An exploration into the relationship of body composition parameters and survival outcomes in patients with resectable colorectal cancer

by

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ABSTRACT

Both tumor biology and host-specific factors play an important role in the prognosis of colorectal cancer. Body composition is an emerging patient-specific factor, which is currently being elucidated. Opportunistic analysis of pre-existing staging computed tomography scans can be used to quantify skeletal muscle and adipose tissue area (cm^2), as well as average skeletal muscle radiodensity (Hounsfield Units). Skeletal muscle area at the third lumbar vertebrae is highly correlated with total body skeletal muscle mass, and can be used as a surrogate marker. Severe loss of skeletal muscle mass, or sarcopenia, has been shown to be predictive of worse perioperative and long-term outcomes in colorectal cancer. Reduced skeletal muscle radiodensity, as a measure of myosteatosis, has also been shown to be associated with worse survival outcomes.

Those patients with sarcopenia are more likely to experience dose-reductions and dose-limiting toxicities during chemotherapy regimens. Therefore, skeletal muscle mass, as measured from cross-sectional imaging, may play a role in personalized dosing of chemotherapy. Furthermore, sarcopenia and myosteatosis have been shown to be associated with poor survival after surgical resection. Unfortunately, there is significant variation in methodology, which prevents comparison between many of the published studies.

This thesis included a large cohort of stage I-III colorectal cancer patients treated with curative intent. All included patients had a preoperative CT scan and were seen at a cancer clinic in Northern Alberta. The primary aim was to quantify effects of sarcopenia and myosteatosis on long-term survival outcomes. A composite phenotype was defined to characterize patients as having sarcopenia alone, myosteatosis alone or concurrent

sarcopenia and myosteatosis. The effect of adipose tissue on survival outcomes was also assessed. Skeletal muscle and adipose tissue mass and skeletal muscle radiodensity were also quantified from 2-year surveillance scans. The rates of change over time, along with presence of sarcopenia at follow-up were then analyzed for their effects on disease recurrence and survival after completion of disease surveillance.

Using cohort specific cut-offs for sarcopenia, myosteatosis, visceral obesity and total adiposity, several conclusions were reached. Sarcopenia was highly predictive of worse overall, recurrence-free and cancer-specific survival. Myosteatosis was predictive of worse overall survival and cancer specific survival. Using a composite phenotype, concurrent presence of sarcopenia and myosteatosis was predictive of significantly worse overall, recurrence-free and cancer-specific survival in an adjusted model. These results were not affected by presence of absence of visceral obesity or elevated total adiposity.

Furthermore, in those patients who survived to their 2-year surveillance scan without evidence of disease recurrence; changes in body composition parameters were quantified. On average, all patients were losing skeletal muscle mass and radiodensity, but gaining adipose tissue. Patients who were sarcopenic at the time of diagnosis, or those patients who lost muscle mass over time had significantly worse overall survival, while increased adiposity had a protective effect. The presence of both sarcopenia and muscle loss over time resulted in increased all-cause mortality.

Overall, this thesis demonstrates that skeletal muscle mass and radiodensity are easily obtainable and quantifiable measurements that can act as reliable prognostic factors in stage I-III colorectal cancer patients treated with curative intent. Furthermore, their change over time may help predict those patients who will have worse survival

outcomes following evidence of late disease recurrence. Identification of sarcopenia and ongoing muscle loss together, represents an increased risk profile, from which patients may benefit from extended disease surveillance. Furthermore, patients found to have sarcopenia at time of diagnosis would be appropriate candidates for an intervention to improve muscle mass and radiodensity, with hopes of improving long-term survival outcomes.

PREFACE

This thesis is an original work by Jessica Hopkins. The research project, of this this thesis is a part, received research ethics approval from the Health Research Ethics Board of Alberta Cancer Committee, Project Name "Effects of body composition in early stage colorectal cancer patients", No. HREBA.CC-16-0034, May 30, 2016.

The identification and design of the research was done in collaboration with Dr. Michael Sawyer, Dr. Vickie Baracos, Dr. David Bigam and Dr. Dean Eurich. Analysis of body composition was done in part by Rebecca Reif, an undergraduate research assistant from the University of Alberta, and the main author, Jessica Hopkins. All other data collection was completed independently by Jessica Hopkins. The statistical analysis, other than the optimal stratification, was completed by Jessica Hopkins. Arsene Zongo completed the optimal stratification analysis in Chapters 4 and 5.

Chapter 2 of this thesis has been published as:
Hopkins JJ, Sawyer MB. A review of body composition and pharmacokinetics in oncology. *Expert Rev Clin Pharmacol* 2017; 10(9): 947-956.
JH was responsible for the literature search, analysis and composition. MB Sawyer was the supervisory author and assisted with concept formation and manuscript composition.

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JH was responsible for the literature review, screening and scoring of articles and paper composition. DS was the second reviewer for scoring of articles. DB and DE contributed to manuscript composition. VB and MS contributed to concept formation and manuscript composition.

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Dr. Dean Eurich has also been a great source of support for study design, statistical analysis and trouble-shooting. Dr. Eurich was consistently available to answer my questions and provide feedback from a methodological point of view.

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LIST OF ABBREVIATIONS

CRC – Colorectal cancer

CT – Computed Tomography

LST – Lean soft tissue

SM – Skeletal muscle

SMR – Skeletal muscle radiodensity

HU – Hounsfield Units

SMA – Skeletal muscle area (cm^2)

SMI – Skeletal muscle index (cm^2/m^2)

TATI – Total adipose tissue index (cm^2/m^2)

BMI – Body mass index

VO – Visceral obesity

BSA – Body surface area

DLT – Dose limiting toxicity

OS – Overall survival

DFS – Disease free survival

CSS – Cancer specific survival

aHR – adjusted hazard ratio

CHAPTER 1: INTRODUCTION

1.1 Statement of the Problem

Colorectal cancer (CRC) is the second most commonly diagnosed cancer in Canadian men and women.[1] Traditionally, tumor specific factors have provided prognostic information for short and long-term outcomes, including survival. This includes depth of tumor penetration and lymph node or distant metastasis, or disease stage.[2,3] Other high-risk features predictive of worse outcomes includes lymphovascular invasion (LVI), perineural invasion (PNI), obstruction or perforation and time of diagnosis and presence of genetic mutations (microsatellite instability, MSI; *BRAF/KRAS* mutations).[4-11] More recently, patient specific factors have emerged as additional or novel prognostic factors. Individual body composition parameters as measured by cross-sectional imaging have been included as valuable prognostic indicators.[12,13] These parameters include measures of skeletal muscle, with the intent of identifying pathological reductions in skeletal muscle (eg. sarcopenia). Other parameters include mean skeletal muscle radiodensity (SMR) as a measure of fatty infiltration into muscle, termed myosteatosis. Adipose tissues can also be quantified, including individual cross sectional area measurements of visceral and subcutaneous adipose tissues. Increased levels of adipose tissue that have been associated with poor outcomes can be defined as visceral obesity or elevated total adiposity. Individually, these parameters each contribute to pathological alterations in patients' body composition. Joint effects of reductions of skeletal muscle mass and radiodensity and elevations in adiposity are currently not well described.

Cross-sectional imaging, specifically computed tomography (CT), is routinely used as a diagnostic and staging modality in many solid organ tumors, including CRC. This has

allowed for the growing interest in utilization of CT-derived body composition parameters as compared to modalities such as dual energy x-ray absorptiometry (DEXA) and bioelectrical impedance analysis (BIA).[14-16] This opportunistic use of CT scans, without incremental radiation exposure, represents a large repository of previously unknown prognostic data. Additionally, patients will continue to undergo CT imaging after initiation or completion of treatment as part of surveillance or treatment monitoring protocols. Patients with CRC will be followed with annual CT scans at a minimum of 2 years, with some guidelines recommending up to 5 years.[2,3] These serial CT scans provide opportunities to quantify patients' body composition across time.[17]

CT imaging provides access to cross-sectional images, which includes skeletal muscle, adipose tissue and bone. Using specifically designed software, a single CT slice can be analyzed with anatomical knowledge and Hounsfield unit (HU) ranges to precisely and accurately define areas of skeletal muscle and visceral and subcutaneous adipose tissues.[18,19] HUs for skeletal muscle typically range from -29 to +150, with those for visceral and subcutaneous adipose tissue ranging from -150 to -50 and -190 to -30, respectively. From this, SMA (cm^2) can be quantified and normalized by height (m^2) to generate a skeletal muscle index (SMI, cm^2/m^2) for comparison between individuals.

In 2004, Shen *et al*, validated skeletal muscle area from a single CT slice at the third lumbar (L3) vertebral level to be linearly related to whole body muscle mass.[18] Later, Mourtzakis *et al*, described an easy to use equation to accurately predict whole body lean soft tissue (LST) mass (kg) from SMA (LST = 0.30*(SMA+6.06)).[19] Based on these validation studies, Prado *et al*, went on to define thresholds for sarcopenia in a cohort of obese cancer patients.[20] Martin *et al*, also defined thresholds for sarcopenia and

myosteatosis in a cohort of respiratory and gastrointestinal tract cancer patients of varying body mass index (BMI, kg/m^2).[21] These threshold values have been the most commonly cited and used sarcopenia and myosteatosis cutoffs within the literature. Through the combined work done to validate this methodology and the creation of large patient cohorts, body composition analysis has become an emerging field of study within the fields of medical and surgical oncology.[15,22] The use of body composition parameters as prognostic factors in cancer patients is a relatively new field of study, and there is ongoing need for standardization of measurements, clarification of cutoff points to define pathological states (eg. sarcopenia, myosteatosis, VO) and investigation into application in the clinical setting.

1.1.1 Computed Tomography Derived Body Composition Analysis in Cancer Patients Receiving Chemotherapy

In current clinical practice, chemotherapy is dosed using body surface area (BSA), which largely ignores a patient's underlying body composition, including total adipose tissue and LST.[23,24] BSA and body mass index (BMI) do not accurately predict drug volume of distribution, metabolism and clearance.[25,26] Reduced skeletal muscle or whole body LST mass may not be recognized by BSA, resulting in overdosing of patients with hydrophilic chemotherapeutics.[27-29] This effect may also be magnified in patients with excess adipose tissue, who have an inflated BSA, which is even less reflective of their underlying LST mass.[30,31] The ultimate effect of inaccurate chemotherapy dosing is increased rates of drug toxicities, dose-reductions or delays and dose-limiting toxicities (DLTs).[28,32-35] The effect of skeletal muscle and adipose tissue is further emphasized in the few studies that have included measures of serum drug levels to describe the

underlying pharmacokinetics.[31,36-38] Taken together, the limitations of BSA-based dosing and the potential role of CT-defined skeletal muscle mass in the use of personalized chemotherapy dosing represent a novel method chemotherapy dosing with the ultimate goal of reducing toxicities and improving treatment completion rates and long-term survival.[39]

1.1.2 Limitations of Computed Tomography Derived Body Composition Analysis for Long-term Survival Outcomes in Colorectal Cancer Patients

Not all CRC patients treated with curative intent will be recommended for adjuvant chemotherapy. Currently, patients with stage I disease or stage II disease without high-risk features will only undergo surgical resection.[2,3] Therefore, alternative patient-specific prognostic factors, including sarcopenia and myosteatosis, will be of interest in terms of long-term survival outcomes irrespective of adjuvant chemotherapy. In a systematic review of the literature, several methodological inconsistencies are highlighted.[40] This includes HU ranges used to identify skeletal muscle and differing thresholds for classification of sarcopenia and myosteatosis. Despite limitations found, there is a consistent theme present within the literature. Both sarcopenia and myosteatosis emerge as significant prognostic factors for worse overall and recurrence free survival in several different cohorts of CRC treated with curative intent.[20,21,30,41-52] Therefore, sarcopenia and myosteatosis appear to represent body composition parameters, which are easily obtainable patient-specific prognostic factors. Further research should focus on consistency of validated methodology, including use of cohort specific cut-off points for sarcopenia and myosteatosis or creation of large body composition databases. This will

add further strength to inclusion of sarcopenia and myosteatosis as high-risk features in CRC.

1.1.3 Body Composition Parameters as Prognostic Factors for Survival in Stage I-III Colorectal Cancer Patients

The long-term survival of patients with resectable, non-metastatic CRC varies based on disease stage and previously defined high-risk features. Body composition parameters, including sarcopenia and myosteatosis, represent potential patient-specific factors that could improve clinician prognostication.[13,22] Recognition of these factors at the time of diagnosis also presents a possible future target for interventions to prolong overall and disease specific survival. There is currently evidence within the literature that presence of sarcopenia or myosteatosis is predictive of significantly worse survival outcomes.[42,43,46] Most of these studies have relied on pre-defined cutoffs, with few defining cohort specific thresholds. While there is ample evidence to support the poor prognostic role of sarcopenia and myosteatosis in resectable CRC, there is little understanding as to what degree these parameters overlap and how they may interact together and impact long-term survival outcomes.

1.1.4 Change in Skeletal Muscle of Colorectal Cancer Patients After Resection

Assessment of change over time is another potential method to understand the response of skeletal muscle to surgical resection and chemotherapy. Few studies have quantified changes in skeletal muscle over time in CRC patient populations after curative resection.[17,53] These studies tend to demonstrate a loss of skeletal muscle over time, but it is often difficult to delineate effects of disease and effects of disease treatments. The

limited evidence that does focus on resectable CRC provides a descriptive analysis of change occurring from diagnosis and through resection and adjuvant chemotherapy.[17,53] It also provides an analysis of features, which are associated with ongoing muscle losses or gains. There is currently lack of data that looks at the association of pre-existing sarcopenia, skeletal muscle losses over time and long-term survival outcomes (OS, DFS, CSS) or does so using validated measures.[53]

CRC patients will ideally have a preoperative diagnostic/staging CT scan, as well as surveillance CT scans at a minimum of 1 and 2 years postoperatively. These scans can be used to serially quantify skeletal muscle in patients from time of diagnosis to end of surveillance. At the 1-year surveillance CT scan, there is the possibility that patients are still recovering their skeletal muscle losses.[17] The 2-year surveillance CT scan may be the final cross-sectional imaging required for patients that remain recurrence free. The timing of this scan also allows for a significant time interval between their resection and adjuvant treatment to allow for recovery of lost skeletal muscle mass. Therefore, both preoperative and 2-year surveillance scan can be analyzed for SMI at each time point, as well as any changes occurring between scans. Unfortunately, opportunistic use of CT scans results in non-standardized time intervals. This can be resolved through comparison of percentage changes in a pre-defined time interval (eg. % change per year). Percentage change of SMI will also control for baseline differences in patients. For example, a small loss of SMI may represent a larger proportionate change in patients with pre-existing low levels of skeletal muscle. This small loss may also result in patients going from a classification of not sarcopenic to sarcopenic, and represent a significant loss of minimal skeletal muscle reserves as compared to those patients with higher baseline SMI.

The cause of ongoing skeletal muscle losses after definitive treatment of CRC is not well defined. There are some expected losses (0.5%/year for men; 0.35%/year for women) that can be attributed to normal aging.[54] Greater than physiological losses may be a result of significant comorbidities or other ongoing catabolic drivers.[55] It is unknown if patients with disease recurrence can be expected to have pathological skeletal muscle loss that can be detected prior to detection of their disease recurrence. If ongoing losses were indicative of an elevated risk of disease recurrence, these patients could be followed for an extended period of time with cross-sectional imaging. Extended surveillance would be done with the goal of early detection of disease recurrence after exclusion for other reasons for muscle loss. This would be patients' best option for curative treatment and long-term survival.

1.2 Summary

Body composition parameters are emerging prognostic factors for patients with CRC. Standardized measurements of skeletal muscle using cross-sectional imaging, and determination of cohort specific thresholds are critical to accurate identification of sarcopenia and myosteatosis. Definition of cutoffs in large, disease and population-specific cohorts are needed to analyze effects of skeletal muscle abnormalities on survival outcomes and to compare these effects between populations. An analysis of the independent and overlapping effects of sarcopenia and myosteatosis is currently lacking within the literature. Additionally, description of skeletal muscle changes over time and its association with long-term survival and CRC disease recurrence is an area body composition research that has yet to be studied.

1.3 Objectives

1) Gain insight into the role of skeletal muscle and whole body LST in predicting chemotherapy toxicities, and the potential role of CT-quantified LST mass as an alternative to BSA dosing.

2) Gain insight into the prognostic role of CT-derived measures of sarcopenia and myosteatosis in survival outcomes of CRC patients who underwent surgical resections, and the limitations associated with this methodology.

3) Determine thresholds for sarcopenia, myosteatosis and elevated total adiposity in a cohort of resected CRC patients. Evaluate the role of sarcopenia and myosteatosis as individual and overlapping prognostic features in long-term survival outcomes.

4) Describe changes in skeletal muscle from time of diagnosis to end of surveillance, as measured by CT in non-metastatic CRC patients treated with curative intent. Evaluate effects of sarcopenia and loss of skeletal muscle on long-term survival outcomes (OS, DFS, CSS).

The first objective was addressed through a literature review of the relationship between CT-derived measures of skeletal muscle, sarcopenia, myosteatosis and whole body LST mass in predicting chemotherapy toxicities (Chapter 2). The second objective was met through a systematic review of the literature addressing the prognostic role of sarcopenia and myosteatosis in resectable CRC. This review also highlighted limitations currently faced in body composition research (Chapter 3). The third objective was addressed by a retrospective cohort study with the use of CT-derived body composition parameters, including individual and overlapping effects of sarcopenia and myosteatosis on long-term survival (Chapter 4). The fourth objective was addressed in a retrospective cohort study, which quantified change in skeletal muscle over time, as well as the

presence of sarcopenia at time of diagnosis and end of surveillance, and its association with survival outcomes (Chapter 5).

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CHAPTER 2: A REVIEW OF BODY COMPOSITION AND PHARMACOKINETICS IN ONCOLOGY

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2.1 Introduction

Chemotherapeutic toxicities and adverse events resulting in dose reductions and delays have been noted to be more common in those patients that have significant weight loss and malnutrition.[20,56] This is thought to be a result of increased inflammation, secondary to the cancer itself, and drug therapy.[15,20,57] Secondary to these observation, the role of lean mass and effects of body composition on drug pharmacokinetics have come into question. Concurrently, there has been an influx of research with respect to body composition parameters, including skeletal muscle mass (the main component of the lean mass compartment) and sarcopenia, and their role in predicting chemotherapeutic toxicities and disease specific outcomes in many different tumor types.

Classically cytotoxic chemotherapy has been dosed by adjusting doses by BSA; or more recently monoclonal antibodies have been dosed by body weight and small molecule targeted chemotherapy have been flat dosed. In 1916, Du Bois and Du Bois published a study on 9 patients, from which they derived a formula to calculate body surface area (BSA) based on known weight and height.[23] Several other formulas have been derived since that time, and the Mosteller formula is still used today by medical oncologists for routine dosing of chemotherapeutic agents.[24] The scientific basis of both the derivation of BSA itself, and use of BSA for dosing beyond phase I trials has been questioned in the literature.[25,58-60] Furthermore, body composition research has identified that persons with similar or identical body weight, body surface area (BSA) or body mass index (BMI) do not necessarily have similar body composition parameters. For example, a person considered overweight or obese by BMI may have a similar lean mass to a

person who would clinically be considered cachectic or wasted. In terms of drug dosing, these people may have a lower volume of distribution or reduced protein binding resulting in higher drug concentrations, which is not identified based on BSA measurements.[58] Additionally, lipophilic drugs administered to a person with higher body fat may result in decreased drug efficacy. Potentially, activation of the immune system in cachectic patients may confound relationships between body composition and chemotherapy side effects. In those patients with advanced cancer and associated cancer cachexia or sarcopenia, activation of the immune system may lead to symptoms of fatigue and anorexia, and they may display signs including anemia, in the absence of systemic chemotherapy. Despite this, changes in body composition and our improved ability to accurately quantify these parameters suggests that we should be considering more than just BSA or simple body weight as a method of dosing anti-neoplastic medications in a population that is known to have reduced lean body mass.[25,58] There is no strong evidence that physiologic functions, such as hepatic and renal drug clearance, are directly related to BSA.[58] Furthermore, there is little data on specific drug pharmacokinetics, as they relate to individual BSA.[61] This highlights the unpredictability of dosing by BSA, and risks of under- versus over-dosing individuals, with resultant ineffective treatment or drug toxicities. It also brings into consideration any potential alternate options to more accurately dose chemotherapeutics. This review aims to highlight the expanding literature on the roles of body composition in adverse events secondary to chemotherapeutic agents. Moreover, to identify those studies that have quantified drug pharmacokinetics in association with low lean mass (sarcopenia), or other measures of body composition, in cancer patients.

2.2 Body composition

Body composition parameters are most frequently quantified through cross-sectional imaging, such as CT scans, which are completed for routine diagnostic, staging or surveillance purposes. Historically, bioimpedance analysis (BIA) has been used, but it's accuracy is affected by the patient's fluid status, and is therefore inaccurate in many cancer patients. There is good evidence within the literature that skeletal muscle area from a single slice at the third lumbar vertebrae is related to total body skeletal muscle mass, or lean mass.[18] Historically, the term lean body mass (LBM) has been used to comment on an individual's skeletal muscle mass. There is currently a push to abandon this term and more appropriately define it as lean soft tissue (LST) mass, which from hereon in will be used in this review. From an identified CT, all skeletal muscle in the slice is identified anatomically and with predefined Hounsfield units (HU) from -29 to +150 HU.[15] Subcutaneous and visceral adipose tissues are also identified anatomically and from -190 to -30 HU and -150 to -50 HU, respectively.[15] There are arguments within the literature on whether psoas muscle area alone is could be an accurate representative of lean mass. There is also disagreement with respect to the specific HU cut-offs used to identify the previously defined body compartments. From the area defined (cm^2), skeletal muscle is normalized by height to obtain skeletal muscle index (SMI, cm^2/m^2). This allows researchers to compare SMI between individuals, and has resulted in specific cut off values used to define sarcopenia within different patient populations.[15,18,21] This is in comparison to the definition put forward by European Working Group on Sarcopenia in Older persons. [55] This group suggested that an operation definition of sarcopenia include

a reduction in at least two of muscle mass, muscle strength and physical performance.[55] Muscle can also be assessed for quality by analyzing its average attenuation in HU. As the HU decrease, there is an increase in fatty infiltration, or myosteatosis.

2.3 Lean soft tissue mass and chemotherapeutic agents

Over the last several years, that has been a rapid increase in the number of studies published in the field of body composition. These publications have focused on relationships between sarcopenia, as defined by reduced skeletal muscle density (SMD, also referred to as LST) on cross-sectional imaging, and documented drug toxicities within a variety of different tumor types. Furthermore, they describe relationships found between sarcopenia or reduced LST and drug toxicities. Several published articles also compare the drug dose by BSA as compared to drug dose by LST as a simple way to highlight how different dosing can be when comparing different methods of measuring body composition or LST. A summary of the studies included in this review can be seen in Table 2.1.

2.3.1 Dose by lean mass and drug toxicities

Some of the earliest work was published by Prado *et al*. in 2007, which used CT-derived values of LST in stage II and III colorectal cancer (CRC) patients undergoing adjuvant treatment with a 5-flurouracel (5-FU)/leucovorin regimen.[27] Their results indicated that patients with and without dose-limiting toxicities (DLT) had significantly different doses of 5-FU/kg LST. They defined a cut off of 20 mg 5-FU/kg LST as a threshold for overall toxicity (OR=16.75) that was predictive in their female cohort.[27] Also, those receiving doses above the threshold had significantly lower muscle cross-

sectional areas (cm^2) and SMI (cm^2/m^2). Interestingly, BSA, dose of 5-FU/BSA and dose of 5-FU/body weight did not differ between the two groups.[27] In a second study by Prado *et al*., in a cohort of patients with metastatic breast cancer, those with sarcopenia received a higher dose of capecitabine per kg LST.[62] Furthermore, these women also presented with a significantly higher rate of drug toxicities.[62] These studies provided early evidence to the importance of LST and it's potential use in drug dosing and understanding pharmacokinetics in the cancer population.

