of the physical activity program to appropriately target muscle mass and adipose tissue loss. In addition, the primary goal is centered around a behaviour change in increasing patients’ weekly usual physical activity by 10 MET-hr per week above baseline over the duration of the intervention. Consequently, the study design of the CO.21 Trial allows for participants to choose an individualized type, frequency, intensity and goal of aerobic exercise in order to meet the intervention goal. Allowing this individual personalization of an aerobic exercise plan can potentially make it difficult to compare fitness outcomes across participants, as the variation in the range of exercises is very large. Lastly, changes in body composition are directly related to energy balance, including diet and nutrition.\textsuperscript{107} The current study did not include any data on participant nutrition during the intervention. Future studies investigating changes in body composition should consider the impact of nutrition on results.

### 6.6 Future directions

The limitations addressed in our study should be considered when undertaking a similar analysis in a larger sample of CO.21 study participants. A subsequent analysis of a larger study
sample is required for an appropriately powered study. An appropriately powered analysis would allow for the detection of an effect size of 0.57 for SMI. In order to detect this change in SMI using a similar aerobic intervention to that of the CO.21 trial, it was calculated that a sample size of 2813 is required. SMI is normalized for individual stature allowing for a more accurate representation of muscle. SMI is also used in combination with BMI to define sarcopenia cut-off values, therefore having SMI as a primary outcome for a future analysis would allow researchers to focus specifically on change in muscle and sarcopenia over time. An additional outcome of interest may be skeletal muscle gauge which combines SMI with skeletal muscle density to give a value that represents both skeletal muscle quantity and quality. The skeletal muscle gauge has previously been positively correlated with age which suggests it may be a possible predictor of age-related sarcopenia and could also capture sarcopenia related physical function impairments. As opposed to a strictly aerobic exercise intervention used in the current study, we suggest that future studies incorporate resistance training into their study design, either as a stand-alone intervention or in combination with aerobic activity. A recent RCT conducted by Vikberg et al used a resistance training intervention which aimed to improve functional strength in pre-sarcopenic individuals. Based off the data reported by Vikberg et al, a sample size of 934 is required to detect a 1.05 effect size for lean muscle mass. To our knowledge there has been no studies that have investigated change in lean muscle mass using a resistance training intervention in a colon cancer population. Therefore, in order to fully understand the potential of exercise to address body composition and result impact on physical function and cancer-specific outcomes of recurrence and survival, future research should examine the impact of resistance training in this population. The current Position Statement From the National Strength and Conditioning Association recommends that resistance training for older adults should include an
individualized and periodized approach consisting of 2-3 sets of 1-2 multi-joint exercises for major muscle groups, achieving 70-85% of 1 repetition maximum, 2-3 times per week. In addition, a resistance training intervention must be designed to account for participant learning of proper exercise technique and safety, particularly in an older population. Resistance training has been shown to enhance muscular strength, power and neuromuscular functioning, as well as improve mobility, physical functioning, and performance in activities of daily living. The addition of resistance training may result in more favourable changes in body composition, particularly larger gains in muscle and SMI. Findings from the current study indicate that automated CT image segmentation, in particular the Voronoi Health Analytics ABACS L3 Module, can be used for rapid quantification of patient body composition from usual care CT scans. Continued research should be performed to investigate which frequency, intensity and type of exercise is optimal to produce favourable body compositions in colon cancer patients. In the future, clinical settings may look to incorporate CT image automated segmentation as a time efficient method to analyze and inform the development and refinement of physical activity interventions for colon cancer patients.

