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Comorbidity, body composition and the progression of advanced colorectal cancer

by

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Abstract

The purpose of this work was to further understand nutritional status, especially body weight and composition, during colorectal cancer progression. Population-based studies of colorectal cancer patients were conducted using administrative health data (primary and co-morbid diseases, demographics), and computed tomography (CT) imaging (body composition). In cohort 1, administrative health data was used to study comorbidities and nutritional status in 574 colorectal cancer patients referred for chemotherapy. Multivariate Cox regression revealed several comorbidities, performance status and weight loss ≥ 20% predicted survival. In cohort 2, a serial CT image analysis assessed longitudinal body composition changes during the last 12 months preceding death from colorectal cancer (n=34). Body composition changes were typified by exponential increases in liver metastases with concurrent accelerations of muscle and fat loss. These results have the potential to make a difference in how colorectal cancer patients are treated and researched by dietitians, oncologists, and health services researchers.

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List of Abbreviations

AJCC	American Joint Committee on Cancer
ANOVA	analysis of variance
BIA	bioelectrical impedance analysis
BMI	body mass index
C statistic	concordance statistic
CI	confidence interval
CM	comorbidity
cm^2	centimeter(s) squared
cm^3	centimeter(s) cubed
COPD	chronic obstructive pulmonary disease
CT	computed tomography
CV	coefficient of variation
d	day(s)
DXA	dual energy x-ray absorptiometry
ECOG	Eastern Cooperative Oncology Group
FFM	fat free mass
FM	fat mass
g	gram(s)
HIV/AIDS	Human Immunodeficiency Virus /Acquired Immununodeficiency Syndrome
HR	hazard ratio
ICD	International Classification of Diseases

ICD-O	International Classification of Diseases in Oncology
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
IRR	Incidence rate ratio
kcal	kilocalorie(s)
kg	kilogram
L3	third lumbar vertebrae
L	liter(s)
m^2	meter(s) squared
mg	milligram
mm	millimeter(s)
MNA	Mini Nutritional Assessment
MRI	magnetic resonance imaging
MST	Malnutrition Screening Tool
MUST	Malnutrition Universal Screening Tool
NHANES	National Health and Nutrition Examination Survey
NRS-2002	Nutritional Risk Screening
OR	odds ratio
PEG	percutaneous endoscopic gastrostomy
PG-SGA	Patient Generated Subjective Global Assessment
REE	resting energy expenditure
ROC	receiver operating characteristic
SD	standard deviation

TNM	Tumor, Nodes, and Metastasis
WHO	World Health Organization
yr(s)	year(s)

CHAPTER 1: Introduction and literature review

1.1 Purpose

The main purpose of this chapter is to provide an understanding of nutritional status, more specifically body weight and body composition, during the progression of colorectal cancer, and how it is an important, yet underutilized prognostic indicator.

1.2 Introduction

The Canadian Cancer Society reports that colorectal cancer is the third most common cause of new cancer cases in both males and females and second leading cause of cancer related death in Canada (1). Overall, men have a 1 in 14 chance and women a 1 in 15 chance of having colorectal cancer in their lifetime (1).

Even though colorectal cancer screening processes have improved substantially over the last several years, many patients are still diagnosed in the advanced stages of disease (2), where treatments are only given with the intention to prolong survival time or reduce symptoms. Men have a 1 in 27 chance and women have a 1 in 31 chance of dying from colorectal cancer in Canada (1). Overall 5 year survival rates from 1999-2005 for colorectal cancer were 65.2% for all stages combined and more specifically were 90.8% for localized stages, 69.5% for regional stages and 11.3% for distant stages (2). A representative Kaplan Meier curve depicting survival by American Joint Committee on Cancer (AJCC) stage is shown in **Figure 1-1** (3). Patients with cancer are often very

interested in determining their survival time and often more so than those suffering from other chronic diseases (4).

1.3 Cancer trajectories and prognostication

Cancer trajectories and prognosis are highly related to one another. Trajectories in health can be defined as the course of events following a cancer diagnosis. Specifically, a cancer disease trajectory is the path a patient's health status follows after receiving a cancer diagnosis. Overall, they are commonly characterized by a gradual health/functional decline over a timeframe of months to years, with an accelerated decline in the final weeks to months of life (5-7). Patients, health care professionals, and researchers are interested in determining factors which affect both the length and pattern of the disease trajectory.

Prognostication, which is defined as a prediction or a forecast of the future course of events (i.e., death) based on present status, can also be described as predicting the cancer disease trajectory. Prognosis can be estimated by physicians based on clinical/subjective judgment, or by using statistical methods encompassing a large selection of indicators (8). Disease specific factors including tumor type, stage, and grade (9) are perhaps some of the most important prognostic indicators. Several patient specific prognostic factors also exist which can influence survival. These include age, gender, genetic factors, symptoms, performance status, psychosocial factors, comorbidities (the concurrent presence of non malignant disease) (8) and nutritional status (10). These factors help to explain why survival may be different in patients with similar disease characteristics.

Prognostication is of interest and important for cancer patients, their families and health care professionals. Because both nutritional and medical treatments are based on prognosis, it helps to determine what type of therapies should be used. It also helps to determine when is the appropriate time to transfer patients into different care settings, if necessary (e.g., palliative care) (7) and allows the patient and their friends and family to plan their remaining time.

Comorbidities and nutritional status, which are both important prognostic factors, will be discussed in more detail in this Chapter.

1.4 Comorbidities as a cancer prognostic indicator

The simultaneous presence of non-malignant diseases (comorbidities) is common in colorectal cancer patients and has been shown to be an important contributing prognostic factor to overall survival (11-14). Comorbidity information can be procured from different types of data sources (e.g., self report, medical records, pharmacy records, and administrative data) (15).

Administrative health data is collected primarily for billing purposes after each encounter with the health system. It is especially advantageous in population based studies. This is because it has the ability to capture relatively accurate data at a low cost on populations from diverse geographical areas that were treated at different facilities (15, 16). Compilation of this data begins after a patient has encountered the health system which includes events such hospitalization or visiting a physician. After using the health system, information including demographics, relevant diagnoses and procedures, admission and discharge dates are extracted from patient charts by health records personnel.

Diagnoses relevant to the encounter with the health system are coded using World Health Organization (WHO) International Classification of Disease (ICD) diagnostic codes.

World Health Organization ICD diagnostic codes are an international language used to track information on diseases, signs, symptoms, causes of injury and reasons for using the health care system; it is currently on its 10th version which began use in 1992 (17). Canadian provinces began to phase in this coding system for hospital diagnoses in 2001 (18). In the 10th version, each disease, sign, symptom, cause of injury and reason for using the health care system is given a unique alphanumeric code (e.g., C20: malignant neoplasm of rectum). These codes are used to track and compare health status, causes of death and health utilization patterns from different populations across large geographical regions. They are also used to compile morbidity and mortality information by the WHO which allows comparisons between countries. These codes are used in different settings for diverse purposes including billing, health services research and epidemiology (19). For administrative inpatient hospitalization data in Alberta, each abstract (or summary of the hospitalization event) contains spaces for up to 16 ICD diagnostic codes which can be used to obtain information on comorbidities.

Of interest for nutrition research is that weight and nutrition related conditions can be captured using ICD 10 codes including protein energy malnutrition (ICD 10: E40–E46), obesity (ICD 10: E66) and weight changes (ICD 10: R63.4: abnormal weight loss, R64: cachexia, R63.5: abnormal weight gain).

There are also ICD 10 codes available to capture micronutrient deficiency malnutrition (ICD 10: E50–E64) and micronutrient hyperalimentation (ICD 10: E67). Of note, the ability of administrative health data to properly capture weight and protein energy malnutrition related data has been suggested to be poor (20, 21), but remains unclear.

Comorbidities can be searched in administrative health data by choosing the appropriate data source (e.g., inpatient hospitalization data), the specific index date or event and looking back in the data for comorbidities recorded from encounters with the health system occurring on or before that event. A time period of 1 year from an index date has been commonly used in previous studies to assess comorbidity burden (22-24). Longer look back periods may identify more information on comorbidities (with both an increase in the number of patients with comorbidities and the number of comorbidities per patient). However, others have found that the majority of hospitalizations occur within 6-12 months from an index date (25) and the comorbidities identified only in hospitalizations further from the index date may be less important compared to those identified closer (22, 25).

After the database, index date and look back period have been chosen, ICD codes from the dataset can be aggregated into groupings for different comorbid conditions (22, 26-28). Two of the most popular groupings for comorbidities using administrative health data are the Charlson (29) and Elixhauser (26) methods.

The Charlson method (29) is the most well known measure used to assess and risk adjust for comorbidity burden in administrative health data for cancer and other patient populations. It encompasses 19 conditions which were found to be predictive of 1 year death in 559 hospitalized internal medicine patients. Originally, it was developed using a chart review, but it has been subsequently adapted for use with administrative health data (22, 27, 28). Both the number and severity of conditions are summarized in a single weighted score. Even though the Charlson method has been used to successfully predict different types of outcomes in diverse populations (22, 29), several issues have been raised. These include the inclusion of conditions that may not predict survival (e.g., history of myocardial infarction at a distant prior time), weights for the different conditions that may not be appropriate for use for different populations and outcomes beyond the derivation cohort, and the concern that single score indices are an oversimplification of actual comorbidity complexity (26, 28, 30). It has also been suggested that using each Charlson comorbidity category as an individual binary variable in statistical models may be a superior risk adjustment method compared to the score based measure (31). The Elixhauser method was created as an attempt to address some of these limitations.

The Elixhauser method (26) is a newer approach which encompasses 31 conditions (including two weight related conditions: obesity and weight loss); this technique was developed and validated by predicting hospital charges, in-hospital mortality and length of stay using a large administrative database encompassing all 1992 California adult acute care inpatient hospitalizations (n=1,779,167). The

Elixhauser method is not a single weighted score like the Charlson index; each comorbidity category is treated as a separate entity (or binary variable).

Comorbidities are an important determinant of outcomes and are a very common finding in cancer patients. They are also complex as patients can have different types, combinations, and severities of disease. It is therefore important to consider comorbidities and their differing impact on outcomes when attempting to determine the unbiased relationship between an independent variable and outcome of interest (e.g., survival) in cancer patients. The Charlson and Elixhauser measures are two methods available to address this issue.

Risk adjustment is the process of accounting for differences in population characteristics (e.g., age, sex, comorbidities etc.) with the goal of obtaining the true relationship between a specific independent variable(s) and outcome of interest. This is an important process for most outcome studies (32) and plays an important role in model building.

In statistics, the overall goal of model building is to select the best and minimum number of variables which will lead to a model that predicts an outcome of interest and can be generalized to similar populations (33). When building a multivariate statistical model, in addition to including variables with statistical significance at the univariate level ($p < 0.1$), it is important to include those which have clinical or biological significance (33). Building a model using this method will help to ensure an unbiased relationship between the outcome and independent variable(s) of interest.

The Elixhauser method is suggested to be a superior comorbidity risk adjustment method in hospitalized patients with respiratory and cardiac conditions (25, 34), and osteoarthritis (23) compared to the Charlson method. Studies comparing Elixhauser and Charlson in cancer patients are scarce (24). The Charlson method is more commonly used to risk adjust for comorbidities in cancer studies; however, based on results from other populations, this may not be the best choice. This still requires further investigation.

1.5 Nutritional status as a cancer prognostic indicator

Nutritional status has been described as an important prognostic factor in cancer (10) and other diseases (35). It can be thought of as a person's well being in terms of the balance between intake and use of nutrients.

1.5.1 Malnutrition

Malnutrition can be defined when there is an excess or more commonly a deficiency of calories, protein and other nutrients which causes effects on one or more of the following: body size, shape and composition, function and outcomes (36). In adults from developed countries, malnutrition is most commonly associated with disease (35) (e.g., renal disease, HIV/AIDS, neurogenerative disease, liver disease, chronic heart disease, chronic obstructive pulmonary disease, and cancer, and often more severely if present in the elderly). Disease associated malnutrition frequently results in a loss of body weight and especially fat free mass (FFM) ultimately due to requirements exceeding intakes.

Malnutrition can be caused by a combination of one or more of the following factors depending on the individual and the disease in question: factors

that can alter nutrient intake, factors that increase nutrient losses, and factors that increase nutrient requirements. Factors which may result in altered (or decreased) dietary intakes could include gastrointestinal obstructions or medications which may cause symptoms that hinder dietary intakes or lead to anorexia (35). Inadequate absorption of nutrients from the gastrointestinal tract can result in increased nutrient losses. Systemic inflammation and increases in other catabolic factors can result in altered metabolism (35, 37) and lead to increases in resting energy expenditure (REE), the amount of calories expended at rest, to a hypermetabolic state. A hypermetabolic state is generally regarded as a REE ≥ 110% predicted using methods such as the Harris Benedict Equation (38, 39). Social factors such as living alone and low educational status (40) can also increase the risk of malnutrition.

Typically malnutrition is associated with weight loss and/or low BMI values. However, because of the rise in obesity in the Canadian population (41) and worldwide, this may no longer be completely the case. This rise in obesity is directly relevant to the field of oncology and other chronic diseases because obesity is a well established risk factor for cancer and many other chronic diseases (42, 43). Using colorectal cancer as an example, it was recently estimated using the population attributable fraction method that obesity was responsible for 16.2% and 12.5% of colorectal cancer in men and women, respectively in Canada (43). Therefore, we expect many colorectal cancer patients presenting for treatment are obese. However, it is also important for health care professionals to suspect malnutrition in patients even in the presence

of obesity, especially if there has been involuntary weight loss (44) as this could signal loss of skeletal muscle which may result in sarcopenic obesity. Sarcopenic obesity can be defined as a muscle mass < 2SD below the healthy young adult mean in the presence of obesity (45, 46). It has been associated with poor outcomes (45-47).

Malnutrition has been reported to be associated with several types of outcomes including decreased survival, increased morbidity (including surgical complications, infections, poor wound healing, poor performance status, and increased length of hospital stay) (35), increased complexity (48), and costs of care (49-51). In order for these outcomes to be prevented, it is important that malnutrition is diagnosed and treated early.

1.5.1.1 Detecting Malnutrition with Nutrition Screening

In patients with malnutrition, early intervention with nutritional therapy is important to increase likelihood of positive outcomes. The intention of nutritional screening is to identify patients who are at nutritional risk by searching for factors associated with malnutrition. Different tools such as the Patient Generated Subjective Global Assessment (PG-SGA), Malnutrition Universal Screening Tool (MUST), Nutritional Risk Screening (NRS-2002), the Mini Nutritional Assessment® (MNA®), and the Malnutrition Screening Tool (MST) (52, 53) are available to screen patients which can either be completed by a health care professional or sometimes by the patient themselves. They frequently encompass questions asking about body weight, weight history, height, dietary intakes, symptoms which may interfere with nutrition intake and other factors. Body

weight measures such as body weight standardized to height (body mass index (BMI) [BMI = weight (kg) / height (m^2)]) and weight change, are perhaps the most commonly used variables for this purpose. In cancer patients, the PG-SGA has been the most extensively validated nutrition screening tool, and is currently the most well regarded and common tool in this population (52, 53).

Having different nutritional screening tools and techniques can be regarded as beneficial as they may be better suited to detect malnutrition in different populations. However, the tools use slightly different criteria (such as different BMI and weight loss cutpoints, different ways to classify nutritional intake compared to normal) to determine whether a patient is at nutritional risk. This helps explain why there is a large diversity in reported prevalence rates of malnutrition in different patient populations and can make studies difficult to compare (35, 54).

Patients who are deemed to be at nutritional risk from screening should undergo a full nutrition assessment by a dietitian or other nutrition professional. A nutrition assessment is a more comprehensive examination of the patient to determine their nutritional status which will allow the prescription of proper therapies. It includes medical, social, and diet histories, anthropometry, body composition, and biochemical measures (55, 56) and should be repeated over time to determine the effectiveness of the nutrition therapy (57).

1.5.2 Cancer related malnutrition

Malnutrition is common in cancer patients (58). In clinical settings, no formal criteria exist and it can be assessed in many different ways, but it is

commonly assessed in cancer patients using weight loss (59) starting at ≥ 5% and/or BMI < 20. Weight loss can occur at different times during the cancer trajectory. It can be among the first symptoms of disease for many patients and is known to be highly prevalent near the end of the disease trajectory (60). It is more prevalent in patients with solid tumors, advanced disease, and the elderly (61). Dewys et al. (10) revealed that weight loss 6 months prior to chemotherapy was common in cancer patients where curative options were not possible. Overall, across all tumor groups, a weight loss 5–10% was reported in 17% of patients and a weight loss of > 10% was reported in 15% of patients. Weight loss was most common among patients with gastric and pancreatic cancer. Specifically, in colon cancer patients, 14% reported a weight loss of 5–10%, and 14% reported a weight loss > 10%.

