Nutrition Assessment in Medical and Surgical Oncology

by

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ABTRACT

Introduction:

Cancer-associated cachexia is defined as a multifactorial syndrome characterized by loss of body weight with specific losses of skeletal muscle and adipose tissue. Cachexia is driven by a variable combination of reduced food intake (FI) and distinct tumor-associated metabolic changes, including elevated energy expenditure, excess catabolism, and inflammation. Patients with cachexia experience weakness, fatigue, loss of independence, poor treatment tolerance, and death. Cachexia may be present at the time of cancer diagnosis or develop and worsen with cancer treatment and disease progression. There are no widely agreed upon diagnostic criteria, which have hindered diagnosis, clinical management and development of effective treatments. An International Consensus Framework for the Definition and Classification of Cancer Cachexia made recommendations for development of diagnostic criteria, suggesting *'definitive cutoffs for variables (e.g. weight loss, low muscle mass) could be determined from large contemporary datasets by determining the values that relate optimally to meaningful patient-centered outcomes, such as loss of function or decreased survival'* The objective of my thesis was to advance development of diagnostic criteria for cancer cachexia in at risk patient populations from two cancer treatment settings, medical and surgical oncology.

Methods:

Large contemporary data sets were lacking to study patients with cancer cachexia. International research partners contributed data from clinical cachexia research studies to create aggregated data sets for secondary data analysis. Data included candidate diagnostic criteria (e.g. body mass index (BMI), weight loss (WL), computed tomography (CT)-defined body composition, FI, and C-reactive protein (CRP, as a marker of inflammation), covariates (e.g. cancer type, stage, surgical approach, age, sex, performance status), and patient-centered

outcomes (e.g. overall survival (OS), length of hospital stay (LOS)). In medical oncology, the prognostic impact of candidate diagnostic criteria (WL, BMI, FI, and CRP) on OS was evaluated with Kaplan Meier and multivariable Cox proportional hazard models; FI and CRP were evaluated as etiological criteria for WL with multivariable multinomial logistic regression (MLR) models. In the surgical setting, the prognostic impact of candidate diagnostic criteria (WL, FI, and CT-defined body composition) on LOS, postoperative complications, and 30-day hospital readmission were evaluated with multivariable logistic (LR) and negative binomial (NMR) regression models.

Results:

Large aggregated data sets were created to study patients from medical (N=18,173 patients) and surgical (N=5,739) oncology settings. Three studies were conducted with data from medical oncology. Study 1 demonstrated that increased %WL and decreased BMI independently predicted OS. A grading system combining %WL and BMI was developed based on OS (Grade 0 (longest OS) to 4 (shortest OS)), and was subsequently validated. In studies 2 & 3, FI and CRP were evaluated as etiological criteria for WL. Common values, based on relative risk of weight loss, were determined across the 3 most frequently used clinical measurement scales for FI, which were combined (normal, moderately or severely reduced) and evaluated. Reduced FI significantly associated with increasingly severe WL. The relationship between CRP and WL was also evaluated; CRP values (<10, 10-43, and ≥43 mg/L) associated with distinct degrees of WL were defined. In multivariable MLR both CRP and FI significantly associated with increasingly severe WL, and the combination of WL, FI, and CRP identified patients with significantly different OS.

Two studies were conducted with data from surgical oncology. In the first study, nutrition risk (based on WL and reduced FI) was identified as an independent predictor of low compliance to a standardized multi-modal care pathway, which had a significant negative impact on postoperative complications and LOS. In the second study, age- and sex-specific preoperative body composition profiles were defined based on combinations of CT-defined low skeletal muscle, low skeletal muscle radiation attenuation, and high visceral fat. Multidimensional body composition profiles were at significant risk of longer LOS and increased 30-day hospital readmission.

Conclusions:

Candidate diagnostic available for aggregation were heterogeneous, and represented with variable frequency. Alterations in metabolism were only represented by a single criterion, CRP. Identifying common values between different measurement scales for FI facilitated data aggregation. Evaluation of aggregated data identified WL, BMI, FI, CRP, and CT-defined body composition as candidate diagnostic criteria for cancer cachexia that identified patients at risk for poor outcomes in different care settings. These criteria are a key first step toward development of definitive diagnostic criteria, and require prospective validation.

PREFACE

This doctoral thesis is original work by Lisa Martin. The research presented is based on data collected from human subjects. A portion of the data presented in Chapters 2, 5, 6, 7 and 8 were acquired through national and international collaborations with research partners, who agreed to share their data for secondary analysis as part of an international data aggregation effort. Research partners are listed in the table and all data were collected under the auspices of human ethics approvals from their respective institutions:

Principle Investigator	**Institution**
Pierre Senesse	Institut Régional du Cancer de Montpellier (ICM), France
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*deceased September 3, 2016

Data collected from human subjects in Alberta, Canada, received research ethics approval from the University of Alberta Health Research Ethics Biomedical Panel and the University of Calgary Health Research Ethics Board. Data included in Chapters 2, 5, 6, 7 and 8 were collected with the following ethical approvals: HREBA.CC-16-0308 "Pro00055767 Chart review of nutritional status in colorectal cancer patients undergoing surgery; HREBA.CC-17-0433 "23198 Chart review of nutritional status and involuntary weight loss in advanced cancer patients";

Pro00046864 “Enhancing Patients' Recovery After Surgery: Strategy to Transform Care and Maximize Value”.

The contributions made by the PhD candidate, Lisa Martin, and the co-authors to the completion of work included in this thesis are described here.

Chapter 2 of this thesis has been published as Martin L, Senesse P, Gioulbasanis I, Antoun A, Bozzetti F, Deans C, Strasser F, Thoresen L, Jagoe RT, Chasen M, Lundholm K, Bosaeus I, Fearon K, Baracos VE. Diagnostic criteria for cancer-associated weight loss. J Clin Oncol, 2015; 33:90-99. *Conception and design***:** Lisa Martin, Kenneth H. Fearon, Vickie E. Baracos, *Provision of study materials or patien**ts:*** Pierre Senesse, Ioannis Gioulbasanis, Sami Antoun, Federico Bozzetti, Chris Deans, Florian Strasser, Lene Thoresen, R. Thomas Jagoe, Martin Chasen, Kent Lundholm, Ingvar Bosaeus, Kenneth H. Fearon, *Collection and assembly of data***:** Lisa Martin, Pierre Senesse, Ioannis Gioulbasanis, Sami Antoun, Federico Bozzetti, Chris Deans, Florian Strasser, Lene Thoresen, R. Thomas Jagoe, Martin Chasen, Kent Lundholm, Ingvar Bosaeus, Kenneth H. Fearon, Vickie E. Baracos *Data analysis and interpretation*: Lisa Martin, Pierre Senesse, Vickie E. Baracos *Manuscript writing:* Lisa Martin and Vickie E. Baracos with contribution from other authors *Revision and final approval of manuscript:* All authors.

Chapter 3 of this thesis has been published as Martin L. Diagnostic criteria for cancer cachexia: Data versus dogma. Curr Opin Nutr Metab Care, 2016; 19:188-198. This article was an invited review, and was completed in its entirety (conception, design, collection and assembly of data, interpretation, manuscript writing and approval) by Lisa Martin

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Support Palliat, 2018, Aug. 16; doi:10.1097/SPC.0000000000000379. Lisa Martin was the invited author for this review, and responsible for the content as lead author. *Conception and design***:** Lisa Martin, Catherine Kubrak**,** *Collection and assembly of data***:** Lisa Martin, Catherine Kubrak, *Data analysis and interpretation*: Lisa Martin, Catherine Kubrak, *Manuscript writing*: Lisa Martin, Catherine Kubrak, *Revision and final approval of manuscript:* Lisa Martin, Catherine Kubrak.

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Leah Gramlich, Gregg Nelson, Jessica Hopkins, Georgios Malietzis, Michael Sawyer, Ian Jenkins, Ronald Brisebois, Anthony MacLean, *Collection and assembly of data***:** Leah Gramlich, Gregg Nelson, Jessica Hopkins, Georgios Malietzis, Michael Sawyer, Ian Jenkins, Ronald Brisebois, Anthony MacLean, Vickie E Baracos, *Data analysis:* Lisa Martin, *Interpretation of results*: Lisa Martin, Georgios Malietzis, Ian Jenkins, Vickie E. Baracos, Leah Gramlich, Gregg Nelson *Manuscript writing:* Lisa Martin, Vickie E. Baracos, *Revision and final approval of manuscript:* All authors.

I would like to dedicate my thesis to Emlyn and Henry.

You are my greatest adventure.

“When in doubt, choose the kids. There will be plenty of time later to choose work.”

- Anna Quindlen

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LIST OF ABBREVIATIONS

ADL	Activities of daily living
AHS	Alberta Health Services
AJCC	American Joint Committee on Cancer
ASA	American Society of Anesthesiologists
BMI	Body mass index
CI	Confidence interval
CNST	Canadian nutrition risk screening tool
CRC	Colorectal cancer
CRP	C-reactive protein
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Easter Cooperative Oncology Group performance status
EORTC	European Organization for Research and Treatment of Cancer
ERAS	Enhanced Recovery After Surgery
EIP	ERAS Implementation Program
EIAS	ERAS Interactive Audit System
FI	Food intake
GI	Gastrointestinal
HR	Hazard ratio
HU	Hounsfield Unit
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10^{th} revision
I-VVAS	*Ingesta*- verbal/visual analogue scale
KPS	Karnofsky Performance Scale
L3	Third lumbar vertebrae
LOS	Length of hospital stay
MLR	Multinomial logistic regression
MNA	Mini nutrition assessment
MST	Malnutrition screening tool
NBM	Negative binomial regression
NS	Non-significant
ONS	Oral nutritional supplements
OS	Overall survival
OR	Odds ratio
PG-SGA	Patient generated-subjective global assessment
POD	Postoperative day
PONV	Postoperative nausea and vomiting
PS	Performance status
QOL	Quality of life
SD	Standard deviation
SAT	Subcutaneous adipose tissue
SE	Standard error
SMA	Skeletal muscle area
SMI	Skeletal muscle index
SMR	Skeletal muscle radiation attenuation

TAT	Total adipose tissue
UICC	Union for International Cancer Control
VAS	Visual analogue scale
VAT	Visceral adipose tissue
VO	Visceral obesity
WL	Weight loss

CHAPTER 1: Introduction and research plan

1.1 Introduction

Cachexia was first described by Hippocrates (460-377 BC) as the gradual emaciation of an individual in response to chronic illness that ultimately leads to death, *'The flesh is consumed… the shoulders, clavicles, chest, and thighs melt away… this illness is fatal'*.[1] Such narrative portraits have continued to appear throughout the literature, whereby a cluster of clinical symptoms including weight loss (WL), wasting of fat and muscle, anorexia, and gastrointestinal disturbances have consistently been used to describe cachexia.[1] The etiology of cachexia has been difficult to characterize due to its multifactorial nature, which is thought to be driven by a variable combination of reduced food intake (FI) and metabolic changes, including elevated energy expenditure, excess catabolism, and inflammation.[2-4] Owing to the prominence of reduced FI as well as the presence of inflammation; cachexia is also classified as a form of disease-associated malnutrition.[4-6] Cachexia is distinct from starvation and nutritional deficiencies in otherwise healthy individuals and because of the underlying disease it can only be partly reversed by nutritional interventions.[2-4]

Patients with cancer-associated cachexia have distinctive tumor-related metabolic changes that are believed to drive wasting of skeletal muscle and adipose tissue. The variable contribution of tumor, inflammation, and FI leads to notable heterogeneity in the presentation, clinical course, and outcomes of patients with cancer cachexia, and was best summarized by Professor Kenneth Fearon '*When considering how a tumor might influence the host, one has to account for the heterogeneity of the response to cancer. Some patients will remain weight-stable, and some will become profoundly cachectic. For those who lose weight this may be via a series of metabolic changes, through the development of anorexia, or via a combination of the two. Furthermore, there is tremendous heterogeneity in the metabolic response which a host may*

demonstrate and a whole variety of causes of reduced food intake. In fact, one might almost despair at trying to find one common final pathway to account for all these changes. Nevertheless, I think such heterogeneity gives us a clue. It suggests that for different tumors and even for patients with the same tumor we may be looking at entirely different mechanisms of weight loss"[7]

It seems highly unlikely that a single clinical, laboratory, or radiological feature would support the diagnosis of cancer cachexia.[8] However, researchers and clinicians alike have used multiple definitions and diagnostic criteria to identify patients with cancer cachexia which have ranged from a single overall assessment (i.e. involuntary WL) to various combinations of assessments (i.e. FI, skeletal muscle depletion, and systemic inflammation).[9,10] These inconsistencies were highlighted in a review by Dechaphunkul et al.[10]; 24 different definitions for cancer cachexia were identified in head and neck cancers alone, and the number of criteria used ranged from a single criterion up to six different criteria. Lack of a uniformly accepted definition and diagnostic criteria have been described as impediments to the identification and treatment of cancer cachexia, and for the development of new therapeutic agents.[2,11,12] Inclusion criteria to clinical trials have favored the inclusion of patients with WL of any etiology and near the end of life. Treatment response is difficult to evaluate in patients whose WL was not due to the etiology targeted by the therapy, and who were too close to death to receive a benefit.[12] The importance of diagnosing patients with cancer cachexia cannot be understated; it has a negative impact on patients' physical functioning and quality of life, decreases their ability to tolerate cancer treatments (e.g. surgery and anti-cancer therapies), and reduces survival.[2,13,14] [15] Early identification is key to ensure appropriate clinical, nutritional, and metabolic care.[16-18]

The increasing prevalence of overweight and obesity add an additional layer of complexity to the assessment and diagnosis of cancer cachexia. Overweight and obese patients are not typically recognized as being at nutrition risk, however excess body fat can mask skeletal muscle wasting associated with cancer cachexia placing patients at increased risk of chemotherapy toxicity, surgical complications, and death.[12,19,20] The prevalence of overweight plus obesity combined (i.e. BMI > 25 kg/m^2) in Canada and the US is 60 and 70% respectively, and is a risk factor for the development of many cancers.[21-24] It is therefore not surprising that today's cancer patient is more likely to be overweight or obese at diagnosis than underweight (e.g. 40% vs. 10%).[19,25] Computed tomography (CT) images completed as standard of care in oncology are routinely available, and offer an unprecedented window to noninvasively and precisely quantify skeletal muscle, and adipose tissues. CT-defined body composition has emerged as an important prognostic indicator in oncology, and has been suggested as a biomarker for consideration in all cancer patients.[26-31] The emerging clinical utility of CT images to assess body composition greatly expands the clinicians' toolbox beyond body weight, and contributes to the identification of patients at risk of cancer cachexia.

A unifying set of concepts to define and diagnose cancer cachexia was needed, which could serve to guide clinical management, and to help create more homogeneous cohorts for clinical research studies.[2,8] This need was recognized and addressed within the International Consensus Framework for the Definition and Classification of Cancer Cachexia.[2] In 2010, a group of international experts in cancer cachexia came together with the purpose to develop a definition and diagnostic criteria specific to cancer cachexia. Making the diagnosis of cancer cachexia is the goal, because it allows for prognostication of outcomes and optimal clinical

managment.[16-18] To be able to diagnose cancer cachexia consensus was required with regard to several key elements:

1) **A definition:** a clear definition should describe what cancer cachexia is, and identifies key clinical and etiological characteristics.

2) **Diagnostic criteria:** a set of signs, symptoms, and tests for use in routine clinical care that when applied identify patients with the syndrome, and can guide the care of individual patients.[8] General requirements for diagnostic criteria are that they are broad and reflect the different features of the syndrome (e.g. the heterogeneity).[8]

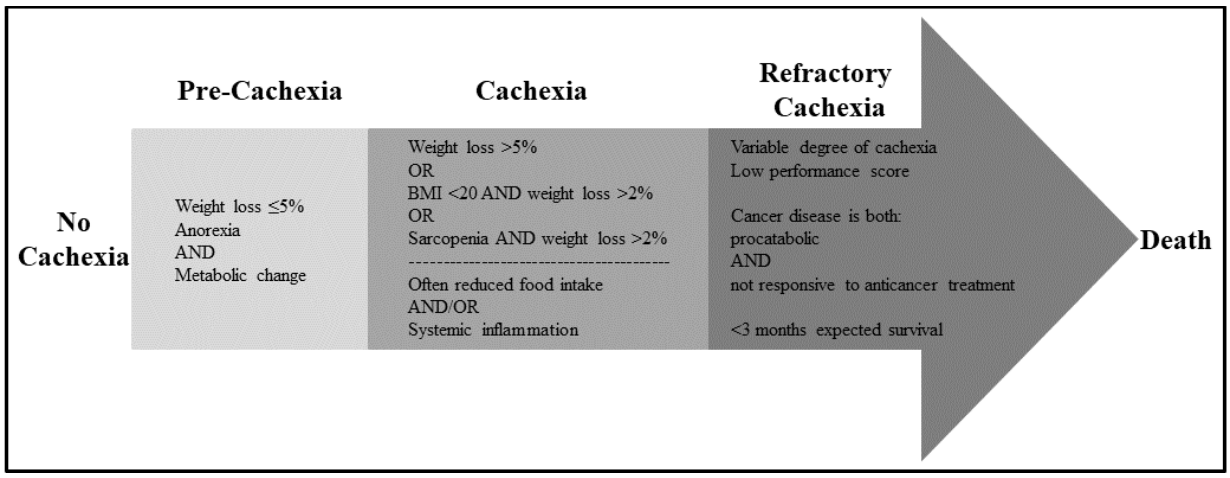
3) **Classification criteria:** are standardized definitions intended to capture the majority of patients with key features of the syndrome, and enables the creation of well-defined, homogeneous cohorts for clinical research.[8]

To gain consensus for these main elements, an international consortium was formed which included 19 experts in clinical cancer cachexia research such as medical and surgical oncologists, palliative medicine specialists, and nutritionists.[2] A formal Delphi consensus process was adopted that included focus groups, discussion, and two Delphi scoring and voting rounds.[2] Consensus was reached for a definition: cancer cachexia is defined as *'a multifactorial syndrome defined by ongoing* ***skeletal muscle loss*** *(with or without fat loss)…characterized by negative protein and energy balance driven by a variable combination of* ***reduced food intake*** *and* ***altered metabolism*** *'*[2] Novel to this definition is the statement that skeletal muscle loss can occur independently from fat mass; therefore the quantification of skeletal muscle mass is critical to the diagnosis of cancer cachexia. This definition acknowledges the specific etiology of cancer cachexia including reduced FI and tumor-driven components that alter metabolism (e.g. tumor-

derived catabolic factors, inflammation, and hypermetabolism) and contribute to excess catabolism of skeletal muscle and adipose tissue as well as to alterations in nutrient intake.[2,32]

Consensus was achieved for the central concepts that will underlie the eventual classification of cancer cachexia according to stages. It was agreed that cancer cachexia is a syndrome that evolves across a continuum characterized by three stages of increasing severity: pre-cachexia, cachexia, and refractory cachexia, which may be variously characterized by severity of WL, reduced FI, altered metabolism, poor functional status, and decreased life expectancy (Figure 1-1).[2] However, there was no consensus with regard to the actual criteria to identify patients for each cachexia stage, and this remains an area for development.

Figure 1-1. Classification of cancer cachexia stage



A schematic for the stages of cachexia, re-drawn from Fearon et al.[2] This figure highlights the concepts that underlie the eventual classification of cancer cachexia, which is represented as a continuum that includes three stages of increasing severity, and presents provisional criteria that may identify patients by cachexia stage. Pre-cachexia is suggested to be characterized by early nutritional (e.g. anorexia) and metabolic changes that precede substantial involuntary loss of body weight and depletion of skeletal muscle (e.g. sarcopenia). Cachexia is characterized by varying degrees of involuntary weight and skeletal muscle depletion that is due to a variable combination of reduced food intake and systemic inflammation. Refractory cachexia is suggested to be characterized by patients with advanced cancers that are no longer responsive to anti-cancer therapies, who have low performance status (e.g. ECOG ≥3) and life expectancy of <3 months.

Given the complexity and multifactorial nature of cancer cachexia the development and validation of diagnostic criteria is expected to be challenging, and consensus was not achieved

for diagnostic criteria.[2,7,8] Involuntary WL and skeletal muscle depletion had some degree of agreement regarding their use as diagnostic criteria, and provisional diagnostic criteria were presented.[2] Involuntary WL as a diagnostic criterion was agreed upon by all participants. However, the severity scale for WL was not agreed upon for the reasons that multiple severity scales are used in clinical practice (e.g. Common Terminology Criteria for Adverse Events (CTCAE)[33] >5%, >10%, >20%), which were arbitrarily defined, and do not consider the severity of WL in combination with initial body weight.[2] A re-evaluation of WL was recommended, to define the impact of the rate of WL in combination with initial body weight in relation to clinical outcomes. There was consensus supporting the routine assessment of skeletal muscle, but no consensus was achieved regarding specific methodology, although preference was given to the quantification of skeletal muscle using CT.[2]

Consensus was not achieved for any diagnostic criteria pertaining to the etiological factors of cancer cachexia. However, an agreed upon list of candidate diagnostic criteria was provided for assessments of FI and altered metabolism.[2] Assessments of FI are recognized to be heterogeneous, and several types of assessments were suggested as possible diagnostic criteria including qualitative (e.g. patient-reported food intake) and quantitative (e.g. calculation of energy and protein intakes) assessments. There are few clinical measures of altered metabolism; however C-reactive protein (CRP, a marker of systemic inflammation) and the assessment of energy expenditure (to determine if patients were hypermetabolic) are recognized as indicators of metabolic change and were suggested as possible diagnostic criteria.[2]

To advance efforts to develop diagnostic criteria for cancer cachexia, authors of the consensus framework recommended a data-driven approach to develop *'definitive cutoffs for variables (e.g. weight loss, low muscle mass) which could be determined from large*

contemporary datasets by determining the values that relate optimally to meaningful patient-centered outcomes, such as loss of function or decreased survival" This statement is the foundation for my thesis.

1.2 Research approach

My research approach has been to aggregate data from clinical research studies, and to conduct secondary analysis to evaluate body weight, WL, FI, CT-defined body composition, and systemic inflammation as diagnostic criteria for cancer cachexia. My goal was to create an aggregated data set large enough for adequately powered statistical and subset analyses. Data was eligible for aggregation based on the following criteria: i) original data were prospectively collected under the auspices of human ethics approvals from respective institutions, ii) data were anonymized, iii) data included a nutrition risk assessment at the point of referral for nutrition care (i.e. prior to nutrition intervention) which could include the following scenarios: at entry to investigational cachexia clinical trials, at cancer diagnosis as of standard of care, prior to undergoing elective surgery, and at entry to supportive/palliative care programs, iii) clinical data including: patient demographics, cancer type and stage, surgical type and approach, performance status, iv) patient centered outcomes (overall survival (OS), length of hospital stay (LOS), postoperative complications, 30-day hospital readmission). Clinical research studies of cachexia include patients most at risk for developing cachexia (i.e. specific cancers and those with locally advanced or metastatic tumors) therefore not all cancer types and stages are represented. Additionally, data on ethnicity is not collected. Details about my research approach are presented in Chapter 3. Cachexia-related data is often already part of standard of care (e.g. CT images; blood work; cancer diagnosis and stage), but is also enriched with data collected from additional nutrition (e.g. WL, FI, appetite) and functional assessments that are not typically found within the medical chart. A main limitation of aggregating data sets for retrospective secondary analysis

is that the data collected can be heterogeneous and difficult to aggregate as different parameters and assessments are used in different studies. I address these limitations throughout my thesis in Chapters 2, 5, 6, and 9.

1.3 Research plan

My overall objective was to advance the development of diagnostic criteria for cancer cachexia. Three specific objectives, sub-objectives and respective hypotheses are outlined:

Objective 1. To evaluate WL as a diagnostic criterion based on the consensus statement that WL *'should be graded according to degree of weight loss and concurrent BMI, and the severity classification should be developed around the predictive value for outcomes such as treatment toxicity, quality of life, hospitalization, and survival'*[2] The aim was to define the prognostic significance of WL and body mass index (BMI) in a large international data set of contemporary cancer patients, using mortality as the outcome.

Sub-Objective 1.1 was to form the International Cancer Cachexia Data Repository (ICCDR) by aggregating data from clinical cancer cachexia research studies made available from international collaborators.

Sub-Objective 1.2 was to test the prognostic significance of WL and BMI in a multivariable Cox proportional survival model, and develop an updated grading system incorporating both WL and BMI. I hypothesized that increased WL and low BMI would be independently predict decreased OS, and that WL would confer a worse prognosis in patients with lower initial BMIs.

Sub-Objective 1.3 was to validate the grading system for cancer-associated WL in an independent sample.

Objective 2 was to evaluate two candidate diagnostic criteria, reduced FI and CRP (a marker of systemic inflammation), as etiological factors for cancer-associated WL.

Sub-objective 2.1 was to describe the relationship between FI, as assessed by three different tools (the Patient-Generated Subjective Global Assessment (PG-SGA)[34,35], the *Ingesta*-Verbal/Visual Analogue Scale (I-VVAS)[36,37], and the Mini-Nutrition Assessment (MNA) [38,39]), and WL to determine if there was equivalency between tools using multinomial logistic regression analysis. I hypothesized the different measurements scales for FI would demonstrate similar associations to WL, and that FI data could be combined. I also hypothesized that increasingly severe reductions in FI would be associated with increasingly severe WL i.e. that FI would explain, in part, the etiology of WL.

Sub-objective 2.2 was to describe the relationship between CRP and WL, and to determine optimal values of CRP associated with increased WL. I hypothesized that higher CRP values would be associated with increased WL.

Sub-objective 2.3 was to evaluate the contribution of CRP *and* FI as etiological criteria for WL using multinomial logistic regression analysis. I hypothesized that both CRP and reduced FI would be independently associated with increased severity of WL.

Sub-objective 2.4 was to determine if the combination of WL, FI, and CRP could be used to stratify patients according to overall survival using the Kaplan Meier method. I hypothesized that increased WL would identify patients with poor OS and that high CRP values and reduced FI would contribute to additional risk stratification.

Objective 3 was to determine if features of cancer cachexia, including WL, reduced FI (as assessed by a nutrition risk screen), and CT-defined body composition (i.e. skeletal muscle depletion, low skeletal muscle radiation attenuation, and high visceral adipose tissue) could

identify surgical patients' poor postoperative outcomes. Outcomes including compliance to standardized surgical care pathways, LOS, postoperative complications, and 30-day hospital readmission were evaluated using logistic and negative binomial regression analysis.

Sub-objective 3.1 was to evaluate surgical data collected from a standardized evidence-based perioperative surgical care pathway (Enhanced Recovery After Surgery (ERAS)) to determine if implementation of ERAS across colorectal surgical programs in Alberta, Canada improved the rate of nutrition risk screening. I hypothesized that nutrition risk screening would be improved, and that patients with nutrition risk (i.e. WL and reduced FI) would be identified.

Sub-objective 3.2 was to determine if patients identified with nutrition risk had worse surgical outcomes, including compliance to surgical pathways, LOS, and postoperative complications using logistic regression. I hypothesized that patients with nutrition risk would have lower compliance to ERAS care pathways, longer LOS, and increased postoperative complications.

Sub-objective 3.3 was to acquire and aggregate clinical data from research studies on cancer cachexia that evaluated preoperative CT-defined body composition in colorectal cancer (CRC) patients eligible for elective surgery.

Sub-objective 3.4 was to establish a sex and age-specific reference group for preoperative CT-defined body composition features in elective CRC patients.

Sub-objective 3.5 was to define sex- and age-specific thresholds for CT-defined low skeletal muscle, low skeletal muscle radiation attenuation, and high visceral adipose tissue that were significantly associated with longer LOS using negative binomial regression. I also wanted to determine if the combination of one, two, or three body composition features conferred increased risk of longer LOS, major complications, and a higher rate of 30-day hospital readmission. I hypothesized that low skeletal muscle, low skeletal muscle radiation attenuation, and high

visceral adipose tissue, would each be associated with longer LOS and that multidimensional profiles would confer additional risk for poor postoperative outcomes.

1.4 Chapter Format

The objectives, sub-objectives, and hypotheses stated above were tested in a series of studies, which have been organized into thesis chapters. Chapters 2 to 4 and 7 & 8 have been published. The thesis chapters will be presented in the order in which the research was completed, and are organized by oncology practice setting (e.g. medical or surgical oncology). Chapters 2 through 6 focus on research conducted in the medical oncology setting, followed by research conducted in the surgical setting (Chapters 7 & 8).

Chapter 2 is the first publication to use data from the ICCDR. This work presents an updated classification system for cancer-associated weight loss based on the prognostic significance of both WL and BMI. Objective 1 and sub-objectives 1.1 to 1.3 are addressed in this chapter.

Chapters 3 & 4 are literature reviews describing recent efforts to develop diagnostic criteria for cancer cachexia according to the principles outlined in the International Consensus Framework for Cancer Cachexia.[2] Chapter 3 provides an in-depth explanation of my research approach and additional context for the work completed in Chapters 2, 5 & 6. Chapter 4 provides discussion about the factors contributing to the etiology of cancer cachexia, as well as context for the research presented in Chapters 5 & 6.

Chapter 5 describes the relationship between FI and WL, and demonstrates how different assessments of FI were aligned based on their associations to WL. FI as an etiological criterion

for WL was also evaluated in multivariate regression. Objective 2 and sub-objective 2.1 are addressed in this chapter.

Chapter 6 describes the association between CRP and WL, and defines optimal values of CRP based on this relationship. CRP as an etiological criterion for WL was evaluated when adjusted for other covariates including reductions in FI. Lastly, the combination of WL, CRP, and FI was evaluated in relation to OS. Objective 2 and sub-objectives 2.2 to 2.4 are addressed in this chapter.

Chapter 7 describes the implementation of a standardized evidence-based perioperative surgical care pathway, ERAS, in colorectal surgeries. This study evaluates changes to nutrition risk screening across surgical programs and evaluates whether nutrition risk screening identifies patients with poor surgical outcomes. Objective 3 and sub-objectives 3.1 to 3.2 are addressed in this chapter.

Chapter 8 describes how the aggregation of clinical data was use to establish age and sex norms for features of body composition specific to preoperative CRC patients, and evaluates features of body composition in relation to postoperative outcomes. Objective 3 and sub-objectives 3.3 to 3.5 are addressed in this chapter.

Chapter 9 provides an overall discussion and directions for future research.

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CHAPTER 2: Diagnostic criteria for the classification of cancer-associated weight loss[1]

2.1 Introduction

Involuntary weight loss (WL) is the cardinal diagnostic criterion of cancer cachexia.[1] WL at the start of chemotherapy is associated with reduced response rates and increased toxicity, and is included as one of the key Common Toxicity Criteria of Adverse Events (CTCAE).[2] Percent WL (%WL) is an index of severity but there are marked inconsistencies as to what %WL oncologists consider clinically important (varying from 5 to >20%).[3, 4] Likewise, levels of body mass index (BMI) used to define clinically underweight and cachexia cited by various authorities and authors are inconsistent (<18.5, <21, <23 kg/m^2).[5]

Individual patients do not start their cancer journey with identical body habitus. The demographics of body weight in cancer patients have changed since most existing grading schemes for WL were established. Overweight and obesity are now prevalent worldwide[6], and the upward shift in body weight renders definitions of clinically significant WL in cancer patients increasingly unclear.[7, 8] Cancer cachexia contributes to poor prognosis through progressive depletion of the body's energy and protein reserves, therefore it is relevant to determine the impact of WL on survival as a function of initial body reserves. Obesity is usually considered a disadvantage based on studies of all-cause mortality.[9] However, obesity confers a survival advantage in patients with several diseases associated with WL (e.g. heart and renal failure).[10] The larger energy reserve of obese persons may confer this advantage.[11]

Diagnostic criteria for cancer cachexia will inevitably include additional information beyond merely assessing WL, such as the presence of skeletal muscle wasting, anorexia and

[1]A version of this chapter has been published: Martin L, Senesse P, Gioulbasanis I, Antoun A, Bozzetti F, Deans C, Strasser F, Thoresen L, Jagoe RT, Chasen M, Lundholm K, Bosaeus I, Fearon K, Baracos VE. Diagnostic criteria for cancer-associated weight loss. J Clin Oncol, 2015; 33:90-99.

inflammation.[12] However, we propose that in the first instance a robust classification of WL is needed, that it should be based on contemporary data and that it should evaluate the prognostic significance of WL in patients who are initially of low, intermediate, and high BMI. Current WL grading schemes do not take into account potential benefit of higher initial body weight in risk assessment of patients with cancer- or treatment-associated WL. The European School of Oncology recommends early recognition of cachexia[13], and an international consensus group[12] recommended the collection of contemporary data to classify the severity of cancer cachexia in relation to outcomes such as treatment toxicity and survival. To that end, we undertook to define the prognostic significance of BMI and WL in a large international data set.

2.2 Methods

2.2.1 Data collection and Handling

Two samples of prospectively collected data were assembled (Table 2-1): a training sample for development of a BMI adjusted WL grading system and a validation sample to assess the performance of the grading system. Data were collected at presentation under the auspices of research ethics approvals at the contributing institutions and were anonymized. Data included: age (>18 years), sex, confirmed cancer site and stage, performance status (PS), WL history, BMI, and time to death or censoring. Cachexia is defined as a continuum with increasing cumulative losses over time to death.[12] To represent this continuum we included patients at most risk for developing cachexia (i.e. specific cancers and those with locally advanced or metastatic tumors). A main point of contact with the health care system at which the data were collected was medical oncology (i.e. consecutively referred patients). The training sample included several previously published population-based cohorts[14-24] and participants in randomized clinical trials.[25-27] Other

data were from screening programs for nutritional risk as part of standard care in medical oncology and integrated supportive/palliative care programs at participating cancer centres. The validation sample included nutritional risk screening data (consecutively referred patients) from a cancer center in Montpellier, France. Compiled data were evaluated against inclusion criteria, and patients were excluded if they were <18 years of age, had a diagnosis of cancer *in situ,* or were missing WL and BMI data.

Weight loss history

Patient-reported weight history was collected over various time frames: previous 1, 2, 3, and/or 6 months, and/or from usual body weight (UBW; Table 2-1). Patient-reported height, weight, and WL history are reliable[28, 29] and patient report is part of the standard medical approach in completing a weight history.[30]

Percent WL was calculated*:*

[(current weight (kg) - previous weight (kg))/previous weight (kg)] x 100

A majority of cases (8396/10768) of all patients (training and validation samples) had WL over the preceding 6 months so we elected to make the initial analysis using this as the primary WL time frame. If 6 month %WL was missing, the next most frequently reported WL time frame was used (UBW, 3, 1 and 2 months). Different WL time frames were evaluated for their ability to predict survival (see results). BMI is reported as current weight (kg) / height^2 (expressed as meters^2).

Performance status and Cancer Stage

Performance status was recorded as Eastern Cooperative Oncology Group Performance Status (ECOG PS). Karnofsky Performance Status (KPS) data were converted to ECOG PS using categories ([31]): KPS 100 (ECOG 0), 90-80 (ECOG 1), 70-60 (ECOG 2), 50-40 (ECOG 3), 0-30 (ECOG 4). Cancer stage was based on the American Joint Committee for Cancer stage groupings.

2.2.2 Statistics

The primary outcome was overall survival, defined as the number of months a patient survived between the date of WL and BMI assessment and the date of death. All patients were followed until death or were censored at their last confirmed contact with the healthcare system. Survival analysis included: Kaplan-Meier method (comparisons with Mantel-Cox log-rank tests) and Cox proportional hazards model (estimated hazard ratios (HR) and 95% confidence intervals (CI)). Concordance (c-)statistics assessed discrimination of the BMI adjusted WL grading system in predicting survival[32] as previously described[15]. C-statistics are applicable to all regression models, including survival models[33], a value of 0.5 indicates a prediction no better than chance and 1.0 is perfect prediction.[32] Analyses were completed using IBM SPSS Statistics for Windows (v22.0, Armonk, NY: IBM Corp.) and C-statistics (95%CI) were estimated using a macro in SAS (v9.1.3, SAS Institute Inc., Cary, NC, U.S.A.). Results were considered significant at the $p<0.05$ level.

Part I: Survival Prediction

The training sample was used to determine the prognostic significance of %WL and BMI (as continuous variables) in a multivariate model controlled for age, sex, cancer site, stage and PS.

Part II: Categorical Assignment of %WL and BMI

Categories were defined for %WL and BMI that related to overall survival from the training sample. Each variable was divided into deciles (i.e. divides the distribution of a continuous variable into ten equal groups) to explore the impact of increasing %WL and decreasing BMI on overall survival. Deciles were compared based on differences in median survival (Kaplan Meier) and prognostic impact on survival (estimated HR from Cox proportional hazard model).

Part III: Grading system

The grading system was created using the training sample based on the combination of %WL and BMI categories. This analysis was laid out in a 5x5 matrix representing 5 different %WL categories within each of the 5 different BMI categories (25 possible combinations of WL and BMI). Grade 0 was assigned to the least risk subgroup in the matrix (longest survival) and Grades 1, 2, 3, 4 were assigned to the subgroups according to decreasing survival and increasing HR.

Part IV: Validation

The %WL and BMI of patients in the validation sample were graded according to BMI adjusted WL grading system, and survival discrimination was evaluated according to median survival and c-statistics, and compared to the training sample.

2.3 Results

2.3.1 Training Sample

Cancer stage for the sample (n=8675) was predominantly (89%) locally advanced or metastatic; the majority (73%) were weight losers (mean WL -9.7%). A few patients (6%) experienced weight gain (defined as >2.4%; mean +8.3%) and 21% were weight stable (within

±2.4% to reflect diurnal variation in body weight; mean -0.2%). Despite prevalent WL, only 10% were underweight (BMI <18.5), 48% normal weight (18.5-24.9), 29% overweight (25.0-29.9) and 13% were obese (≥30.0).

Previous work[14] demonstrated weight gain was prognostic of reduced survival in advanced cancer patients in the last months of life. Several forms of weight gain signal disease progression: edema, ascites, increased organ volume and tumor mass. Given that we could not discriminate the specific nature of weight gain, the main analysis focused specifically on weight stable and weight losing individuals (N=8160). Patient characteristics for the training sample are presented (Table 2-2). There were 6294 deaths (out of 8160 patients), an overall median survival of 8.2 months (95% CI 7.9-8.6), and a median follow-up of 41.3 months (95% CI 39.8-42.8).

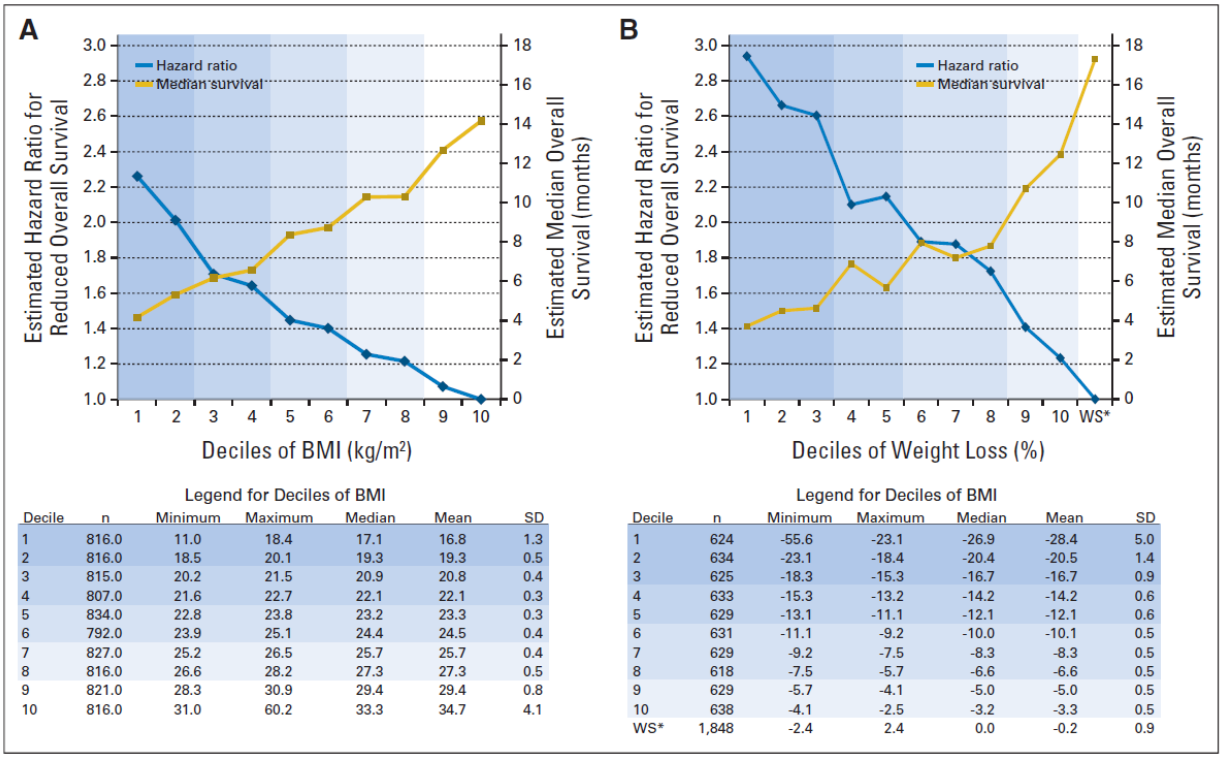
%WL and BMI (continuous variables) were modeled along with conventional covariates known to impact survival (Table 2-3). Predictors of survival in the univariate analysis included %WL, BMI, sex, age (continuous), cancer site, cancer stage, and PS. All variables, except sex, predicted survival at the multivariate level, both increasing %WL (P<0.001) and decreasing BMI (P=0.010) independently predicted survival for the training sample overall. %WL over all time frames was predictive of survival (data not shown): 1 month (P<0.001), 2 months (P<0.001), 3 months (P=0.003), 6 months (P<0.001), and UBW (P<0.001). A multivariate model including advanced stages only (III+IV) controlled for diagnosis, sex, age, BMI, and %WL (not shown) was not different from the overall multivariate model presented in Table 2-3.

2.3.2 BMI adjusted WL grading system

Figure 1 depicts the relationship between deciles of %WL and BMI to overall survival. For BMI deciles (n=816/decile), there were no differences in median survival between deciles

1+2, 3+4, 5+6, 7+8, 9+10 (Figure 2-1A). Therefore, 5 categories of BMI (<20.0, 20.0-21.9, 22.0-24.9, 25.0-27.9, ≥28.0 kg/m^2) were considered that differed in overall survival (P<0.001). Weight stable (± 2.4%) patients were grouped into one category (N=1847) and weight losing patients (N=6290) were split into deciles (n=629/decile). There were no differences in median survival between deciles 1+2+3, 4+5, 6+7+8, 9+10, and 11 (Figure 2-1B). Thus 5 categories of WL were considered that differed in overall survival: weight stable (± 2.4%) and %WL (2.5 to -5.9%, -6.0 to -10.9%, -11.0 to -14.9%, and ≥-15.0%, P<0.001).

Figure 2-1: Line graphs representing the relationships between deciles of BMI (1A) and percent weight loss (%WL, 1B) to overall survival.