Later studies also highlighted the difference in drug dosing by LST. Data from a randomized controlled trial (RCT) on advanced NSCLC showed that in those patients receiving gemcitabine and vinorelbine, there was a very large variation in the dose per LST administered (23.2-53.1 mg/kg and 1.5-3.3 mg/kg, respectively).[35] The variation in dose was also seen in patients with otherwise identical BSA but differences in LST. Also, those patients presenting with grade 3-4 toxicities had statistically significant higher doses per LST for both chemotherapeutics.[35] Another multicenter RCT in advanced NSCLC found that in these patients, doses of carboplatin, gemcitabine, pemetrexed and vinorelbine all had large variations per kg LST as compared to BSA dosing.[34] In their analysis, doses of non-platinum based drugs per kg LST were associated with grade 3-4 hematological toxicities.[34] In a two-center prospective cohort of patients with CRC, the range of oxaliplatin per LST varied significantly throughout the population (2.55 – 6.60 mg/kg).[32] In these CRC populations cut-offs of 3.09 mg/kg LBM and 3.55 mg/kg LST were associated with development of DLT, including sensory neuropathy. Patients above this threshold also had elevated levels of 5-FU/kg LST.[32] Notably, the BSA did not differ between groups. In a more recent study, of metastatic treated with sunitinib, patients that

experienced any DLT had significantly lower SMI and LST, but not sarcopenia, as defined by previously established cut offs.[63] Additionally, those patients with DLTs had significantly higher doses of sunitinib based on their CT-measured LST (0.9 mg/kg vs 0.8 mg/kg).[63] This eloquently demonstrates that patients with identical BSA receiving identical drug doses do not necessarily have the same ability to metabolize the drug, and that this may be secondary to differing body compartments, such as their lean mass.

2.3.2. Sarcopenia and drug toxicities

While the rest of the literature does not define a dose per kg LST for comparison, it does strongly demonstrate associations of DLTs in those patients with sarcopenia. For example, in 2010 Antoun *et al*. used Prado *et al*.'s cut offs for sarcopenia in a population of patients receiving sorafenib for metastatic renal cell carcinoma (RCC).[64] They found that men with sarcopenia had significantly more DLTs (37 vs. 5%. $p<0.04$). Also, men with DLTs had significantly lower SMI, and all but one met the threshold for sarcopenia.[64] Conversely, in another cohort of metastatic RCC being treated with sunitinib both LST and BSA has a statistically significant association with early DLT, but sarcopenia (as defined by specific cut offs from Prado *et al.*) was not significantly different in patients with and without DLTs.[38] In a subgroup analysis of sarcopenic patients with a BMI<25 kg/m^2, there was a significant increase in the number of DLTs (55.5 vs. 23.1%).[38]

Effects of body composition on drug toxicities are not limited to specific cancer type or chemotherapy. In an analysis of patients enrolled in a phase I study, regardless of their tumor or drug type, low SMI was the sole factor found to be associated with DLT, and patients with severe toxic events had significantly lower SMI (42.4 vs. 48.4

cm^2/m^2).[65] This was also seen in patients with low or normal BMI, compared to those patients with a BMI>25 kg/m^2.[65] Other studies have looked at gastrointestinal cancers, and treatment with standard chemotherapeutic agents and with novel immunotherapy, which also rely on weight based dosing. Despite the broad disease types and differences in anti-neoplastic agents used, these studies are all able to reveal an association between toxicities and changes in body composition. A cohort of stage III CRC patients receiving adjuvant FOLFOX, psoas index (PI) was found to be predictive of all grade 3-4 toxicities and grade 3-4 neutropenia in both univariate and multivariate analyses.[66] In a cohort of patients receiving neoadjuvant treatment for esophago-gastric cancer the presence of sarcopenia, as defined by cut offs from Prado *et al.,* was significantly associated with DLTs (54.5 vs. 28.9%), and sarcopenia remained the only independent predictor of DLTs after controlling for other variables.[67] In a subsequent study evaluating esophago-gastric cancer patients undergoing neoadjuvant chemo-radiation, those who had DLT had a significantly lower SMA, LST and reduced muscle attenuation (MA), but not SMI or BMI.[68] Those with sarcopenia (based on Prado's cut-offs) had a significantly lower BMI, SMI and LST. In this cohort, patients with sarcopenia and an elevated BMI had a higher risk of DLT than obese, non-sarcopenic patients (OR 5.54). Overall, sarcopenic patients were more likely to develop a DLT (OR 2.47), even if they were of normal weight (OR 1.60).[68] Daly *et al*. looked at a population of patients with metastatic melanoma being treated with ipilimumab, which is dosed in terms of mg/kg.[69] They found that sarcopenia was predictive of overall, but not immune-related, high-grade toxicities (OR 3.54), and more specifically, that fatigue was more prevalent in sarcopenic patients.[69] An important point that needs to be made in regards to studies of immunotherapy is that fatigue can be

a side effect of activation of the immune system. Interestingly, they also quantified MA, a marker for fatty infiltration, and found that those patients with reduced MA were even more likely to have high-grade toxicities (OR 7.46) and DLT.[69] This provides another aspect of body composition that may play an important role in both disease outcomes and the body's ability to metabolize and clear drugs.

There have been studies that have demonstrated that effects of LST are also seen beyond conventional chemotherapy drug administration. Chemotherapeutic toxicities are also seen in patients undergoing cytoreductive surgery and heated intraperitoneal chemotherapy (CRS-HIPEC) for peritoneal carcinomatosis from CRC.[70] Sarcopenic patients had significantly more toxicities, and sarcopenia was the only independently predictive factor for toxicity in a multivariate regression (OR 3.97).[70] The concept of body composition affecting LST and chemotherapeutic toxicities has also been extended to hepatic arterial infusion (HAI) chemotherapy in a cohort of patients with metastatic disease to the liver.[71] But, they were unable to demonstrate any differences in grade 3-4 toxicities secondary to HAI in sarcopenic versus non-sarcopenic patients, or between those that were in the first and fourth quartiles for normalized oxaliplatin dose (mg/kg LST).[71]

Several studies have demonstrated a significant decrease in LST in those with DLTs, yet at the same time unable to show a statistically significant association with sarcopenia except within subgroups analysis of sarcopenic patients. In a population of advanced NSCLC patients receiving first-line chemotherapy, there was no observed relationship between toxicities and sarcopenia.[72] Rather, weight loss in the preceding 6 months, concentration of protein and albumin levels, as compared to sarcopenia were

found to be the most significant predictors for toxicities.[72] In another study looking at stage IV NSCLC, specifically those being treated with afatinib, those patients with lower LST and an increased ratio of LST to afatanib dose was significantly associated with increased DLTs. Despite this trend, sarcopenia was not predictive of DLTs.[56] In a cohort of patients with advanced, relapsed ovarian cancer treated with pegylatyed liposomal doxorubicin and trabectedin, there was no demonstrable association between cross-sectional muscle area or LST with toxicity unless the cohort was restricted to patients with a BMI>25 kg/m^2.[73] Within that subset, patients with DLT had significantly lower BMI and whole body fat mass (FM). Also, their ratio of FM/LBW was significantly lower in the group with DLTs. Conversely, LST was the only significant predictor of DLTs in normal weight patients.[73] Similarly, in a population of patients with metastatic CRC being treated with chemotherapy, sarcopenia was the only factor associated with grade 3-4 toxicities in a multivariate logistic regression model (OR 13.55).[74] While these toxicities tended to be more common in sarcopenic patients than non-sarcopenic patients, this did not reach statistical significance.[74] Most recently, sarcopenic metastatic breast cancer patients receiving taxane-based chemotherapy were shown to be significantly more likely to develop grade 3-4 toxicities and require hospitalization and have any adverse event (74 vs. 35%).[75] LST, BMI and BSA did not demonstrate any relationship with toxicity in this group.[75]

2.4 Body composition and pharmacokinetics

In contrast to the work done on body composition and drug toxicities, there has been significantly less work directly quantifying drug levels and pharmacokinetics as they relate to body composition parameters from cross-sectional CT-imaging. Despite

this, the data that has come out of those studies demonstrates the importance of both whole body FM and LST in drug pharmacokinetics. A summary of the published studies included in this review can be seen in Table 2.2.

Again, the literature is quite broad in tumor type and specific chemotherapeutic agents included. In the four studies included, three different tumor types and four different drugs were evaluated. Prado *et al*. were one of the earliest groups to bring attention to this phenomenon. In a study of stage II-III breast cancer patients, they found that the LST of patients varied widely, even in patients with identical BSA.[37] Concurrently, the epirubicin dose per kg LST also widely varied (3.3-5.1 mg/kg) and LST was higher in patients that did not experience any DLTs. In terms of epirubicin pharmacokinetics, drug clearance was positively associated with increasing LST, but not BSA.[37] In their final model, 33% of epirubicin clearance was explained by LST and AST alone.[37] In their study, they are able to demonstrate that BSA does not predict LBM. This is important as drug clearance was related to LST and not BSA. This study emphasizes the importance of body composition and the lack of differentiation to these different parameters by the measure of BSA.

Later, Mir *et al.* found somewhat similar results in regards to pharmacokinetics of sorafenib in advanced hepatocellular carcinoma (HCC) patients.[36] They demonstrated that sarcopenic patients had a significantly higher median dose-adjusted area under the curve (AUC) (102.4 vs. 53.7 mg/l.h) and that patients with DLTs in the same time period also had significantly higher AUC (106.4 vs. 56.7 mg/l.h).[36] While there was no significant difference in sorafenib dose per kg LST, sarcopenic patients were more likely to be started on the lower dose (200 mg bid) and had significantly higher rates of DLTs,

compared to non-sarcopenic patients.[36] In an attempt to expand upon the knowledge of body composition and pharmacokinetics, Massicotte *et al*., looked to create a predictive model of drug toxicity.[76] In a population of patients with metastatic medullary thyroid carcinoma receiving vandetinib, body composition parameters were considered in a continuous fashion in relation to DLTs and vandetanib serum concentrations.[76] Patients experiencing DLTs had significantly lower SMI (37.2 vs. 44.3 cm^2/m^2) and a SMI of 43.1 cm^2/m^2 was found to be predictive of DLTs using a ROC analysis. This group also had a significantly elevated serum concentration of vandetinib (1091 vs. 739 ng/mL). Of note, patients with SMI <43.1 cm^2/m^2 and BMI$\leq$25 kg/m^2 had an even higher rate of DLTs (83%).[76] The cut off predicted in this study is similar to cut off thresholds used to define sarcopenia. [20,21,76]

Wong *et al*. attempted to unveil a relationship between adipose tissue components of the body and drug toxicities.[31] In an Asian cohort with locally advanced or metastatic breast cancer, intra-abdominal fat volume and visceral fat volume to total fat volume (VFV:TFV) ratio was found to be significantly correlated with hematological toxicities, specifically grade 4 leukopenia.[31] This same group had preservation of the correlation in low (<18.5 kg/m^2) and high (>30 kg/m^2) BMI subgroups, but did not demonstrate any direct correlation between toxicities and BMI or BSA. Furthermore, pharmacokinetic evaluation of doxorubicin in these patients showed a significant positive correlation of VFV and TFV with doxorubicin AUC (r^2 = 0.324, r=0.262, respectively).[31]

2.5 Expert commentary

Development of tools to accurately quantify LST and fat mass through cross-sectional imaging has opened a new avenue of investigation within oncology research.

The current body of literature describing roles of body composition in oncology is rapidly increasing. As evident in this review, there has been an increased interest in the importance of lean mass as it pertains to anti-neoplastic drug pharmacokinetics and toxicities. It has become clear that BSA and BMI do not accurately predict volume of distribution and drug metabolism and clearance. Consequently, the ability to quantify lean body mass differences in persons of identical BSA suggests the unpredictability of chemotherapeutic toxicities is likely secondary to an interaction between body composition and drug pharmacokinetics.

While there has been significant work done to standardize this research, there is still variation in the acquisition of data. Most groups are using 1-2 slices from approximately the L3 region of CT scans. Beyond this, there are differences in whether total skeletal muscle area versus psoas muscle area is calculated. Only one of the studies included in this review utilized psoas muscle area and index as their marker of sarcopenia. The inherent issue in ignoring the rest of the abdominal musculature is the chance of poor representation of lean mass by a single muscle, especially one that is small and therefore at risk of large variation through minor changes in area or mean HU attenuation. There is also a paucity of research that validates its use, or defines a specific cut off point to define sarcopenia in cancer patient populations. Furthermore, HU cut-offs for skeletal muscle, subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) differ between studies. Only one study included analyzed relationships between MA and drug toxicities. While there appears to be an association present, there is currently no predefined cut-offs to define myosteatosis, and there remains work to be done to identify thresholds within different populations, including age groups.

The vast majority of the published literature looks solely at associations of sarcopenia and chemotherapy toxicities. Several of these studies have compared drug dose per kg of LST, as predicted by a formula from Mourtzakis *et al*.[19] This calculation is based on skeletal muscle area at L3 in cross-sectional imaging and was shown to be predictive of total body LST. The comparison of drug dose by BSA to LST is of interest, as it highlights inaccuracies of BSA in dosing, while concurrently demonstrating a possible replacement measure with LST. In fact, all studies that reported these measures found that as LST decreased, there was a concurrent increase in drug dose per kg LST. They also found that those with higher doses per LST had higher rates of drug toxicities and DLTs. This lends support to the hypothesis that reduced LST results in a reduced volume and distribution and increased likelihood of over-dosing when relying on a BSA dosing method. This concept is exceedingly important within the cancer population for several reasons. The prevalence of sarcopenia within cancer-specific populations tends to higher then the general population, and is often upwards of 40-50%.[20,21] This is due to a combination of disease factors, medication side effects, comorbid conditions and increasing age. Therefore, there is a need for awareness of this phenomenon for patients receiving cancer therapies. Also, anti-neoplastic agents tend to have more frequent and severe toxicities than other classes of medications. Patients that have severe enough adverse events from these drugs will often have dose reductions, treatment delays or treatment discontinuations, all of which will have an impact on their overall disease outcome. Finally, the ability to quantify an individual's LST has become increasingly easier, as CT scans are readily done for diagnostic purposes, and individuals can be easily

trained to extract this data. It is for those reasons that awareness of body composition is of utmost importance and that further work needs to be done in directly measuring drug pharmacokinetics within these patient populations.

Pharmacokinetic studies included in this review support this conclusion. They demonstrate that drug concentrations measured from patient blood samples are elevated in patients with lower LST and in patients experiencing DLTs. Furthermore, studies reviewed were completed on different tumor and drug types, suggesting that effects of LST on drug pharmacokinetics is not limited to a specific cancer or chemotherapeutic agent.

2.6 Five-year view

We predict that over the course of the next five years, the exact role of body composition will become more defined in the clinical setting. As the research being published consistently highlights the clinical relevance, in treatment and disease specific outcomes, we expect a push to include LST in calculating chemotherapy dosing. The definition or threshold values for sarcopenia may not be identical between populations of different ages or ethnicities. Regardless, an increase in drug dose per LST has consistently been shown to be predictive of DLTs, and future research should focus on how this can be translated into clinical practice. The role of body composition fits within the model of molecular pathologic epidemiology (MPE) for CRC. Quantification of individual lean soft tissue mass and muscle quality will help understand interactions between these parameters and drug distribution and side effects. Overall, this will allow clinicians to practice precision, individualized medicine.

2.7 Conclusion

Body composition, specifically sarcopenia as measured by LST, has been strongly supported within the literature as being a relevant factor in chemotherapeutic drug toxicities. A reduction in LST is thought to affect pharmacokinetics by reducing the volume of distribution, protein binding, metabolism and clearance of drugs. The strong association of sarcopenia with drug toxicities and increased dose per kg of LST, which is not predicted by BSA dosing, greatly supports the need to alter or change the method of drug dosing within medical oncology. There is also a need to identify interventions to reduce loss and improve gain of lean mass in these patients. This review provides an up to date summary of the literature, and specifically highlights the feasibility of using routing staging investigations as a modality for individualized chemotherapeutic dosing without further radiation exposure.

Table 2.1: Body composition and chemotherapy toxicities

Authors	Study population	Chemotherap-eutic agent included	BC measurem-ents	BC parameter/ sarcopenia cutoff	Toxicity parameters	Main findings
Prado et al., 2007[15]	Resected, high-risk stage II & stage III CRC N=62	Six 28-day cycles of **5-FU** (425 mg/m^2) and leucovorin IV bolus daily x 5d (20 mg/m^2)	CT, average of 2 slices at L3	SMA SAT VAT	NCI CTCAE V2.0 (only cycle 1) Grade3-4 toxicity Dose delay Dose reductions	Increased overall DLTs in those receiving a dose of >20 mg 5-FU/kg LBM Reduced LST a significant predictor for 5-FU toxicity
Prado et al., 2009[16]	Metastatic breast cancer N=55	Capecitabine (1,250 mg/m^2 bid or 1,000 mg/m^2 bid)	CT, average of 2 consecutive slices at L3 LST (kg) = [(L3 muscle area cm^2 x 0.3] + 6.06	SMA SMI M<52.4 cm^2/m^2 F<38.5 cm^2/m^2	NCI CTCAE v2.0 Grade 2-4 toxicities; First cycle only	Sarcopenia associated with increased toxicities. Only independent predictive factor in a logistic regression (HR 4.1)
Antoun et al., 2010[21]	Metastatic renal cell carcinoma N = 55	**Sorafenib** (800 mg/day)	CT, average of 2 slices at L3	SMA SMI SAT VAT M<52.4 cm^2/m^2 F<38.5 cm^2/m^2	NCI CTCAE v3.0 – severe toxicity leading to dose reduction or discontinuation	Increased DLTs in patients with sarcopenia Men with DLTs had significantly lower BMI, SMI

Parsons et al., 2012[29]	Metastatic liver lesions (CRC) N=57	HAI oxaliplatin (60-175 mg/m^2), leucovorin (200 mg/m^2), 5-FU (300 mg/m^2 bolus and 600 mg/m^2 infusion)	CT, single slice at L3 LST (kg) = [(L3 muscle area cm^2 x 0.3] + 6.06 Whole body FM (kg) = 0.042 x [fat tissue at L3 (cm^2)] + 11.2	SMA SMI SAT VAT M<52.4 cm^2/m^2 F<38.5 cm^2/m^2	NCI CTCAE v3.0 ≥Grade 3	There was no difference in grade 3-4 toxicities between the sarcopenic and non-sarcopenic groups. There was also no difference between those in the 1st and 4th quartiles of normalized oxaliplatin dose (mg/kg LST)
Huillard et al., 2013[22]	Metastatic renal cell carcinoma N=61	Sunitinib (25, 37.5 or 50 mg/day based on ECOG)	CT, single slice at L3 LST (kg) = [(L3 muscle area cm^2 x 0.3] + 6.06	SMA SMI M<55.4 cm^2/m^2 F<38.9 cm^2/m^2	NCI CTCAE v3.0 Grade 3-4 DLT = dose reduction; temporary or permanent discontinuation	Sarcopenic patients with a BMI<25 kg/m^2 were more likely to have DLTs. Decreasing LST and BSA had a significant association with increasing DLTs.
Cousin et al., 2014[23]	Any SOT or hematological malignancy, enrolled in a phase I trial N=93	Receiving any chemotherapeutic agent	CT, single slice at L3	SMA SMI SAT VAT M<54.1 cm^2/m^2 F<40.8 cm^2/m^2	NCI CTCAE v3.0/4.0 DLT = postponement of treatment, drug dose reduction, drug discontinuation First cycle only	In patients with any malignancy and any drug type, a low SMI and BMI (<25 kg/m^2) was significantly associated with DLTs. In a multivariate analysis, only low SMI remained significant.
Barret et	Metastatic	As per French	CT, single	SMA	NCI CTCAE	Sarcopenia independently

al., 2014[32]	CRC Multicenter (9) N=51	guidelines	slice at L3	SMI SAT VAT	v4.0 Grade 3-4 toxicities	predictive of grade 3-4 toxicities. Tendency to more grade 3-4 toxicities in sarcopenic patients.
Prado et al., 2014[31]	Advanced, relapsed ovarian cancer N=74	Pegylated liposomal doxorubicin, **PLD** (30 mg/m^2) +/- trabectedin	CT, average of 2 consecutive slices at L3 LST (kg) = [(L3 muscle area cm^2 x 0.3] + 6.06 Whole body FM (kg) = 0.042 x [fat tissue at L3 (cm^2)] + 11.2	SMA SMI SAT VAT	NCI CTCAE v3.0 DLT $\geq$ grade 3 toxicity First cycle only	In patients with a BMI$\geq$25 kg/m^2, patients with DLTs had significantly lower BMI and FM lower FM/LBW ratios. In this subset the risk of DLTs increased with decreasing FM (OR 0.87). LST was a significant predictor of toxicity in normal weight patients.
Tan et al., 2015[25]	Potentially curative esophago-gastric cancer, receiving neoadjuvant therapy N=89	SCC: Cisplatin (80 mg/m^2) 5-FU (1000 mg/m^2) Adenocarcinoma: Epirubicin (50 mg/m^2) Cisplatin (60 mg/m^2)	CT, average of 2 consecutive images at L3 LST (kg) = [(L3 muscle area cm^2 x 0.3] + 6.06	SMA SMI M$\leq$52.4 cm^2/m^2 F$\leq$38.5 cm^2/m^2	DLT = drug reduction, drug discontinuation, postponement of treatment	Sarcopenia associated with increased DLTs. Sarcopenia was only independent predictor of DLTs in multivariate analysis.