Cancer patients develop weight loss at diagnosis and throughout the rest of the disease trajectory due to several factors including tumor type and stage (62). The tumor itself may require energy for its own needs and may also cause changes in host metabolism which can result in inefficient use of nutrients and an increase in whole body metabolic needs (63). Overall, resting energy expenditure (REE) is suggested to be higher in cancer patients than healthy individuals, but high levels of variability have been reported (60, 64-66). This variability is not completely understood. Factors that predict hypermetabolism in cancer patients include advanced stage disease, a longer duration of disease, and an acute phase protein response (60, 66, 67). Symptoms from the tumor itself and the treatment (such as abdominal fullness, taste changes, vomiting, and mouth dryness) have

also been found to be more common in patients with weight loss (68). These symptoms may cause insufficient dietary intakes. When we combine inadequate dietary intakes in a person with increased needs, weight loss will occur because the body is forced to draw upon peripheral energy stores to meet needs.

Malnutrition in cancer patients is associated with many different types of consequences throughout the disease trajectory; decreased survival, reduced treatment response and poor quality of life are among the most commonly reported (10, 69). Body weight loss generally mirrors the cancer trajectory, with an accelerated decline in the final weeks to months of life (5), with cachexia appearing in the end stage.

1.5.2.1 Cancer cachexia

Cachexia is a Greek term, kakos (bad) hexis (condition), which translates into 'bad condition' (i.e., severe skeletal muscle and fat loss). Hippocrates (460-370 BC) first described cachexia as a condition where "…the flesh is consumed and becomes water… the abdomen fills with water, the feet and legs swell, the shoulders, clavicles, chest, and thighs melt away… This illness is fatal". In addition to severe weight loss, patients with cachexia frequently possess a group of unfavorable symptoms including anorexia, early satiety, edema, weakness and anemia which results in several unfavorable outcomes including decreased quality of life, diminished performance status, poor treatment tolerance and decreased survival (70-72). A classic post mortem analysis study from the 1930s revealed that cachexia was the cause of death in ~20% of colorectal cancer patients (73),

which is likely due to the loss of respiratory muscle function (70) and poor immune status.

Despite the number of advanced cancer patients affected with severe weight loss, a formal definition of cancer cachexia has been lacking. This lack of a formal definition was recently highlighted by Fox et al. who found that the prevalence of cachexia varied substantially depending on the definition (74). Fearon et al. (75) suggested that cancer cachexia could be considered present if a patient had a 10% weight loss, a dietary intake < 1500 kcal/d, and a c-reactive protein (a marker of inflammation) > 10mg/L. To remedy the lack of formal criteria to define cachexia, a consensus definition was recently released which defined cachexia as a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass (76). Using the new definition, a diagnosis of cachexia can be made if a patient has a weight loss of ≥ 5% in 12 months (or a BMI < 20) and three or more of the following criteria: decreased muscle strength, fatigue, anorexia, low FFM index, and abnormal biochemistry (increased c-reactive protein, anemia, low serum albumin) (76).

1.5.2.2 Obesity and cancer weight loss

Obesity and cancer related weight loss is a contemporary topic and merits a special discussion. Currently, it remains unclear to health professionals how to evaluate the nutritional status of cancer patients who are obese. Moreover, obese patients and their families frequently believe cancer associated weight loss is beneficial (77) which is not the case, especially when weight loss encompasses

skeletal muscle. There is also considerable debate on how to best feed obese cancer patients. Should these patients lose weight during their disease, should they maintain their weight, or should they try to gain weight? One new phenomenon we are beginning to better understand and may help to partially answer this question is that obesity may confer a survival advantage in some patients. Over the past 5–10 years, research suggests that being overweight or obese is associated with prolonged survival in patients with a diagnosis of a wasting disease (78-80). This is because these patients are more likely to die from the wasting disease rather than the risks associated with excess body weight such as type 2 diabetes and cardiovascular disease. In wasting diseases, excess adipose tissue becomes an energy reserve which can be mobilized in response to catabolic processes. This has been termed the "obesity paradox" or "reverse epidemiology" phenomenon because this is opposite from how obesity affects survival in the general population. Obesity in the general population is generally associated with decreased survival.

1.5.2.3 Body weight, weight loss and cancer summary

Some weight loss mechanisms may be overtly evident in some patients, such as a patient who is not eating. Unfortunately, despite the number of people affected by both mild and more severe weight loss (i.e., cachexia), many aspects are still poorly understood. Further understanding of body composition and the composition of cancer associated weight change is likely still needed to help increase understanding of cancer associated weight loss.

1.6 Body Composition

Human body composition is a field of study over 150 years old (81). It can be studied on 5 different levels: atomic, molecular, cellular, tissue-organ, and whole-body (82). The sum of all components at each level of study is equal to body weight.

1.6.1 Body composition assessment

Body weight is considered the easiest, lowest cost, and crudest measure of body composition. It is a one compartment model as there is no measure of the composition of the body. It does not even make a distinction between the fat mass (FM) and fat free mass (FFM) (which encompasses all non fat tissues in the body including bone) compartments. Body weight is frequently standardized to height and reported as BMI. Body mass index is commonly used to determine weight related health risk as it is correlated with total body fat. A high total body fat is associated with diseases including diabetes, hypertension, heart disease, gallbladder disease and some types of cancer (83, 84). When using BMI, it should be understood that it has several limitations (83) including masking quantities and/or changes in different body tissues which may be associated with different levels of risk and benefit. Body composition measures are therefore needed as they can provide more detail on the different body components associated with different levels of risk.

Body composition assessment partitions the body into two or more components. Many body composition studies use a two component molecular model that separates the body into FFM and FM compartments. Different

techniques are available to provide a whole body estimate of FFM and FM including bioelectrical impedance analysis (BIA) and air displacement plethysmography (BOD POD®) (85, 86).

Dual energy x-ray absorptiometry (DXA) is a criterion standard method that uses a three compartment molecular model. It partitions the body into the lean soft tissue (muscle, organs, and all other non fat tissues excluding bone mineral), fat mass, and bone mineral compartments (86). Unlike the two compartment methods, DXA also has the ability to provide information on the regional composition of areas such as the head, trunk and appendages. As such, appendicular skeletal muscle mass, which is the total lean soft tissue mass in the arms and legs, can be used as a surrogate for whole body skeletal muscle. Appendicular skeletal muscle represents ~73–75% of whole body skeletal muscle (87). When standardized to height (m^2), it is commonly used as a measure for sarcopenia (or low muscle mass usually defined as < 2SD below the healthy young adult mean) (88).

Some advantages of tools that partition the body into two or three compartments are the relatively low cost after the initial equipment expense, the ability to perform rapid testing, and low risks associated with the testing procedures. Some disadvantages are lack of ability to account for alterations in hydration status, which is important in individuals with edema and ascites (89). In addition, they do not partition the lean soft tissue compartment into different components with distinct relevance, such as organ tissue and skeletal muscle, and the adipose tissue into subcutaneous, visceral and intermuscular depots.

The tissue organ level examines the mass and proportion of different tissues and organs in the body including adipose tissue (visceral, intermuscular, and subcutaneous depots), skeletal muscle (specific muscles), organs (e.g., liver, spleen, heart, kidneys) and bone (82). This level of study emphasizes that FM and FFM are not homogenous compartments. Specifically, FFM encompasses muscle and organs which have different functions and specific metabolic rates. For example, the specific metabolic rate of skeletal muscle is 13kcal/kg/d which is much lower than the specific metabolic rates for organs (e.g., 200kcal/kg/d for liver, 240kcal/kg/d for brain, and 440kcal/kg/d for heart and kidneys) (90). It is also known that high metabolic rate organs such as liver, brain, spleen, and kidneys encompasses ~5–6% of body weight despite being responsible for ~60% of REE (90, 91). Because body composition (and more specifically FFM (92)) is the largest determinant of REE and organ mass is a significant contributor, this level of body composition has been used in the past to successfully model REE in healthy individuals (91, 93).

Computed tomography (CT) and magnetic resonance imaging (MRI) are criterion standard tools capable of measuring body composition at the tissue organ level. These methods involve taking a series of images which can be used in different ways to determine body composition. A series of images can be analyzed to determine the tissue volume (94); the volume can then be multiplied by tissue specific densities to determine tissue mass (87, 95). In addition, muscle and adipose tissue cross sectional areas (cm^2) from transverse images taken at standard vertebral landmarks (such as the 3^{rd} lumbar vertebrae (L3)) can be used

to provide estimates of whole body muscle and adipose tissue stores in both healthy adults (96) and cancer patients (97). The advantages of CT and MRI are their high validity and reliability (94, 98), however, the disadvantages are that they are expensive, can have long testing times, and may or may not be able to scan individuals with a BMI $\geq$ 40 (89). CT imaging also requires exposure to a radiation dose that would be considered unethical for healthy individuals. This is not an issue in cancer populations as they require CT scanning as part of routine care. This part of the patient record is usually electronically stored and available for secondary body composition assessment (97). This avoids having the patient undergo extra body composition tests for research purposes. This is important as studies with advanced cancer patients with multiple tests and interventions can have high withdrawal rates (99, 100).

1.6.2 Body composition and cancer

Body composition research in colorectal cancer, advanced cancer, and advanced colorectal cancer can still be considered in its infancy especially when looking at measurement at the tissue organ level. In Asia, a few studies used CT imaging to measure the impact of visceral adipose tissue on overall survival (101) and surgical outcomes (102-105) in patients with resectable colorectal cancer. In advanced cancer patients, clinical trial studies using body composition as an outcome measure or research assessing nutritional status of this population from the past 10 years have relied primarily on BIA (106-109) and occasionally DXA (100) to assess body composition. In addition, longitudinal studies of body composition changes in advanced cancer patients are relatively scarce (100, 110).

Despite how commonly two compartment molecular methods are used in the literature to assess body composition, they may not be the best approaches based on work from 25 years ago when CT imaging was first used for body composition assessment (111). Heymsfield and McManus (110) reported in their classic prospective case study evaluation of the body composition changes in cancer patients that different lean soft tissue compartments (i.e., organ, muscle) change in dissimilar ways over the cancer disease trajectory. Specifically in colorectal cancer patients, they found that liver and spleen (which represent high specific metabolic rate tissues) increased as skeletal muscle mass simultaneously decreased. This increase in liver mass may be due to two possible reasons. The first is that liver metastases, which affect ~50% of all colorectal cancer patients (112), can cause increases in liver mass (113). Others also report that the increases in liver size in cancer patients may be due to elevated rates of substrate recycling, gluconeogenesis, and acute phase protein synthesis (70, 114). These findings suggest that if body composition is measured where different lean soft tissues are considered a composite (such as in two or three compartment molecular methods), changes in one type of lean soft tissue may mask changes in another. This may have occurred in a study by Fouladiun et al. (100) who found that the lean soft tissue mass in the trunk increased as time to death neared, whereas in the limbs of the same patients, lean soft tissue was found to have decreased, which would be expected with cachexia.

The work by Heymsfield and McManus (110), although only a case study approach, suggests that body composition assessment in colorectal cancer patients

should be performed at the tissue organ level. Despite these findings, most recent body composition work in advanced cancer patients uses BIA (or DXA) which are not able to discern quantities or changes in different lean soft tissue components. Furthermore, longitudinal studies are missing. This suggests further work is needed in this area.

1.7 Summary

Many factors have the ability to affect cancer related outcomes which may or may not be considered important by researchers, medical and nutrition professionals. Comorbidities are known to affect cancer related outcomes and are frequently accounted for in cancer studies. However, the best method to risk adjust for comorbidities in cancer patients is unknown and previous work suggests that the most commonly used method may not be the best choice. Nutritional status, despite being an important cancer prognostic indicator has not been consistently used by the medical community including oncologists in the past (48, 115-119). Nonetheless, poor nutritional status is often considered a concern by patients and their families (120). For nutritional status to be considered to be an important cancer prognostic indicator, it is essential to further develop our understanding in this area.

1.8 Hypothesis

The purpose of this thesis is to investigate the following two hypotheses in colorectal cancer patients:

1) Proper risk adjustment for unbiased survival prediction will encompass disease stage, performance status, age, sex and comorbidities (both body weight- and non body weight related conditions).
2) Colorectal cancer patients are affected by a viscerally driven cachexia syndrome originating from increasing masses of high metabolic rate tissues, especially liver, spleen, and tumor. The increase in high metabolic rate tissues will result in an elevated resting energy expenditure which will lead to loss of peripheral tissues (i.e., skeletal muscle and adipose tissue).

1.9 Objectives

The objectives of this thesis are as follows:

Investigated in Chapter 2:

1) To assess how well the Charlson and Elixhauser comorbidity methods risk adjust for comorbidities derived from administrative inpatient hospitalization data.
2) To assess the quality of obesity and weight loss data captured using inpatient hospitalization administrative health data compared to prospectively collected clinical data.
3) To evaluate whether replacing the Elixhauser body weight-related comorbidities derived with inpatient hospitalization administrative health data with cancer-appropriate weight variables and performance status derived using clinical data improves the predictive power of the comorbidity measure.

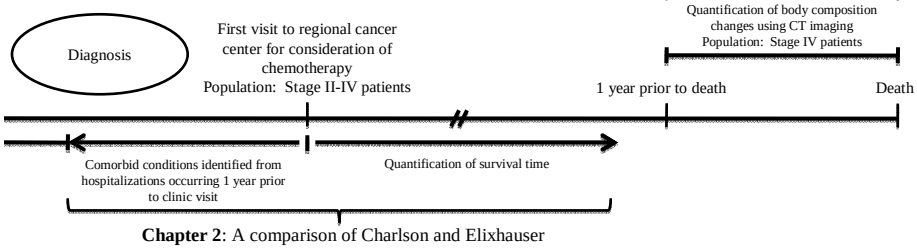
Investigated in Chapter 3:

4) To retrospectively measure with CT imaging longitudinal changes in both peripheral (i.e., muscle and adipose tissue) and high metabolic rate (i.e., liver and spleen) tissues in a cohort of patients during the last year of life.
5) To estimate the effect of liver and spleen changes on whole body resting energy expenditure during the last year of life using a computational model of human metabolism.
6) To prospectively evaluate the relationship between resting energy expenditure determined by indirect calorimetry and organ mass.

A timeline showing where these studies are situated in the colorectal cancer disease trajectory is shown in Figure 1-1.

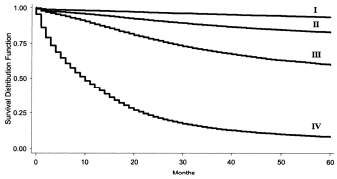
Figures

Figure 1-1: Study timeline and typical Kaplan Meier curves for colorectal cancer survival by stage



Chapter 3: A viscerally-driven cachexia syndrome in patients with advanced colorectal cancer: contributions of organ and tumor mass to whole body energy demands

Chapter 2: A comparison of Charlson and Elixhauser comorbidity measures to predict colorectal cancer survival using administrative health data



Stage	0 mo		30 mo			60 mo		
	Survival (%)	N	Survival (%)	N	P	Survival (%)	N	P
I	100	14500	96.1	8591	—	93.2	4515	—
II	100	34361	89.2	19492	<.0001	82.5	10105	<.0001
III	100	26949	72.7	12192	<.0001	59.5	5514	<.0001
IV	100	20802	17.3	1832	<.0001	8.1	432	<.0001

Sample Kaplan Meier curves for survival by AJCC stage

From: O'Connell et al. Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging
J Natl Cancer Inst 2004;96(19):1420-5 (by permission of Oxford University Press and Journal of the National Cancer Institute)

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CHAPTER 2: A comparison of Charlson and Elixhauser comorbidity measures to predict colorectal cancer survival using administrative health data

2.1 Introduction

Cancer survival is related to primary malignancy characteristics such as site and stage, and patient variables such as sex, age, and performance status. The concurrent presence of non-malignant diseases (comorbidities) is common and has been shown to be an important contributing factor to cancer survival (1-4). Cancer patients who are ≥ 70 years typically have 3 comorbidities (5), of which cardiovascular disease and hypertension are among the most common (6). Importantly, weight-related conditions such as underweight, obesity and involuntary weight loss also predict cancer survival (7, 8). Exclusion of any of these relevant explanatory variables would result in biased estimates of survival. We suggest that disease features, demographics, and comorbidities including weight-related conditions should all be considered in cancer risk adjustment models.