6.7 Impact

In observational studies higher physical activity levels and higher skeletal muscle mass are associated with improved outcomes, namely cancer recurrence and survival. The proposed study provides novel information on changes in body composition with a physical activity intervention in colon cancer survivors by using an ideal approach to capturing total muscle area and muscle quality compared to a small number of prior studies. This new evidence will provide the foundation for further research to explore the impact of changes in physical activity and change in body composition on cancer outcomes. Future directions from this work
could include conducting a similar analysis in a larger sample from the multi-site CO.21 trial to investigate if favourable changes in body composition can be obtained to reduce sarcopenia within intervention participants. Automated CT scan analysis for body composition quantification is feasible, and if the type of intervention that is efficacious at improving body composition is identified, this could result in a trial to examine the potential of referral to supportive care services in those who present with sarcopenia or develop sarcopenia during treatment to improve cancer outcomes and overall patient health.
7 Conclusion

In conclusion, the collection and analysis of CT scan images of individuals with colon cancer who have completed primary adjuvant cancer treatment and are participating in the BC Cancer site of the CO.21 Trial is feasible. Strong reliability for measuring body composition parameters in a colon cancer population was observed for the use of the manual segmentation of body composition using SliceOmatic, and established for automated segmentation of body composition using Voronoi Health Analytics ABACS L3 Module when. There was no evidence of a significant change among the various measures of body composition in the intervention group compared to control across the 12-month study. Despite study findings, changes in muscle and adipose tissue remain a central pathway in which exercise is thought to alter cancer outcomes. A larger, properly powered study that aims to detect changes in SMI with automated CT image segmentation is warranted to investigate if favourable changes in body composition can be achieved and sustained with resistance training in a population of colon cancer patients.
## Tables and Figures

**Table 1.** Commonly used body composition imaging techniques.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Principle &amp; Body Compartment Measured</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>DXA</td>
<td>- The generation of a high- and low-energy emission by an x-ray source differentiates between soft tissue and bone. Fat mass is then estimated from specific attenuation characteristics of soft tissues.</td>
<td>- Differentiates fat, lean, and bone tissue. - Regional measures can be obtained. - Safe for repeated measures; fast and non-invasive. - High precision and accuracy.</td>
<td>- Differences within and between manufacturers and software versions. - Inability to differentiate compartments within fat and lean tissues. - Measurements are influenced by thickness of tissue and lean tissue hydration.</td>
</tr>
<tr>
<td>CT</td>
<td>- X-ray attenuation through tissues is detected and an image is reconstructed. Adipose tissue, skeletal muscle, bone, visceral organs, and brain tissue can be identified by different x-ray attenuation.</td>
<td>- Highly accurate quantitative &amp; qualitative measure of body composition at the tissue-organ level. - High image resolution. - Consistent image attenuation value within and between scans. - Useful in clinical settings where images are acquired for medical purposes.</td>
<td>- Limited to highly specialized settings. - Costly, and requires specialized skills to operate. - Large radiation exposure. - Cannot accommodate very large subjects.</td>
</tr>
<tr>
<td>MRI</td>
<td>- Atomic protons become aligned in a magnetic field. These protons are then activated by a radio frequency wave, absorbing energy. The signal generated is used to develop regional and whole-body cross-sectional images. Quantifies adipose tissue, skeletal muscle, edema, and visceral organs.</td>
<td>- High image resolutions. - Highly accurate method to determine body composition at the tissue-organ level. - Safe across age range and groups.</td>
<td>- Limited to highly specialized settings. - Costly, and requires specialized skills. - Procedure requires individuals to hold breath. Cannot accommodate very large subjects.</td>
</tr>
</tbody>
</table>