Legend for Deciles of BMI

Decile	n	Minimum	Maximum	Median	Mean	SD
1	816.0	11.0	18.4	17.1	16.8	1.3
2	816.0	18.5	20.1	19.3	19.3	0.5
3	815.0	20.2	21.5	20.9	20.8	0.4
4	807.0	21.6	22.7	22.1	22.1	0.3
5	834.0	22.8	23.8	23.2	23.3	0.3
6	792.0	23.9	25.1	24.4	24.5	0.4
7	827.0	25.2	26.5	25.7	25.7	0.4
8	816.0	26.6	28.2	27.3	27.3	0.5
9	821.0	28.3	30.9	29.4	29.4	0.8
10	816.0	31.0	60.2	33.3	34.7	4.1

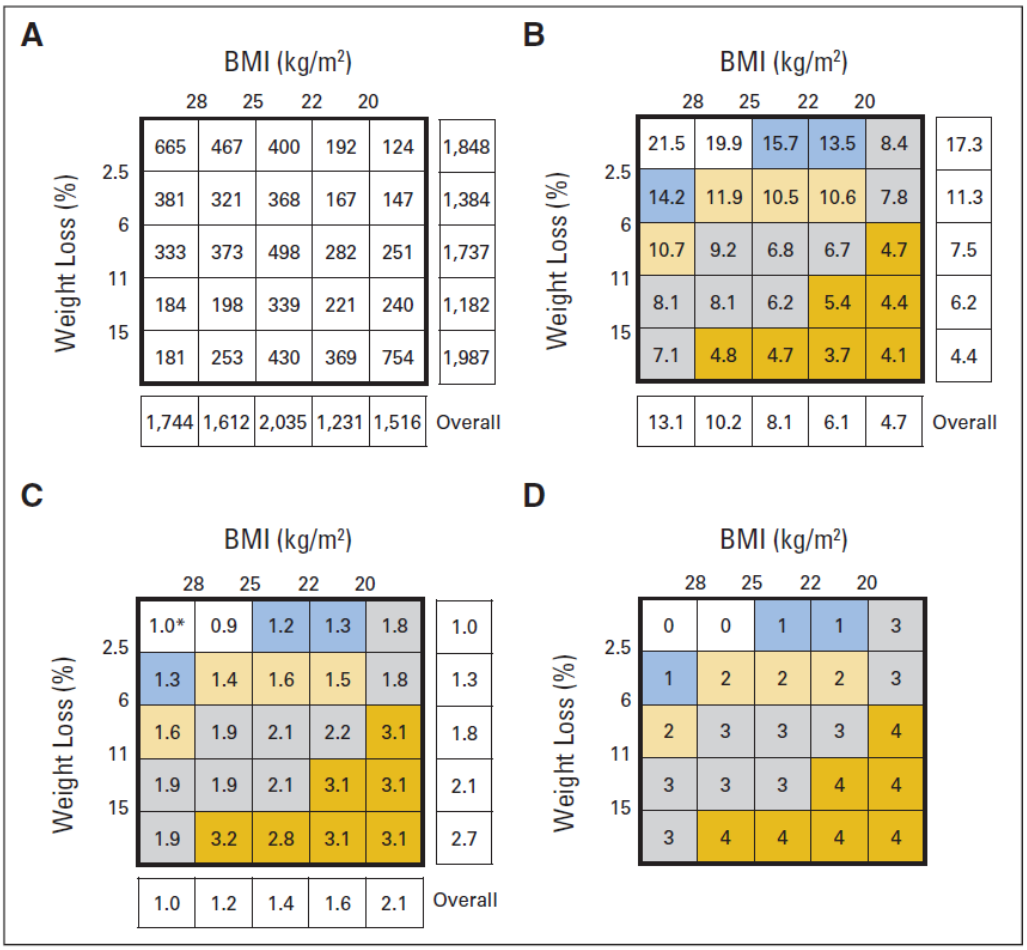
Legend for Deciles of BMI

Decile	n	Minimum	Maximum	Median	Mean	SD
1	624	-55.6	-23.1	-26.9	-28.4	5.0
2	634	-23.1	-18.4	-20.4	-20.5	1.4
3	625	-18.3	-15.3	-16.7	-16.7	0.9
4	633	-15.3	-13.2	-14.2	-14.2	0.6
5	629	-13.1	-11.1	-12.1	-12.1	0.6
6	631	-11.1	-9.2	-10.0	-10.1	0.5
7	629	-9.2	-7.5	-8.3	-8.3	0.5
8	618	-7.5	-5.7	-6.6	-6.6	0.5
9	629	-5.7	-4.1	-5.0	-5.0	0.5
10	638	-4.1	-2.5	-3.2	-3.3	0.5
WS*	1,848	-2.4	2.4	0.0	-0.2	0.9

Decile 1 represents the lowest BMI (1A) and the highest %WL (1B), decile 10 represents the highest BMI (1A) and lowest %WL (1A). Blue lines represent unadjusted estimated hazard ratios associated with reduced overall survival. Reference categories are BMI decile 10 (BMI >30.9, HR=1.0, 1A) and weight stable (±2.4%, HR=1.0, 1B). The risk of reduced survival increases with decreasing BMI (1A) and increasing %WL (1B). Yellow lines represent the estimated median overall survival in months. Median survival decreases with decreasing BMI (1A) and increasing %WL (1B). Different shades of blue in the line graphs and legends indicate significant differences (P<0.05) in median survival between deciles.

The 5x5 matrix analysis representing 25 possible combinations for %WL and BMI are presented (Figure 2-2). Sample size (n), median survival and unadjusted HRs (see below for adjusted HRs) are shown in Figures 2-2A-C, respectively. Combining groups with similar HRs yielded 5 distinct grades with significantly different survival (Figure 2-2D). A gradient of decreasing survival was observed with increasing %WL and decreasing BMI; the highest risk in the lower right hand corner (Grade 4, median survival 4.3 months) and the least risk in the upper left corner (Grade 0, 20.9 months).

Figure 2-2: Risk of reduced survival is a function of body mass index *and* percent weight loss (%WL).



Panels A-C represent a 5x5 matrix analysis of the 5 categories of BMI and 5 categories of %WL for a total 25 possible combinations. The sample size (A), median overall survival (months; B), and unadjusted estimated hazard

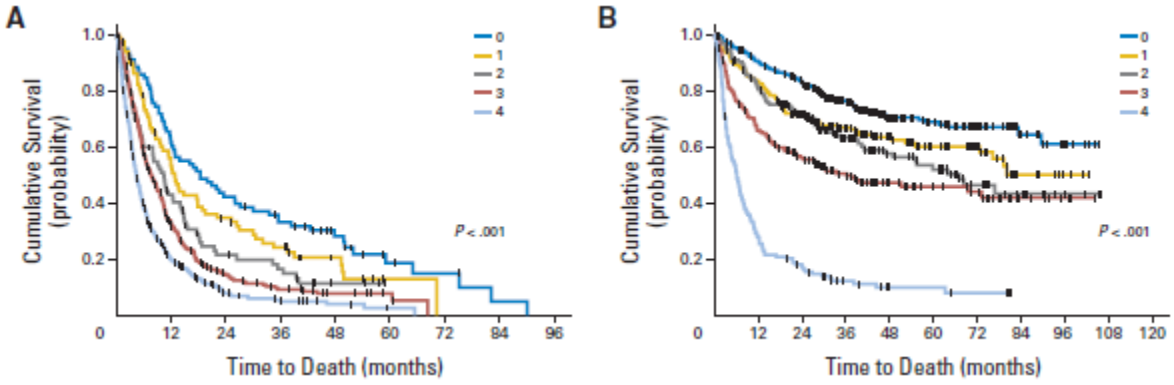
ratios (*reference category BMI ≥28.0/weight stable ±2.4%, HR=1.0; 2C) are presented for each cell. Different colors (A-C) represent significant differences (P<0.05) in median overall survival and HRs within and between cells of the matrix. Figure 3-2D represents the BMI adjusted WL grading system (grades 0 to 4). Grade 0 (20.9 months (95%17.9-23.9), unadjusted HR=1.0), Grade 1 (14.6 months (12.9-16.2), HR=1.3), Grade 2 (10.8 months (9.7-11.9), HR=1.5), Grade 3 (7.6 months (7.0-8.2), HR=2.0), Grade 4 (4.3 months (4.1-4.6), HR=3.1, P<0.001). Figures 3-2E,F represent cumulative survival curves from the sub-group analysis of the training sample for gastro-esophageal (E) and head & neck (F) cancers by grade.

The grading system showed good discrimination of survival (c-statistic 0.88 (95% CI 0.86-0.89)). The BMI adjusted WL grades were entered into a multivariate analysis controlled for age, sex, cancer site, cancer stage, and performance status and they were independent predictors of survival: Grade 0 (adjusted HR=1.0, reference category), Grade 1 (HR=1.1 (95% CI 1.0-1.3), P=0.02), Grade 2 (HR=1.2 (1.1-1.3), P<0.001), Grade 3 (HR=1.4 (1.2-1.5), P<0.001), Grade 4 (HR=1.7 (1.5-1.9), P<0.001). These results are similar to the model presented in Table 2 with %WL and BMI as continuous variables.

2.3.3 Subgroup analyses

The training sample included a range of cancer sites, stages and PS and each of these were independent predictors of survival (Table 2-3). Clinically, we evaluate prognosis within specific cancer sites and stages. Therefore the grades were assessed for survival discrimination within major sub-groups of the training sample for which there was adequate sample size and number of events (Table 2-4). Overall, the grades showed good survival discrimination (Figure 2-3 A,B) and were independent predictors of survival when the multivariate analysis was stratified according to cancer site, cancer stage, age, PS, and health care setting (Table 2-4). WL grades were independently predictive of survival in patients with both good (0-2) and poor (3-4) performance status when controlled for age, sex, cancer diagnosis and stage (Table 2-4).

Figure 2-3: Cumulative survival curves from the subgroup analysis of the training sample for (A) garteoesophageal and (B) head and neck cancers.



2.3.4 Validation Sample

A total of 2093 patients were included (Table 2-2). Median overall survival was 12.3 months (95% CI 11.4-13.3) with a median follow-up of 25.7 months (95% CI 24.7-26.8). BMI and %WL (continuous variables) were independently predictive of survival in multivariate analysis (Table 2-3). Patients in the validation sample had a different case mix, however the BMI adjusted WL grades when applied to this sample gave a c-statistic of 0.89 (95% CI 0.87-0.92), concordant with the training sample. The grades gave good survival discrimination overall and was a significant independent predictor of survival in a multivariate analysis (Table 2-4).

2.4 Discussion

Ours is the first systematically developed cancer WL grading system that incorporates the 2 dimensions of WL and BMI and links them to survival. We assembled data representing the spectrum of these features in contemporary cancer patients, and demonstrated that both %WL and BMI predict survival independently of conventional prognostic factors including cancer site, stage, and PS. This large study validates the concept proposed within the international cachexia

classification framework[12] that the severity of WL should be evaluated based on the rate of loss *and* the level of depletion of body reserves. The proposed grading system takes into account the impact of high versus low initial BMI in the risk assessment of patients with WL. On average there was a 4.9 fold difference in median survival between grades 0 and 4 (20.9 versus 4.3 months, Table 2-4), and these differences were even higher in patient subgroups with the greatest long term nutritional risk, such as cancers of the head and neck (12.8 fold difference) which are notorious for impairment of food intake. Energy deficits of ~120,000 total calories during chemoradiation have been reported for patients with head and neck cancer[34], thus substantial energy reserves may confer an advantage. In patients nearing the end of their cancer trajectory (e.g. supportive/palliative care setting) it might be speculated that the quantity of energy reserves are less important in predicting survival, as death may ensue from tumor invasion of vital organs and processes. While indeed the magnitude of difference in median survival between grades 0 and 4 was less in poor prognosis subgroups, they still gave good survival discrimination at later stages of the disease trajectory. Survival prediction at the end of life is important for clinicians to make decisions regarding patient care i.e. placement into palliative care.

The power of this exercise lies in the assembly of a large sample of patients to clarify interactions between simple markers of nutritional status. BMI and %WL can be combined to provide a severity grade related to the risk of shortened survival. This is most clearly understood and presented in a matrix of combinations of BMI and %WL. The least risk category (longest survivors) comprises individuals with a high BMI who are weight stable or have minimal WL. Likewise, the highest risk category (lower right corner of the matrix) has low initial BMI and high %WL. It has been conventional to use one or more %WL cutoffs in grading systems applied to cancer patients, including CTCAE, cachexia scores, and screening tools for malnutrition.

Using a single cutoff has the pitfall of subgrouping patients with disparate degrees of risk. For example, in Figure 3-2B within all patients with WL <10.9%, there are significantly different subsets of patients with characteristic median survivals as long as 21.5 months (weight stable with high BMI) and as short as 4.7 months (initial BMI <20 kg/m^2).

Our results reinforce the interest of documenting WL and BMI, which when assembled into a meaningful classification scheme, can reclaim their clinical utility. Loss of ability to maintain body weight, even subtle WL >2.4% is significantly related to decreased survival, and is consistent with the recently proposed notion of "pre-cachexia"[12]. This could be a useful time to start preventative nutrition and metabolic interventions, rather than delaying intervention for WL until some arbitrarily defined high level. Clinical management of obese patients with cancer is a developing sphere of cancer research.[7] Here we note that for individuals with the highest BMI (i.e. largest energy reserves) the risk of mortality associated with any degree of WL is less than for individuals with lower initial BMI. We caution that this does not mean their WL has no clinical consequence. Separate work clearly demonstrates that skeletal muscle loss is particularly detrimental in obese and overweight cancer patients.[15, 35] In obese patients with advanced solid tumors, sarcopenia (severe muscle depletion)[14] or sarcopenia and concurrent WL[34], associated with poor prognosis compared with obese patients without these features.

We suggest that our BMI adjusted WL grading system is a useful tool in efforts to predict survival as it is independent of cancer site, stage, and PS, and strongly discriminates survival differences. Grade 4 carries a particularly poor prognosis (Table 2-4). Grade 4 is thus of value in identifying individuals whose expected survival is too short to be consistent with certain specific treatment plans or interventions. In current CTCAE criteria, grade 4 (life-limiting toxicity) is undefined for WL. The consistently short median survival for grade 4 BMI adjusted WL across a

broad range of cancer sites, stages, and settings, is a potentially useful and consistent criterion for grade 4 toxicity. The grades will assist in more effective stratification of patients to clinical trials involving interventions for cachexia as well as investigations of cancer therapy, allowing inclusion of more homogeneous populations with respect to expected survival.

There are some limitations to our work. Although our data sets were all collected prospectively there are differences in the time frame of WL and types of PS measures. Concerns about these differences are partly addressed by the subgroup analysis within our large training (n=8160) and validation (n=2693) samples. It would seem that as long as %WL is recorded over a consistent time frame within a given setting, WL during 1, 3, or 6 months should have clinical utility with our grading scheme. Given the broad array of cancer sites and stages, we are unable to exactly account for previous and present cancer treatments in the current survival analysis. It is not clear to what extent WL is specifically cancer associated, as it may also be associated with acute illness, comorbid conditions, or side effect of treatment. We speculate that this simply may not matter, if the WL is analogous to the expenditure of capital (body reserves of energy and protein) and it culminates in metabolic bankruptcy regardless of why it was spent.

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Table 2-1. Descriptions of data contributed to the training and validation samples.

	Training Samples												Validation Sample
Ref	13	14, UP	15	21	18,19	24,25	22	26	20	23	16,17	UP	UP
Country	Canada[1a]	Canada[1b]	Canada[2]	Canada[3]	Greece	Scotland	UK	Sweden	Italy	Switzer-land	Norway	France	France
Data Source	Nutrition risk screening	Nutrition risk screenin g	Base-line data, clinical study	Nutrition risk screening	Base-line data, clinical study	Base-line data, RCT	Base-line data, clinical study	Base-line data, RCT	Base-line data, clinical study	Base-line data, clinical study	Base-line data, clinical study	Base-line data, clinical study	Nutrition risk screening
Health Care Setting*	Support/ Palliat care	Med oncol	Med oncol	Support/ Palliat care	Med oncol	Support/ Palliat care; Med oncol	Surgica l oncol	Support / Palliat care	Support / Palliat care	Support/ Palliat care	Support/ Palliat care	Med oncol	Med oncol
Total N	1631	3815	529	151	738	706	215	486	180	112	92	82	3075
Exclude	133	274	56	18	39	4	0	32	3	7	0	11	382

N†													
Include N	1498	3541	473	133	699	702	215	454	177	105	92	71	2693
Weight History	Prior 1,6 months	Prior 1,6 months	Prior 2,6 months	Prior 6 months	Prior 3 months	UBW	UBW	UBW	Prior 6 months	Prior 6 months	Prior 3 months	Prior 6 months	Prior 1, 6 months & UBW

Med Oncol, medical oncology; Palliat, palliative; RCT, Randomized Clinical trial; Support, supportive; UK, United Kingdom; UBW usual body weight; UP, unpublished; *Description of the treatments delivered in the health care setting to which patients were referred: **Supportive/Palliative Care:** these samples represent patients referred for multidisciplinary pain and symptom management in routine clinical practice. This setting includes patients with metastatic disease who were receiving treatment with palliative intent and/or no longer receiving active treatment. **Medical Oncology:** these samples represent patients referred for chemotherapy treatment in routine clinical practice, chemotherapy was administered according to cancer site, stage, and performance status. This setting includes patients newly diagnosed or with recurrent disease. Samples included patients who were treatment naïve and who had received prior surgery, chemotherapy, and/or radiation.

†Exclusions: <18 years of age, cancer in situ, missing weight loss and BMI, missing survival information, weight gain (>2.4%)

Table 2-2. Characteristics of training and validation samples

	Training Sample (N=8160)			Validation Sample (N=2693)		
Continuous Variables	**N**	**Mean**	**SD**	N	**Mean**	**SD**
Age (years)	8160	65.3	11.8	2693	61.3	12.7
Weight (kg)	7848	69.6	16.9	2693	65.9	14.6
Height (m)	7532	1.69	0.1	2690	1.67	0.09
BMI (kg/m^2)	8160	24.4	5.1	2690	23.4	4.6
% weight loss*	8138	-9.7	8.4	2693	-7.0	6.7
Categorical Variables	**N**	**Percent**		**N**	**Percent**	
Sex						
male	4949	60.6		1367	50.7	
female	3211	39.4		1326	49.2	
Cancer Site						
colorectal	1395	17.1		300	11.1	
breast	227	2.8		453	16.8	
gastro-esophageal	947	11.6		222	8.2	
genitourinary	300	3.7		544	20.2	
head & neck	997	12.2		308	11.4	
other cancers	285	3.5		339	12.6	
other gastrointestinal	207	2.5		27	1.0	
pancreas	831	10.2		162	6.0	
respiratory	2561	31.4		234	8.7	
unknown primary	121	1.5		1	0.0	
hematological	148	1.8		54	2.0	
liver & intrahepatic bile ducts	141	1.7		49	1.8	
Cancer Stage						
stage I	279	3.4		77	3	

stage II	555	6.8	127	4.9
stage III	1274	15.7	221	8.5
stage IV	6010	74.0	2173	83.6
ECOG Performance Status				
score 0	1234	17.6	571	21.2
score 1	2560	36.5	899	33.4
score 2	1551	22.1	767	28.5
score 3	1494	21.3	434	16.1
score 4	176	2.5	18	0.7
WHO BMI Categories				
<18.5	817	10.0	320	11.9
18.5-24.9	3974	48.7	1504	55.8
25.0-29.9	2325	28.5	656	24.4
≥30.0	1044	12.8	210	7.8
Weight change				
weight stable (±2.4%)	1847	22.6	808	30.0
weight loss (>-2.4%)	6290	77.1	1885	70.0

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; N, number; SD, standard deviation; WHO, World Health Organization

*% weight loss based on weight reported in previous 6 months, if missing, the next the longest time frame for reported %WL was substituted where available i.e. UBW, 3, 2, or 1 months respectively: %WL = [(current weight-previous weight (kg))/previous weight (kg)]x100%

Table 2-3. Median survival and hazard ratios with 95% confidence intervals for proportional hazard model assessing the effect of variables associated with survival.

Variables	Number of Deaths	Median Survival (months, 95% CI)	Univariate		Multivariate		Multivariate	
			HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-Value
% weight loss (continuous)*	6279/8137	8.2 (7.9-8.6)	0.96 (0.96-0.96)	<0.001	0.98 (0.98-0.99)	<0.001	0.98 (0.97-0.99)	<0.001
BMI (kg/m^2, continuous)	6294/8160	8.2 (7.9-8.6	0.95 (0.95-0.96)	<0.001	0.99 (0.99-1.00)	.010	0.97 (0.96-0.99)	<0.001
Age (years, continuous)	6294/8160	8.2 (7.9-8.6)	1.01 (1.01-1.01)	<0.001	1.01 (1.01-1.01)	<0.001	1.01 (1.01-1.02)	<0.001
Sex								
Male	3768/4949	8.5 (8.1-9.0)	1.00		1.00		1.00	
Female	2526/3211	7.7 (7.2-8.2)	1.08 (1.02-1.13)	.004	0.96 (0.90-1.01)	.133	0.86 (0.77-0.96)	0.008
Cancer Site				<0.001		<0.001		<0.001
colorectal	903/1395	16.3 (14.6-18.1)	1.00		1.00		1.00	
breast	194/227	7.5 (5.8-9.1)	1.85 (1.59-2.17)	<0.001	1.24 (1.04-1.47)	.014	1.18 (0.96-1.46)	0.123
gastro-esophageal	805/948	6.8 (6.1-7.5)	1.82 (1.66-2.00)	<0.001	1.88 (1.70-2.10)	<0.001	1.62 (1.29-2.05)	<0.001
genitourinary	275/300	4.0 (3.3-4.7)	2.83 (2.47-3.24)	<0.001	1.52 (1.30-1.76)	<0.001	1.13 (0.94-1.37)	0.199
head & neck	455/997	64.3 (48.1-80.5)	0.45 (0.40-0.51)	<0.001	0.58 (0.51-0.66)	<0.001	0.89 (0.71-1.12)	0.321

other cancers	240/276	6.0 (4.5-7.4)	1.96 (1.70-2.26)	<0.001	1.28 (1.10-1.49)	.001	1.32 (1.07-1.64)	0.01
other gastrointestinal	192/215	4.2 (3.3-5.1)	2.49 (2.13-2.91)	<0.001	1.81 (1.54-2.13)	<0.001	1.09 (0.65-1.82)	0.75
pancreas	731/831	4.3 (3.8-4.8)	2.79 (2.53-3.09)	<0.001	1.98 (1.75-2.25)	<0.001	1.91 (1.51-2.41)	<0.001
respiratory	2144/2561	6.9 (6.4-7.3)	1.96 (1.81-2.12)	<0.001	1.80 (1.65-1.96)	<0.001	1.47 (1.18-1.83)	0.001
unknown primary	114/121	4.0 (3.1-4.9)	2.67 (2.20-3.25)	<0.001	1.67 (1.31-2.13)	<0.001	7.29 (1.01-52.4)	0.048
hematological	107/148	6.1 (3.8-8.4)	1.56 (1.28-1.91)	<0.001	0.95 (0.77-1.18)	.647	0.46 (0.28-0.74)	0.001
liver & intrahepatic bile ducts	134/141	4.8 (3.5-6.1)	3.01 (2.51-3.61)	<0.001	2.40 (1.85-3.11)	<0.001	1.75 (1.20-2.56)	0.004
Cancer Stage				<0.001		<0.001		<0.001
I	84/279	72.0[†](66.3-77.7)	1.00	<0.001	1.00		1.00	
II	231/555	45.6 (39.1-52.1)	1.73 (1.35-2.22)	<0.001	1.16 (0.89-1.51)	.277	1.30 (0.601-2.82)	0.504
III	860/1274	16.2 (14.4-18.0)	3.29 (2.63-4.11)	<0.001	1.76 (1.40-2.22)	<0.001	2.43 (1.21-4.86)	0.012
IV	5093/6010	5.9 (5.6-6.2)	6.70 (5.39-8.32)	<0.001	3.95 (3.17-4.93)	<0.001	6.98 (3.61-13.49)	<0.001
ECOG PS				<0.001		<0.001		<0.001
score 0	636/1234	33.3 (29.6-37.0)	1.00	<0.001	1.00		1.00	
score 1	1790/2560	13.2 (12.4-14.1)	1.86 (1.70-2.04)	<0.001	1.29 (1.17-1.41)	<0.001	1.66 (1.41-1.97)	<0.001
score 2	1276/1551	5.4 (4.9-5.9)	3.50 (3.17-3.85)	<0.001	1.92 (1.73-2.13)	<0.001	2.44 (2.06-2.90)	<0.001
score 3	1369/1494	3.2 (2.9-3.4)	5.17 (4.70-5.69)	<0.001	2.92 (2.63-3.24)	<0.001	4.24 (3.51-5.14)	<0.001

score 4	167/176	1.3 (0.9-1.7)	8.44 (7.11-10.02)	<0.001	5.05 (4.23-6.05)	<0.001	6.48 (3.91-10.74)	<0.001

BMI, body mass index; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio

Table 2-4. Sub-group analysis: median survival by grade, and overall p-values from cox proportional hazards models assessing the prognostic significant of the BMI adjusted WL grading system.

	BMI adjusted WL grades					**Prognostic significance of BMI adjusted WL grades stratified by covariate**	
	Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Overall Uni-variate P-Value**	**Overall Multi-variate P-Value‡**
Training Sample							
Overall							
N deaths	696/1132	678/973	858/1189	1853/2326	2195/2518		
Median Survival (months)	20.9	14.6	10.8	7.6	4.3	<0.001	<0.001
95% CI	(17.9-23.9)	(12.9-16.2)	(9.7-11.9)	(7.0-8.2)	(4.1-4.6)		
Subgroup analysis stratified by covariate							
Cancer Site							
Colorectal							
N deaths	95/170	97/167	146/251	297/472	268/335		
Median Survival (months)	28.3	22.8	21.6	17.3	7.3	<0.001	0.002
95% CI	(18.9-37.6)	(17.7-27.9)	(17.2-26.0)	(13.8-20.8)	(5.5-9.2)		
Gastro-esophageal							
N deaths	63/78	63/81	67/83	243/288	368/417		
Median Survival (months)	18.4	12.8	10.3	7.6	4.4	<0.001	0.003
95% CI	(9.8-27.0)	(10.7-14.9)	(7.8-12.9)	(6.1-9.0)	(3.8-5.0)		
Head & Neck							
N deaths	85/304	73/195	66/155	94/184	137/155		
Median Survival (months)	77.9*	66.4*	67.0	36.2	6.1	<0.001	<0.001
95% CI	(73.0-82.8)	(59.9-72-9)	(45.6-88.4)	(6.5-66.0)	(4.7-7.6)		
Respiratory tract							
N deaths	296/389	273/330	350/434	620/709	592/684		
Median Survival (months)	11.3	9.9	8.2	5.6	4.2	<0.001	<0.001
95% CI	(9.7-12.9)	(7.9-11.9)	(7.1-9.3)	(4.9-6.3)	(3.5-4.9)		
Cancer Stage							
I + II†							
N deaths	70/217	52/165	36/123	76/200	81/127		

Median Survival (months)	70.2*	67.3*	57.6*	45.9	13.0	<0.001	0.047
95% CI	(63.9-76.6)	(60.2-74.5)	(50.6-64.6)	(23.2-68.6)	(8.8-17.3)		
III							
N deaths	99/185	105/176	114/199	248/373	293/340		
Median Survival (months)	30.4	26.9	24.5	17.1	7.3	<0.001	<0.001
95% CI	(19.8-41.0)	(20.8-33.1)	(17.4-31.7)	(13.4-20.7)	(6.1-8.5)		
IV							
N deaths	525/722	514/620	702/860	1522/1743	1817/2047		
Median Survival (months)	12.2	9.1	7.6	5.6	3.8	<0.001	<0.001
95% CI	(10.6-13.7)	(8.0-10.2)	(6.7-8.4)	(5.1-6.0)	(3.6-4.1)		
Age							
<65							
N deaths	268/526	262/431	346/523	766/999	996/1144		
Median Survival (months)	30.9	19.5	12.6	8.7	4.7	<0.001	<0.001
95% CI	(24.5-37.4)	(16.2-22.9)	(10.5-14.6)	(7.8-9.7)	(4.2-5.1)		
≥65							
N deaths	428/606	416/542	512/666	1087/1327	1199/1374		
Median Survival (months)	15.2	12.0	9.3	6.6	4.1	<0.001	<0.001
95% CI	(12.7-17.8)	(10.1-13.9)	(8.1-10.6)	(5.9-7.3)	(3.8-4.5)		
Performance Status							
good (ECOG 0-2)							
N deaths	510/912	461-732	562/866	1073/1481	1085/1336		
Median Survival (months)	27.8	19.7	15.0	10.7	6.0	<0.001	<0.001
95% CI	(24.0-31.7)	(17.3-22.0)	(13.1-17.0)	(9.7-11.7)	(5.5-6.5)		
poor (ECOG 3-4)							
N deaths	116/133	109/124	175/188	465/513	670/710		
Median Survival (months)	6.1	4.4	3.5	2.9	2.6	<0.001	<0.001
95% CI	(3.6-8.6)	(3.2-5.7)	(2.8-4.1)	(2.4-3.4)	(2.3-2.9)		
Health Care Setting							
Medical Oncology							
N deaths	529/949	475/756	592/902	1115/1544	1116/1384		

Median Survival (months)	28.3	19.8	14.9	11.0	6.4	<0.001	<0.001
95% CI	(24.2-32.3)	(17.5-22.2)	(13.1-16.8)	(10.0-12.0)	(5.8-6.9)		
Supportive/Palliative Care							
N deaths	167/183	203/217	266/287	738/782	1079/1134		
Median Survival (months)	5.8	5.0	3.9	3.7	3.2	<0.001	0.002
95% CI	(4.0-7.6)	(4.1-5.9)	(3.2-4.6)	(3.3-4.1)	(2.9-3.4)		
Validation Sample							
Overall							
N deaths	166/353	245/430	260/450	568/842	474/615		
Median Survival (months)	25.1	15.7	17.6	11.5	6.9	<0.001	<0.001
95% CI	(19.0-31.3)	(12.5-18.9)	(13.7-21.4)	(9.9-13.2)	(5.9-8.0)		

BMI, body mass index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; WL, weight loss
*median survival not reached, estimated mean overall survival is reported
†Stage I and II were combined as they represent patients earlier in the cancer trajectory
‡Multivariate P-values for the prognostic significance of the BMI adjusted WL grades are adjusted for covariates including: age, sex, cancer site,
cancer stage, and ECOG performance status

CHAPTER 3: Diagnostic Criteria for Cancer Cachexia: Data versus Dogma[1]

3.1 Key Points

- There are notable disparities in diagnostic criteria for cancer cachexia, and there are no agreed upon diagnostic criteria.
- Through international consensus, a cancer cachexia framework was proposed to address disparities in diagnostic criteria. Candidate diagnostic criteria for cancer cachexia include: weight loss, muscle mass, reductions in food intake, and alterations in metabolism.
- Definitive diagnostic criteria for cancer cachexia can be developed with large contemporary data sets that include variables related to cancer cachexia. Clearly defined statistical methods will identify candidate diagnostic criteria with the best utility.
- A new grading system for cancer-associated weight loss has been proposed confirming the concept that severity of weight loss should be classified according to the degree of weight loss and current body weight.
- Further levels of refinement for diagnostic criteria include advancements related to skeletal muscle depletion (and other features of body composition), and causes of cancer cachexia including reduced food intake, and alterations in metabolism. Development in these areas will enrich cancer cachexia classification systems and improve their utility.

3.2 Cachexia has been known since ancient times but lacks agreed upon diagnostic criteria

Historical descriptions of cachexia as a wasting syndrome date back to Hippocrates, and are full of rich observations about dramatic weight loss, the experience of anorexia, weakness and fatigue that eventually lead to death. Unintended weight loss (WL) has always been a key clinical sign, and often triggers investigations for malignancy as a possible explanation. Often cachexia is defined by a single criterion based on its cardinal clinical feature, WL, which is typically classified as being above a certain threshold (>5%, >10%).[1-4] There has been a

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renaissance in cancer cachexia research over the last decade, with support from a Society on Cachexia and Wasting Disorders, a series of international conferences, and an expanding research community. There have been advancements in basic science, clinical research, and in the identification of therapeutic targets for cachexia therapies. Advancements have improved our understanding of the pathophysiology of cachexia, also termed disease-associated malnutrition, now invariably described as a multifactorial syndrome of ongoing loss of muscle (with or without fat), driven by variable impairments of food intake and metabolic alterations that elicit excess catabolism (e.g. inflammation) (Table 3-1).[1-5] These metabolic changes explain why cachexia cannot be reversed by conventional nutritional support alone, and are the key difference between cachexia and starvation-related malnutrition.[1,4,5]

Criteria to define cachexia, in addition to WL, now include variable combinations of low body mass index (BMI), skeletal muscle mass, reduced dietary intake, and biological indicators of inflammation as markers of metabolic change (Table 3-1). Measurement of these dimensions is increasingly specific, precise, clinically available, and can be related to diverse clinically relevant outcomes including risk of chemotherapy toxicity, surgical complications, functional impairment, patient-family psychological distress, attrition from clinical trials, and mortality.[1,4]

This new knowledge has been variably understood and translated producing an abundance of clinical tests and assessments. As a result, there is a heterogeneous mix of available diagnostic criteria for cancer cachexia which have been applied in a dogmatic fashion.[6] Further to the possible combinations of diagnostic criteria, is an added layer of heterogeneity within each individual criterion (Table 3-2). For example, WL can be collected over various time frames and defined according to different thresholds. Overall, there are not widely agreed upon diagnostic criteria for cancer cachexia, and disparities among the existing ones are notable in

published research, clinical trials, clinical assessments, and practice guidelines.[3,4,7-11] A main challenge is to identify the most robust diagnostic criteria among a sea of credible candidates.

3.3 Progress toward consensus diagnostic criteria for cancer cachexia

Several authors and consensus groups flagged disparities among cachexia diagnostic criteria as a detriment to the identification and treatment of cachectic patients, and for the development of therapeutic agents.[1,4,9,10] International consensus groups[1,4] have addressed these disparities, and proposed frameworks for the general classification of cachexia associated with chronic disease[1], and specifically for cancer cachexia.[4] This review focuses on the cancer cachexia framework[4] where agreement was reached on several main themes: an etiology-based definition for cancer cachexia, the concept of cachexia as a continuum with three stages of clinical relevance, the presentation of provisional diagnostic criteria, and recommendations for assessments to describe cancer cachexia**.**

The cancer cachexia framework[4] proposes a series of next steps, notably a call for data resulting in a data-driven approach for the development of a robust set of diagnostic criteria, *"definitive cutoffs for variables (e.g. weight loss, low muscle mass) could be determined from large contemporary datasets by determining the values that relate optimally to meaningful patient-centered outcomes, such as loss of function or decreased survival… the criteria suggested in the present consensus remain arbitrary".*

With this task is underway, several authors[7,9-12] adopted the provisional diagnostic criteria[4] and compared classification of cachectic patients to other definitions for cachexia.[1,3] Not surprisingly different classifications yield different results, stratification of patients according to cachexia stage improved with combinations of criteria (e.g. WL + reduced food intake, WL + inflammation), but development of more clearly defined diagnostic criteria is necessary.

Deployment of the right diagnostic criteria and their combinations may improve identification of cachexia patient subsets to guide clinical decisions and therapeutic research. For example, identification of subsets of cachectic patients with poor prognosis unlikely to live long enough to receive benefit from cancer therapies or withdraw from clinical trials, but who may be candidates for supportive therapies such as nutrition support.[13]

3.4 Methods and principles for the development of diagnostic criteria

The cancer cachexia framework[4] provides an agreed upon list of potential candidates to classify cancer cachexia (e.g. WL, skeletal muscle (SM) depletion, reduced food intake, metabolic alterations). The first set of candidate diagnostic criteria includes descriptions of the clinical manifestation of cachexia including WL and SM depletion. The next set includes etiologically based criteria that explain WL and SM depletion including reductions in food intake and alterations in metabolism. Candidate diagnostic criteria must be clinically relevant, practical, and readily available. To define definitive diagnostic criteria, data sets of similarly collected variables are necessary and should be large enough to capture representative distributions of candidate diagnostic criteria, important covariates, and outcomes for adequately powered statistical analyses, including subset analyses. Inclusion of contemporary cancer patients ensures representation from a variety of cancer populations, body weight demographics, and treatment plans. Survival is a key outcome, clinically relevant in oncology and is unambiguous in its collection and interpretation. However, other outcomes must be considered including treatment complications, functional impairment, quality of life, and attrition from clinical trials.

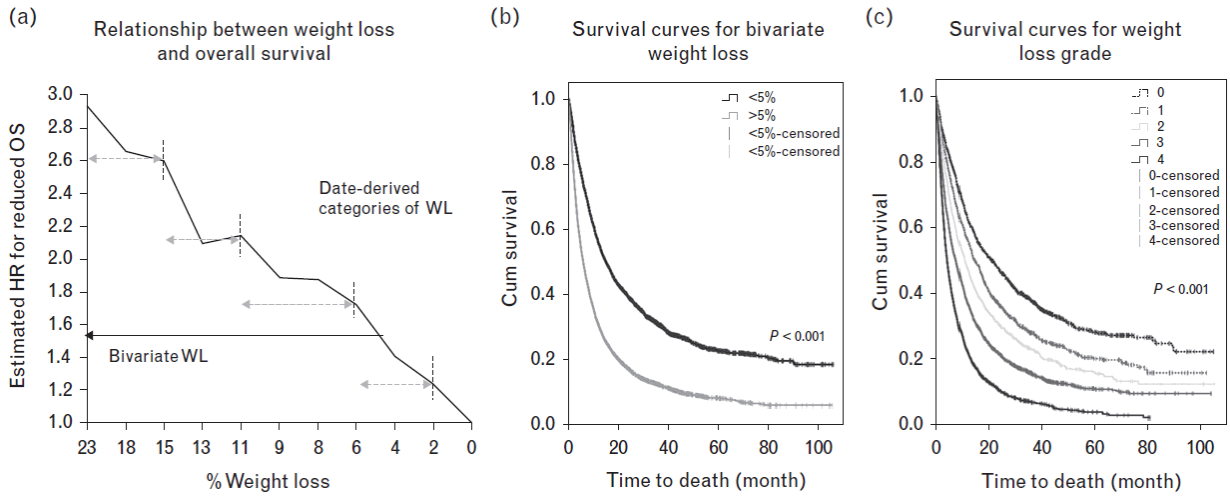
A typical analytical approach applies clearly defined statistical methods (i.e. regression analysis) to examine the distribution of candidate diagnostic criterion and the relationship to relevant outcomes (Figure 3-1A). This approach encourages examination of the shape of the

distribution and changes in risk across a variable (e.g. linear vs. non-linear) to generate risk stratifications and optimal values linked to an outcome, which can then be adjusted for other covariates. New values for diagnostic criteria and/or their combinations require independent validation for proof of concept and applicability in different populations. This review will discuss recent work on data driven approaches to define diagnostic criteria for WL, SM depletion, reduced food intake, and altered metabolism.

3.5 Re-defining weight loss as a diagnostic criterion for cancer cachexia

The cancer cachexia framework[4] suggested that **"***severity should be graded according to degree of weight loss and concurrent BMI, and the severity classification should be developed around the predictive value for outcomes such as treatment toxicity, quality of life, hospitalization, and survival*"

Figure 3-1. The relationship between percent weight loss and overall survival



a) A line graph illustrating the shape of the relationship between % weight loss, divided in to deciles, and overall survival in a sample of cancer patients (N=8138).[14] The black arrow represents the cutoff for a bivariate classification for weight loss above 5%[4], and the gray dotted arrows represent the data-derived cutoffs for five categories of weight loss wherein risk of reduced survival significantly (P<0.001) increases for each category. (b) Cumulative survival curve (Kaplan-Meier Method, log rank tests) representing the bivariate classification for weight loss.[14] (c) Cumulative survival curves for weight loss grades (0–4) defined by combining five categories of weight loss (Fig. 1a) and five categories of BMI (not shown).[14] The weight loss grades add several levels of stratification when compared with a bivariate classification for weight loss.

The conventional, but arbitrary provisional diagnostic criterion[4] for cancer cachexia is unintentional WL of >5% in the previous 6 months. This bivariate classification is recognized to be an oversimplification, it assumes an equal risk for all degrees of WL >5% that disregards all notions of severity (Figure 3-1A, B). WL is actually understood with a greater level of sophistication; increased WL equals increased risk of poor outcome (Figure 3-1A).[14] A concept first proposed by De Wys et al.[15] and represented in the Common Terminology Criteria for Adverse Events (CTCAE v4)[2], a system to grade the severity of an adverse event in oncology, including three levels of clinically relevant WL (Table 3-1). Additionally, 7 classes of BMI with clinical relevance are accepted. The importance of WL is not the same across the distribution of BMI; people with little energy and protein reserves to begin with, experience a greater impact of WL. These concepts were confirmed by Martin et al.[14], who compiled a large data set of similarly collected variables on >11,000 cancer patients from Europe and Canada, which was used to develop and validate a new grading system for cancer-associated WL based on a risk stratification with survival as the outcome. WL and BMI independently predicted overall survival, and when considered together provide excellent stratification of patients with disparate survivals, confirming that severity of WL should be evaluated based on the rate of WL and current BMI (Figure 3-1C). The WL grading system remains to be validated according to cancer type, treatment setting, and for other outcomes such as treatment complications or attrition from clinical trials. Next levels of refinement include diagnostic criteria for SM, food intake, and altered metabolism.

3.6 Skeletal muscle is an emerging diagnostic criterion for cancer cachexia

The cancer cachexia framework[4] specifies that "*cancer cachexia is characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass)*…" and includes SM

depletion, in addition to WL, as a provisional diagnostic criterion.[4] There is no consensus regarding methodology for assessment of muscle mass, however preference was given to computed tomography cross-sectional images taken at the L3 region (CT L3).[4] CT images are completed as standard of care in oncology, are routinely available, and offer an unprecedented window to non-invasively and precisely quantify SM. When CT images are unavailable another modality should be considered (e.g. DEXA).

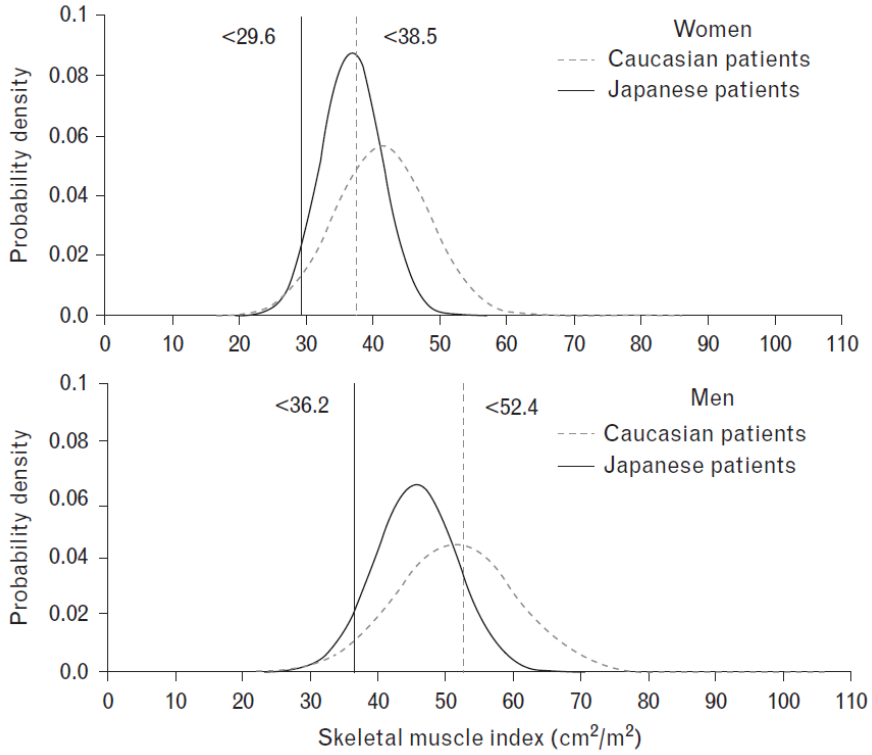
The rapidity with which CT analysis has been adopted for the quantification of SM in oncology made it the topic of several reviews in 2015.[16-19] The most extensive review by Kazemi-Bejestani et al.[17] included 53 studies (from 2000 to Jan.2015) on a total of 9,138 patients. The authors concluded there is a consistent association between SM depletion and outcomes including chemotherapy response and toxicity, increased post-surgical complications and length of hospital stay, and mortality. Quantification of other tissues (e.g. fat) is an evolving area of research, but not sufficiently refined to be included as diagnostic criterion at this time. From Jan. 2015-Nov. 2015, an additional 19 publications on 5,124 patients were evaluated for SM using CT analysis (Table 3-3). These studies[20-37] corroborate the concepts highlighted by Kazemi-Bejestani et al.[17] including associations between SM depletion and increased chemotherapy-related toxicity[20] and post-surgical complications[21-24], and decreased survival[25-28]. Treatment induced changes in SM is an emerging theme, and recent work highlights significant SM loss during the course of chemotherapy[29-34], which associated with reduced survial in four studies.[30-33]

Up for debate is the application of pre-defined cutoffs for SM depletion in patient populations with different demographics (e.g. race, obesity rates, muscularity, tumor types). The provisional diagnostic criteria[4] includes sex-specific cutoffs for CT L3 defined SM depletion

(skeletal muscle index (SMI) Men: <52.4 cm^2/m^2; SMI Women: <38.5 cm^2/m^2) associated with reduced survival.[4,38] These cut offs were derived from a Caucasian sample of obese (BMI ≥30.0, N=250) cancer patients, and may have limited relevance when applied to other populations. Development of appropriate reference populations and data derived cutoffs specific to sex, age, and race are clearly needed to advance the concepts of SM depletion.[4,17]

Martin et al.[39] completed an analysis including all BMI classes in a large sample (N=1473) of Caucasian cancer patients. BMI and sex specific cutoffs for SM depletion (SMI Men: <43 cm2/m2 (BMI<25.0), <53 cm2/m2 (BMI≥25.0); Women: <41 cm2/m2) were defined in relation to survival, demonstrating SM differs by sex and body weight. More recent studies include analyses to define cutoffs for SM depletion specific to their patient populations (Table 3-3).[21,25,30,32] Fujiwara et al.[25] offer an excellent example in a large (N=1257) sample of Japanese hepatocellular carcinoma patients. Sex-specific cutoffs for skeletal muscle depletion (SMI Men: ≤36 cm^2/m^2; SMI Women: ≤30 cm^2/m^2) were defined based on survival. Notably, these cutoffs are lower than those derived from a Caucasian population, confirming careful consideration should be given to the choice of cutoffs applied to a given population (Figure 3-2).