Inpatient administrative health data is an information source often used to identify comorbidities recorded with International Classification of Disease (ICD) diagnostic codes. The Charlson index (9) is the most common measure to assess comorbidity in cancer patients with ~1000 citations since 2005. It was originally based on the risk of 1 year death for 19 conditions in 559 hospitalized internal medicine patients. The Elixhauser method is a more recent approach which

encompasses 31 conditions; this technique was developed and validated by predicting in-hospital mortality, length of stay, and hospital charges using an administrative database encompassing all adult acute care inpatient hospitalizations that occurred in 1992 in California (n=1,779,167) (10). Elixhauser is suggested to be a superior risk adjustment model in hospitalized patients with cardiac and respiratory conditions (11, 12), and osteoarthritis (13). About 70 citations using Elixhauser in cancer studies have appeared since 2005, showing its emerging popularity. Only one study to date has compared Elixhauser with Charlson in cancer patients (14).

Weight loss and obesity are included in the Elixhauser, but not the Charlson measure. Involuntary weight loss is an independent prognostic factor for poor treatment response and reduced survival in cancer patients (7). Obesity (defined as a body mass index (BMI) $\geq 30 kg/m^2$) is normally regarded as a risk factor for decreased survival in the general population when all-cause mortality is considered (15); however, recent reports suggest that in wasting diseases (including cancer and renal disease) patients with obesity have longer, not reduced survival, compared to patients with a lower BMI (8, 16, 17). It is also presently uncertain how body weight features should be included for risk adjustment in cancer survival models and whether the manner in which they are captured in administrative data and included in the Elixhauser method corresponds to what is currently known about their impact on survival in cancer patients based on clinical data.

We studied a population-based cohort of stage II-IV colorectal cancer patients to further develop our understanding of optimal risk adjustment procedures in cancer survival research. Building upon a base model which included age, sex, and stage, we sought to improve the model by adding either Charlson or Elixhauser comorbidities to determine the better risk adjustment tool. We also evaluated whether adding performance status and replacing Elixhauser weight-related conditions with more cancer-appropriate weight variables derived using clinical data improved the model's predictive power.

2.2 Methods

Ethical approval was obtained from the Alberta Cancer Board Research Ethics Board.

2.2.1 Patient population, demographics and cancer-related variables

All Alberta residents with stage II-IV colorectal cancer (ICD-O: C18-C20 excluding appendix cancer) (18) who visited a new patient medical oncology clinic at the Cross Cancer Institute (Edmonton, Canada) between June 8, 2004 and March 31, 2006 were included. This single tertiary cancer facility in northern Alberta (population 1.8 million) handles almost all (> 95%) referrals for consideration of chemotherapy or radiation therapy. Age, sex, stage, tumor site, and date of death were obtained from the Alberta Cancer Registry. The first clinic visit date was our index date and the point in time at which stage was established and from which survival time was quantified. All patients were followed for > 3yrs. Cancer stage was defined using the American Joint

Committee on Cancer (6th Edition) stage groupings I, II, III, and IV (19). The end date of our study was June 9, 2009.

Height, weight and weight history were patient-reported variables obtained from the Patient Generated Subjective Global Assessment (PG-SGA) (20). The PG-SGA is a clinical tool used for nutritional screening of cancer patients and is completed at this clinic visit. Self-reported height, weight and weight history have been found to be reliable measures in healthy adults (21, 22) and cancer patients (23). The PG-SGA includes a performance status score (patient-reported version of the Eastern Cooperative Oncology Group (ECOG) performance status): 0 = normal with no limitations; 1 = not my normal self, but able to be up and about with fairly normal activities; 2 = not feeling up to most things, but in bed or chair less than half the day; 3 = able to do little activity and spend most of the day in bed or chair; 4 = pretty much bedridden, rarely out of bed.

2.2.2 Comorbidities

Comorbidities were obtained from inpatient hospitalization administrative data provided by Alberta Health and Wellness, the agency responsible for administering the provincial health care plan. This dataset includes all inpatient hospitalizations that occurred in any Alberta hospital and includes up to 16 ICD-10 diagnostic codes for each hospitalization. Hospitalizations that occurred in the year prior to the index date were included in the calculation of comorbidities.

2.2.2.1 Charlson and Elixhauser methods

Comorbidity burden was quantified using the Charlson and Elixhauser methods which have validated coding algorithms available for ICD-10 codes (24). All diagnostic codes from each hospitalization were searched to identify codes specified in the Charlson and Elixhauser algorithms. Binary variables were created indicating presence or absence of each Charlson and Elixhauser comorbidity. Patients who were not hospitalized in the year prior to the index date were considered to have no comorbidities. Comorbidity categories involving cancer were excluded and those with ≤ 3 occurrences were omitted for statistical reasons.

2.2.2.2 *Augmented* Elixhauser method

Both ECOG performance status and clinical body weight data were used to *augment* the Elixhauser method. All comorbidities not related to body weight were derived using administrative data. Two weight-related variables were created using PG-SGA data for the *augmented* Elixhauser method: abnormal weight loss, and abnormal BMI. These variables are important because colorectal cancer patients are normally a weight-losing population (mean 6 month weight loss for our population 6.7 ± 7.8%) and risk of death in cancer patients increases at lower BMI values (1, 25, 26). Abnormal weight loss was defined as loss of ≥ 20% within the past six months (i.e., Grade 3 weight loss from the National Cancer Institute Common Terminology Criteria for Adverse Events (v3.0)). Abnormal BMI was defined as < 20kg/m^2, a value consistent with a diagnosis of cachexia (27).

2.2.3 Statistical Analysis

Analysis was conducted in three stages. In each stage, regression models were fitted and comorbidities were determined and grouped using each of the following methods: 1) Charlson; 2) Elixhauser; or 3) *augmented* Elixhauser. Two- and 3yr survival (robust Poisson regression), and overall survival (Cox regression) were the outcome variables. Because > 10% of the population had the outcome, robust Poisson regression was used instead of logistic regression to avoid overestimation of risk ratios (28, 29).

First, unadjusted hazard ratios (HR) and incidence rate ratios (IRR) were calculated for each Charlson and Elixhauser comorbidity variable using Cox and robust Poisson regression models; corresponding 95% confidence intervals for each estimate were also determined.

Second, adjusted Cox and robust Poisson regression models were fitted. Models included variables with well-accepted associations with survival (i.e., age, sex, and stage), as well as all the comorbidity variables using Charlson, Elixhauser, and *augmented* Elixhauser approaches. For each individual comorbidity, we calculated adjusted HR, IRR, and corresponding 95% confidence intervals. Age was treated as a continuous variable (30) and performance status was dichotomized by combining scores 0–1 and 2–4 to represent good and poor performance status, respectively (7, 23).

Finally, robust Poisson regression models were compared to determine which of Charlson, Elixhauser, or *augmented* Elixhauser best predicts 2- and 3yr survival. Each regression model encompassed one of the three comorbidity

methods as well as age, sex, and stage. We also evaluated a base model which included only age, sex, and stage.

To determine which comorbidity method was the best predictor of survival, change in the concordance (c) statistic was tested using the roccomp command in Stata (31). This command tests for differences between two correlated receiver operating characteristic (ROC) curves (32), a graph of the true positive rate vs. the false positive rate. The c statistic is equivalent to the area under the ROC curve (33); in this case, the probability that someone who died has a higher predicted probability of dying than someone who did not die in the specified timeframe. A c statistic of 0.5 indicates the model predicts the outcome as well as chance (i.e., equal numbers of true and false positives), 0.7 to <0.8 is acceptable discrimination, 0.8 to <0.9 indicates excellent discrimination, 0.9 to <1.0 is outstanding discrimination and, 1.0 is perfect prediction (34). Other comorbidity measure validation studies with binary outcomes have used this method (11, 12, 14). To ensure that our model was not overfitting, we internally validated our robust Poisson regression models using ten-fold cross validation (35). We then took all of the predicted probabilities generated from the 10 models and generated a single ROC curve. This process was carried out separately for 2- and 3-year survival for each model.

SPSS v17.0 (SPSS Inc, Chicago, IL) and Stata v10.0 (Stata Corp, College Station, TX) were used for statistical analysis. All tests were two sided and α was set at 0.05.

2.3 Results

2.3.1 Demographic and cancer-related variables

There were 574 patients included, 486 (85%) of whom were hospitalized in the year prior to the index date in a total of 764 hospitalizations. Population characteristics are listed in **Table 2-1**. No differences in age, sex, and performance status were observed between hospitalized and non hospitalized patients.

2.3.2 Comorbidities

2.3.2.1 Charlson and Elixhauser Comorbidities

Overall, 25.6% had ≥ 1 Charlson comorbidities and 7.5% of those patients had ≥ 3 comorbidities. **Table 2-2** presents the frequency of each Charlson comorbidity and their unadjusted and adjusted HR and IRR. The following Charlson comorbidities were dropped from statistical analyses due to low counts (i.e., ≤ 3 patients affected): peripheral vascular disease, rheumatic disease, hemiplegia or paraplegia, moderate or severe liver disease, and HIV/AIDS. Diabetes without complications, chronic pulmonary disease and myocardial infarction were the most common conditions. In the unadjusted Cox regression models, congestive heart failure, dementia, and renal disease were significant predictors of survival but only renal disease was significant in the adjusted model.

Overall, 46.5% had ≥ 1 Elixhauser comorbidities and 26.9% of those patients had ≥ 3 comorbidities. **Table 2-3** presents the frequency of each Elixhauser comorbidity and their unadjusted and adjusted HR and IRR. The following Elixhauser comorbidities were dropped from statistical analyses due to

low counts (i.e., ≤ 3 patients affected): peripheral vascular disorders, paralysis, peptic ulcer disease, rheumatoid arthritis, coagulopathy, drug abuse, alcohol abuse, psychosis and HIV/AIDS. The most frequent Elixhauser conditions were uncomplicated hypertension, uncomplicated diabetes, and cardiac arrhythmias. In unadjusted Cox regression models, congestive heart failure, cardiac arrhythmias, renal failure and fluid and electrolyte disorders were significant predictors of survival. Cardiac arrhythmias, uncomplicated hypertension and fluid and electrolyte disorders were significant predictors in the adjusted Cox regression model. Unlike other comorbidities, uncomplicated hypertension was positively associated with survival.

Pair wise correlations between the comorbidities did not reveal any collinearity issues amongst different conditions within the Charlson and Elixhauser measures.

2.3.2.2 *Augmented* Elixhauser comorbidities

Only 1.0% of hospitalized patients had an ICD 10 diagnosis of weight loss recorded, however 4.5% of our cohort reported a weight loss of ≥ 20%. Weight loss derived using only administrative health data was not a significant predictor of survival. However, weight loss derived using the 20% cutpoint from the self-reported data was significant in both the adjusted and unadjusted Cox regression models. Approximately, 6.6% of patients had a BMI < 20kg/m^2 (27). Low BMI was significant predictor of survival in the unadjusted Cox regression model and tending towards significance in the adjusted model. Performance status was a

significant predictor of survival in the unadjusted and adjusted Cox regression models.

2.3.3 Robust Poisson regression model discrimination

The c statistics for Elixhauser and Charlson comorbidity measures adjusted for age, sex, and stage for 2- and 3-yr survival are reported in **Table 2-4**. A base model (age, sex, and stage) with no comorbidities already demonstrated excellent discrimination (i.e., c statistics > 0.8) for 2- and 3yr survival. Adding Charlson comorbidities as individual binary variables generated a model that was not different from the base model (2yr: p=0.14, 3yr: p=0.17). The addition of Elixhauser comorbidities to the base model, however, increased the c statistic by 0.027-0.028 compared to the base model (2yr: p=0.0051, 3yr: p=0.0017). The c statistic for the Elixhauser comorbidities was 0.021 higher compared to the Charlson comorbidities and significantly different (2yr: p=0.018, 3yr p=0.016). The addition of the *augmented* Elixhauser variables to the base model also had higher discrimination compared to the base model alone (2yr p=0.0003, 3yr p=0.0001). The *augmented* Elixhauser method achieved a higher c statistic than the standard Elixhauser method for 2yr (p=0.026), but not 3yr (p=0.13) survival. The c statistics for models with either the Charlson (9) or Elixhauser (36) weighted scores added to the base model were not significantly different from those of the base model alone. The ten-fold cross-validated c statistics ranged from 0.804 to 0.839 for all models, including the base model, Charlson, and Elixhauser (normal and *augmented*) for both 2- and 3yr survival.

As stage is a variable with substantial discrimination power in this population (c statistics: 2yr: 0.777, 3yr: 0.790), we tested the differences in comorbidity measure performance adjusted for age and sex separately by stage (**Table 2-5**). The highest c statistic in the base models was observed in stage III patients. For all stages and survival times, the Elixhauser and *augmented* Elixhauser methods had significantly higher discrimination compared to the base model (i.e., age, sex). The greatest increase in c-statistic contributed by the addition of the Elixhauser comorbidities was for 2yr survival in stage II patients (increased from 0.683 to 0.838). Overall, the *augmented* Elixhauser had higher c statistics compared to the standard Elixhauser method; however, this did not reach statistical significance except for stage IV, 3yr survival. This analysis clarifies that c statistics vary by stage, but that the overall conclusions stated above were also true within stage, including a lack of discrimination by Charlson model and statistically increased discrimination by Elixhauser method.

2.4 Discussion

As cancer is largely a disease of the elderly who frequently possess multiple comorbidities, it is essential that the best measure is used to control for additional conditions which may impact survival. Emerging recent evidence, largely from non-cancer populations suggests that the Elixhauser method is a superior comorbidity risk adjustment model compared to the Charlson method (11, 12). Despite these findings, the Elixhauser method has not been popular in cancer studies perhaps due to few reported comparisons with the Charlson

measure and concerns regarding the inclusion of too many explanatory variables (i.e., 30+), thus requiring a fairly large sample size.

We found that the Elixhauser measure is a superior comorbidity risk adjustment method with a significantly higher c statistic for both 2- and 3-year survival than the Charlson measure (Table 2-4). Some reasons for this may be due to the lack of comprehensiveness of the Charlson comorbidities and because it was designed to predict one year survival. Survival studies with colorectal cancer patients are generally focused on 2 to 5 year survival. Baldwin *et al*. is the only published comparison of the Charlson and Elixhauser methods in cancer patients (14). A strength of that study is that it included both outpatient and inpatient administrative records data; however, we believe our analysis better addresses the question of whether Charlson or Elixhauser is a better comorbidity risk adjustment model in cancer patients. Our population encompassed patients of all ages (i.e., not just those $\geq$ 66 years) with different stages of disease (i.e., stage II–IV, not just stage III), used different survival times to determine when comorbidities exert their influence, used all cause mortality, and most importantly, compared unbiased estimates (c statistic) to identify the best prediction model. Although Baldwin *et al*. examined whether the different comorbidity measures significantly add to a base model containing standard risk adjustment variables including age, sex and race, they did not conduct statistical comparisons from which concrete conclusions could be drawn about which method is best.

Overall, the c statistics for all cause mortality for the different comorbidity measures are similar to or slightly higher than values reported in other patient populations (11, 12, 24, 37); it will be of interest to determine how the two approaches compare for other cancers than the types studied here. It is important to do this analysis by cancer stage, since stage by itself already exerts substantial survival discrimination. This analysis clearly revealed that the addition of comorbidities has a larger improvement on survival prediction for stage II patients and the magnitude of this effect decreased for stages III and IV. This would be expected as stage II patients have substantially higher 5-year cancer-specific survival rates compared to stage III and IV patients and, therefore, are more likely to die from a condition other than their cancer than a person with more advanced disease. The increased importance of comorbidity in less aggressive compared to more aggressive cancers has been previously suggested (38). Regardless of stage, however, the Elixhauser method was better than the Charlson method.

In spite of the likely under-reporting of weight loss and obesity in administrative data noted in this study and others (10, 24, 37, 39,40), the replacement of administrative data with clinical weight data for obesity and weight loss Elixhauser comorbidities did not improve the predictive performance of the method. Two conditions significantly related with survival (congestive heart failure and renal failure) are well-known causes of cachexia and wasting (27) and it may be that the addition of weight loss data adds little to an analysis where these conditions are already accounted for. Under-reporting of weight-related data in administrative data sources may be due to poor recording of these

features in medical records, the ICD codes available to identify weight related conditions (i.e., abnormal weight loss (ICD 10: R83.4)) have no specific defining cutpoints, and/or the lack of incentive to record this information.