Table adapted from Prado & Heymsfield (2014).
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>PA Intervention</th>
<th>Measurement of Body Composition</th>
<th>Mean Change in Body Composition</th>
<th>Change in Fitness</th>
<th>Other Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Courneya et al. (2003)</td>
<td>102</td>
<td>Participants chose preferred exercise: 3-5 times/week for 20-30 min at 65% to 75% of predicted HR$_{\text{max}}$ for 16-weeks</td>
<td>Sum of skinfolds (mm)</td>
<td>P = 0.607</td>
<td>Treadmill time (s) P = 0.330 Resting HR (bpm) P = 0.361</td>
<td>Increased fitness group vs. decreased fitness group self-reported QOL P = 0.038*</td>
</tr>
<tr>
<td>Devin et al. (2016)</td>
<td>47</td>
<td>Participant cycle ergometer exercise: Moderate intensity group – 50min at 50% to 70% HR$<em>{\text{max}}$ High intensity group – 38min at 85% to 95% HR$</em>{\text{max}}$ 3 times/week for 4-weeks</td>
<td>DXA</td>
<td></td>
<td>High intensity: VO$_{2\text{max}}$ (ml/kg/min) &amp; Relative PPO (W/kg) – P &lt; 0.05*</td>
<td>Mean change in Godin PA index: P = 0.932</td>
</tr>
<tr>
<td>Brown et al. (2017)</td>
<td>39</td>
<td>Participant treadmill exercise: Low dose group – 150min/week High dose group – 300min/week 50% to 70% predicted HR$_{\text{max}}$ for 6-months</td>
<td>DXA (cm$^2$)</td>
<td>VAT: P = 0.008* SAT: P = 0.222 Fat mass (kg): P = 0.238 Lean mass (kg): P = 0.450</td>
<td>MET hours/week change between groups p &lt; 0.001</td>
<td>BMI – P = 0.354 Waist circumference – P &gt; 0.001* Hip circumference – P = 0.518 Waist to hip ratio – P = 0.054</td>
</tr>
</tbody>
</table>

Legend: * Statistically significant finding
Table 3. Baseline comparisons of demographic, medical and intervention adherence characteristics of participants.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=18)</th>
<th>Control (n=8)</th>
<th>Intervention (n=10)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%)</td>
<td>Number (%)</td>
<td>Number (%)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10 (56%)</td>
<td>4 (50%)</td>
<td>6 (60%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Female</td>
<td>8 (44%)</td>
<td>4 (50%)</td>
<td>4 (40%)</td>
<td></td>
</tr>
<tr>
<td>Treatment type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capecitabine</td>
<td>2 (11.1%)</td>
<td>0 (0%)</td>
<td>2 (20%)</td>
<td>0.41</td>
</tr>
<tr>
<td>FOLFOX</td>
<td>14 (77.8%)</td>
<td>7 (87.5%)</td>
<td>7 (70%)</td>
<td></td>
</tr>
<tr>
<td>CAPOX</td>
<td>2 (11.1%)</td>
<td>1 (12.5%)</td>
<td>1 (10%)</td>
<td></td>
</tr>
<tr>
<td>Completed expected number of treatment cycles (Y/N)</td>
<td>16 (88.9%)</td>
<td>8 (100%)</td>
<td>8 (80%)</td>
<td>0.48</td>
</tr>
<tr>
<td>&gt; 90% of expected treatment exposure</td>
<td>12 (66.7%)</td>
<td>7 (87.5%)</td>
<td>5 (50%)</td>
<td>0.15</td>
</tr>
<tr>
<td>&gt; 90% Physical Activity Intervention Adherence</td>
<td>-</td>
<td>-</td>
<td>10 (100%)</td>
<td>-</td>
</tr>
<tr>
<td>BMI &lt;25kg/m2</td>
<td>6 (33.3%)</td>
<td>1 (12.5%)</td>
<td>5 (50%)</td>
<td>0.08</td>
</tr>
<tr>
<td>BMI ≥25kg/m2 &lt;30kg/m2</td>
<td>9 (50%)</td>
<td>4 (50%)</td>
<td>5 (50%)</td>
<td></td>
</tr>
<tr>
<td>BMI ≥30kg/m2</td>
<td>3 (16.7%)</td>
<td>3 (37.5%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, (years)</td>
<td>59.1 ± 9.7</td>
<td>57.1 ± 8.8</td>
<td>60.7 ± 10.4</td>
<td>0.45</td>
</tr>
<tr>
<td>BMI, (kg/m2)</td>
<td>26.9 ± 3.1</td>
<td>28.5 ± 2.9</td>
<td>25.6 ± 2.7</td>
<td>0.91</td>
</tr>
<tr>
<td>Days since end of treatment</td>
<td>144.3 ± 43.3</td>
<td>121.9 ± 44.5</td>
<td>162.2 ± 34.5</td>
<td>0.49</td>
</tr>
</tbody>
</table>

*Abbreviations: body mass index - BMI*
Table 4. CT L3 slice analysis feasibility measures.