		Capecitabine (625 mg/m^2)				
Arrieta et al., 2015[1]	Stage IV NSCLC who received at least 1 cycle of platinum-based therapy N=84	**Afatinib** (40 mg/day)	CT, single slice at L3 LST (kg) = [(L3 muscle area cm^2 x 0.3] + 6.06	SMA	NCI CTCAE v4.0 Grade 3-4 toxicities Dose reduction Dose discontinuation Disease progression	Reduced LBM BMI and LST/afatanib ratio associated with increased DLTs. Sarcopenia not predictive of increased DLTs.
Jung et al., 2015[24]	Stage III CRC receiving adjuvant chemotherapy N=229	FOLFOX (12 cycles) Oxaliplatin (85 mg/m^2) Leucovorin (200 mg/m^2) 5-FU (600 mg/m^2)	CT, single slice at L4	PA PI Sex-adjusted lowest quartile	NCI CTCAE v3.0 Grade 3-4	PI predictive of overall grade 3-4 toxicities in univariate and multivariate analysis.
Sjoblom et al., 2015[17]	Stage IIIB-IV NSCLC N=153	**Gemcitabine** (1000 mg/m^2), **vinorelbine** (60 mg/m^2)	CT, single slice at L3 LST (kg) = [(L3 muscle area cm^2 x 0.3] + 6.06	SMA SMI	NCI CTCAE v3.0 Grade 3-4 Dose reduction $\geq$20% Discontinuation after first cycle	Higher doses of gemcitabine or vinorelbine per kg LST associated with increased risk of grade 3-4 toxicities.
Sjoblom et al., 2016[18]	Stage IIIB-IV NSCLC N=424	Carboplatin and permetrexed (500 mg/m^2)	CT, single slice at L3 LST (kg) =	SMA SMI	NCI CTCAE v3.0	Drug dose per kg LST varied widely as compared to BSA dosing. Those patients with elevated dose per kg LST had

		Or Gemcitabine (1000 mg/m^2) +/- Vinorelbine (60 m g/m^2)	[(L3 muscle area cm^2 x 0.3] + 6.06			higher rates of grade 3-4 hematological toxicities.
Chemama et al., 2016[28]	CRC with PC undergoing CRS-HIPEC N=97	Intraperitoneal oxaliplatin (300 mg/m^2) and irinotecan (200 mg/m^2) in 2L/m^2 of dextrose at 43 C Intravenous 5-FU (400 mg/m^2) and leucovorin (20 mg/m^2)	CT, single slice at L3	SMA SMI MA VAT SAT M<43 cm^2/m^2 if BMI<25 kg/m^2 and <53 cm^2/m^2 if BMI>25 kg/m^2 F<41 cm^2/m^2	NCI CTCAE v3.0 Grade III-IV neutropenia = event	Sarcopenia associated with increased overall toxicities and neutropenia.
Anandavadivelan et al., 2016[26]	Esophageal or gastric cardia cancer, treated with neoadjuvant chemother	Cisplatin (100mg/m^2) on day 1, 5-FU (750 mg/m^2) infusion days 1-5 Oxaliplatin (130 mg/m^2) substituted for	CT, single slice at L3 LST (kg) = [(L3 muscle area cm^2 x 0.3] + 6.06	SMA SMI SAT VAT M<52.4 cm^2/m^2 F≤38.5 cm^2/m^2	NCI CTCAE v3.0 DLT – any toxicity leading to reduction, delay or permanent discontinuation	Increased DLTs in sarcopenic and sarcopenic obese patients. Patients with toxicities were more likely to have lower MA, SMI and LST.

	apy N=72	adenocarcinoma Carboplatin (AUC 5) substituted for squamous cell				
Ali et al., 2016[19]	Histologically-confirmed metastatic CRC Two centers N=138	Folinic acid (200 mg/m^2), 5-FU bolus (400 mg/m^2), infusional 5-FU x 46 hr (2400 mg/m^2), biweekly for up to 12 weeks Combined with **oxaliplatin**, irinotecan and/or cetuximab	CT, average of 2 adjacent images at L3 LST (kg) = [(L3 muscle area cm^2 x 0.3] + 6.06	SMA SMI	Sensory neuropathy Levi Scale Considered DLT if ≥grade 3 (first 3 cycles) or change in treatment plan	Increased DLTs in patients with oxaliplatin normalized by LST rather than BSA.
Srdic et al., 2016[30]	Stage IIIB-IV NSCLC N=100	First-line chemotherapy: gemcitabine, paclitaxel or etoposide	CT, average of 2 consecutive slices at L3	SMA SMI	NCI CTCAE v2.0 Grade 2-4 toxicities First cycle only Dose reduction or discontinuation	No relationship between sarcopenia and chemotherapy toxicities.
Shachar et al.,	Metastatic breast	Paclitaxel (80-90 mg/m^2)	CT, L3	SMA SMI	NCI CTCAE v4.03	Increased DLTs and need for hospitalization in patients with

2017[33]	cancer, being treated with a taxane-based regimen N=40	Docetaxel (60-100 mg/m^2) *nab*-paclitaxel (100-260 mg/m^2)	LST (kg) = [(L3 muscle area cm^2 x 0.3] + 6.06	SMD (mean HU) SMG = SMI*SMD <41 cm^2/m^2	Hospitalization Grade 3-4 toxicity Dose reduction or delay	sarcopenia
Cushen et al., 2017[20]	Metastatic renal cell carcinoma N=55	Sunitinib (50 mg/day)	CT, average of 2 slices at L3 LST (kg) = [(L3 muscle area cm^2 x 0.3] + 6.06	SMA SMI SAT VAT M<55.4 cm^2/m^2 F<38.9 cm^2/m^2	NCI CTCAE v4.0 DLT = dose reduction, temporary or permanent drug discontinuation All 4 cycles	Low SMI and LST, but not sarcopenia, were significantly associated with increased DLTs. Patients with DLTs had significantly higher doses of sunitinib per kg LST.
Daly et al., 2017[27]	Metastatic melanoma N=84	Ipilimumab	CT, average of 2 consecutive slices at L3 LST (kg) = [(L3 muscle area cm^2 x 0.3] + 6.06 Whole body FM (kg) = 0.042 x [fat	SMA SMI MA TAT M<43 cm^2/m^2 if BMI<25 kg/m^2 and <53 cm^2/m^2 if BMI>25	NCI CTCAE v4.0 Grades I1-2 vs. 3-4 (high grade) irAE = immune related AE DLT = any dose delay or drug discontinuation (grade 3-4)	Sarcopenia and low MA were significantly associated with overall AE. There were significantly more DLTs in patients with low MA, but not sarcopenia.

			tissue at L3 (cm^2)] + 11.2	kg/m^2 F<41 cm^2/m^2		

Abbreviations: BC: body composition; CRC: colorectal cancer; SMA: skeletal muscle area; SMI: skeletal muscle index; SAT: subcutaneous adipose tissue; VAT: visceral adipose tissue; NCI CTCA: common terminology criteria for adverse events; DLT: dose-limiting toxicity; MA: muscle attenuation; SMD: skeletal muscle density; SMG: skeletal muscle; FM: fat mass; PA: psoas area; PI: psoas index; PC: peritoneal carcinomatosis; CRS-HIPEC: cytoreductive surgery and heated intraperitoneal chemotherapy; NCSLC: non-small cell lung cancer; TAT: total adipose tissue; AE: adverse event

Table 2.2: Body composition, chemotherapy toxicities and pharmacokinetics

Authors	Study population	Chemother-apeutic agent included	BC measurem-ents	BC parame-ters	Toxicity parameters	Pharmacokinetic parameters	Main findings
Prado et al., 2011[34]	Stage II-III breast cancer N=24	**Epirubicin** (100 mg/m^2) 5-FU (500 mg/m^2) Cyclophosphamide (500 mg/m^2)	CT, average of 2 slices at L3 LST (kg) = [(L3 muscle area cm^2 x 0.3] + 6.06	SMA Liver volume	NCI CTCAE v2.0 DLT = $\geq$ Grade 3 Only first cycle	Epirubicin concentrations at 1 and 24 hr post-infusion Epirubicin clearance (one-compartment models)	LST significantly associated with epirubicin clearance. Patients without DLTs had significantly higher LST.
Mir et al., 2012[35]	Advanced HCC N=40	Sorafenib (200-400 mg bid)	CT, average of 2 consecutive slices at L3 LST (kg) = [(L3 muscle area cm^2 x 0.3] + 6.06	SMA SMI Cut offs: M<55.4 cm^2/m^2; F<38.5 cm^2/m^2	NCI CTCAE v3.0 DLT = dose reduction (grade 3-4), temporary or permanent drug discontinuation First month of treatment only	Sorafenib plasma concentration on day 14, 28 (one-compartment model)	Sarcopenic patients had higher overall rates of DLTs (specifically grade 2 diarrhea) and sarcopenia was the only independent predictor of DLTs. Median sorafenib dose-adjusted AUC was significantly higher in sarcopenic patients and in patients with DLTs.
Massicotte et al.,	Metastatic medullary thyroid	Vandetanib (300 mg/day)	CT, single slice at L3	SMA SMI SAT	DLT = dose reduction, treatment	Vandetanib serum concentration	Patients with DLTs had significantly higher level of serum

2013[36]	carcinoma N=33	versus placebo (ZETA trial)	LST (kg) = [(L3 muscle area cm^2 x 0.3] + 6.06 Whole body FM (kg) = 0.042 x [fat tissue at L3 (cm^2)] + 11.2	VAT	withdrawal	(closest to documented toxicity)	vandetinib and lower SMI. ROC analysis gave an SMI cut-off of 43.1 cm^2/m^2as being predictive of DLT. SMI below this cut-off and BMI≤25 kg/m^2 had highest incidence of DLTs.
Wong et al., 2014[37]	Locally advanced and metastatic breast cancer N=84	Doxorubicin (75 mg/m^2) Docetaxel (75 mg/m^2)	CT, average of 2 consecutive slices at L3	SMA VFV TFV Fat ratio (VFV:TFV)	NCI CTCAE v2.0	Plasma levels of doxorubicin and doxorubicionol at 0, 1, 2, 4, 7, 24h after 1st treatment (two-compartment model for doxorubicin and one sequential compartment for doxorubicionol)	Doxorubicin AUC positively correlated with VFV and TFV. Higher VFV and fat ratio in patients presenting with grade 4 leukopenia, which was maintained in subgroups with BMI<18.5 kg/m^2 or >25 kg/m^2

CT: computed tomography; LBM: lean body mass; SMA: skeletal muscle area; SMI: skeletal muscle index; NCI CTCAE: common terminology criteria for adverse events; DLT: dose-limiting toxicity; SAT: subcutaneous adipose tissue; VAT: visceral adipose tissue; VFV: visceral fat volume; TFV: total fat volume

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CHAPTER 3: BARRIERS TO THE INTERPRETATION OF BODY COMPOSITION IN COLORECTAL CANCER: A REVIEW OF THE METHODOLOGICAL INCONSISTENCY AND COMPLEXITY OF THE CT-DEFINED BODY HABITUS

Hopkins JJ, Skubleny D, Bigam DL, Baracos VE, Eurich DT, Sawyer MB. Barriers to the Interpretation of Body Composition in Colorectal Cancer: A Review of the Methodological Inconsistency and Complexity of the CT-Defined Body Habitus. *Ann Surg Oncol.* 2018. Epub ahead of print.

3.1 Introduction

In our currently aging population, validated prognostic factors for colorectal cancer (CRC) outcomes are needed to allow clinicians to risk stratify patients in terms of short and long-term outcomes. Host-related factors, including body composition as measured by computed tomography (CT), have an important association with survival. Reduced skeletal muscle mass, or sarcopenia, has been shown to be associated with worse overall, disease-free and cancer-specific survival (OS, DFS, CSS). Sarcopenia can be quantified through a reduced skeletal muscle index (SMI, cm^2/m^2; i.e. cross-sectional skeletal muscle area at the 3^{rd} lumbar vertebra and normalized by patient height). Myosteatosis, quantified by reduced skeletal muscle radiodensity, and visceral obesity (VO), defined by elevated cross-sectional visceral adipose tissue (VAT), have also been associated with survival outcomes in CRC.

Currently, the literature for defining body composition parameters is heterogeneous, with variable statistical methods and cut-off points being utilized. This review was performed to provide a comprehensive update on associations of body composition parameters and survival outcomes in CRC treated with curative intent. We also aim to highlight current methodological inconsistencies within this literature.

3.2 Methods

3.2.1 Data sources

This systematic review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. MEDLINE and Pubmed databases were searched using terms related to CRC (colon cancer, rectal cancer, neoplasia, malignancy, tumour), body composition (sarcopenia, sarcopenic obesity, skeletal muscle, visceral obesity, adipose tissue, myosteatosis), cross-sectional imaging (CT, computed tomography, MRI, magnetic resonance imaging) and survival (outcomes, survival, mortality, recurrence, progression). All human-based studies published from January 2000 to September 2017 were included.

3.2.2 Study selection

All original studies that studied CT-measured body composition and survival outcomes of resectable or early-stage CRC were included. Articles that exclusively quantified psoas muscle or perinephric fat were excluded, as these are not representative of whole body values.[77] Any non-English articles and conference abstracts were excluded. If the cohort was primarily non-resectable metastatic disease it was also excluded. Reviews and commentaries were assessed for relevant references, but were not included. All reference lists were searched for any additional relevant publications. All articles were grouped on the basis of body composition parameters defined.

3.2.3 Data extraction

Data was directly abstracted from papers, which included year of publication, study method, study population (number of patients, disease stage, surgical intervention,

medical treatments, disease outcomes), body composition analysis (timing of CT, level of CT analysis, image software, tissue types analyzed, continuous or cut-off values used), risk estimates with 95% confidence intervals (95% CI) or p-values, and factors adjusted for in analysis. Study authors were contacted when necessary for any missing information.

3.2.4 Quality assessment

Study quality was assessed independently by two reviewers (JH, DS), using the Newcastle-Ottawa Scale (NOS) for cohort studies. Differences in scoring categories was reviewed and agreed upon by both reviewers. Key areas of quality assessment included selection and comparability of study groups and assessment of outcome. Specific criteria used are defined in the footnotes of Table 3.1. A total score of 5 or less was considered low, 6-7 was considered moderate and 8-9 was considered high quality.[78]

3.3 Results

3.3.1 Search outcome

A total of 20 studies were included (Figure 3.1, Table 3.1) with a total of 8895 patients. Ten studies considered sarcopenia [21,30,42-44,46,47,50-52] and 12 considered VO. Four studies included sarcopenic obesity (SO)[20,30,46,51] and 3 considered myosteatosis.[21,43,46] Five studies were excluded as they only reported total psoas area (TPA).[79-83] Two studies reported on outcomes in patients with resectable CRC liver metastases.[51,52] All studies reported on at least one of OS, CSS or DFS.

3.3.2 Quality assessment

Table 3.1 contains study quality characteristics, as per NOS criteria. Eight of 20 studies scored as low quality. Only 2 studies included prospective cohorts. [20,21] All but 1 study reported the number of patients with CT scans available[52], with only 4 reporting at least 90% of CT scans being available in their cohort. [44,47,48,51] Ascertainment of body composition parameters varied. Thirteen studies used a CT slice at L3 to quantify SM and VAT. Of the remaining studies, 6 used a CT slice at the umbilicus [45,48,84-87] and 1 used multiple measurements at 3 cm intervals in the lumbar region.[88] All studies reporting on sarcopenia normalized SM by height (m^2) to compare muscularity SMI (cm^2/m^2). VO was reported by VFA (cm^2) or VFA/SFA ratio.

Continuous data (SMI, VFA, VFA/SFA ratio) was converted to binary data using previously reported cut-off points, [30,43,44,46,49,51,86,87] optimal stratification analysis [20,21,30,41,89] or separated by median value [47,48,84,85,88] or into quartiles [42,90] or tertiles[30,44]. Continuous data was used in 1 study.[45] Two studies reported an elevated ratio of visceral to subcutaneous fat (V/S ratio) as their measure of VO.[84,85] Sex-specific cutoffs are important, as male and female differences in muscle and adipose tissues have been well characterized. Sex-specific cut-offs were used in 13 studies.[20,21,30,41-44,46,47,50-52,86] Those not using sex-specific cutoffs used a median value [45,48,88], a single cut-off point [49], a visceral to total fat ratio [87] or visceral to subcutaneous fat ratio.[84,85,88] A summary of methodology can be seen in Tables 3.2 and 3.3.

There was a consistent HU range used to define SM. The range of HU used to define adipose tissue ranged from a lower limit of -400 to -140 and an upper limit range

of -30 to -50. HU ranges were not specified in 4 studies [45,84-86], and VAT was not defined separately from SAT in 2 studies.[48,88] The cut-off value to define visceral obesity ranged from >80 cm^2 [91] to >280 cm^2 [41], with one study using cutoffs for TAT.[30] All 3 studies that included myosteatosis used previously identified BMI-specific HU cutoffs.[21,43,46]

3.3.3 Baseline Body Composition Parameters

Overall prevalence of sarcopenia was 15-60%.[21,30,42-44,46,47,50-52] As these studies were based in heterogeneous populations with differing methodology and cut points, comparison of sarcopenia prevalence is limited. The reported prevalence of myosteatosis was 19-78%.[21,43,46] Similarly to sarcopenia data, either a cutoff point previously defined in the literature [43,46] or cohort specific cutoff point was used.[21] Prevalence of VO ranged from 13.9-71%. [30,41,43-45,48,49,84,86-88,92,93] There are no well defined cut points for VO, and authors often separate their data based on percentiles.

3.3.4 Association of sarcopenia and myosteatosis with survival

A summary of studies including sarcopenia and myosteatosis can be seen in Table 3.2. Prado *et al.*, reported that SO was an independent predictor of OS in obese patients with cancers of GI and respiratory tracts.[20] Similarly, Martin *et al*. found that sex- and BMI-specific cut-off points for sarcopenia and myosteatosis were associated with a significant reduction in OS.[21] Miyamoto showed a significant increase in disease recurrence related to reduced SMI in males.[50]

Malietzis *et al.*, found sarcopenia was predictive of worse OS and DFS. Conversely, McSorley *et al.,* analyzed sarcopenia using Prado's and Martin's cut-offs, and found that regardless of cut-off point used, there was no significant relationship to OS or DFS.[43] A second group also used Martin's cut-offs for sarcopenia in a cohort of CRC and esophagogastric cancer patients, and found a non-significant increased risk of death.[44]

In the C-SCANS cohort, sarcopenic patients have a higher overall and CRC-specific risk of death. The highest risk of CRC-specific death was in women with low muscle mass and high adiposity.[30] From the same cohort, sarcopenia resulted in increased risk of all cause or CRC-specific mortality.[42] Additionally, the authors found that the highest risk of death was in those patients who were sarcopenic and had a neutrophil to lymphocyte ratio (NLR) of 3 or more (HR=2.12, 95% CI, 1.70, 2.65; HR=2.43, 95% CI, 1.79, 3.29, respectively.[42]

Martin *et al.*, defined cut-offs for SMR associated with reduced OS, especially in obese patients that had concurrent low SMI.[21] McSorley *et al.*, found that myosteatosis was significant for OS and CSS. [43] Malietzis *et al.,* used the same HU cutoffs, and found that myosteatosis was not predictive of OS or DFS.[46]

3.3.5 Association of visceral obesity with survival

Moon *et al.*, found a VSR ratio greater than the 50th percentile was significantly associated with DFS.[84] In a study by Lee *et al.*, a VSR>0.4 was not predictive of DFS or OS, but a VFA>130 cm^2 was independently predictive of 5-year OS and DFS.[49] Conversely, Yamamoto *et al.,* found no relationships between survival and VO, using

cut-offs from a Japanese population.[86] Rickles *et al.*, demonstrated a nearly threefold reduction in DFS in patients with VO and stage II disease.[88] Using Prado's cut offs, Malietzis *et al.,* demonstrated a significant effect of SO, but not VO, on 30-day mortality.[91,94] In a second study, the same author also demonstrated that individuals with VO and metabolic syndrome had worse OS and CSS (HR 1.45).[94] Similarly, Boer *et al.,* demonstrated SMI below the sex-specific median at L4 had shorter OS in univariate analysis. This contrasted an earlier study by Ballian *et al.*, which found improved OS with increasing VFA/SFA ratio (VSR).[85] But, they were unable to demonstrate a survival benefit after dichotomizing VSR at 0.5.[85] Park *et al.*, defined VO as a VFA/TFA ratio of greater than 29%, and found a significantly improved OS by K-M curve.[87]

In the C-SCANS study the authors categorized TAT in tertiles, and found elevated TAT resulted in reduced OS and CSS, which was magnified with concurrent low SMI.[30] Using the same cohort, Cespedes-Feliciano *et al.*, used the sex-specific highest quartile of VAT to define obesity and found that metabolically dysregulated and obese patients had reduced OS and CSS, once adjusted for underlying SM mass.[41] This cohort is significantly larger (m=4.465) than previously studied populations with resultant statistical power. McSorley *et al.*, using Doyle's cut off points, were unable to demonstrate a significant change in OS or CSS.[43] Conversely, Black *et al.*, looked at SFA rather than VFA and found that patients with reduced SFA had worse OS.[44] Choe *et al.*, analyzed changes in adipose tissue (VFA, SFA) over time. They found that patients who had an increased VAT from staging to follow-up CT scans had improved OS. [48]

3.4 Discussion

Body composition has become a topic of interest within surgical and medical oncology. Published studies have concluded that patients with sarcopenia or myosteatosis have worse survival. The relationship between VO and survival is less clear. But, previous studies demonstrating a paradoxical increase in survival with obesity-defined BMI, may be explained by higher underlying muscle mass. [30]

There are limitations in the strength of conclusions due to significant methodological heterogeneity. Lumbar tissue areas have been validated as linearly related to whole body SM, VAT and SAT[18], yet several studies utilized the umbilicus as a landmark. The umbilicus results in measurement error, as it is a non-static landmark. There has also been a trend to use psoas muscle as a measure of muscularity. This is not a validated methodology and risks significant bias. [77,95]. Psoas muscle measurements are biased through high measurement error, weak correlation to total lumbar SMA and known psoas-specific muscle atrophy related to spinal pathologies. [77,95]

Variation is seen in the HU ranges to identify tissues compartments (SM, VAT, SAT), which can result in discrepancies of cross-sectional area. It will also affect the average SMR, with a higher minimum SM HU failing to identify potential fatty infiltration of muscle, and therefore a reduced detection of myosteatosis. The use of intravenous contrast also significantly affects average SMR detected.[96,97] Studies included in this review had a homogenous SM HU range, but the prevalence of non-contrast CTs is not reported. The HU range for VAT may affect the area defined, but to a smaller degree as most VAT will be detected from -120 to -50 HU.

There is a lack of consensus for specific cut-offs used to define sarcopenia as a dichotomous variable. The most commonly used cut-off points come from Prado *et al*.

(M<52.4 cm^2/m^2; F<38.5 cm^2/m^2)[20] and Martin *et al*. (M<43 cm^2/m^2 if BMI<25 kg/m^2; M<53 cm^2/m^2 if BMI>25 kg/m^2; F<41 cm^2/m^2).[21] These studies both used optimal stratification to define their cut-off points in a Canadian population of obese and mixed BMI cohort of GI and respiratory tract, respectively.[20,21] Optimal stratification has been used by other groups to identify cohort specific cutoffs, and is one known and validated statistical tool.[30,41,42] Applying Martin or Prado's cut-offs, the prevalence of sarcopenia in published cohorts ranges from 41-47% and 15-60%, respectively.[20,21,43,46,51] In our own early-stage CRC cohort, using published cutoffs, prevalence of sarcopenia ranged from 35-52%. Therefore, identification of population specific cut-off points by optimal stratification may be ideal if they have not been previously defined in a similar population. For example, several Japanese groups have validated sarcopenia cut-offs in a cohort of Japanese patients with gastric cancer that differ from those by Prado *et al*.[98-100]

The same issues are identified for VO and myosteatosis, as summarized in Table 3.3. There is no widely accepted cut-off for VO, and we can expect Asian cohorts to have a lower cutoff than their Caucasian counterparts. Furthermore, use of a VFA/SFA ratio to define VO is subject to bias. Those patients with large VFA and concurrent SFA may fall below the "elevated" cutoff, whereas those with generally low VFA, but considerably lower SFA may fall above this cutoff. Again, applying cutoffs to our own cohort resulted in a VO prevalence from 3-88%. Values used for low MA to define myosteatosis have not been adequately defined and can be expected to vary in studies based on HU limits used to define skeletal muscle and the population being studied. Until there is a standardized process for obtaining body composition parameters with validated cut-off

points in varying populations, we can expect to continue to see inconsistencies in data collection and analysis that will make the study results difficult to compare.

These studies consistently demonstrated the ease of using routine staging CT scans as a tool to measure body composition in CRC patients. The issue of radiation exposure is irrelevant as patients will already have been required imaging for diagnostic or staging purposes, and body composition parameters can readily be extracted from the same scan.

Mechanisms resulting in changes in body composition are unknown. It is hypothesized to be related to the host inflammatory response. There is ongoing research into body composition and systemic inflammation in cancer, as measured through plasma markers, such as calprotectin.[101] One group has demonstrated an elevated a neutrophil to lymphocyte ratio (NLR) in CRC patients undergoing resection was an independent predictors of sarcopenia.[94] They also showed that individuals with an NLR>3 had significantly lower SMI and MA than those with an NLR<3. The relationship between CRC outcomes and NLR has been independently demonstrated to have a significant association and potential to be another predictor of oncologic outcomes in CRC.[102] The association of elevated NLR with myopenia supports the proposed connection between myosteatosis and systemic inflammation. [102] Ongoing research is needed to fully elucidate the mechanism of inflammation and body composition in CRC survival.

3.4.1 Conclusion

The literature on body composition is rapidly expanding, and there is a clear need for standardized protocols and definitions. Despite this, skeletal muscle mass and radiodensity appear to consistently be associated with survival outcomes in CRC. Body

composition is therefore a clinically important factor to be considered in treatment and prognosis.