Figure 3-2: Distributions for skeletal muscle index (cm^2/m^2), evaluated by CT image analysis, for Caucasian and Japanese cancer patients



Normal distributions for skeletal muscle index (cm^2/m^2), evaluated by CT image analysis, for Caucasian (gray dotted lines)[39] and Japanese (black solid lines) cancer patients.[25] Also depicted are the sex-specific cutoff values derived from Caucasian (vertical grey dotted lines) and Japanese (vertical black solid lines) patient populations.[4,25]

CT analysis provides a plethora of prognostic information, and these findings are of such importance they should be accepted as a standard oncology biomarker.[40] It is acknowledged that SM, which is the focus of this section, is not the only information of importance. CT analyses reveal the highly dimensional nature of body composition, including different tissue amounts and distributions (e.g. total, subcutaneous, and visceral fat), and tissue specific radiation attenuation values. For SM in particular, low attenuation values indicate fatty infiltration to the muscle. All of these dimensions can potentially relate to clinical outcomes as well as functionality of muscle.[22,24,25,27,28,30,33-35,38] Other areas for development include evaluating the interplay between

SM (and other tissues) with candidate diagnostic criteria including food intake, and altered metabolism.

3.7 Reduced food intake is a candidate diagnostic criterion in development

The cancer cachexia framework[4] specifies two factors responsible for the development of cancer cachexia, which *"is driven by a variable combination of reduced food intake and abnormal metabolism."* Characterization of these features is necessary to identify patients with cachexia. The assessment of food intake or anorexia is recommended, but there is no consensus regarding measurements of food intake, and no provisional diagnostic criteria were presented.[4] However, reduced food intake or anorexia have been included as diagnostic criteria in other definitions of cachexia[1,3] (Table 3-1), and when combined with other diagnostic criteria (e.g. WL, inflammation) demonstrate improved identification of cachexic patient subsets.[3,7,9,11]

A notable limitation in defining diagnostic criteria for food intake and anorexia is the heterogeneity of available assessments (Table 3-2). It is unknown which assessments are most associated with the features defining cachexia such as WL, SM depletion, and altered metabolism, or how they relate optimally to clinical outcomes. Recent work highlights the clinical utility of food intake measures within existing assessment tools commonly collected in cachexia research[41-43], and Solheim et al.[43] point out that assessments of anorexia and food intake are both necessary to fully describe the food intake of cachectic patients due to conscious control over appetite loss. Linkages between actual food intake and clinical assessments remain to be evaluated and may offer validation to various classifications of food intake such energy intake <1500 kcal[3], and commonly used categorical estimations of food intake (e.g. normal, less than normal, etc). As well, capturing actual food intake inclusive of macronutrients (energy, protein, fat) and micronutrients (vitamins, minerals) may allow for the identification of specific nutrient

deficiencies associated with cancer cachexia. Refining food intake as a diagnostic criterion will be enabled by the emergence of rich data sets to identify assessments with the best utility.

3.8 Biologic Aberrations (i.e. inflammation) in Cachexia - How do we factor them in to cachexia classifications?

To date classification work has centered on the effects of cachexia (e.g. WL, SM depletion) and not causation. Current oncology research, is marrying genetic and other biologic information with traditional clinical findings to determine patient subsets which may respond to tailored cancer therapies. A similar approach is needed to enable us to establish cachexia patient subsets to guide therapeutic research.

The cancer cachexia framework[4] describes altered metabolism as a variable combination of factors (e.g. inflammation, tumor metabolism, tumor mediated effects) leading to a hypercatabolic state resulting in cachexia. There is no consensus regarding measurements for altered metabolism. However, inflammation an important driver of tumor growth and metastasis has also emerged as an important driver of energy imbalance and muscle wasting in cancer cachexia.[4] C-reactive protein (CRP) is the most widely accepted index of systemic inflammation.[4] Inclusion of other routinely available clinical markers of inflammation (e.g. neutrophils and lymphocytes) also predict the effect of inflammation on cancer progress and survival. The most accepted scale to characterize systemic inflammation is the Glasgow Prognostic Score (GPS). McMillan[44] together with other investigators[45,46] have clearly shown the devastating effect of systemic inflammation on survival and development of cancer-related symptoms.[47] Adding systemic inflammation to traditional clinical findings offers improved identification of patient subsets with worse prognosis and unlikely to benefit from treatment.[7,9,13,46] Efforts to understand systemic inflammation as a cause of SM depletion in cancer cachexia are emerging (Table 3-3). Two studies[36,48] showed systemic inflammation to be

an independent predictor of SM depletion, as well as a contributor to accelerated muscle loss during treatment.[48]

Measures of systemic inflammation are clinically available, have been collected on a large number of patients, and it is possible to compile this data to explore their interplay with other features of cachexia. Subsequent biologic information such as evidence of altered autonomic function, immune and hormonal activity, microbiota, and genetic background may enrich cachexia classification, albeit with increasing complexity. For example, preliminary evidence determined a series of s*ingle nucleotide polymorphisms* (SNPs) either confer susceptibility or resistance to cancer cachexia[49] Cancer cachexia is complex but it is anticipated that our advancing knowledge of cachexia causation will enrich our classification systems and improve their utility.

To summarize, there are limitations to what is presented here. Cancer cachexia research has many facets, however the focus of this review highlights where we have data to address disparities in diagnostic criteria as outlined in the cancer cachexia framework. Other areas of assessment such as physical function and quality of life are outcomes or consequences of cancer cachexia and continuing areas for development. Data collection efforts towards a large international data repository with an expanded number of clinical variables are ongoing with support from the cancer cachexia consensus group. Of particular interest is the development of prospective treatment related outcomes for cancer therapies and surgery. Ultimately, new values for diagnostic criteria will require validation and adoption into practice.

3.9 Conclusion

There is a consensus definition and framework outlining assessments necessary to diagnose cancer cachexia[4], and extensive collaboration produced an international data set to enable development and refinement of diagnostic criteria for cancer cachexia, with potential to

influence other spheres of cachexia research. Identification of cachectic patient subsets may lead to better inclusion criteria for clinical trials, decreased attrition rates, improved outcomes, and approval of therapeutics. As well, better identification of patients who are likely to benefit from treatment (aggressive vs. supportive) and earlier deployment of beneficial therapies. Developing diagnostic criteria for cancer cachexia using methodologies similar to those that have been used in other chronic conditions[50] indicates the potential of a data driven approach to define diagnostic criteria with clinical utility.

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Table 3-1. A summary of narrative definitions for cachexia and diagnostic criteria

Narrative Definitions		Diagnostic Criteria
Cachexia Associated with Chronic Disease		
ICD-10 cachexia (R64)*	A wasting syndrome, associated with an underlying condition e.g. HIV, cancer	None specified
Consensus definition disease-associated cachexia[1]	"A complex metabolic syndrome associated with underlying illness... characterized by loss of muscle with or without loss of fat mass... prominent clinical feature is weight loss... Anorexia, inflammation, insulin resistance and increased muscle protein breakdown frequently associated with wasting disease."	Weight loss >5 % AND 3 of the following: ● decreased muscle strength, ● fatigue, ● anorexia, ● low fat-free mass index, ● abnormal biochemistry (inflammation, low albumin, anemia)
Cancer Cachexia		
NCI CTCAE v4.0[2]	A decrease in overall body weight	Grade 1: 5 to 10% from baseline; intervention not indicated; Grade 2: 10 to <20% from baseline; nutritional support indicated; Grade 3: ≥20% from baseline; tube feeding or TPN indicated; Grade 4: not defined, life threatening; Grade 5: not defined, fatal
3-factor classification for cancer cachexia[3]	"A multifactorial syndrome characterized by ongoing weight loss, low food intake, and presence of systemic inflammation"	At least 2 of the following factors: ● weight loss ≥10%, ● food intake <1500 kcal/day, ● CRP ≥10 mg/L
Consensus Definition Cancer cachexia[4]	"A multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass)... not fully reversed by conventional nutritional support... leading to progressive functional impairment. Its pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism."	Weight loss >5% over past 6 months OR BMI <20 AND any degree of weight loss >2% OR Muscle depletion AND any degree of weight loss >2%

*ICD-10, International Classification of Disease, http://apps.who.int/classifications/icd10/browse/2016/en#/R6; HIV, human immunodeficiency virus; NCI CTCAE v4.0, National Cancer Institute Common Terminology Criteria for Adverse Events; CRP, C-reactive protein; BMI, body mass index.

Table 3-2. A summary of candidate diagnostic criteria[4] and the heterogeneity that exists within each criterion.

Diagnostic Criteria	Examples of heterogeneity in data collection and in the reporting of diagnostic criteria
Weight Loss	**Data collection**: ● clinical tools e.g. SGA, PG-SGA, MNA, MST, MUST, SNAQ, NRS 2002, NCI CTCAE v.4.0 ● different time frames e.g. WL (actual or %) over previous 1, 2, 3, 6 months, or from pre-illness weight **Reported as:** ● continuous variable e.g. % or amount (kg., lbs.) ● bivariate categorization e.g. WL present (yes or no), WL > than a defined threshold (>5%, >10%, >3kg, >5kg) ● multiple categories of increasing severity e.g. Grade 1 (5-10%), Grade 2 (10-20%), Grade 3 (>20%)
Reduced food intake	**Data Collection:** ● clinical tools e.g. SGA, PG-SGA, MNA, MUST, SNAQ, NRS 2002, FAACT, VAS (estimated food intake), and food records, food frequency questionnaires (recorded food intake) ● different time frames e.g. retrospectively (previous day, 1 week, 1 or 3 months) or prospectively (over 1 to 7 days) **Reported as:** ● continuous variable e.g. kcal energy, g protein, g fat from recorded food intake, or VAS (0-100) for estimated intake ● bivariate classification e.g. < or > 1500kcal/d from recorded food intake, or estimated food intake less than usual (yes or no) ● multiple categories of increasing severity e.g. estimated food intake (normal, reduced, severely reduced)
Appetite Loss / Anorexia	**Data Collection:** ● clinical tools e.g. SGA, PG-SGA, MST, FAACT, ESAS, EORTC QLQ-C30, NCI CTCAE v.4.0 ● different time frames e.g. same day, previous 1-2 weeks or month **Reported as :** ● continuous variable e.g. VAS (0-100) ● bivariate categorization e.g. appetite loss/anorexia present (yes or no) ● multiple categories of increasing severity e.g. Likert scales (0, no loss; 4, severe loss)
Inflammation	**Data Collection:** ● biological indicators for systemic inflammation: CRP, albumin, neutrophils, lymphocytes, cytokines **Reported as:** ● continuous individual parameters e.g. CRP, albumin, neutrophils, lymphocytes, cytokines ● continuous composite parameters e.g. NLR, PINI ● bivariate categorization e.g. CRP (>5 or > 10 mg/L), NLR (>3 or >5) ● multiple categories of increasing severity e.g. GPS, mGPS, PINI

SGA, Subjective Global Assessment; PG-SGA, Patient Generated-Subjective Global Assessment; MNA, Mini-Nutritional Assessment; MST, Malnutrition Screening Tool; MUST, Malnutrition Universal Screening Tool; SNAQ, Short Nutritional Assessment Questionnaire; NRS 2002, Nutrition Risk Screening; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; FAACT, Functional Assessment of Anorexia Cachexia Therapy; VAS, visual analogue scale; ESAS, Edmonton Symptom Assessment Scale; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; CRP, C-reactive protein; PINI, prognostic inflammatory and nutritional index; NLR, neutrophil to lymphocyte ratio; GPS, Glasgow

Prognostic Score; mGPS, modified Glasgow Prognostic Score. *This is not intended to be an exhaustive list of all possible assessments and biological indicators.

Table 3-3. A Summary of results from 19 articles (n=5,124 patients) published between Jan. 2015 to Nov. 2015 evaluating skeletal muscle using CT L3 image analysis.

Authors	(n) Patients/cancer type/therapy	Definition of Sarcopenia* (SMI cm^2/m^2)	% sarcopenic	Major findings related to skeletal muscle
Skeletal muscle and chemotherapy toxicity				
Sjoblom[20]	153/non-small cell lung/ chemotherapy	_	_	Chemotherapy dosed as mg/kg LBM independently associated with grade 3–4 haematological toxicity (OR = 1.15, P=0.018).
Skeletal muscle pre-surgery and post-surgical outcomes				
Harada[21]	325/esophageal/surgery or chemoradiation	Men: <44.5 Women: <36.5	33	Anastomotic leak higher in sarcopenic vs. non-sarcopenic (25% vs. 14%, P = 0.032); no difference for other complications.
Huang[22]	142/colorectal/surgery	[25]	12	Sarcopenia (OR 4.5, P = 0.007) independent risk factor for post-surgical complications.
Tegels[23]	152/gastric/surgery	[39]	57	Sarcopenia did not predict in-hospital mortality (P=0.52), severe complications (P=1.00) or 6-month mortality (P=0.69).
van Vught[24]	206/colorectal /surgery + chemotherapy	[38]	44	SMI lower in patients with severe postoperative complications (86.6 vs. 110.2 cm^2/m^2; p = 0.008). SMI (cm^2/m^2) independently associated with severe postoperative complications (OR 0.9, P=0.018), higher SMI less complications
Skeletal muscle and survival prediction				
Fujiwara[25]	1257/liver/treatment	Men: ≤36.2 Women: ≤29.6	11	Sarcopenia independent predictor of reduced OS (HR 1.5, P=0.001).
Fukishima[26]	63/renal/prior treatment	[39]	68	Sarcopenia independent predictor of OS (HR 2.6, p=0.015). Three-year OS for sarcopenic vs. non-sarcopenic were 31% and 73% (P <0.001).
Psutka[27]	387/renal/surgery	[38]	47	Sarcopenia independently associated with increased cancer specific mortality (HR 1.70, p=0.047) and all-cause mortality (HR 1.5, p=0.039).
Tamandl[28]	200/oesophageal + gastro-oesophageal junction/surgery	[38]	65	Reduced OS (HR 1.9, P=0.011) for sarcopenic vs. non-sarcopenic post-surgery.
Treatment induced changes in skeletal muscle				
Antoun[29]	120/prostate/treatment	[39]	70	Significant SMI loss from baseline to 3 months (-2.5 cm^2/m^2, P<0.001), and baseline to 6 months (-2.8 cm^2/m^2, P< 0.001). Sarcopenia not associated with OS, PFS.

Choi[30]	484/pancreas/chemotherapy	Men: <42.2 Women: <33.9	21	Significant SMI loss (-2.8 cm^2/m^2, P<0.001) from baseline to progression. Baseline sarcopenia (HR 1.7, P<0.001), loss of SMI (HR 1.4, P=0.004) independent predictors of OS.
Cooper[31]	89/pancreas/chemotherapy or chemoradiation	[39]	52	Significant SMI loss (-1.2 cm^2/m^2, P<0.01) from baseline to post-treatment. Post-treatment SMI independently predicted DFS (HR=0.9, P=0.04), higher SMI for improved DFS.
Kimura[32]	134/non-small cell lung / chemotherapy	Men: <41 Women: <38	38	Significant SMI loss from baseline to 3 months (-1.6 cm^2/m^2, p<0.01), 6 months (-1.3 cm^2/m^2, p<0.01), 12 months (-1.5 cm^2/m^2, p<0.01). Increase SMI independently predicted better OS after 6 months (0.92, P<0.01), and 12 months (0.90, P<0.01) of treatmen..
Miyamoto[33]	182/colorectal/chemotherapy	-	29	Change in SMI was +4.2% and not associated with OS. When SMI loss examined as quartiles, the highest quartile of SMI loss (>5%) independently predicted reduced OS (HR 2.1, P=0.010).
Rollins[34]	228/pancreas + cholangiocarcinoma/ chemotherapy	[39]	61	Significant loss SMI (-2.4 cm^2/m^2, P<0.001) from baseline to follow-up. Sarcopenia did not predict OS (p=0.739) or chemotherapy completion or toxicity.
Skeletal muscle and inflammatory markers				
Aust[35]	140/ovary/surgery + chemotherapy	[39]	29	Sarcopenia (HR 1.23, p=0.565) did not predict OS. There were no correlation between inflammatory markers and SMI.
Malietzis[36]	763/colorectal/surgery	[39]	65	Patients with NLR>3 had lower SMI (P=0.002) than those with NLR <3. NLR >3 (OR 1.8, p<0.001) an independent predictor of low SMI.
Reisinger[37]	87/colorectal/surgery	-	-	Low pre-operative SMI significantly predicted high concentrations for calprotectin (a biological indicator of inflammation) on PO days 2-5.
Rollins[34]	228/pancreas + cholangiocarcinoma/ chemotherapy	[39]	60	No correlation between inflammatory markers and SMI.

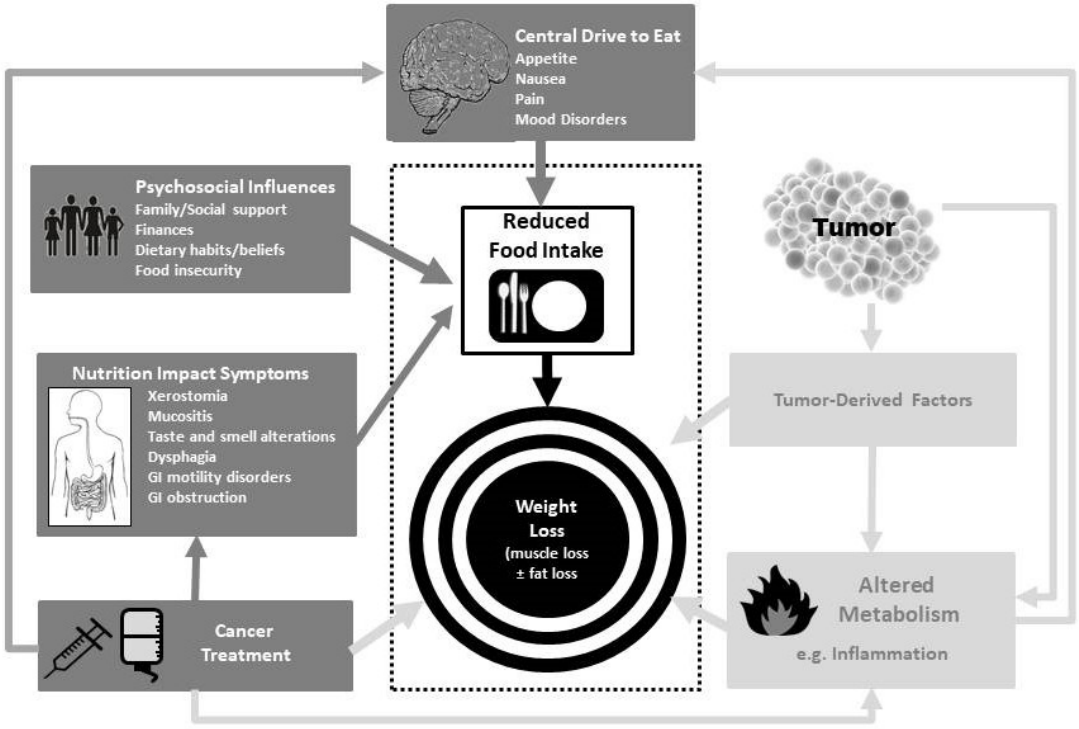
SMI, skeletal muscle index (cm^2/m^2); LBM, lean body mass; OR, odds ratio; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; C-index, concordance index; DFS, disease-free survival; NLR, neutrophil to lymphocyte ratio; PO, post-operative.
*Sarcopenia = skeletal muscle depletion (measured by CT L3 image analysis) defined by cutoffs for skeletal muscle index (cm^2/m^2) associated with a clinical outcome (e.g. overall survival).

CHAPTER 4: How much does reduced food intake contribute to cancer-associated weight loss?[1]

4.1 Introduction

In 2011, an international consensus group defined cancer cachexia as a syndrome of involuntary weight loss (WL), characterized by the loss of skeletal muscle (with or without fat loss), which is driven by a variable combination of reduced food intake (FI) and altered metabolism.[1] Many factors conspire to impair FI and to alter metabolism, resulting in WL (Figure 4-1).

Figure 4-1. A conceptual diagram representing the pathophysiology of cancer cachexia



A conceptual diagram representing the pathophysiology of cancer cachexia**,** which is driven by a variable combination of reduced food intake (FI) and altered metabolism.[1] The focus of this review, identified by the dotted black box, is the contribution of reduced FI to cancer-associated weight loss (WL). There are many factors that conspire to reduce FI resulting in involuntary WL in patients with cancer cachexia (represented by dark grey boxes). Many of these factors are directly or indirectly related to the presence of the tumor e.g. nutrition impact symptoms due to location of the tumor in the gastrointestinal tract or development of symptoms in response to cancer therapies; decreased central drive to eat in response to pro-inflammatory tumor-mediated factors, and/or cancer-related pain or

[1] A version of this chapter will be published: Martin L, Kubrak C. How much does reduced food intake contribute to cancer-associated weight loss? Curr Opin Support Palliat Care, 2018; 12, doi:10.1097/SPC.0000000000000379

nausea. Non-cancer related psychosocial factors can also act as barriers to FI e.g. mood disorders, food insecurity, lack of social support for assistance with meal preparation, poor dietary habits, etc. Metabolic alterations (represented by light grey boxes) are also key drivers of cancer-associated WL, and include tumor-mediated catabolic factors that act directly on skeletal muscle and adipose tissue, or via pro-inflammatory factors arising from interactions with the immune system. The specific nature of these metabolic alterations continues to evolve and requires further elucidation. Ultimately our understanding of the factors contributing to cancer-associated WL will only be fully described when both reductions in food intake and alterations in metabolism are accounted for.

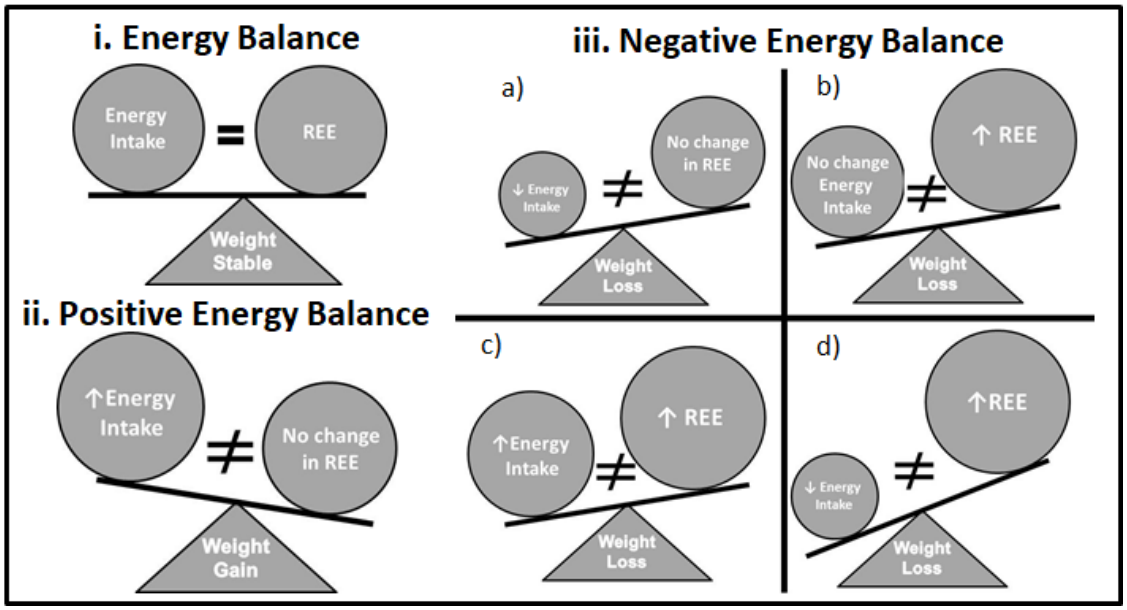
Reduced FI may be instigated by pain, nausea, anxiety, depression, or inflammation as examples, whereby the central drive to eat within the brain (appetite center) is decreased or abolished.[2-4] Additionally, other clinically distinct causes of reduced FI (referred to as nutrition impact symptoms) including decreased upper gastrointestinal motility (early satiety and nausea), dysphagia, stomatitis, bowel obstruction, dental issues, and psychosocial factors may also contribute to a diminished FI.[1,2,4-6] Altered metabolism is characterized by tumor-derived catabolic factors and inflammation, which promote skeletal muscle and adipose tissue catabolism, and increased energy expenditure, resulting in WL (Figure 5-1).[2,4] The extent to which FI is reduced and metabolism is altered is not currently known.[1,2,4,5] However, early identification of reduced FI is the dominate theme within clinical practice guidelines for nutrition care in patients with cancer, since it's treatment has the potential to stem continued WL, improve patient outcomes (i.e. quality of life (QOL)), and reduce patients' and family's distress[1,5,7-11]

There is a paucity of research studies evaluating the contribution of reduced FI to cancer-associated WL. Lack of emphasis in the current research on reduced FI is disproportionate to its' importance to clinicians, patients, and families.[11] In this review, using cancer-associated WL as the model (Figure 4-1), we will present recent studies focusing on the assessment of FI and its association with cancer-associated WL.

4.2 Identification of Reduced Food Intake

An individual's energy intake must align with their energy expenditure (i.e. sum of resting energy expenditure, physical activity, and diet-induced thermogenesis) to maintain energy balance and weight stability (Figure 4-2).[2,5] Cancer can alter the homeostatic control of energy balance[2]; tumor derived catabolic factors, inflammation, and cancer treatments can increase energy expenditure and reduce energy intake resulting in negative energy balance and WL (Figure 4-2).

Figure 4-2. A diagram representing the energy balance framework.



A diagram representing the energy balance framework. Energy intake represents the sum total calories ingested and metabolized from the diet; energy expenditure represents the sum total calories of resting energy expenditure (REE), physical activity, and diet-induced thermogenesis. Total energy expenditure is difficult to measure; therefore REE is often used to represent energy expenditure. There are several scenarios within the energy balance framework that will impact on body weight. **i.** Energy balance refers to a net balance between energy intake and energy expenditure, resulting in overall weight stability, **ii.** Positive energy balance occurs with an increase in energy intake relative to energy expenditure resulting in weight gain. **iii.** Negative energy balance occurs when there is an imbalance between energy intake and energy expenditure resulting in weight loss (WL). Four scenarios highlight how the variable contributions of food intake and altered metabolism (represented by REE) can result in WL: a) decreased energy intake, no change in REE, b) no change in energy intake, increased REE, c) disproportionate increase in both energy intake and REE, d) decreased energy intake, increased REE.

To understand the factors contributing to the continuum of cancer-associated WL, information about energy intake and energy expenditure over time is essential. A variety of methods exist to quantify both energy intake and expenditure, each with inherent advantages and limitations.[12-14] However, as Chow & Hall[12] eloquently point out, a main barrier to our understanding of energy balance is the lack of precise and accurate information about daily fluctuations in both energy intake and expenditure that can capture persistent changes over time. Quantification of energy expenditure is complex and challenging, and at present we have an incomplete understanding about the role of altered energy expenditure in weight losing cancer patients.[5,13,15-17] In absence of routine, clinically expedient assessments of energy expenditure, current recommendations are to evaluate and manage energy intakes according to clinical effects on body weight and muscle mass.[5]

There are a variety of clinical tools used to assess FI, which can be divided into three main types: 1) Screening for reduced FI using clinical questionnaires: patients compare their current or recent FI to what is normal (i.e. adequate) for them using various categorical or numerical responses (Table 4-1), 2) Assessment of food and fluid intake using recall or diaries: patients record their current food and fluid intake; macro- and micro-nutrient intakes can be calculated, and information about diet quality, food patterns, and preferences can be obtained (Table 4-1). A main limitation for these types of tools is the short time frame (e.g. 1 day to 1 month) over which FI is captured relative to the period of WL (e.g. 1 to 6 months, from pre-illness), which cannot capture the day-to-day variations in FI. 3) A third approach is to use appetite as a surrogate for FI, for which there are also a variety of clinical assessments.[18] However, appetite is unlikely to be adequate surrogate of FI. Measures of appetite and FI have been demonstrated to be only moderately correlated[19,20], likely because appetite and FI represent

different aspects of FI behavior; appetite is a dimension of ingestive behavior that also includes hunger and satiety, which together influence the outcome which is FI.[21] There is currently no agreement for how to measure or define reduced FI; however, given the variability in available assessments, reduced FI has been variously classified as patient reported reductions in FI, or energy intakes that are either below a measured energy expenditure or below the recommended energy and protein intakes outlined in clinical practice guidelines.[5]

4.3 Food Intake and Cancer-Associated Weight Loss

The specific contribution of FI to cancer-associated WL has not been extensively studied. Therefore, it is not possible to draw definitive conclusions regarding the magnitude of the contribution of reduced FI to cancer-associated WL; results were difficult to aggregate due to differences in study design (cross-sectional vs. longitudinal; observational vs. intervention), definitions for WL as an outcome (e.g. continuous, >5%), FI measures (questionnaire vs. food/fluid records), and limited presentation of statistical information. However, common themes were identified and will be discussed.

4.3.1 Comparing food intake between patients with and without cancer-associated weight loss

Four studies compared the FIs of patients with or without cancer cachexia (i.e. patients with or without WL).[22-25] Similar to what Blum et al.[15] had previously reported, the use of prospectively collected FI records to estimate energy intakes in cancer patients was limited.[22,23,25] Overall, mean energy (and protein) intakes were not different between cachectic or non-cachectic patients, although a higher proportion of cachectic patients reported reductions in FI (measured by the PG-SGA)[24] and energy intakes of <20kcal/kg/d.[22] Small sample sizes limit the ability to detect differences due to large inter-individual variations in FI, and energy expenditure

was either not quantified[22,25] or quantified inappropriately[23] so the gap between energy intake and energy expenditure could not be adequately assessed as an explanatory factor for WL.

4.3.2 The association between food intake and cancer-associated weight loss

Four studies evaluated the association between FI and WL (Table 4-2).[19,20,26,27] Vagnildhaug et al.[27] observed increasingly severe reductions in FI (measured by the PG-SGA) with increased severity of WL. Two studies[19,20] sought to evaluate the association of FI to cancer-associated WL using multivariable linear regression analysis. These studies demonstrated that reduced FI (measured by the PG-SGA as normal vs. reduced) or low energy and protein intakes (continuous as kcal/kg/d; g/kg/d) had significant, independent associations with WL. Notably, both studies also sought to evaluate the association of altered metabolism to WL by including a measure of systemic inflammation, C-reactive protein (CRP), but did not find an association.[19,20]

Two studies[19,26] undertook specific interventions to improve FI in cancer patients (Table 4-2). Kapoor et al.[26] randomized 63 female cachectic patients into two groups, both groups received nutritional and physical activity counseling and the intervention group (N= 30) received 100 g/d of fortified flour for 6 months. Patients were assessed 3 and 6 months after initial visit. The intervention group significantly increased total energy (kcal/d) and protein (g/d) intakes at each visit, resulting in a trend towards body weight gain. In the study by Nasrah et al.[19], cachexic patients (N=320) attending a multi-disciplinary cancer nutrition rehabilitation program received, pain, symptom, and psychosocial management, exercise training, and individualized nutrition counseling to achieve target dietary intakes of at least 30 kcal/kg and 1.3 g protein/kg. Patients were seen approximately 6 and 12 weeks after initial visit. Overall, researchers found as mean energy (from 25 to 32 kcal/kg/d) and protein (from 1.0 to 1.4 g/kg/d) intakes increased, weight

stabilized (weight change from -2 to 0.4 kg) over time. Interestingly, researchers observed an unpredictable weight change response with a given change in energy intake suggesting that unaccounted for alterations in metabolism (e.g. increased energy expenditure) might be contributing to WL. Taken together these two studies suggest that reduced FI is an important contributor to cancer-associated WL, which can be mediated with efforts to improve FI in subsets of patients. Identifying patients likely to respond to nutritional interventions will require further characterization.

A single study[28] assessed resting energy expenditure (REE kcal/d; portable indirect calorimetry) and energy intake (24hr recall, kcal/d) in a heterogeneous group of cancer patients (Table 4-2). Interestingly, when patients were classified as hypermetabolic (defined as an REE >110% of predicted REE), hypometabolic, or normometabolic, the mean energy intakes (kcal/d) were not different between groups, and thus not surprisingly hypermetabolic patients had the greatest WL. This observation suggests patients with hypermetabolism fail to augment their energy intakes in relation to their increased energy expenditure resulting in negative energy balance and WL. In a multivariable linear regression analysis hypermetabolism, low energy intake (kcal/d), and elevated CRP had significant, independent associations with WL >5% (Table 4-2). Although the magnitude of the association for each of these factors was not reported, this study suggests that both reduced FI and alterations in metabolism associate with WL.

4.3.3 Nutrition impact symptoms and Cancer-associated weight loss

In the current literature, researchers recorded results of self-perceived symptoms that associated with reduce FI in weight losing patients with cancer. Appetite loss (measured with a variety tools) related to reduced FI (measured by food/fluid records, VAS FI scores) in a majority of weight losing patients.[19,20,24,26,29-31] Patients with cachexia often described dysgeusia,

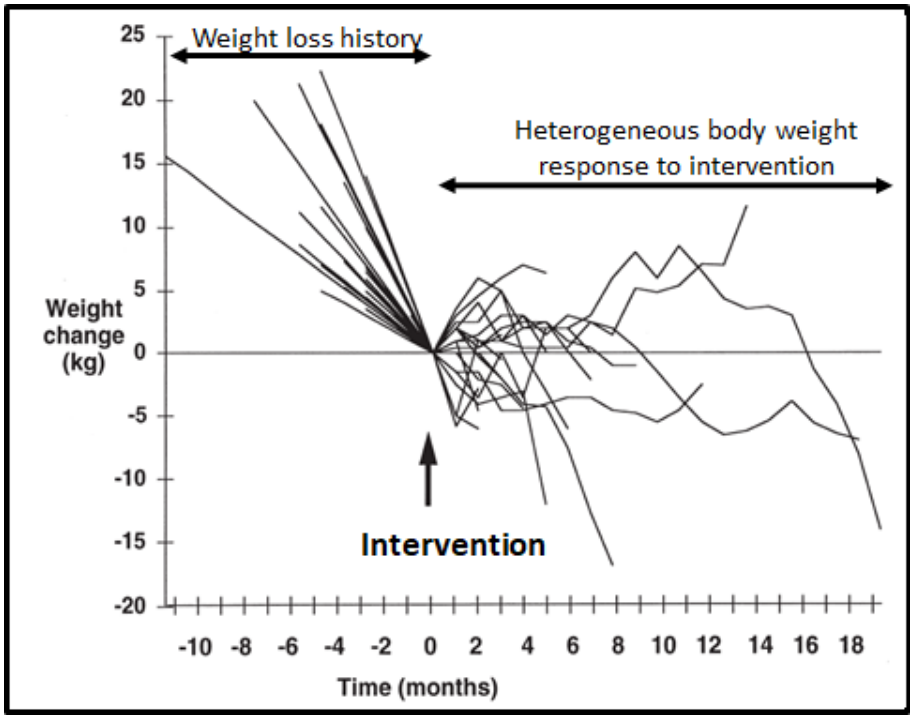
nausea, vomiting, pain, fatigue, depression, weakness, and meat aversion, as reasons for reduced FI.[19,26,29-33] These symptoms are consistent with our current understanding of the factors likely to interfere with FI in patients with cancer (Figure 4-1).[1,2]

4.4 Discussion

A key feature of cancer cachexia is reduced FI that leads to progressive WL, which is the subject of this review. The current literature does not dispute this concept, but lack of consensus regarding the assessment of FI is a principal factor confounding this area of research and limits our ability to explain the magnitude of the association with WL. It is improbable that reductions in FI alone will explain the progression of WL in all patients with cachexia, and without adequate consideration of the factors driving alterations metabolism (e.g. increased energy expenditure, systemic inflammation, and tumor-derived catabolic factors), we have an incomplete understanding about the magnitude by which these alterations also contribute to cancer-associated WL (Figure 4-1).

Diminishing FI is recognized to be a dominant driver of WL, and efforts to improve FI with the intention to promote maintenance or gain of weight are regarded as the first line of treatment for cancer cachexia.[2,4-6,34] It is our understanding that cancer cachexia cannot be fully reversed by nutrition support alone due to metabolic alterations that independently contribute to WL, and because of this variable combination of reduced FI and altered metabolism attempts to correct FI alone will result in variable body weight responses (Figure 4-3).[1,2,10,19,35-37]

Figure 4-3. Heterogeneous body weight responses to a nutritional intervention



Body weight response to a nutritional intervention. The line graph, from Wigmore et al.[35], shows the variable progression (rate) of WL before and after introducing a nutritional intervention and highlights the variability in body weight responses, which include weight stability, weight gain, WL, and fluctuation between all three of body weight responses. Monitoring body weight responses in conjunction food intake provides information about energy balance; which essentially, quantifies the gap between energy intake and expenditure. For example patients in negative energy balance scenario iii. c) from Fig 2A) increase their energy intake but continue to lose weight because energy intake remains below REE.

A recent meta-analysis did find that nutrition interventions promoted weight gain in subsets of patients undergoing chemotherapy or chemoradiation. This positive effect on body weight was attributed to interventions with energy dense high protein oral nutritional supplements enriched with n-3 fatty acids, which aim to improve both energy and protein intakes as well as modulate alterations in metabolism.[10] Understanding which patients are likely to respond to specific nutrition interventions requires further investigation, and many additional factors (e.g. patient compliance, high symptom burden, increased tissue catabolism, proximity to death) can also affect individual response to a given intervention[10,19] de van der Schueren et al.[10]

made a series of recommendations to improve the design of future clinical trials studying nutrition interventions in cancer cachexia, including the study of interventions in the context of multimodal care plans, which is also the recommend treatment approach for cancer cachexia.[6,34,38-40] Core components of multimodal care include the medical management of pain and symptoms, and combined interventions to improve FI, increase exercise to promote anabolism, modulate inflammation, and establish adequate psychosocial supports.[4,10,34,39,40] Indeed specialized multimodal cachexia clinics have demonstrated positive impacts on body weight, improved FI, and other important patient outcomes such as quality of life, physical function, pain and distress.[19,41-45] Although not every center will have access to specialist cachexia clinics, Maddocks et al.[40] suggest effective multimodal care can be practical and incorporated into the clinical practice of health care professionals. Key components for the successful adoption of multimodal care plans include patient engagement, communication between health care professionals, consistent messaging regarding the treatment plan, and practical and individualized interventions.[40,41]

In order to provide the right nutrition interventions at the right time, identification of patients at risk of nutrition problems is an essential first step.[6,38] Clinical practice guidelines recommend regularly screening cancer patients for nutrition risk (i.e. weight loss, reductions in FI, nutrition impact symptoms) and if identified, followed-up with a comprehensive nutrition assessment, and appropriate interventions defined in the context of individual prognosis and treatment goals[5] This review, albeit limited in scope, demonstrates current research is aligned with international consensus and clinical guidelines to assess FI in patients with cancer, but there is no agreement on how to best measure FI in clinical practice, which has been a longstanding issue.[1,15,36,37] Future studies to evaluate equivalency between different measures of FI based on

their association to cancer-associated WL are needed to enhance our ability to aggregate and compare research results, reduce heterogeneity, and improve our ability to draw conclusions about the impact of FI on features of cancer.

4.5 Conclusion

The etiology of cancer cachexia is driven by a variable combination of reduced FI and altered metabolism. In the clinical setting, identifying reductions in FI is the predominant theme, but few studies have examined the magnitude of the association to WL. Additionally, research studies have adopted a variety of different tools to evaluate FI in patients with cancer, rendering the comparison of available studies challenging. The literature reviewed here points to reductions in FI as an important driver of cancer-associated WL, which is independent of alterations in metabolism. Until there is a more complete understanding about the alterations in metabolism that occur in patients with cancer and how they relate to WL, multimodal interventions that remove barriers to FI should remain a focus of care.

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Table 4-1. Assessments used to measure food intake in the oncology setting.

Measures of Food Intake in Clinical Practice	Example Tools	Example Data	Advantages	Limitations
Food intake as a component of clinical questionnaires	PG-SGA	Food intake in the past month: Normal / less than usual/ more than usual Current food intake: Normal food, in normal amount/ normal food, reduced amount/ little solid food/ only oral nutritional supplements/ only liquids/ very little anything	Completed by patient or health care providers Screens for nutritional problems Can be used to track changes over time Clinically expedient Current food intake is benchmarked to past intake	No estimate of macro- and micronutrient intakes None or limited information about patient food patterns and preferences Food intake assessed over different time frames (e.g. intake now, past week, or over one or 3 months)
	MNA	Food intake over the past 3 months: Normal vs. moderately or severely reduced		
	Food intake VAS	Current food intake VAS (0-none at all to 10-as normal)		
	NRS-2002	Food intake in the preceding week: 50-75% of normal requirement/ 25-50% of normal requirement/		

		0-25% of normal requirement		
Food and fluid records	24-hour recall (food and fluids consumed the previous day) Food and fluid intake diaries (food and fluids consumed over 1-7 days)	Macronutrients: Energy intake (kcal/d) Protein intake (g/d) Fat intake (g/d) Micronutrients	Completed by patient or care giver and health care provider Information about food type, patterns, and preferences Useful for in-depth nutritional assessment and for guiding individualized nutrition interventions	Requires specialized software and country-specific nutrient database Time consuming and burdensome to patient/caregiver Accuracy declines with increased recording days Resource intensive (health care provider must collect, verify, and enter data) Potential for mis-quantification of food items, and underestimation of nutrients

MNA, Mini-Nutrition Assessment; NRS 2002, Nutrition Risk Screening; PG-SGA, Patient Generated-Subjective Global Assessment; VAS, visual analogue scale.

Table 4-2. A summary of studies that have examined the contribution or food intake to cancer-associated weight loss.