Testing comorbidity measure performance in different cancer cohorts is worthy of future work. This will ensure that the best risk adjustment model is used to test the relationships between emerging variables and cancer survival. The lack of significance in most of the comorbidities in the adjusted models shown in Table 2-3 suggests a good predictive model for survival may only need to include a few comorbidities. Now that we have established the value of the Elixhauser method, it can now be used to risk-adjust in future cancer studies evaluating the effects of various treatment modalities on survival.

2.5 Conclusion

Our study is the first to directly compare the Charlson and Elixhauser comorbidity measures using the appropriate unbiased estimate in patients with colorectal cancer. Choosing optimal risk adjustment methods is essential to ensuring the report of unbiased relationships between an independent variable and outcome of interest. Standardized and comprehensive risk adjustment protocols to control for differences in baseline status will have important future applications in many domains of oncology and will allow for better comparison between studies.

Tables

Table 2-1: Population characteristics (n=574)

Age (years)	
	64 ± 12 Range: 32–90
Sex (%)	
Male	**58.4**
Female	**41.6**
Primary Tumor Site (%)	
Colon	**62.2**
Rectum	**25.6**
Rectosigmoid Junction	**12.2**
Cancer Stage (%)	
II	**27.7**
III	**33.3**
IV	**39.0**
BMI Category (%)	
BMI < 20	**6.6**
BMI 20-24.9	**36.1**
BMI 25.0-29.9	**37.6**
BMI ≥ 30	**19.7**
Performance Status Score (%)	
0	**24.4**
1	**52.3**
2	**13.2**
3	**8.5**
4	**1.6**

Table 2-2: Prevalence of Charlson comorbidities and relationship with all cause mortality in stage 2-4 colorectal cancer patients (n=574)

	n (%) with CM	Cox Regression		Robust Poisson Regression			
				Died ≤ 2yrs (184 died, 390 survived)		Died ≤ 3yrs (230 died, 344 survived)	
		Unadjusted HR [95%CI]	Adjusted HR† [95% CI]	Unadjusted IRR [95%CI]	Adjusted IRR† [95% CI]	Unadjusted IRR [95%CI]	Adjusted IRR† [95% CI]
Myocardial infarction	31 (5.4)	1.1 [0.69, 1.9]	0.98 [0.54, 1.8]	1.1 [0.68, 1.8]	0.96 [0.61, 1.5]	1.1 [0.76, 1.7]	1.1 [0.75, 1.5]
Congestive heart failure	19 (3.3)	**2.2 [1.3, 3.8]**	*1.9 [0.99, 3.8]*	**2.0 [1.4, 2.9]**	1.6 [0.87, 3.0]	**1.6 [1.1, 2.3]**	1.2 [0.70, 2.1]
Cerebrovascular disease	7 (1.2)	0.27 [0.038, 1.9]	0.21 [0.024, 1.8]	0.44 [0.072, 2.7]	0.85 [0.11, 6.4]	0.35 [0.057, 2.2]	0.67 [0.095, 4.7]
Dementia	6 (1.1)	**3.1 [1.4, 7.0]**	1.7 [0.61, 4.7]	**2.6 [1.8, 3.9]**	2.0 [0.83, 4.9]	**2.5 [2.3, 2.8]**	**2.3 [1.1, 5.1]**
Chronic pulmonary disease	37 (6.4)	1.4 [0.89, 2.2]	0.94 [0.58, 1.5]	1.3 [0.86, 1.9]	0.84 [0.55, 1.3]	**1.4 [1.0, 1.9]**	0.98 [0.69, 1.4]
Peptic ulcer disease	5 (0.9)	1.3 [0.42, 4.1]	1.5 [0.48, 4.7]	0.62 [0.11, 3.6]	0.63 [0.14, 2.8]	1.0 [0.34, 2.9]	0.96 [0.56, 1.6]
Mild liver disease	6 (1.0)	0.30 [0.042, 2.1]	0.51 [0.071, 3.7]	0.52 [0.086, 3.1]	0.78 [0.32, 1.9]	0.41 [0.069, 2.5]	0.62 [0.24, 1.6]
Diabetes without complications	65 (11.3)	1.1 [0.73, 1.6]	1.1 [0.72, 1.5]	1.1 [0.74, 1.5]	1.0 [0.75, 1.4]	1.1 [0.80, 1.5]	1.0 [0.80, 1.3]
Diabetes with complications	7 (1.2)	1.9 [0.69, 5.0]	0.83 [0.19, 3.6]	1.8 [0.94, 3.5]	0.62 [0.34, 1.1]	1.4 [0.75, 2.7]	0.70 [0.42, 1.2]
Renal disease	11 (1.9)	**2.5 [1.2, 5.0]**	**3.3 [1.2, 9.1]**	**2.0 [1.3, 3.2]**	**1.9 [1.2, 3.0]**	**1.6 [1.0, 2.5]**	*1.5 [0.99, 2.2]*

Bold values were significant ($p<0.05$), values in *italics* represent marginal p values ($0.05 < p < 0.1$).

†HR (hazard ratio) and IRR (incidence rate ratios) adjusted for age (continuous variable), sex, stage, and all comorbidities listed in table.

Table 2-3: Prevalence of Elixhauser comorbidities and relationship with all cause mortality in stage 2-4 colorectal cancer patients (n=574)

	n (%) with CM	Cox Regression		Robust Poisson Regression			
				Died ≤ 2yrs (184 died, 390 survived)		Died ≤ 3yrs (230 died, 344 survived)	
		Unadjusted HR [95% CI]	Adjusted HR† [95% CI]	Unadjusted IRR [95% CI]	Adjusted IRR† [95% CI]	Unadjusted IRR [95% CI]	Adjusted IRR† [95% CI]
Elixhauser							
Congestive Heart Failure	19 (3.3)	**2.2 [1.3, 3.8]**	1.7 [0.87, 3.4]	**2.0 [1.4, 2.9]**	**2.1 [1.1, 3.8]**	**1.6 [1.1, 2.3]**	1.6 [0.88, 2.8]
Cardiac arrhythmias	52 (9.1)	**1.6 [1.1, 2.3]**	**1.6 [1.0, 2.5]**	**1.5 [1.1, 2.1]**	*1.4 [0.98, 1.9]*	1.2 [0.91, 1.7]	1.1 [0.79, 1.4]
Valvular disease	10 (1.7)	1.8 [0.83, 3.7]	0.58 [0.21, 1.6]	1.6 [0.84, 3.0]	0.65 [0.32, 1.3]	1.3 [0.67, 2.3]	0.63 [0.34, 1.2]
Pulmonary circulation disorders	11 (1.9)	1.7 [0.80, 3.6]	1.4 [0.61, 3.2]	1.4 [0.74, 2.8]	0.92 [0.49, 1.7]	**1.6 [1.0, 2.5]**	0.99 [0.63, 1.6]
Hypertension without complications	140 (24.4)	0.92 [0.69, 1.2]	**0.60 [0.43, 0.84]**	0.89 [0.66, 1.2]	**0.62 [0.46, 0.85]**	0.88 [0.69, 1.1]	**0.68 [0.53, 0.88]**
Hypertension with complications	12 (2.1)	*2.0 [0.98, 4.0]*	0.60 [0.12, 2.9]	**1.9 [1.1, 3.0]**	1.1 [0.55, 2.1]	1.5 [0.90, 2.4]	0.98 [0.58, 1.7]
Other neurological disorders	11 (1.9)	1.3 [0.57, 2.9]	1.1 [0.47, 2.7]	1.4 [0.74, 2.8]	1.3 [0.65, 2.6]	1.4 [0.79, 2.4]	1.2 [0.79, 2.0]
Chronic pulmonary disease	37 (6.4)	1.4 [0.89, 2.2]	1.0 [0.61, 1.7]	1.3 [0.86, 1.9]	0.93 [0.61, 1.4]	**1.4 [1.0, 1.9]**	1.1 [0.79, 1.5]
Diabetes without complications	65 (11.3)	1.1 [0.74, 1.6]	1.1 [0.71, 1.6]	1.1 [0.74, 1.5]	1.1 [0.78, 1.6]	1.1 [0.80, 1.5]	1.2 [0.86, 1.5]
Diabetes with complications	7 (1.2)	1.9 [0.69, 5.0]	0.45 [0.095, 2.2]	*1.8 [0.94, 3.5]*	**0.52 [0.28, 0.96]**	1.4 [0.75, 2.7]	*0.60 [0.36, 1.0]*
Hypothyroidism	35 (6.1)	1.1 [0.64, 1.8]	1.0 [0.59, 1.8]	0.98 [0.59, 1.6]	*0.70 [0.47, 1.0]*	1.1 [0.72, 1.6]	0.90 [0.63, 1.3]
Renal failure	11 (1.9)	**2.5 [1.2, 5.0]**	*4.9 [0.87, 27.7]*	**2.0 [1.3, 3.2]**	**2.0 [1.1, 3.6]**	**1.6 [1.0, 2.5]**	**1.6 [1.0, 2.6]**

	n (%) with CM	Cox Regression		Robust Poisson Regression			
				Died ≤ 2yrs (184 died, 390 survived)		Died ≤ 3yrs (230 died, 344 survived)	
		Unadjusted HR [95% CI]	Adjusted HR† [95% CI]	Unadjusted IRR [95% CI]	Adjusted IRR† [95% CI]	Unadjusted IRR [95% CI]	Adjusted IRR† [95% CI]
Liver disease	8 (1.4)	0.78 [0.25. 2.4]	1.3 [0.39, 4.3]	1.2 [0.48, 2.9]	1.7 [0.74, 3.9]	0.94 [0.38, 2.3]	1.3 [0.59, 3.0]
Obesity	16 (2.8)	0.71 [0.32, 1.6]	1.4 [0.57, 3.4]	0.78 [0.33, 1.8]	1.3 [0.62, 2.9]	0.62 [0.26, 1.5]	0.96 [0.47, 2.0]
Weight loss	6 (1.0)	0.62 [0.15, 2.5]	0.46 [0.11, 2.0]	0.52 [0.086, 3.1]	0.75 [0.099, 5.7]	0.41 [0.069, 2.5]	0.45 [0.060, 3.4]
Fluid & electrolyte disorders	29 (5.1)	**2.2 [1.4, 3.4]**	**2.0 [1.2, 3.3]**	**1.7 [1.1, 2.4]**	1.2 [0.78, 2.0]	**1.7 [1.3, 2.2]**	**1.4 [1.0, 1.9]**
Blood loss anemia	6 (1.0)	0.66 [0.16, 2.6]	*0.26 [0.061, 1.1]*	0.52 [0.086, 3.1]	**0.26 [0.078, 0.88]**	0.83 [0.27, 2.6]	0.49 [0.19, 1.2]
Deficiency anemia	27 (4.7)	1.4 [0.82, 2.3]	1.3 [0.75, 2.2]	1.2 [0.70, 1.9]	1.2 [0.67, 2.0]	1.2 [0.81, 1.8]	1.3 [0.94, 1.8]
Depression	17 (3.0)	1.5 [0.79, 2.8]	1.8 [0.88, 3.6]	1.5 [0.89, 2.5]	**2.2 [1.2, 4.2]**	*1.5 [0.99, 2.2]*	**2.1 [1.3, 3.4]**
Augmented* Elixhauser							
ECOG performance status scores 2-4	134 (23.3)	**2.1 [1.6, 2.7]**	**2.5 [1.9, 3.3]**	**1.9 [1.5, 2.4]**	**1.6 [1.3, 1.9]**	**1.7 [1.4, 2.1]**	**1.5 [1.2, 1.7]**
BMI < 20	38 (6.6)	**1.7 [1.1, 2.7]**	*1.6 [0.94, 2.6]*	**1.8 [1.3, 2.5]**	1.3 [0.91, 1.8]	**1.4 [1.0, 1.9]**	1.0 [0.75, 1.4]
6 month weight loss ≥ 20%	26 (4.5)	**1.9 [1.2, 3.1]**	**1.7 [1.0, 3.0]**	**1.7 [1.2, 2.5]**	1.3 [0.92, 1.9]	**1.5 [1.0, 2.1]**	1.2 [0.88, 1.6]

Bold values were significant (p<0.05), values in *italics* represent marginal p values (0.05 < p < 0.1).

†HR (hazard ratio) and IRR (incidence rate ratios) adjusted for age (continuous variable), sex, stage, and all comorbidities listed in table.

**Augmented* Elixhauser includes performance status and substitutes clinical body weight data for administrative records weight data, with low body weight defined as BMI < 20kg/m^2 and abnormal weight loss defined as > 20% loss in 6 months.

Table 2-4: Elixhauser and Charlson comorbidity method discrimination for 2- and 3-year all cause mortality in stage 2-4 colorectal cancer patients

	C statistics for 2- and 3-year survival	
	2yr (184d, 390a)†	**3yr (230d, 344a)†**
Base Model (age, sex, stage)	0.824[a]	0.827[a]
Charlson‡	0.831[a]	0.833[a]
Elixhauser‡	0.852[b]	0.854[b]
Augmented* Elixhauser‡	0.864[c]	0.862[b]

C statistics in the same column with different superscript letters are different, $p < 0.05$ (Stata roccomp test).

†d=deceased, a=alive

‡Adjusted for age (continuous variable), sex, and stage

**Augmented* Elixhauser includes performance status and substitutes clinical body weight data for administrative records weight data, with low body weight defined as BMI < 20kg/m^2 and abnormal weight loss defined as > 20% loss in 6 months.

Table 2-5: Elixhauser and Charlson comorbidity method discrimination for 2- and 3-year all cause mortality by stage in colorectal cancer patients

	C statistics for 2 and 3 year survival					
	Stage 2 (n=159)		Stage 3 (n=191)		Stage 4 (n=224)	
	2yr (17d, 142a)†	3yr (23d, 136a)†	2yr (28d, 163a)†	3yr (41d, 150a)†	2yr (139d, 85a)†	3yr (166d, 58a)†
Base Model (age, sex)	0.683[a]	0.664[a]	0.783[a]	0.692[a]	0.571[a]	0.585[a]
Charlson‡	0.709[a]	0.686[a]	0.817[a]	0.726[a]	0.581[a]	0.610[b]
Elixhauser‡	0.838[b]	0.799[b]	0.872[b]	0.789[b]	0.679[b]	0.724[c]
***Augmented* Elixhauser*‡**	0.859[b]	0.807[b]	0.891[b]	0.793[b]	0.717[b]	0.787[d]

C statistics in the same column with different superscript letters are different, $p<0.05$ (Stata roccomp test).

†d=deceased, a=alive

‡adjusted for age (continuous variable), sex, and functional status (dichotomous variable)

**Augmented* Elixhauser includes performance status and substitutes clinical body weight data for administrative records weight data, with low body weight defined as BMI < 20 kg/m^2 and abnormal weight loss defined as > 20% loss in 6 months.

Endnote

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CHAPTER 3: A viscerally-driven cachexia syndrome in patients with advanced colorectal cancer: contributions of organ and tumor mass to whole body energy demands

3.1 Introduction

The etiology of cancer cachexia and other wasting syndromes is not clearly understood, but several hypotheses exist (1-4). One theory is that peripheral stores of fat and protein are mobilized from adipose tissue and skeletal muscle to be used as a fuel for energetically demanding visceral organs, which have increased activity in the tumor-bearing state. The energetic demands of the liver are particularly substantial. Liver represents ~2% of body weight in healthy individuals, but its specific metabolic rate is high (200 kcal/kg/d) (5); consequently, it represents ~20% of whole-body resting energy expenditure (REE). Organ mass has been used to model and predict REE (6, 7) and liver size is a significant predictor of REE (7).

The potential significance of the mass of high-metabolic-rate organs on REE and the development of cancer cachexia has only been suggested (4); however, we suspect that it could be important in colorectal cancer. The presence of hepatomegaly and splenomegaly is common knowledge to oncologists, however, the changes in size of these organs has only been directly quantified in case reports (8). Tumors, as unresectable hepatic metastases, may represent an additional burden of high metabolic rate tissue; importantly, ~50% of all colorectal cancer patients develop this complication (9) which has been associated

with weight loss (10, 11). There is currently very few quantitative data on the contribution of high metabolic rate organs to cancer cachexia-associated weight loss (4, 8, 12); this would require extensive body composition and REE measurements. However, we know small changes in organ mass have the potential to account for a substantial quantity of energy expenditure over time. If liver mass increased by only 500g and this change persisted, this would add an incremental REE of 100kcal/d.

We hypothesized that patients with colorectal cancer may be especially affected by a viscerally driven cachexia syndrome, originating from increasing masses of high-metabolic-rate tissues, especially liver, spleen, and tumor. Several approaches were used to investigate this question. A retrospective serial computed tomography (CT) image analysis was completed to assess longitudinal body composition changes (i.e., liver, spleen, skeletal muscle, adipose tissue) in subjects with colorectal cancer. Using data from this cohort, we used a computational model of human metabolism (13, 14) to estimate the effect of organ changes on whole-body REE. In a second cross-sectional cohort, we evaluated the relationship between REE determined by indirect calorimetry and organ mass.