Table 3.1: Summary of quality of included studies based on the Newcastle-Ottawa Scale

First author, year	Selection				Compar-ability	Outcome			Total score	N
	Represen-tativeness of exposed cohort (1)	Selection of non-exposed cohort (2)	Ascerta-inment of exposure (3)	Demonstr-ation that outcome not present at study start (4)	Compar-ability of cohorts (5) [a]	Assess-ment of outcome (6)	Long enough follow up (7)	Adequ-acy of follow up (8)		
Caan, 2017[3]	0	1	1	0	2	1	1	0	6	3262 [b]
Cespe-des Felicia-no, 2017[4]	0	1	1	0	2	1	1	1	7	2470 [b]
McSorl ey, 2017[5]	0	1	1	0	2	1	1	0	6	322
Black, 2017[6]	1	1	0	0	2	1	1	0	6	447
Jeong, 2016[24]	0	1	0	0	0	0	0	1	2	346
Malietz is, 2016[7]	0	1	1	0	2	1	1	1	7	805
Boer 2016[8]	1	1	0	0	1	1	0	0	4	91
Choe,	1	1	0	0	2	0	1	1	6	630

2016[19]										
Cespedes Feliciano, 2016[28]	0	1	1	0	2	1	1	0	6	3276 [b]
Lee, 2015[26]	0	1	0	0	0	1	1	0	3	62
Park, 2015[23]	0	1	0	0	0	0	1	0	2	186
Miyamoto, 2015[9]	0	1	1	0	1	1	1	1	6	220
Lodewick, 2014[12]	1	1	1	0	1	0	1	0	5	171
Martin, 2013[10]	0	1	1	1	2	1	1	1	8	1473
Rickles, 2012[25]	0	1	0	0	1	1	0	0	3	219
Ballian, 2012[21]	0	1	0	0	0	0	1	0	2	113
Yamamo-to, 2012[22]	0	1	1	0	1	1	1	1	6	273
van Vledder, 2012[11]	0	1	1	0	1	0	1	0	4	196
Prado, 2008[13]	0	1	1	1	2	1	1	1	8	250

Moon, 2008[20]	0	1	0	0	0	0	1	0	2	161

Key quality criteria assessed: (1) representativeness of exposed cohort (eg. consecutive cohort with ≥90% of CT scans available for analysis, (2) selection of non-exposed cohort (eg. patients drawn from same community as exposed patients), (3) ascertainment of exposure (eg. CT-assessed body composition using single slice at L3 to determine total cross-sectional area or radiodensity and applying sex specific cut-offs), (4) demonstration that outcome of interest was not present at start of study (eg. must be prospective cohort study, no recurrent disease), (5) comparability of cohorts (eg. at minimum adjusted for sex and age, additional points if adjusted for comorbidities, disease stage), (6) assessment of outcome (eg. independent, blinded assessment with record linkage), (7) length of follow-up (eg. minimum 3 year follow up for DFS/OS), (8) adequacy of follow-up (eg. completeness, minimal loss to follow-up)

[a] Max of 2 points assigned for comparability

[b] Patients came from same study cohorts (Colorectal Cancer: Sarcopenia, Cancer, and Near-term Survival, C SCANS)

Table 3.2 Summary of studies investigating association between sarcopenia, sarcopenic obesity, myosteatosis and colorectal cancer

Author (year)	Study population	Body composition analysis method (type, level, parameter measured, timing)	Software, HU range	Sarcopenia/SO/ myosteatosis cut off points	Outcome measured	HR (95% CI)	Adjustment factors
Prado *et al.* (2008)[13]	All new diagnoses of gastrointestinal or respiratory tract cancers and classified as obese Stage I-IV N=250 (57% CRC pts)	CT L3, average of 2 consecutive slices SMA Within 30 days of BMI measurement	Slice-O-Matic SM: -29 to +150	Used optimal stratification to establish sex-specific cut offs associated with mortality in their cohort **SO:** M<52.4 cm^2/m^2; F<38.5 cm^2/m^2 with BMI>30 kg/m^2	OS (SO)	4.2 (2.4, 7.2)	Functional status, cancer type, stage
van Vledder *et al.* (2012)[11]	Resectable CRCLM N=196	CT L3 SMA Preoperative	MeVisLab v 2.2.1 (MeVis Medical Solutions) SM: -30 to +150	Used optimal stratification to establish sex-specific cut offs **Sarcopenia:** M<43.75 cm^2/m^2; F<41.1 cm^2/m^2	OS DFS	2.69 (1.67,4.32) 1.96 (1.29,2.97)	OS: Number of metastases, RFA, resection margin RFS: number of metastases,

							CEA, RFA, resection margin
Martin *et al.* (2013)[10]	GI or respiratory tract cancer referred to outpatient medical oncology N=1473 (52% CRC pts)	CT L3, average of 2 adjacent slices SMA Prior to referral	Slice-O-Matic SM: -29 to +150	Used optimal stratification to establish sex-specific cut offs associated with mortality **Sarcopenia:** SMI: M<43 cm^2/m^2 if BMI<25 kg/m^2; M<53 cm^2/m^2 if BMI>25 kg/m^2; F<41 cm^2/m^2 **Myosteatosis**: <41 HU if BMI<25 and <33 if BMI>25	OS Sarcopenia Myosteatosis	1.20 (1.04,1.37) 1.36 (1.19,1.55)	BMI, weight loss, SMI
Miyamoto *et al.* (2015)[9]	Primary resectable CRC Stage I-III N=220	CT L3, single slice SMA Preoperative	SYNPASE VINCENT SM: -30 to +150	SMI in sex specific lowest quartile **Sarcopenia**: M<49.5 cm^2/m^2; F<42.1 cm^2/m^2	OS DFS CSS	2.27 (1.15,4.49) 2.17 (1.20,3.94) 2.50 (1.00,6.24)	Sex, age at surgery, ASA tumor location, grade, tumor location, preoperative CEA
Lodewick *et al.* (2015)[1]	Partial hepatectomy for CRCLM	CT L3, average of 2 adjacent	OsiriX SM: -30 to +110	**Sarcopenia:** M<43 cm^2/m^2 for BMI<25	OS: Sarcopenia	0.90 (0.57,1.41)	Not adjusted (not included in

[2]	N=171	slices SMA Preoperative		kg/m^2 and <53 cm^2/m^2 for BMI>25 kg/m^2; F<41 cm^2/m^2 **SO**: SMI as above with body fat % M>35.7%; F>44.4% (Lodewick)	SO DFS: Sarcopenia SO	0.66 (0.39,1.14) 0.87 (0.69,1.28) 0.81 (0.52,1.25)	multivariate analysis)
Malietzis *et al*. (2016)[7]	Primary resectable CRC Stage I-IV N = 805	CT L3 single slice SMA, VFA Preoperative	Slice-O-Matic v4.3 (Tomovision) SM: -29 to 150	**Sarcopenia**: M<52.4 cm^2/m^2; F<38.5 cm^2/m^2 (Prado) **SO**: SMI cut offs + BMI>30kg/m^2 **Myosteatosis:** SMD<41 HU if BMI<25 and <33 HU if BMI<25	OS: Sarcopenia SO Myosteatosis DFS Sarcopenia SO Myosteatosis	 1.70 (1.25,2.31) 1.88 (0.92,3.26) 1.42 (1.09,2.50) 1.53 (1.06,2.39) 1.73 (0.81,3.68) 1.14 (0.67,1.93)	Only sarcopenia adjusted for ASA, surgical approach, stage, grade, LVI, adjuvant therapy
Boer *et al.* (2016)[8]	Primary resectable CRC Stage I-III N=91	CT Mid-L3, superior and inferior L4 slices (each considered individually) TPA, TAMA	TeraRecon SM: -29 to +150	**Sarcopenia:** sex-specific cut off < median (cm^2/m^2)	OS (TAMA at L3)	8.54 (1.07,68.3)	Not adjusted

		Preoperative					
Black *et al.* (2017)[6]	Primary resectable esophagus, stomach or CRC Stages I-IIII N=447 (N=339 for CRC)	CT L3, single slice Preoperative or before neoadjuvant CRT	ImageJ v 1.47 (NIH) SM: -29 to +150	**Sarcopenia:** M<43 cm^2/m^2; F<41 cm^2/m^2	OS (in CRC patients)	1.21 (0.82,1.79)	Age, sex, stage, neoadjuvant/ adjuvant therapy, LVI, neutrophil count, SFI, VFI
Caan *et al.* (2017)[3]	Primary, resectable CRC Stages I-III N=3262	CT L3, single slice SMA, VFA, VAT Within 4 mo of diagnosis	Slice-O-Matic v 5.0 (Tomovision) SM: -29 to +150	Optimal stratification to establish sex- and BMI-specific sarcopenia cut-points **Sarcopenia:** M<52.3 cm^2/m^2if normal <54.3 cm^2/m^2 if overweight; F<38.6 cm^2/m^2 if normal, <46.6 cm^2/m^2 if overweight Sex-specific tertiles for SMA + TAT for body composition	Sarcopenia: OS CSS Low muscle + high adiposity phenotype: OS CSS	1.27 (1.09,1.48) 1.46 (1.19,1.79) 1.40 (1.03,1.90) 1.79 (1.20,2.67)	Age at diagnosis, sex, race, stage, chemotherapy, radiation, site of tumor; sarcopenia adjusted for total adiposity in tertiles

				phenotypes			
Cespedes Feliciano *et al.* (2017)[4]	Primary, resectable CRC Stages I-III N=2470	CT L3, single slice Pre-chemo/RT SMA	Slice-O-Matic v 5.0 (Tomovision) SM: -29 to +150	Optimal stratification to establish sex- and BMI-specific sarcopenia cut-points **Sarcopenia:** SMI M<52 cm^2/m^2 if BMI<30 and <54 cm^2/m^2 if BMI>30; F<38 cm^2/m^2 if BMI<30 and <47 cm^2/m^2 if BMI>30	OS CSS	1.28 (1.10,1.53) 1.42 (1.13,1.78)	Race, cancer site, age at diagnosis, BMI category, sex, stage
McSorley *et al.* (2017)[5]	Primary, resectable CRC Stages I-III N=322	CT L3, single slice VFA, SFA, SMA SMD	ImageJ v 1.47 (NIH) SM: -29 to +150	**Sarcopenia:** M<52.4 cm^2/m^2; F<38.5 cm^2/m^2 and M<43 cm^2/m^2 if BMI<25 and <53 cm^2/m^2 if BMI>35; F<41 cm^2/m^2 **Myosteatosis**: SMD<41 HU if BMI<25 and <33 HU if	OS: Prado cutoffs Martin cutoffs Myosteatosis CSS: Prado cutoffs Martin	 1.26 (0.79,2.00) 1.40 (0.88,2.24) 2.29 (1.38,3.81) 0.89 (0.49,1.59) 0.90	Myosteatosis adjusted for age, sex, ASA, mGPS, NLR, stage, BMI Sarcopenia included in multivariate analysis

				BMI<25	cutoffs Myosteatosis	(0.50,1.62) 2.11 (1.14,3.92)	

TPA, total psoas area; TPV, total psoas volume; VFA, visceral fat area (cm^2); VFI: visceral fat index (cm^2/m^2); SFA, subcutaneous fat area (cm^2); SFD subcutaneous fat density; SFI: subcutaneous fat index (cm^2/m^2); TAT: total adipose tissue; TBF, total body fat; SMI, skeletal muscle index; SMA, skeletal muscle area; SM, skeletal muscle; TAMA, total abdominal muscle area; PI, psoas index; HU, Hounsfield units; HUAC, Hounsfield unit average calculation (representing total psoas density); BIA, bioelectrical impedance analysis; PNF, perinephric fat thickness; OS: overall survival; CSS: cancer specific survival; RT: radiation therapy; SMD: skeletal muscle radiodensity; mGPS: modified Glasgow Prognosis Score; NLR: neutrophil lymphocyte ratio; CRT: chemoradiation therapy; LVI: lymphovascular invasion; CRCLM: colorectal cancer liver metastases; RFA: radiofrequency ablation; CEA: carcinoembryonic antigen; ASA: American Society of Anesthesia performance status

Table 3.3: Summary of studies investigation association between visceral obesity and colorectal cancer

Author (year)	Study population	Body composition analysis method (type, level, parameter measured, timing)	Software, HU range	VO definition	Outcome measured	HR (95% CI)	Adjustment factors
Moon *et al.* (2008)	Primary resectable CRC, N=161	CT Average of umbilicus (L3-3) and iliac crest (L4-5) VAT, SAT Preoperative	Software not specified, HU not specified	**VO:** VFA/SFA >50th percentile	OS DFS	K-M curves (log-rank) P=0.24 P=0.008 Favoring non-VO pts	Not adjusted
Ballian *et al.* (2012)	Primary rectal adenocarci-noma Stage I-IV N=254	CT At umbilicus VAT, SAT Preoperative	Ziosoft®, HU range not specified	VFA/SFA treated as continuous variable **VO:** VFA/SFA $\geq$0.5	OS DFS	K-M curves (log-rank) P=0.003 P=0.17 Favoring VO pts	Not adjusted
Yamamoto *et al. (*2012)	Primary resectable CRC Duke A-C N=273	CT At umbilicus VAT, SAT Preoperative	FatScan Software HU not specified	**VO:** M$\geq$130 cm^2; F$\geq$90 cm^2	OS RFS	K-M curves (log-rank) P=0.52 P=0.54	Not adjusted
Rickles, *et al.*	Primary resectable	CT Most cranial	Aquarius 3D	**VO:** VFV>50th	OS Stage I	0.67	Major complication,

(2013)	CRC Stage I-III N=219	slice including S1 cephalad 12cm at 3cm intervals (Maurovich-Horvat) TFV, VFV, SFV Preoperative	VAT/SAT: centered at -120 HU with 140 HU width	percentile	Stage II Stage III DFS Stage I Stage II Stage III	(0.18, 2.59) 1.97 (0.78, 5.02) 0.43 (0.17, 1.07) 0.50 (0.23, 1.06) 2.72 (1.21, 6.10) 0.50 (0.23, 1.06)	intraoperative blood transfusion, laparoscopic approach, smoking history, sex, age, neoadjuvant/adjuvant therapy, tumor size
Park *et al.* (2015)	Primary resectable colon cancer Stage I-III N=186	CT Umbilicus VFA, SFA, TFA Preoperative	Fat Assessment Tool v 4.5 (Philips Healthcare) VAT: -400 to 0 Histogram method	**VO:** V/T>29%	OS	K-M curve (log rank test, p=0.057) Favoring VO pts	Not adjusted
Lee *et al.* (2015)	Resected CRC requiring adjuvant chemother-apy with no evidence of distant metastases Stage II-III	CT L3-4 intervertebral space VFA, SFA Preoperative	Leonardo Workstation VAT: -150 to -50	**VO:** VFA>130 cm^2 Alternate VO: VFA/SFA >0.4 (Clark)	OS DFS	7.0 (2.0, 24.6) 4.2 (1.6, 11.0)	T stage, N stage

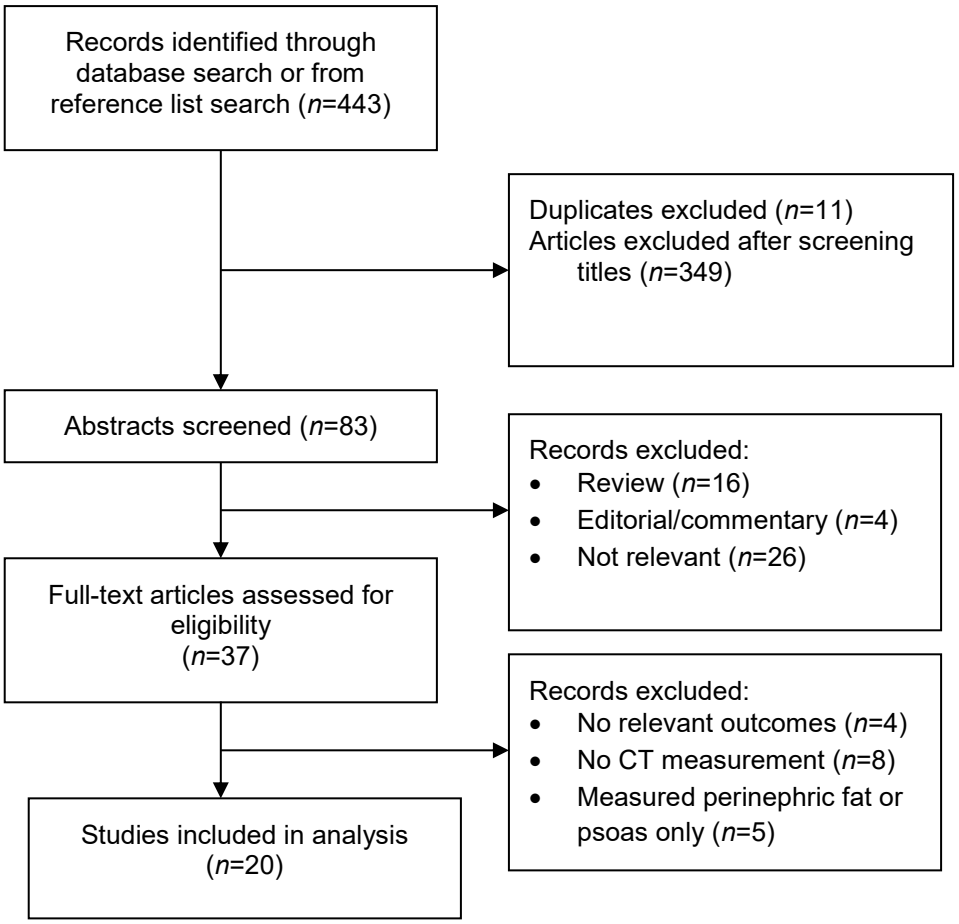
	N=62						
Choe *et al.* (2016)	Primary resectable CRC Stage I-III N=630	CT Umbilicus, single slice VFA, SFA Preoperative	Rapidia 2.8 (INFINITT) VAT/SAT: -250 to -50	**VO:** VFA>median value	OS DFS MFS	1.13 (0.65, 1.98) 1.23 (0.77, 1.95) 1.26 (0.76, 2.11)	Sex, age, stage, grade, venous invasion, preoperative SAT, VAT change, SAT change, preoperative BMI, adjuvant chemotherapy
Malietzis *et al.* (2016)	Primary resectable CRC Stage I-IV N = 805	CT L3 single slice SMA, VFA Preoperative	Slice-O-Matic v4.3, SM: -29 to 150 VAT: -150 to -50 SAT: -190 to -30	**VO:** M>163.8 cm^2; F>80.1 cm^2 (Doyle)	OS DFS	0.80 (0.57, 1.07) 0.68 (0.44, 1.05)	Not adjusted
Cespedes Feliciano *et al.* (2016)	Primary resectable early stage CRC Stage I-III N=2,446	CT L3, single slice VAT Perioperative	Slice-o-Matic VAT: -190 to -30	Used VAT in highest sex specific quartile **VO:** M>280 cm^2; F>164	OS: Obese Obese + metsyn DSS Obese	 1.09 (0.83, 1.44) 1.45 (1.12, 1.82) 1.20 (0.83, 1.73)	Race, age, smoking history, stage, grade, CRT, cancer site, sex-specific tertile of muscle mass

				cm^2	Obese + metsyn	1.49 (1.09, 2.02)	
Jeong *et al.* (2016)	Primary resectable CRC in non-cachectic patients (Jeong) N= 258 Comparison cachectic group N=88	CT At umbilicus, single slice VAT, SAT Preoperative	Rapidia, INFINITT HU not specified	**VO:** treated VFV as a continuous variable	VFV significan-tly correlated with cancer size, T stage, CEA	No difference in DFS, OR	-
Black *et al.* (2017)	Primary resectable esophagus, stomach or CRC Stages I-IIII N=447 (N=339 for CRC)	CT L3, single slice Preoperative or before neoadjuvant CRT	ImageJ v 1.47 (NIH) VAT: -190 to -30	**VO:** highest sex-specific tertile of VFI	OS (CRC patients)	1.00 (0.80, 1.26)	Age, sex, stage, neoadjuvant/a-djuvant therapy, LVI, neutrophil count, SFI, SMI
Caan *et al.* (2017)	Primary resectable CRC Stage I-III N=3,262	CT L3, single slice SMA, VFA, VAT Within 4 mo of diagnosis	Slice-O-matic v 5.0 (Tomovisio n) VAT: -190 to -30	Highest sex-specific tertile of TAT **VO:** M>463cm^2;	OS CSS For low muscle + high adiposity	1.21 (1.01, 1.46) 1.28 (1.00, 1.64) 1.40 (1.03, 1.90) 1.79	Age at diagnosis, sex, race, stage, chemotherapy, radiation, cancer site

				F>423cm^2 Body compositi on phenotype s (high fat, low muscle)	phenotype	(1.20, 2.67)	
McSor-ley *et al.* (2017)	Primary, resectable CRC Stages I-III N=322	CT L3, single slice VFA, SFA, SMA SMD	ImageJ v 1.47 (NIH) VAT: -190 to -30	**VO:** M>160cm ^{2}; F>80cm^2	OS CSS	0.76 (0.49, 1.17) 0.90 (0.51, 1.60)	Not adjusted VO not included in multivariate model

TAT, total adipose tissue; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; VFA, visceral fat area (cm^2); VSR. VFA/SFA ratio; SFA, subcutaneous fat area (cm^2); SFD subcutaneous fat density; TBF, total body fat; SMI, skeletal muscle index (cm^2/m^2); SMA, skeletal muscle area; SM, skeletal muscle; TAMA, total abdominal muscle area (cm^2); HU, Hounsfield units; MetSyn, metabolic syndrome; VFI: visceral fat index (cm^2/m^2); SFI: subcutaneous fat index (cm^2/m^2); LVI: lymphovascular invasion; MFS: metastasis free survival; metsyn: metabolic syndrome/dysregulation; V/T: visceral to total fat ratio

Figure 3.1: Flow diagram to illustrate study inclusion or exclusion in this systematic review.



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CHAPTER 4: THE IMPACT OF MUSCLE AND ADIPOSE TISSUE ON LONG-TERM SURVIVAL IN STAGE I-III COLORECTAL PATIENTS

Hopkins JJ, Reif R, Bigam DL, Baracos VE, Eurich DT, Sawyer MB. The impact of muscle and adipose tissue on long-term survival in stage I-III colorectal cancer patients. *Dis Colon Rectum.* 2018 (Accepted March 25, 2018; publication pending)

4.1 Introduction

There is mounting evidence that body composition parameters, specifically skeletal muscle mass and radiodensity (SMR) and visceral adipose tissue (VAT) provide prognostic implications for patients with colorectal cancer (CRC).[30,44,46,94] These patient-specific factors could help to risk stratify patients, which may predict those patients requiring more aggressive adjuvant treatment or prolonged disease surveillance. Several studies have looked at CRC survival outcomes and have shown that reduced skeletal muscle mass, or sarcopenia, reduced skeletal muscle radiodensity (SMR), or myosteatosis, and elevated VAT, or visceral obesity (VO), result in worse overall (OS) and recurrence-free survival (RFS).[30,42-44,46] This is of interest, as staging computed tomography (CT) scans are done routinely, and offer an opportunistic way to accurately measure body composition without exposing to patient to excess radiation.[18] Myosteatosis is defined by a reduced SMR, which is a measure of fatty infiltration into the skeletal muscle. While sarcopenia, myosteatosis and visceral obesity may be important independently, joint effects of these parameters may confer the worst survival risk in patients with stage I-III CRC, being treated with curative intent.[30] Overlapping effects of these parameters may identify body composition phenotypes with increased risks of death or disease recurrence. Therefore, the aim of this study was to determine relationships between CT-derived body composition parameters and their effects on long-term survival outcomes in a cohort of patients with stage I-III, resectable CRC. We also

aimed to identify body composition phenotypes based on these parameters, which identified those patients at highest risk of reduced survival.

4.2 Materials & Methods

4.2.1 Cohort and endpoints

This retrospective cohort study included all patients identified from the Alberta Cancer Board (ACB) Registry with stage I-III CRC who underwent surgical resection with curative intent from January 2007 – December 2009 and were seen in a comprehensive cancer clinic (*n*=1,418). Patients were excluded if they were duplicated in the database (n=72), did not have a preoperative CT scan (*n*=356) or if they had recurrent disease (*n*=22). The final sample size was 968 patients. Excluded patients were significantly older, and more likely to be stage I disease.