Study	N/Setting/Cancer Type	Variables	Measure of WL	Correlation with Weight Change	Outcome(s)
Vagnildhaug / **Prospective observational cross-sectional multi-center**	1406/Palliative Care Program/Heterogeneous, incurable, 60% receiving treatment	**Food Intake (current):** PG-SGA; 5 sub-categories **Appetite loss (previous week)**: EORTC QLQ-C15 PAL **Function:** EORTC-QLQ-C15 PAL, KPS **Fatigue:** EORTC-QLQ-C15-PAL **Emotional Functioning:** EORTC-QLQ-C15-PAL	Weight loss grades (WLG) (0-4)	Not reported	**One way ANOVA:** compared differences between WLG 0-4 Worsening of parameters with increasing WLG: Food intake (P<0.001) Appetite loss (P<0.001) KPS (P<0.001) Fatigue (P<0.001) Physical function (P<0.001) Emotional functioning (P<0.001)
Solheim/ **Prospective, observational, cross-sectional multi-center**	885/Palliative Care Program/Heterogeneous, incurable, 75% receiving treatment	**Food Intake (past month):** PG-SGA; normal vs. reduced **Appetite loss (previous week)**: EORTC QLQ-C30 **Function:** EORTC-QLQ-C30, KPS **Inflammation:** CRP_{log} (mg/L)	% weight loss past 6 months	Reduced food intake R_s=0.34, P<0.01 Appetite loss R_s=0.34, P<0.01	**Multivariable linear regression:** %WL (dependent variable): Reduced food intake (β=0.15, P<0.01) Appetite loss (β=-0.16, p<0.01) Physical function (β=0.15, P<0.01) Gender (β=0.11, P<0.01) (adjusted model R^2=0.13) age, gender, cancer site, metastatic sites, cancer treatment, CRP_{log} associated with %WL at the univariable level
Nasrah/ **Retrospective,**	320/Cancer Nutrition Rehabilitation Program/	**Energy intake (kcal/kg/d)**: 24-hour recall	***Visit 1(Baseline)***: weight change (kg)	Energy intake (kcal/kg/d) (R=0.25, P<0.001)	**Multivariable linear regression:** weight change in kg (dependent

intervention, longitudinal, moncentric	Heterogeneous, advanced (Stage III-IV), 35% not receiving treatment *Intervention = individualized diet counselling and exercise training	**Protein intake (g/kg/d):** 24-hour recall **Appetite loss:** VAS 0-10 **Performance Status:** ECOG **Inflammation**: CRP_{log} (mg/L), Albumin (g/L)	past 6 weeks	Protein intake (g/kg/d) (R=0.28, P<0.001) Appetite loss (R_s= -0.24, P<0.001) PS (R_s=-0.24, P<0.001) CRP_{log} (R=-0.11, P<0.05)	variable): Significant independent predictors of weight change: Energy intake† (P=0.002) Performance status (P=0.002) Appetite loss score (P<0.05) (adjusted model R^2= 0.12) age, sex, tumor type, chemotherapy treatment, and CRP_{log} did not associate with weight change
			Visit 2: weight change (kg) past 6 weeks (V2-V1)	Energy intake (R=0.26, P<0.001) Protein intake (R=0.19, P<0.01) Appetite loss (R_s= -0.31, P<0.001), PS (R_s=-0.18, P<0.01) CRP_{log} (R=-0.09, P=NS)	Significant independent predictors of weight change: Energy intake† (P=0.004) Appetite loss score (P=0.005) only predictors at V2 (adjusted model R^2= 0.10) age, sex, tumor type, chemotherapy treatment, and $CRP_{log,}$ PS, did not associate with weight change
			Visit 3: weight change (kg) past 6 weeks (V2-V3)	Energy intake (R=0.35, P<0.001) Protein intake (R=0.23, P<0.01) Appetite loss (R_s= -0.38, P<0.001) PS (R_s=-0.28, P<0.001) CRP_{log} (R=-0.06, P=NS)	Significant independent predictors of weight change: Energy intake (P=0.0005) Appetite loss score (P=0.001) only predictors at V3 (adjusted model R^2= 0.17) age, sex, tumor type, chemotherapy treatment, and $CRP_{log,}$ PS, did not associate with

					weight change
Kapoor/ **prospective, intervention, longitudinal, moncentric**	N=33/Heterogeneous tumor group, all female, palliative care clinic Treatment group N=17; Control Group, N=15 * Both groups individualized diet counselling; Intervention group received 14 packets of 100 g of Enhanced Atta (flour), providing approximately 400 kcal/d	**Energy intake (kcal/d):** 24-hour recall **Protein intake (g/kg/d**): 24-hour recall **Food Frequency Questionnaire (FFQ) by Indian Migrant FFQ** **EORTC-QLQ-C30 measured (**fatigue, nausea and vomiting, pain, appetite loss, constipation, diarrhea) **Physical Activity Questionnaire (Indian Migrant study – PAQ)**	***Visit 1 (Baseline):*** weight (kg)	Not reported	Student's t-test compared differences between intervention and control groups for each time point, and repeated measures ANOVA determined changes within groups overtime:
			Visit 2: weight change (kg) past 3 months (V2-V1)	Not reported	Compared to the control group, the intervention groups significantly increased (t-test): Energy intake (P=0.003) Protein intake (P<0.001) Physical activity (P=0.007) Appetite loss (P<0.001) and Reduced pain (P<0.001) Reduced fatigue (P<0.001)
			Visit 3: weight change (kg) past 3 months (V3-V2)	Not reported	Compared to the control group, the intervention groups significantly increased (t-test): Energy intake (P=0.001) Protein intake (P<0.001) Physical activity (P<0.007) Appetite loss (P=0.001) and Reduced fatigue (P<0.001) **At the end of 6 months**

					(repeated measures ANOVA): Intervention group increased: Body weight (P=0.081) Energy intake (P<0.001) Macronutrient intake (P<0.001) Appetite loss (P=0.006) and Reduced pain (P=0.012) Reduced fatigue (P=0.002) No change in performance status (NS) Control group decreased: Body weight (P=0.003), PS (P=0.004) and showed no improvement in energy or macronutrient intakes, and appetite loss.
Vazeille/ **Cross-sectional, observational, monocentric**	390/Multi-disciplinary risk assessment program/Heterogeneous, solid tumors, any stage, prior to systemic therapy	**Energy intake (kcal/d):** 24-hour recall **Measured REE (kcal/d)**: indirect calorimetry (portable) **Predicted REE (kcal/d):** Harris-Benedict Equation **Energy Balance (kcal/d):** energy intake– measured REE **Inflammation:** CRP (mg/L), Albumin (g/L), **Nutrition Status:** NRI	% weight loss from UBW	Energy balance R=-0.23, P<0.001) NRI score R=0.27, P<0.001 Albumin (R=0.22, P<0.001) CRP R=-0.20, P<0.001	**Multivariable linear regression:** WL >5% (dependent variable): Significant independent predictors of WL >5%: Energy intake (OR 0.9998 [95% CI 0.9997-0.9999), P=0.013) CRP (OR 1.0019 [1.0006, 1.0032], P=0.004), Hypermetabolism† (OR 1.1742 [95% CI 1.0428, 1.3223], P=0.008)

Abbreviations: ANOVA, analysis of variance; BW, body weight; CI, confidence interval; CRP, C-reactive protein; DI, dietary intake; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; EORTC-QLQ-C15 PAL/C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FFQ, Food Frequency Questionnaire; Ingesta-VAS, Ingesta visual analogue scale; KPS, Karnofsky Performance Scale; NS, non-significant; NRI, nutrition risk index; OR, odds ratio; PG-SGA, Patient-Generated Subjective Global Assessment; PS, Performance Status; PAQ, Physical Activity Questionnaire; QOL, Quality of life; R, pearson correlation; Rs spearman correlation; REE, resting energy

expenditure; UBW, usual body weight; VAS, visual analogue scale; WL, weight loss, WLG, weight loss grade. *dietary intake in this model was not specified as energy, protein or diet category; †Hypermetabolism measured REE >110% of predicted REE.

CHAPTER 5: Reduced food intake as an explanatory variable for cancer-associated weight loss

5.1 Introduction

Cancer cachexia is defined, as a multifactorial syndrome of involuntary weight loss (WL) characterized by skeletal muscle loss (with or with fat loss), which is driven by "a variable combination of reduced food intake (FI) and altered metabolism".[1] Reduced FI is an important and, in some cases the dominant driver of cancer-associated WL, and quantifying the severity of FI impairment is recommended as an essential first step to guide nutrition care.[1-10] Impairments to FI are multifactorial, and can include decreased central drive to eat, uncontrolled pain and symptoms, physical obstruction or gastrointestinal tract dysfunction, reduced physical function, and/or psychosocial factors [2]. Some of these limitations may be reversible, and their identification can assist care teams to determine appropriate feeding strategies.[2,11,12]

Despite the importance placed on the early identification of reduced FI, its specific contribution to WL has not been fully elucidated.[13] There is a lack of consensus with regard to how reduced FI ought to be measured due to significant heterogeneity of available assessments.[13] FI data acquired from the clinical setting is predominantly acquired from validated patient-reported nutrition risk assessment questionnaires, *e.g.* the Patient-Generated Subjective Global Assessment (PG-SGA) [14,15], the *Ingesta*-Verbal/Visual Analogue Scale (I-VVAS)[16,17], and the Mini-Nutrition Assessment (MNA) [18,19], as opposed to the more labor intensive food and fluid records.[20] A concept inherent to all of these tools is to capture the quantity of FI anchored to an individual's perceived normal food intake; however the ratings of severity are numerical or descriptive and have a 3-, 7- or 10-levels to describe intake.

Our international research groups have been involved in the aggregation of an International Cancer Cachexia Data Repository (ICCDR) of patients with cancers of advanced

stage who are at risk for cancer cachexia. Our goal is to generate samples of sufficient size to capture representative distributions of key patient features, including FI and WL history, and clinical outcomes for adequately powered statistical and subset analyses. The ICCDR includes FI data for 11,704 cases (evaluated by PG-SGA (n=6161), *I*-VVAS (n=3186) and MNA (n=2357)), and is therefore suited to answer our research questions: what is the association between FI as assessed by three different tools and WL?

5.2 Methods

5.2.1 Study population

The ICCDR includes prospective clinical and nutrition risk assessment data collected from 1999 to 2016. Nutrition risk assessment occurred at several points of referral for nutrition care (i.e. prior to nutrition intervention): at entry to investigational cachexia clinical trials, at cancer diagnosis as of standard of care, and at entry to supportive/palliative care programs. Martin et al.[21] provide a description of the study cohorts initially included in the ICCDR, to which additional data have subsequently been added. The ICCDR has specific inclusion criteria intended to facilitate data pooling: i) Original study data were prospectively collected under the auspices of human ethics approvals from respective institutions, ii) data are anonymized and iii) clinical data include age (≥18 years), sex, confirmed cancer site (based on International Classification of Diseases (ICD)-10 classifications) and stage (based on the American Joint Committee on Cancer (AJCC) stage groupings versions 6 to 7), performance status (PS; Eastern Cooperative Oncology Group (ECOG), Karnofsky Performance Status (KPS), or other measures of PS), WL history, measures of FI, body mass index (BMI), and if available time to death/censoring.

For this study, patients were selected from the ICCDR with complete data for the following: demographic and clinical data (age, sex, cancer diagnosis and stage, PS, BMI, WL history), and nutrition risk assessments that included a measure of FI. Data for these patients was collected between 2004 and 2014. Patients with data from 2004 to 2010 used AJCC staging version 6.0, from 2011 onwards version 7.0 was used. We did not select patients with weight gain (e.g. ≥2.5%) for the reasons that our primary outcome is cancer-associated WL, and we previously showed that weight gaining patients in this population had different prognoses compared to weight stable patients.[22]

5.2.2 Assessments of Food Intake

Three data sets were identified each with a different assessment for measuring reductions in FI: the PG-SGA, the 10-point *I*-VVAS, and the MNA.

The PG-SGA data includes data pooled from 5 study cohorts (Table 5-1). The PG-SGA has 7 categories of FI, and patients choose the category that best represents their current FI compared to what is normal for them. The categories of FI capture the severity of FI impairment, represented by both quantity (e.g. less than normal, very little of anything) and quality indicators (normal food, little solid food, only liquids/ONS). Patients who reported receiving "only tube feedings or nutrition by vein" were excluded (N=69) as they were no longer relying on volitional FI.

The *I*-VVAS data was collected from a nutrition risk screening program at the Cancer Institute of Montpellier, France (Table 5-1).[21] FI was assessed at patients' first visit using the patient reported 10-point *I*-VVAS[16,17], and patients could respond to the question verbally or visually. The 10-point scale conveys the severity of current FI impairment based on quantity (normal to nothing at all). Patients rating their FI as 0 were excluded (N=47) as they were

receiving artificial nutrition support and no longer relying on volitional FI; an *I*-VVAS of 1 was therefore defined as the lowest level of volitional FI.

MNA data includes data pooled from two study cohorts (Table 5-1). [21,23,24] The MNA includes a question about FI in the screening portion of the tool, which assesses reductions in the quantity of FI over the previous 3 months. Patients relying on artificial nutrition support were excluded (N=47) as they were no longer relying on volitional food intake.

5.2.3 Statistics

Summary statistics were used to describe patients. The primary outcome was WL history, recorded as the percentage of WL over the previous 6 months or from usual body weight and calculated as:

% weight loss (%WL) =

*[(current weight in kg -previous weight in kg)/previous weight in kg]*100*

Statistical analysis was carried out in two parts:

1) The relationship between assessments of FI (PG-SGA, I-VVAS, MNA) and %WL were evaluated. Mean %WL was calculated for each of the three FI measurement scales; statistical differences in mean %WL were evaluated using one-way ANOVA (post-hoc tests: Games-Howell), a difference of >2% was recognized to be clinically meaningful WL (i.e. account for measurement error).

2) Multinomial logistic regression (MLR) was used to evaluate the association between reductions in food intake and %WL; MLR is an extension of logistic regression and is a robust statistical approach when the dependent variable has more than two categories. The dependent variable in this analysis is WL, which has 5 categories of severity (±2.4%, 2.5-5.9%, 6.0-10.9%, 11.0-14.9%, and ≥15.0%), as outlined in the diagnostic criteria for cancer-associated WL.[21] The

reference group for the dependent variable was weight stable (±2.4%), to which all other categories of WL were compared. MLR models were adjusted for age (continuous), sex, cancer site (ICD-10), cancer stage (AJCC), PS (ECOG or MNA mobility score), and BMI (<20.0, 20.0-21.9, 22.0-27.9, ≥28.0).[21] Results are reported as odds ratios (OR) and 95% confidence intervals (CI).

All analyses were completed using IBM SPSS Statistics for Windows version 23.0 (SPSS, Chicago, IL) and were considered statistically significant at the $P<0.05$ level. Figures were drawn with GraphPad Prism version 7.04 for Windows (GraphPad Software, La Jolla California USA).

5.3 Results

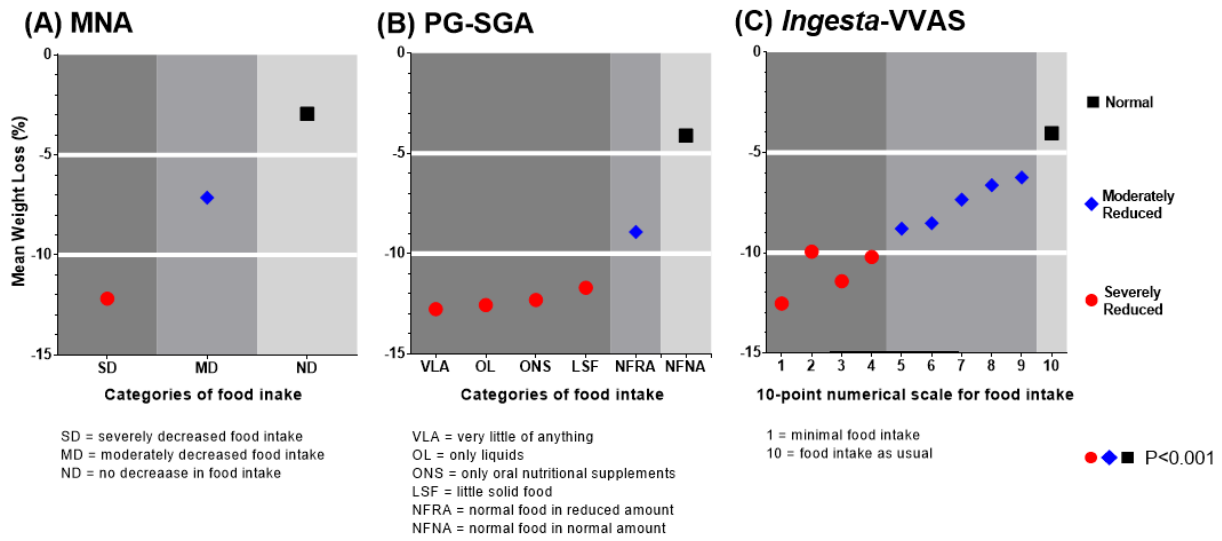
5.3.1 Patient Characteristics

Characteristics for the PG-SGA, *I*-VVAS, and MNA data sets are presented in Table 5-2. Each data set represents patients with cancer cachexia: patients with predominantly locally advanced or metastatic disease and losing weight.

5.3.2 The association between food intake and cancer-associated weight loss

Figure 5-1 depicts the mean %WL for each of the FI measurement scales from the MNA, PG-SGA, and *I*-VVAS respectively. Within each tool, measurement scales represent clinical and statistical differences in %WL (P<0.001).

Figure 5-1. The relationship between percent (%) weight loss (WL) and three food intake (FI) measurement scales



Three graphs depict the relationship between percent weight loss (%WL) and food intake (FI) measurement scales collected from different nutrition risk assessment tools: (A) MNA, (B) PG-SGA, and (C) *Ingesta*-VVAS. For each graph (A,B,C), different shades of gray represent significant differences (P<0.001) in mean %WL within the respective measurement scales. The 3 categories of FI measured by the (A) MNA associated with significantly different degrees of WL (p<0.001). Based on differences in %WL, three levels of FI were defined for the (B) PG-SGA, and (C) *Ingesta*-VVAS, which aligned with the categories of FI from the (A) MNA. Each measurement scale has a category representative of normal FI (black box). Moderately reduced FI (blue diamond) is represented by the following categories: (A) MNA "moderately decreased food intake"; (B) PG-SGA "normal food in reduced amount"; and (C) *Ingesta*-VVAS numeric scores 5 to 9. Severely reduced FI (red circle) is represented by the following categories: (A) MNA "severely decreased food intake"; (B) PG-SGA "little solid food", "only oral nutritional supplements", "only liquids", and "very little of anything"; and (C) *Ingesta*-VVAS numeric scores 1 to 4. White lines highlight regions of similar mean %WL values for normal, moderately reduced, and severely reduced FI descriptors, which align the three tools.

The MNA (Figure 5-1A) has 3 FI categories associated with different degrees of WL (P<0.001; Table 5-1). The PG-SGA and *I*-VVAS also had three distinct homogeneous subsets within their measurement scales that associated with different degrees of WL (P<0.001; Figure 5-1 B,C). Therefore, the measurement scales of the PG-SGA and *I*-VVAS were each combined into three categories of FI, similar to the MNA: normal, moderately reduced, and severely reduced, which associated with significantly different degrees of WL (P<0.001; Table 5-3). Each category of FI (normal, moderately reduced, severely reduced) was compared across tools. There

were some significant statistical differences between similar categories of FI (P<0.05), however the mean differences in %WL were <2%, and therefore not clinically meaningful (Table 5-3).

Three MLR models, one for each of the PG-SGA, *I*-VVAS and MNA data sets, evaluated the association between reduced FI and WL. The univariable analysis can be found in Appendix III, Suppl Table 1. In multivariable MLR analysis, all models were adjusted for the same variables: age, sex, cancer diagnosis, cancer stage, PS, and BMI, and the full models can be found in Appendix IV, Suppl Table 2. Table 5-4 depicts the adjusted odds ratios (OR) of experiencing weight loss with different levels of severity, in patients with moderately and severely reduced FI, as compared to those with normal intake. In each of the adjusted MLR models, reduced FI had the strongest association to WL, and each of the models demonstrated similar associations (i.e. overlapping OR with 95% CI; no differences between beta coefficients) between FI categories and WL severity (Table 5-4; Appendix IV Suppl Table 2). The odds of belonging to the most severe WL category (≥15.0%) for patients reporting severely reduced FI (vs. normal) were overlapping for each of the 3 tools: the PG-SGA **(**OR 15.3 (95% CI 11.3-20.7), P<0.001), the *I*-VVAS (OR 14.4 (95% CI 9.3-22.2), P<0.001), and the MNA: OR 26.9 (95% CI 14.3-50.5), P<0.001; Table 5-4). Likewise the odds of WL ≥15.0% for patients reporting moderately reduced FI (vs. normal) also overlapped for the PGSGA **(**OR 5.02 (95% CI 3.95-6.38), P<0.001), the *I*-VVAS **(**OR 5.62 (95% CI 3.83-8.26, P<0.001)), and the MNA (OR 7.1 (95% CI 4.3-11.6), P<0.001; Table 5-4).

Reductions in FI did not account for WL in all patients with cancer (Table 5-5). For example, the majority of patients with weight stability reported a normal FI (76% MNA; 61% PG-SGA; 63% *I*-VVAS), however patients with weight stability also reported moderately or severely reduced FI (24% MNA; 39% PG-SGA; 37% *I*-VVAS; Table 5-5). Similarly, a small

proportion of patients with ≥15% WL reported a normal FI (13% MNA; 12% PG-SGA; 11% *I*-VVAS; Table 5-5). These results are not unexpected given that the etiology of cancer-associated WL is driven by a variable combination of reduced FI and altered metabolism.

5.4 Discussion

The pathophysiology of cancer cachexia is said to be "….characterized by a negative protein and energy balance driven by a variable combination of 2 major etiologies, reduced FI and abnormal metabolism".[1] The identification of reduced FI is suggested to be a diagnostic criterion for cancer cachexia, yet there has been no consensus regarding how reductions in FI ought to be measured.[1] We evaluated the quantitative significance of reduced FI as a driver of cancer-associated WL. This is the first study to demonstrate equivalency between three different assessments of FI, the MNA, PG-SGA, and *I*-VVAS, and their association to cancer-associated WL. We approached this using MLR analyses to determine the probability of weight loss (categorical dependent variable) in patients with varying levels of FI. Our findings suggest that reduced FI had the strongest association to WL, in models adjusted for age, sex, cancer site, cancer stage, performance status, and BMI. These findings were consistent across three independent, international samples totaling 11,704 patients. Patient-reported "severely reduced food intake" captured subsets of patients with a high likelihood (OR>14) of having already lost ≥15% of their body weight at first assessment. This is not surprising, as mean daily energy intakes for patients with the lowest *I*-VVAS scores (≤4) are estimated to between 5-13 kcal/kg/day, which is grossly insifficient.[17]

The MNA, PG-SGA, and *I*-VVAS are major clinical assessments recommended in oncology nutrition clinical practice [2], and despite their diversity of concept and scales, the questions used to identify low levels of FI associated with WL. These tools assess FI based on

patients' own estimates of current or recent FI in relation to what is normal for them, which allows patients to directly convey the impact cancer has on them.[25] There are however, limitations to this analysis. The data used in this study was collected at a single point in time (i.e. to determine the need for nutrition care), and as a result there are discrepancies between the time frames for which reductions in FI (e.g. current or past 3 months) were recorded in relation to the time frame over which WL occurred (e.g. previous 6 months or from usual body weight). We do not have information regarding the actual onset of FI problems or about fluctuations in intake and body weight that may have occurred up until the point of assessment. Additionally, we did not account for alterations in metabolism (e.g. tumor mediated catabolic factors, systemic inflammation, and/or increased energy expenditure), which are also important in the etiology of cancer-associated WL.

In cancer cachexia, the respective contributions of FI and altered metabolism are painted as a spectrum; most patients experience both to some degree, and in others it is reduced FI or hypermetabolism that have the predominant effect on weight loss.[26] Our results indirectly support this concept; a subset of patients (N=2089, 18%; Table 5-5) reported normal FI but also had WL of varying degrees. WL in these patients may be attributable to various alterations in metabolism that have not been accounted for which has also been observed by others.[27-29] However, at present we have an incomplete understanding about how to clinically identify or evaluate alterations in metabolism and there are currently no viable treatment options, therefore treatment for cancer cachexia has predominantly focused on improving FI to support weight maintenance and weight gain, albeit with limited sucess.[30-32]

There are many factors that conspire to reduce FI in patients with cancer including a decreased central drive to eat (anorexia), various symptoms (stomatitis, early satiety,

constipation, nausea, vomiting, pain), depression, anxiety, functional impairment, social isolation, lack of finances, poor dentition and dietary habits, all of which should be recognized early. [26,30] Identification of specific issues affecting FI should be prioritized, as they may be readily managed and reversed by appropriate treatments. Optimization of nutritional intake can be achieved when cachexia is managed within a multimodal context.[27,33] This includes medical management of pain and symptoms, interventions to increase physical activity to promote anabolism, modulation of inflammation, and psychosocial support.[34] When barriers to FI are removed, the escalation of nutrition care (e.g. from oral to enteral feeding) should be viewed as an iterative process based on changes to FI and body weight response.[27]

In order to provide the right nutrition interventions at the right time, identification of patients at risk of nutrition problems (WL and reductions in FI) is an essential first step [3,35], and if identified, followed-up with a comprehensive nutrition assessment, and appropriate interventions defined in the context of individual prognosis and treatment goals.[2] Our findings underscore the clinical importance of assessing patients' FI using clinically expedient assessments as patients with reduced food intake have a high probability of presenting with severe WL.

5.5 References

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Table 5-1. A description of study cohorts that were selected from the International Cachexia Database (ICDR) for this study.

	PG-SGA Data Set N=6161					***I*-VVAS Data Set N=3186**	**MNA Data Set N=2357**	
Contributor	Martin[21]	Kubrak[21, UP]	Gagnon[36]	Chasen[33]	Laird[37]	Senesse[38]	Senesse[UP]	Muscaritoli[39]
Data Collection	Nutrition Risk Screening in Prospective Observational Cohorts							
Country	Canada				Europe	France	France	Italy
Health Care Setting	Medical Oncology / Palliative Care	Medical Oncology	Medical Oncology	Palliative Care	Palliative Care	Medical Oncology	Medical Oncology	Medical Oncology
Total N	4647	494	382	150	488	3186	605	1752

MNA, Mini-Nutrition Assessment; N, number; PGSGA, Patient-generated subjective global assessment; *I*-VVAS, *Ingesta*-verbal/visual analogue scale; WL, weight loss; UP, unpublished

Table 5-2. Patient characteristics for the three study cohorts

Variables	Current Food Intake Measured with PGSGA Food Intake Categories (N=6161)		Current Food Intake measured with a 10-point Visual Analogue Scale (N=3186)		Past Food Intake Measured with MNA Food Intake Categories (N=2357)	
	N	%	N	%	N	%
Region						
Canada	5373	92.1	-	-		
Europe	488	7.9	-	-		
France	-	-	3186	100	605	26
Italy	-	-	-	-	1752	74
Sex						
Male	3603	58.5	1633	51.3	1150	48.8
Female	2558	41.5	1553	48.7	1207	51.2
Age, years (mean, SD)	64.6 (12.1)		62.1 (12.4)		66.2 (12.9)	
Status						
Censored	1522	24.7	728	22.8	-	-
Dead	4639	75.3	2458	77.2	-	-
Overall Survival, months (median, 95% CI)	9.6 (9.2-10.1)		10.9 (10.1-11.7)		-	-
Cancer Diagnosis*						
Head & neck	1191	19.3	346	10.9	99	4.2
Breast	258	4.2	533	16.7	481	20.4
Upper gastrointestinal	950	15.4	433	13.6	384	16.3
Lower gastrointestinal	1009	16.4	519	16.3	403	17.1
Genitourinary organs	386	6.3	478	15.0	433	18.4
Respiratory	1913	31.1	363	11.4	364	15.4
Other	454	7.4	514	16.1	193	8.2
Cancer Stage†						
1	280	4.5	85	2.7	240	10.0
2	442	7.2	166	5.2	274	11.6
3	859	13.9	299	9.4	423	17.9
4	4580	74.3	2636	82.7	1420	60.2
ECOG PS						
PS 0	1387	22.5	554	17.4	-	-
PS 1	2110	34.2	1055	33.1	-	-
PS 2	1181	19.2	994	31.2	-	-
PS 3	1327	21.5	567	17.8	-	-
PS 4	156	2.5	16	0.5	-	-

MNA Section C: Mobility						
bed or chair bound					225	9.5
able to get out of bed / chair but does not go out					417	17.7
goes out					1715	72.8
% WL (mean, SD)	-8.0 (7.5)		-7.2 (6.7)		-5.8 (6.1)	
WL Categories						
±2.4% (weight stable)	1777	28.8	928	29.1	864	36.7
2.5-5.9%	1139	18.5	655	20.6	534	22.7
6.0-10.9%	1347	21.9	818	25.7	537	22.8
11.0-14.9%	816	13.2	376	11.8	211	9.0
≥15.0%	1082	17.6	409	12.8	211	9.0
BMI, kg/m2 (mean, SD)	25.0 (5.3)		23.5 (4.6)		24.6 (4.4)	
BMI Categories						
<20.0	935	15.2	707	22.2	278	11.8
20.0-21.9	863	14.0	551	17.3	337	14.3
22.0-24.9	1540	25.0	890	27.9	792	33.6
25.0-27.9	1289	20.9	571	17.9	528	22.4
≥28.0	1534	24.9	467	14.7	422	17.9
WL Grade						
Grade 0	1066	17.3	417	13.1	453	19.2
Grade 1	900	14.6	510	16.0	462	19.6
Grade 2	992	16.1	538	16.9	396	16.8
Grade 3	1766	28.7	973	30.5	697	29.6
Grade 4	1437	23.3	748	23.5	349	14.8
PGSGA Box 2: current food intake						
normal food	2112	34.3	-	-	-	-
normal food, less amount	2765	44.9	-	-	-	-
little solid food	588	9.5	-	-	-	-
only liquids or ONS	289	4.7	-	-	-	-
very little anything	407	6.6	-	-	-	-
***I*-VVAS**						
1	-	-	113	3.5	-	-
2	-	-	171	5.4	-	-
3	-	-	233	7.3	-	-
4	-	-	220	6.9	-	-
5	-	-	481	15.1	-	-
6	-	-	212	6.7	-	-

7	-	-	281	8.8	-	-
8	-	-	229	7.2	-	-
9	-	-	53	1.7	-	-
10	-	-	1193	37.4	-	-
MNA Section A: food intake past 3 months						
severe decrease	-	-	-	-	267	11.3
moderate decrease	-	-	-	-	1000	42.4
no decrease	-	-	-	-	1090	46.2

BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; ; *I*-VVAS, *Ingesta*-Verbal/Visual Analogue Scale; MNA, mini-nutrition assessment; N, number; PG-SGA, Patient-Generated Subjective Global Assessment; SD, standard deviation; WL, weight loss

*Upper gastrointestinal (esophageal, stomach, pancreas, liver, biliary tract, small bowel); lower gastrointestinal (colon, rectum, anus); genitourinary (kidney, bladder, adrenal, prostate, testes, penis); Other (gynecological, hematological, peritoneum, unknown, thyroid)

†based on AJCC version 6 or 7

(-) indicates there is no data for these fields

Table 5-3. Mean percent (%) weight loss by category of food intake for each measurement tool.

Categories for severity of reduced food intake				Comparison between categories of food intake within each assessment tool	Mean differences in %WL between food intake assessments tools for each category of food intake			Comparisons between food intake assessment tools for each category of food intake
PG-SGA		**N**	**Mean %WL (SD)**	**P-Value***	***I*-VVAS[a]**	**MNA[b]**	**PG-SGA[c]**	**P-Value***
●	severely reduced	1284	-12.2 (7.8)	■◆● <0.001	1.3	0.0		[a] P<0.05
◆	moderately reduced	2765	-8.9 (7.2)		1.0	1.8		[a,b,c] P<0.05
■	normal	2112	-4.1 (5.8)		0.1	0.3		[b] P<0.05
***I*-VVAS**								
●	severely reduced	737	-10.9 (7.2)	■◆● <0.001		-1.3	-1.3	[a, b] P<0.05
◆	moderately reduced	1256	-7.9 (6.3)			0.8	-1.0	[a,b,c] P<0.05
■	normal	1193	-4.0 (5.1)			1.0	-0.1	[b] P<0.05
MNA								
●	severely reduced	267	-12.2 (7.8)	■◆● <0.001	1.3		0.0	[a] P<0.05
◆	moderately reduced	1000	-7.1 (5.4)		-0.8		-1.8	[a,b,c] P<0.05
■	normal	1090	-3.0 (4.4)		-1.0		-1.1	[a,c] P<0.05
Overall								
●	severely reduced	2288	-12.1 (11.5)	■◆● <0.001				
◆	moderately reduced	5021	-8.3 (8.1)					
■	normal	4395	-3.8 (5.3)					

MNA, Mini-Nutrition Assessment; PG-SGA, Patient-Generated Subjective Global Assessment; *I*-VVAS, *Ingesta* Verbal/Visual Analogue Scale; WL, weight loss *Comparison of means with One-way ANOVA

Table 5-4. Data from three multivariable multinomial logistic regression (MLR) models highlighting the association between assessments of food intake and cancer-associated weight loss (WL).

Values for Food Intake Categories from Fully Adjusted Multivariable MLR Analysis													
PG-SGA MLR model[1]		**WL 2.5-5.9% N= 1139 (28.8%)**			**WL 6.0-10.9% N= 1347 (21.9%)**			**WL 11.0-14.9% N= 816 (13.2%)**			**WL ≥15.0% N= 1082 (17.6%)**		
Current Food Intake	**N (%)**	**β (SE)**	**OR (95% CI)**	**P-Value**	**β (SE)**	**OR (95% CI)**	**P-Value**	**β (SE)**	**OR (95% CI)**	**P-Value**	**β (SE)**	**OR (95% CI)**	**P-Value**
severely reduced*	1284 (20.8)	1.09 (0.14)	2.98 (2.26-3.92)	<0.001	1.79 (0.13)	5.98 (4.59-7.78)	<0.001	2.37 (0.16)	10.70 (7.85-14.58)	<0.001	2.73 (0.16)	15.27 (11.25-20.73)	<0.001
normal food, reduced amount	2765 (44.9)	0.66 (0.09)	1.94 (1.63-2.30)	<0.001	1.08 (0.09)	2.93 (2.46-3.50)	<0.001	1.45 (0.12)	4.25 (3.36-5.38)	<0.001	1.61 (0.12)	5.02 (3.95-6.38)	<0.001
normal food, normal amount	2112 (34.3)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
I-VVAS MLR model[2]		**WL 2.5-5.9% N= 655 (20.6%)**			**WL 6.0-10.9% N= 818 (25.7%)**			**WL 11.0-14.9% N= 376 (11.8%)**			**WL ≥15.0% N= 409 (12.8%)**		
Current Food Intake	**N (%)**	**β (SE)**	**OR (95% CI)**	**P-value**	**β (SE)**	**OR (95% CI)**	**P-value**	**β (SE)**	**OR (95% CI)**	**P-value**	**β (SE)**	**OR (95% CI)**	**P-value**
severely reduced intake (scores 1-4)	736 (23.1)	0.86 (0.18)	2.37 (1.68-3.35)	<0.001	1.53 (0.16)	4.62 (3.36-6.37)	<0.001	2.13 (0.21)	8.41 (5.63-12.58)	<0.001	2.67 (0.22)	14.36 (9.28-22.23)	<0.001
moderately reduced intake (scores 5-9)	1256 (39.4)	0.82 (0.12)	2.28 (1.79-2.90)	<0.001	1.13 (0.12)	3.10 (2.45-3.92)	<0.001	1.45 (0.17)	4.25 (3.04-5.94)	<0.001	1.73 (0.20)	5.62 (3.83-8.26)	<0.001
normal (score 10)	1193 (37.5)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
MNA MLR model[3]		**WL 2.5-5.9% N=534 (22.7%)**			**WL 6.0-10.9% N=537 (22.8%)**			**WL 11.0-14.9% N=211 (9.0%)**			**WL ≥15.0% N=211 (9.0%)**		
Past Food Intake	**N (%)**	**β (SE)**	**OR (95% CI)**	**P-value**	**β (SE)**	**OR (95% CI)**	**P-value**	**β (SE)**	**OR (95% CI)**	**P-value**	**β (SE)**	**OR (95% CI)**	**P-value**
severely	267	0.78	2.17	0.007	1.93	6.87	<0.001	2.28	9.73	<0.001	3.29	26.86	<0.001

reduced	(11.3)	(0.29)	(1.24-3.80)		(0.26)	(4.12-11.46)		(0.31)	(5.33-17.75)		(0.32)	(14.29-50.49)	
moderately reduced	1000 (42.4)	1.32 (0.13)	3.74 (2.89-4.83)	<0001	2.00 (0.14)	7.38 (5.57-9.78)	<0.001	1.78 (0.20)	5.94 (3.99-8.86)	<0.001	1.95 (0.25)	7.05 (4.29-11.60)	<0.001
not reduced	1090 (46.2)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	

β, beta coefficient; ; *I*-VVAS, *Ingesta*-verbal/visual analogue scale, MNA, Mini-Nutrition Assessment; MLR, multinomial logistic regression; N, number; OR, odds ratio; PGSGA, Patient-generated subjective global assessment; SE, standard error; WL, weight loss

*Severely reduced includes the following PG-SGA categories (little solid food, only liquids/oral nutritional supplements, very little of anything)

[1]PG-SGA MLR Model - Reference weight stable (+/- 2.4%) N=1777 (28.8%); Intercept only model: –2 log likelihood (LL)=18682.909, AIC 18690.909; Final Model: -2LL=16403.448, AIC=16555.448, $\chi 2$=2279.461 (df=72), P<0.001; Pseudo R2 (Nagelkerke) = 0.323; Pearson goodness-of-fit P=0.063

[2]*I*-VVAS MLR Model - Reference weight stable (+/-2.4%) N=928 (21.9%); Intercept only model: -2 LL=9671.159, AIC=9679.159; Final Model: -2LL=8658.277, AIC=8818.277, $\chi 2$=1012.883 (df=76), P<0.001; Pseudo r2 (Nagelkerke)=0.285; Pearson goodness-of-fit P=0.792

[3]MNA MLR Model - Reference weight stable (±2.4%) N=864 (36.7%); Intercept only model: -2 log likelihood (LL)= 6755.457, AIC 6763.457; Final Model: -2LL=5533.028, AIC=5677.028, $\chi 2$=1222.429 (df=68), P<0.001; Pseudo R2 (Nagelkerke)=0.427, Pearson goodness-of-fit P=0.198

Table 5-5. The crosstabulation for categories of weight loss (WL) by categories of food intake (FI) for each of the food intake assessment tools: PG-SGA, *I*-VVAS, MNA

WL Categories		PG-SGA FI Categories				I-VVAS FI Categories				MNA* FI Categories			
		Severe	**Moderate**	**Normal**	**Total**	**Severe**	**Moderate**	**Normal**	**Total**	**Severe**	**Moderate**	**Normal**	**Total**
≥ -15.0%	N	426_a	532_b	124_c	1082	195_a	168_b	46_c	409	95_a	89_b	27_c	211
	% within WL Categories	39.4%	49.2%	11.5%	100%	47.7%	41.1%	11.2%	100%	45.0%	42.2%	12.8%	100%
	% within FI Categories	33.2%	19.2%	5.9%	17.6%	26.5%	13.4%	3.9%	12.8%	35.6%	8.9%	2.5%	9.0%
	% of Total	6.9%	8.6%	2.0%	17.6%	6.1%	5.3%	1.4%	12.8%	4.0%	3.8%	1.1%	9.0%
-11.0 to -14.9%	N	257_a	431_b	128_c	816	138_a	169_b	69_c	376	46_a	116_b	49_c	211
	% within WL Categories	31.5%	52.8%	15.7%	100%	36.7%	44.9%	18.4%	100%	21.8%	55.0%	23.2%	100%
	% within FI Categories	20.0%	15.6%	6.1%	13.2%	18.7%	13.5%	5.8%	11.8%	17.2%	11.6%	4.5%	9.0%
	% of Total	4.2%	7.0%	2.1%	13.2%	4.3%	5.3%	2.2%	11.8%	2.0%	4.9%	2.1%	9.0%
-6.0 to -10.9%	N	309_a	704_a	334_b	1347	207	376_a	235_b	818	68_a	340_b	129_c	537
	% within WL Categories	22.9%	52.3%	24.8%	100%	25.3%	46.0%	28.7%	100%	12.7%	63.3%	24.0%	100%
	% within FI Categories	24.1%	25.5%	15.8%	21.9%	28.1%	29.9%	19.7%	25.7%	25.5%	34.0%	11.8%	22.8%
	% of Total	5.0%	11.4%	5.4%	21.9%	6.5%	11.8%	7.4%	25.7%	2.9%	14.4%	5.5%	22.8%
-2.5 to -5.9%	N	167_a	530_b	442_b	1139	109_a	285_b	261_b	655	30_a	274_b	230_c	534
	% within WL Categories	14.7%	46.5%	38.8%	100%	16.6%	43.5%	39.8%	100%	5.6%	51.3%	43.1%	100%
	% within FI Categories	13.0%	19.2%	20.9%	18.5%	14.8%	22.7%	21.9%	20.6%	11.2%	27.4%	21.1%	22.7%
	% of Total	2.7%	8.6%	7.2%	18.5%	3.4%	8.9%	8.2%	20.6%	1.3%	11.6%	9.8%	22.7%

±2.4% (weight stable)	N	125_a	568_b	1084_c	1777	88_a	258_b	582_c	928	28_a	181_b	655_c	864
	% within WL Categories	7.0%	32.0%	61.0%	100%	9.5%	27.8%	62.7%	100%	3.2%	20.9%	75.8%	100%
	% within FI Categories	9.7%	20.5%	51.3%	28.8%	11.9%	20.5%	48.8%	29.1%	10.5%	18.1%	60.1%	36.7%
	% of Total	2.0%	9.2%	17.6%	28.8%	2.8%	8.1%	18.3%	29.1%	1.2%	7.7%	27.8%	36.7%
Total	N	1284	2765	2112	6161	737	1256	1193	3186	267	1000	1090	2357
	% within WL Categories	20.8%	44.9%	34.3%	100%	23.1%	39.4%	37.4%	100%	11.3%	42.4%	46.2%	100%
	% within FI Categories	100%	100%	100%	100%	100%	100%	100%	100%	100.0 %	100.0%	100.0%	100%
	% of Total	20.8%	44.9%	34.3%	100%	23.1%	39.4%	37.4%	100%	11.3%	42.4%	46.2%	100%

FI, food intake; MNA, Mini-Nutrition Assessment; N, number; PGSGA, Patient-generated subjective global assessment; *I*-VVAS, *Ingesta*-verbal/visual analogue scale; WL, weight loss

$_{a,b,c}$ Subscript letters denote significant differences ($P<0.05$; Pearson Chi-Square, Bonferroni correction) in column proportions between categories of food intake within each weight loss category for each assessment tool.

Chapter 6: The variable contribution of reduced food intake and systemic inflammation to cancer-associated weight loss

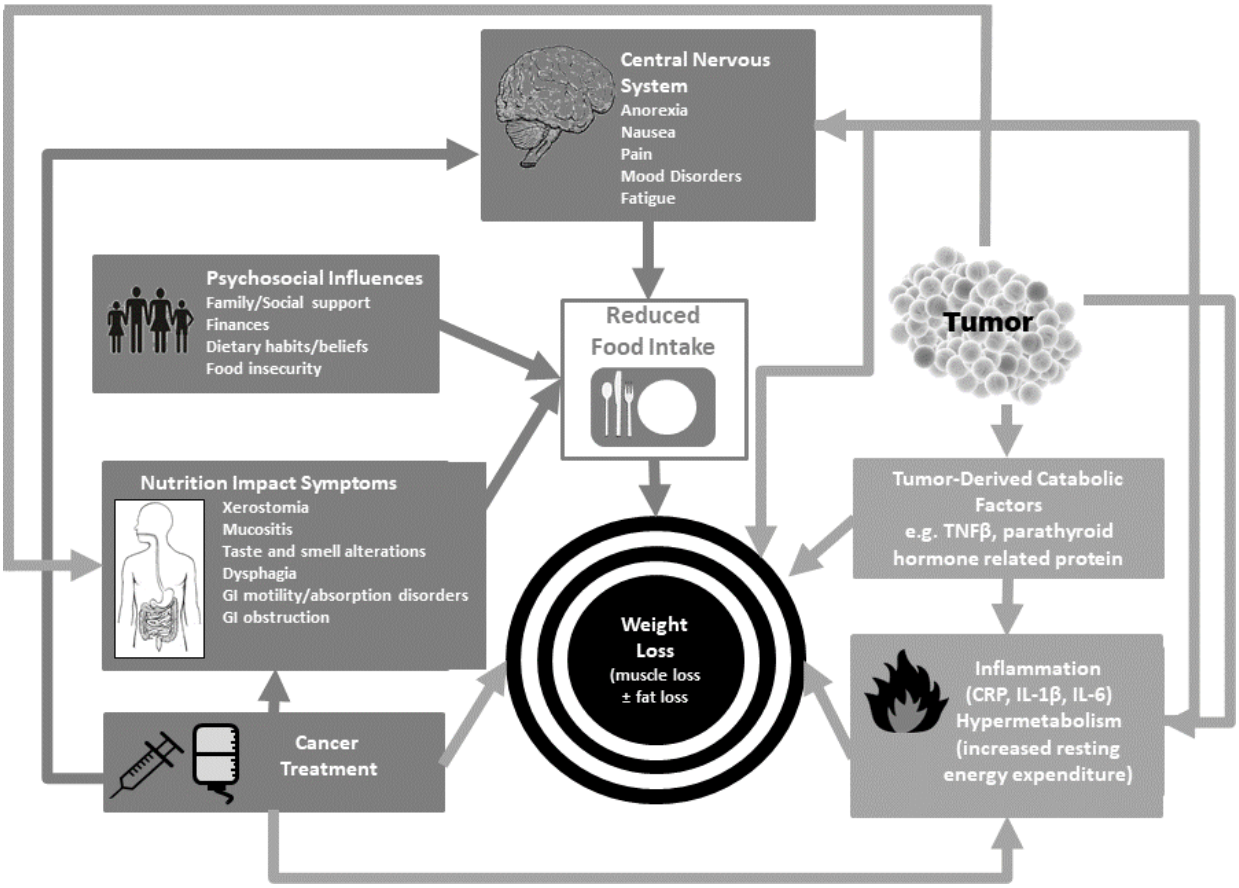
6.1 Introduction

Cancer cachexia is defined as a syndrome of involuntary weight loss (WL), which is characterized by the progressive loss of skeletal muscle, which can occur with or without loss of fat mass.[1] The etiology of cancer-associated WL is suggested to be driven by a variable combination of reduced food intake (FI) and altered metabolism. We previously demonstrated that reductions in FI independently associated with increased probability of WL in a multivariable regression model adjusted for covariates including age, sex, cancer site, cancer stage, performance status, and body mass index (BMI).[2] However, this model did not explain all the variation in WL, and one explanation was that we did not account for alterations in metabolism. We hypothesized that the addition of covariates related to altered metabolism would contribute to explaining the etiology of WL in cachectic patients.