<table>
<thead>
<tr>
<th>Feasibility Measure</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>L3 slice analysis total time (min:sec)</td>
<td>17:20 ± 4:30</td>
</tr>
<tr>
<td>L3 slice land marking time (min:sec)</td>
<td>2:30 ± 2:30</td>
</tr>
<tr>
<td>L3 slice manual segmentation time (min:sec)</td>
<td>15:20 ± 3:30</td>
</tr>
<tr>
<td>L3 slice automated segmentation* time (min:sec)</td>
<td>0:57 ± 0:10</td>
</tr>
<tr>
<td>L3 slice automated analysis total time* (min:sec)</td>
<td>3:27 ± 2:40</td>
</tr>
<tr>
<td>L3 slice quality score:</td>
<td>No (%)</td>
</tr>
<tr>
<td>0 (not available)</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>1 (not suitable for analysis)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>2 (major quality issues)</td>
<td>3 (5.6%)</td>
</tr>
<tr>
<td>3 (minor quality issues)</td>
<td>25 (46.3%)</td>
</tr>
<tr>
<td>4 (high quality)</td>
<td>18 (33.3%)</td>
</tr>
<tr>
<td>L3 slice retention (%)</td>
<td>46/47 (97.9%)</td>
</tr>
</tbody>
</table>

Legend:
*Automated segmentation performed with Voronoi Health Analytics ABACS L3 Module.
#Automated total time includes L3 slice land marking time
### Table 5. Reliability of body composition measures.

<table>
<thead>
<tr>
<th>Measure</th>
<th>ICC</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Muscle</strong> ((cm^2))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-rater&lt;sub&gt;a&lt;/sub&gt;</td>
<td>1.000</td>
<td>0.998 – 1.000</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Inter-rater&lt;sub&gt;b&lt;/sub&gt;</td>
<td>0.999</td>
<td>0.997 – 0.999</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Inter-rater&lt;sub&gt;c&lt;/sub&gt;</td>
<td>0.981</td>
<td>0.873 – 0.994</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>IMAT</strong> ((cm^2))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-rater&lt;sub&gt;a&lt;/sub&gt;</td>
<td>0.971</td>
<td>0.161 – 0.994</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Inter-rater&lt;sub&gt;b&lt;/sub&gt;</td>
<td>0.928</td>
<td>0.190 – 0.981</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Inter-rater&lt;sub&gt;c&lt;/sub&gt;</td>
<td>0.710</td>
<td>0.320 – 0.874</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>VAT</strong> ((cm^2))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-rater&lt;sub&gt;a&lt;/sub&gt;</td>
<td>1.000</td>
<td>1.000 – 1.000</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Inter-rater&lt;sub&gt;b&lt;/sub&gt;</td>
<td>1.000</td>
<td>1.000 – 1.000</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Inter-rater&lt;sub&gt;c&lt;/sub&gt;</td>
<td>0.997</td>
<td>0.993 – 0.999</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>SAT</strong> ((cm^2))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-rater&lt;sub&gt;a&lt;/sub&gt;</td>
<td>0.999</td>
<td>0.998 – 1.000</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Inter-rater&lt;sub&gt;b&lt;/sub&gt;</td>
<td>0.999</td>
<td>0.968 – 1.000</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Inter-rater&lt;sub&gt;c&lt;/sub&gt;</td>
<td>0.992</td>
<td>0.978 – 0.997</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>MA (mean HU)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-rater&lt;sub&gt;a&lt;/sub&gt;</td>
<td>1.000</td>
<td>1.000 – 1.000</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Inter-rater&lt;sub&gt;b&lt;/sub&gt;</td>
<td>0.999</td>
<td>0.997 – 0.999</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Inter-rater&lt;sub&gt;c&lt;/sub&gt;</td>
<td>0.992</td>
<td>0.982 – 0.996</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**Legend:**
- **Intra-rater<sub>a</sub>**, analyst 1 vs. analyst 1 one month after original values;
- **Inter-rater<sub>b</sub>**, analyst 1 vs. analyst 2;
- **Inter-rater<sub>c</sub>**, analyst 1 vs. the Voronoi Health Analytics ABACS L3 Module.