Primary endpoints included recurrence, recurrence-free survival, overall survival (RFS, and OS) and CRC-specific survival (CSS). Recurrence was defined as pathological or radiological evidence of recurrence of disease whichever came first. Date of death, last date of contact, cause of death, tumor site and American Joint Committee on Cancer (AJCC, 6^{th} edition) stage were obtained from the ACB registry. Anthropometric data (height and weight closest to time of CT), tumor characteristics, surgical procedure, treatment and comorbidities were obtained from the institutional electronic medical record (EMR). Any patients that developed distant disease within 3 months of diagnostic/staging CT were considered stage IV disease. This study was approved by the Health Research Ethics Board of Alberta (HREBA) Cancer Committee at the University of Alberta.

4.2.2 Body composition

Muscle and adipose tissue were quantified from diagnostic or staging CT scans taken at time of diagnosis and prior to any radiation treatment, chemotherapy or surgical intervention. Two trained and blinded individuals (JH, RR) identified a single CT slice at the L3 level, which was subsequently segmented in Matlab for total cross-sectional muscle and adipose tissue analysis.[103] Each scan was manually corrected by two individuals (JH, RR), trained to accurately identify and quantify visceral and subcutaneous fat, as well as the following muscles at the 3rd lumbar vertebrae: rectus abdominus, external/internal obliques, transversus abdominus, psoas, and paraspinal (quadratus lumborum, erector spinae). Calculated coefficients interobserver of variation for SMA, SMR and VAT were 1.2, 1.1 and 1.3%, respectively. Hounsfield unit (HU) ranges were -29 to +150 for muscle, -190 to -30 for subcutaneous adipose tissue and -150 to -50 for visceral adipose tissue. Total cross-sectional skeletal muscle area (SMA) and total adipose tissue (TAT) area was measured in cm^2 and both was normalized by height (m^2) and reported as lumbar skeletal muscle index (SMI, cm^2/m^2) and total adipose tissue index (TATI, cm^2/m^2). Mean SMR in HU was reported for total cross-sectional muscle area.

4.2.3 Definition of sarcopenia, myosteatosis, visceral obesity

Sarcopenia and reduced skeletal muscle radiodensity (SMR) have been previously defined in a similar population using optimal stratification to identify BMI-specific cut-offs related to OS.[21] These cut-off values (Sarcopenia in females SMI <41 cm^2/m^2;

Sarcopenia in males SMI <43 cm^2/m^2 if BMI <25 kg/m^2 or SMI <53 cm^2/m^2 if BMI ≥25 kg/m^2; Myosteatosis in males/females <41 HU if BMI <25 kg/m^2; <33 HU if BMI ≥25 kg/m^2) were also applied to our population. VO, as quantified in a cohort of patients undergoing surgical resection for a gastrointestinal malignancy with associated metabolic syndrome, was defined as VAT cross-sectional area >160 cm^2 or >80 cm^2 in males and females, respectively.[91] These cut-offs were used for descriptive and comparative purposes. We also defined sarcopenia, myosteatosis, VO and elevated total adiposity specifically to our population through an optimal stratification analysis. Optimal stratification is a previously described method used to identify population-specific cut-off points in continuous data.[21,104] We determined cut-off points from sex-specific ranges of SMI, MA, VAT and TATI in our own population, which was associated with OS. Optimal stratification is based on log-rank statistics to test for a threshold value of a continuous variable with respect to a time to event outcome. OS was used based on previous research and it was our primary endpoint.[104,105] This is a common statistical test used to identify cut off points for low muscle mass and increased VAT.[21,30,42] These cut-off points were used in our statistical modeling.

We use the term body phenotypes to describe sub populations affected by different combinations of sarcopenia, myosteatosis and obesity i.e. sarcopenia alone (1), myosteatosis alone (2) or sarcopenia and myosteatosis together (3). Cut-offs for VO and total adiposity were also applied to this phenotype. Our population specific cutoff points from an optimal stratification analysis were used to define all parameters (sarcopenia, myosteatosis, VO, elevated total adiposity). These varying body composition phenotypes were considered in a multivariate analysis for the joint effect on survival. This body

composition phenotype was considered in the same statistical models, but replaced sarcopenia and myosteatosis as independent variables.

4.2.4 Statistical analysis

Differences between groups were tested using Student's t-test, chi^2 test or Fisher's exact test. Patient follow-up began at the date of surgery and continued until their death, loss to follow-up or September 1, 2017. RFS was defined as time from surgery until time of recurrence, or time to end of study or loss to follow up. CSS and OS were defined as time from surgery to time of CRC-specific death or death from any cause, respectively, or until loss to follow up or end of study. All statistical modeling was done with purposeful selection, and inclusion of biologically important covariates.

Kaplan-Meier (K-M) curves were used to establish effects of variables on survival outcomes. Log rank tests were used to compare difference in survival curves. Univariate and multivariate survival analyses were conducted using Cox proportional hazards model. Hazard ratios (HR) and 95% confidence intervals (CIs) were obtained. Schoenfeld residuals demonstrated no evidence that the proportional hazards assumption was violated. We created 2 separate multivariate models using the skeletal muscle phenotype. One model considered only skeletal muscle attributes. The second model adjusted for total fat (TATI).

In multivariate analysis, the cohort was adjusted for covariates established *a priori*, including sex, age at diagnosis, disease stage, comorbities (Charlson Comorbidity Index, CCI) and high-risk tumor characteristics (lymphovascular/perineural invasion, obstruction/perforation). Further covariates considered during rational model building

included neoadjuvant and adjuvant treatment (chemotherapy, radiotherapy) and body mass index (BMI, kg/m^2). Patients were considered to have received neo/adjuvant treatment if they completed >50% of the intended protocol. Tumor and patient's genetics were not included in the analysis due to insufficient data available. A secondary analysis of the cohort stratified by tumor location (colon versus rectum) was also considered, with the same model building.

Statistical analyses were performed using Stata 15.0 software (College Station, TX:StataCorp LLC). Statistical significance was established with two-sided tests at $p<0.05$. Optimal stratification analysis was performed using SAS software (version 9.3; SAS Institute Inc., Carey, NC).

4.3 Results

4.3.1 Baseline characteristics

There were a total of 968 patients included in our cohort. We excluded 356 of 1,418 potential patients (25%), as they did not have a preoperative CT scan. Excluded patients tended to be older and have less advanced (stage I) disease. They also had a lower rate of recurrence (11.6 vs. 26.2%) and a similar rate of death (37.6 vs. 36.3%). Table 4.1 describes baseline characteristics. At time of censoring, there were 254 disease recurrences and 350 deaths during follow-up, with no post-operative deaths recorded (30 day mortality). The median length of follow-up was 5.2 years (range 0.01-10.25). The median length of time from CT to surgery was 21 days. Most patients had stage III disease, and just over half of patients received adjuvant treatment. Men had more rectal cancers and had more comorbidities. Men also had significantly higher SMA, SMI and

SMR. On average 10% of the cohort presented emergently with obstruction or perforation at time of diagnosis. The mean BMI for this cohort was 27.7 kg/m^2, which did not differ by gender (Table 4.1). Preoperative weight loss was unknown.

Table 4.2 is a summary of cut-off points found specific to our population, using optimal stratification. They are slightly lower than previously published cut-off points in the literature.[20,21] A visual representation of the overlap of sarcopenia, myosteatosis and VO is shown (Figure 4.1). A cut-off for TATI was also included in this analysis (Table 4.2). There was no difference in disease stage in patients that were sarcopenic or myosteatotic (p=0.716, p=0.850, respectively). Independently, patients who were either sarcopenic or myosteatotic were significantly older (p<0.001) with more comorbidities (p<0.001) and were less likely to receive adjuvant treatment (OR=0.67, p=0.006; OR=0.54, p<0.001, respectively).

4.3.2 Association of single body composition parameters with overall survival

Kaplan-Meier curves demonstrated significantly worse OS for patients with sarcopenia and myosteatosis (log-rank, p<0.001) (Figure 4.2). OS was not reduced in patients with VO or elevated total adiposity (TATI). In univariate analysis (Table 4.3), sarcopenia and myosteatosis predicted an increased risk of death. Clinically and statistically significant variables were included in a multivariate analysis (Table 4.3). In an adjusted model, both sarcopenia and myosteatosis remained associated with worse OS (adjusted HR (aHR) 1.45, 95% confidence intervals (CI) 1.15, 1.84; aHR 1.54, 95% CI 1.19, 1.98, respectively). OS was not associated with VO or BMI, but elevated total adiposity was associated with a protective effect (aHR 0.76, 95% CI 0.60, 0.96).

4.3.3 Association of single body composition parameters with cancer specific survival

Of 350 deaths, 223 (63.7%) died secondary to their CRC. Those patients with myosteatosis or sarcopenia both had significantly more deaths from CRC and non-cancer causes ($p<0.001$) than those without myosteatosis or sarcopenia. Kaplan-Meier curves demonstrated reduced CSS in patients with either sarcopenia (log-rank, $p<0.001$, Figure 4.3) or myosteatosis (log-rank, $p<0.001$, Figure 4.3). In univariate analysis both sarcopenia (HR 1.76, 95%CI 1.34, 2.31) and myosteatosis (HR 1.65, 95%CI 1.25, 2.17) were identified as significant predictors of CSS (Table 4.3). In multivariate analysis, sarcopenia and myosteatosis remained a significant predictor of worse CSS (aHR 1.39, 95%CI 1.04, 1.86; aHR 1.42, 95%CI 1.04, 1.93). In both univariate and multivariate analysis, measures of adiposity (VO, TATI, BMI) did not result in significantly worse CSS.

4.3.4 Association of single body composition parameters with recurrence free survival

Of 254 patients who developed disease recurrence, 186 subsequently died, of which 174 (68.5%) were secondary to CRC. The median time to recurrence was 14.2 (IQR=9.5-36.8) months. Kaplan-Meier curves demonstrated worse RFS in patients with sarcopenia (log-rank, $p=0.023$, Figure 4.4). As seen in Table 4.3, in univariate and multivariate analysis, only presence of sarcopenia resulted in a significantly worse RFS (HR 1.36, 95%CI 1.05, 1.78; HR 1.35, 95%CI 1.02, 1.79, respectively).

4.3.5 Myosteatosis/Sarcopenia composite phenotype association with outcomes

We identified 72 patients with sarcopenia alone, 343 patients with myosteatosis alone and 194 patients with both sarcopenia and myosteatosis. When this phenotype was included in our multivariate Cox proportional hazards model, patients with both sarcopenia and myosteatosis were associated with worse OS (aHR 2.24, 95%CI 1.63, 3.09), RFS (1.57, 95%CI 1.09, 2.28) and CSS (1.96, 95%CI 1.32, 2.90). Myosteatosis alone predicted significantly worse OS and CSS, whereas sarcopenia alone only predicted significantly worse OS (Table 4.4). As survival outcomes were not significantly associated with the presence of VO in our original models (Table 4.3), we adjusted our body composition phenotype model by total adiposity, using TATI cutoffs from an optimal stratification analysis (Table 4.2). High levels of total adiposity significantly added to our OS model, and were protective against overall mortality (aHR=0.76, 95%CI 0.60, 0.96). Similarly to VO, adjusting for TATI in patients with sarcopenia and myosteatosis did not alter their risk of recurrence or cancer-specific mortality (Table 4.4). In our composite phenotype analysis, adjustment, AJCC sub-stages were considered. When included in the multivariate analysis, CRC sub-stage did not change HRs for our composite phenotype.

4.3.6 Myosteatosis/Sarcopenia composite phenotype association with outcomes, stratified by tumor location

In a stratified analysis of survival outcomes, effects of the composite phenotype on rectal cancer patients was predictive of poor survival outcomes (Table 4.5). Patients with concurrent sarcopenia and myosteatosis had significantly OS (aHR 2.76, 95%CI 1.65, 4.62) and CSS (2.42, 95%CI 1.32, 4.49). Patients with colon cancer and both

features also had significantly worse OS (aHR 1.94, 95%CI 1.29, 2.94). The body composite phenotype trended towards worse RFS, but was not significant, regardless of tumor location. Of note, elevated total adiposity in colon cancer patients was predictive of significantly improved OS (aHR 0.74, 95%CI 0.54, 0.99).

4.4 Discussion and Conclusions

This study reinforces the importance of skeletal muscle mass and radiodensity in long-term survival outcomes for CRC patients treated with curative intent. In our cohort, those patients with sarcopenia were found to have poorer OS, RFS and CSS, even after adjusting for clinically and pathologically important covariates. Conversely, BMI was not a significant factor in any models or in univariate analysis. This is an important result as BMI was an unreliable predictor of body composition, as compared to CT-derived muscle measurements, in the current era where obesity is highly prevalent. While our findings are consistent with previously published work, which has demonstrated that sarcopenia is associated with reduced OS, CSS and RFS, we have introduced the idea of a composite phenotype that highlights overlapping effects of sarcopenia and myosteatosis.[30,42,44,46,47,106] Furthermore, the difference found between our cohort's and pre-existing sarcopenia and myosteatosis cutoffs emphasizes the risk of using a universal threshold. The cutoffs defined will be influenced by the cohort being characterized, including patient ethnicity and disease process, as well as the outcomes being studied. While there is data within the literature that suggests that sarcopenia is not associated with survival outcomes, these studies relied on cut-off points from different patient populations than their own.[43] McSorley *et al.*, used SMI cut-offs defined by Martin *et al.*,

in a population of respiratory and gastrointestinal cancer patients.[43] These cut-offs may not be specific enough to the population defined by McSorley, and therefore unable to predict worse survival outcomes. These cut-offs were also unable to predict poor prognosis in our patient cohort. Our sarcopenia cutoffs were lower for females and males with a BMI$\geq$25 kg/m^2, as compared to Martin *et al*.[21] This difference is likely due to the fact that our patient cohort was solely CRC patients with resectable disease rather than a heterogeneous cohort, of which 50% had stage IV disease. Despite the lack of a widely accepted cutoff, sarcopenia can be further supported as a validated prognostic factor as it is predictive of poor survival outcomes in several different tumor types,[13,16,107,108] and has been associated with mortality in a large meta-analysis.[14] In this study, cutoffs for SMI and SMR were obtained for sarcopenia and myosteatosis, respectively. SMI and SMR were not considered as continuous variables in the analysis as we aimed to give clinicians a defined cutoff point below which risk of mortality increased significantly, rather than an arbitrary decrease in these variables. This is especially true as there are many publications in the literature which have previously demonstrated that loss of muscle mass is detrimental to survival outcomes.

Myosteatosis has not been as well characterized as sarcopenia in the literature. In this study, there was an association of myosteatosis with OS, but not RFS or CSS. Prevalence of myosteatosis did not differ by or correlate to tumor stage (correlation coefficient 0.0075), but was related to increasing age, worse overall health and a significantly reduced likelihood of receiving adjuvant chemotherapy. More deaths occurred in patients with myosteatosis, which suggests that it may be a marker of reduced capacity to withstand stresses of disease. While sarcopenia and myosteatosis often occur

together, they are not mutually inclusive and additive effects of both parameters on muscle may be predictive of significantly worse outcomes.[21] It has been demonstrated that effects of myosteatosis on survival may outweigh effects of sarcopenia.[21,43] This was not reflected in our study, and may have been a result of differing patient cohorts and subsequent cutoff points used to define a threshold for myosteatosis. Martin *et al*, included all respiratory and gastrointestinal tract tumors in their analysis. The effect of myosteatosis may have been magnified by the inclusion of tumor types with a well-known cachectic effect, such as pancreatic or lung cancer. Despite this, myosteatosis was a significant factor in our OS and CSS model and should therefore be included in CT-derived body composition analysis.

We found that VO alone was not predictive of any survival outcomes. While VAT is known to be metabolically active and to contribute to insulin resistance and increased systemic inflammation,[109,110] the underlying role of muscle mass may play a more important role in survival, thereby outweighing effects of VO in our population. We also considered the role of high total adiposity (TATI) in our population. Patients who had high levels of TAT experienced a protective effect for OS, but not RFS or CSS. This differs from previously published studies. For example, in a large cohort of patients with early-stage CRC, those with elevated adiposity were found to at increased risk of death, especially if they had concurrent sarcopenia.[30] The majority of other studies looking at associations of VO and survival in CRC were published in Asian populations,[48,49,84,86,87] or were restricted to specific disease stages[49,88] or tumor location,[85] and did not concurrently assess muscle mass or quality. Furthermore, as suggested by Caan *et al.*, survival benefit associated with high fat mass or BMI may be an effect of lower

prevalence of sarcopenia in those patients with elevated BMI, rather than a protective effect of increased weight or adipose tissue.[30] The significant overlap of VO and myosteatosis may limit the ability of VAT to further predict survival outcomes. In the current literature, VAT is not normalized by height, in contrast to skeletal muscle. Our data was analyzed by visceral obesity using VAT and VATI, with no difference in outcomes found. We also analyzed our total adiposity using TATI. The lack of normalization of VAT in the literature may be secondary to convention. Alternatively, VAT may be less affected by body height than SMA. This is an area of potential future investigation.

In the sub-analysis, stratifying patients by tumor location demonstrated a magnified effect of the body composite phenotype in patients with rectal cancer. Rectal cancer patients with sarcopenia and myosteatosis had significantly worse OS and CSS. Stratification of tumor location suggests that survival in rectal patients may have been confounding results, despite tumor location being adjusted for in the original analysis. A diagnosis of rectal cancer will often require a patient to undergo neo- and adjuvant treatment. Surgical resection of rectal cancers also have a higher risk of complication and at the time of this cohort were more likely to have been open rather than laparoscopic. All of these factors combined may have influenced the effect of sarcopenia and myosteatosis on survival outcomes in rectal cancer patients.

There are limitations to our study. It is a retrospective cohort study, and was therefore dependent on data that was present within patient charts and raises the possibility of unknown confounders. Furthermore, any patient not seen in a cancer clinic was not included in the study, which in combination with lack of preoperative CT scan

excluded approximately 30% of our cohort. As previously stated, excluded patients tended to be older and have more stage I disease. Had those patients been included, the effects of sarcopenia and myosteatosis may have been magnified, as muscle and frailty is known to increase with age. We did not have sufficient data on genetic markers, including microsatellite instability and BRAF mutations, to include this in our analysis. Knowledge of these genetic mutations would have allowed for further risk stratification, and strengthened our conclusions. However, we were still able to include a large population, and our results are similar to those found in other patient cohorts.[21,30,46]

Confirmation of sarcopenia as a prognostic factor for survival in CRC will allow for patients and clinicians to better understand disease trajectory. The ability to identify sarcopenia and myosteatosis preoperatively will also benefit those patients who require neoadjuvant or adjuvant chemotherapy. As cancer patients maintain an anabolic potential, preoperative identification of reduced muscle mass or density represents a secondary treatment target prior to definitive surgery. Patients with colon cancer and sarcopenia are more likely to have dose-limiting toxicities and be unable to complete their chemotherapy regimens.[27,32,66,74] Once identified by CT, the potential window to improve muscle mass and quality, and thereby survival, begins. There is evidence that patients with sarcopenia still maintain anabolic potential and the ability to reduce muscle loss or potentially even have muscle gains during treatment.[111,112] Therefore, an intervention at time of diagnosis, which could potentially include anti-inflammatories, omega-3 fatty acids and physical activity, would allow for clinicians to improve patients' long term survival outcomes. Furthermore, lean soft tissue mass, as determined through CT body composition analysis, may replace standard body surface area dosing for chemotherapy.[18,19,29] Body

composition quantified on staging CT scan would therefore represent a targetable prognostic factor as well as a more accurate way of dosing patients requiring neo/adjuvant chemotherapy. This study emphasizes the need for both surgeons and medical oncologists to be aware of differing body composition parameters and how they predict long-term patient outcomes.

Table 4.1: Patient Clinical Characteristics, by Sex

Characteristic	Total (n=968)	Men (n=589)	Women (n=379)	*P*
	No. (%)	No. (%)	No. (%)	
Age (yr)				
Mean	65.8	65.5	66.4	0.232
SD	11.8	11.6	12.0	
AJCC stage				
I	100 (10.3)	67 (11.4)	33 (8.7)	0.124
II	374 (38.6)	236 (40.1)	138 (36.4)	
III	494 (51.0)	286 (48.6)	208 (54.9)	
T stage				
1	40 (4.1)	24 (4.1)	16 (4.2)	
2	114 (11.8)	69 (11.7)	45 (11.9)	0.462
3	645 (66.6)	402 (68.3)	243 (64.1)	
4	169 (17.5)	94 (15.9)	75 (19.8)	
Primary site				
Colon	587 (60.6)	324 (55.0)	263 (69.4)	***<0.001***
Rectum	381 (39.4)	265 (45.0)	116 (30.6)	
Tumor grade				
Well-moderately differentiated	838 (86.6)	526 (89.3)	312 (82.3)	***0.002***
Poorly differentiated	126 (13.0)	60 (10.2)	66 (17.4)	
Unknown	4 (0.4)	3 (0.5)	1 (0.3)	
Perineural/lymphovascular invasion				
Present	203 (21.0)	118 (20.0)	85 (22.4)	0.420
Absent	764 (78.9)	470 (79.8)	294 (77.6)	
Unknown	1 (0.1)	1 (0.2)	-	

Adjuvant treatment				
Yes	503 (52.0)	306 (52.0)	197 (52.0)	0.895
No	465 (48.0)	283 (48.0)	182 (48.0)	
Charlson comorbidity index				
0	582 (60.1)	330 (56.0)	253 (66.8)	***0.002***
1-2	321 (33.2)	212 (36.0)	108 (28.5)	
≥3	65 (6.7)	47 (8.0)	18 (4.7)	
L3 total skeletal muscle area (cm^2)				
Mean	133.6	154.0	101.8	***<0.001***
SD	35.3	28.3	16.7	
Skeletal muscle index (cm^2/m^2)				
Mean	46.9	51.3	40.3	***<0.001***
SD	9.9	9.0	7.0	
Skeletal muscle radiodensity (HU)				
Mean	32.5	33.2	31.5	***0.005***
SD	9.3	9.4	9.0	
Total visceral fat area (cm^2)				
Mean	171.5	208.7	113.9	***<0.001***
SD	111.9	113.9	79.8	
Sarcopenia [a]				
Yes	266 (27.5)	170 (28.9)	96 (25.3)	0.239
No	702 (72.5)	419 (71.1)	283 (74.7)	
Sarcopenia (Martin cutoffs)				
Yes	488 (50.5)	262 (44.5)	226 (59.6)	***<0.001***
No	478 (49.5)	327 (55.5)	153 (40.4)	

Myosteatosis [a]				
Yes	537 (55.5)	304 (51.6)	233 (61.5)	***0.003***
No	431 (44.5)	285 (48.4)	146 (38.5)	
Myosteatosis (Martin cutoffs)				
Yes	590 (61.1)	334 (56.7)	256 (67.5)	***0.001***
No	376 (38.9)	255 (43.3)	123 (32.5)	
Visceral obesity [a]				
Yes	494 (51.0)	352 (59.8)	142 (37.5)	***<0.001***
No	474 (49.0)	237 (40.2)	237 (62.5)	
Visceral obesity (Doyle cutoffs)	594 (61.4)	377 (64.0)	217 (57.3)	***0.031***
Yes	374 (38.6)	212 (36.0)	162 (42.7)	
No				

[a] Cohort specific cutoffs from optimal stratification; Sarcopenia and myosteatosis stratified by sex and BMI (</≥25kg/m^2), VO stratified by sex

Table 4.2: Cohort specific threshold values significantly associated with low survival

BMI category (kg/m^2)	SMI (cm^2/m^2)		SMR (HU)		VAT (cm^2)		TATI (cm^2/m^2)	
	Males	Females	Males	Females	Males	Females	Males	Females
< 25	45.7	31.6	38.2	35.7	171.4	128.2	>98.3	>103.6
≥ 25	47.1	38.5	31.9	33.6				