Alterations in metabolism are a defining characteristic of cancer cachexia, and their manifestations are thought to explain why cancer cachexia cannot be fully reversed by nutrition support alone (Figure 6-1).[1] Alterations in metabolism arise from a variable combination of factors including tumor metabolism, tumor-derived catabolic factors, and pro-inflammatory mediators. The majority of our understanding about metabolic alterations in response to malignancy is from animal studies, which are not always consistent with findings in human subjects[3], and at present the identification and characterization of metabolic alterations in patients with cancer remains elusive. There is no consensus regarding a measure that best represents altered metabolism in patients with cancer. There is, however, clinical evidence suggesting an independent contribution of systemic inflammation (e.g. elevated C-reactive protein (CRP)), hypermetabolism (i.e. increased energy expenditure), and tumor-derived factors

such as parathyroid hormone-related peptide (PTHrP) to an increased risk of cancer-associated WL.[4-6]

Figure 6-1. A conceptual diagram representing the pathophysiology of cancer cachexia



A conceptual diagram representing the pathophysiology of cancer cachexia**,** which is driven by a variable combination of two major etiologies: reduced food intake (FI) and altered metabolism.[1] There are many factors that conspire to cause involuntary WL in patients with cancer cachexia. Reductions in FI can be directly or indirectly related to the presence of the tumor e.g. nutrition impact symptoms due to location of the tumor in the gastrointestinal tract or development of symptoms in response to cancer therapies; decreased central drive to eat in the central nervous system in response to pro-inflammatory tumor-mediated factors, and/or cancer-related pain or nausea. Non-cancer related psychosocial factors can also act as barriers to FI e.g. mood disorders, food insecurity, lack of social support for assistance with meal preparation, poor dietary habits, etc. Metabolic alterations (represented by light grey boxes) are also key drivers of cancer-associated WL, and include tumor-mediated catabolic factors that act directly on skeletal muscle and adipose tissue, or via pro-inflammatory factors arising from interactions with the immune system. Tumor metabolism and inflammation lead to hypermetabolism resulting in increased proteolysis and lipolysis to support the increased energy requirements. Inflammation in the CNS can elicit the production of glucocorticoids from the adrenal glands, which acts directly on skeletal muscle. However, the specific nature of these metabolic alterations continues to evolve and requires further elucidation. Ultimately our understanding of the factors contributing to cancer-associated WL will only be fully described when both reductions in FI and alterations in metabolism are accounted for. (figure adapted from Martin & Kubrak[7], Baracos et al.[3])

CRP is the most common clinically available indicator of systemic inflammation reported in the cachexia literature, and has been included as a diagnostic criterion in prior definitions of cachexia.[8,9] CRP has also been demonstrated to be an important prognostic marker in oncology, and when combined with clinical characteristics such as WL, performance status (PS), and FI improves the identification of patient subsets with worse prognosis and who are unlikely to benefit from treatment.[9-17] Threshold values for CRP (≥5, ≥10 mg/L) commonly used in the oncology setting have been defined based on their association to overall survival, and while weight losing cancer patients often have higher CRP levels, values of CRP that relate optimally to WL as an outcome have not been extensively studied.[6,8,9,18,19]

Our international research groups have aggregated clinical data of patients with advanced cancers who are at risk of cancer cachexia to create the International Cancer Cachexia Data Repository (ICCDR).[2,20,21] Data from the ICCDR was used for this analysis, to address the following primary objectives: 1) evaluate the relationship between CRP and WL, and determine optimal CRP values for risk stratification based on WL, 2) evaluate the contribution of CRP *and* FI as explanatory variables for WL. A secondary objective was to determine if we could stratify patients according to overall survival based on the combination of CRP, FI, and WL.

6.2 Methods

6.2.1 Study population

Patients were selected from the ICCDR. A detailed description of the ICCDR has been provided elsewhere.[2,20,21] Briefly, the ICCDR is an international effort to pool original study data that has been collected at several points of referral for nutrition care within the oncology setting: at entry to investigational cachexia clinical trials, at cancer diagnosis as standard of care, and at entry to supportive/palliative care programs. This analysis includes original study data that were

prospectively collected from 2002 to 2014, under the auspices of human ethics approvals from their respective institutions. To be included in the current analysis, patients required complete data for the following: demographic and clinical data (age, sex, cancer diagnosis (ICD-10) and AJCC stage (version 6.0 prior to 2011, version 7.0 thereafter), performance status (PS), body mass index (BMI), WL history), and a nutrition risk assessment that included a measure of FI and serum CRP (g/ml). For each original study cohort, high sensitivity serum CRP was collected at the same time as the nutrition risk assessment was completed, and analyzed in laboratories with automated analyzers that were standardized according to international certified reference material.[22]

We did not select patients with weight gain (e.g. ≥2.5%) for the reasons that our primary outcome is cancer-associated WL, and we previously showed that weight gaining patients in this population had different prognosis from weight stable patients.[23]

6.2.2 Assessments of food intake and C-reactive protein

Patient-reported FI was collected from one of two nutrition risk assessment tools: the Patient Generate Subjective Global Assessment (PG-SGA), and the *Ingesta*-Verbal/Visual Analogue Scale (*I*-VVAS). We previously demonstrated that each of these measurements scales could be combined into three distinct FI categories: normal, moderately, or severely reduced FI based on their association to %WL.[2]

6.2.3 Statistics

Summary statistics were used to describe patients. The primary outcome was WL history, recoded as the percentage of WL over the previous 6 months calculated as:

$$\%\ weight\ loss\ (\%WL) =$$

*[(current weight in kg -previous weight in kg)/previous weight in kg]*100*

Statistical analysis was carried out in three parts:

1) The relationship between serum CRP (mg/L) and %WL was evaluated, and optimal values were defined for CRP that related to %WL as follows: the distribution of CRP values was divided into deciles (i.e. 10 equal groups) and the mean %WL was calculated for each decile to explore the impact of increasing CRP on WL. A similar approach to define optimal values for WL and BMI has been previously reported.[21] Deciles were compared based on differences in mean %WL using one-way ANOVA (post-hoc tests: Games-Howell). Deciles of CRP that did not have statistical differences for mean %WL were combined in to categories.

2) Multinomial logistic regression (MLR) evaluated the association between CRP and %WL adjusted for other variables likely to associate with WL including: FI, age (continuous), sex, cancer site (ICD-10), cancer stage (AJCC version 6.0 or 7.0), PS (ECOG), and BMI (<20.0, 20.0-21.9, 22.0-27.9, ≥28.0)).[21] MLR is an extension of logistic regression and is a robust statistical approach when the dependent variable has more than two categories. The dependent variable in this analysis is WL, which has 5 categories of severity (±2.4%, 2.5-5.9%, 6.0-10.9%, 11.0-14.9%, and ≥15.0%), as outlined in the diagnostic criteria for cancer-associated WL.[21] The reference group for the dependent variable was weight stable (±2.4%), to which all other categories of WL were compared. Results are reported as odds ratios (OR) and 95% confidence intervals (CI).

3) Survival analysis evaluated differences in overall survival (OS) for patients stratified by categories of CRP, FI, and %WL. OS was defined as the number of months a patient survived between the date of nutrition risk assessment and the date of death; patients were observed until

death or censored at their last confirmed contact with the health care system. Survival analysis was performed with the Kaplan-Meier method (comparisons with Cox-Mantel log-rank tests).

All analyses were completed using IBM SPSS Statistics for Windows version 23.0 (SPSS, Chicago, IL) and were considered statistically significant at the $P<0.05$ level. Figures were drawn with GraphPad Prism version 7.04 for Windows (GraphPad Software, La Jolla California USA).

6.3 Results

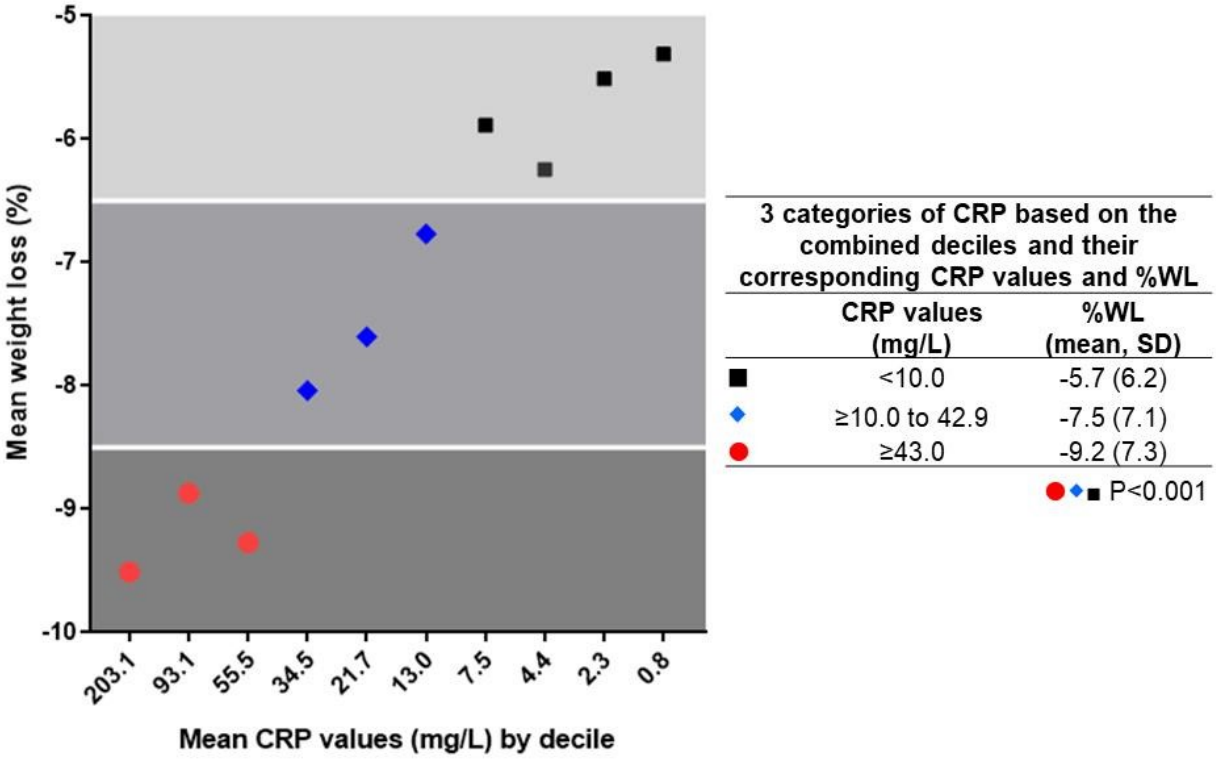
6.3.1 Patient characteristics

A total of 3443 patients were selected and included in this analysis (Table 6-1). Patients represented patients with cancer cachexia: they had predominantly locally advanced or metastatic disease, with an average weight loss of -7.3% ±7.3 over the previous 6 months.

6.3.2 CRP and cancer-associated weight loss

The relationship between CRP and % WL was examined by dividing serum CRP values (mg/L) into deciles (i.e. 10 equal groups), and calculating the mean %WL for each decile (Figure 6-1).

Figure 6-1. Mean %WL by decile of serum CRP (mg/L) values.



A graph depicting the mean %WL by decile of serum CRP (mg/L) values (mean CRP values are indicated for each decile). Different colored symbols (●◆■) represent significant differences in mean %WL (P<0.05) between deciles; deciles with similarly colored symbols were not significantly different, and were combined into three distinct CRP categories, highlighted by different shades of gray. The legend indicates the corresponding range of CRP vales and mean % WL for each of the 3 CRP categories.

There were three distinct subsets with significant differences (P<0.001) in mean %WL (Figure 6-1). Deciles of CRP were therefore combined, and 3 categories of CRP were defined (<10.0 mg/L, 10.0-42.9 mg/L, and ≥43.0 mg/L), representing increased CRP values that associated with increased WL. The values and mean % WL for each CRP category are listed in Figure 6-1.

The association between categories of CRP and increased severity of WL was evaluated with MLR analysis. The univariable MLR analysis can be found in Appendix V Suppl Table 1. In the multivariable analysis, the MLR model was adjusted for age, sex, cancer diagnosis, cancer stage, PS, BMI, and categories of food intake (Table 6-2). At the multivariable level, age and

cancer stage were not associated with WL and were not included in the final MLR model. In the final MLR model, both reduced FI and CRP independently associated with increased probability of WL, demonstrating progressively increasing ORs as the severity of WL increased. Table 6-2 presents the adjusted odds ratio (OR) of experiencing WL with different levels of severity, for patients with moderate or severely reduced FI compared to those with normal intake, and with moderate (10.0-42.9 mg/L) or high (≥43.0 mg/L) CRP values compared to CRP values <10.0 mg/L. CRP did not associate with WL below 6%, whereas reductions in FI had strong associations within each category of WL (i.e. larger beta coefficients and ORs as severity of WL increased). Even moderately reduced FI had stronger associations to WL (ORs from 2.4 to 4.6, P<0.001) compared with moderate (ORs from 1.3 to 1.8, P<0.05) or high (ORs from 1.7 to 2.4, P<0.001) CRP values. Other covariates that were significantly associated with increased probability of WL included cancer diagnosis (lung, head & neck, upper and lower GI cancers), PS ≥1, male sex, and BMI <25.0.

Our MLR model, adjusted for sex, cancer diagnosis, performance status, BMI, reductions in FI *and* CRP did not explain all the variation in WL. Patients experienced variable combinations of FI and CRP values across WL categories; overall, patients with elevated CRP values (>10 mg/L) and/or reduced FI (moderate or severe), had a greater % of patients with WL ≥6.0% compared to those with normal FI (37% vs. 12%, P<0.001, Table 6-3). For example, a subset of patients (N=384, 10%) reported normal FI *and* CRP values <10.0 mg/L but also had some degree of unexplained WL (i.e. WL >2.4%; Table 6-3). It is possible that other unaccounted factors (e.g. tumor mediated pro-catabolic factors, increased energy expenditure) may explain WL in these patients.

6.3.3 Risk stratification for overall survival

Median overall survival (OS) for this patient cohort was 9.5 months (95% CI 8.9-10.1; Table 6-1). The combined impact of increased CRP values, reduced FI, and WL on OS was evaluated. Patients were stratified by WL category (±2.4%, 2.5-5.9%, 6.0-10.9%, 11.0-14.9%, ≥15.0%), and for each WL category a 3x3 matrix was created including 3 categories of FI (normal, moderately, and severely reduced) , and 3 categories of CRP (< 10 mg/L, 10-42.9 mg/L, ≥43.0 mg/L). There was a total of 9 combinations per WL category for which median OS was calculated (Table 6-3). Patients with weight stability, normal FI, and CRP values <10 mg/L had the longest median OS of 25.9 months (95% CI 20.8-31.0). In each WL category, patients with severely reduced FI and CRP values >43 mg/L had the lowest median OS ranging from 1.1 to 4.1 months (Table 6-3).

6.4 Discussion

Cancer cachexia is driven by a variable combination of two major etiologies, reduced FI and altered metabolism.[1] We had previously demonstrated that patient-reported reductions in FI associated with increased probability of WL independent of age, sex, cancer diagnosis and stage, and performance status.[2] In this analysis, our regression model did not explain all the variation in WL, and a possible explanation was that we had not accounted for alterations in metabolism. In the ICCDR, the only marker of metabolic alteration available for evaluation as an explanatory factor for WL was CRP (i.e. systemic inflammation). We characterized the relationship between CRP and WL, and defined three categories for CRP (<10; 10-43; ≥43 mg/L) based on values related to increased WL; patients with CRP <10 mg/L had the lowest WL (mean 5.7±6.2%). CRP values of ≥10 are a common threshold used in oncology for prognostication of survival, and here we demonstrated they were also associated with increased WL.[17]

In an adjusted MLR analysis, both CRP and reduced FI independently associated with increased probability of WL, as did other covariates including cancer diagnoses of the lung, head & neck, and gastrointestinal tract, PS ≥1, male sex, and BMI <25.0. These covariates contributed to the variation in WL explained by our model, and likely capture other reasons for WL beyond what we can measure with FI and CRP. Cancer diagnoses involving the GI tract including head & neck and upper and lower GI tract, as well as their treatments (e.g. GI toxicity) can impair ingestion, digestion, and absorption of nutrients, contributing to WL and not captured by our FI measures. Similarly, CRP may not capture the full scope of the underlying inflammatory processes contributing to WL in different tumor types, treatments, or in some cases behaviors (e.g. smoking).[24,25] As well, tumor invasion of metabolically active organ tissue (e.g. liver) may lead to increased energy expenditure (i.e. hypermetabolism), which represents an additional contribution to WL beyond measures of FI and CRP.[26,27] Reduced performance status may contribute to WL and muscle atrophy as a result of disuse and fatigue in response to cancer treatment and inflammation in the central nervous system.[3,27] Sex differences in immune response may, in part, contribute to higher WL in men.[28] For example, estrogen can modulate inflammatory responses (e.g. inhibit production of interleukin-6, NfκB and tumor necrosis factor-α), which have been linked to WL and muscle wasting in cancer patients, and are not captured by CRP.[28,29]

Some of the unexplained variation in WL may also be due to methodological limitations. There are discrepancies between the time frames for which reduced FI (e.g. current) was recorded in relation to the time frame over which WL occurred (e.g. previous 6 months). We do not know how FI and CRP values fluctuated over the period of time period during which WL occurred. These patterns may be revealed with longitudinal data collected using repeated

assessments. Some of the unexplained variation in WL may be the result of an incomplete set of relevant covariates in our statistical models. In cancer cachexia, the contribution of FI and altered metabolism to WL are painted as a spectrum; most patients experience both to some degree, and in others it is reduced FI or hypermetabolism or tumor-derived catabolic factors that have the predominant effect on WL.[30] We do not currently have a full accounting of factors that contribute to altered metabolism including assessments of energy expenditure (overall and of the tumor), measures of tumor-derived catabolic factors, or information about the tumor or cancer treatment. In our analysis, cancer stage did not associated with WL but information about tumor mass and metabolism may improve our understanding about the factors contributing to WL.[26,31] At present, clinical data representing some of these factors is limited, although there is evidence to suggest they are important to the etiology of WL. A recent meta-analysis suggests there is an overall small increase (8-9%) in the resting energy expenditure (REE) of cancer patients compared to healthy controls, with larger elevations in cancers of the head & neck, esophageal, pancreas and liver.[32] Two longitudinal studies demonstrated that patient's positive for PTHrP, which is thought to increase REE through adipose tissue browning, independently increased the risk of weight loss when adjusted for CRP, PS, cancer stage, albumin, and serum calcium.[4,5] There is a long list of catabolic factors arising from animal studies, and more are currently being investigated but we do not have confirmatory studies or values for these factors in humans.[3] A way forward would be to conduct prospective studies in a single tumor group with the aim to characterize factors that are likely to related to reductions in FI and metabolic alterations (REE, inflammation, tumor-mediated catabolic factors, cancer treatment) leading to cancer cachexia.

In oncology, patients are faced with a life limiting disease, and we therefore require information about their prognosis to determine the most appropriate type of clinical

interventions.[33-36] CRP continues to be an important prognostic indicator in this patient cohort, and when combined with reduced FI, subsets of patients are identified with significantly reduced OS across different severities of WL (Table 6-3). This information is clinically available, and may facilitate identification of individuals entering end of life phase, which requires important consideration of treatments and care planning. These results suggest clinical assessments of patient-reported FI and a widely available clinical marker of systemic inflammation are associated with cancer-associated WL and provide useful prognostic information.

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Table 6-1. Patient characteristics

Variables	N	%
Region		
Canada	513	14.9
Europe	2930	85.1
Sex		
Male	1873	54.4
Female	1570	45.6
Age, years (mean, SD)	63.6 (12.3)	
Status		
Censored	754	21.9
Dead	2689	78.1
Overall Survival, months (median, 95% CI)	9.5 (8.9-10.1)	
Cancer Diagnosis*		
Head & neck	307	8.9
Breast	429	12.5
Upper gastrointestinal	685	19.9
Lower gastrointestinal	276	8.0
Genitourinary organs	607	17.6
Respiratory	786	22.8
Other	353	10.3
Cancer Stage†		
1	86	2.4
2	177	5.1
3	482	14.0
4	2698	78.4
ECOG PS		
PS 0	734	21.3
PS 1	1081	31.4
PS 2	1058	30.7
PS 3	546	15.9
PS 4	24	0.7
% WL (mean, SD)	-7.3 (7.0)	
WL Categories		
±2.4% (weight stable)	1019	29.6
2.5-5.9%	711	20.7
6.0-10.9%	822	23.9
11.0-14.9%	390	11.3
≥15.0%	501	14.6
BMI, kg/m2 (mean, SD)	24.1 (4.9)	

BMI Categories		
<20.0	655	19.0
20.0-21.9	566	16.4
22.0-24.9	953	27.7
25.0-27.9	646	18.8
≥28.0	623	18.1
WL Grade‡		
Grade 0	512	14.9
Grade 1	542	15.7
Grade 2	590	17.1
Grade 3	1028	29.9
Grade 4	771	22.4
Reduced Food Intake		
normal	686	19.9
moderately reduced	1380	40.1
severely reduced	1377	40.0
Food Intake Tool Used		
PG-SGA	1001	29.1
I-VVAS	2247	70.9
CRP, mg/L (mean, SD)	43.6 (64.3)	
CRP_{log} (mean, SD)	2.7 (1.7)	
CRP <10 mg/L	1375	39.9
CRP ≥10 mg/L	2068	60.1

BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; *I*-VVAS, *Ingesta*-Verbal/Visual Analogue Scale; N, number; PG-SGA, Patient-Generated Subjective Global Assessment; SD, standard deviation; WL, weight loss

*Upper gastrointestinal (esophageal, stomach, pancreas, liver, biliary tract, small bowel); lower gastrointestinal (colon, rectum, anus); genitourinary (kidney, bladder, adrenal, prostate, testes, penis); Other cancers (gynecological, hematological, peritoneum, unknown, thyroid)

†based on AJCC version 6 or 7

‡based on WL grades by Martin et al.[4]

Table 6-2. A multivariable multinomial logistic regression model to evaluate the association of CRP and food intake to weight loss.

Variables in model	N (%)	WL 2.5-5.9% N= 711 (20.7%)			WL 6.0-10.9% N= 822 (23.9%)			WL 11.0-14.9% N= 390 (11.3%)			WL >=15.0% N= 501 (14.6%)		
		β (SE)	OR (95% CI)	P-Value	β (SE)	OR (95% CI)	P-Value	β (SE)	OR (95% CI)	P-Value	β (SE)	OR (95% CI)	P-Value
CRP Categories													
≥43.0 mg/L	1032 (30.0)	0.18 (0.14)	1.19 (0.91-1.56)	0.193	0.51 (0.13)	1.67 (1.29-2.15)	<0.001	0.56 (0.16)	1.75 (1.27-2.42)	<0.001	0.87 (0.16)	2.39 (1.74-3.29)	<0.001
10.0-42.9 mg/L	1036 (30.1)	0.20 (0.12)	1.22 (0.97-1.55)	0.088	0.26 (0.12)	1.30 (1.03-1.65)	0.028	0.32 (0.16)	1.37 (1.01-1.87)	0.045	0.59 (0.16)	1.80 (1.32-2.45)	<0.001
<10.0 mg/L	1375 (39.9)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
Current Food Intake													
severely reduced intake	686 (19.9)	0.92 (0.17)	2.52 (1.80-3.53)	<0.001	1.37 (0.16)	3.94 (2.87-5.40)	<0.001	2.02 (0.20)	7.51 (5.12-11.02)	<0.001	2.29 (0.19)	9.84 (6.76-14.33)	<0.001
moderately reduced intake	1380 (40.1)	0.87 (0.11)	2.40 (1.92-2.99)	<0.001	1.12 (0.11)	3.07 (2.46-3.84)	<0.001	1.36 (0.16)	3.90 (2.88-5.29)	<0.001	1.52 (0.16)	4.59 (3.37-6.24)	<0.001
normal	1377 (40.0)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
Cancer Diagnosis													
respiratory	786 (22.8)	0.43 (0.19)	1.54 (1.06-2.25)	0.025	0.27 (0.19)	1.32 (0.91-1.90)	0.141	0.65 (0.26)	1.91 (1.15-3.17)	0.012	0.64 (0.27)	1.90 (1.12-3.22)	0.017
other	353 (10.3)	0.05 (0.22)	1.06 (0.69-1.61)	0.800	-0.18 (0.21)	0.83 (0.55-1.25)	0.379	0.17 (0.29)	1.19 (0.68-2.09)	0.544	0.15 (0.30)	1.17 (0.65-2.08)	0.603
genitourinary	607 (17.6)	0.34 (0.20)	1.41 (0.96-2.07)	0.081	0.01 (0.19)	1.01 (0.70-1.47)	0.947	0.24 (0.26)	1.27 (0.76-2.12)	0.362	0.43 (0.26)	1.54 (0.92-2.58)	0.099

upper GI	685 (19.9)	0.58 (0.20)	1.79 (1.20-2.66)	0.004	0.45 (0.19)	1.56 (1.07-2.28)	0.022	1.04 (0.26)	2.83 (1.70-4.70	<0.001	1.63 (0.26)	5.11 (3.07-8.49)	<0.001
lower GI	276 (8.0)	0.24 (0.24)	1.27 (0.80-2.04)	0.314	0.26 (0.23)	1.30 (0.83-2.02)	0.251	0.72 (0.30)	2.06 (1.15-3.70)	0.016	0.59 (0.31)	1.80 (0.97-3.34)	0.062
head & neck	307 (8.9)	0.33 (0.25)	1.39 (0.85-2.27)	0.183	0.53 (0.23)	1.70 (1.08-2.69)	0.022	0.63 (0.32)	1.87 (1.00-3.49)	0.050	1.25 (0.31)	3.50 (1.92-6.37)	<0.001
breast	429 (12.5)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
ECOG PS													
PS 3-4	570 (16.6)	0.12 (0.19)	1.12 (0.77-1.63)	0.541	0.44 (0.19)	1.56 (1.07-2.25)	0.019	0.54 (0.24)	1.72 (1.07-2.77)	0.026	0.93 (0.25)	2.54 (1.57-4.10)	<0.001
PS 2	1058 (30.7)	0.12 (0.15)	1.13 (0.83-1.53)	0.432	0.67 (0.16)	1.95 (1.44-2.64)	<0.001	0.75 (0.21)	2.13 (1.42-3.18)	<0.001	0.99 (0.22)	2.69 (1.77-4.11)	<0.001
PS 1	1081 (31.4)	0.30 (0.14)	1.35 (1.03-1.77)	0.032	0.52 (0.15)	1.69 (1.27-2.26)	<0.001	0.53 (0.20)	1.69 (1.14-2.51)	0.009	0.68 (0.21)	1.97 (1.30-2.99)	0.001
PS 0	734 (21.3)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
Sex													
male	1873 (54.4)	0.20 (0.11)	1.23 (0.98-1.53)	0.072	0.20 (0.11)	1.23 (0.98-1.53)	0.069	0.45 (0.14)	1.57 (1.19-2.08)	0.002	0.70 (0.14)	2.02 (1.53-2.66)	<0.001
female	1570 (45.6)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
BMI Categories (kg/m2)													
<20.0	655 (19.0)	0.60 (0.18)	1.82 (1.28-2.59)	0.001	0.96 (0.18)	2.62 (1.85-3.70)	<0.001	1.86 (0.24)	6.42 (3.98-10.36)	<0.001	2.17 (0.21)	8.75 (5.76-13.29)	<0.001
20.0 to 21.9	566 (16.4)	0.37 (0.17)	1.45 (1.04-2.02)	0.029	0.92 (0.17)	2.52 (1.82-3.49)	<0.001	1.48 (0.24)	4.40 (2.74-7.06)	<0.001	0.94 (0.23)	2.55 (1.64-3.98)	<0.001

22.0 to 24.9	953 (27.7)	0.45 (0.14)	1.57 (1.19-2.07)	0.002	0.59 (0.15)	1.80 (1.35-2.40)	<0.001	1.18 (0.22)	3.24 (2.09-5.02)	<0.001	0.75 (0.20)	2.12 (1.42-3.15)	<0.001
25.0 to 27.9	646 (18.8)	0.11 (0.15)	1.12 (0.83-1.51)	0.460	0.32 (0.16)	1.38 (1.01-1.88)	0.040	0.73 (0.24)	2.08 (1.30-3.33)	0.002	-0.05 (0.23)	0.95 (0.60-1.51)	0.839
≥28.0	643 (18.1)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	

β, beta coefficient; BMI, body mass index; CRP, C-reactive protein; MLR, multinomial logistic regression; N, number; OR, odds ratio; PS, performance status; SE, standard error; WL, weight loss

MLR Model adjusted for age, sex, cancer diagnosis, cancer stage, performance status, and BMI - Reference weight stable (±2.4%) N=1019 (29.6%); Intercept only model: –2 log likelihood (LL)=10598.216, AIC 10606.21; age (P=0.259) and cancer stage (P=0.843) were not significant at the multivariable level and not included in the final model.

Final Model: -2LL=9592.50, AIC=9744.50, $\chi 2$=1005.71 (df=72), P<0.001; Pseudo R^2: Nagelkerke=0.265, Cox and Snell=0.253, McFadden's=0.094, Pearson goodness-of-fit P=0.694

Table 6-3. Median overall survival (OS) for patients stratified by categories of weight loss (WL), food intake (FI), and CRP categories

	WL Categories*														
	±2.4% N=1019 (29.6%)			2.5-5.9% N=711 (20.7)			6.0-10.9% N=822 (23.9%)			11.0-14.9% N=390 (11.3%)			WL ≥15.0% N=501 (14.6%)		
	CRP (mg/L) categories			CRP (mg/L) categories			CRP (mg/L) categories			CRP (mg/L) categories			CRP (mg/L) categories		
Food Intake Categories	**<10.0**	**10.0-42.9**	**≥43.0**	**<10.0**	**10.0-42.9**	**≥43.0**	**<10.0**	**10.0-42.9**	**≥43.0**	**<10.0**	**10.0-42.9**	**≥43.0**	**<10.0**	**10.0-42.9**	**≥43.0**
Normal															
N events/N	222/385	146/189	68/81	97/159	73/82	47/57	85/127	57/67	58/61	32/43	25/31	13/14	20/25	22/25	31/34
%N within WL category	37.8%	18.5%	7.9%	22.4%	11.5%	7.6%	15.5%	8.2%	7.4%	11.0%	7.9%	3.6%	5.0%	5.0%	6.8%
OS, months	25.9[a]	12.2[b]	5.6[c]	21.9[a]	11.9[a]	7.1[a]	19.0[a]	8.6[b]	4.9[c]	8.5[a]	9.9[a]	6.3b	9.2a	8.6a	5.0a
(95% CI)	(20.8-31.0)	(9.5-14.9)	(1.9-9.3)	(16.3-27.5)	(6.9-16.9)	(5.9-8.4)	(13.1-24.9)	(5.9-11.3)	(2.9-6.9)	(3.7-13.2)	(8.4-11.4)	(1.8-10.8)	(2.5-15.9)	(3.0-14.2)	(2.7-7.3)
Moderately reduced															
N events/N	76/117	68/81	73/80	82/118	89/112	72/82	91/132	105/127	121/132	36/56	41/51	64/71	44/58	64/72	87/91
%N within WL category	11.5%	7.9%	7.9%	16.6%	15.8%	11.5%	16.1%	15.5%	16.1%	14.4%	13.1%	18.2%	11.6%	14.4%	18.2%
OS, months	22.2[a]	10.7[b]	3.8[c]	19.7[a]	8.8[b]	5.0[c]	19.3[a]	8.1[b]	4.0[c]	13.8[a]	7.5[b]	3.5[c]	13.0[a]	6.4[b]	3.1[c]
(95% CI)	(14.9-29.5)	(8.6-12.8)	(1.8-5.8)	(16.2-23.2)	(6.8-10.9)	(3.6-6.5)	(13.5-25.1)	(5.9-10.3)	(3.2-4.8)	(4.6-23.0)	(4.9-10.1)	(2.6-4.3)	(6.8-19.2)	(5.5-7.3)	(1.5-4.7)
Severely reduced															
%N within WL category	2.2%	2.1%	4.2%	4.1%	4.4%	6.2%	4.3%	6.6%	10.6%	6.7%	8.7%	16.4%	8.6%	11.8%	18.8%
N events/N	13/22	16/21	41/43	24/29	28/31	36/44	23/35	46/54	78/87	17/26	29/34	59/64	34/43	53/59	85/94

%N within WL category	2.2%	2.1%	4.2%	4.1%	4.4%	6.2%	4.3%	6.6%	10.6%	6.7%	8.7%	16.4%	8.6%	11.8%	18.8%
OS, months	13.2[a]	12.1[a]	1.1[b]	8.7[a]	5.3[b]	2.2[b]	14.5[a]	6.2[b]	3.1[b]	14.4[a]	6.6[a,b]	4.1[b]	5.9[a]	5.2[a,b]	2.5[b]
(95% CI)	(11.5-14.9)	(0.0-24.8)	(0.6-1.6)	(6.1-11.3)	(3.8-6.8)	(0.0-5.0)	(10.5-18.5)	(5.1-7.3)	(2.3-3.9)	(0.0-30.5)	(5.1-8.1)	(2.5-5.7)	(4.8-7.0)	(3.8-6.6)	(1.7-3.3)
Overall															
OS, months	24.4	11.8	3.8	19.7	8.8	5.7	18.4	7.3	3.8	12.0	7.9	3.8	9.2	6	3.0
(95% CI)	(20.0-28.8)	(9.8-13.9)	(2.8-4.8)	(16.6-22.8)	(6.9-10.8)	(4.3-7.1)	(14.4-22.3)	(6.0-8.6)	(3.1-4.4)	(9.3-14.7)	(6.0-9.8)	(2.9-4.7)	(6.2-12.2)	(5.1-6.9)	(2.2-3.8)

CI, confidence interval; CRP, C-reactive protein; N, number; OS, median overall survival; WL, weight loss

*WL categories as defined by Martin et al.(ref)

[a,b,c] Superscript letters indicate significant differences (P<0.05) between median OS (Kaplan Meier with log rank (Mantel-Cox) tests) within a food intake category when stratified by CRP, for each WL category.

CHAPTER 7: Implementation of an Enhanced Recovery After Surgery program can change nutrition care practice: A multi-center experience in elective colorectal surgery[1]

7.1 Clinical Relevancy Statement

Enhanced Recovery After Surgery (ERAS) programs are multimodal surgical care pathways that optimize patient care to promote recovery and improve postoperative outcomes. ERAS programs are emerging as the standard in perioperative management around the world. A key component is integration of evidence-based perioperative nutrition care into overall patient management. Implementation of an ERAS program for elective colorectal surgeries had a positive impact on the optimization of nutrition care and is a step towards greater quality of nutrition care throughout surgical programs in Alberta, Canada. ERAS implementation aligns surgical care with clinical practice guidelines for perioperative nutrition care.

7.2 Introduction

Suboptimal nutrition status has long been recognized as an independent predictor of poor surgical outcomes.[1] Unfortunately, surgical nutrition care practices have not been well characterized, especially with regard to nutrition risk screening, nutrition diagnoses, and in characterizing effective nutrition interventions.[2] Several nutrition and surgical societies have called for significant improvements to perioperative nutrition care practices[1,3-6], with a consistent take home message: implementation of evidence-based perioperative nutrition care pathways that are integrated into overall management of the surgical patient improve nutrition care practices and clinical outcomes.[1]

[1]A version of this chapter had been published: Martin L, Gillis C, Atkins M, Gillam M, Sheppard C, Buhler S, Basualdo Hammond C, Nelson G, Gramlich L. Implementation of an Enhanced Recovery After Surgery Program can change nutrition care practice: A multi-center experience in elective colorectal surgery. JPEN J Parenter Enteral Nutr, 2018; Jul 23; doi.org/10.1002/jpen.1417

Enhanced Recovery After Surgery (ERAS) programs are increasingly being adopted as the standard of perioperative care around the world.[1] ERAS programs are multimodal, evidence-based care improvement processes that bundle more than 20 care elements throughout the perioperative period, and consistently demonstrate improved postoperative outcomes in a variety of surgical settings.[7-12] The goals are to manage the stress response to surgery, maintain body stores, and improve physiologic function for early recovery.[7,8] These goals are achieved by standardizing care elements related to surgical practices including analgesia, anesthesia, fluid and symptom management, and perioperative nutrition care.[7,8] Central to ERAS programs is recognition that nutritional status affects outcomes of surgery and must be optimized for recovery; therefore, perioperative nutrition care is integrated into the overall management of the patient.[1,13] ERAS programs are recognized as important drivers of standardized perioperative nutrition care, and have provided the foundation of key perioperative nutrition care elements, which have been incorporated in to clinical practice guidelines for surgical patients.[1-4,6,14]

Despite the recognized benefits of ERAS programs[1,3,4], implementation of evidenced-based guidelines is a continual challenge.[2,4,8] ERAS programs are complex, they must be adapted to local contexts and require extensive education, cooperation, and collaboration between the patient, health care provider, and health system.[7,15] To facilitate education and training for successful adoption of ERAS protocols, the ERAS Society has a formalized ERAS Implementation Program (EIP).[16] To be effective at improving postoperative outcomes, compliance to ERAS care elements is essential. This requires multidisciplinary teams to cooperate to carry out the care processes throughout the perioperative period, and for patients to take part in their recovery.[7] Higher compliance (e.g. >70%) to ERAS care processes is an independent predictor of improved postoperative outcomes including reduced LOS and

complications.[17-19] Within any ERAS program a minority of patients will not benefit from these strategies, and their identification is not well characterized.[18] Identifying patients likely to deviate from an ERAS program, and therefore at risk of poor postoperative outcomes, is of interest as it may inform development of alternative care elements that would benefit these patients.[18]

In 2013, Alberta Health Services (AHS), a provincial health system, led an EIP[16] in elective colorectal surgeries as a strategic initiative to enhance the quality of surgical care with a focus on efficiency, effectiveness, safety, accessibility, and cost.[20] [16] Initial results demonstrated reductions in length of hospital stay and cost, similar to other ERAS programs in colorectal surgery. [9-12,20-22] Prior to ERAS implementation, perioperative nutrition care practices for colorectal surgeries were not standardized and ill-defined. The AHS EIP provided opportunity to standardize and initiate several perioperative nutrition care processes.[23] The goal of this work is to generate knowledge regarding the impact of an EIP on the local adoption of perioperative nutrition care practices for elective colorectal surgeries, and identify patients who were more likely to deviate from the EIP. Outcomes of implementation studies focus on the rate of adoption of evidence-based practices,[15]Our primary focus is nutrition risk screening, and characterizing patients with nutrition risk in relation to adherence to ERAS care elements, and a secondary focus on postoperative outcomes. Our first objective describes the perioperative nutrition care elements implemented as part of the AHS EIP and the rate of compliance to these elements. The second objective was to evaluate whether nutrition risk affected compliance to the EIP and impacted postoperative outcomes.

7.3 Methods

7.3.1 ERAS Implementation Program

A description of the AHS EIP undertaken as a quality improvement project has been published.[22] AHS is a provincial health system servicing ~4.4 million people in Alberta, Canada. In 2013, AHS implemented ERAS Society guidelines for colorectal surgery[23] in 6 acute care centers in the cities of Edmonton and Calgary.[22] The AHS EIP was implemented according to a formalized process outlined by the ERAS Society[16] and includes 22 evidence-based clinical care elements implemented by a multidisciplinary team throughout the perioperative period (Table 7-1). A core component of AHS EIP is data collection for the purposes of auditing and evaluating care processes, which in turn support and enhance practice change at both the provider and system level. Patient, surgery, compliance, and outcome data are prospectively collected by dedicated ERAS nurse coordinators (N=6) using the ERAS Interactive Audit System (EIAS, a secure online data capture tool) and data definitions developed by the ERAS Society.[24,23] Compliance to each of the 22 care elements is recorded as compliant vs. non-compliant, according to pre-specified criteria, and overall compliance is calculated as the number of elements achieved (Table 7-2).[22] Short-term postoperative outcomes include: 1) length of hospital stay (LOS) defined as the period between primary surgical date and discharge from hospital (readmissions were not included in the calculation), 2) complications recorded as any complication occurring during the index hospitalization (graded according to the Clavien-Dindo classification[25]); serious complications defined as grade ≥3, 3) 30-day readmission and mortality rates are also recorded. This quality improvement data captured within the EIAS was analyzed to assess the impact on nutrition care.

7.3.2 Study Design

The study population included consecutive, adult (≥18 years) patients (from September 2013-December 2016) who underwent elective colorectal surgeries as part of AHS EIP.

Multiple ERAS care elements contribute to patients' nutrition and metabolic status (e.g. fluid balance, anesthesia/analgesia), we chose to evaluate the care elements specific to nutrition care practices: nutrition risk screening, minimizing pre-operative fasting, use of pre-operative carbohydrate loading, prevention of postoperative nausea and vomiting, initiation of nutrition support when appropriate, early oral feeding, and mobilization (Tables 7-1, 7-2).[1,7,8,13,23] Changes to perioperative nutrition care practices were evaluated using pre- and post-comparisons between 2 groups: 1) Pre-ERAS group: data collection prior to ERAS implementation to assess baseline compliance, 2) ERAS group: data collection with full ERAS implementation.

From a nutrition care perspective, the adoption of nutrition risk screening is a significant benefit of the AHS EIP. ERAS care elements, including nutrition risk screening tools, are adapted to meet local needs, hence centers selected nutrition risk screening tools best suited to their local context. For the ERAS Group, nutrition risk screening is completed by a health care provider at a preadmission visit with one of two validated tools: the Malnutrition Screening Tool[26] (MST; nutrition risk defined as an MST score ≥2, which equates to eating poorly and/or recent weight loss) or the Canadian Nutrition Screening Tool[27] (CNST, nutrition risk defined based on responding "yes" to two questions, which equates to eating poorly and recent weight loss). Nutrition risk refers to a nutritional problem with potential to negatively impact nutritional status resulting in malnutrition. For the ERAS Group, patients' deemed to be at nutrition risk based on either tool were grouped together for analysis. We evaluated the impact of nutrition risk on compliance to ERAS care elements, and on short-term postoperative outcomes. Additional nutrition care elements included use of postoperative nutrition support prescribed by a Registered

Dietitian (e.g. enteral or parenteral nutrition), monitoring of patient's body weight, time taken for the patient to experience flatus, have a bowel movement, tolerate solid food (defined as consuming a solid diet in normal portions without vomiting, excludes use of nasogastric tube), and achieve activities of daily living (ADL; defined as the number of days after surgery when able to independently physically perform basic ADL to the same extent as before surgery). These data were evaluated as indicators of recovery.

The AHS EIP had ethical approval from institutional research ethics boards as a health system quality improvement initiative, individual consent from patients was not sought or required. Individual patient data were anonymized prior to inclusion in the EIAS.

7.3.3 Statistical Analysis

Frequencies and summary statistics describe the patient sample. Differences between groups were assessed with parametric (Independent T-tests, Chi-Square Tests and Fisher Exact Tests with post-hoc Bonferroni corrections) or non-parametric (Mann-Whitney) tests where appropriate. Binary logistic regression models evaluated the association between patient and surgical variables, and hospital site with dependent variables: low overall compliance to ERAS care elements (defined as <70%[19]), extended length of hospital stay (defined as >5 days), and postoperative complications (yes vs. no). Relationships between these outcomes and study variables were assessed at the univariable level, and variables significantly associated with an outcome ($P<0.1$) were entered into multivariable analyses (full model). Non-significant variables were removed in a backward step-wise manner, and the most parsimonious model was retained as the final model. Results are reported as odds ratios (OR with 95% CI) and considered

significant at the P<0.05 level (two-tailed). Data analysis was performed with IBM SPSS Statistics for Windows (v.23, Armonk, NY: IBM Corp).

7.4 Results

7.4.1 The influence of ERAS implementation on the adoption of perioperative nutrition care practices

7.4.1.1 Patient characteristics

4023 patients were included in the AHS EIP (pre-ERAS group, N=476; ERAS group, N=3536; Table 7-3). There were few differences between these groups. Overall, 3% of patients were underweight (BMI <18.5), 36% of patients were overweight (BMI 25.0-29.9), and 33% were obese (BMI ≥30.0). The ERAS group had more laparoscopic surgeries compared to the pre-ERAS group (46% vs. 36%, P<0.001), due to changes in surgical practice as a result of AHS EIP. Mean overall compliance to the EIP was 71% in the ERAS group vs. 51% in the pre-ERAS group (Table 7-3). Pre- and intra-operative elements had the highest compliance while postoperative elements had the lowest compliance. More than half (67%) of patients in the ERAS group achieved good overall compliance (>70%), compared to essentially no patients (1%) in the pre-ERAS group.

7.4.1.2 Changes to perioperative nutrition care practices

AHS EIP had a significant impact on nutrition care (Table 7-4). In the pre-operative period, the ERAS group had significant improvements with regard to nutrition screening, carbohydrate loading, and postoperative nausea and vomiting prophylaxis (PONV). Nutrition risk screening increased from 8% (pre-ERAS group) to 74% (ERAS group, P<0.001). However,

a high proportion of patients in the ERAS group (N=908, 26%) were not screened for nutrition risk.

In the postoperative period, the ERAS group had improvements with regard to the adoption of strategies to stimulate gut motility, initiate early oral feeding, and obtaining patient weights (Table 7-4). Calories from oral nutritional supplements (ONS) on postoperative day (POD) 0-3 were increased (P<0.001). The ERAS group reduced the number of days to tolerate solid food, from 5.9 to 2.3 days (p<0.001). Use of artificial nutrition increased from 2% (Pre-ERAS Group) to 25% (ERAS Group, (P<0.001). More patients in the ERAS group met targets for mobilization on POD 0-3 (P<0.001), and time to return to ADL was reduced (3.4 days vs. 7.7 days, P<0.001).