**Abbreviations:** IMAT – intramuscular adipose tissue, VAT – visceral adipose tissue, SAT – subcutaneous adipose tissue, MA – muscle attenuation
### Table 6. Time and group interactions on body composition outcomes measured via baseline and 12 months CT scans.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Control (mean ± SD)</th>
<th>Intervention (mean ± SD)</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 months</td>
<td>Mean Δ</td>
</tr>
<tr>
<td><strong>Muscle (cm²)</strong></td>
<td>148.9 ± 25.0</td>
<td>151.0 ± 28.0</td>
<td>2.1 ± 11.1</td>
</tr>
<tr>
<td><strong>IMAT (cm²)</strong></td>
<td>11.1 ± 5.7</td>
<td>12.4 ± 6.7</td>
<td>1.3 ± 1.6</td>
</tr>
<tr>
<td><strong>VAT (cm²)</strong></td>
<td>151.2 ± 99.2</td>
<td>157.3 ± 103.5</td>
<td>6.1 ± 17.8</td>
</tr>
<tr>
<td><strong>SAT (cm²)</strong></td>
<td>207.0 ± 72.3</td>
<td>213.8 ± 70.2</td>
<td>6.8 ± 31.2</td>
</tr>
<tr>
<td><strong>TAT (cm²)</strong></td>
<td>369.3 ± 103.5</td>
<td>383.5 ± 110.0</td>
<td>14.2 ± 42.4</td>
</tr>
<tr>
<td><strong>MA (mean HU)</strong></td>
<td>42.2 ± 7.6</td>
<td>41.2 ± 8.8</td>
<td>-1.0 ± 2.7</td>
</tr>
<tr>
<td><strong>SMI (cm²/m²)</strong></td>
<td>52.4 ± 8.3</td>
<td>53.0 ± 8.3</td>
<td>0.6 ± 3.5</td>
</tr>
<tr>
<td><strong>No (%)</strong></td>
<td>2 (25%)</td>
<td>1 (12.5%)</td>
<td>-1</td>
</tr>
<tr>
<td><strong>Probable sarcopenia</strong></td>
<td>0 (0%)</td>
<td>5 (50%)</td>
<td>-3</td>
</tr>
</tbody>
</table>

Table 7. Time and group interactions on body mass index and performance outcomes.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Control (mean ± SD)</th>
<th>Intervention (mean ± SD)</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 months</td>
<td>12 months</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.5 ± 2.9</td>
<td>28.7 ± 2.2</td>
<td>28.2 ± 2.9</td>
</tr>
<tr>
<td>Estimated VO₂max (ml/kg/min)</td>
<td>33.9 ± 8.1</td>
<td>31.2 ± 8.6</td>
<td>27.7 ± 4.8</td>
</tr>
<tr>
<td>Treadmill time (min:sec)</td>
<td>14:40 ± 3:50</td>
<td>14:40 ± 5:20</td>
<td>14:40 ± 7:10</td>
</tr>
<tr>
<td>6MWT (m)</td>
<td>556.8 ± 56.3</td>
<td>564.7 ± 73.5</td>
<td>600.1 ± 92.0</td>
</tr>
</tbody>
</table>

Abbreviations: BMI - body mass index, 6MWT – six-minute walk test.
Table 8. Correlations between change (baseline – 12 months) in body composition measures and change (baseline – 12 months) in exploratory measures.