3.2 Subjects and Methods

3.2.1 Retrospective cohort

The study was approved by the Alberta Cancer Board Research Ethics Board (Edmonton, Canada). Our region encompasses Northern Alberta, Canada. A database of all cancer cases in the region (Alberta Cancer Registry) codes

primary cancers by their site and morphology, along with clinical and demographic information. We searched the database with the following criteria: 1) deceased from colorectal cancer (ICD-9-CM codes: 153.X, 154.0, 154.1) between June 1, 2001 and August 31, 2004, and 2) evaluation by CT imaging at least twice between colorectal cancer diagnosis and death. With the understanding that cachexia is most prominent at the end of life and to take advantage of the statistical power of repeated measures, we focused on patients with ≥ 4 CT scans on record during the year preceding death.

3.2.2 CT image analysis

Muscle and adipose tissue surface areas were evaluated at a standard vertebral landmark (the 3rd lumbar vertebrae; L3), because tissue areas in this region are significantly related to whole-body muscle and fat masses (15-17). Tissues were analyzed on 2 consecutive transverse CT images extending inferiorly from L3 with Slice-O-Matic V4.3 (Tomovision, Montreal, Canada), which permitted specific tissue demarcation by using Hounsfield unit thresholds of –29 to +150 for skeletal muscles (*psoas, erector spinae, quadratus lumborum, transversus abdominus*, external and internal obliques, *rectus abdominus*) (18), –150 to –50 for visceral adipose tissue (19), and –190 to –30 for subcutaneous and intermuscular adipose tissues (18). Thresholds were manually adjusted as necessary. Cross-sectional areas (cm^2) were computed for each tissue by summing tissue pixels and multiplying by the pixel surface area. Mean tissue areas for 2 consecutive images were calculated; the mean coefficient of variance

(CV) of paired images was 1.5% for skeletal muscle and 2.7% for adipose tissue areas.

Regression equations derived from an advanced cancer patient cohort were used to estimate whole-body fat-free mass (FFM) and fat mass from L3 skeletal muscle and total adipose tissue surface areas (17):

- Whole body FFM (kg) = 0.30 * (skeletal muscle at L3 using CT (cm^2)) + 6.06; r^2=0.88 (17)
- Whole body fat mass (kg) = 0.042 * (total adipose tissue at L3 (cm^2)) + 11.2; r^2=0.77 (17)

Muscle surface area was also used to estimate whole body muscle using an algorithm derived from a healthy population (15) as no equation currently exists to predict this compartment from L3 muscle surface area in advanced cancer patients

- Whole body skeletal muscle volume (L) = 0.166 * (skeletal muscle 5 cm above L4-L5 (cm^2)) + 2.142, r^2=0.855 (15)

A density of 1.04g/cm^3 was used to convert muscle volume to mass (20).

Liver and spleen volumes (cm^3) were also measured with CT images. Because the images encompassed the entire liver and spleen, the organ tissue surface area on each image was analyzed. Liver and spleen surface areas on each consecutive image, the image thickness (usually 6.5mm) and separation (usually 5mm) were then used by the Slice-O-matic *db volumes* function to calculate volume. Liver volume included metastases if present. To estimate organ mass

from volume, a density of 1.05g/cm^3 was used for liver and 1.054g/cm^3 for spleen (20, 21).

3.2.3 Prospective Cohort

We investigated the relationship between organ mass and measured REE in a second cohort of patients with metastatic colorectal cancer (n=18). Subjects were recruited from the Cross Cancer Institute (Edmonton, Canada) between April 1, 2005 and October 31, 2006 and provided written informed consent. Each participant had a REE measurement by indirect calorimetry (VMax 29N, SensorMedics, Yorba Linda, California). Prior to the REE assessment, subjects were asked to fast for 12 hours and refrain from strenuous exercise and alcohol for 24 hours. Participants rested for 30 minutes after which a canopy was placed over their head and shoulders for 30 minutes to analyze O_2 consumption and CO_2 production. Breath samples were measured until a steady state was reached for 15 minutes. The Weir equation was used to calculate REE (22). On the same morning as the REE assessment, all participants also underwent a dual energy x-ray absorptiometry (DXA) scan (LUNAR Prodigy High Speed Digital Fan Beam X-Ray-Based Densitometer with enCORE 9.20 software; General Electric, Madison, Wisconsin) (23) to measure whole-body FFM. All subjects also had a CT scan 14 ± 7 days from this date which was used to quantify organ mass as described above.

3.2.4 Mathematical Model Simulations

A mathematical model has been developed which simulates the dynamics of whole-body metabolism, body composition changes, and REE during semi-

starvation and refeeding (13). This model was also used to integrate data on the metabolic changes in patients with cancer cachexia to show how these derangements synergize with reduced energy intake to result in progressive loss of body constituents and alterations in energy metabolism (14). The initial conditions of the cachexia simulation (14) were selected to represent a typical cancer patient before disease onset: a 69 year old male with an initial body weight of 77.7 kg, 32% body fat, a dietary intake of 2400kcal/d and a REE of 1606 kcal/d (30.6 kcal/kg FFM/d). In the previously reported simulation (15), we applied several reported metabolic derangements defining cancer cachexia, including an increase in rates of lipolysis (+50 ± 30%), proteolysis (+40 ± 10%), and Cori cycle (+300 ± 100%), a tumor mass of 200 ± 100g; and an energy intake that linearly decreased to 1700 kcal/d by the end of the 12 month simulation. We also assumed that the liver and spleen remained the same as those of healthy adults (1.8kg for liver, 250g for spleen), rather than shrinking in response to reduced energy intake (8, 13). In all simulations, the liver- and spleen-specific metabolic rates were 200kcal/kg/d (5) and 80kcal/kg/d (24), respectively. Direct measures of tissue-specific metabolic rates are calculated by pairing blood flow with the arteriovenous oxygen concentration difference over a tissue of interest (5).

In the current study, we modified the original cancer cachexia simulation (14) using the directly determined liver and spleen masses, in place of our prior assumptions. Furthermore, we adjusted the decline of dietary energy intake to match the average measured body composition changes of the retrospective cohort. We found that a linear decrease of energy intake from 2400 kcal/d to

2150 kcal/d at the end of the 62 week simulation allowed the simulations to match the retrospective body composition changes.

3.2.5 Data Analysis

Statistical analysis was completed using SPSS Version 15.0 (Chicago, Illinois) and Stata Version 10.0 (College Station, Texas). All values are presented as means ± standard deviation, significance was taken at $\alpha=0.05$ and all tests were two sided. Two sample t-tests and $\chi 2$ tests were used to compare patient cohorts. For statistical analysis of absolute tissue masses in the retrospective cohort, we completed repeated measures analysis of variance (ANOVA) with Bonferroni pairwise comparisons. Simple linear regression was used to examine relations in the prospective cohort.

Tissue rates of change were calculated for the retrospective cohort. Tissue changes in each scan interval were expressed as a percentage and divided by the number of days in each interval as the timing of CT imaging was unique for each individual. The daily rate of loss or gain was multiplied by 100 to form a standard unit, % change/100d to allow for comparisons.

3.3 Results

3.3.1 Retrospective Cohort

Our initial search criteria identified 262 patients. There were 1108 CT scans available in this cohort (range 2–16 per patient), which had been conducted for diagnosis, staging or follow-up. We focused on a subset of 34 patients who had ≥ 4 CT scans in the year preceding death. This subset was 35% female, died at 60 ± 8 years of age after surviving a median of 22 months. The distribution of

primary tumor sites was 68% colon (ICD-9-CM: 153.X), 6% rectosigmoid junction (ICD-9-CM: 154.0), and 26% rectum (ICD-9-CM: 154.1); 91% of this group had adenocarcinomas. In total, this group had 156 scans available for assessment; all images were analyzed with the exception of subcutaneous adipose tissue data from 2 obese patients, which was not fully visible in the image field of view. In addition, liver and spleen could not be accurately identified in 2 different patients, and liver was not assessed in 2 additional individuals due to either a resection or images not covering the entire organ. Selection bias was not apparent in this subset (n=34); we found that the sex distribution, age at death, survival time, primary tumor site, tumor morphology and body composition features (i.e., muscle and adipose tissues) in the last 2 months of life were not different from the overall cohort (p values > 0.1).

The changes in liver, spleen, muscle, and adipose tissue over time are shown (**Table 3-1**). Representative cases of liver and spleen gain (**Figure 3-1A**) and muscle and adipose tissue loss (**Figure 3-1B**) are illustrated. At the earliest studied time point (10.7 ± 2.7 months from death), the liver and spleen of the cancer patients (Table 1) were larger than those reported for healthy adults (i.e., liver: 1.4 – 1.8kg; spleen 0.15 – 0.25kg) (8, 20). Liver increased thereafter (mean gain +0.74 kg) over 9.5 months ($p=0.010$); there was a trend towards increased spleen mass ($p=0.077$). Over the same period, ~4.2kg of muscle ($p<0.001$) and ~3.5kg of fat ($p=0.004$) were lost, and the percentage of estimated FFM occupied by the liver increased from 4.5% to 7.0% ($p<0.001$). The range of liver masses at

1.2 ± 0.5 months from death was considerable (interquartile range: 2.0kg – 3.8kg), and many patients had evidence of liver metastases (Figure 3-1A).

The largest tissue changes occurred in the last interval studied; 80% of the mean gain in liver, 69% of the mean loss in muscle and 91% of the mean loss in adipose tissue occurred during this time. The rates of tissue loss or gain over time (% change/100d) are shown in **Figure 3-2**; maximal rates were observed close to death. Mean skeletal muscle tissue loss accelerated logarithmically (r^2=0.99) to –13%/100d at 2 months from death. Mean adipose tissue loss also accelerated logarithmically (r^2=0.95) to –41%/100d at 2 months from death. Mean liver gain followed a polynomial relationship (r^2=0.90) to +39%/100d at 2 months from death.

3.3.2 Prospective Cohort

The cohort (n=18) was 45% female and 60 ± 11 years of age at time of assessment. On average, participants had 46.2 ± 12kg FFM, which included a 1.9 ± 0.5kg liver (range: 1.1kg – 3.2kg) and 0.31 ± 0.1kg spleen (range: 0.12kg – 0.71kg). Participants had a measured REE of 1503 ± 295kcal/d (33 ± 6 kcal/kg FFM/d). Resting energy expenditure was higher in patients with larger livers (r^2=0.35, p=0.010) (**Figure 3-3A**). Moreover, as liver occupied a larger percentage of whole body FFM, REE/kg FFM/d increased (r^2=0.35, p=0.010) (**Figure 3-3B**- dashed line).

The slope of the regression between liver mass and REE (Figure 3-3A) is a value of interest, which potentially indicates a high composite metabolic rate of the liver and metastases (i.e., 343 kcal for each 1kg increase). This is

considerably higher than 200kcal/kg/d reported for healthy human liver *in situ*. However, this must be considered with caution because no data exist for the metabolic rate *in situ* of liver with metastases. While this awaits direct measurement, done by pairing blood flow with the arteriovenous oxygen concentration difference over the tissue of interest (5), a high metabolic rate may be inferred from the relatively high rates of glucose uptake; this is the basis for detecting metastases by imaging using ^{18}F-deoxyglucose (**Figure 3-4**).

3.3.3 Simulation Results

Key assumptions in our earlier model (stable liver mass, tumor mass ≤ 200g) appear to have been quite conservative relative to the directly determined values (Table 3-1), which we used to refine the model. Model simulations of the healthy reference condition (dotted curves) compared with reduced energy intake alone (dashed dotted curves), our previous cachexia simulation (14) (dashed curves), and the new cachexia simulation based on the directly determined liver and spleen masses of our retrospective colorectal cancer cohort (from Table 3-1) (solid curves) are illustrated in **Figure 3-5**. The new cachexia simulation culminated at an REE of 1900kcal/d (39.7kcal/kg FFM/d), which is 294kcal/d (9.3kcal/kg FFM/d) above the healthy reference condition, 331kcal/d (9.7kcal/kg FFM/d) above the reduced energy intake simulation, and 144kcal/d (3.8kcal/kg FFM/d) above the previous cachexia simulation. Notably, the late rapid increase of liver mass measured in the retrospective colorectal cancer patient cohort was related to a steep increase in estimated metabolic rate during the last 3 months of the simulation. The estimated contribution of spleen was negligible, because of

the small overall size, lower specific metabolic rate, and relative constancy in size of this organ. During the last 3 months of the simulation, the cumulative energy expended by the liver was estimated to be 31,900 kcal for the healthy reference condition, 31,400 kcal for reduced energy intake alone, and 49,600 kcal for the new cachexia simulation (i.e., an increment of 17,700 kcal in the liver).

We also plotted the relation between the percentage of FFM occupied by the liver and REE (kcal/kg FFM/d) from the cachexia simulation incorporating the changes in organ mass from Table 3-1 (Figure 3-3B- solid line); this appeared to follow a similar relationship to the prospective cohort.

3.4 Discussion

Our study captured detailed progressive body composition changes occurring in patients with colorectal cancer during disease progression until death. These changes were typified by exponential increases in the size of the liver and hepatic metastases, with concurrent accelerations of muscle and fat loss. The longitudinal CT image review provides a basis for a quantitative estimation of the contribution of visceral organs and metastases to REE. Our results suggest that a considerable catabolic influence underlying colorectal cancer cachexia is exerted by the energetic demands of liver and metastases and to a lesser extent the spleen. This is supported by estimates based on a computational model of human metabolism as well as direct measures of REE and body composition in advanced colorectal cancer patients. In patients with extensive metastatic disease and organomegaly, these visceral changes could exert a quantitatively important catabolic effect by virtue of their size and consumption of energy. This increased

energy expenditure occurs during the period of most rapid weight loss, but importantly, also in the end stages of anorexia and hence very low food intake, which likely results in a substantial energy deficit. In a healthy individual, energy balance is maintained by an increase in energy intake, but in patients with advanced cancer, it may be difficult to envisage an increased energy expenditure being covered by an incremental oral intake in a population with reduced energy intakes sometimes less than basal metabolism (25). This increased energy expenditure and consequent energy imbalance should be included among the major causes of colorectal cancer cachexia in individuals with metastatic disease.

Cachexia has often been attributed to the catabolic actions of humoral mediators (i.e., cytokines, proteolysis–inducing or lipolytic factors), insulin resistance and low dietary intakes as outlined in current review articles (1-3); consequently, most treatments have focused on these factors. In patients with substantial tumor burden and organomegaly, these treatments may have limited efficacy, since the primary problem (extensive disease burden) is not corrected by these agents. Quantitative analysis of disease burden may be included in future studies to help to explain why some treatments are ineffective in certain individuals.

3.4.1 Methodological Considerations

A longitudinal retrospective CT image review was a realistic approach to evaluate body composition changes; patients had frequent scans throughout their illness and were not required to undergo additional testing for this research. Prospective studies of body composition using other methods are comparatively

difficult to conduct as participation rates are low and withdrawal rates are high in patients with very advanced disease (26, 27). The group studied in the present study was not different from a regional cohort of patients who died from colorectal cancer with respect to disease characteristics, demographics and body composition, and is thus likely a representative sample.

Computed tomography imaging allows discrimination between different FFM components (i.e., muscle, liver, spleen) which appears important as we saw that different constituents change in opposite directions. These distinctions cannot be made with other methods such as DXA or bioelectrical impedance. The quantification of organ volume with CT images is reasonably precise, and our interobserver CV values (3.6% for liver and 4.0% for spleen) are similar to previously reported values for organs (28). Muscle and adipose tissue areas determined from CT images have a typical CV of 1-2% (17) and whole body tissue masses estimated from the CT images are correct to the nearest 3.5kg for fat mass and 3.0kg for FFM (17). One limitation of our analysis is the inability to quantitatively discriminate liver tissue and metastases. We suspect the majority of progressive increases in liver were metastases; however, liver parenchyma has been reported to increase in colorectal cancer patients with liver metastases (29), which may be connected with increased gluconeogenesis and synthesis of acute-phase proteins (4).

Our study is strengthened by the use of a mathematical model (13, 14) that allowed us to estimate the effect of organ mass changes on REE (Figure 3-5). Computational modeling is a new tool that can integrate clinical data to build a

conceptual framework for the understanding of altered energy balance states. This is especially useful in contexts where patient vulnerability limits the use of invasive tests and compliance is limited by disease progression. Using this model, we showed that the range of increases in REE computed with the new cancer cachexia simulation (up to 1900kcal/d or 39.7kcal/kg FFM/d) (Figure 3-5-solid line) is consistent with reported values for patients with advanced cancer (26, 30).