Table 4.3: Body composition and survival

Variable	Overall Survival				Recurrence Free Survival				Cancer Specific Survival			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
BMI	0.77 (0.62, 0.96)	***0.021***	[a]	-	1.11 (0.85, 1.45)	0.440	[a]	-	0.94 (0.71, 1.24)	0.6523	[a]	-
Sarcopenia	2.01 (1.67, 2.50)	***<0.001***	1.45 (1.15, 1.84)	***0.002***	1.36 (1.04, 1.78)	***0.027***	1.35 (1.02, 1.79)	***0.039***	1.76 (1.34, 2.31)	***<0.001***	1.39 (1.04, 1.86)	***0.028***
Myosteatosis	2.03 (1.61, 2.54)	***<0.001***	1.54 (1.19, 1.98)	***0.001***	1.11 (0.87, 1.43)	0.404	[a]	-	1.65 (1.25, 2.17)	***<0.001***	1.42 (1.04, 1.93)	***0.026***
Visceral obesity	0.98 (0.80, 1.21)	0.862	[a]	-	1.07 (0.84, 1.38)	0.578	[a]	-	0.98 (0.75, 1.27)	0.879	[a]	-
Total adiposity [b]	0.91 (0.73, 1.14)	0.422	0.76 (0.60, 0.96)	***0.020***	1.01 (0.77, 1.32)	0.949	[a]	-	0.95 (0.71, 1.25)	0.694	[a]	-

All models adjusted for age at diagnosis, sex, Charlson Comorbidity Index, disease stage, tumor sidedness (right, left, rectum) perineural/lymphovascular invasion, obstructed or perforated at presentation and adjuvant treatment

[a] Not significant in multivariate model

[b] Defined by total adipose tissue index cutoff from optimal stratification analysis

Table 4.4: Survival based on differing body composition phenotypes

Variable	Overall Survival				Recurrence Free Survival				Cancer Specific Survival			
	Univariate		Multivariate [a]		Univariate		Multivariate [a]		Univariate		Multivariate [a]	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Body composition phenotype model 1 [ac]												
1	1.96 (1.27, 3.04)	***0.002***	1.77 (1.13, 2.77)	***0.012***	1.48 (0.93, 2.34)	0.097	1.46 (0.92, 2.32)	0.112	1.73 (1.02, 2.94)	***0.041***	1.52 (0.89, 2.60)	0.127
2	1.88 (1.42, 2.49)	***<0.001***	1.55 (1.15, 2.09)	***0.004***	1.09 (0.81, 1.47)	0.573	1.23 (0.89, 1.70)	0.204	1.55 (1.11, 2.16)	***0.010***	1.43 (1.00, 2.04)	0.051
3	3.20 (2.40, 4.27)	***<0.001***	2.24 (1.63, 3.09)	***<0.001***	1.40 (0.99, 1.96)	0.052	1.57 (1.09, 2.28)	***0.017***	2.40 (1.69, 3.42)	***<0.001***	1.96 (1.32, 2.90)	***0.001***
Body composition phenotype model 2 [bc]											1.49 (0.87, 2.56)	0.144
1	1.96 (1.27, 3.04)	***0.002***	1.70 (1.09, 2.66)	***0.019***	1.48 (0.93, 2.34)	0.097	1.47 (0.92, 2.34)	0.108	1.73 (1.02, 2.94)	***0.041***	1.46 (1.02, 2.10)	***0.038***
2	1.88 (1.42, 2.49)	***<0.001***	1.63 (1.21, 2.21)	***0.001***	1.09 (0.81, 1.47)	0.573	1.22 (0.88, 1.69)	0.225	1.55 (1.11, 2.16)	***0.010***	1.97 (1.33, 2.92)	***0.001***

3	3.20 (2.40, 4.27)	***<0.001***	2.26 (1.64, 3.11)	***<0.001***	1.40 (0.99, 1.96)	0.052	1.57 (1.09, 2.28)	***0.017***	2.40 (1.69, 3.42)	***<0.001***	0.87 (0.65, 1.17)	0.355
Obese [d]	0.91 (0.73, 1.14)	0.422	0.76 (0.60, 0.96)	***0.020***	1.01 (0.77, 1.32)	0.949	1.05 (0.79, 1.38)	0.740	0.95 (0.71, 1.25)	0.694		

[a] All models adjusted for age at diagnosis, sex, comorbidities, disease stage, tumor sidedness (right, left, rectum), adjuvant treatment, obstruction/perforation at time of diagnosis and perineural/lymphovascular invasion

[a] Did not consider visceral or total adiposity.

[b] Also adjusted for elevated total adiposity (TATI)

[c] 1=sarcopenia, 2=myosteatosis, 3 = sarcopenia & myosteatosis; reference = no sarcopenia or myosteatosis

[d] TATI cutoffs: M>98.3 cm^2/m^2; F>103.6 cm^2/m^2

Table 4.5: Multivariate survival analysis based on differing body composition phenotypes, stratified by tumor location

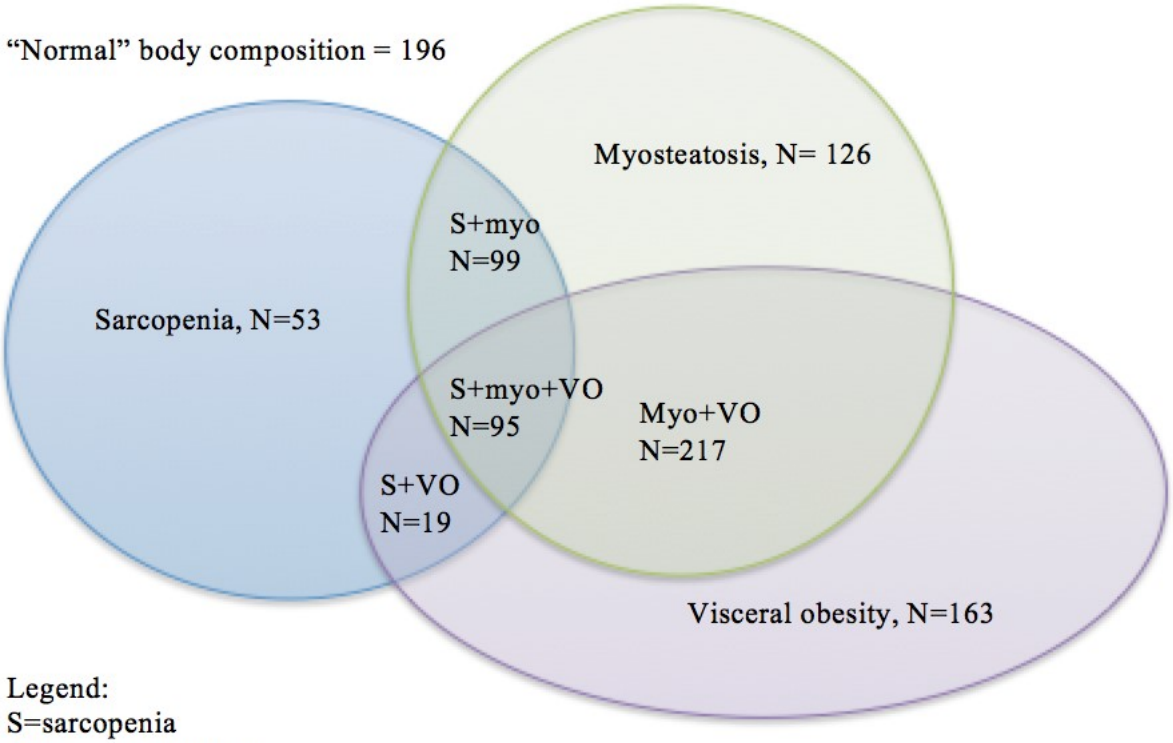
Variable	Overall Survival [a]				Recurrence Free Survival [a]				Cancer Specific Survival [a]			
	Colon		Rectum		Colon		Rectum		Colon		Rectum	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Body composition phenotype model 1 [ab]												
1	1.49 (0.83, 2.68)	0.180	2.01 (1.00, 4.02)	***0.049***	1.66 (0.92, 3.02)	0.095	1.01 (0.45, 2.25)	0.978	1.45 (0.73, 2.87)	0.283	1.38 (0.56, 3.38)	0.485
2	1.41 (0.95, 2.08)	0.084	2.06 (1.29, 3.29)	***0.003***	1.08 (0.69, 1.68)	0.742	1.30 (0.81, 2.10)	0.278	1.07 (0.66, 1.73)	0.783	2.09 (1.21, 3.59)	***0.008***
3	1.94 (1.29, 2.94)	***0.001***	2.76 (1.65, 4.62)	***<0.001***	1.52 (0.93, 2.50)	0.098	1.54 (0.87, 2.74)	0.138	1.65 (0.98, 2.75)	0.058	2.42 (1.32, 4.49)	***0.005***
Obese [c]	0.74 (0.54, 0.99)	***0.049***	0.77 (0.53, 1.12)	0.171	1.25 (0.85, 1.83)	0.250	0.88 (0.59, 1.32)	0.555	0.92 (0.62, 1.35)	0.658	0.82 (0.52, 1.29)	0.391

[a] All models adjusted for age at diagnosis, sex, comorbidities, disease stage, tumor sidedness (right, left, rectum), adjuvant treatment, obstruction/perforation at diagnosis and perineural/lymphovascular invasion

[b] 1=sarcopenia, 2=myosteatosis, 3 = sarcopenia & myosteatosis; reference = no sarcopenia or myosteatosis

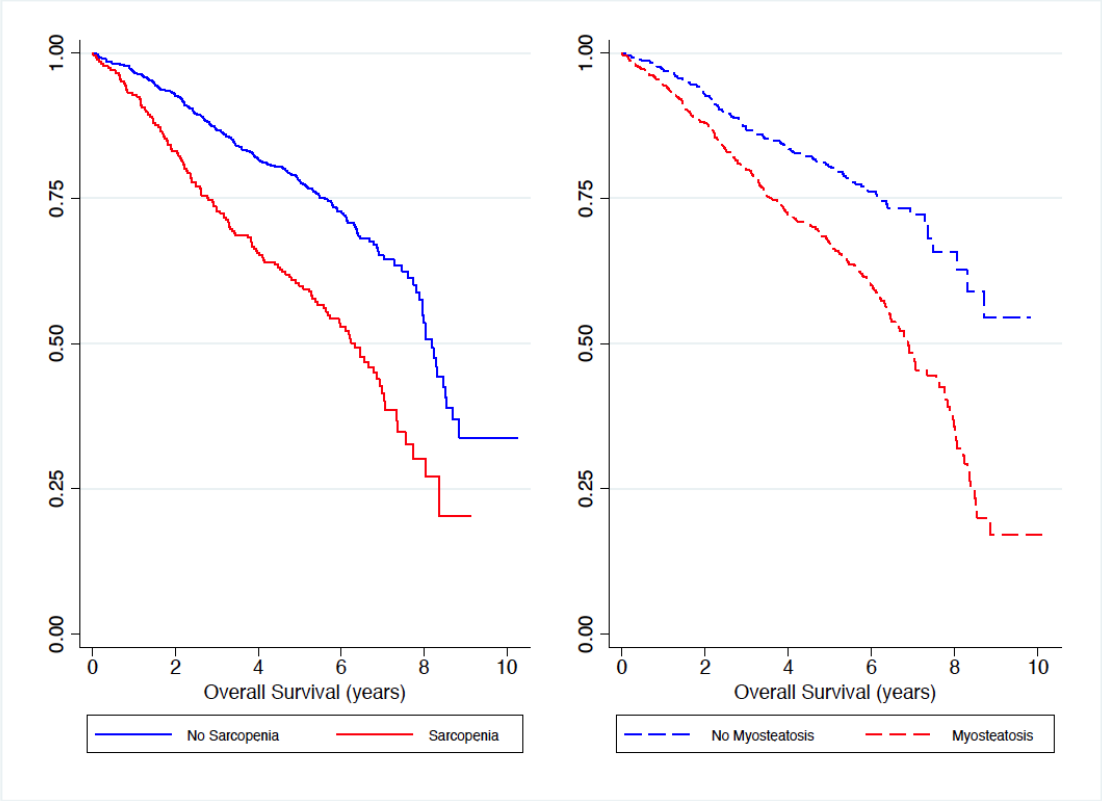
[c] TATI cutoffs: M>98.3 cm^2/m^2; F>103.6 cm^2/m

Figure 4.1: Venn diagram of overlapping body composition parameters



Legend:
S=sarcopenia
Myo = myosteatosis
VO=visceral obesity

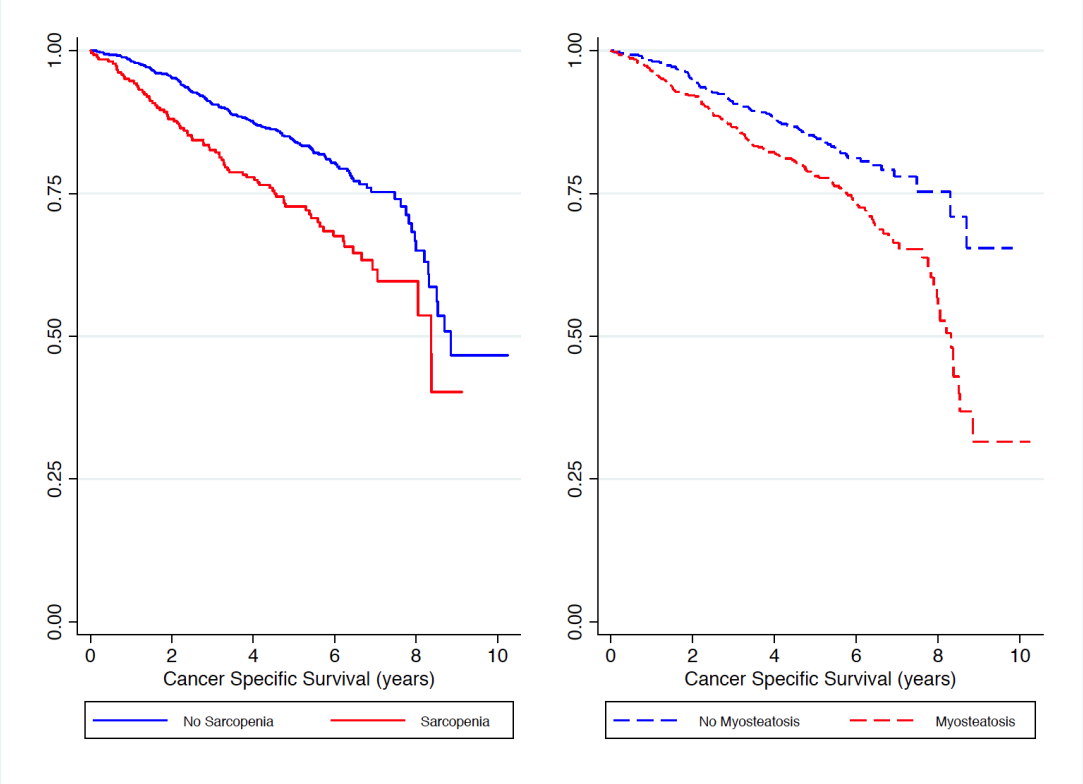
Figure 4.2: Kaplan-Meier curve for OS by presence of sarcopenia or myosteatosis



Left – OS by presence of sarcopenia (solid blue = no sarcopenia, solid red = sarcopenia)

Right – OS by presence of myosteatosis (dash blue = no myosteatosis, dash red = myosteatosis)

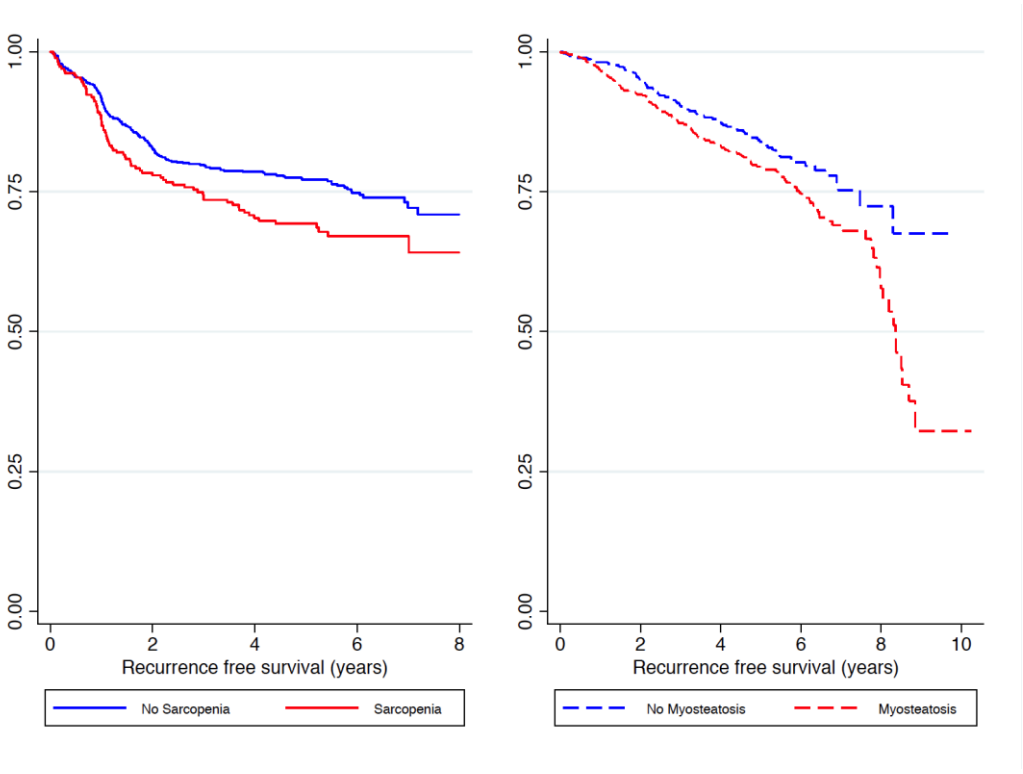
Figure 4.3: Kaplan-Meier curve for CSS by presence of sarcopenia or myosteatosis



Left – CSS by presence of sarcopenia (solid blue = no sarcopenia, solid red = sarcopenia)

Right – CSS by presence of myosteatosis (dash blue = no myosteatosis, dash red = myosteatosis)

Figure 4.4: Kaplan-Meier curve for RFS by presence of sarcopenia or myosteatosis



Left – RFS by presence of sarcopenia (solid blue = no sarcopenia, solid red = sarcopenia)

Right – RFS by presence of myosteatosis (dash blue = no myosteatosis, dash red = myosteatosis)

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CHAPTER 5: SKELETAL MUSCLE CHANGES DETECTED IN SURVEILLANCE OF RESECTABLE COLORECTAL CANCER IS PREDICTIVE OF POOR SURVIVAL

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5.1 Introduction

Patient specific body composition parameters, as measured by computed tomography (CT), play an important role in cancer survival.[20,21,43,46] Reduced skeletal muscle mass, or sarcopenia, has been well described as a poor prognostic factor that is associated with reduced overall, recurrence-free and cancer specific survival (OS, RFS, CSS) in colorectal cancer (CRC). [21,42,46] Additionally, myosteatosis, as measured by reduction in CT-derived skeletal muscle radiodensity (SMR), has also been shown to predict poor survival outcomes in CRC.[21,43,93] Visceral, subcutaneous and total adipose tissues (VAT, SAT, TAT) are additional body composition parameters that have been explored in relation to survival outcomes.[30,41,46] These parameters have traditionally been quantified at a single point in time, typically prior to treatment, and related to both short and long-term outcomes.[13,15,113-115]

CT-derived measures of muscle and adipose tissue are an opportunistic way to measure a patient specific factor. Post-operative surveillance of these patients includes annual CT scans, which presents an attractive option for quantification of change in muscle and fat over time. Repeated measures of body composition have been reported, with quantification of change over time in both palliative and curative settings.[17,116,117] Loss of muscle mass during neoadjuvant treatment in esophageal and ovarian cancer or during palliative treatment in metastatic CRC is predictive of worse outcomes, including death.[116-118] In early-stage CRC after surgical resection, loss of skeletal muscle over time has been shown in older patients and those who underwent open procedures.[17] Currently, there is a lack of studies that explore relationships between longitudinal muscle and fat changes and long-term survival outcomes in CRC patients treated with curative intent.

Based on the natural history of CRC, most patients will experience their disease recurrence within 2 years, and surveillance protocols suggest annual CT scan for up to 2-5 years.[119,120] There are currently no well-described risk factors to predict recurrence beyond 2 years. Therefore, the primary aim of this study was to evaluate the role of changes in muscle mass over time, in conjunction with presence or absence of sarcopenia, in relation to survival in patients with resected CRC. It was hypothesized that loss of muscle mass over time, in patients with sarcopenia, would be predictive of worse OS, RFS and CSS after completion of CRC surveillance. It was also hypothesized that elevated adiposity would result in worse survival outcomes after 2-year CT scan. Secondary aims included analysis of changes in SMR and adiposity over time.

5.2 Methods and Materials

5.2.1 Cohort and endpoints

This study included a retrospective cohort of resectable (I-III) CRC patients that were identified from the Alberta Cancer Board (ACB) Database as undergoing surgical resection and seen in a comprehensive cancer clinic from January 2007-December 2009, inclusive. Any patients that were duplicated in the database, originally presented with recurrent disease or did not have a preoperative CT scan were excluded. From these patients, anyone who developed disease recurrence or died prior to or did not complete a surveillance CT scan at approximately 2 years were excluded. Any CT scans that were unenhanced at only one time point were also excluded, as SMA may vary up to 7 cm^2.[96]

Primary endpoints considered were disease recurrence, OS, RFS, and CSS. All endpoints were measured from time of 2-year surveillance CT scan, unless otherwise stated.

Date of death, date of last contact, cause of death, American Joint Committee on Cancer (AJCC, 6th edition) stage, disease recurrence and anthropometric data (height, weight) were obtained from the ACB database. All other data, including tumor and patient characteristics, surgical procedure and neoadjuvant/adjuvant treatment were obtained from an institutional electronic medical record (EMR). This study was approved by the Health Research Ethics Board of Alberta (HREBA) Cancer Committee at the University of Alberta. The STROBE guidelines were followed for reporting of observational studies.[121]

5.2.2 Body composition analysis

Routine CT scans completed for staging and surveillance were identified. This included one preoperative scan, and a second surveillance CT closest to the 2-year time point. A single image from each scan was obtained from the third lumber (L3) level, as it has been shown to correlate highly with total body skeletal muscle and fat.[18] Each image was subsequently segmented in Matlab software for total cross-sectional muscle and adipose tissue analysis.[103] All scans were manually edited by 2 blinded individuals (JH, RR), who were trained to accurately identify and quantify skeletal musculature, and visceral and subcutaneous fat. Hounsfield unit (HU) ranges for each body compartment were -29 to +150 for skeletal muscle, -190 to -30 for subcutaneous fat and -150 to -30 for visceral fat. All compartments were measured as total cross sectional areas in squared centimeters. Total adipose tissue (TAT) was defined as the sum of VAT and SAT. Skeletal muscle and TAT were normalized by height (m^2) and reported as lumbar skeletal muscle index (SMI, cm^2/m^2) and total adipose tissue index (TATI, cm^2/m^2) in order to quantify prevalence of sarcopenia and elevated total adiposity at both time points. Mean skeletal muscle radiodensity (SMR) in

HU was reported for the total skeletal muscle cross-sectional area. Inter-observer coefficients of variation for measurements of skeletal muscle area (SMA), skeletal muscle radiodensity (SMR), visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) were 1.2, 1.1, 1.3 and 1.2%, respectively.

5.2.3 Definition of body composition parameters and change over time

Optimal stratification was used to define cohort specific cut-off points from sex-specific ranges of SMI, SMR and TATI measured at the initial time point (preoperatively). These cut-off points were used to define threshold values for sarcopenia (SMI), myosteatosis (SMR), VO (VAT) and elevated total adiposity (TATI). Presence of each body composition parameter was reassessed at follow-up CT scan.

Change in body composition was measured between time points. As time points were not static, change was measured as a percentage change per year (365 days) for skeletal muscle area, VAT, SAT and TAT. Change in SMR was defined by absolute change in HU per year. While percentage change per 100 days has been previously defined, change per year allows for easy correlation to patients' annual surveillance CTs. All of these change in body composition variables were then divided into equal tertiles and defined as losing (tertile 1), stable (tertile 2) or gaining (tertile 3), unless otherwise specified. After creating tertiles, the mean values of change were assessed to ensure that they represented true loss and gain, as a change of +/-2% has been previously shown to represent measurement error.[19,117]

5.2.4 Statistical analysis

Group differences were tested using paired Student's t-test, Fisher's exact test or Kruskal-Wallis test. Patient follow-up began at the time of their surveillance CT scan and continued until their death, loss to follow-up or October 31, 2017. Disease recurrence was defined as first objective evidence on endoscopy or diagnostic imaging of recurrent disease, as per RECIST (Response Evaluation Criteria in Solid Tumors) guidelines.[122] RFS was defined as the time from surveillance CT scan until the identification of recurrent disease, loss to follow up or end of study. OS and CSS were defined as the time from surveillance CT scan until the time of death from any cause or death secondary to CRC, respectively, or until loss to follow up or study end.