<table>
<thead>
<tr>
<th>Δ in Measure</th>
<th>Group</th>
<th>Age#</th>
<th>BMI</th>
<th>Estimated VO_{2max}</th>
<th>Treadmill time</th>
<th>6MWT</th>
<th>Program adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>INT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>INT</td>
<td>-0.12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>-0.19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated VO_{2max} (ml/kg/min)</td>
<td>INT</td>
<td>0.24</td>
<td>-0.43</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>0.83*</td>
<td>-0.09</td>
<td></td>
<td>0.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treadmill time (min.sec)</td>
<td>INT</td>
<td>-0.09</td>
<td>-0.80*</td>
<td>0.44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>0.35</td>
<td>0.01</td>
<td>-1.17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWT (m)</td>
<td>INT</td>
<td>-0.78**</td>
<td>-0.16</td>
<td>0.13</td>
<td>0.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>-0.13</td>
<td>-0.22</td>
<td>-0.58</td>
<td>0.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Program adherence (%)</td>
<td>INT</td>
<td>0.23</td>
<td>0.01</td>
<td>0.34</td>
<td>-0.21</td>
<td>-0.43</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>0.15</td>
<td>0.21</td>
<td>0.10</td>
<td>0.24</td>
<td>-0.03</td>
<td>0.28</td>
</tr>
<tr>
<td>Muscle (cm²)</td>
<td>INT</td>
<td>-0.05</td>
<td>0.76*</td>
<td>0.02</td>
<td>-0.12</td>
<td>-0.44</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>-0.21</td>
<td>0.56</td>
<td>-0.79*</td>
<td>-0.47</td>
<td>-0.12</td>
<td>-0.15</td>
</tr>
<tr>
<td>IMAT (cm²)</td>
<td>INT</td>
<td>0.76*</td>
<td>-0.39</td>
<td>0.90**</td>
<td>0.10</td>
<td>-0.12</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>0.04</td>
<td>0.42</td>
<td>0.60</td>
<td>0.39</td>
<td>-0.06</td>
<td>-</td>
</tr>
<tr>
<td>VAT (cm²)</td>
<td>INT</td>
<td>-0.09</td>
<td>0.90**</td>
<td>-0.29</td>
<td>-0.77*</td>
<td>-0.14</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>0.40</td>
<td>0.42</td>
<td>0.60</td>
<td>0.39</td>
<td>-0.06</td>
<td>-</td>
</tr>
<tr>
<td>SAT (cm²)</td>
<td>INT</td>
<td>0.40</td>
<td>0.15</td>
<td>0.29</td>
<td>-0.01</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>0.04</td>
<td>0.15</td>
<td>0.15</td>
<td>0.29</td>
<td>-0.01</td>
<td>-</td>
</tr>
<tr>
<td>TAT (cm²)</td>
<td>INT</td>
<td>0.39</td>
<td>-0.05</td>
<td>-0.12</td>
<td>0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>0.39</td>
<td>0.45</td>
<td>0.66</td>
<td>0.21</td>
<td>-0.25</td>
<td>-</td>
</tr>
<tr>
<td>MA (mean HU)</td>
<td>INT</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>-0.06</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>0.39</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>-</td>
</tr>
<tr>
<td>SMI (cm²/m²)</td>
<td>INT</td>
<td>0.16</td>
<td>0.15</td>
<td>0.15</td>
<td>0.29</td>
<td>-0.01</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>0.07</td>
<td>0.79*</td>
<td>-0.01</td>
<td>-0.12</td>
<td>-0.40</td>
<td>-</td>
</tr>
</tbody>
</table>

Legend: *Indicates a significant p value < 0.05; ** Indicates a significant p value < 0.01.; # the variable age is a fixed factor for patients at 12 months.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Images that were not available for analysis.</td>
</tr>
<tr>
<td>1</td>
<td>Images that were deemed not suitable for analysis. Ex: images were visual tissue differentiation could not be done due to noise or other factors.</td>
</tr>
<tr>
<td>2</td>
<td>Images that were deemed as having major quality issues. Ex: images were noise has distrubted visual tissue differentiation in certain image regions.</td>
</tr>
<tr>
<td>3</td>
<td>Images that were deemed as having minor quality issues. Ex: images were certain anatomical objects (i.e. floating rib) or otherwise (i.e. metal) are visable.</td>
</tr>
<tr>
<td>4</td>
<td>Images that were deemed as high quality. Ex: images without visual noise or objects.</td>
</tr>
</tbody>
</table>
Figure 1. Consort diagram of patients and their CT scans.
**Figure 2.** Time to complete the first 5 and the last 5 L3 slice manually and with the Voronoi Health Analytics ABACS L3 Module.
**Figure 3.** Muscle tissue surface area change from baseline to 12 months between individuals in the INT group (n=9) and CON group (n=8).
Figure 4. Skeletal muscle index (muscle tissue surface area adjusted for patient stature) change from baseline to 12 months between individuals in the INT group (n=9) and CON group (n=8).