A further strength of our study was the simultaneous measurement of different FFM components and REE in the prospective cohort to explore the relation between body composition and REE in advanced colorectal cancer. This also provided information to help authenticate results from the model. These data suggest that liver mass is proportional to REE (Figure 3-4A). The metabolic rate of the liver and metastases merits further study, because our results suggest that 200 kcal/kg/d may be a conservative estimate. There are several possible reasons for an increased liver-specific metabolic rate in this population. The liver plays a pivotal role in systemic inflammation, acute phase protein synthesis and gluconeogenesis which have been documented in advanced cancer (1, 31-33). Moreover, increases in tumor are associated with higher substrate turnover and oxygen consumption (34).

3.4.2 Implications of High Metabolic Rate Tissues on Body Composition and Resting Energy Expenditure

The largest observed changes in body composition in the retrospective cohort occurred between 4.2 and 1.2 months from death. Liver increased and

muscle decreased especially rapidly during this time. This resulted in a shift to an increased proportion of FFM occupied by higher-metabolic-rate tissues. In healthy populations, the relationship between the proportions of higher metabolic rate organ mass relative to FFM has been found to explain some of the variance in REE (6, 7, 28). Our study affirms that this relationship is quantitatively important in colorectal cancer cachexia, and perhaps other cancers where organomegaly and liver metastases are common.

Tables

Table 3-1: Absolute tissue masses quantified with computed tomography (CT) imaging in patients who died of colorectal cancer

Mean months to death at time of CT image	Visceral Organ Mass + Tumor**		Peripheral Tissues***	
	Liver + Metastases Volume (cm^3) *(Estimated Mass (kg))*	Spleen Volume (cm^3) *(Estimated Mass (kg))*	Skeletal Muscle L3 Surface Area (cm^2) *(Estimated Whole Body Mass (kg))*	Fat Mass L3 Adipose Tissue Surface Area (cm^2) *(Estimated Whole Body Fat Mass (kg))*
n*	30	32	34	32
10.7 ± 2.7	2153 ± 629 [b,†] *(2.3 ± 0.7)*	302 ± 204 *(0.32 ± 0.2)*	151 ± 38[bc] *(28.3 ± 6.6)*	339 ± 206[b] *(25.4 ± 8.7)*
7.1 ± 1.3	2245 ± 692 [b] *(2.4 ± 0.7)*	326 ± 220 *(0.34 ± 0.2)*	149 ± 37[b] *(28.0 ± 6.4)*	345 ± 208[b] *(25.7 ± 8.7)*
4.2 ± 1.2	2291 ± 771 [b] *(2.4 ± 0.8)*	345 ± 237 *(0.36 ± 0.3)*	144 ± 37[c] *(27.0 ± 6.4)*	330 ± 214[b] *(25.1 ± 9.0)*
1.2 ± 0.5	2857 ± 1435[a] *(3.0 ± 1.5)*	366 ± 238 *(0.39 ± 0.3)*	127 ± 36[a] *(24.1 ± 6.3)*	255 ± 190[a] *(21.9 ± 8.0)*
Overall change in 9.5 months‡	+704 cm^3 *(+0.74 kg)* *p=0.010*	+64 cm^3 *(+0.067 kg)* *p=0.077*	-24 cm^2 *(-4.2 kg)* *P < 0.001*	-84 cm^2 *(-3.5 kg)* *p=0.004*

Means in the same column with different superscript letters are significantly different, $p < 0.05$ (repeated-measures ANOVA with Bonferroni pairwise comparisons).

*The number of subjects varies because of missing data, as outlined in Results.

**Liver and spleen masses were quantified as outlined in Subjects and Methods.

***L3 tissue cross-sectional areas (cm^2) were used to estimate whole-body skeletal muscle and fat mass from regression equations reported by Shen et al (15) and Mourtzakis et al (17), respectively.

†Mean ± SD (all such values).

‡p value for change between 10.7 and 1.2 mo from death (repeated-measures ANOVA with Bonferroni pairwise comparison).

Figures

Figure 3-1: Representative patients showing change in (a) liver and spleen and (b) skeletal muscle and adipose tissue

Transverse computed tomography images from (a) a 54 year old woman at the 12th thoracic vertebrae (i) 10.0 and (ii) 1.5 months from death; the liver with metastases (LM) increased by 1.3kg to 3.1kg and spleen (SP) increased by 0.30kg to 0.50kg, and (b) a 52 year old man at the 3rd lumbar vertebrae (i) 7.7 and (ii) 0.8 months from death; estimated whole body muscle (SM) decreased by 8.8kg to 17.0kg and whole body adipose tissue (AT) decreased by 2.0kg to 16.7kg.

LM, liver and metastases; SP, spleen; SM, skeletal muscle; AT, adipose tissue.

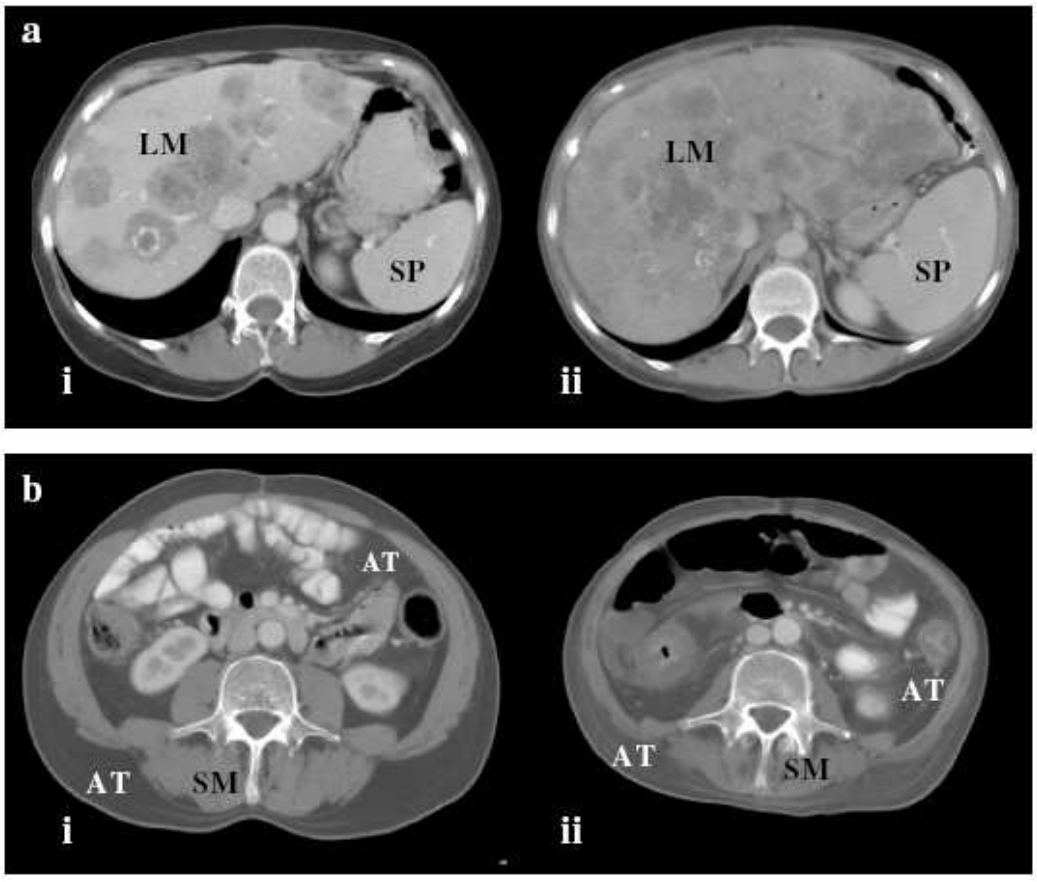
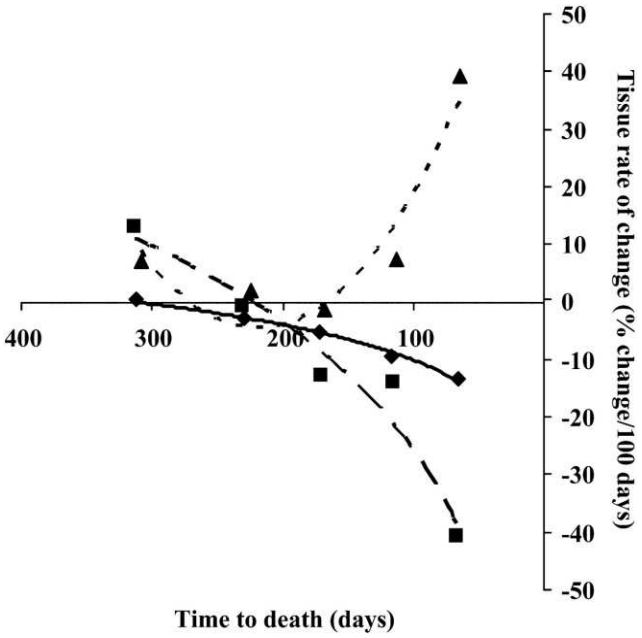
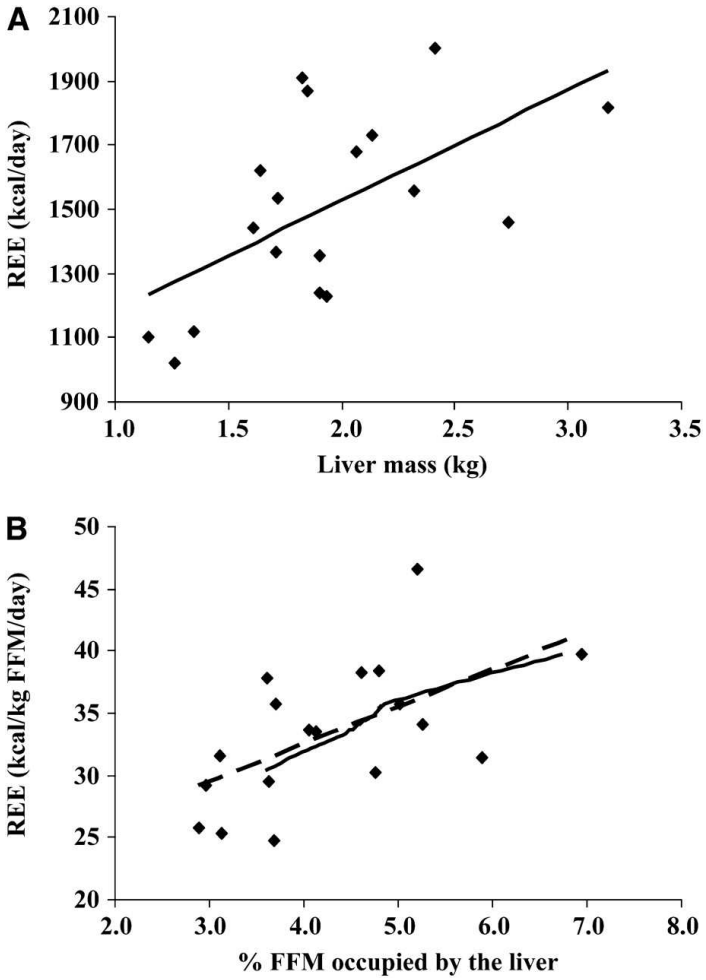


Figure 3-2: Time course rates of gain or loss for liver (including metastases), muscle, and adipose tissue from the retrospective colorectal cancer patient cohort (n=34)



Scan intervals were categorized relative to the time of death and divided into 5 categories. Mean rates of change (% change/100days) were determined for each tissue at each time point. Best-fit regression lines were used to determine the overall rate of change relation over time. The rate of change in liver followed a polynomial relation: liver %change/100days = $0.0017(\text{time to death (days)})^2 - 0.7316(\text{time to death (days)}) + 75.56$, $r^2=0.90$ (triangles and dotted curve). The loss of skeletal muscle was logarithmic: skeletal muscle %change/100days = $8.8303\text{Ln}(\text{time to death (days)}) - 50.746$, $r^2=0.99$ (diamonds and solid curve). Loss of adipose tissue was also logarithmic: adipose tissue %change/100days = $32.029\text{Ln}(\text{time to death (days)}) - 172.92$, $r^2=0.95$ (squares and dashed curve).

Figure 3-3: Relation between measured resting energy expenditure (REE) and liver mass in the prospective colorectal cancer patient cohort (n=18)



Liver mass (including metastases) was determined by computed tomography image analysis. REE was determined by indirect calorimetry and fat-free mass (FFM) was determined by dual energy x-ray absorptiometry. Simple linear regression was used to assess relations. (A) REE (kcal/day) = 343.52(liver mass (kg)) + 841.49, (r^2=0.35, p=0.010). (B) REE (kcal/kg FFM/day) = 3.0011(%FFM occupied by the liver) + 20.513, (r^2=0.35, p=0.010) (dashed line). The solid line indicates a similar relation occurring in the new cancer cachexia simulation incorporating the measured liver masses from the retrospective cohort (Table 3-1).

Figure 3-4: ^{18}F-Deoxyglucose positron emission tomography (PET) scan of a patient with extensive liver metastases

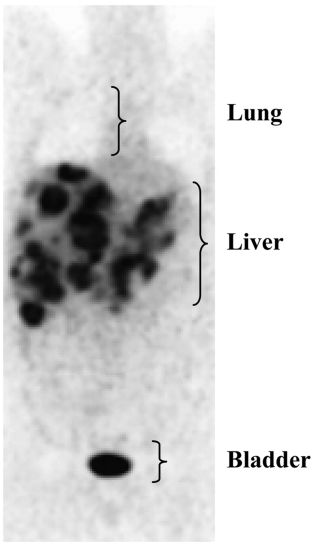
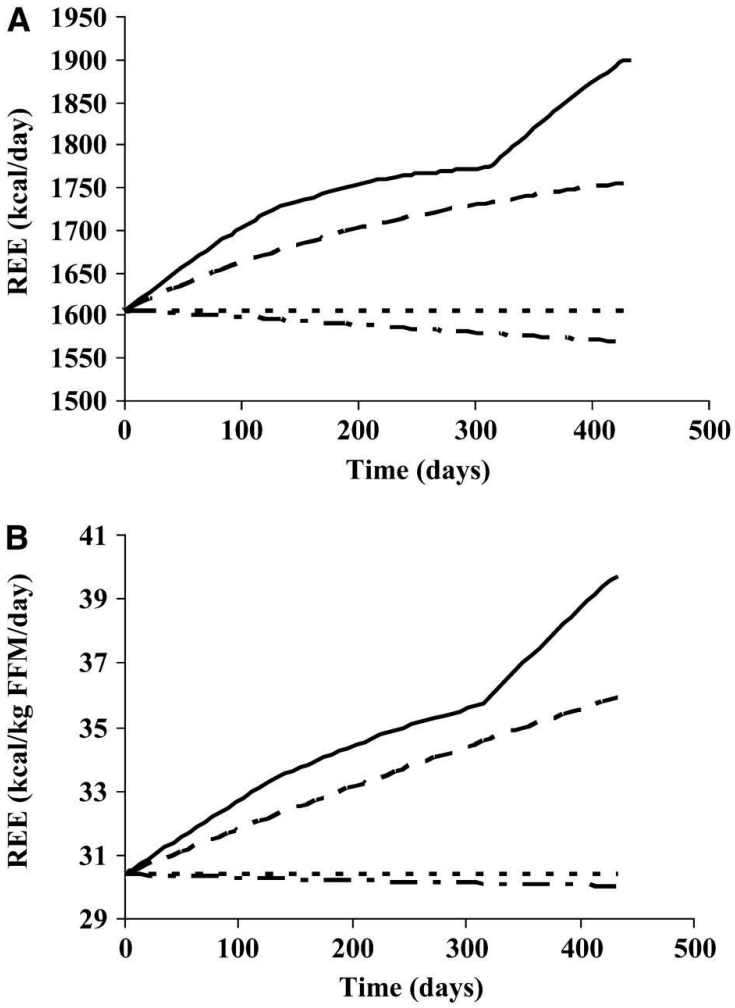


Figure 3-5: Simulation of resting energy expenditure (REE) over 62 weeks based on measured liver and spleen masses from the retrospective colorectal cancer patient cohort (n=34)



All calculations are based on an assumed liver-specific metabolic rate of 200 kcal/kg/day and spleen specific-metabolic rate of 80kcal/kg/day. The original cachexia simulation (constant 1.8kg liver and 250g spleen) (14) (dashed curve) can be contrasted to the cachexia simulation specifying the organ masses match the data at different time points from the retrospective cohort computed tomography images (Table 3-1) (solid curve). The healthy reference simulation in energy balance (constant 1.8kg liver and 250g spleen) (dotted curve) and the reduced energy intake simulation (dashed dotted curve) are also shown (13). (A) Resting energy expenditure (REE) (kcal/day) and (B) REE (kcal/kg fat free mass (FFM)/day).