Optimal stratification is a statistical method used to identify population specific cut-off points from continuous data, and has previously been used in the body composition literature.[20,21] It is based on the use of log-rank statistics to determine a threshold value from a continuous variable that is related to a time to event outcome.[104,105] OS was used as a time to event outcome, as it was one of the primary endpoints and has been used in previous publications.[21] Optimal stratification thresholds were used to dichotomize SMI, SMR, VAT and TATI and defined sarcopenia, myosteatosis, VO and elevated total adiposity, respectively.

Both univariate and multivariate Cox proportional hazards models were used for survival analyses. Multivariate modeling was done with purposeful selection and *a priori* inclusion of biologically and clinically important covariates, including: sex, age at follow-up CT scan, disease stage, comorbidities (Charlson Comorbidity Index, CCI) and high-risk tumor characteristics (lymphovascular/perineural invasion, high grade histology, adjuvant treatment). Sarcopenia at diagnosis and follow up were both included in the multivariate

analysis to control for regression to the mean.[123,124] Hazard ratios (HR) and 95% confidence intervals (CIs) were obtained and Schoenfeld residuals showed no evidence of violating the proportional hazards assumption. Post-estimation linear combinations were used to determine overlapping effects of sarcopenia and muscle loss, or elevated total adiposity.

SAS software (version 9.3; SAS Institute Inc., Carey, NC) was used for optimal stratification analysis. All other statistical analyses were performed using Stata 15.0 software (College Station, TX: StataCorp LLC). Statistical significance was established with two-sided tests and $p<0.05$.

5.3 Results

5.3.1 Baseline characteristics

From the ACB database, 1,418 patients were identified who were also seen in a tertiary care center (Figure 5.1). From these, 968 were included at the initial time point with an analyzable CT scan. After excluding patients who were lost to follow up (n=19), had no 2 year CT scan (n=48), had an unenhanced CT at one time point (N=10) or had disease recurrence or died prior to their 2 year CT (n=224), the cohort had a total of 667 patients. In the cohort, the mean age was 67 and patients were primarily male (Table 5.1). Most patients had stage II or II disease (91%), and 377 (55.7%) received adjuvant chemotherapy. Disease recurrence was detected in 75 (11.1%) patients. Prevalence of sarcopenia and myosteatosis at follow up were 28.8 and 72.7%, respectively. Prevalence of visceral obesity and total adiposity at follow up were 50.4 and 71.7%, respectively. Those patients with disease recurrence were no different in age, sex, CCI score, disease stage, tumor location or use of adjuvant chemotherapy (Table 5.1). They were more likely to die (64 vs. 19%, $p<0.001$) and

had shorter survival (3.68 vs. 5.56 years) after end of surveillance. Prevalence of sarcopenia, myosteatosis, visceral obesity and elevated total adiposity were not significantly different in patients with disease recurrence (Table 5.1).

5.3.2 Change in muscle mass, radiodensity and fat mass

On average, skeletal muscle mass (-0.415% change/year) and SMR (-5.77 HU/year) decreased over time, regardless of patient sex. Conversely, adipose tissue tended to increase over time, whether it was visceral (+8.96% change/year), subcutaneous (+7.71% change/year) or total (7.06% change/year) adipose tissue.

In the tertiles of muscle change, patients who had lost, maintained stable or gained muscle mass had average SMIs of 43, 47 or 49 cm^2/m^2, respectively. The mean rate of change of skeletal muscle was -5.01, -0.46 and +4.33% SMI/year. Patients who were gaining muscle over time were significantly more likely to have a left-sided primary and less likely to have a rectal primary (Table 5.1). With respect to those who were losing muscle, these patients were more likely to have a non-cancer related death, decreased OS and increased prevalence of both sarcopenia and myosteatosis at follow up (Table 5.1). Furthermore, patients gaining muscle mass were on average also losing SMR (-2.89 HU/year), but at a rate less than those patients losing muscle mass (-9.09 HU/year) (Table 5.2). Notably, patients gaining muscle mass had a significantly greater rate of increase in adipose tissue ($p<0.001$).

The tertiles of SMR change had a mean rate of change (HU/100 days) of -17.33, -6.03 and +6.11 and average HU of 24, 28 and 33 for SMR losing, stable and gaining groups, respectively. Those patients who were decreasing their absolute SMR had significantly less deaths (22 vs. 30%, $p=0.031$). They were also significantly more likely to have stage III disease and have received adjuvant chemotherapy (64 vs. 52%, $p=0.009$). Those patients who

were gaining SMR were significantly less likely to be viscerally obese (43 vs. 58%, p=0.009) or have elevated total adiposity (65 vs. 77%, p=0.024). Those patients gaining fat (VAT, SAT, TAT) were gaining muscle at a faster rate, and were concurrently losing SMR at a significantly greater rate (Table 5.2). Measures of TATI strongly correlated with both VAT (0.706) and SAT (0.838).

There were 199 patients who were sarcopenia at time of follow up. Of these, 134 (67%) were sarcopenic at diagnosis. Within this group, there were 26 (13%) patients with disease recurrence, of which 16 died from CRC. In the 65 patients who became sarcopenic sometime after their diagnostic CT, there were 6 (9%) disease recurrences and 4 of these patients died of their CRC. In comparison, the 134 patients who were sarcopenic at both time points had 19 (14%) disease recurrences and 12 died of their CRC. There were a total of 36 patients who were sarcopenic at diagnosis, but not at follow up. In this group, 4 (11%) patients developed disease recurrence and all died of their disease.

5.3.3 Survival Analysis

In a univariate model, sarcopenia (at diagnosis and follow up) and loss of skeletal muscle over time were both associated with worse OS. Presence of sarcopenia at either time point was also associated with worse CSS in the univariate model (Table 5.3). Neither sarcopenia or muscle loss were significant in univariate analysis of RFS.

In the multivariate model, adjusting for clinically important patient and disease factors, both sarcopenia at time of diagnosis (HR 1.80, p=0.013) and skeletal muscle loss over time (HR=1.55, p=0.044) were both independently predictive of worse OS (Figure 5.2). Sarcopenia and loss of skeletal muscle over time demonstrated trends towards worse RFS

(HR 1.62, p=0.185; HR 1.68, p=0.118, respectively) and CSS (HR 1.44, p=0.325; HR=1.34, p=0.389, respectively), but never reached significance (Figure 5.2).

Comparison of total adiposity across in the multivariate analysis for OS, RFS and CSS demonstrated differing patterns. Elevated total adiposity tended to be protective in terms of OS (HR 0.66, p=0.024). In the RFS and CSS analyses, elevated total adiposity was no longer a protective factor and predicted neither worse nor improved survival (HR 1.07, p=0.802; HR=1.01, p=0.980, respectively) (Table 5.3).

In order to understand how sarcopenia interacted with change in skeletal muscle mass over time, linear combinations were generated from the multivariate model (Table 5.2). The combination of sarcopenia at diagnosis with loss of muscle over time resulted in significantly worse OS (HR=2.73, p=0.007). The same combination predicted worse RFS (HR 4.56, p=0.051) that neared significance. No combinations predicted worse CSS (Table 5.2). While total adiposity and sarcopenia at either point in time did not reach significance, a pattern did emerge. Elevated total adiposity tended towards a protective effect in patients who were sarcopenic at follow up, with the reverse effect for those who were sarcopenic at diagnosis (Table 5.2). Linear combinations of elevated total adiposity and muscle loss over time did not reach significance, but trended towards worse RFS (HR 1.80, p=0.169).

5.4 Discussion

This study highlights the changes in body composition that occur from time of diagnosis to end of surveillance, including changes in skeletal muscle, SMR and adipose tissue. In this large cohort of CRC patients treated with curative intent, those who lived to complete their surveillance without disease recurrence were more likely to have worse OS if they had sarcopenia and loss of skeletal muscle over time. These associations were

independent of important clinical and pathological features, including patient age and sex, comorbidities, disease stage, high-risk features and use of adjuvant chemotherapy. This is a novel finding, as previous studies have been limited to weight loss or body mass index (BMI) change over time in early-stage disease.[125-128] Others have only demonstrated worse survival outcomes in advanced CRC, or other advanced solid organ and hematological malignancies[116,117,129,130]. While loss of muscle with aging is expected, pre-existing sarcopenia compounded by an accelerated loss of muscle after treatment, represents a pathological state resulting in poor survival.

In a recent study, which included a similar cohort of patients with resectable CRC, serial CT scans from diagnosis to 60 months were analyzed.[17] Several patterns from this study emerged, including muscle loss over time in those with open procedures, rectal cancer, stage III or IV disease and age greater than 65 years.[17] Based on these findings, changes in skeletal muscle mass are expected over time in many patients treated for CRC. The current study attempted to build from this previous work by also describing change in adipose tissue over time and by relating changes in muscle and adipose tissues to risk of recurrence and mortality after completion of surveillance. CT-derived measures of body composition have not previously been analyzed in this manner, and may provide a method of risk stratification for those patients who successfully complete their post-treatment surveillance.

In healthy adult patients, muscle loss of 1-2% per year is expected.[131] In this cohort, there was a mean loss of roughly 0.5% per year. When the cohort was considered by tertiles of muscle loss, those in the first tertile had the greatest loss of muscle (-5.01% per year) while those in the third tertile actually demonstrated gain of muscle (+4.33% per year). This suggests that one group of patients has an ongoing muscle loss beyond the expected rate,

while another group is demonstrating anabolic potential through ongoing muscle gain. Both surgery and adjuvant chemotherapy are major catabolic hits occurring after the time of diagnostic CT. By their 2-year surveillance scan, patients can be expected to have recovered from the effects of surgery and chemotherapy, and to no longer be losing muscle at a pathological rate. The results from this study show that some patients will recover from their losses and go on to gain back muscle, while others will continue to lose muscle. As expected, those patients with ongoing losses had significantly worse OS (HR 1.53, CI 1.00, 2.34) independent of all other important prognostic factors. Increased all-cause mortality was further worsened by pre-existing sarcopenia (HR 2.73, CI 1.32, 5.65). Interestingly, sarcopenia at time of diagnosis demonstrated a consistently stronger effect on survival outcomes as compared to sarcopenia at follow up. While the cause behind this is unknown, there are possible explanations for this phenomenon. Those patients that are still alive without disease recurrence at 2 years inherently have a decreased risk of disease recurrence, based on the known natural history of CRC. Therefore, despite being sarcopenic at follow up, they have bypassed an important threshold for long-term recurrence free survival. Secondly, those patients that were sarcopenic and diagnosis and remained so at follow up not only lack the potential for a meaningful anabolic response to improve their muscle mass but also have reduced reserves as compared to those patients who went from having normal muscle mass to being sarcopenic. Finally, the potential causes of sarcopenia at time of diagnosis versus follow-up may differ, specifically affecting the RFS and CSS associations found.

As the effect of sarcopenia and ongoing muscle loss was the primary aim of this study, SMR was not included in the survival analysis. In the descriptive statistics, SMR did demonstrate some unexpected patterns. Patients in the lowest tertile of SMR change (eg.

SMR loss) had significantly less deaths than those in the third tertile (eg. SMR gain). While counterintuitive, this result can best be explained by the fact that patients with ongoing SMR losses were significantly more likely to have stage III disease and to have received adjuvant chemotherapy. There is evidence in the literature that over time chemotherapy not only results in reduction of skeletal muscle mass, but also reduction in SMR and gain of VAT, and that these changes may be predictive of survival.[106,129,132-135] Patients who received chemotherapy would have ended their anti-cancer treatment significantly later than those who were treated solely with surgical resection. Chemotherapy may be causing prolonged systemic inflammation resulting in these patients having ongoing SMR loss, as compared to those who did not receive adjuvant chemotherapy.

Throughout the analysis, the role of fat as a prognostic marker has not been clear. As TATI was highly correlated to both VAT and SAT, it was the sole marker of adiposity used in the univariate and multivariate models. Elevated total adiposity acted as a protective factor and was significantly predictive of improved OS (HR 0.66, CI 0.46, 0.95), independent of all other important covariates. Despite having a protective effect against all cause mortality in the adjusted model, its effect essentially became null in the models for RFS and CSS. When considered in conjunction with pre-existing sarcopenia, presence of elevated total adiposity demonstrated a trend towards increased risk of all-cause and cancer-specific mortality. Conversely, presence of sarcopenia at follow up combined with elevated adiposity trended towards an improvement in OS. Perhaps towards the end of life, all cause mortality is reduced by increased adiposity, which may be acting as a functional reserve, especially in those patients that have skeletal muscle loss.[136] In the setting of CRC, obesity is a risk factor for initial development of CRC.[137] Adiposity may act in a similar manner for disease recurrence

and CSS, or through interaction with skeletal muscle. Unfortunately, the pathophysiology behind the role of adipose tissue in disease recurrence and survival is not well understood.

While the exact effect of adipose tissue on survival outcomes is not yet clear, the ability to accurately quantify adipose tissues independent of skeletal muscle further diminishes the role of BMI as a reliable prognostic factor. The relationship between BMI and survival outcomes in CRC has demonstrated worse outcomes in those with an underweight BMI and a protective effect or no difference in those with overweight and obese BMI.[127,128,138] A more recent study evaluating weight change after early-stage CRC diagnosis in a large cohort demonstrated an increase risk of mortality with significant weight loss, but no mortality risk with weight gain.[125] Previously, the obesity paradox argument would suggest that elevated BMI or adiposity was providing some kind of mortality benefit to these patients. With the advent CT-derived body composition analysis and the increased awareness of the role of muscle mass on outcomes, it has become clearer that the mortality benefit is derived from increased muscle, rather than fat, mass.[30] Those studies limited to weight change or BMI classification are unable to quantify the type of weight loss (eg. skeletal muscle vs. adipose tissue) occurring or patients underlying body composition (eg. sarcopenia vs. normal SMI). Therefore, use of CT-derived body composition analysis is superior to measurement of weight and height alone in prediction of survival outcomes for cancer patients, and the specific parameters that are affecting measured outcomes.

This study is not free of limitations. It is a retrospective cohort study of prospectively collected data, and was restricted to patients who were seen at a tertiary cancer center. The data collection was limited to what data was collected and inputted into the EMRs. Therefore, there is missing data on patient performance status and ASA score at time of surgery. Also,

patients who did not have a preoperative CT scan or surveillance CT scan were excluded from the study, risking bias. It is not known if those patients developed disease recurrence, what their body composition parameters were or how they changed over time. While the total cohort of patients is large, for purposes of this study only a subset of patients who were alive without disease recurrence at their 2-year surveillance CT were considered. This limited the total number of patients included. Furthermore, most CRC disease recurrence occurs in the first 2 years after diagnosis, while this study only considered recurrences after that point in time. Those patients were excluded in the hopes of avoiding bias in change in skeletal muscle and fat from patients that had a known diagnosis or were near the end of life. Despite these limitations, this study still included a relatively large cohort with many clinically important variables and good long-term follow up.

5.4.2 Conclusions

In patients with resected CRC who survive recurrence-free to their 2-year surveillance CT scan, the presence of sarcopenia at diagnosis followed by loss of muscle after surgery are predictive of worse OS independently and in combination. This represents a novel consideration of skeletal muscle as a prognostic factor in CRC, and a potential indicator for prolonged surveillance. Staging and surveillance CT scans provide the opportunistic chance to recognize these body composition abnormalities at time of diagnosis and intervene. Surveillance imaging allows for easy recognition of ongoing losses, which may suggest prolonged follow up.

Table 5.1: Clinical and pathological characteristics of cohort based on disease recurrence and change in muscle mass and radiodensity

Characteristic No. (%)	By disease recurrence			By change in muscle [a]			
	Recurrence (N=75)	No recurrence (N=592)	*P*	SMI losing (N=223)	SMI stable (N=222)	SMI gaining (N=222)	*P*
Age (years)	68	67	0.464	68	68	66	0.355
Sex							
Male	48 (64)	344 (58.1)	0.384	141 (63.2)	123 (55.4)	128 (57.7)	0.230
Female	27 (36)	248 (41.9)		82 (36.7)	99 (44.6)	94 (42.3)	
Charlson Comorbidity Index							
0	40 (53.3)	381 (64.4)	0.121	129 (57.8)	148 (66.7)	144 (64.9)	0.070
1-2	31 (41.3)	176 (29.7)		73 (32.8)	65 (29.3)	69 (31.1)	
≥3	4 (5.3)	35 (5.9)		21 (9.4)	9 (4.0)	9 (4.0)	
Stage							
I	9 (12.0)	51 (8.6)	0.062	20 (9.0)	25 (11.3)	15 (6.8)	0.547
II	23 (20.7)	263 (44.4)		99 (44.4)	91 (41.0)	96 (43.2)	
III	43 (57.3)	278 (47.0)		104 (46.6)	106 (47.7)	111 (50.0)	
Location							
Right	24 (32.0)	207 (35.0)	0.280	65 (29.2)	82 (36.9)	84 (37.8)	***0.002***
Left	27 (36.0)	161 (27.2)		62 (27.8)	50 (22.5)	76 (34.2)	
Rectal	24 (32.0)	224 (37.8)		96 (43.0)	90 (40.5)	62 (28.0)	
Adjuvant chemo							
No	34 (45.3)	256 (43.2)	0.805	108 (48.4)	93 (41.9)	89 (40.1)	0.177
Yes	41 (54.7)	336 (56.8)		115 (51.6)	129 (58.1)	133 (59.9)	
Recurrences	75	0	***<0.001***	28 (12.6)	28 (126)	19 (8.6)	0.298
Deaths	48 (64.0)	111 (18.8)	***<0.001***	65 (29.2)	47 (21.2)	47 (21.2)	0.079
Survival after	3.68	5.56	***<0.001***	4.84	5.22	5.91	***<0.001***

follow up CT (years)							
Sarcopenia[c] at diagnosis	23 (30.7)	143 (24.2)	0.256	52 (23.3)	44 (19.8)	70 (31.5)	***0.015***
Sarcopenia[c] at follow up	25 (33.3)	167 (28.2)	0.347	105 (47.1)	51 (23.0)	36 (16.2)	***<0.001***
Myosteatosis[c] at diagnosis	41 (54.7)	307 (51.9)	0.713	118 (52.9)	110 (49.6)	120 (54.1)	0.621
Myosteatosis[c] at follow up	53 (70.7)	432 (73.0)	0.681	179 (80.3)	150 (67.6)	156 (70.3)	***0.006***
Visceral obesity[c] at diagnosis	44 (58.7)	296 (50.0)	0.178	135 (60.5)	110 (49.6)	95 (42.8)	***0.001***
Visceral obesity[c] at follow up	45 (60.0)	291 (49.2)	0.086	114 (51.1)	112 (50.5)	110 (49.6)	0.952
Elevated total adiposity[c] at diagnosis	49 (65.3)	408 (68.9)	0.513	171 (76.7)	144 (64.9)	142 (64.0)	***0.005***
Elevated total adiposity[c] at follow up	55 (73.3)	423 (71.5)	0.787	155 (69.5)	161 (72.5)	162 (73.0)	0.690

[a] % change in SMI per 1 year

[b] absolute change in Hounsfield Units per 100 days

[c] Using cohort specific cut-offs determined from optimal stratification analysis; at follow up CT scan

Table 5.2: Rate of change of muscle and fat parameters based on tertiles of skeletal muscle and adipose tissue change

Mean % change per year	Muscle % change tertiles				SMR absolute change tertiles				Visceral adipose % change tertiles				Subcutaneous adipose % change tertiles				Total adipose % change tertiles			
	3	2	1	*P*	3	2	1	*P*	3	2	1	*P*	3	2	1	*P*	3	2	1	*P*
SMI	4.3	-0.5	-5.1	[a]	0.6	0.1	-2.0	[a]	1.1	-0.8	-1.6	[a]	1.5	-0.7	-2.1	[a]	1.4	-0.6	-2.1	[a]
SMR	-2.9	-5.3	-9.1	[a]	6.1	-6.0	-17	[a]	-7.6	-7.0	-2.7	[a]	-8.4	-7.3	-1.6	[a]	-8.5	-6.8	-2.0	[a]
VAT	21	5.9	-0.4	[a]	8.4	9.6	8.9	[a]	41	1.6	-15	[a]	33	2.4	-8.6	[a]	39	1.7	-14	[a]
SAT	15	6.6	1.6	[a]	7.1	7.6	8.4	[a]	22	4.7	-3.5	[a]	27	4.4	-8.1	[a]	25	4.7	-6.7	[a]
TAT	16	5.6	-0.2	[a]	6.6	7.4	7.2	[a]	27	2.8	-8.7	[a]	27	3.3	-9.1	[a]	28	3.1	-10	[a]

[a] $P<0.001$

1: Losing

2: Stable

3: Gaining

Table 5.3: Survival analysis based on changes in skeletal muscle composition and total adiposity

Variable	Overall Survival				Recurrence Free Survival				CRC Specific Survival			
	Univariate		Multivariate [a]		Univariate		Multivariate [a]		Univariate		Multivariate [a]	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Sarcopenia Diagnosis	2.20 (1.60, 3.03)	<0.001	1.80 (1.13, 2.85)	0.013	1.44 (0.88, 2.36)	0.143	1.62 (0.80, 3.29)	0.185	1.67 (1.01, 2.75)	0.044	1.44 (0.69, 2.99)	0.325
Follow up	2.15 (1.57, 2.94)	<0.001	0.93 (0.58, 1.50)	0.773	1.36 (0.84, 2.20)	0.211	0.86 (0.42, 1.78)	0.685	1.71 (1.052 .78)	0.030	1.04 (0.49, 2.19)	0.918
Elevated total adiposity [b]	0.88 (0.63, 1.23)	0.457	0.66 (0.46, 0.95)	0.024	1.07 (0.64, 1.78)	0.802	1.07 (0.63, 1.83)	0.807	1.28 (0.74, 2.25)	0.379	1.01 (0.69, 2.63)	0.980
Change in muscle [c]												0.145
Stable	1.12 (0.74, 1.67)	0.593	1.21 (0.79, 1.86)	0.385	1.57 (0.88, 2.82)	0.128	1.67 (0.92, 3.07)	0.094	1.57 (0.88, 2.82)	0.132	1.58 (0.85, 2.92)	
Losing	1.65 (1.13, 2.39)	0.010	1.55 (1.01, 2.37)	0.044	1.63 (0.91, 2.91)	0.102	1.68 (0.88, 3.24)	0.118	1.51 (0.83, 2.76)	0.180	1.34 (0.69, 2.63)	0.389

[a] Model adjusted for age, sex, disease stage, high risk factors (high grade, lymphovascular invasion), adjuvant treatment,
[b] Elevated total adiposity based on sex-specific optimal stratification cutoffs of total adipose tissue index (M>98.3 cm^2/m^2; F>103.6 cm^2/m^2)
[c] Tertiles of percentage change in skeletal muscle index per year; reference = muscle gaining tertile

Table 5.4: Linear combinations of sarcopenia and change in skeletal muscle mass over time from multivariate model

Variable	Overall Survival [c]				Recurrence Free Survival [c]				Cancer Specific Survival [c]			
	Sarcopenia at diagnosis		Sarcopenia at follow up		Sarcopenia at diagnosis		Sarcopenia at follow up		Sarcopenia at diagnosis		Sarcopenia at follow up	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Change in muscle mass[a]												
Losing	2.73 (1.32, 5.65)	***0.007***	1.45 (0.89, 2.35)	0.136	2.72 (0.89, 8.35)	0.080	1.45 (0.68, 3.07)	0.332	1.94 (0.62, 6.06)	0.255	1.40 (0.64, 3.04)	0.401
Losing & stable	3.18 (1.15, 8.78)	***0.026***	1.69 (0.82, 3.47)	0.157	4.56 (1.00, 20.89)	0.051	2.42 (0.80, 7.37)	0.117	3.06 (0.65, 14.44)	0.157	2.21 (0.72, 6.74)	0.165
Elevated total adiposity [b]	1.22 (0.68, 2.20)	0.499	0.65 (0.35, 1.21)	0.176	1.72 (0.71, 4.23)	0.230	0.92 (0.36, 2.34)	0.861	1.45 (0.58, 3.65)	0.425	1.05 (0.39, 2.81)	0.927