The frequency of unknown/missing data nutrition care elements was highly variable. Elements missing <10% of cases included: carbohydrate loading, oral bowel prep, and PONV prophylaxis, mobilization on POD 0, time to tolerating solid food (Table 7-4). Elements missing >20% of cases included: nutrition risk screening, patient weights, energy intake from ONS on POD 2-3, use of artificial nutrition, and mobilization on POD 1-3 (Table 7-4). The ERAS group had fewer missing data compared to the pre-ERAS group.

7.4.2 Impact of nutrition risk on compliance to AHS EIP and short-term postoperative outcomes

7.4.2.1 Patient characteristics

A total of N=2628 (74%) patients from the ERAS group were screened for nutrition risk and included in this analysis. The majority (88%, N=2317) of patients were not at nutrition risk, and 12% (N=311; MST N=218, CNST N=93) were at nutrition risk. Characteristics of these two groups are presented in Table 7-3. Patients at nutrition risk had more smokers (P<0.001), cancer

diagnoses (P=0.004), open surgeries (P=0.016), complex surgical procedures (P=0.034), and BMIs <25.0 (P<0.001). More than half (53%) of patients at nutrition risk were also overweight or obese.

7.4.2.2 Nutrition risk and compliance to AHS EIP

Patients at nutrition risk had lower overall compliance compared to those not at nutrition risk (68% vs. 74 %, P<0.001, Table 7-3). There was no difference in compliance for patients at nutrition risk as defined by the MST or CNST (P=0.623). For nutrition care elements, the nutrition risk group had less patients with morning weights (P<0.05), able to meet energy intake targets for early oral feeding (e.g. ONS consumption on POD 0-3, P<0.05), more patients requiring postoperative nutrition support (31% vs. 25%, P<0.001, Table 7-4), and a trend to take longer to return to solid food (P=0.079). Patients at nutrition risk had reduced mobility on POD 0-2, and took longer to recover ADL (4.5 vs. 3.1 days, P=0.046, Table 7-4). In multivariable logistic regression (Table 7-5), low compliance to AHS EIP (<70%) was predicted by nutrition risk (OR 2.3 95% CI 1.8-3.0, P<0.001), sex, age, surgical complexity, ASA ≥3, postoperative complications, and hospital site. Patients with BMI ≥30.0 were more likely to have good compliance (>70%) to ERAS care elements.

7.4.2.3 Nutrition risk and short-term postoperative outcomes

Short-term postoperative outcomes are listed in Table 7-3. Overall, AHS EIP significantly reduced LOS (median 5.0 days (IQR 4.0) vs 6.0 days (IQR 5.0), P<0.001), and the proportion of patients with LOS >5 days (58% vs. 49%, P<0.001), but had no effect on the rate of postoperative complications (44 vs. 48%, P=0.069), 30-day readmission (11% vs. 10%, P=0.364), or 30-day mortality (0.2% vs. 0.7%, P=0.388).

In contrast, patients at nutrition risk in the ERAS group had longer LOS (median 6.0 days (IQR 5.0) vs. 5.0 days (IQR 4.0), P<0.001, Table 7-3). LOS did not differ between patients with nutrition risk defined by MST or CNST (P=0.396). In multivariable logistic regression (Table 7-6), LOS >5 days was predicted by postoperative complications, surgical approach, surgical complexity, ASA class, sex, age, hospital site, and overall compliance to AHS EIP. Nutrition risk trended towards significance for longer LOS (OR 1.40 95% CI 1.00-1.97, P=0.052).

Patients at nutrition risk had more postoperative complications (56% vs. 49%, P=0.016), and more serious (Grade ≥3) postoperative complications (14% vs. 8%, P=0.022). Postoperative complications differed (P<0.001) between patients with nutrition risk defined by MST (N=135 (62%)) or CNST (N=39 (42%)) but not for serious complications (P=0.955). In multivariable logistic regression (Appendix VI), postoperative complication were predicted by surgical approach (open or converted procedures), greater surgical complexity, ASA class ≥3, age, male sex, low compliance to AHS EIP, and hospital site. ERAS care elements. Overall nutrition risk (and as defined by MST or CNST) did not predict of postoperative complications.

There was no difference in readmission rates for patients with or without nutrition risk (P=0.156, Table 7-3), nor when nutrition risk was defined by MST or CNST (P=0.447). Thirty-day mortality was low for this patient cohort (N=22, 0.8%), however 30-day mortality was higher for patients at nutrition risk (2.2% vs. 0.6%, P<0.001, Table 7-3). There was no difference in mortality for patients with nutrition risk defined by MST or CNST (P=0.805).

7.5 Discussion

AHS EIP for elective colorectal surgeries had a positive impact on the adoption of standardized perioperative care practices with an overall compliance rate of 72%. This is of

significance as enhanced adherence (>70%) to ERAS protocols are associated with improved surgical outcomes[19]. Adoption of an EIP aligned AHS more closely with clinical practice guidelines for perioperative nutrition care in surgical patients. Prior to ERAS implementation, the majority of perioperative nutrition care elements were either not practiced, or were highly variable. Key areas of improvement included nutrition risk screening, pre-operative carbohydrate loading, stimulation of gut motility, obtaining morning weights, early oral feeding, and mobilization. Nutrition risk screening, increased from 8% to 74%, and identified a subset of patients (12%) who were less compliant with the ERAS protocol, slower to recover oral intake and physical functioning, and had longer LOS and increased mortality. Collectively these results suggest patients at nutrition risk have difficulty recovering from elective surgery, which is independent of postoperative complications.

A limitation of our study was 26% of patients in the ERAS group were not screened for nutrition risk, potentially introducing a selection bias, which may explain, in part the lower rate of nutrition risk compared to other studies in similar patient populations (20-47%). However, the rate of nutrition risk is largely dependent on the case mix within the patient cohort and the tool selected for screening.[13,28-30] There is heterogeneity in nutrition risk screening tools used across surgical programs, and for this reason results are not directly aggregable. Importantly, in programs where validated nutrition risk screening tools were used (e.g. Patient Subjective Global Assessment (PGSGA), Nutrition Risk Screen (NRS)-2002, Malnutrition Universal Screening Tool (MUST)), nutrition risk was associated with worse postoperative outcomes including longer LOS and increased postoperative complications, similar to our findings.[13,28-30] In this study, nutrition risk was defined by two different screening tools, the MST and CNST,[26,27] and it is possible the rate of nutrition risk detection differed between the tools. However, the MST and

CNST use similar criteria to identify nutrition risk (reduced food intake and weight loss), and have similar sensitivity and specificity versus the subjective global assessment (MST sensitivity = 39-93%, specificity = 55-93%; CNST sensitivity 67-73%, specificity 80-86%).[31] Outcomes were not different whether patients were screened with the MST or CSNT. This is an important finding as both tools are designed to detect patients with pre-existing nutritional problems, (weight loss and reduced food intake), and when these problems are identified patients were less able to comply with AHS EIP, and importantly for nutritional professionals, had lower compliance to nutrition care elements. It seems plausible when nutritional problems pre-exist they continue to be problematic in the postoperative period and for patient recovery. We did observe an increase of 6% in the use of postoperative nutrition support for patients at nutrition risk, but it is not clear if this can be attributed to nutrition risk screening. A better understanding of care processes related to nutrition support in AHS is needed and is an opportunity for study to develop standardized nutrition care pathways. ERAS guidelines include recommendations for pre-operative nutrition interventions for patients at nutrition risk, these guidelines are not sufficiently developed in the AHS EIP, and this has been identified as a major gap in nutrition care and an area for development.

With any large scale quality improvement program there are limitations to consider. Nutrition risk was an important patient factor in identifying low compliance to AHS EIP; however other factors may also impact compliance to perioperative nutrition care elements. The AHS EIP achieved highest compliance in the preoperative period (86%) and lowest in the postoperative period (57%), similar to other colorectal ERAS programs.[18,32] Possible explanations include development of postoperative complications, which can result in deviations from protocols, and the high degree of patient and multidisciplinary involvement in the

postoperative period, which may explain reported differences in the rates of adherence to ERAS care elements, and in data recording.[7,8,33] Some ERAS elements are more easily tracked and recorded by health care professionals, for example ERAS elements found in the medical record or included on order sets e.g. PONV prophylaxis were missed less frequently by the multidisciplinary teams.[33] Data for elements not found in the medical record, and collected using other methodologies such as patient journals (e.g. mobility and nutrition) had lower rates of adherence.[33] Barriers to nutrition care within the AHS EIP have been identified and are related to care processes at individual hospital sites, and information and communication for providers and patients related to eating and drinking after surgery.[33,34] Strategies to enhance nutrition care include process improvement for ensuring delivery of appropriate snack and ONS, and encouragement and education for patients and health care providers.[33] Improved adherence to other ERAS elements that influence oral intake and bowel function (e.g. optimal management of pain/nausea, fluid balance, non-opioid analgesia) will contribute to improved postoperative oral intake.

Strengths of this study include the large, representative patient cohort, with data collected over a whole health system. Our results are consistent with other EIPs, and studies examining the impact of nutrition risk on outcomes of surgery. ERAS care elements may need to be modified and expanded to account for the growing literature identifying the many factors that influence compliance and impact on postoperative outcomes.[7,8] This study highlights nutrition risk as one of these factors, and development of alternate standardized care pathways may benefit these patients.[35,36] For example, evidence-based multimodal prehabilitation programs have demonstrated some efficacy in contributing to improved patient outcomes within ERAS programs.[37,38] Prehabilitation offers individualized nutrition (e.g. counselling and supplemental

protein, n-3 fatty acids), function (exercise program), and anxiety-reduction to promote metabolic preparation and optimization of health status beginning pre-operatively and extending into recovery.[37] AHS is working towards a standardized perioperative nutrition care pathway within the ERAS paradigm.

Ultimately, AHS EIP changed practice with the successful introduction of nutrition risk screening, and basic aspects of nutrition care that align with clinical guidelines for surgical patients. Areas for further development include reducing the number of missing nutrition risk screens, and development of processes that link nutrition screening to assessment, provision of nutrition support for at risk patients, and development of nutrition care elements tailored to patients likely to deviate from the standard ERAS care protocol.

7.6 References

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Table 7-1. Enhanced recovery after surgery (ERAS) care elements for people undergoing major colorectal surgeries in Alberta, Canada

Preoperative Care Elements	Intraoperative Care Elements	Postoperative Care Elements
Preadmission counselling	**Nausea and vomiting prophylaxis**	*Mid-thoracic epidural anesthesia/analgesia*
Nutrition risk screening	Short acting anesthetic agents	No nasogastric tubes
Fluid and carbohydrate loading	*Mid-thoracic epidural anesthesia/analgesia*	**Prevention of nausea and vomiting**
No prolonged fasting	No drains	*Avoidance of salt and water overload*
No/selective bowel preparation	*Avoidance of salt and water overload*	Early removal of catheter
Antibiotic prophylaxis	Maintenance of normothermia (body warmer/warm intravenous fluids)	**Early oral nutrition**
Thromboprophylaxis		*Non-opioid oral analgesia/NSAIDs*
No premedication		**Early mobilization**
		Stimulation of gut motility
		Audit of compliance and outcomes

NSAIDs, non-steroidal anti-inflammatory drugs

*Nutrition care elements related to nutrition care practices are listed in bold

ERAS elements in italics are recognized to have an important impact on nutrition status and metabolism but do not fall under the purview of nutrition care practices

Table 7-2. Criteria for compliance to ERAS nutrition care elements

Nutrition Care Elements	ERAS Guideline	ERAS Guideline Compliant	ERAS Guideline Non-compliant
Nutrition risk* screening‡	Nutrition risk score recorded: Malnutrition Screening Tool OR Canadian Nutrition Screening Tool	yes	no
Fluid and carbohydrate loading‡	Patient treated with a preoperative carbohydrate rich drink: At least 50g of carbohydrates together with at least 400 ml fluid, be given up until 2 hours prior to anesthesia	yes	no
No prolonged fasting‡	Patient allowed solid food up to 6 hours before and clear fluids up to 2 hours before induction of anesthesia	yes	no
No/selective bowel preparation‡	Patient received oral bowel preparation /cleansing preoperatively	no	yes
Postoperative nausea and vomiting prophylaxis‡	PONV prophylaxis given before end of operation	yes	no
Stimulation of gut motility‡	Patient received gut motility stimulation (gum, laxative or both)	yes	no
Early oral nutrition§			
POD 0	Energy from ONS on POD 0 until early morning POD 1	≥300 kcal	< 300 kcal
POD 1	Energy from ONS on POD 1 until early morning POD 2	≥600 kcal	<600 kcal
POD 2	Energy from ONS on POD 2 until early morning POD 3	≥600 kcal	<600 kcal
POD 3	Energy from ONS on POD 2 until early morning POD 4	≥600 kcal	<600 kcal
Early mobilization§			
POD 0	Patient mobilized at all	yes	no
POD1	Number of hours, in total, patient mobilized	≥4 hours	< 4 hours
POD 2 to 3	Number of hours, in total, patient mobilized	≥6 hours	< 6 hours

ERAS, Enhanced Recovery After Surgery; g, grams; ml, milliliters; ONS, oral nutritional supplements; POD, postoperative day

*Nutrition risk defined as ≥2 on the Malnutrition Screening Tool (MST) or two "yes" answers on the Canadian Nutrition Screening Tool (CNST); completed by a health care professional

†Mobile refers to a patient who can rise from bed to walk, or to sit in chair

‡Data collected and recorded in medical chart by a health care professional; data abstracted and entered in to EIAS by ERAS nurse coordinator according to ERAS standardized data definitions

[§]Data collected from patient report: patients recorded in an ERAS journal the amount of ONS consumed/day and time spent mobilizing/day for a total of 3 days; data was entered into EIAS by ERAS nurse coordinator, calories from ONS were estimated based on reported volume of ONS consumed.

Table 7-3. Characteristics of patients who underwent elective colorectal surgery within an ERAS implementation program.

Patients Characteristics	Pre-ERAS (N=487)	ERAS (N=3536)	P-Value †	Not At Nutrition Risk (N=2317)	At Nutrition Risk* (N=311)	P-Value †
Sex (N, %)			0.372			0.306
female	222 (46)	1539 (43)		994 (43)	143 (46)	
male	264 (54)	1996 (57)		1322 (57)	168 (54)	
Age, years (mean, SD)	62.4 (13.7)	61.4 (14.3)	0.128	61.6 (14.1)	62.5 (14.9)	0.296
AgeCategory			0.105			0.091
18-25	3 (0.6)	49 (1)		27 (1)	6 (2)	
26-50	81 (17)	631 (18)		400 (17)	53 (17)	
51-75	311 (64)	2317 (66)		1539 (66)	190 (61)	
76-100	92 (19)	539 (15)		351 (15)	62 (20)	
Height, cm (mean, SD)	168.4 (10.5)	168.2 (10.2)	0.762	168.4 (10.1)	167.9 (9.7)	0.395
Weight, kg (mean, SD)	80.5 (21.0)	80.2 (19.8)	0.798	80.5 (19.6)	74.5 (20.2)	**<0.001**
BMI, kg/m^2 (mean, SD)	28.3 (6.4)	28.2 (6.2)	0.923	28.3 (5.9)	26.3 (6.4)	**<0.001**
BMI class (N,%)			0.060			**<0.001**
<18.5 (underweight)	20 (4)	81 (2)		43 (2)	14 (5)	
18.5-24.9 (normal weight)	138 (28)	1019 (29)		658 (28)	131 (42)	
25.0-29.9 (overweight)	159 (33)	1269 (36)		846 (37)	97 (31)	
≥30.0 (obese)	170 (35)	1167 (33)		770 (33)	69 (22)	
Alcohol use (N, %)			**<0.001**			0.470
no	393 (81)	3191 (90)		2101 (91)	277 (89)	
yes	78 (16)	299 (9)		190 (8)	29 (9)	
stopped due to surgery	2 (0.2)	8 (0.4)		5 (0.2)	0 (0)	
unknown	15 (3)	38 (1)		21 (1)	5 (2)	
Smoker (N ,%)			0.487			**<0.001**
no	402 (82)	2900 (82)		1929 (83)	231 (74)	
yes	84 (17)	613 (17)		379 (16)	76 (24)	
unknown	1 (1)	23 (1)		9 (0.4)	4 (1)	
Diabetes (N, %)			0.700			0.708
no	413 (85)	2964 (84)		1934 (83)	258 (83)	
yes	74 (15)	564 (16)		380 (16)	52 (17)	
unknown	0 (0)	8 (0.2)		3 (0.1)	1 (0.3)	
ASA Class (N, %)			0.523			0.067
1 to 2	326 (67)	2385 (67)		1582 (68)	192 (62)	
3 to 4	137 (28)	1074 (30)		68 (30)	111 (36)	
unknown	24 (5)	76 (2)		47 (2)	8 (3)	
Cancer Diagnosis (N, %)			0.204			**0.004**

non-cancer diagnosis	244 (50)	1880 (53)		1105 (48)	175 (56)	
cancer diagnosis	243 (50)	1656 (47)		1212 (52)	136 (44)	
Diagnosis (N, %)			**<0.001**			**<0.001**
benign tumor including polyp(s)	54 (11)	531 (15)		402 (17)	23 (7)	
Crohn's disease	25 (5)	51 (1)		28 (1)	7 (2)	
diverticular disease	50 (10)	236 (7)		148 (6)	31 (10)	
functional disorder	23 (5)	152 (4)		86 (4)	9 (3)	
inflammatory bowel disease	22 (5)	266 (8)		168 (7)	25 (8)	
other benign disease or disorder	68 (14)	644 (18)		380 (16)	41 (13)	
other primary malignancy	9 (2)	48 (1)		29 (1)	6 (6)	
primary adenocarcinoma	222 (46)	1574 (45)		1053 (45)	164 (53)	
metastasis or recurrence malignancy	12 (3)	34 (1)		23 (1)	5 (2)	
Procedure Type (N, %)			0.627			0.143
rectal procedure	327 (67)	2335 (66)		818 (35)	123 (40)	
colon and small bowel procedure	160 (33)	1201 (34)		1499 (65)	188 (60)	
Surgical approach (N, %)			**<0.001**			**0.016**
laparoscopic	174 (36)	1628 (46)		1198 (52)	145 (47)	
open	232 (48)	1336 (38)		795 (34)	135 (43)	
stoma approach	48 (10)	410 (11)		213 (9)	19 (6)	
converted	26 (5)	134 (4)		101 (4)	12 (4)	
unknown	7 (1)	28 (1)		10 (0.4)	0 (0)	
Surgical Complexity‡ (N, %)			0.863			**0.034**
less complex procedures	286 (59)	2062 (58)		1324 (57)	158 (51)	
more complex procedures	201 (41)	1474 (42)		993 (43)	153 (49)	
Acute Care Centre			**<0.001**			**<0.001**
Hospital Site #1	50 (13)	502 (14)		196 (9)	31 (10)	
Hospital Site #2	75 (19)	1182 (33)		1003 (43)	86 (28)	
Hospital Site #3	56 (14)	504 (14)		415 (18)	44 (14)	
Hospital Site #4	48 (12)	513 (15)		251 (11)	66 (21)	
Hospital Site #5	97 (25)	389 (11)		227 (10)	50 (16)	
Hospital Site #6	61 (16)	446 (13)		225 (10)	34 (11)	
Short-term post-operative outcomes						
Length of hospital stay (days)						
mean (SD)	8.8 (18.1)	7.6 (8.8)	**<0.001**	7.4 (7.6)	8.1 (7.6)	**<0.001**
median (IQR)	6.0 (5.0)	5.0 (4.0)		5.0 (4.0)	6.0 (5.0)	
Extended LOS (N, %)						

<5 days	204 (42)	1800 (51)	**<0.001**	1228 (53)	121 (39)	**<0.001**
>5 days	280 (58)	1706 (49)		1104 (47)	191 (61)	
Complication(s) during primary stay (N, %)			0.069			**0.016**
yes	212 (44)	1707 (48)		1127(49)	174 (56)	
no	273 (56)	1829 (52)		1190 (51)	137 (44)	
Complication severity‡ (N, %)			0.764			**0.022**
non-serious (Grade I to II)	184 (90)	1537 (90)		1027 (92)	149 (86)	
serious (Grade III to IV)	21 (10)	163 (10)		95 (8)	24 (14)	
30-day readmission rate (N,%)	52 (11)	343 (10)	0.364	236 (10)	27 (9)	0.156
30-day mortality rate (N, %)	1 (0.2)	26 (0.7)	0.388	15 (0.6)	7 (2.2)	**<0.001**
Compliance to ERAS care elements, % (Mean, SD)						
pre-operative care elements	61.5 (13.3)	86.3 (13.8)	**<0.001**	86.7 (13.6)	87.6 (13.2)	0.274
intra-operative care elements	69.5 (15.2)	77.7 (16.5)	**<0.001**	79.5 (15.7)	75.4 (17.9)	**<0.001**
post-operative care elements	34.8 (10.8)	58.5 (16.7)	**<0.001**	59.1 (16.3)	55.0 (16.0)	**<0.001**
overall	51.3 (7.0)	71.8 (10.1)	**<0.001**	73.6 (9.5)	68.1 (9.3)	**<0.001**
Overall Compliance to all ERAS care elements						**<0.001**
>70% (good compliance)	4 (1)	2245 (63)	**<0.001**	1642 (71)	154 (50)	
<70% (low compliance)	483 (99)	1291 (37)		675 (29)	157 (50)	

ASA, American Society of Anesthesiologists physical status classification; BMI, body mass index; ERAS, Enhanced Recovery After Surgery; IQR, interquartile range; LOS, length of hospital stay; N, number; SD, standard deviation

*Nutrition risk defined as ≥2 on the Malnutrition Screening Tool (MST) or two "yes" answers on the Canadian Nutrition Screening Tool (CNST), patients in the ERAS implementation group whose nutrition screen status was unknown (N=908) were excluded from this analysis

†P-value based on comparison between groups (Pre-ERAS vs. ERAS; Not at Nutrition Risk vs. At Nutrition Risk) Chi-square, Fischer's exact test, or independent t-test were used where appropriate

‡Surgical complexity = more complex procedures: abdominoperineal resection, anterior resection of rectum, total/subtotal colectomy, reversal of Hartmann's procedure; less complex procedures: right hemicolectomy, left hemicolectomy, other large/small bowel resection, ileostomy reversal

§ based on Clavien-Dindo complication classification

Table 7-4. The impact of ERAS implementation and nutrition risk on nutrition care elements.

ERAS Protocol Nutrition Care Elements	Pre-ERAS (N=487)	ERAS (N=3536)	P-Value	Not At Nutrition Risk (N=2317)	At Nutrition Risk* (N=311)	P-Value
Pre-Surgery						
Nutrition screen (N, %)			**<0.001**	-	-	-
yes	43 (9)	2628 (74)		-	-	-
no	445 (91)	908 (26)		-	-	-
Carbohydrate treatment (N, %)			**<0.001**			0.377
yes	18 (4)	2142 (61)		1425 (62)	196 (63)	
no	467 (96)	1238 (35)		810 (35)	100 (32)	
unknown	2 (0)	156 (4)		82 (4)	15 (5%)	
Oral bowel preparation (N, %)			**<0.001**			0.310
no	270 (55)	2561 (72)		1691 (73)	236 (76)	
yes	210 (43)	951 (27)		619 (27)	73 (23)	
unknown	7 (1)	24 (1)		7 (0.3)	2 (1)	
PONV prophylaxis administered (N, %)			**<0.001**			0.193
yes	386 (79)	3133 (89)		2069 (89)	267 (86)	
no	94 (19)	369 (10)		231 (10)	41 (13)	
unknown	7 (1)	34 (1)		17 (1)	3 (1)	
Post-Surgery						
Stimulation of gut motility (N, %)			**<0.001**			**<0.001**
yes (laxatives or gum or both)	67 (14)	2559 (72)		1715 (74)	216 (69)	
no stimulation given	420 (86)	445 (13)		195 (8)	51 (16)	
unknown	0 (0)	532 (15)		407 (18)	44 (14)	
POD 0 ONS Intake ≥300 kcal (N, %)			**<0.001**			**<0.001**
yes	0 (0)	709 (20)		507 (22)	61 (20)	
no	287 (59)	2243 (63)		1477 (64)	178 (57)	
unknown	300 (41)	584 (17)		333 (14)	72 (23)	
POD 0 Energy intake (kcal) from ONS (Mean, SD)	1.6 (18.3)	156.3 (148.1)		173.1 (147.1)	145.8 (153.7)	**0.007**
POD 0 Mobile† at all (N, %)			**<0.001**			**<0.001**
yes	209 (43)	2150 (61)		1528 (66)	162 (52)	
no	253 (52)	1300 (37)		739 (32)	145 (47)	
unknown/not applicable	25 (5)	86 (2)		50 (2)	4 (1)	
POD 1 Patient's Morning Weight Measured‡			**<0.001**			**0.001**
yes	40 (8)	2269 (64)		1626 (70)	189 (61)	

no	447 (92)	1267 (36)		691 (30)	122 (39)	
POD 1 ONS Intake ≥600 kcal (N, %)			**<0.001**			**<0.001**
yes	1 (0)	1061 (30)		775 (33)	77 (25)	
no	286 (59)	1977 (56)		1266 (55)	174 (56)	
unknown	200 (41)	498 (14)		276 (12)	60 (19)	
POD 1 Energy intake (kcal) from ONS (Mean, SD)	8.3 (58.0)	359.3 (245.7)		389.9 (235.2)	343.5 (242.8)	**0.003**
POD 1 Hours mobile ≥4 hours (N, %)			**<0.001**			**<0.001**
yes	32 (7)	1650 (47)		995 (43)	134 (43)	
no	89 (18)	695 (18)		401 (17)	83 (27)	
unknown / not applicable	366 (75)	1191 (34)		921 (40)	94 (30)	
POD 1 Hours mobile (mean, SD)	2.8 (2.7)	4.8 (2.5)	**<0.001**	4.9 (2.6)	4.1 (2.6)	**<0.001**
POD 2 Patient's Morning Weight Measured			**<0.001**			
yes	53 (11)	2195 (62)		1545 (67)	187 (60)	0.026
no	434 (89)	1341 (38)		772 (33)	124 (40)	
POD 2 ONS intake ≥600 kcal (N, %)			**<0.001**			**0.002**
yes	0 (0)	427 (12)		303 (13)	29 (9)	
no	288 (59)	2543 (72)		1686 (73)	216 (69)	
unknown	199 (41)	566 (14)		328 (14)	66 (21)	
POD 2 Energy intake (kcal) from ONS (Mean, SD)	10.0 (57.4)	299.6 (250.2)		319.2 (247.4)	305.1 (243.4)	0.400
POD 2 Hours mobile ≥6 hours (N, %)			**<0.001**			**<0.001**
yes	21 (4)	1074 (30)		661 (29)	84 (27)	
no	85 (18)	1075 (30)		604 (26)	122 (39)	
unknown / not applicable	381 (78)	1387 (39)		1052 (45)	105 (34)	
POD 2 Hours mobile (mean, SD)	3.6 (2.7)	5.4 (2.7)	**<0.001**	5.4 (2.7)	4.9 (2.7)	**0.001**
POD 3 Patient's Morning Weight Measured			**<0.001**			0.060
yes	56 (11)	1657 (47)		1182 (51)	141 (45)	
no	431 (89)	1879 (53)		1135 (49)	170 (55)	
POD 3 ONS intake ≥600 kcal (N, %)			**<0.001**			0.066
yes	2 (0)	511 (15)		1419 (61)	183 (60)	
no	282 (58)	2177 (62)		521 (23)	187 (60)	
unknown	203 (42)	848 (24)		527 (23)	86 (28)	
POD 3 Energy intake (kcal) from ONS (Mean, SD)	14.37 (98.5)	224.9 (244.1)		244.9 (246.7)	211.4 (235.1)	**0.046**
POD 3 Hours mobile ≥6			**<0.001**			**<0.001**

hours (N, %)						
yes	20 (4)	855 (24)		494 (21)	75 (24)	
no	70 (14)	822 (23)		470 (20)	89 (29)	
unknown / not applicable	397 (82)	1859 (53)		1353 (58)	147 (47)	
POD 3 Hours mobile (mean, SD)	3.9 (2.7)	5.4 (2.7)	**<0.001**	5.4 (2.7)	5.2 (2.8)	0.289
Use of artificial nutrition (N, %)			**<0.001**			**<0.001**
none	140 (29)	1763 (50)		1233 (53)	118 (38)	
ONS only	7 (1)	659 (19)		418 (18)	68 (22)	
enteral nutrition only	0 (0)	9 (0)		4 (0.2)	2 (1)	
enteral and parenteral nutrition	0 (0)	47 (1)		21 (1)	8 (3)	
parenteral nutrition only	5 (1)	171 (5)		130 (6)	16 (5)	
unknown	335 (69)	887 (25)		511 (22)	99 (32)	
Days to recover ADL[§] (mean, SD)	7.7 (24.2)	3.4 (4.7)	**<0.001**	3.1 (10.0)	4.5 (6.1)	**0.046**
assessed (N, %)				1738 (75)	198 (64)	
unknown / not applicable (N, %)				579 (25)	113 (36)	
Days to first flatus (mean, SD)	3.4 (16.9)	2.1 (2.5)	0.078	2.1 (2.9)	2.1 (1.7)	0.938
assessed (N, %)	481 (99)	3426 (97)		2259 (97)	299 (96)	
unknown / not applicable (N, %)	6 (1)	110 (3)		58 (3)	12 (4)	
Days to first stool (mean, SD)	3.7 (3.6)	3.1 (3.3)	**0.004**	3.1 (3.3)	3.2 (3.1)	0.417
assessed (N, %)	413 (85)	2871 (81)		1820 (78)	266 (86)	
unknown / not applicable (N, %)	74 (15)	665 (19)		497 (22)	45 (15)	
Days to tolerating solid food[ǁ] (mean, SD)	5.9 (18.4)	2.3 (4.6)	**0.001**	2.8 (4.5)	3.3 (6.4)	0.079
assessed (N, %)	461 (95)	3377 (96)		2234 (96)	288 (93)	
unknown / not applicable (N, %)	26 (5)	159 (4)		83 (4)	23 (7)	

ADL, activities of daily living; ERAS, Enhanced Recovery After Surgery; kcal, calories; N, number; ONS, oral nutritional supplments; PONV, post-operative nausea and vomiting; POD, post-operative day; SD, standard deviation; VAS, visual analogue scale;

*Nutrition risk defined as ≥2 on the Malnutrition Screening Tool (MST) or two "yes" answers on the Canadian Nutrition Screening Tool (CNST), patients in the ERAS implementation group whose nutrition screen status was unknown (N=908) were excluded from this analysis

[†]Mobile refers to a patient who can rise from bed to walk, or to sit in chair

[‡]Morning weights = patient's were weighed each morning using an electric scale located on the surgical wards (calibrated weekly), weight was recorded in medical chart by health care professional

[§]Days to achieve ADL = the number of days after surgery until patient was out of bed for more than 6 hours per day and at same level of independence with respect to daily living as before surgery.

[ǁ]Tolerating solid food = consuming solid food in normal portions without vomiting and excludes the use of a nasogastric tube

Table 7-5. Logistic regression model of the factors associated with low compliance (<70%) to ERAS care elements for patients in the ERAS implementation group (N=2628)

Outcome = low overall compliance to ERAS care elements (<70%)

Factors	N	Univariable		Final Multivariable		
		OR (95% CI)	P-Value	N	OR (95% CI)	P-Value
Nutrition Screen*						
not at nutritional risk	2317	1.0 (ref)		2316	1.0 (ref)	
at nutritional risk	311	2.48 (1.95-3.15)	**<0.001**	311	2.77 (2.11-3.64)	**<0.001**
Sex						
female	1137	1.0 (ref)				
male	1490	0.95 (0.81-1.12)	0.559	-	-	-
Age (years)	2627	1.0 (0.99-1.00)	0.227	-	-	-
ASA Class						
1 to 2	1774	1.0 (ref)		1774	1.0 (ref)	
3 to 4	798	1.51 (1.27-1.80)	**<0.001**	798	1.38 (1.13-1.68)	**0.001**
unknown	55	1.20 (0.68-2.13)	0.528	55	1.61 (0.83-3.15)	0.161
Cancer Diagnosis						
non-cancer diagnosis	1280	1.0 (ref)	0.496	-	-	-
cancer diagnosis	1348	1.06 (0.90-1.24)		-	-	-
Procedure Type						
colon and small bowel procedure	1687	1.0 (ref)		-	-	-
rectal procedure	914	1.42 (1.20-1.68)	**<0.001**	-	-	-
Surgical approach						
laparoscopic	1343			1342	1.0 (ref)	
open	930	2.72 (2.28-3.25)	<0.001	930	3.08 (2.50-3.81)	**<0.001**
stoma approach	232	0.67 (0.47-0.96)	0.028	232	0.75 (0.50-1.10)	0.142
converted	113	2.75 (1.86-4.07)	<0.001	113	2.72 (1.77-4.18)	**<0.001**
unknown	10	0.78 (0.17-3.69)	0.753	10	2.24 (0.45-11.18)	0.324
Surgical Complexity						
less complex procedures	1482	1.0 (ref)		-	-	-
more complex procedures	1146	1.56 (1.32-1.84)	**<0.001**	-	-	-
Complication(s) during primary stay						
no	1327	1.0 (ref)		1327	1.0 (ref)	
yes	1301	3.05 (2.56-3.62)	**<0.001**	1300	2.53 (2.09-3.04)	**<0.001**
BMI class						
<18.5 (underweight)	57	1.64 (0.95-2.81)	0.074	57	1.35 (0.74-2.43)	0.328
18.5-24.9 (normal weight)	789	1.0 (ref)		789	1.0 (ref)	
25.0-29.9 (overweight)	943	0.80 (0.66-0.98)	**0.033**	942	0.83 (0.67-1.04)	0.110
≥30.0 (obese)	839	0.71 (0.58-0.88)	**0.001**	839	0.74 (0.59-0.94)	**0.014**

Acute Care Center						
Hospital #1	227	1.0 (ref)		277	1.0 (ref)	
Hospital #2	1089	2.33 (1.68-3.23)	**<0.001**	1088	4.56 (3.14-6.62)	**<0.001**
Hospital #3	459	0.81 (0.55-1.18)	0.263	459	1.10 (0.73-1.66)	0.653
Hospital #4	317	1.03 (0.70-1.54)	0.853	317	1.37 (0.89-2.12)	0.153
Hospital #5	277	1.18 (0.79-1.77)	0.414	277	2.01 (1.27-3.16)	**0.003**
Hospital #6	259	1.01 (0.66-1.52)	0.981	259	1.19 (0.76-1.86)	0.456
Diabetes						
no	2192	1.0 (ref)		-	-	-
yes	432	1.14 (0.91-1.41)	0.249	-	-	-
unknown	4	0.73 (0.08-7.08)	0.790	-	-	-

ASA, American Society of Anesthesiologists physical status classification; BMI, body mass index ; CI, confidence interval; ERAS, Enhanced Recovery After Surgery; LOS, length of hospital stay; N, number; OR, odds ratio;

*Nutrition risk was only calculated for pateints in the ERAS Group and defined as ≥2 on the Malnutrition Screening Tool (MST) or two "yes" answers on the Canadian Nutrition Screening Tool (CNST), patients in the ERAS Group whose nutrition screen status was unknown (N=908) were excluded from this analysis

(-) dash indicates variables that were not included in the logistic regression models because they were not significant at univariable or multivariable level

Logistic Regression Full model (included all variables significant at univariable level) -2 LL = 2770.997, Negelkerke R^2 = 25%, Hosmer & Lemeshow test P= 0.318, Classification = 73%; Fitted Model (retains variables significant at multivariable level) -2LL = 2775.011, Negelkerke r^2 = 25%, Hosmer & Lemeshow test P=0.131, Classification = 73%

Chapter 8: Assessment of CT-defined muscle and adipose tissue features in relation to short term outcomes after elective surgery for colorectal cancer: a multicenter approach[1]

8.1 Introduction

Computed tomography (CT)-defined features of skeletal muscle and adipose tissue have emerged as a new prognostic tools for postoperative complications, length of hospital stay (LOS), readmissions and mortality.[1-6] In colorectal cancer (CRC) surgery, 36 reports (N=7,666 patients) on CT-defined body composition features and post-surgical outcomes have appeared, focusing on skeletal muscle (SM, 17 studies) and visceral adipose tissue (VAT, 20 studies).[1,3,7-30] Sarcopenia, visceral obesity (VO) and reduced muscle radiodensity (myosteatosis) have been associated with post-operative complications, extended LOS, and survival.[131-25] However, there is a lack of methodological consistency[31-34], and threshold values to define these features have been derived in from non-surgical, non-CRC patients. Threshold values associated with increased risk of mortality have been published[5,25,35,36], but were derived in unresectable cancers and their application to surgical settings is questionable[37] because features such as SM may have unique relationships with different outcomes.[38] Furthermore, effects of aging on body composition has largely been ignored in developing thresholds; SM declines after the age of 50, whereas fat mass increases with age, and declines into extreme old age.[39,40] Use of standardized scores (z-scores) is an approach used to account for age and sex specific effects on body composition, but applying standardized scores requires a large study population.[41] Lastly, sarcopenia, VO, and myosteatosis have been most often evaluated in isolation[1,3,7-13,15], and we suggest this is inadequate to describe a given individual. For example, in CRC, sarcopenic obesity associated with poorer postoperative outcomes, when compared to either feature

[1]A version of this chapter has been published: Martin L, Hopkins J, Malietzis G, Jenkins JT, Sawyer MB, Brisebois R, MacLean A, Nelson G, Gramlich L, Baracos VE. Assessment of CT-defined muscle and adipose tissue features in relation to short term outcomes after elective surgery for colorectal cancer: a multicenter approach. Ann Surg Oncol, 2018; 25:2669-2680

alone.[2,4,7,9] We propose a full assessment of all possible combinations of sarcopenia, VO and myosteatosis is needed.

Large data sets for CT-defined body composition features of resectable CRC patients are lacking, and heterogeneity of CT image analysis methodologies and differences defining surgical outcomes (e.g. complications) create difficulty aggregating existing data.[31] As a result, the generalizability of results is difficult to determine. Development of a data set specific to CRC is necessary to characterize what is usual for CRC patients with respect to body composition features, and to evaluate these features in relation to postoperative outcomes.

We aimed to establish a large, pooled sample consisting of pre-operative CT-defined body composition in CRC patients eligible for elective surgery. Study cohorts with similar characteristics were identified, and sex and age norms for body composition features specific to CRC were developed. Thresholds for sarcopenia, myosteatosis, and VO were defined based on their association with LOS, and the combination of body composition features on LOS, major complications, and readmissions was evaluated. Post-operative complications are recognized to be a main driver of LOS and readmissions; however patients with altered body composition profiles may have extended LOS independent of postoperative complications.[42-44] We adjusted for major complications in our analysis of LOS and readmissions.

8.2 Methods

8.2.1 Study design & participants

Our pooled analysis (see statistics for pooling criteria) includes data from Canadian and UK cohorts: The Canadian Cohort includes consecutive primary CRC patients who underwent elective surgical resection from August 2013 to March 2015[45] (Cohort 1) and January 2007 to December 2009 (Cohort 2) and in Alberta, Canada (population ~4 million). The UK Cohort

included consecutive patients with primary CRC who underwent surgery at St. Mark's Hospital, London, UK from January 2006 to December 2011.[9] Included patients were adults (≥18 years) with primary CRC who underwent elective colorectal resection surgery, and had a preoperative CT image. Patients were excluded if they had recurrent disease confirmed before or during surgery, had emergency surgery or did not have a preoperative CT image available for analysis. The Canadian and UK cohorts had ethical approval from their respective institutional Research Ethics Boards.

8.2.2 Clinical data

For all study cohorts, demographic, surgical, and outcome data were prospectively collected over the perioperative period, and recorded in institutional surgical databases. Common baseline characteristics included: age, sex, weight, height, cancer site (colon vs. rectum, classified using the International Statistical Classification of Diseases and Related Health Problems *10th* Revision) and stage (American Joint Committee on Cancer (AJCC) or Union for International Cancer Control's (UICC)), American Society of Anesthesiologists (ASA) class, surgical approach (laparoscopic, open, or converted procedures). Definitions for short-term surgical outcomes were: 1) LOS: period between primary operation date and discharge from hospital (readmissions not included), 2) Major post-operative complications: any complication with Clavien-Dindo[46] Grade ≥3, 3) Hospital readmission: hospital admission within 30 days of discharge for a primary CRC surgery, 4) Survival: mortality occurring within 30 days of surgery.

8.2.3 Computed tomography

CT images acquired for cancer staging prior to surgery were used for quantitative assessment of SM and adipose tissue. The average time between CT image acquisition and surgery was 30 days. CT image analysis was done in Canada and UK using identical

methodology: SliceOmatic© (TomoVision, Magog, Quebec, Canada) with a single axial abdominal CT image landmarked at the 3rd lumbar vertebra (L3). For each cohort, a single trained observer, blinded to patient outcomes reviewed all images. Pre-determined Hounsfield Unit (HU) thresholds were: -29 HU to +150 HU for SM, -50 to -150 HU for VAT and -30 to -190 HU for subcutaneous adipose tissue (SAT). SM area (SMA), mean skeletal muscle radiodensity (SMR) and areas of VAT and SAT were reported. SMA, VAT, and SAT were normalized for height^2 and reported as: SM index (SMI, cm^2/m^2), VAT index (VATI, cm^2/m^2) and SAT index (SATI, cm^2/m^2). Inter-rater coefficients of variation were within the expected ranges: SMI (2%), SMR (4%), VATI (4-7%).[47,48] Contrast agents can significantly alter SMR values[49,50], therefore only contrast enhanced images were used.

8.2.4 Statistics

Frequencies and summary statistics are reported. Variables were tested for normality using the Shapiro-Wilk test. Comparisons were assessed with parametric (Independent T-tests, ANOVA (Tukey post-hoc test), Chi-Square or Fischer's Exact Tests (post-hoc Bonferroni corrections)) or non-parametric (Mann-Whitney, Kruskal-Wallis Test) tests where appropriate.

Criteria for pooling cohorts was the absence of significant differences (using Z-tests) in age and sex-specific regression coefficients for SMI, SMR and VATI between linear regression models for individual cohorts.[51] The pooled CRC cohort was stratified by sex and age (<50, 50-59, 60-69, 70-79, ≥80 years) and Z-scores for each body composition feature were calculated using the pooled sex- and age- specific means and population standard deviations.

The primary outcome was postoperative LOS. LOS has a naturally skewed distribution and was treated as count data, hence we used a generalized linear model with a negative binomial distribution (NBM), appropriate for skewed distributions.[52] Relationships between LOS

and Z-scores for each body composition feature were evaluated. Threshold values were defined by examining the tissue-specific Z-score distributions, and determining the value that significantly associated with longer LOS using NBM. Z-score values significantly associated with longer LOS were defined for patients with low SMI (sarcopenia), low SMR (myosteatosis) and a high VATI (viscerally obese). Relationships between LOS and other relevant patient and surgical characteristics, including the geographic region (Canada, UK) were also evaluated. Results from NBMs are reported as incidence rate ratios (IRR with 95% CI), and as adjusted estimated marginal mean LOS. Logistic regression models evaluated the relationship of body composition features to major complications (none vs. ≥Grade 3) and hospital readmissions (none vs. readmitted) experienced with 30 days of discharge after primary surgery. Results are reported as odds ratios (OR with 95% CI).

For all regression analyses variables significant ($P<0.1$) at the univariable level were entered into multivariable analyses. The most parsimonious model was retained based on variables significant at the multivariable level and contributing to goodness of fit statistics (e.g. lowest Akaike Information Criteria, AIC). Results were considered significant at the $P<0.05$ level (two-tailed). Analysis was performed with IBM SPSS Statistics for Windows (v.23, Armonk, NY: IBM Corp).

8.3 Results

8.3.1 Patient characteristics

The pooled CRC cohort (Table 8-1) included 1,345 Canadian patients (Cohort 1 (N=384) & 2 (N=961)), and 755 patients from the UK. A majority had stage II+III cancers (76%), tumor in the colon (61%) and underwent laparoscopic surgeries (75%), with a low conversion rate of 4%.