Endnote

A version of this chapter has been published in the *American Journal of Clinical Nutrition*. The citation is as follows:

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CHAPTER 4: Final Discussion

4.1 Introduction

The purpose of this work was to further understand nutritional status, especially body weight and composition during colorectal cancer progression. A population-based study of colorectal cancer patients was conducted using administrative health data to collect information on the primary disease, comorbidities, demographics, CT imaging to assess body composition, and the PG-SGA questionnaire to obtain information on height, body weight, weight history, and performance status. These studies occurred at different places in the cancer disease trajectory; Figure 1-1 situates the studies on a time line. Results from Chapter 2, which occurred around the time patients were first considered for systemic chemotherapy and involved patients in stages II-IV, revealed which disease conditions predicted survival, and showed that weight related conditions (e.g., underweight and weight loss) lost some independent predictive power when they were placed in statistical models with other comorbid conditions. This chapter also revealed that weight related conditions (e.g., obesity and weight loss) were not captured in administrative health data. In Chapter 3, a serial CT image analysis assessed longitudinal body composition changes during the last 12 months preceding death from colorectal cancer in 34 patients with stage IV cancer. Body composition changes were typified by exponential increases in tumor with concurrent accelerations of muscle and fat loss.

These results have the potential to make a difference in how colorectal cancer patients are treated and how they are researched, which will lead to better patient outcomes and more accurate research findings. This following discussion outlines key points related to the work described in the previous chapters organized into topics of particular interest to three different groups of professionals who treat and research colorectal cancer patients: dietitians, oncologists, and health services researchers. I will also present suggestions for further research and changes to practice in these disciplines.

4.2 Key points for the Dietitian

Nutritional status is a complex phenomenon because it is determined by multiple factors. The work presented in Chapters 2 and 3 has revealed some key findings around comorbidities, the importance of tissue organ level body composition assessment, and the impact of body composition on resting energy expenditure (REE). Dietitians may want to consider these findings when conducting nutrition assessments and performing interventions.

- **Comorbidities are an important part of a complete nutritional assessment in cancer patients**

It is widely accepted that comorbidities affect the ongoing health of colorectal cancer patients, as would be expected since > 50% of new colorectal cancer diagnoses occur in individuals ≥ 70 years (1). One previous study suggested that colon cancer patients 65–74 years and ≥ 75 years have a median of ~4 and ~5 comorbidities, respectively (2). Comorbidities in cancer patients, especially those that may be longstanding and/or uncontrolled, have the potential

to explain and/or exacerbate the development of malnutrition, weight loss and cachexia (3). Several conditions, other than cancer, are known to be associated with wasting syndromes such as chronic heart failure, renal failure, and chronic obstructive pulmonary disease (COPD) (4). From the results presented in Chapter 2, some colorectal cancer patients have these conditions.

It is known that patients present with both low and high body weights (i.e., underweight and obesity) when they are first seen by a medical oncologist for consideration of systemic chemotherapy as found in the cohort presented in Chapter 2. Rates of underweight from this cohort (BMI < 18.5: 3.1%) were just slightly higher than the general Canadian adult population (2%) (5). Rates of obesity from the cohort in Chapter 2 (19.7%) were slightly lower than the general adult population (23.1%). This is a bit of a surprise because obesity is a risk factor for this type of cancer. However, this low prevalence may be due to the fact that many patients had lost weight in the time prior to coming to the new patient medical oncology clinic. Examination of the 6 month weight history in this cohort finds that 29.8% of patients were obese within the 6 months preceding the clinic visit.

Sarcopenia (or low muscle mass generally regarded as < 2 standard deviations below the healthy young adult sex specific mean (6)) is also common when patients are first seen in medical oncology. In the same patient cohort presented in Chapter 2 and by using the method described by Prado et al. (7), it was found that~46% of patients were sarcopenic. Even though the mean age of this population was 64 ± 12 years, the prevalence of sarcopenia is much higher

than reported for the healthy elderly < 70 years (13.5–24.1%) and similar to what is reported for healthy elderly > 80 years (43.2–60.0%) (6). Because of this high prevalence of sarcopenia, determining the origin of low muscle mass is relevant as it is unlikely to be caused entirely by the cancer itself. It remains unclear if and how comorbidities may explain sarcopenia, underweight, and obesity.

Table 4-1 presents a univariate analysis to determine how comorbidities classified according to the Elixhauser categories predict three different body weight conditions: sarcopenia, underweight, and obesity at the time of presentation to new patient medical oncology clinics. This is the same cohort presented in Chapter 2 except that it only includes patients who had a CT scan near to the clinic visit date. The comorbidities were collected from hospitalizations occurring in the one year prior to the clinic visit date from inpatient administrative hospitalization data as described in Chapter 2. Renal failure was the only significant predictor of sarcopenia. This makes sense as this has been linked with wasting disease (8). Chronic pulmonary disease (a known risk factor for wasting diseases), pulmonary circulation disorders (which are linked with lung diseases such as COPD), hypertension with complications (which is a risk factor for renal failure and heart failure, two well known wasting diseases), and renal failure were significant predictors of underweight. Diabetes with complications, which is well known to be associated with excess body weight, was a significant predictor of obesity. Although some of the comorbidities listed in this table might be expected to predict sarcopenia, underweight or obesity, there may be other factors that might be responsible for

these conditions that may not be listed in this table. One such factor that may be associated with sarcopenia is prolonged best rest (9). This was also tested in the same patient cohort from Table 4-1. Patients who spent < 5 days (including no days) in hospital had significantly more muscle than those who spent ≥ 30 days in hospital in the year prior to the clinic visit date. Females who spent < 5 days (or no days) in hospital had a L3 skeletal muscle index of 43.8cm^2/m^2 which is higher compared to those who spent ≥ 30 days in hospital (38.8cm^2/m^2) (p=0.0075). Males who spent < 5 days (or no days) in hospital had a L3 skeletal muscle index of 53.6cm^2/m^2 compared to those who spent ≥30 days in hospital (46.3cm^2/m^2) (p < 0.001). Specifically for sarcopenia, other comorbidities such as previous fractures and infections may also be related to low muscle mass. This is a topic worthy of further investigation.

When dietitians are looking to evaluate the impact of comorbidities on nutritional status in cancer patients, it is important that they have knowledge of where to procure this information and that a comprehensive identification method is chosen. Comorbidities are rarely included as part of nutrition screening tools, but are part of a complete nutritional assessment. In clinical settings, dietitians can obtain comorbidities from asking the patient and searching medical records. Administrative health data would not be an appropriate source in clinical settings because it is not available until long after the patient has used the health care system. Therefore, it should be reserved for research purposes. Administrative health data, with proper ethical approvals, can be obtained in Canada from the provincial ministry of health or the Canadian Institutes for Health Information.

The results presented in Chapter 2 suggest that the Elixhauser measure (10) is a comprehensive tool that should be considered for use by dietitians instead of the more commonly used Charlson comorbidities (11). In dietetic practice and research, the Elixhauser measure has been rarely used, but it has important potential uses as a more comprehensive risk adjustment method by researchers or simply a tool to identify more relevant conditions that may impact nutritional status in the clinical setting compared to the comorbidities identified using the Charlson method (11).

Clinical dietitians will see patients who possess different types and combinations of conditions which may have dissimilar nutritional treatments and goals. The results presented in Chapter 2 revealed that colorectal cancer patients commonly have comorbidities where those nutritional treatments and recommendations may be different from those suggested for the cancer. For example, a patient with type 2 diabetes who is diagnosed with advanced cancer might be recommended in one regard to consume more energy dense foods to maintain weight (for the advanced cancer) and in another regard to consume more lower energy dense foods to lose weight (for the type 2 diabetes). Patients with different illnesses may also be assigned care from different dietitians, who specialize in the treatment of the different conditions which may have dissimilar nutritional aims. Dietitians are trained to assess and provide personalized guidance on how to best meet the nutritional needs of the patients, even when they have many different conditions with conflicting nutrition recommendations. However, it is possible recommendations may vary depending on the reason for

the visit (see example above). Ideally, all recommendations provided by dietitians should consider all relevant conditions to best meet the care of the patient, but this is not always the case as reported by Orrevall et al. (12). They found that patients felt confused and uncertain when information given by different dietitians about different conditions (e.g., poor intake and diabetes or short bowel syndrome or an ileostomy) was conflicting. Conflicting information about nutrition is an added source of stress for patients at a time when consuming an adequate diet is already difficult. Dietitians treating cancer patients in oncology settings and likewise dietitians treating cancer patients in clinics specializing in other diseases may wish to consult with one another to best meet patient needs.

Although comorbidities have the potential to affect nutritional recommendations, dietitians need to consider patient prognosis when deciding the best nutritional treatment for the patient. In patients who have earlier stages of disease, comorbidities are something that likely needs to be considered by the dietitian and treated nutritionally if appropriate and necessary. However, in later stages of disease, especially when the disease becomes refractory to treatment (as seen in Chapter 3), aggressive nutrition interventions of any sort would not be possible or appropriate. At this point, the risk and burden of artificial nutritional support likely offsets any potential benefit. When patients are in the last few months of life and cared for in palliative settings, nutritional goals are to maximize quality of life and decrease suffering (13). At this time, the patient and family also need support and knowledge to properly cope with the situation (14).

- **Body composition is an important part of a complete nutritional assessment and a significant determinant of resting energy expenditure in cancer patients**

Fat free mass (FFM) encompasses all non-fat containing tissues in the body, which includes organs and skeletal muscle. It is the most important determinant of resting energy expenditure (REE) (15). Fat free mass is not a homogenous compartment; the tissues in this compartment occupy different proportions, and have unique functions and specific metabolic rates (16, 17). Even though muscle encompasses the largest proportion of the FFM compartment (> 50%), it is only responsible for 20-25% of REE (16). Conversely, organ tissue (e.g., liver, kidney, heart and brain) encompasses ~60% of REE, despite only accounting for ~7% of overall FFM mass (16, 18). Variations in both the mass and proportion of different body constituents, especially high specific metabolic rate organ mass, has the ability to explain differences in REE among healthy individuals (18-20). It may also be able to explain a portion of the variation reported in cancer patients (21, 22). Although this relationship has been previously suggested to be important in cancer patients (17), the work presented in Chapter 3 provides among the first evidence to support this hypothesis in advanced colorectal cancer patients. Dietitians should be aware of the relationship between FFM and REE in this patient population, because it can affect both nutritional requirements and treatment.

- **Body composition assessment**

Common tools to measure body composition in clinical and research settings (e.g., BIA, BOD POD®, ***hydrodensitometry***) use a two compartment molecular approach, which partitions the body into two compartments, FFM and fat mass (FM), and gives a whole body measure of these tissues (23, 24). Because muscle occupies a large proportion of FFM, FFM is sometimes assumed to represent skeletal muscle. The findings in Chapter 3 clearly reveal this assumption needs to be used with caution when assessing nutritional status in colorectal cancer patients nearing the end of life because there is a redistribution of FFM from skeletal muscle to central tissues such as the tumor in the liver during this time. Therefore, increases in organ mass have the potential to overshadow a decrease in skeletal muscle or similarly, a large proportion of organ mass may hide a small musculature (e.g., sarcopenia) if only whole body FFM is measured.

When body composition assessment is deemed to be appropriate in colorectal cancer patients and with the knowledge of the possible changes in FFM components, dietitians should perhaps look beyond two compartment molecular methods. Dual energy x-ray absorptiometry (DXA) is a criterion standard body composition measurement tool that uses a three compartment molecular model which partitions the human body into three components: lean soft tissue (which contains muscle, organs, and other non-fat tissues excluding bone), fat mass, and bone mineral (24). Unlike the two compartment methods listed above which can only provide information at the whole body level, DXA also has the ability to

provide information on the regional composition of certain areas such as the head, trunk, and appendages. Using the appendages as a surrogate for whole body muscle is one option that could be considered. The disadvantages of DXA are that it is not commonly available in cancer settings (25) and inaccuracies could be present in cancer patients with severe edema. Although this method is a better choice, it may not be completely ideal.

Computed tomography and MRI imaging are other criterion standard tools used for body composition assessment; however, because of their cost, lack of availability, and radiation exposure with CT imaging, they are not frequently considered feasible methods in non-malignant disease or healthy individuals. These are not issues in an oncology setting because CT imaging is routinely used by physicians for diagnostic purposes (25). Dietitians working in oncology or other areas of practice where this test is routine should be educated on the ability of this method to precisely quantify body composition at the tissue organ level. Dietitians should not consider it a tool exclusively for physician use. Computed tomography imaging may be able to help dietitians to precisely assess initial body composition features which will allow for a more comprehensive nutritional assessment. When serial scans are taken, they can monitor the effectiveness of nutrition interventions. In order for this method to be integrated into dietetic practice, training programs and simplification of analysis procedures are likely needed. It should also not be forgotten that anthropometry is always a potentially useful means of acquiring some idea of muscle mass. Mid upper arm muscle circumference may be an option to assess muscle stores (26); measured values can

be compared to normative Health Canada (27) or NHANES data. Individuals falling below the 5th percentile are considered at risk for poor nutritional status (26).

- **Resting energy expenditure**

In colorectal cancer patients, the work described in Chapter 3 suggests that especially in advanced disease, there is an increase in both mass and proportion of high metabolic rate organs including liver and tumor which may be responsible for a large increase in and a substantial proportion of REE. Although patients at the very end of life would not be candidates for body composition measurement, REE assessment with indirect calorimetry, and aggressive nutritional support, this phenomenon reminds dietitians about the implications of estimating REE using prediction methods such as the Harris Benedict equation (28). It also reminds dietitians about the importance of measurement of REE with indirect calorimetry if appropriate and possible.

The Harris Benedict equation predicts REE based on height, weight, and age (28). One key drawback of this method is that it does not take into account body composition which is the largest determinant of REE. If the proportion of organ mass has a higher relative contribution, such as I demonstrated in colorectal cancer patients, these equations would underestimate REE. Alternatively, if REE was to be predicted in a sarcopenic patient compared to a non sarcopenic patient with the same organ mass, body weight, height, and age using the Harris Benedict equation, it would likely over- predict REE. The relationship between measured and predicted REE from the prospective cohort from Chapter 3 is shown in

Figure 4-1. Despite the r^2 being 0.77, there are some individuals whose REE was not predicted accurately. In this dataset, in the two individuals where measured REE was the most under predicted by the Harris Benedict equation, the liver occupied approximately ~5.2% of FFM; in the two individuals where measured REE was the most over predicted by the Harris Benedict equation, the liver occupied ~3.1% of FFM. Differences in size and proportion of other body composition components as well as the systemic inflammatory response (29) may be additional reasons why the Harris Benedict equation may not accurately predict REE in cancer patients.

4.3 Key Points for the Oncologist

Nutrition information, including body weight and composition, has been frequently ignored by physicians and oncologists. This may be due to lack of nutrition training in medical programs, the lack of consistent criteria to diagnose and treat malnutrition, the lack of knowledge or guidelines on what to do with information on nutritional status, the belief that nutrition is not important, and the lack of time to document nutrition information in medical records (12, 30-35). Despite this oversight, nutritional issues have been associated with many cancer related outcomes of interest such as surgical complications (36-39), chemotherapy toxicity (40, 41), disease recurrence (42), decreased survival (7, 43, 44) and are considered important and a source of worry to patients (12, 45).

- **Oncologists should have an understanding of body weight and body composition and its effects on cancer related outcomes**

Obesity and cachexia are likely the most familiar nutritional issues to oncologists. Obesity is a well known risk factor for many types of cancer (46); consequently, many patients who present for cancer treatment are obese. Obesity associates with increased likelihood of recurrence and decreased disease free survival (42). It was present in ~20% of the cohort used for the study in Chapter 2 at the time of the clinic visit. Cachexia is a well known consequence of advanced disease (47) especially after treatment is no longer effective. Both obesity and cachexia are visible by observing the patient and can be measured using BMI. However, oncologists should be aware that BMI cannot detect all nutritional abnormalities associated with risk and should understand that a normal BMI does not mean an absence of risk.