[a] Percentage change in skeletal muscle index per year in tertiles; reference = muscle gaining
[b] Sex-specific cutoff based on optimal stratification analysis of total adipose tissue index (M>98.3 cm^2/m^2; F>103.6 cm^2/m^2)
[c] Multivariate model adjusted for age, sex, disease stage, high risk factor (high grade, lymphovascular invasion), and adjuvant treatment

Figure 5.1: Flow diagram of patient inclusion to study cohort

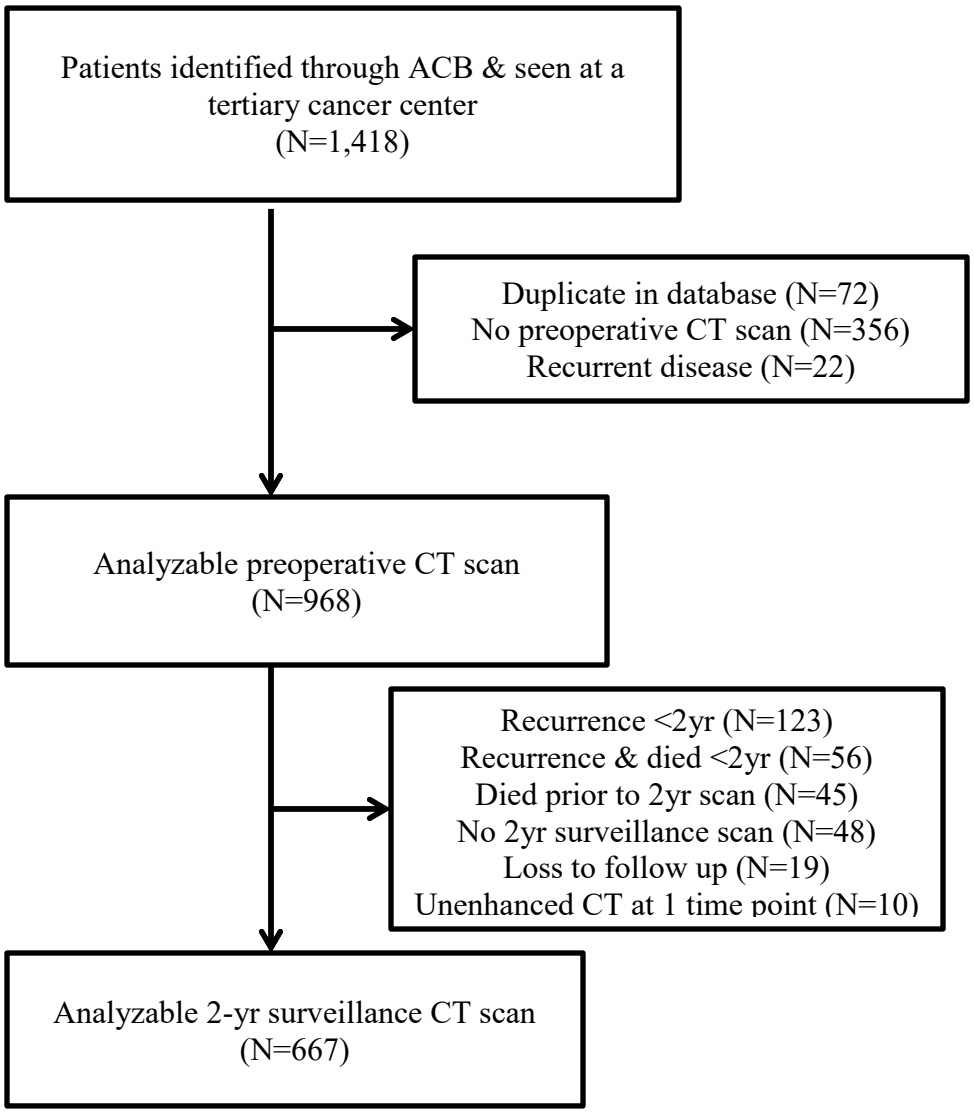
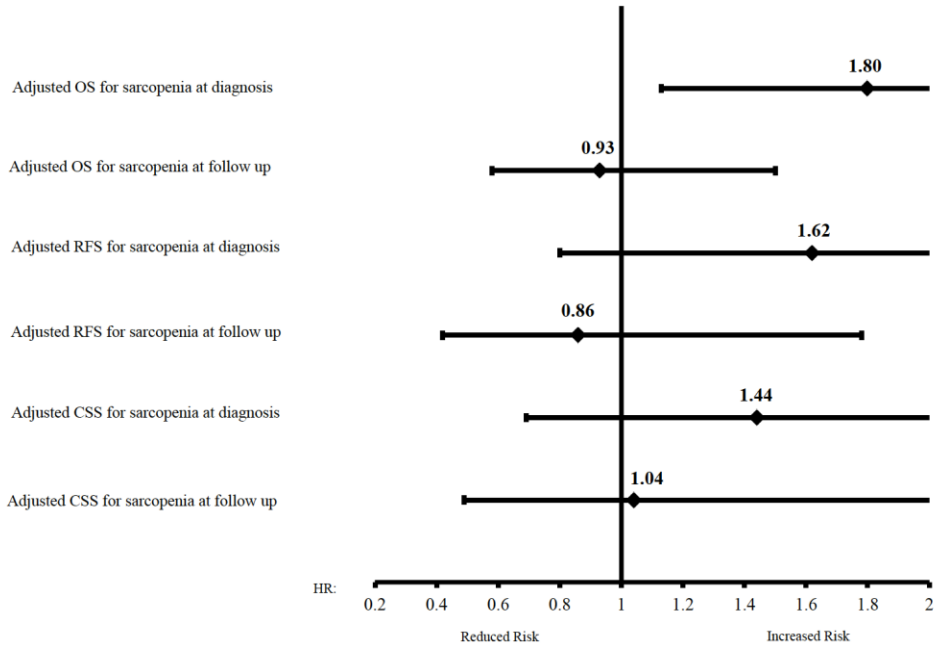


Figure 5.2: Effect of sarcopenia on survival outcomes from multivariate analysis



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CHAPTER 6: SUMMARY

6.1 Overview of Research

Despite a decline in incidence and death rates in recent years, CRC remains the second most common cancer diagnosis in Canada, and the second and third leading cause of cancer related deaths in men and women, respectively.[70,139] Furthermore, cancer diagnoses are occurring in an aging population, where anti-cancer treatments are being administered to older patients with increasingly more comorbidities. The average BMI of patients has also increased, adding obesity to the complexity of patient management. Consequently, the recognition and study of patient-specific prognostic factors has become of increased importance to improve both short and long-term outcomes in patients diagnosed with cancer. CRC prognosis, in particular, is affected by patient age and body habitus, as curative treatment requires patients to undergo surgical resection with possible neo/adjuvant chemo/radiotherapy. Patient-specific prognostic factors allow for the clinician to recognize and understand poor outcomes in patients beyond standard disease-related factors currently used for staging and treatment guidance.

Although BMI is a tempting factor to consider, and is often cited as an increased risk modifier, it does not provide a truly accurate description of the underlying body composition.[30] The advent of CT-derived body composition analysis has created an up and coming field of research which allows for accurate quantification of skeletal muscle and adipose tissue using cross-sectional imaging done for diagnostic or treatment planning purposes.[15,22,140] CT-derived measures of skeletal muscle and adipose tissue can be used directly, or as a prediction of whole body LST and fat mass, respectively.[18,19]

This is based on the validation of a single CT slice being linearly related to whole body muscle and fat.[18] Subsequently, the measurement of body composition parameters has multiple applications within the field of oncology, including CRC.[15,42,43,46,141,142] Accurate measures of LST mass may be a superior method of dosing chemotherapy, as compared to BSA.[27,36-38,74,143] Identification of reduced skeletal muscle, or sarcopenia, has also been shown to be predictive of chemotherapy toxicities, post-operative complications and poor survival outcomes.[20,21,27,28,46,94,144,145] Despite these demonstrated associations, there is a lack of awareness to the limitations surrounding CT-derived body composition analysis and the importance for standardization of measurements.[40] There is also ongoing need to define the overlap and potential interactions of sarcopenia and myosteatosis as prognostic factors in CRC treated with curative intent. Furthermore, there are few studies that have quantified the change in skeletal muscle over time and investigated its association with long-term survival outcomes in stage I-III CRC patients who are disease free at the end of surveillance. [53]

6.1.1 Previous Literature on Body Composition in Patients Receiving Chemotherapy

As discussed in detail in Chapter 2, there is ample evidence that patients who experience grade 3 or 4 toxicities or DLTs during chemotherapy are significantly more likely to have a lower SMI or whole body LST mass.[38,62-65,67-71,73-75] The majority of these studies have reported on CT-derived measures of skeletal muscle and adipose tissue, and how these are associated with chemotherapy toxicities.

In those studies which dichotomized patients by presence or absence of sarcopenia, predefined cutoffs were most commonly applied. [20,21,38,62-64,67-71] This was

done without comparison of the studied cohort and the cohort from which the cutoffs were derived.[20,21] In general, reductions of LST mass or presence of sarcopenia was associated with increased prevalence or risk of toxicities. Quantification of LST also allowed for comparison of relative dosing based on LST mass versus BSA, with wide variations in dose per kg LST demonstrated.[27,32,34,35,56,63,71,73] Few studies included an analysis of pharmacokinetics and direct serum drug measurements. Those that did found that in patients with similar doses by BSA, absolute serum drug levels were higher and whole body LST was lower in patients with toxicities.[36,37,76]

As previously discussed, the currently published literature presents a strong argument for the use of CT-derived LST mass over BSA-based dosing. Ideally, the use of LST-based dosing would represent a more accurate picture of each individual patient's body composition, resulting in dosing that is based on the true volume of drug distribution. In order to convince clinicians to move from BSA to LST-based dosing, additional pharmacokinetic studies may be necessary. Feasibility studies, which would demonstrate the ease of acquiring LST and applying in to chemotherapy regimens, may also improve uptake in the clinical realm.

6.1.2 Limitations of CT-Derived Body Composition Parameters in CRC

In order to gain an understanding of how body composition affects survival outcomes in CRC patients, we aimed to first recognize how CT-derived measurements are being derived, and subsequently applied, in CRC patient populations similar to our own.[20,21,30,41-52,84-88] With that in mind, a systematic review of the literature was undertaken. Notably, sole use of the psoas muscle as being representative of total abdominal skeletal muscle area was considered inaccurate, and excluded.[77,95]

Review of the literature suggests that body composition, specifically relating to skeletal muscle, is an important predictor of survival outcomes in CRC. The strength of this conclusion is still not fully elucidated due to the heterogeneity in the methodology used to investigate the association between sarcopenia and survival.[40] Other limitations in this area of research include the retrospective design, reliance on CT scans completed for clinical purposes and application of cutoffs derived from dissimilar cohorts. There has also been little investigation into how different body composition parameters overlap and interact in CRC patients. Therefore, further research in body composition will require standardization of methodologies and protocols, as well as exploration into composite body composition phenotypes.

6.2 Summary of Findings

Our objectives were to establish cohort specific threshold values for sarcopenia, myosteatosis and VO, and to determine their independent effect on long-term survival outcomes, including OS, DFS and CSS. We also aimed to develop a further understanding of the extent of overlap in patients with sarcopenia, myosteatosis and obesity, and how these factors may interact to effect survival. Finally, we described the change in body composition parameters over time, and analyzed the effect of muscle change on survival after completion of disease surveillance. Our ultimate goal was to identify patients at increased risk of disease recurrence, so that they may undergo prolonged CT-surveillance for early detection of recurrence. These objectives were accomplished by evaluating the impact of a composite body composition phenotype on

survival in stage I-III CRC patients (Chapter 4) and determining the effects of skeletal muscle loss in patients who remained disease free at the end of surveillance (Chapter 5).

Prevalence of sarcopenia in our cohort varied significantly based on the threshold used. From our cohort specific cutoffs, the 27.5% of patients were sarcopenic, as compared to 50.5% when using Martin *et al.'s* cutoffs.[21] Both of these values fit within the published range of sarcopenic prevalence (15-60%).[40] Prevalence of myosteatosis (55.5 vs. 61.1%) and VO (51.0 vs. 61.4%) varied less between the 2 cutoffs applied.[91] As expected, our cohort specific thresholds for sarcopenia were significantly lower than those previously published, despite our mean sex-specific SMI being nearly identical.[21] As the same methodology and statistical analyses used to derive these values, the disparity is best explained by the patient cohorts from which the raw body composition data was derived.[21,104,105] Our cohort was a homogeneous group of stage I-III CRC patients from Northern Alberta who all underwent surgical resection and treatment with curative intent. In contrast, Martin *et al.'s* cohort included patients with any respiratory or gastrointestinal tract cancer, of whom 50% had stage IV disease.[21] The median survival in this study for males and females was 17.0 and 15.9 months, respectively, as compared to 60 months in our cohort.[21] Therefore, determination of threshold values for sarcopenia using log rank statistics separating patients based on time to death in patients with significantly different disease-specific trajectories allowed for the output of cutoff values that widely differed. The importance of this phenomenon is that cutoff values from a single cohort cannot be blindly applied to all disease types and stages. This conclusion can also be extended to include cohorts differing by patient ethnicity.

The individual effects of sarcopenia and myosteatosis on survival are consistent with previous literature, giving further support to the role of skeletal muscle as a patient-specific prognostic factor.[21,41,46] We found that both sarcopenia and myosteatosis are predictive of significantly DFS. There is some previously published evidence that suggests myosteatosis plays a more important role poor survival outcomes. In our cohort, sarcopenia was more globally predictive of worse survival outcomes than myosteatosis. This may be a result of how sarcopenia and myosteatosis overlapped in our population. Of those patients with sarcopenia, only 20.7% were sarcopenic alone, while 73.7% also had concurrent myosteatosis. In patients with myosteatosis, 23.5% were myosteatotic alone and 36.1% had concurrent sarcopenia. This demonstrates a significant overlap of myosteatosis in patients with sarcopenia. Therefore, it is difficult to assess the independent effects of sarcopenia and myosteatosis on our patient cohort. This same conclusion can be drawn for previous studies that considered each variable in isolation.

In order to overcome this limitation in the research, we created a composite phenotype. Patients were considered as having normal skeletal muscle parameters, sarcopenia alone, myosteatosis alone or overlapping sarcopenia and myosteatosis. In our multivariate analysis using our composite phenotype, individual or overlapping presence of sarcopenia and myosteatosis predicted significantly worse OS. Concurrent sarcopenia and myosteatosis also predicted significantly worse RFS and CSS. When elevated total adiposity was adjusted for in the model, myosteatosis alone was also a significant predictor of worse CSS. These results suggest that development of both skeletal muscle abnormalities imparts a significantly worse prognosis, and clinicians should recognize any overlapping of these features. While the HRs for sarcopenia alone tended to be

greater than those for myosteatosis alone, myosteatosis was the only independent predictor of significantly worse CSS (aHR = 1.46, 95%CI 1.02, 2.10). This is more congruent with the previous literature, in which myosteatosis played a greater roll in predicting survival outcomes.

Although there is currently literature on change in skeletal muscle in patients receiving chemotherapy, there exists a paucity of published data on change in CRC patients treated with curative intent and its association with survival outcomes.[17,53] Our study described changes occurring in patients who remained recurrence free at end of surveillance, and is the first to suggest that loss of muscle from time of diagnosis is predictive of significantly worse survival. We found that patients who had sarcopenia at time of diagnosis and those who lost skeletal muscle from time of diagnosis to end of follow up were had significantly worse OS independently, and in combination. We also demonstrated a trend towards significantly worse RFS in patients who were sarcopenic at diagnosis and went on to lose skeletal muscle after treatment (aHR=4.56, 95%CI 1.00, 20.89). These results suggest that those patients who are found to have both of these features at their 2-year annual surveillance CT may be at an increased risk of disease recurrence, and are significantly more likely to die from any cause. This represents a potential risk feature to identify patients who would benefit from extended surveillance with cross-sectional imaging. Or, perhaps the increased risk of all-cause mortality in these patients is a reason to stop surveillance if they would not be offered any curative treatment in the setting of late disease recurrence. Future follow-up of our cohort to see which patients received curative treatment, palliative chemotherapy or purely symptom control would add help to clarify. Alternatively, these patients may have had ongoing

skeletal muscle loss from comorbid conditions or subsequent hospital admissions, resulting in increased risk of all-cause mortality secondary to causes other than their CRC.

From previous work, measurement error in quantification of serial CT scans is roughly 1-2%.[19,117,146,147] We also know that with advancing age, patients can be expected to lose some muscle mass, and this has been estimated to be up to 1-2% per year, with higher rates at ages greater than 70 years. [148-150] But, as of yet, there is no current standard for defining significant muscle loss over time in cancer patients. We opted to divide our cohort into tertiles of percentage muscle change per year. We found that patients who were in the lowest tertile were on average losing 5.10% of their SMI per year, with a range of -1.92 to -27.1% per year. When considering measurement error and physiological losses, this value is likely pathological and represents a potential guide for monitoring future patients.

The combined effect of these studies demonstrates strong evidence for the prognostic importance of body composition parameters at time of CRC diagnosis and change in skeletal muscle over time. The presence of sarcopenia is highly prognostic of long-term survival outcomes, which we have demonstrated to be true even if patients survive disease free to the end of surveillance. The consequences of sarcopenia can also be effectively modified by the coinciding presence of myosteatosis, resulting in significantly worse survival.

As both were retrospective cohort studies, there are limitations that are inherent to this methodology. This includes the possibility of selection bias and the inability to control collection of specific variables. In our cohort, while we were able to identify a

large group of patients (n=1,418) diagnosed with stage I-III CRC who underwent surgical resection, we had to exclude 356 patients (25%) who did not have a preoperative CT scan. We also only included patients that were seen in a tertiary care center, in order to be able to collect clinical variables. Both of these exclusion criteria may have resulted in a selection bias for those who were ultimately included in the study. Despite the fact that all patients were seen in a tertiary care cancer clinic, there were still limitations as to what data was available for each patient. We were unable to collect complete information on laparoscopic versus open surgery, postoperative complications and tumor genetics. We also did not have data on hospital admissions close to the time of surveillance CT. Immobilization for other causes may result in ongoing skeletal muscle loss that is independent of losses seen from recurrent disease. Regardless, we were able to define a large cohort (n=968) with sufficient long-term follow up (median OS = 5.0 years) in order to detect disease recurrences (n=254, 26.2%) and all cause mortality (n=350, 36.2%).

6.3 Implications for Future Research and Clinical Implications

Our results have important implications for both future research and clinical practice. Body composition, as derived from cross-sectional imaging, is a highly accurate and reproducible method of quantifying skeletal muscle and adipose tissues.[15,18,19,22] Pathological reductions in skeletal muscle mass are highly prevalent in cancer patient populations and have significant effect on patient outcomes. Thus, recognition of skeletal muscle changes allows for improved disease prognostication and a specific target to improve disease outcomes. While there appears to be a strong association of skeletal muscle mass and its change over time with respect to survival

outcomes, we are unable to demonstrate a causal relationship. Even in the absence of a causal relationship, skeletal muscle may be a proxy for some other factor resulting in poor survival. Research demonstrating improved outcomes with increased skeletal muscle mass and radiodensity would add strength to the association of body composition and survival outcomes.

This is especially important in an aging population, where anti-cancer treatments are being administered to older persons on average. Elderly patients are at risk of having lower baseline levels of skeletal muscle based on normal physiological losses over time. Using CT scans completed for clinical purposes to quantify skeletal muscle and whole body LST mass is a novel way to dose chemotherapy. BSA is poorly validated and does not differentiate between muscle and adipose tissues.[25,26] CT-derived measurements could be implemented into clinical practice, by analysis of pre-treatment scans and calculating dose per kg of LST, as opposed to BSA.[39] In order for body composition analysis to be successfully integrated into clinical care, there is still need for dosing methods based on skeletal muscle mass or LST and evidence that this type of dosing would reduce toxicities while still maintaining treatment standards. Future research in this area should focus on pharmacokinetic analysis of chemotherapeutics, including whole body LST mass as the volume of distribution for hydrophilic drugs. The primary goal of using LST-based dosing would be to reduce toxicities resulting in dose reduction, delays or termination. By minimizing the time patients are not receiving treatments secondary to toxicities, and maximizing the dose tolerated, patients will ideally be treated with the optimal chemotherapy dose. This would include the ability of patients to complete chemotherapy regimens as they are intended.

As previously discussed, there are inconsistencies in the field of body composition analysis. Standardization of image analysis and clarification of cutoff values for sarcopenia and myosteatosis will allow for this area of research to have a larger clinical impact.[40] There currently exists data that rebuts the use of the psoas muscle as predictive of whole body skeletal muscle and validates the use of total abdominal muscle area.[77] Unfortunately, there is still a lack of clarification in the determination and use of cutoff values. Moving forward, cohort characteristics, such as disease stage and patient ethnicity, should be considered before application of pre-defined cutoffs. Amalgamation of similar cohorts into large data repositories may help to clarify these threshold values and to generate more globally applicable cutoff values.

CT scans used for diagnostic purposes in CRC represent a wealth of data that is currently not being used in the clinical domain. As demonstrated in the literature, analysis of a single slice to quantify skeletal muscle mass and average SMR is easily done.[18,19] This is especially true with the use of segmentation software, requiring only manual editing.[103] Providing clinicians with specific values of their patients' skeletal muscle indices (SMI, SMR) would improve their ability to prognosticate survival outcomes.[42,46] Additional quantification over time would also help clinicians to identify those patients who are at increased risk of disease recurrence. In our results, we defined a group in which patients were losing skeletal muscle over time. We reported this value as a percentage change per year, rather than per 100 days, to allow for easy application to clinical populations. Patients identified as losing muscle at or greater than this rate (mean -5.10% SMI/year) could be selected for extended CT surveillance, with the aim of diagnosing disease recurrence at an early, treatable state.

Sarcopenia represents more than just a prognostic factor, which predicts poor survival outcomes. From previous research, it is clear that cancer patients maintain an anabolic potential, with the ability to improve their baseline skeletal muscle mass.[111,151,152] Therefore, sarcopenia is a patient-specific treatment target that may modify disease outcomes. Within the nutrition literature there are previous attempts to target cachexia and modify skeletal muscle loss, which have had poor results. This is likely due to interventions being applied to palliative cancer populations with baseline refractory cachexia.[111,152-154] Interventions in these patient populations are significantly less likely to effect disease outcomes, particularly when the median survival is often less than one year. Conversely, in stage I-III CRC, the average patient will survive well beyond one year, and the subsequent effects of interventions to improve skeletal muscle mass may have a more measurable effect.[17] Current research looking into the role of anti-inflammatories, omega-3 fatty acids and physical activity may provide promising results for future interventions.[155] These interventions could easily be applied to patients identified to be sarcopenic or at-risk of developing sarcopenia from the time of diagnosis and throughout their treatment trajectory. This would allow patients to play an even more active role in their treatment.

6.4 Conclusions

CT-derived measurement of skeletal muscle and adipose tissue represents a novel patient specific prognostic factor that can be incorporated into clinical practice. Our research has demonstrated the ease of measurement and the significant effects of sarcopenia and myosteatosis on survival outcomes. Furthermore, the presence of serial CT scans done for clinical purposes and quantification of change over time further

strengthens the association of body composition parameters and poor survival. The research presented here strengthens the argument for inclusion of sarcopenia and myosteatosis as prognostic factors in stage I-III CRC. Our results also imply that loss of skeletal muscle over time in the face of pre-existing sarcopenia represents a state of increased cancer recurrence risk and significantly worse survival outcomes.

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