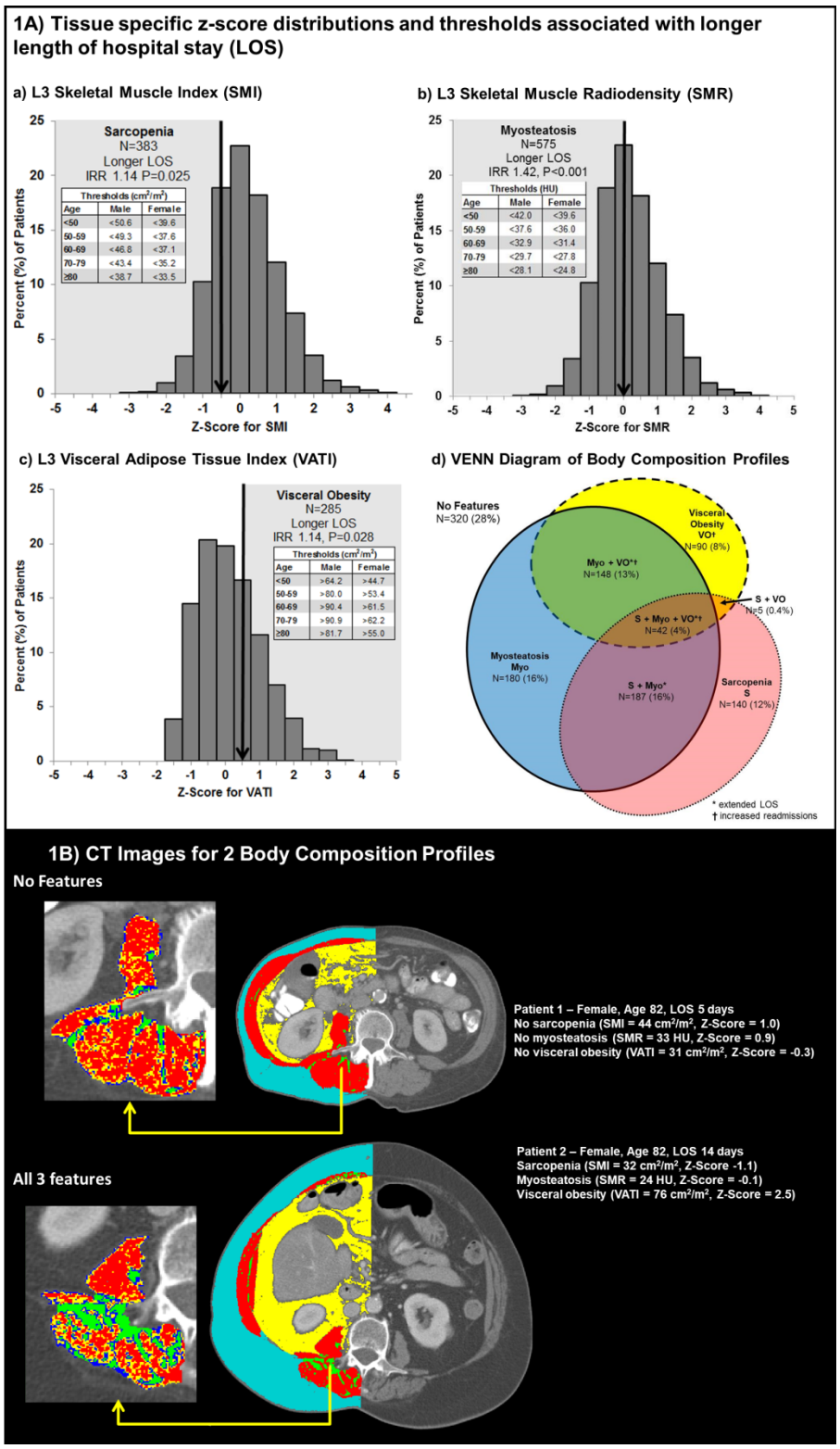
Sex and age significantly associated with features of body composition. There was no significant difference in age and sex-specific regression coefficients for SMI, SMR and VATI in linear regression models between individual cohorts (Appendix VII Suppl Table 1), hence the cohorts were pooled. Pooled data was used for Z-score calculation, and is shown in Table 8-2.

8.3.2 Individual body composition features associate with LOS

This analysis included N=1139 patients (Canadian Cohort 1 N=384; UK Cohort N=755) for whom LOS, postoperative complications, and readmission rates were available. Z-score distributions for SMI, SMR, VATI, and the univariable thresholds for z-scores that significantly associated with LOS, are presented (Figure 8-1).

Sarcopenia was defined as a z-score below -0.5 for SMI (Figure 8-1A_a), myosteatosis was defined as a z-score below 0 for SMR (Figure 8-1A_b) and VO was defined as a z-score above 0.5 for VATI (Figure 8-1A_c).

Figure 8-1. Description of body composition features related to length of hospital stay



Panel 1A) Tissue-specific Z-Score distributions for: a) Skeletal Muscle Index (SMI), b) Skeletal Muscle Radiation Attenuation (SMR), c) Visceral Adipose Tissue Index (VATI). Z-scores were calculated using specific values for sex and age decade (<50, 50-59, 60-69, 70-79, ≥80) for each tissue feature, from the aggregated CRC data set. Z-score values that significantly associated with increased LOS are indicated by black arrows. The shaded areas in Panel A_{a-c} denote the proportion of the distribution at risk for longer LOS. Tissue-specific threshold values, stratified by sex and age, are presented in the tables inset in Panel A_{a-c}. d**)** A proportional VENN diagram depicting overlap between different features of body composition (sarcopenia, myosteatosis, viscerally obese), representing 8 distinct body composition profiles. **Panel 1B)** L3 axial CT scans for two females of the same age. Patient 1 has none of the features sarcopenia, obesity, or myosteatosis. Patient 2 has all three features. *Main panels:* The L3 region includes: skeletal muscle, subcutaneous adipose tissue, visceral adipose tissue, and intramuscular adipose tissue (IMAT). *Insets:* A zoomed in view of the psoas and paraspinal muscles highlights fat infiltration to the muscle represented by different ranges of skeletal muscle attenuation and intramuscular adipose tissue area. Attenuation ranges were defined: normal attenuation (+30 to +150 HU), abnormal (low) attenuation (+1 to +29 HU and 0 to -29 HU). Patient 1, stage I colon cancer, has 65% of their psoas and paraspinal muscle area within the normal attenuation range, and minimal IMAT infiltration. Patient 2, stage IIA rectal cancer, has 49% of their skeletal muscle within the normal attenuation range, and extensive IMAT infiltration.

8.3.3 Multidimensional body composition profiles associate with LOS

Patients were classified as being affected by sarcopenia, myosteatosis, and/or VO; individual patients had none, 1, any 2, or all 3 features (Figure 8-1A_d). Figure 8-1B illustrates two female patients of the same sex and age, with none, and all 3 features, respectively.

In multivariable analysis (Table 8-3), surgical approach (P<0.001), major complications (P<0.001), Canada *vs* UK (P<0.001), age (P<0.001) and 3 body composition profiles were associated with LOS. These profiles were characterized by myosteatosis + sarcopenia (IRR 1.27 (95% CI 1.12-1.43), P<0.001), myosteatosis + VO (IRR 1.25 (1.10-1.42), P=0.001) and myosteatosis + sarcopenia + VO (IRR 1.58 (1.29-1.93), P<0.001). Patients with myosteatosis trended toward longer LOS (P=0.054). As expected, major postoperative complications predicted longer LOS (IRR 2.42 (95% CI 2.18-2.68), P<0.001) however, the 3 body composition profiles predicted longer LOS in patients *with* and *without* major complications (Table 8-4), or if they were from Canada or the UK (Appendix VIII Suppl Table 2).

8.3.4 Post-surgical complications

The rate of 30-day hospital readmission was 9% (N=96; Canadian Cohort 1 N=42; UK Cohort N=54). Three body composition profiles predicted readmission in multivariable analysis

(Table 8-5): VO only (P=0.018), myosteatosis + VO (P=0.005), and sarcopenia + myosteatosis + VO (P=0.038). Other variables predictive of readmission included open surgical approach (P=0.002), major complications (P<0.001), and stage III cancer (P=0.027). The rate of major complications was 15% (N=175; Canadian Cohort N=73; UK Cohort N=102). None of the body composition profiles predicted major complications (Appendix IV Suppl Table 3). Mortality within 30 days post-surgery occurred in too few patients (Canadian Cohort N=0, UK Cohort N=10 (0.9%) to make statistical inferences.

8.4 Discussion

Multiple prior studies in CRC have assessed single features (SM, SMR, and VAT) as stand-alone measures, or at most examined 2 features at the same time.[7,9,12,14] While these studies identified a portion of patients at risk for poor outcomes, our analysis demonstrates without consideration of all three abnormalities, not all of the patients at risk are identified. We found body composition profiles characterized by abnormal skeletal muscle (myosteatosis + sarcopenia) negatively impacted on LOS, whereas body composition profiles characterized by VO predicted hospital readmission. Clearly the worst case body composition is the simultaneous presence of sarcopenia, myosteatosis and VO. A number of patients had sarcopenia, VO, or myosteatosis in isolation, which might reflect an early stage of the development toward a more deleterious body composition. The isolated presence of VO was significantly and independently associated with short-term hospital readmission and the isolated presence of myosteatosis showed a trend for increased LOS.

In prior work, we presented sex-specific threshold values for reduced SMI[5,36] and SMR[5], based on risk of mortality, not LOS. The current analysis was predicated on LOS as the primary outcome, for the reasons that mortality rates are low post-elective CRC surgery and thresholds

defined in relation to mortality may not be relevant for short-term postoperative outcomes.[31,37] We recognize major complications to be a major driver of LOS and readmissions, and our analyses were adjusted accordingly. Importantly, body composition profiles at risk of longer LOS and readmission were independent of major complications, whether patients were from Canada or the UK, surgical approach, and age. As expected, major complications significantly extended LOS for all body composition profiles; however at risk body composition profiles extended LOS by an additional 4 (myosteatosis + sarcopenia or VO) to 9 days (myosteatosis + sarcopenia + VO).When in the longer term, cancer-related mortality data become available for these cohorts, it will be possible to evaluate in what manner mortality and pre-surgery body composition may be associated.

The radiological definition of body habitus is an emerging theme, with considerable recent proliferation in surgical oncology. However, this area is rife with differing approaches, and it is not possible to aggregate results or directly compare relevant outcomes.[31,34] The need to standardize recording of surgical outcomes is an acknowledged issue[53], and the need to standardize body composition measures has become equally apparent[31,34] in the recent CRC surgical literature relating postoperative complications to body composition.[7-9,11-14,17-19,21,26-30,54] In our approach we sought to develop an understanding of body composition common to 2 regional patient populations. We selected 2 regions likely to be comparable with regard to body composition, and determined that regardless of patients being from Canada or UK they had the same postoperative risks conferred by body composition, even though the surgical practices differ between countries. Ethnicity has been described in the literature as factor related to various body composition features[25], however, data on ethnicity is not available at an individual level in our patient samples; we acknowledge that it should become part of future data collection efforts.

In CRC, CT body compositions analysis could be implemented as a pre-operative risk assessment to assist in treatment decision making. Body composition profiles identified here are pre-existing, we do not know their provenance or if they are reversible. Further clinical characterization of patient subsets showing abnormal body composition would be valuable to determine whether their surgical risk is associated with specific comorbidities[55], inflammation[56], or metabolic abnormalities.[57] Given that myosteatosis and VO are key risk factors, investigations for insulin resistance and metabolic syndrome might be of interest. Specific interventions remain to be investigated for their ability to support CRC patients with altered body compositions, and it is unknown whether and over what timescale these features could be modified. It is plausible that sarcopenia and myosteatosis have implications through reduced physical functioning and delayed return to activities of daily living.[42,43] In the future it will be of interest to evaluate the physical functioning of patients with altered body composition profiles. Evidence-based multimodal pre-habilitation programs have demonstrated some efficacy in contributing to improved cancer patient outcomes, including functional capacity and return to activities of daily living within ERAS programs.[58] It is unknown what effect such interventions would have on patients with altered body composition profiles, or would improve surgical outcomes.

This study contributes to advancing the understanding of CT data interpretation and suggests CT-defined features can help identify patients at risk for longer LOS and hospital readmission. Development of better risk stratification is essential to link patients to the appropriate therapeutic interventions.

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Table 8-1. Characteristics for the pooled colorectal surgical cohort.

Variables	Pooled CRC Cohort
Sample Size (N)	2100
Data Collection Time Frame	2006-2015
Study Type	Retrospective, cohort
Sex (N, %)	
Female	830 (39)
Male	1270 (61)
Age (years; mean ±SD)	66.6 ±11.9
BMI* (kg/m^2; mean ±SD)	27.7 ±5.6
Tumor Site (N, %)	
Colon	1279 (61)
Rectum	821 (39)
Surgical Approach (N, %)	
Laparoscopic Surgery	1580 (75)
Open Surgery	413 (20)
Converted	83 (4)
Unknown	24 (1)
Cancer Stage§ (N, %)	
I	385 (18)
II	713 (34)
III	887 (42)
IV	109 (5)
CT Analysis Software	SliceOmatic
HU range for muscle	-29 to 150
HU range for visceral adipose tissue	-150 to -50
HU range for subcutaneous adipose tissue	-190 to -30
Number of CT image observers	3
Outcomes Investigated	
Primary*	LOS
Secondary†	major complications (Grade ≥3)‖
	hospital readmission
	30-day mortality
LOS for Primary Admission	
Mean ±SD	9.42 ±10.79
Median (IQR)	6.00 (6.00)
30-day major complications (Grade ≥3) (N, %)	175 (15)
30-day hospital readmission (N, %)	96 (9)
30-day Mortality	10 (1)

BMI, body mass index; CRC, colorectal cancer; HU, Hounsfield Unit; IQR, interquartile range; L3, third lumbar vertebrae; LOS, length of hospital stay; N, number; SD, standard deviation

*† available for N=1136 patients from Canadian Cohort 1 (N=384) and UK Cohort (N=755)

‖ Complications graded according to the Clavien-Dindo classification

Table 8-2. Pre-surgical L3 CT-defined body composition features by sex and age for the pooled colorectal cancer (CRC) cohort (N=2100).

Body Composition Feature	Sex	Age Categories					P-Values†	Total
		<50	50-59	60-69	70-79	≥80		
Skeletal Muscle Area (SMA, cm^2)	Female (mean, SD)	113.8 (21.4)	105.9 (17.1)	104.2 (17.7)	97.2 (15.2)	90.6 (15.2)	P<0.001	
	N	75	138	238	245	134		830
	Male (mean, SD)	169.7 (32.1)**	165.3 (29.9)**	153.9 (24.7)**	141.5 (23.0)**	125.8 (20.5)**	P<0.001	150.0 (28.5)**
	N	97	219	422	378	154		1270
Skeletal Muscle Index (SMI, cm^2/m^2)	Female (mean, SD)	43.0 (8.1)	41.0 (6.7)	40.5 (6.7)	38.6 (6.4)	36.9 (5.9)	P<0.001	39.7 (6.8)
	N	75	138	238	245	134		830
	Male (mean, SD)	55.1 (9.9)**	53.8 (9.2)**	51.3 (8.3)**	47.9 (8.1)**	43.2 (7.4)**	P<0.001	50.0 (9.1)**
	N	97	219	422	378	154		1270
Skeletal Muscle Radiation Attenuation (SMR, HU)	Female (mean, SD)	39.6 (9.3)	36.0 (8.8)	31.4 (8.5)	27.8 (8.5)	24.8 (7.5)	P<0.001	30.8 (9.6)
	N	75	138	238	245	134		830
	Male (mean, SD)	42.0 (7.8)	37.6 (8.8)	32.9 (8.6)*	29.7 (8.3)*	28.1 (8.7)**	P<0.001	32.9 (9.4)**
	N	97	219	422	378	154		1270
Visceral Adipose Tissue Area (VAT, cm^2)	Female (mean, SD)	78.0 (69.8)	98.8 (72.3)	119.1 (79.1)	119.4 (77.2)	98.0 (71.0)	P<0.001	108.7 (76.4)
	N	75	136	235	240	131		817
	Male (mean, SD)	140.3 (93.1)**	189.8 (106.5)**	216.9 (114.9)**	214.4 (113.8)**	184.0 (95.7)**	P<0.001	201.6 (111.4)**
	N	97	218	419	374	153		1261
Visceral Adipose Tissue Index (VATI, cm^2/m^2)	Female (mean, SD)	29.6 (26.7)	38.3 (28.3)	46.5 (30.5)	47.1 (30.4)	40.0 (29.7)	P<0.001	42.7 (30.1)
	N	75	136	235	240	131		817
	Male (mean, SD)	45.7 (29.5)**	61.6 (34.0)**	71.9 (37.5)**	72.5 (38.5)**	63.3 (33.1)**	P<0.001	67.3 (36.9)**
	N	97	218	419	374	153		1261
Subcutaneous Adipose Tissue Area (SAT, cm^2)	Female (mean, SD)	242.5 (139.3)	231.9 (118.6)	255.1 (130.5)	229.7 (111.0)	186.5 (93.1)	P<0.001	231.6 (120.2)
	N	74	133	235	238	131		811
	Male (mean, SD)	192.8 (107.8)*	185.0 (85.4)**	188.2 (102.5)**	180.3 (79.2)**	146.4 (58.1)**	P<0.001	180.6 (89.8)**
	N	97	218	420	375	153		1263
Subcutaneous Adipose Tissue Index (SATI, cm^2/m^2)	Female (mean, SD)	92.1 (53.6)	89.8 (46.0)	99.7 (51.7)	90.5 (43.3)	39.5 (47.2)	P<0.001	91.0 (47.2)
	N	74	133	235	238	131		811
	Male (mean, SD)	62.4 (34.8)*	60.2 (27.9)**	62.5 (33.3)**	61.0 (26.9)**	50.1 (19.4)**	P<0.001	60.2 (29.5)**

	N	97	218	420	375	153		1263
Total Adipose Tissue Area (TAT, cm^2)	**Female (mean, SD)**	318.1 (192.7)	329.1 (175.2)	374.2 (188.2)	347.6 (168.5)	284.5 (144.9)	P<0.001	339.4 (176.6)
	N	74	133	235	236	131		809
	Male (mean, SD)	333.1 (185.6)	374.8 (174.5)*	403.0 (180.4)	393.5 (164.1)**	330.4 (132.8)*	P<0.001	381.1 (171.7)
	N	97	218	419	374	153		1261**
Total Adipose Tissue Index (TATI, cm^2/m^2)	**Female (mean, SD)**	120.8 (74.1)	127.4 (68.5)	146.1 (74.2)	137.4 (65.3)	116.7 (61.2)	P<0.001	133.4 (69.4)
	N	74	133	235	236	131		809
	Male (mean, SD)	107.7 (59.4)	121.8 (55.9)	133.8 (58.7)*	133.1 (55.8)	113.4 (45.0)	P<0.001	127.0 (56.6)
	N	97	218	419	374	153		1261*

CT, computed tomography; HU, Hounsfield Unit; L3, third lumbar vertebrae; N, number; SD, standard deviation
*P<0.05, **P<0.001 (Independent T-test) for the comparison between males and females within each age category and overall

† One-way ANOVA for the comparison between age categories within each sex

Table 8-3. Regression models for variables associated with extended length of hospital stay (LOS) and 30-hospital readmission in patients with colorectal cancer undergoing elective surgery

	Negative Binomial Regression Model† Outcome = Length of hospital stay (days)						Logistic Regression Model‡ Outcome = 30-day hospital readmission (yes vs. no)					
	Univariable			Multivariable			Univariable			Multivariable		
Variables	**N**	**IRR (95% CI)**	**P-Value**	**N**	**IRR (95% CI)**	**P-Value**	**N**	**OR (95% CI)**	**P-Value**	**N**	**OR (95% CI)**	**P-Value**
Pre-surgical Body Composition Profiles												
no features												
No Sarcopenia, No myosteatosis, No Visceral Obesity	320	1.0 (ref)		319	1.0 (ref)		320	1.0 (ref)		316	1.0 (ref)	
1 feature												
Sarcopenic	140	1.05 (0.92-1.20)	0.472	139	1.13 (0.99-1.29)	0.070	140	0.71 (0.28-1.82)	0.474	139	0.87 (0.33-2.30)	0.786
Visceral Obesity	90	1.17 (1.00-1.35)	**0.045**	90	1.01 (0.86-1.18)	0.909	90	2.44 (1.14-5.24)	**0.022**	89	2.66 (1.18-6.00)	**0.018**
Myosteatosis	181	1.46 (1.23-1.72)	**<0.001**	181	1.13 (1.00-1.27)	**0.054**	181	1.43 (0.71-2.89)	0.317	180	1.44 (0.69-3.03)	0.333
2 features												
Sarcopenia + Visceral Obesity	5	1.37 (0.89-2.12)	0.152	5	1.15 (0.63-2.10)	0.657	-	-	-	-	-	-
Sarcopenia + Myosteatosis	187	1.53 (1.32-1.78)	**<0.001**	186	1.27 (1.12-1.43)	**<0.001**	186	1.09 (0.52-2.30)	0.816	186	1.18 (0.54-2.57)	0.677
Myosteatosis + Visceral Obesity	148	1.29 (1.09-1.52)	**0.003**	148	1.25 (1.10-1.42)	**0.001**	147	2.79 (1.46-5.33)	**0.002**	146	2.72 (1.36-5.46)	**0.005**
3 features												
Sarcopenia + Myosteatosis + Visceral Obesity	42	1.73 (1.34-2.24)	**<0.001**	42	1.58 (1.29-1.93)	**<0.001**	42	2.64 (0.99-7.04)	0.052	42	2.98 (1.06-5.46)	**0.038**
Cancer Site												

Colon	728	1.0 (ref)		-			727	1.0 (ref)				
Rectum	408	1.11 (1.01-1.22)	**0.026**	-	-	NS	407	1.50 (0.99-2.29)	0.059	-	-	NS
Surgical Approach												
Laparoscopic	648	1.0 (ref)		640	1.0 (ref)		648	1.0 (ref)		635	1.0 (ref)	
Open	411	1.80 (1.64-1.96)	**<0.001**	397	1.85 (1.70-2.01)	**<0.001**	409	2.30 (1.47-3.59)	**<0.001**	390	2.08 (1.29-3.34)	**0.003**
Converted	77	1.74 (1.47-2.06)	**<0.001**	73	1.53 (1.31-1.79)	**<0.001**	77	2.19 (1.01-4.72	**0.047**	73	1.56 (0.67-3.68)	0.304
ASA Class (N, %)												
ASA 1	117	1.0 (ref)		-			117	1.0 (ref)				
ASA 2	794	1.32 (1.14-1.55)	**<0.001**	-	-	NS	794	1.54 (0.65-3.65)	0.327	-	-	NS
ASA 3+4	221	1.30 (1.09-1.55)	**0.004**	-	-	NS	219	2.82 (1.14-7.01)	**0.025**	-	-	NS
Major Complication within 30 days post-surgery												
no	960	1.0 (ref)		941	1.0 (ref)		960	1.0 (ref)		934	1.0 (ref)	
yes	173	2.20 (1.96-2.46)	**<0.001**	169	2.42 (2.18-2.68)	**<0.001**	172	4.65 (2.97-7.26)	**<0.001**	164	4.67 (2.89-7.56)	**<0.001**
Cancer Stage*												
I	281	1.0 (ref)		-			280	1.0 (ref)		275	1.0 (ref)	
II	342	1.02 (0.91-1.16)	0.702	-	-	NS	341	1.05 (0.56-1.99)	0.875	330	1.15 (0.58-2.28)	0.69
III	398	1.05 (0.93-1.84)	0.415	-	-	NS	398	1.86 (1.05-3.28)	**0.033**	389	2.10 (1.14-3.87)	**0.018**
IV	109	1.00 (0.84-1.19)	1.00	-	-	NS	109	1.15 (0.49-2.74)	0.747	104	0.87 (0.33-2.30)	0.886
Geographic Region												
Canada	384	1.0 (ref)		381	1.0 (ref)		382	1.0 (ref)				
UK	752	1.26	**<0.00**	729	1.33	**<0.001**	752	0.63	**0.030**	-	-	NS

		(1.15-1.39)	**1**		(1.22-1.46)			(0.41-0.96)				
Sex												
Female	450						449	1.0 (ref)				
Male	686	1.20 (1.09-1.31)	**<0.001**	-	-	NS	685	1.22 (0.79-1.88)	0.382	-	-	NS
Age (years)	1136	1.01 (1.01-1.01)	**0.001**	1110	1.01 (1.01-1.01)	**<0.001**	1134	1.01 (0.99-1.03)	0.260	-	-	NS
Diabetes												
no	1031	1.0 (ref)		-			1029	1.0 (ref)				
yes	105	0.92 (0.79-1.08)	0.310	-	-	NS	105	0.88 (0.42-1.87)	0.744	-	-	NS

ASA, American Society of Anesthesiologists; CI, confidence interval; IRR, incident rate ratio; LOS, length of stay; N, number; OR, odds ratio
Canadian cohort used American Joint Committee on Cancer (AJCC) version 6, UK cohort used Union for International Cancer Control's (UICC) version 5
†Model = Generalized linear model with negative binomial distribution, dependent variable = LOS; Best fit final model (Full Model (all variables significant at the univariable level) AIC = 6588.963, Fitted Model (removed non-significant variables from multivariable model) AIC = 6584.190). Variables not significant at univariable level = Cancer Stage, Diabetes; Variables non-significant at multivariable level = ASA Class (P=0.881), Cancer Site (P=0.681), Sex (P=0.110)
‡Model = Binary logistic regression model, dependent variable = 30-day hospital readmission (no. vs. yes; N=92 were readmitted); Best fit final model (Full Model (all variables significant at the univariable level) AIC =391.737, Fitted Model (removed non-significant variables from multivariable model) AIC = 390.808). Variables not significant at univariable level = sex, age, diabetes; Variables non-significant at multivariable level = study cohort (P=0.655), ASA Class (P=0.161)

Table 8-4. Estimated marginal mean LOS derived from the final adjusted NBM for each body composition profile demonstrating the independent effect of the three body composition profiles on LOS with or without major post-operative complications

Body composition profiles based on the absence or presence of sarcopenia, myosteatosis, or visceral obesity	Major Complication within 30 days post-surgery	Estimated Marginal Mean LOS (95% CI)	Mean Difference (days)	P-Value
no features				
No Sarcopenia, No Myosteatosis, No Visceral Obesity	yes	16.44 (14.62-18.48)[c]	9.64	<0.001
	no	6.80 (6.22-7.44)[a]		
1 feature				
Sarcopenic	yes	18.58 (16.05-21.52)	10.90	<0.001
	no	7.69 (6.81-8.68)		
Visceral Obesity	yes	16.59 (14.03-19.62)	9.73	<0.001
	no	6.86 (5.94-7.94)		
Myosteatosis	yes	18.53 (16.28-21.09)	10.86	<0.001
	no	7.66 (6.86-8.56)		
2 features				
Sarcopenia + Visceral Obesity	yes	18.85 (10.24-34.70)	11.05	0.002
	no	7.80 (4.27-14.23)		
Sarcopenia + Myosteatosis*	yes	**20.86 (18.21-23.89)[d]**	**12.23**	**<0.001**
	no	**8.63 (7.74-9.61)[b]**		
Myosteatosis + Visceral Obesity*	yes	**20.57 (18.03-23.47)[d]**	**12.06**	**<0.001**
	no	**8.51 (7.63-9.49)[b]**		
3 features				
Sarcopenia+ Myosteatosis + Visceral Obesity*	yes	**25.90 (21.12-31.78)[d]**	**15.19**	**<0.001**
	no	**10.72 (8.86-12.97)[b]**		

*profiles identified from negative binomial regression that are significantly (P<0.05) associated with extended LOS (compared to no features) independent of major complications, study cohort, surgical approach, and age

[a,b] Significantly different from no features (No sarcopenia, No myosteatosis, No Visceral Obesity) with no major complications

[c,d] Significantly different from no features (No sarcopenia, No myosteatosis, No Visceral Obesity) with major complications

CHAPTER 9: Discussion and future directions

9.1 The status of diagnostic criteria

Cachexia has devastating effects on patients including weakness, fatigue, loss of independence, poor treatment tolerance, and death. Over the course of history, up until the present day, cachexia has been described by several signs and symptoms including involuntary weight loss (WL), wasting of skeletal muscle (SM) and adipose tissues, anorexia, and gastrointestinal symptoms.[1] However, the specific etiology has been difficult to define due to its complex and multifactorial origins related to the underlying disease and its treatment. Owing to the prominence of reduced food intake (FI) as well as the presence of inflammation; cachexia is also classified as a form of disease-associated malnutrition.[2-4] There is no widely agreed upon definition or diagnostic criteria for cachexia or disease-associated malnutrition, which is consequently reflected within the International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10), which sets the international standard for reporting disease and health conditions.[5] The ICD-10 includes a core description of cachexia as a condition of involuntary WL >10% associated with chronic illness, characterized by atrophy of SM, due to inadequate dietary intake, malabsorption, or hypermetabolism, but lacks diagnostic criteria.[5,6]

International research consortia including the Global Leadership on Malnutrition (GLIM) and the Society on Sarcopenia, Cachexia and Wasting Disorders,[7-9] have focused research efforts on developing international consensus for a definition and diagnostic criteria for disease-associated malnutrition, cachexia, and cancer cachexia.[7-9] These efforts are complimentary and have produced consensus definitions with overlapping core concepts, which are common to definitions outlined in the ICD-10, but that also include a minimum set of diagnostic criteria which require development and validation (Table 9-1).[7-9]

The overarching theme of this thesis has been to advance the development of diagnostic criteria for the diagnosis of cancer cachexia based on the International Consensus Framework for the Definition and Classification of Cancer Cachexia.[9] Key requirements for diagnostic criteria include clinical availability, cost and time effectiveness, and clinical utility.[3,8-10] The research presented throughout this thesis includes several advances related to the development of diagnostic criteria for cancer-associated WL, computed-tomography (CT)-defined SM and adipose tissue, FI, and inflammation.

9.1.1 Diagnostic criteria for cancer-associated weight loss

In the ICD-10, cachexia is diagnosed based on WL >10%.[5] The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) has a grading scheme (Grade 1-5) intended to capture the severity of an adverse event, along with recommendations for appropriate interventions.[11]WL is included as an adverse event (Grade 1: 5-10%; Grade 2: 10-20%; Grade 3: >20%), but grades 4 and 5 WL are not defined, the etiology of WL is unaccounted for, and the impact of WL based on initial body weight is not considered. In Chapter 2, I presented and validated an updated classification for cancer-associated WL by combining %WL and BMI (Grades 0 to 4), which stratified patients according to overall survival (OS). An important finding from this analysis is that even small amounts of weight loss (i.e. 2.5-5.0%) associated with reduced OS, which may go undetected when using the classifications suggested in the ICD-10 and NCI CTCAE. The updated WL grades have been validated in three additional cohorts representing different care settings (palliative care, medical oncology) and cancer types (e.g. head and neck and lung cancers).[12-14] Vagnildhaug et al.[14], further demonstrated that higher WL grades (i.e. more severe) identified patients likely to progress to worsening stages of cancer cachexia; with worsening of physical function, food intake, and

appetite. The WL grades have also been included in the most recent European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on nutrition in cancer patients.[15] Grading the severity of WL with consideration for initial body weight is an improvement over the bivariate classification of >10% used in the ICD-10, and contributes to refining the severity grades used in the NCI CTCAE. But questions remain, the WL grades were based on mortality as an outcome and will need to be validated against other outcomes that are important to patients including activities of daily living, quality of life, and tolerance to cancer treatment. Furthermore, we will have to consider how WL grades can be adopted into clinical practice.

9.1.2 Diagnostic criteria for CT-defined skeletal muscle

Provisional diagnostic criteria for cancer cachexia include the identification of SM depletion, based on thresholds defined for several different assessment methods including cross-sectional imaging (CT or magnetic resonance imaging (MRI)), dual energy x-ray imaging (DEXA), anthropometry (mid upper-arm muscle area), and bioelectrical impedance analysis.[9] There was no consensus for any one assessment method, but preference was given to SM quantified using computed tomography (CT). Sex-specific thresholds related to mortality were presented for CT-defined SM that were originally developed in obese patients with advanced cancer.[16]. The use of CT to quantify SM and adipose tissue is a new and developing area of assessment. Since these provisional criteria were presented our knowledge and research efforts have greatly expanded. There has been a proliferation of different methods (e.g. tissue-specific thresholds, software packages, tissue attenuation ranges, and CT image landmarks) used in the quantification of SM as well as adipose tissues using CT, which has contributed significant heterogeneity in the literature.[17,18] Additional CT metrics have appeared including SM radiation attenuation, adipose tissue (visceral and subcutaneous) areas and attenuation, which appear to

have different associations to different clinical outcomes.[19-26] We are beginning to appreciate how patient characteristics such as age, sex, and total adiposity impact on features of body composition and need to be factored into our analyses.[25-27] This new knowledge has presented a great challenge in attempting to identify data sets for aggregation in order to explore some of these concepts. In chapter 8, I present an advanced analysis using body composition metrics derived from CT image analysis in preoperative colorectal cancer patients. I created a large aggregated data set of pre-operative CT images to facilitate the comparison of body composition features by sex and age within a similar patient population. I defined thresholds for SM, SM attenuation, and visceral obesity that related to surgical outcomes. Lastly, I was able to explore the impact of a multidimensional body composition profile and demonstrate an increased risk of longer length of hospital stay (LOS) and 30-day hospital readmission. This analysis advanced our understanding of how age and sex affect features of body composition and that multidimensional assessments of body composition beyond SM mass are necessary to capture patients with the greatest risk of poor surgical outcomes. Adoption of CT-defined body composition into routine clinical practice remains to be determined. There are efforts underway in Edmonton, Alberta and Queensland, Australia to understand if using CT as an assessment of body composition is feasible in clinical practice. Once demonstrated to be feasible, it would then be possible to determine how CT-body composition could augment nutrition clinical practice in areas such as the identification of patients with altered body composition, tailoring of nutrition support (e.g. calculation of protein needs based on lean body mass (LBM)), and improved monitoring of effectiveness of nutrition interventions (e.g. gains in LBM).[28]

9.1.3 Diagnostic criteria for food intake

There are many assessments of FI to explore as diagnostic criteria for the etiology of involuntary WL.[9] Reduced FI is a key feature of cancer cachexia for which there are multiple possible etiologies, and identifying reductions in FI is recommended as an essential first step to guide nutrition care.[15] Information about FI is collected on the majority of nutrition screening tools used in the oncology setting. However there are differences in measurement scales and time frames for how reductions in FI are captured. In Chapter 5, I demonstrated that despite differences in measurement scales there are points of alignment between tools that allows them to be combined into a single diagnostic criterion for FI. I further demonstrated in multivariable analysis adjusted for cancer type, cancer stage, functional status, age, and sex that reductions in food intake had the strongest overall association to WL, suggesting that reduction in FI play an important role in the etiology of WL. Few studies have provided a quantitative value for energy and protein intake corresponding to patient reported categories of food intake, however "severely reduced" FI appear to be associated with energy intakes <500 kcal per day which is grossly insufficient to support the maintenance of body weight.[29] This supports the conceptual validity of these patient-reported categories to identify patients with low intakes.

9.1.4 Diagnostic criteria for systemic inflammation

Alterations in metabolism are the most difficult criteria to define. They are driven by an individual patient's response to the presence of a tumor and cancer treatment, which induce inflammation, excess catabolism, and hypermetabolism to a variable extent. There is tremendous heterogeneity in tumor characteristics (e.g. grade, specific mutations, metabolic rate) and in how a patient will respond to both the tumor and its treatment, which makes the characterization of individual metabolic alterations incredibly difficult.[30] There is potentially a long list of tumor-derived factors and mechanisms contributing to SM and adipose tissue wasting.[31,32] These factors

can be proteolytic (e.g. IL-6, growth/differentiation factor 15 (GDF15) and/or lipolytic (e.g. leukemia inhibitory factor (LIF), parathyroid hormone-related protein (PTHrP)) in their actions and can be produced directly by the tumor, or may arise from crosstalk between the tumor and host immune system.[31,32] However, clinical evidence is limited; clinical measures for many of these factors are not available, the prevalence of these factors and the magnitude of their contribution to weight loss in humans is not well characterized. If we move out from the molecular etiologies and examine the overall metabolic processes such as the rates of protein synthesis, protein degradation, and energy expenditure there are clinical studies in patients with cancer cachexia suggesting increased rate of whole-body protein turnover and increased resting energy expenditure.[31] However, these types of measurements are limited to the research setting as they are invasive, time consuming, and expensive and unlikely to be adapted into clinical practice. The evidence related to the identification of metabolic alterations is in a rudimentary state of development, and their measurement for the time being is limited to the research setting. Treatment response is a clinically relevant indicator of altered metabolism, whereby the presence of tumor is driving the underlying metabolic changes.[9,33] However, it has not been collected as part of cancer cachexia research studies, but moving forward would seem an essential piece of information to understand responsiveness to nutrition interventions.

The most widely accepted clinical proxy for altered metabolism is C-reactive protein (CRP).[9] CRP was not frequently part of the data collected in the aggregated clinical cachexia studies (e.g. <40% of patients in the aggregated data set had a measure of CRP). In Chapter 6, I demonstrated that CRP was significantly independently associated with WL in multivariable analyses when reductions in FI were also accounted for. These results indicate that CRP is, in part, contributing to the development of cancer-associated WL. However, it was clear that

neither CRP nor reductions in FI explained all of the WL in cancer patients. This was not surprising given the other factors likely to contribute to WL. As an example PTHrP, a tumor-derived factor, was demonstrated to independently increase the risk of WL in a multivariable model adjusted for CRP, PS, cancer stage, albumin, and serum calcium. Although this study did not account for reductions in FI, it is preliminary evidence that other, and possibly tumor-derived, factors are contributing to WL.[34,35] At present what these other factors might be is largely unknown, and substantial advancement with regard to their identification and characterization will be required before they can be considered as diagnostic criteria. In the meantime, the addition of CRP to assessments of FI may help the clinician differentiate patients with different etiologies for their WL (e.g. predominantly reduced FI, or combination inflammation and reduced FI), which might also provide an initial indication about their ability to respond to nutrition interventions.[8,36,37]

9.2 Strengths and limitations of a data driven approach

Health-related data is highly valued, as it can be used to provide information about disease characteristics, prevalence, risk factors, clinical practice, and outcomes of treatment.[38] However, availability of data sets large enough to fully examine these features is limited, and therefore aggregation of health-related data from multiple studies is necessary. Data aggregation for secondary analysis enhances our ability to compare patient populations and to answer research questions quickly and inexpensively.[39] Additionally, findings generated from secondary analyses may be more generalizable than findings from a single center.

I adopted a data-driven approach, a priori, to advance the development of diagnostic criteria for cancer cachexia. However, there were no large aggregated data sets specific to cancer cachexia available for analysis, and therefore a main objective of my thesis was to create large

aggregated data sets from clinical research studies conducted in cancer cachexia. In the process of aggregating data, it was evident that data related to candidate diagnostic criteria were not collected systematically: a heterogeneous mix of measures and assessments were used and criteria were collected with varying frequency across data sets (e.g. most frequent = WL; least frequent = metabolic alterations). The type of information gathered within these datasets highlights that our understanding pertaining to the different concepts of cancer cachexia are in various stages of progress. The balance of data included criteria related to weight loss and qualitative assessments of food intake, and few data sets included criteria related to skeletal muscle depletion, and metabolic alterations. The heterogeneity and lack of data pertaining to some of these concepts is particularly challenging. Data related to metabolic alterations were limited to a single clinical measure of inflammation, which was influenced by the prevailing ordering practices of a given country. For example, CRP (an acute phase protein produced in the liver) was common among European data sets, but not typical of Canadian data sets, which were more likely to have included neutrophils and lymphocytes (immune cells made in the bone marrow). Both of these measures are demonstrated to be strong prognostic indicators for overall survival[40,41], but they represent different aspects of the inflammatory process, and it is not clear if they can be compared as etiological criteria for WL. The relationship between neutrophils, lymphocytes and WL needs to be evaluated to determine if these measures could be used interchangeably as etiological diagnostic for WL.

A way forward for cachexia researchers would be to generate an agreed upon minimum data set that would facilitate data sharing and aggregation, similar to the approach adopted by the GLIM group.[8] There are some excellent examples of systematic data collection using minimum data sets that could guide and inform this process. nutritionDay worldwide is a large scale,

international data collection effort with the goal to reduce disease-associated malnutrition among hospitalized individuals and nursing home residents.[42] Nutrition Day is a 1-day data collection initiative involving 7,000 institutions, the same data is collected across participating sites using a standardized online data capture tool, and includes additional data capture elements for hospitalized oncology patients. Enhanced Recovery After Surgery (ERAS) protocols are also excellent examples of international systematic data collection initiatives in the surgical setting.[43] In addition to standardized data collection the ERAS Society recently developed a framework to facilitate standardization for reporting ERAS related studies.[44] Although the type of nutrition data collected within these different initiatives may not capture data relevant to the diagnosis of cancer cachexia, they provide a model and platform of how to accomplish standardized data collection. Additionally, there are numerous examples of how these initiatives used standardized data to demonstrate improved clinical outcomes, influence health systems, and change clinical practice.[45-51]

There are however known limitations with aggregated data that include the lack of control over the types of patients originally included, which variables were collected, how variables were measured and recorded, completeness of the data collected, and limited longitudinal follow-up.[39] Other limitations can arise when changes to the standardized data fields are made, and while these are necessary to capture new developments and advancement, it can limit the evaluation of trends over time. In my work with Alberta Health Services' ERAS implementation program (AHS EIP), presented in Chapter 7, obtaining data that was not part of the medical record (e.g. weight loss history, postoperative nutritional supplement consumption, and mobility), was a challenge, and these fields had the highest rate of missing values. Some of these challenges can be mitigated through data linkages with other data sources where essential data

can be acquired. For example, a portion of the data presented in Chapter 8 was acquired from data linkages between our AHS EIP data and our provincial Picture Archiving Communication System (PACS). A subset of patients from AHS EIP were linked with CT images stored in PACS, and this data was used to identify CT-defined body composition features that predicted surgical outcomes. Development of minimum data sets for cachexia could be informed and aligned with these efforts and vice versa, our efforts to develop more robust diagnostic criteria for cancer cachexia may improve the type of nutritional data captured in these large standardized data collection initiatives.

Lastly, a main recommendation for the development of diagnostic criteria is that they relate to meaningful patient-centered outcomes. Reporting of patient centered outcomes also suffers from heterogeneity. In 2012, the International Consortium for Health Outcomes Measurement (ICHOM) Initiative was created to develop standard sets of patient-centered outcomes according to medical condition.[52] The standard recommended set of outcome measures were defined based on the need to encompass overall disease control (e.g. overall survival (OS), cancer-specific survival (CSS), and recurrence-free survival (RFS), treatment complications (US National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE); Clavien-Dindo classification), and quality of life (European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life C30 tool), in addition to condition specific assessments.[52-56] Similar efforts are underway to standardize outcome measurement in anaesthesia and perioperative medicine trials.[57] These core outcomes include those related to surgical complications, organ failure and survival, cancer-specific and long term survival, patient-reported outcomes (e.g. QOL, satisfaction), health resource utilization (e.g. LOS, cost, fitness for discharge).[58]

In our approach to the development of diagnostic criteria, we have considered these larger ongoing efforts of outcome standardization, and have evaluated diagnostic criteria in relation to outcomes that are of interest to medical and surgical oncologists to help support their validity and use. Identification of SM depletion using CT has gained particular attention in both medical and surgical oncology. The identification of SM depletion has been associated with outcomes related to disease control, treatment complications, and important patient reported outcomes (e.g. physical function, quality of life).[22,26,59,60] The assessment of SM may change how oncologists dose chemotherapy, and new clinical trials are underway to test this paradigm.[61,62]

9.3 Future development and implementation

9.3.1 Future development: acquisition of data relevant to cancer cachexia

Currently available data sets for the development of diagnostic criteria for cancer cachexia are limited with regard to the breadth and depth of data they contain. Additional data will be required to expand our understanding in specific areas, such as metabolic alterations. A clear distinction must be made between what kind of data are feasible to collect in the clinical versus research setting. Large scale initiatives such as nutritionDay, ERAS programs, and GLIM have provided valuable information related to the type of clinical and nutrition data that currently collected, as well as to what is feasible in large scale data collection efforts.[2,3,63,64] Missing assessments include SM (adipose tissue), biological indicators of inflammation, and assessments of physical function and quality of life. The feasibility of acquiring this type of data in different practice settings needs to be determined. One such effort is currently underway, the International Nutrition Audit in FORegut TuMors (INFORM), to understand what types of data collection specific to nutrition care practices are feasible to collect as part of clinical practice, which will help generate a common minimum data set.[65]

Large organizations such as the Southwest Oncology Group (SWOG) Cancer Research Network[66], or the Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN)[67] design and conduct large multi-center clinical trials, and as a consequence collect large amounts of in-depth clinical, treatment, biospecimen, and outcome data. These networks are uniquely positioned to contribute to the understanding of alterations in metabolism. Linkages between clinical data and biological samples may allow for the exploration of underlying mechanisms of SM catabolism, tumor-derived factors, and the effects cancer treatment. For example, data available for retrospective analysis enables longitudinal assessments of SM changes using CT in response cancer treatments, which provides information about the impact of treatment regimens on SM. Knowledge about the types of treatments that affect SM could inform development of future clinical trials for interventions to support the maintenance of SM.