Legend: * Indicates sarcopenia measured by pre-established SMI cut-off values. One participant did not have a baseline CT scan L3 image available for analysis and therefore is not included in the figure. The excluded participant was identified as having sarcopenia at 12 months.
Figure 5. Intra-muscular adipose tissue surface area change from baseline to 12 months between individuals in the INT group (n=9) and CON group (n=8).
**Figure 6.** Visceral adipose tissue surface area change from baseline to 12 months between individuals in the INT group (n=9) and CON group (n=8).
Figure 7. Subcutaneous adipose tissue surface area change from baseline to 12 months between individuals in the INT group (n=9) and CON group (n=8).
Figure 8. Total Adipose tissue surface area change from baseline to 12 months between individuals in the INT group (n=9) and CON group (n=8).
Figure 9. Muscle attenuation mean Hounsfield unit change from baseline to 12 months between individuals in the INT group (n=9) and CON group (n=8).
**Figure 10.** 30 second chair sit to stand change from baseline to 12 months between individuals in the INT group (n=9) and CON group (n=8).

*Legend.* * Indicates probable sarcopenia measured by 30 second chair sit to stand score age-adjusted cut off values. 30 second chair sit to stand values were unavailable for one participant in the PA intervention group and thus are not displayed.
Figure 11. Absolute change from baseline to 12 months in BMI between groups.
Figure 12. Absolute change from baseline to 12 months in estimated VO2max between groups.
Figure 13. Absolute change from baseline to 12 months in treadmill time between groups.
Figure 14. Absolute change from baseline to 12 months in 6MWT distance between groups.


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91. CT Radiographic Techniques | Radiology |SUNY Upstate Medical University. (2018).


from the CHALLENGE Trial. *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology*, 25(6), 969–977. https://doi.org/10.1158/1055-9965.EPI-15-1267


Appendix

Figure 15. Bland-Altman plot. The difference between muscle surface area (cm²) quantified with manual segmentation and muscle surface area (cm²) quantified with automated segmentation is drawn against the mean of manual and automated segmented muscle surface area in 46 CT images.

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\text{Muscle Difference (manual-automated)} = \frac{\text{Muscle}_{\text{manual}} + \text{Muscle}_{\text{automated}}}{2}
\]

--- Mean difference
--- 95% limits of agreement
Figure 16. Bland-Altman plot. The difference between IMAT surface area (cm²) quantified with manual segmentation and IMAT surface area (cm²) quantified with automated segmentation is drawn against the mean of manual and automated segmented IMAT surface area in 46 CT images.
Figure 17. Bland-Altman plot. The difference between VAT surface area (cm²) quantified with manual segmentation and VAT surface area (cm²) quantified with automated segmentation is drawn against the mean of manual and automated segmented VAT surface area in 46 CT images.

\[
\text{Mean difference} \\
\text{95% limits of agreement}
\]

\[
\frac{\text{VAT}_{\text{manual}} + \text{VAT}_{\text{automated}}}{2}
\]
Figure 18. Bland-Altman plot. The difference between SAT surface area (cm²) quantified with manual segmentation and SAT surface area (cm²) quantified with automated segmentation is drawn against the mean of manual and automated segmented SAT surface area in 46 CT images.
Figure 19. Bland-Altman plot. The difference between MA (mean HU) quantified with manual segmentation and MA (mean HU) quantified with automated segmentation is drawn against the mean of manual and automated segmented MA in 46 CT images.