Computed tomography imaging, a tool used daily in oncology practice to provide diagnostic information and monitor the progress of treatment, has uncovered significant findings about the body composition in cancer patients as revealed in Chapter 3. In other studies, it has also revealed that sarcopenia, defined using sex specific muscularity cutpoints roughly < 2 SD below the healthy young adult mean (7, 25), is associated with decreased survival (7), and increased risk of treatment toxicity (41) in cancer patients. In the elderly, sarcopenia has been associated with poorer physical function (6) and nosocomial infections (48). Sarcopenia cannot be detected easily detected visually or by using only body weight indicators (such as BMI) as it can appear at any BMI including in patients who are obese (7).

Table 4-2 presents a population based cohort of deceased colorectal cancer patients seen in new patient medical oncology clinics at the Cross Cancer Institute, Edmonton, Canada, (n=527) grouped by survival time. Mean BMI is a relatively stable measure; it remains consistently in the overweight category throughout all survival times. There are also substantial proportions of patients who are overweight and obese in all survival times. Underweight is not common in this cohort; even in patients who presented < 90 days from death, it was only found in 9.0% of the population. If BMI was used as the only indicator of nutritional status in this cohort, nutritional status may not appear very problematic. A different situation is uncovered when body composition is measured. The prevalence of sarcopenia in this cohort is high; it ranges from 41.7% (in patients who survived longer than 3 years) to 60.5% (in patients who survived ≤ 90 days). This table clearly shows that if BMI is the only indicator of nutritional status that is used, it would miss a large number of patients who are suffering from sarcopenia and compromised nutritional status.

Because abnormal body composition types such as sarcopenia are common in colorectal cancer patients, and can affect outcomes in different domains of oncology (e.g., medical oncology, surgical oncology), oncologists should be interested in using CT imaging to measure different body composition features in their patients. This information might affect how they treat patients and has the potential to explain outcomes in certain patients such as why some patients experienced chemotherapy toxicity or why others had more surgical complications. Perhaps in the future, the impact of body composition on cancer-

related outcomes and the use of CT imaging as a body composition assessment tool could be added into medical school curricula.

Because oncologists (and dietitians) may not have the practical means to work with CT images to assess body composition features, simpler methods are perhaps needed to provide this type of information. New techniques such as automated CT image analysis programs to assess muscle and adipose tissue stores (49) and linear dimensions are promising methods which have the potential to provide this information expediently and potentially at a low cost (especially for linear measurements which could be done in standard image viewing software packages). Radiologists may also be able to provide body composition information on radiology reports that are already routinely completed after CT imaging.

- **Dietitians are available to help oncologists treat nutritional issues throughout the disease trajectory**

Cancer patients have evolving nutritional issues throughout the disease trajectory. Oncologists should have a good understanding of when to refer patients to see a dietitian for nutritional intervention as this may result in better treatment (e.g., decreased likelihood of treatment toxicity and recurrence) and survival outcomes. Nutrition screening tools should be systematically applied. Oncologists should also understand that nutrition goals depend on both the patient body weight and composition and their disease stage.

Obesity is known to be associated with poor outcomes listed above and there is likely some temptation by oncologists to recommend weight loss to their

obese patients. However, we also know that sarcopenia is common and associated with poor cancer related outcomes (7, 41, 50). Patients who are obese and are deemed to be in a position where weight loss would be appropriate and beneficial, should see a dietitian to be prescribed a hypocaloric, high protein diet to help ensure a preservation of skeletal muscle (51, 52). In overweight and obese head and neck cancer patients, a prophylactic percutaneous endoscopic gastrostomy (PEG) tube has been shown be an effective way to allow patients to slowly lose body weight so that it becomes within or closer to the healthy BMI range (53). Simply instructing patients to lose weight without supervision may result in undesirable losses of skeletal muscle protein which may lead to a worsening of sarcopenia and the poor outcomes associated with it.

Although treatments for sarcopenia are still in their infancy, nutritional therapy with higher protein diets is one option. Higher protein diets, and protein spaced evenly throughout the day (54) may help to prevent or reverse muscle loss. Further research is still required in this area.

4.4 Key Points for the Health Services Researcher

Administrative health data has the potential to be an efficient and low cost way to study large populations that span diverse geographical areas and use different health facilities (55, 56). Although this data source is convenient and perhaps the only way to efficiently study large populations, it does have some disadvantages such as incompleteness and inability to capture the severity of diseases (55, 56). Specifically in relation to nutrition and body weight variables, evidence is mounting that administrative health data does not properly capture this

information (57, 58) and it has become clear that it may not be suitable for this task. It has been suggested that obesity identified in hospitalized children using administrative health data was associated with different population characteristics and health services utilization patterns compared to patients who only had obesity identified using height and weight from their medical record (57). Changes in the protocols for recording body weight information at the front line in addition to development of new ways to capturing body weight and composition information using ICD codes are likely needed to make administrative health data ready for such an endeavor.

- **Administrative health data underestimates the true prevalence of weight related conditions in cancer patients**

Weight and protein-energy malnutrition recorded by ICD diagnostic codes in administrative health data has been suggested to underestimate the true population prevalence of these features (57, 58). Current information on the completeness of this data is scarce. In the work presented in Chapter 2 and others which use administrative health data to calculate the Elixhauser comorbidity measure, obesity is reported to be prevalent in 1–5% of the population (10, 59-61) even in diseases where obesity is a risk factor (e.g., type 2 diabetes) while overall population prevalence rates are typically > 20% (5).

This poor capture may be the result of several possible causes (55) including improper coding and failure to identify diagnosis by the health records personnel, but the more plausible cause is likely due to missing documentation of body weight, its change, and interpretation in patient medical records. Of specific

interest to health services researchers is that the completeness of administrative health data is verified according to medical record (55). However, if weight related variables are not recorded and/or are not interpreted compared to any standard (such as recording BMI and its classification according to the WHO guidelines (62) instead of just recording height and weight, which would not give any indication there is a problem) in patient medical records, this method would not identify a discrepancy.

Health services researchers should be aware of poor capture of weight related variables and use them with caution in population based studies, such as for the identification of patient cohorts. The probable first step to better capture is to ensure health professionals record body weight information routinely and an interpretation in patient medical records. In order for this to happen, the importance of these variables and their ability to predict outcomes of interest needs to be emphasized to physicians and other health professionals. Also, perhaps incentives are needed to capture this information.

- **International Classification of Diseases (ICD) codes for body weight related diagnoses may need modification**

To make administrative health data more useful for the study of weight related conditions, modification of the current ICD diagnostic codes for these features may be necessary. The current codes as they stand do not allow for the collection of useful body weight related data. One issue is that the ICD diagnostic codes for abnormalities in body weight contain no severity indicator or if they do contain a severity indicator, it is difficult to use. Specifically for weight loss,

there are codes to define abnormal weight loss (ICD 10: R63.4) and abnormal weight gain (ICD 10: R63.5), however, there are no criteria on the magnitude of change that needs to occur to use this code. Oncologists have trouble determining important degrees of weight loss in cancer patients (35) and this also seems to be due to the absence of a clear and widely accepted grading system for weight loss. The current code format does not allow discrimination of 5%, 10%, 20% or even larger weight losses.

The current codes available to track abnormalities in body weight are perhaps also in need of revision. There are codes available to capture obesity (ICD 10: E66) but they have been described to be problematic (63, 64). Perhaps one way to better capture body weight information would be to have a grading system for body weight (such as codes for different WHO BMI (62) categories) and a grading system indicating the percentage of weight change. A new obesity clinical staging system which accounts for both BMI and obesity related comorbidities (64) might be another option to consider.

The other issue with the ICD body weight codes specifically relevant for cancer is that there is no code specifically for cancer cachexia. For very low body weights, there are codes for cachexia (not including nutritional marasmus, cancer cachexia and HIV disease resulting in wasting syndrome) (ICD 10: R64) and HIV disease resulting in wasting syndrome (ICD 10: B22.2). Cancer cachexia is considered part of the code for malignant neoplasm without specification to site (ICD 10: C80). Therefore, tracking cancer cachexia with ICD codes in their

current form is therefore nearly impossible. Cancer cachexia could be considered as a candidate to have its own unique code.

With knowledge that sarcopenia and sarcopenic obesity may be associated with poor outcomes including poor performance status (6) and nosocomial infections (48) in the elderly and poor survival (7) and treatment toxicity (40, 41) in cancer patients, it is important that ICD codes are available to capture this information. Currently, no ICD diagnostic codes are available to capture sarcopenia. With increased consensus on how to define this condition (4, 65) this seems like a worthwhile and perhaps feasible addition. Without addition of these codes, study of the impact of these features at the population level would not be possible.

Tables

Table 4-1: The prevalence of Elixhauser comorbidities (CM) and their relationship with the presence of sarcopenia, underweight, and obesity in colorectal cancer patients seen in new patient medical oncology clinics (n=489)

	n (%) with CM	**Sarcopenia† (n=221)**		**BMI < 20 (n=34)**		**Obesity (BMI > 30) (n=97)**	
		n (%) of sarcopenic patients who have CM	Univariate OR [95% CI]	n (%) of underweight patients who have CM	Univariate OR [95% CI]	n (%) of obese patients who have CM	Univariate OR [95% CI]
Congestive Heart Failure	16 (3.3)	7 (3.2)	0.94 [0.35, 2.6]	2 (5.9)	2.0 [0.43, 9.0]	5 (5.2)	1.9 [0.64, 5.6]
Cardiac arrhythmias	44 (9.0)	26 (11.8)	1.9 [0.99, 3.5]	3 (8.8)	0.98 [0.29, 3.3]	6 (6.2)	0.61 [0.25, 1.5]
Valvular disease	8 (1.6)	5 (2.3)	2.0 [0.48, 8.7]	0 (0)	-*	1 (1.0)	0.57 [0.070, 4.7]
Pulmonary circulation disorders	8 (1.6)	5 (2.3)	2.0 [0.48, 8.7]	3 (8.8)	**8.7 [2.0, 38.1]**	1 (1.0)	0.57 [0.070, 4.7]
Hypertension without complications	126 (25.8)	61 (27.6)	1.2 [0.79, 1.8]	5 (14.7)	0.48 [0.18, 1.3]	29 (29.9)	1.3 [0.79, 2.1]
Hypertension with complications	9 (1.8)	7 (3.2)	4.4 [0.90, 21.2]	3 (8.8)	**7.2 [1.7, 30.4]**	2 (2.1)	1.2 [0.24, 5.7]
Other neurological disorders	10 (2.0)	6 (2.7)	1.8 [0.51, 6.6]	2 (5.9)	3.5 [0.71, 17.1]	1 (1.0)	0.443 [0.055, 3.5]
Chronic pulmonary disease	29 (5.9)	14 (6.3)	1.1 [0.54, 2.4]	5 (14.7)	**3.1 [1.1, 8.7]**	5 (5.2)	0.83 [0.31, 2.2]
Diabetes without complications	59 (12.1)	31 (14.0)	1.4 [0.81, 2.4]	2 (5.9)	0.44 [0.10, 1.9]	12 (12.4)	1.0 [0.53, 2.0]

	n (%) with CM	Sarcopenia† (n=221)		BMI < 20 (n=34)		Obesity (BMI > 30) (n=97)	
		n (%) of sarcopenic patients who have CM	Univariate OR [95% CI]	n (%) of underweight patients who have CM	Univariate OR [95% CI]	n (%) of obese patients who have CM	Univariate OR [95% CI]
Diabetes with complications	5 (1.0)	2 (0.9)	0.81 [0.13, 4.9]	0 (0)	-*	3 (3.1)	**6.2 [1.0, 37.8]**
Hypothyroidism	27 (5.5)	14 (6.3)	1.3 [0.61, 2.9]	4 (11.8)	2.5 [0.81, 7.7]	6 (6.2)	1.2 [0.46, 3.0]
Renal failure	8 (1.6)	7 (3.2)	**8.7 [1.1, 71.5]**	3 (8.8)	**8.7 [2.0, 38.1]**	2 (2.1)	1.4 [0.27, 6.8]
Liver disease	8 (1.6)	4 (1.8)	1.2 [0.30, 4.9]	1 (2.9)	1.9 [0.23, 16.2]	1 (1.0)	0.57 [0.070, 4.7]
Fluid & electrolyte disorders	24 (4.9)	14 (6.3)	1.7 [0.76, 4.0]	2 (5.9)	1.2 [0.28, 5.5]	1 (1.0)	0.17 [0.022, 1.3]
Blood loss anemia	5 (1.0)	2 (0.9)	0.81 [0.13, 4.9]	0 (0)	-*	2 (2.1)	2.7 [0.45, 16.6]
Deficiency anemia	24 (4.9)	14 (6.3)	1.7 [0.76, 4.0]	3 (8.8)	2.0 [0.56, 7.1]	2 (2.1)	0.35 [0.082, 1.5]
Depression	14 (2.9)	5 (2.3)	0.67 [0.22, 2.0]	2 (5.9)	2.3 [0.50, 10.8]	2 (2.1)	0.67 [0.15, 3.0]

Numbers in **bold** represent significant values ($p < 0.05$)

The following Elixhauser comorbidities were dropped due to low counts (i.e., ≤ 3 patients affected in the overall sample): peripheral vascular disorders, paralysis, peptic ulcer disease, rheumatoid arthritis, coagulopathy, drug abuse, alcohol abuse, psychosis, and HIV/AIDS.

†Sarcopenia was measured using the method and cutpoints described by Prado et al. (41). CT scans were taken on average 24 ± 22 days from the new patient medical oncology clinic visit date.

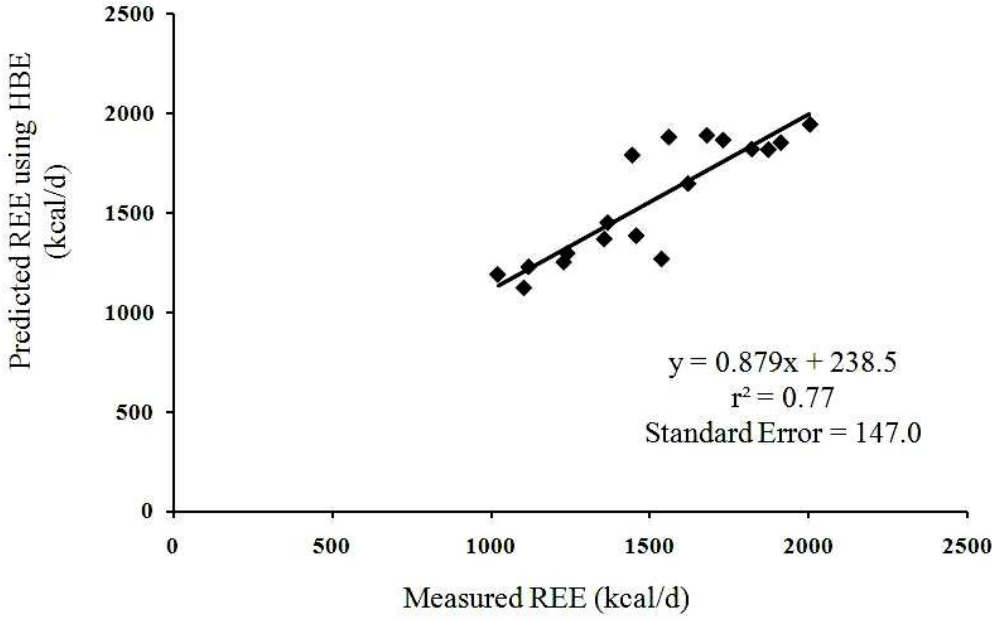
*Cannot be calculated.

Table 4-2: Body weight and composition characteristics in deceased colorectal cancer patients seen in new patient medical oncology clinics categorized by time to death (n=527)

	Time to death						
	≤ 90d (n=67)	**91d-180d (n=56)**	**181d-365d (n=111)**	**366d-545d (n=98)**	**545d-730d (n=61)**	**730d-1095d (n=73)**	**≥ 1096d (n=61)**
Mean BMI	25.4	25.6	25.2	25.4	26.1	25.9	27.3
WHO BMI Categories (%)							
< 18.5	9.0	7.1	4.5	5.1	1.6	2.7	1.6
18.5-24.9	43.3	46.4	50.5	45.9	42.6	46.6	36.1
25.0-29.9	29.9	28.6	31.5	31.6	34.4	37.0	37.7
≥ 30	17.9	17.9	13.5	17.3	21.3	13.7	24.6
Body Composition							
Sarcopenia (%)	60.5	50.0	61.1	52.5	47.6	54.2	41.7

Figures

Figure 4-1: Relationship between measured and predicted REE (using the Harris Benedict equation (HBE)) from the prospective cohort (n=18) described in Chapter 3



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