9.3.2 Future development: how can diagnostic criteria be used to advance nutrition care

Goals for nutrition care in cancer patients are to identify and treat nutrition and metabolic alterations to maintain SM and function, to limit interruptions in treatment, and improve quality of life.[15] Nutrition interventions include dietetic counseling, oral nutrition supplements (ONS), and enteral or parenteral nutrition. Unfortunately, few high quality studies (e.g. randomized clinical trials) demonstrate effectiveness of these types of interventions in patients with cancer cachexia.[68,69] In a meta-analysis by de van der Schueren et al.[68] patient selection criteria (e.g. included patients with weight loss of any etiology and near the end of life), lack of clinically relevant patient-centered outcomes, and low compliance to nutrition prescriptions have limited interpretations regarding the effectiveness of nutrition interventions. In a sub-set analysis patients consuming a high protein oral nutritional supplement (ONS) enriched with omega-3 fatty acids,

demonstrated improved body weight and SM while undergoing chemoradiation therapy.[68] The authors offered that omega-3 fatty acids may have contributed to the attenuation the inflammatory response and the high protein content contributed to maintenance of target protein intakes. Multimodal treatment approaches are recommended for the treatment of cancer cachexia, which includes symptom management, nutrition interventions, physical therapy, and psychosocial support, and these types of approaches have reported significant improvements in body weight, physical function, and quality of life.[70-73] A randomized clinical trial investigating the effect of a multimodal intervention that includes nutrition counseling, a protein dense ONS enriched with omega-3 fatty acids, and an anti-inflammatory agent is currently underway.[74]

Early identification of nutrition and metabolic alterations is essential to guide appropriate interventions. The diagnostic criteria developed and presented in this thesis identify patients with disparate clinical outcomes, and offer an initial clue about to characterize the etiology of WL. In Chapters 5 & 6, reductions in FI and CRP were identified as etiological criteria for WL, with reductions in FI having the strongest association. Nutrition interventions aimed at augmenting food intake with dietary counseling and ONS typically fall short of recommended energy intakes by 300-800 kcal/day, at this point in time it is not clear how to overcome this gap.[68] The use of artificial nutrition support (enteral or parenteral) in cancer patients is somewhat controversial, although it is recommended in cases where FI is severely compromised, the benefits and risks must be weighed carefully and commencement of artificial nutrition support is not recommended a prognosis of less than 2 months.[15] Validated diagnostic criteria could be applied to identify patients for whom artificial nutrition support should not be initiated (i.e. patients with poor prognosis), but it is not clear how they could be used to identify patients who would benefit this approach. Therapeutic agents that enhance FI by targeting appetite centers in the brain are

promising treatment strategies. Agents such as ghrelin or ghrelin analogues (e.g. anamorelin)[75-77] have been tested in clinical trials and demonstrated significant improvements in the LBM of advanced lung cancer patients. Other molecules of interest currently under investigation in animal models include melanocortin receptor antagonists (e.g. Melanocortin-4 Receptor Antagonists)[78], and antagonists to GDF15.[79] These types of therapies offered as part of multimodal interventions that include nutrition support could offer significant improvements in the treatment of cancer cachexia. Carefully designed clinical trials are required to test these classes of agents. Diagnostic criteria could be applied to help select patients likely to receive a benefit of the therapy (i.e. targeted etiology of WL and good prognosis).

Well-designed clinical trials are essential to test whether treatments for cancer cachexia are safe and effective. As these efforts continue to advance what can be done in the meantime to ensure that patients with cachexia are correctly identified, and that they receive nutrition and metabolic care?[80] The development of diagnostic criteria that are linked to patient-centered outcomes is progress towards more effective identification and treatment of patients with cancer cachexia. Advancement of clinical trial design for nutrition interventions are beginning to appear, where the effectiveness of nutrition care is being evaluated against the limiting of Grade ≥3 treatment toxicities as a primary outcome.[81]

The assessments proposed within this thesis include WL, FI, CT-defined body composition, and CRP, which are acquired by different people involved in the care of patients with cancer. Alignment of these assessments in a common way would require leadership from the health system and across disciplines, headed by the oncologist physician or surgeon to foster interdisciplinary collaboration to ensure care providers are aware of what information is needed to identify a patient a risk of cancer cachexia and what steps should follow thereafter.[82] ERAS

programs offer excellent examples of how to develop capacity within the health system and for care providers. ERAS programs require health systems and care providers to examine current care practices and how care is delivered to develop implementation strategies that are best suited to the local context. This implementation process contributes to the successful implementation of multimodal evidence based guidelines, and collection of data to evaluate implementation processes, evaluate change in clinical practice and improve outcomes.[64] It seems plausible that a similar type of process could be applied to oncology, where efforts to integrate supportive/palliative care (inclusive of nutrition) alongside cancer care pathways have proven effective.[83,84] There are evidenced based care pathways for the diagnosis and treatment of different cancer types, but these pathways do not incorporate nutrition care alongside cancer care.[85,86] I see an opportunity to align diagnostic criteria with nutrition care guidelines to create standardized nutrition care pathways for patients with cancer cachexia. Standardized nutrition care pathways could contribute the development of the nutrition intervention component that is essential for the multimodal treatment of cancer cachexia.[87-91] Standardized nutrition care pathways are risk stratified, and identify the need for increased levels of nutrition intervention based on risk of an outcome.[92] Within this thesis I have identified candidate diagnostic criteria based on nutrition assessments that help identify patients at risk of poor outcomes, which could be used to develop an algorithm for nutrition care. This is an area that is open for development and future work will be directed toward this opportunity.

9.4 Conclusion

In conclusion the research presented in this thesis offers an initial step toward the development of diagnostic criteria for cancer cachexia. Identifying patients with increased risk of poor outcomes in different care settings can help guide care. Prospective validation of these

concepts is required. Health data are essential to the development of diagnostic criteria and the hope is the data collection efforts will continue and begin to incorporate additional parameters essential to the diagnosis of cancer cachexia.

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Table 9-1. A summary of proposed diagnostic criteria for cancer cachexia, cachexia, and malnutrition.

Diagnostic Criteria	Cancer Cachexia[9]	Cachexia[7]	Malnutrition[8]
Weight loss	>5% previous 6 months	>5% in previous 12 months or less	>5% previous 6 months
	>2% if BMI<20		>10% if longer than previous 6 months
BMI (kg/m^2)	<20	<20	<20 if <70 years
			<22 if >70 years
			<18.5 if <70 years (Asia)
			<20 if >70 years (Asia)
Skeletal muscle	Appendicular SMI consistent with sarcopenia (males <7.26 kg/m2; females <5.45 kg/m2) MUMA by anthropometry (men <32 cm2, women <18 cm2);31 CT lumbar SMI (men <55 cm2/m2; women <39 cm2/m2);33 whole body FFM BIA (men <14.6 kg/m2; women <11.4 kg/m2).	Low fat free mass	Reduced by validated body composition measuring techniques (DEXA, BIA, CT, MRI)
Muscle Strength	None	Decreased	None
Food Intake	Reduced food intake Anorexia	Anorexia	<50% of estimated requirements for > 1 week, or any reduction for >2 weeks, or any chronic GI condition that adversely impacts food assimilation or absorption
Inflammation	Systemic inflammation	CRP IL-6	Acute disease – severe Chronic disease – mild to moderate
Fatigue	None	Fatigue	None
Other Biochemistry		Hemoglobin <120 g/L Albumin <35 g/L	

BIA, bioelectrical impedance analysis; BMI, body mass index; CRP, c-reactive protein; CT, computed tomography; DEXA, dual energy x-ray absorptiometry; FFM, fat free mass ; GI, gastrointestinal; IL, interleukin; MUMA, mid upper-arm muscle area; L3, third lumbar vertebrae; SMI, skeletal muscle index

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Appendix I

Chapter 2 Supplementary Table 1. Predictive value of BMI and WL as continuous variables in a multivariable Cox proportional hazard model applied to advanced cancer stages only (stages III+IV).

	B	SE	Wald	df	P-value	HR	95.0% CI for HR	
							Lower	Upper
BMI	-.010	.003	11.885	1	.001	.990	.984	.996
%WL	-.015	.002	64.564	1	.000	.985	.981	.989
Sex								
Male								
Female	-.044	.030	2.086	1	.149	.957	.902	1.016
Age	.006	.001	21.687	1	.000	1.006	1.003	1.008
Cancer Diagnosis			545.429	11	.000			
colorectal								
breast	.361	.089	16.582	1	.000	1.434	1.206	1.706
gastro-esophageal	.637	.057	124.677	1	.000	1.891	1.691	2.115
genitourinary	.569	.077	54.269	1	.000	1.766	1.518	2.055
Hean & neck	-.428	.066	41.882	1	.000	.652	.573	.742
other	.365	.080	21.091	1	.000	1.441	1.233	1.684
other GI	.718	.085	72.112	1	.000	2.050	1.737	2.419
pancreas	.765	.067	132.426	1	.000	2.150	1.887	2.449
respiratory	.637	.046	194.634	1	.000	1.890	1.729	2.067
unknown primary	.663	.123	29.021	1	.000	1.940	1.525	2.470
hematological	.062	.111	.311	1	.577	1.064	.856	1.322
liver/intrahepatic bile ducts	.987	.132	55.670	1	.000	2.683	2.070	3.476
Performance Status			798.326	4	.000			
0								
1	.287	.050	32.292	1	.000	1.332	1.207	1.471
2	.730	.055	177.605	1	.000	2.076	1.864	2.311
3	1.149	.055	437.338	1	.000	3.155	2.833	3.514
4	1.727	.093	344.410	1	.000	5.622	4.685	6.747

B, beta coefficient; BMI, body mass index; df, degrees of freedom; GI, gastrointestinal; HR, hazard ratio; SE, standard error; %WL, percent weight loss.

Appendix II

Chapter 2 Supplementary Table 2. Predictive value of BMI adjusted WL Grades in a multivariable Cox proportional hazard model applied to advanced stages only (stage III + IV)

	B	SE	Wald	df	P-value	HR	95.0% CI for HR	
							Lower	Upper
BMI adjusted WL Grades			144.225	4	.000			
0								
1	.118	.062	3.670	1	.055	1.125	.997	1.270
2	.204	.057	12.621	1	.000	1.226	1.096	1.372
3	.323	.051	39.507	1	.000	1.381	1.249	1.527
4	.541	.052	108.573	1	.000	1.717	1.551	1.901
Sex								
Male						1.000		
Female	-.058	.030	3.607	1	.058	.944	.890	1.002
Age	.006	.001	22.239	1	.000	1.006	1.003	1.008
Cancer Diagnosis			544.858	11	.000			
colorectal								
breast	.373	.089	17.697	1	.000	1.452	1.220	1.727
gastro-esophageal	.641	.057	126.234	1	.000	1.899	1.698	2.123
genitourinary	.571	.077	54.473	1	.000	1.769	1.520	2.059
head & neck	-.410	.066	38.387	1	.000	.664	.583	.756
other	.363	.080	20.737	1	.000	1.437	1.230	1.680
other GI	.713	.085	71.159	1	.000	2.040	1.728	2.407
pancreas	.774	.066	135.918	1	.000	2.168	1.904	2.469
respiratory	.646	.046	200.856	1	.000	1.908	1.745	2.086
unknown primary	.690	.123	31.360	1	.000	1.994	1.566	2.538
hematological	.073	.111	.433	1	.510	1.076	.866	1.337
Liver/intrahepatic bile ducts	.994	.132	56.440	1	.000	2.701	2.084	3.500
Performance Status			780.587	4	.000			
0								
1	.269	.051	28.344	1	.000	1.309	1.186	1.446
2	.706	.055	166.165	1	.000	2.025	1.819	2.254
3	1.126	.055	421.047	1	.000	3.085	2.770	3.435
4	1.694	.093	330.672	1	.000	5.443	4.535	6.534

B, beta coefficient; BMI, body mass index; df, degrees of freedom; GI, gastrointestinal; HR, hazard ratio; SE, standard error; %WL, percent weight loss.

Appendix III

Chapter 5 Supplementary Table 1. Univariable multinomial logistic regression analysis for the association of selected variables to cancer-associated weight loss for three different models based on food intake assessments from three data sets: PG-SGA, I-VVAS, and the MNA

PG-SGA MLR model		**Univariable MLR Analysis**											
		WL 2.5-5.9%			**WL 6.0-10.9%**			**WL 11.0-14.9%**			**WL ≥15.0%**		
Variables in model	**N (%)**	**N= 1139 (28.8%)**			**N= 1347 (21.9%)**			**N= 816 (13.2%)**			**N= 1082 (17.6%)**		
		β (SE)	**OR (95% CI)**	**P-Value**	**β (SE)**	**OR (95% CI)**	**P-Value**	**β (SE)**	**OR (95% CI)**	**P-Value**	**β (SE)**	**OR (95% CI)**	**P-Value**
Current Food Intake													
severely reduced*	1284 (20.8)	1.19 (0.13)	3.28 (2.53-4.24)	<0.001	2.08 (0.12)	8.02 (6.30-10.21)	<0.001	2.86 (0.14)	17.41 (13.14-23.07)	<0.001	3.39 (0.14)	29.79 (22.69-39.13)	<0.001
normal food, reduced amount	2765 (44.9)	0.83 (0.08)	2.29 (1.95-2.69)	<0.001	1.39 (0.08)	4.02 (3.41-4.74)	<0.001	1.86 (0.11)	6.43 (5.15-8.02)	<0.001	2.10 (0.11)	8.19 (6.57-10.21)	<0.001
normal food, normal amount	2112 (34.3)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
Cancer Diagnosis*													
respiratory	1913 (31.1)	0.53 (0.10)	1.70 (1.40-2.08)	<0.001	0.80 (0.11)	2.23 (1.81-2.74)	<0.001	1.14 (0.14)	3.12 (2.38-4.08)	<0.001	1.14 (0.13)	3.12 (2.42-4.03)	<0.001
other	712 (11.6)	0.24 (0.14)	1.27 (0.97-1.67)	0.078	0.72 (0.13)	2.06 (1.59-2.67)	<0.001	0.91 (0.17)	2.49 (1.78-3.49)	<0.001	1.19 (0.16)	3.27 (2.41-4.43)	<0.001
genitourinary	386 (6.3)	0.61 (0.18)	1.83 (1.28-2.62)	0.001	1.20 (0.17)	3.30 (2.36-4.63)	<0.001	1.39 (0.21)	4.02 (2.66-6.08)	<0.001	1.88 (0.19)	6.58 (4.58-9.46)	<0.001
upper GI	950 (15.4)	0.92 (0.15)	2.52 (1.89-3.36)	<0.001	1.65 (0.14)	5.20 (3.96-6.84)	<0.001	2.23 (0.16)	9.27 (6.72-12.79)	<0.001	2.65 (0.15)	14.10 (10.47-19.00)	<0.001

lower GI	1009 (16.4)	0.86 (0.13)	2.37 (1.86-3.03)	<0.001	1.35 (0.12)	3.84 (3.02-4.90)	<0.001	1.59 (0.16)	4.90 (3.61-6.66)	<0.001	1.49 (0.15)	4.42 (3.29-5.94)	<0.001
head & neck	1191 (19.3)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
ECOG PS													
PS 3-4	1483 (24.1)	0.81 (0.12)	2.24 (1.77-2.84)	<0.001	1.68 (0.12)	5.39 (4.28-6.78)	<0.001	2.38 (0.14)	10.84 (8.17-14.37)	<0.001	3.28 (0.16)	26.60 (19.42-36.44)	<0.001
PS 2	1181 (19.2)	0.73 (0.12)	2.07 (1.64-2.62)	<0.001	1.55 (0.12)	4.69 (3.72-5.90)	<0.001	1.95 (0.15)	7.00 (5.23-9.39)	<0.001	2.75 (0.16)	15.63 (11.32-21.57)	<0.001
PS 1	2110 (34.2)	0.60 (0.09)	1.82 (1.52-2.19)	<0.001	1.04 (0.10)	2.84 (2.34-3.45)	<0.001	1.22 (0.14)	3.40 (2.61-4.43)	<0.001	1.86 (0.15)	6.43 (4.75-8.71)	<0.001
PS 0	1387 (22.5)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
Cancer Stage													
stage 4	4580 (74.3)	0.47 (0.11)	1.60 (1.29-1.98)	<0.001	0.89 (0.11)	2.44 (1.95-3.06)	<0.001	1.06 (0.14)	2.89 (2.18-3.84)	<0.001	1.51 (0.15)	4.54 (3.39-6.08)	<0.001
stage 3	856 (13.9)	0.47 (0.14)	1.60 (1.23-2.10)	0.001	0.64 (0.14)	1.90 (1.44-2.51)	<0.001	0.73 (0.18)	2.08 (1.47-2.95)	<0.001	0.82 (0.18)	2.27 (1.59-3.25)	<0.001
stage 1-2	725 (11.8)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
Sex													
female	2558 (41.5)	-0.02 (0.08)	0.98 (0.84-1.14)	0.788	0.12 (0.07)	1.12 (0.97-1.30)	0.110	0.03 (0.09)	1.03 (0.87-1.22)	0.720	0.02 (0.08)	1.02 (0.88-1.19)	0.787
male	3603 (58.5)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
Age (years)	6161 (100)	-0.002 (0.00)	1.00 (0.99-1.00)	0.554	-0.004 (0.00)	1.00 (0.99-1.00)	0.223	0.001 (0.00)	1.00 (0.99-1.01)	0.757	-0.01 (0.00)	0.99 (0.98-1.00)	0.004
BMI Categories (kg/m2)													

<20.0	935 (15.2)	0.50 (0.14)	1.65 (1.24-2.19)	0.001	1.10 (0.13)	3.00 (2.31-3.90)	<0.001	1.64 (0.15)	5.14 (3.84-6.88)	<0.001	2.56 (0.14)	12.97 (9.85-17.08)	<0.001
20.0 to 21.9	863 (14.0)	0.26 (0.13)	1.29 (1.00-1.68)	0.054	0.92 (0.12)	2.52 (1.99-3.20)	<0.001	1.16 (0.14)	3.20 (2.41-4.25)	<0.001	1.62 (0.14)	5.05 (3.83-6.66)	<0.001
22.0 to 24.9	1540 (25.0)	0.45 (0.10)	1.56 (1.28-1.91)	<0.001	0.74 (0.10)	2.10 (1.72-2.57)	<0.001	0.99 (0.12)	2.69 (2.11-3.43)	<0.001	1.25 (0.13)	3.48 (2.72-4.46)	<0.001
25.0 to 27.9	1289 (20.9)	0.26 (0.10)	1.30 (1.06-1.59)	0.011	0.43 (0.10)	1.54 (1.25-1.89)	<0.001	0.39 (0.13)	1.47 (1.13-1.92)	0.004	0.69 (0.13)	1.99 (1.53-2.59)	<0.001
≥28.0	1534 (24.9)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
***I*-VVAS MLR model**	**Univariable MLR Analysis**												
Variables in model	**N (%)**	**WL 2.5-5.9% N= 655 (20.6%)**			**WL 6.0-10.9% N= 818 (25.7%)**			**WL 11.0-14.9% N= 376 (11.8%)**			**WL ≥15.0% N= 409 (12.8%)**		
		β (SE)	**OR (95% CI)**	**P-Value**	**β (SE)**	**OR (95% CI)**	**P-Value**	**β (SE)**	**OR (95% CI)**	**P-Value**	**β (SE)**	**OR (95% CI)**	**P-Value**
Current Food Intake													
severely reduced intake (scores 1-4)	736 (23.1)	1.02 (0.16)	2.76 (2.01-3.79)	<0.001	1.76 (0.15)	5.83 (4.35-7.80)	<0.001	2.58 (0.19)	13.23 (9.18-19.07)	<0.001	3.33 (0.20)	28.04 (18.95-41.48)	<0.001
moderately reduced intake (scores 5-9)	1256 (39.4)	0.90 (0.11)	2.46 (1.97-3.08)	<0.001	1.28 (0.11)	3.61 (2.90-4.49)	<0.001	1.71 (0.16)	5.53 (4.03-7.58)	<0.001	2.11 (0.18)	8.24 (5.76-11.78)	<0.001
normal (score 10)	1193 (37.5)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
Cancer Diagnosis													
respiratory	363 (11.4)	0.32 (0.19)	1.06 (0.69-1.65)	0.780	0.30 (0.18)	0.88 (0.59-1.32)	0.541	0.83 (0.25)	0.99 (0.60-1.64)	0.969	0.84 (0.25)	0.68 (0.42-1.11)	0.121

other	514 (16.1)	-0.04 (0.17)	0.74 (0.49-1.11)	0.151	0.01 (0.16)	0.66 (0.46-0.95)	0.026	0.57 (0.23)	0.76 (0.48-1.22)	0.259	0.39 (0.24)	0.44 (0.28-0.69)	<0.001
genitourinary	478 (15.0)	0.45 (0.17)	1.21 (0.81-1.82)	0.354	0.25 (0.17)	0.84 (0.58-1.23)	0.379	0.51 (0.24)	0.72 (0.43-1.18)	0.190	0.76 (0.24)	0.63 (0.40-0.99)	0.046
upper GI	519 (16.3)	0.95 (0.19)	1.99 (1.29-3.07)	0.002	0.88 (0.18)	1.58 (1.06-2.36)	0.025	1.69 (0.23)	2.33 (1.44-3.77)	0.001	2.05 (0.23)	2.28 (1.47-3.53)	<0.001
lower GI	433 (13.6)	0.16 (0.18)	0.91 (0.59-1.38)	0.647	0.13 (0.17)	0.75 (0.51-1.10)	0.142	0.77 (0.23)	0.93 (0.58-1.51)	0.780	0.72 (0.24)	0.60 (0.38-0.95)	0.031
head & neck	346 (10.9)	0.26 (0.20)	0.77 (0.52-1.15)	0.197	0.42 (0.18)	0.65 (0.46-0.94)	0.021	0.84 (0.26)	0.43 (0.26-0.71)	0.001	1.22 (0.25)	0.29 (0.18-0.48)	<0.001
breast	533 (16.7)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
ECOG PS													
PS 3-4	583 (18.3)	0.58 (0.17)	1.78 (1.29-2.47)	0.001	1.07 (0.17)	2.93 (2.11-4.07)	<0.001	1.89 (0.25)	6.65 (4.05-10.92)	<0.001	2.22 (0.24)	9.19 (5.72-14.78)	<0.001
PS 2	994 (31.2)	0.54 (0.15)	1.71 (1.29-2.28)	<0.001	1.22 (0.15)	3.39 (2.54-4.53)	<0.001	2.01 (0.23)	7.49 (4.73-11.87)	<0.001	2.08 (0.23)	8.02 (5.11-12.59)	<0.001
PS 1	1055 (33.1)	0.32 (0.14)	1.37 (1.05-1.80)	0.021	0.85 (0.14)	2.33 (1.77-3.08)	<0.001	1.39 (0.23)	4.01 (2.53-6.35)	<0.001	1.17 (0.24)	3.22 (2.03-5.10)	<0.001
PS 0	554 (17.4)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
Cancer Stage													
stage 4	2635 (82.7)	0.37 (0.17)	3.36 (1.96-5.77)	<0.001	0.75 (0.18)	2.71 (1.62-4.54)	<0.001	1.00 (0.26)	2.12 (1.49-3.01)	<0.001	1.21 (0.28)	1.45 (1.03-2.04)	0.032
stage 3	299 (9.4)	0.39 (0.23)	3.11 (1.63-5.93)	0.001	0.59 (0.23)	2.62 (1.40-4.92)	0.003	0.96 (0.32)	1.81 (1.15-2.86)	0.011	1.13 (0.33)	1.48 (0.94-2.33)	0.090
stage 1-2	251 (7.9)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	

Sex													
female	1553 (48.8)	-0.19 (0.10)	0.83 (0.68-1.01)	0.064	-0.12 (0.10)	0.89 (0.74-1.08)	0.229	-0.32 (0.12)	0.73 (0.57-0.93)	0.010	-0.55 (0.12)	0.58 (0.46-0.73)	<0.001
male	1632 (51.2)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
Age (years)	3185 (100)	0.01 (0.00)	1.01 (1.00-1.02)	0.072	0.01 (0.00)	1.01 (1.00-1.01)	0.186	0.004 (0.01)	1.00 (0.99-1.01)	0.373	-0.002 (0.01)	1.00 (0.99-1.01)	0.662
BMI Categories (kg/m2)													
<20.0	707 (22.2)	0.70 (0.18)	2.0 (1.4-2.9)	<0.001	1.15 (0.17)	3.2 (2.3-4.5)	<0.001	1.80 (0.23)	6.0 (3.8-9.5)	<0.001	2.81 (0.25)	16.6 (10.1-27.1)	<0.001
20.0 to 21.9	551 (17.3)	0.30 (0.18)	1.3 (1.0-1.9)	0.095	0.80 (0.17)	2.2 (1.6-3.1)	<0.001	1.18 (0.23)	3.2 (2.1-5.1)	<0.001	1.33 (0.27)	3.8 (2.2-6.4)	<0.001
22.0 to 24.9	890 (27.9)	0.49 (0.15)	1.6 (1.2-2.2)	0.001	0.55 (0.15)	1.7 (1.3-2.3)	<0.001	0.67 (0.22)	2.0 (1.3-3.0)	0.003	1.10 (0.25)	3.0 (1.8-4.9)	<0.001
25.0 to 27.9	571 (17.9)	-0.04 (0.17)	1.0 (0.7-1.3)	0.793	0.28 (0.16)	1.3 (1.0-1.8)	0.087	0.62 (0.23)	1.9 (1.2-2.9)	0.007	0.26 (0.29)	1.3 (0.7-2.3)	0.374
≥28.0	467 (14.7)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
MNA MLR model	**Univariable MLR Analysis**												
Variables in model	**N (%)**	**WL 2.5-5.9% N= 534 (22.7%)**			**WL 6.0-10.9% N= 537 (22.8%)**			**WL 11.0-14.9% N= 211 (9.0%)**			**WL ≥15.0% N= 211 (9.0%)**		
		β (SE)	**OR (95% CI)**	**P-Value**	**β (SE)**	**OR (95% CI)**	**P-Value**	**β (SE)**	**OR (95% CI)**	**P-Value**	**β (SE)**	**OR (95% CI)**	**P-Value**
Current Food Intake													
severely decreased	267 (11.4)	1.12 (0.27)	3.05 (1.78-5.22)	<0.001	2.51 (0.24)	12.33 (7.64-19.91)	<0.001	3.09 (0.28)	21.96 (12.64-38.15)	<0.001	4.41 (0.29)	82.31 (46.51-145.65	<0.001

												)	
moderately decreased	1000 (42.4)	1.46 (0.12)	4.31 (3.39-4.58)	<0.001	2.26 (0.13)	9.54 (7.35-12.38)	<0.001	2.15 (0.19)	8.57 (5.90-12.43)	<0.001	2.48 (0.24)	11.93 (7.52-18.91)	<0.001
no decrease	1090 (46.2)		1.0 (ref)										
Cancer Diagnosis													
respiratory	364 (15.4)	0.97 (0.18)	2.64 (1.85-3.75)	<0.001	1.33 (0.20)	3.78 (2.55-5.59)	<0.001	1.43 (0.34)	4.20 (2.15-8.19)	<0.001	1.46 (0.65)	4.32 (2.18-8.59)	<0.001
other	292 (12.4)	0.63 (0.20)	1.88 (1.28-2.76)	0.001	0.92 (0.22)	2.52 (1.64-3.86)	<0.001	1.55 (0.34)	4.69 (2.41-9.13)	<0.001	1.65 (0.35)	5.21 (2.65-10.25)	<0.001
genitourinary	433 (18.4)	0.78 (0.17)	2.18 (1.56-3.06)	<0.001	1.20 (1.19)	3.32 (2.28-4.83)	<0.001	1.27 (0.33)	3.55 91.85-6.81)	<0.001	1.30 (0.34)	3.67 (1.88-7.17)	<0.001
upper GI	384 (16.3)	1.64 (0.22)	5.15 (3.38-7.85)	<0.001	2.47 (0.22)	11.83 (7.68-18.24)	<0.001	3.20 (0.32)	24.63 1305-43.50)	<0.001	3.45 (0.33)	31.42 (16.54-59.71)	<0.001
lower GI	403 (17.1)	1.19 (0.19)	3.29 (2.28-4.74)	<0.001	1.86 (0.20)	6.44 (4.36-9.51)	<0.001	2.36 (0.32)	10.58 (5.70-19.65)	<0.001	2.21 (0.33)	9.11 (4.77-17.42)	<0.001
breast	481 (20.4)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
MNA Section C: Mobility													
bed or chair bound	225 (9.5)	0.58 (0.23)	1.78 (1.13-2.80)	0.012	1.02 (0.22)	2.78 (1.82-4.24)	<0.001	1.54 (0.25)	4.67 (2.87-7.60)	<0.001	2.13 (0.23)	8.41 (5.34-13.24)	<0.001
able to get out of bed/chair but does not go out	417 (17.7)	0.58 (0.15)	1.79 (1.32-2.43)	<0.001	0.93 (0.15)	2.54 (1.90-3.39)	<0.001	0.87 (020)	2.38 (1.60-3.55)	<0.001	1.11 (0.20)	3.03 (2.03-4.51)	<0.001
goes out	1715 (72.8)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
Cancer Stage													
stage 4	1420 (60.2)	0.95 (0.14)	2.58 (1.97-	<0.001	1.68 (0.16)	5.37 (3.93-	<0.001	1.85 (0.25)	6.34 (3.89-	<0.001	2.04 (0.27)	7.70 (4.57-	<0.001

			3.38)			7.33)			10.33)			12.96)	
stage 3	423 (17.9)	1.00 (0.17)	2.71 91.95-3.77)	<0.001	1.15 (0.20)	3.15 (2.15-4.63)	<0.001	1.30 (0.30)	3.68 (2.05-6.600	<0.001	1.40 (0.32)	4.07 (2.19-7.56)	<0.001
stage 1-2	514 (21.8)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
Sex													
female	1207 (51.2)	-0.44 (0.11)	0.64 (0.52-0.80)	<0.001	-0.51 (011)	0.60 (0.48-0.75)	<0.001	-0.45 (0.15)	0.64 (0.47-0.87)	0.004	-0.41 (0.15)	0.67 (0.49-0.90)	0.008
male	1150 (48.8)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
Age (years)	2357 (100)	0.01 (0.00)	1.01 (1.00-1.02)	0.005	0.01 (0.00)	1.01 (1.00-1.02)	0.003	0.03 (0.01)	1.03 (1.02-1.04)	<0.001	0.03 (0.01)	1.03 (1.02-1.04)	<0.001
BMI Categories (kg/m2)													
<20.0	278 (11.8)	0.83 (0.25)	2.29 (1.42-3.72)	0.001	1.61 (0.24)	5.02 (3.17-7.96)	<0.001	2.78 (0.37)	16.17 (7.83-33.39)	<0.001	4.17 (0.43)	64.43 (28.00-148.31)	<0.001
20.0 to 21.9	337 (14.3)	0.06 (0.21)	1.06 (0.70-1.61)	0.784	1.03 (0.20)	2.81 (1.91-4.12)	<0.001	1.98 (0.35)	7.22 (3.64-14.30)	<0.001	2.72 (0.42)	15.16 (6.65-34.54)	<0.001
22.0 to 24.9	792 (33.6)	0.82 (0.15)	2.28 (1.69-3.06)	<0.001	0.85 (0.17)	2.34 (1.69-3.24)	<0.001	1.71 (0.32)	5.51 (2.92-10.41)	<0.001	1.75 (0.42)	5.77 (2.55-13.07)	<0.001
25.0 to 27.9	528 (22.4)	0.23 (0.17)	1.26 (0.90-1.75)	0.173	0.65 (0.18)	1.91 (1.36-2.70)	<0.001	1.51 (0.33)	4.53 (2.35-8.74)	<0.001	1.36 (0.44)	3.88 (1.65-9.16)	0.002
≥28.0	422 (17.9)		1.0 (ref)			1.0 (ref)			1.0 (ref)				

β, beta coefficient; BMI, body mass index; *I*-VVAS, *Ingesta*-verbal/visual analogue scale GI, gastrointestinal; MNA, Mini-Nutrition Assessment; MLR, multinomial logistic regression; N, number; OR, odds ratio; PGSGA, Patient-generated subjective global assessment; PS, performance status; WL, weight loss
*Severely reduced includes the following PG-SGA categories (little solid food, only liquids/oral nutritional supplements, very little of anything)

Appendix IV.

Chapter 5 Supplementary Table 2. Multivariable multinomial logistic regression (MLR) analysis for the association of selected variables to cancer-associated weight loss for three different models based on food intake assessments from three data sets: PG-SGA, *I*-VVAS, and the MNA

PG-SGA MLR model[1]		**Multivariable MLR Analysis**											
Variables in model	**N (%)**	**WL 2.5-5.9% N= 1139 (28.8%)**			**WL 6.0-10.9% N= 1347 (21.9%)**			**WL 11.0-14.9% N= 816 (13.2%)**			**WL >=15.0% N= 1082 (17.6%)**		
		β (SE)	**OR (95% CI)**	**P-Value**	**β (SE)**	**OR (95% CI)**	**P-Value**	**β (SE)**	**OR (95% CI)**	**P-Value**	**β (SE)**	**OR (95% CI)**	**P-Value**
Current Food Intake													
severely reduced*	1284 (20.8)	1.09 (0.14)	2.98 (2.26-3.92)	<0.001	1.79 (0.13)	5.98 (4.59-7.78)	<0.001	2.37 (0.16)	10.70 (7.85-14.58)	<0.001	2.73 (0.16)	15.27 (11.25-20.73)	<0.001
normal food, reduced amount	2765 (44.9)	0.66 (0.09)	1.94 (1.63-2.30)	<0.001	1.08 (0.09)	2.93 (2.46-3.50)	<0.001	1.45 (0.12)	4.25 (3.36-5.38)	<0.001	1.61 (0.12)	5.02 (3.95-6.38)	<0.001
normal food, normal amount	2112 (34.3)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
Cancer Diagnosis*													
respiratory	1913 (31.1)	0.43 (0.11)	1.53 (1.23-1.90)	<0.001	0.59 (0.12)	1.80 (1.43-2.27)	<0.001	0.89 (0.15)	2.45 (1.81-3.31)	<0.001	0.94 (0.15)	2.56 (1.89-3.46)	<0.001
other	712 (11.6)	-0.05 (0.15)	0.95 (0.70-1.29)	0.753	0.16 (0.15)	1.17 (0.87-1.59)	0.299	0.29 (0.20)	1.34 90.91-1.96)	0.136	0.49 (0.19)	1.63 (1.13-2.35)	0.009
genitourinary	386 (6.3)	0.30 (0.20)	1.35 (0.92-1.99)	0.124	0.62 (0.19)	1.85 (1.28-2.69)	0.001	0.67 (0.23)	1.96 (1.24-3.10)	0.004	1.13 (0.22)	3.09 (2.02-4.73)	<0.001
upper GI	950 (15.4)	0.55 (0.16)	1.73 (1.27-2.34)	<0.001	1.02 (0.15)	2.77 (2.05-3.73)	<0.001	1.51 (0.18)	4.54 (3.19-6.46)	<0.001	1.88 (0.17)	6.57 (4.67-9.26)	<0.001

lower GI	1009 (16.4)	0.76 (0.13)	2.13 (1.65-2.76)	<0.001	1.27 (0.14)	3.56 (2.73-4.64)	<0.001	1.59 (0.17)	4.92 93.51-6.89)	<0.001	1.66 (0.17)	5.25 (3.73-7.39)	<0.001
head & neck	1191 (19.3)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
ECOG PS													
PS 3-4	1483 (24.1)	0.38 (0.14)	1.47 (1.12-1.92)	0.005	0.89 (0.14)	2.44 (1.87-3.18)	<0.001	1.38 (0.16)	3.97 (2.88-5.49)	<0.001	2.00 (0.18)	7.36 (5.16-10.51)	<0.001
PS 2	1181 (19.2)	0.44 (0.13)	1.55 (1.20-2.01)	0.001	0.97 (0.13)	2.63 (2.03-3.40)	<0.001	1.23 (0.17)	3.42 (2.48-4.73)	<0.001	1.82 (0.18)	6.15 (4.31-8.79)	<0.001
PS 1	2110 (34.2)	0.39 (0.10)	1.48 (1.22-1.79)	<0.001	0.64 (0.11)	1.90 (1.54-2.35)	<0.001	0.73 (014)	2.07 (1.56-2.75)	<0.001	1.23 (0.17)	3.43 (2.47-4.75)	<0.001
PS 0	1387 (22.5)					1.0 (ref)			1.0 (ref)			1.0 (ref)	
Cancer Stage													
stage 4	4580 (74.3)	0.21 (0.12)	1.23 (0.97-1.56)	0.086	0.40 (0.13)	1.50 (1.16-1.93)	0.002	0.33 (0.17)	1.39 (1.00-1.93)	0.047	0.49 (0.18)	1.63 (1.15-2.30)	0.006
stage 3	856 (13.9)	0.30 (0.14)	1.35 (1.02-1.80)	0.036	0.41 (0.16)	1.50 (1.11-2.04)	0.009	0.45 (0.19)	1.57 (1.08-2.30)	0.019	0.53 (0.21)	1.71 (1.14-2.56)	0.009
stage 1-2	725 (11.8)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
Sex													
female	2558 (41.5)	-0.16 (0.08)	0.85 (0.72-1.00)	0.056	-0.14 (0.08)	0.87 (0.74-1.03)	0.101	-0.29 (0.10)	0.75 (0.62-0.90)	0.003	-0.39 (0.09)	0.68 (0.56-0.81)	<0.001
male	3603 (58.5)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
Age (years)	6161 (100)	-0.01 (0.00)	0.99 (0.99-1.00)	0.016	-0.00 (0.00)	0.99 (0.98-0.99)	<0.001	-0.01 (0.00)	0.99 (0.98-1.00)	0.005	-0.02 (0.00)	0.98 (0.97-0.98)	<0.001
BMI Categories (kg/m2)													

<20.0	935 (15.2)	0.47 (0.15)	1.61 (1..20-2.15)	0.001	1.02 (0.14)	2.76 (2.09-3.66)	<0.001	1.53 (0.16)	4.62 (3.36-6.34)	<0.001	2.41 (0.16)	11.10 (8.14-15.12)	<0.001
20.0 to 21.9	863 (14.0)	0.26 (0.14)	1.29 (0.99-1.69)	0.063	0.92 (0.13)	2.52 (1.95-3.26)	<0.001	1.15 (0.16)	3.15 (2.31-4.28)	<0.001	1.58 (0.16)	4.87 (3.57-6.64)	<0.001
22.0 to 24.9	1540 (25.0)	0.41 (0.11)	1.50 (1.22-1.85)	<0.001	0.68 (0.11)	1.97 (1.59-2.44)	<0.001	0.89 (0.13)	2.44 (1.88-3.18)	<0.001	1.13 (0.14)	3.10 (2.36-4.08)	<0.001
25.0 to 27.9	1289 (20.9)	0.26 (0.11)	1.30 (1.06-1.60)	0.014	0.43 (0.11)	1.53 (1.23-1.91)	<0.001	0.36 (0.14)	1.43 (1.08-1.90)	0.013	0.65 (0.15)	1.92 (1.43-2.56)	<0.001
≥28.0	1534 (24.9)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
***I*-VVAS MLR model[2]**		**Multivariable MLR Analysis**											
Variables in model	**N (%)**	**WL 2.5-5.9% N= 655 (20.6%)**			**WL 6.0-10.9% N= 818 (25.7%)**			**WL 11.0-14.9% N= 376 (11.8%)**			**WL >=15.0% N= 409 (12.8%)**		
		β (SE)	**OR (95% CI)**	**P-Value**	**β (SE)**	**OR (95% CI)**	**P-Value**	**β (SE)**	**OR (95% CI)**	**P-Value**	**β (SE)**	**OR (95% CI)**	**P-Value**
Current Food Intake													
severely reduced intake (scores 1-4)	736 (23.1)	0.86 (0.18)	2.37 (1.68-3.35)	<0.001	1.53 (0.16)	4.62 (3.36-6.37)	<0.001	2.13 (0.21)	8.41 (5.63-12.58)	<0.001	2.66 (0.22)	14.36 (9.28-22.23)	<0.001
moderately reduced intake (scores 5-9)	1256 (39.4)	0.82 (0.12)	2.28 (1.79-2.90)	<0.001	1.13 (0.12)	3.10 (2.45-3.92)	<0.001	1.45 (0.17)	4.25 (3.04-5.94)	<0.001	1.73 (0.20)	5.62 (3.83-8.26)	<0.001
normal (score 10)	1193 (37.5)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
Cancer Diagnosis													
respiratory	363 (11.4)	0.25 (0.21)	1.29 (0.85-1.96)	0.235	0.21 (0.21)	1.24 (0.83-1.85)	0.296	0.65 (0.28)	1.91 (1.10-3.31)	0.021	0.48 (0.30)	1.62 (0.90-2.91)	0.106
other	514 (16.1)	-0.04 (0.19)	0.97 (0.67-1.39)	0.851	0.01 (0.18)	1.01 (0.72-1.44)	0.937	0.55 (0.25)	1.74 (1.07-2.83)	0.027	0.26 (0.27)	1.29 (0.76-2.21)	0.345

genitourinary	478 (15.0)	0.43 (0.20)	1.53 (1.03-2.27)	0.034	0.22 (0.20)	1.24 (0.85-1.83)	0.266	0.38 (0.28)	1.46 (0.84-2.52)	0.179	0.53 (0.29)	1.70 (0.97-2.99)	0.065
upper GI	519 (16.3)	0.85 (0.22)	2.35 (1.54-3.58)	<0.001	0.74 (0.21)	2.10 (1.39-3.16)	<0.001	1.51 (0.27)	4.52 (2.64-7.73)	<0.001	1.87 (0.28)	6.51 (3.73-11.35)	<0.001
lower GI	433 (13.6)	0.28 (0.20)	1.33 (0.89-1.98)	0.164	0.37 (0.20)	1.45 (0.98-2.13)	0.061	1.11 (0.27)	3.04 (1.79-5.15)	<0.001	1.07 (0.29)	2.90 (1.65-5.12)	<0.001
head & neck	346 (10.9)	0.27 (0.24)	1.31 (0.82-2.07)	0.257	0.45 (0.22)	1.57 (1.01-2.42)	0.043	0.84 (0.30)	2.32 (1.28-4.22)	0.006	1.07 (0.31)	2.92 (1.58-5.37)	0.001
breast	533 (16.7)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
ECOG PS													
PS 3-4	583 (18.3)	0.18 (0.20)	1.20 (0.81-1.77)	0.358	0.45 (0.20)	1.56 (1.05-2.32)	0.026	1.28 (0.29)	3.59 (2.02-6.38)	<0.001	1.47 (0.30)	4.33 (2.42-7.77)	<0.001
PS 2	994 (31.2)	0.21 (0.17)	1.23 (0.89-1.70)	0.215	0.68 (0.17)	1.98 (1.42-2.75)	<0.001	1.35 (0.26)	3.85 (2.32-6.39)	<0.001	1.23 (0.26)	3.42 (2.03-5.74)	<0.001
PS 1	1055 (33.1)	0.16 (0.15)	1.17 (0.88-1.56)	0.282	0.59 (0.15)	1.80 (1.34-2.43)	<0.001	1.09 (0.25)	2.97 (1.83-4.83)	<0.001	0.77 (0.26)	2.16 91.30-3.58)	0.003
PS 0	554 (17.4)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
Cancer Stage													
stage 4	2635 (82.7)	0.14 (0.18)	1.15 (0.80-1.65)	0.459	0.36 (0.19)	1.43 (0.98-2.08)	0.065	0.39 (0.28)	1.48 (0.85-2.58)	0.164	0.46 (0.31)	1.58 (0.86-2.91)	0.141
stage 3	299 (9.4)	0.23 (0.24)	1.26 (0.78-2.03)	0.348	0.32 (0.25)	1.38 (0.84-2.25)	0.205	0.47 (0.35)	1.59 (0.81-3.14)	0.179	0.54 (0.37)	1.72 (0.83-3.58)	0.146
stage 1-2	251 (7.9)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
Sex													
female	1553 (48.8)	-0.15 (0.13)	0.86 (0.67-	0.234	-0.18 (0.12)	0.84 (0.66-	0.150	-0.38 (0.15)	0.68 (0.51-	0.013	-0.71 (0.16)	0.49 (0.36-	<0.001

			1.10)			1.07)			0.92)			0.67)	
male	1632 (51.2)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
Age (years)	3185 (100)	0.00 (0.00)	1.00 (0.99-1.01)	0.546	0.00 (0.00)	1.00 (0.99-1.01)	0.838	0.00 (0.01)	1.00 (0.98-1.01)	0.386	-0.01 (0.01)	0.99 (0.98-1.00)	0.095
BMI Categories (kg/m2)													
<20.0	707 (22.2)	0.64 (0.19)	1.90 (1.31)	0.001	0.98 (0.18)	2.66 (1.85)	<0.001	1.56 (0.25)	4.76 (2.94-7.72)	<0.001	2.57 (0.27)	13.12 (7.70-22.37)	<0.001
20.0 to 21.9	551 (17.3)	0.21 (0.18)	1.23 (0.86-1.77)	0.249	0.67 (0.18)	1.94 (1.38-2.75)	<0.001	1.01 (0.25)	2.73 (1.69-4.43)	<0.001	1.13 (0.29)	3.10 (1.77-5.43)	<0.001
22.0 to 24.9	890 (27.9)	0.47 (0.15)	1.60 (1.18-2.17)	0.002	0.51 (0.16)	1.67 (1.22-2.28)	0.001	0.60 (0.23)	1.83 (1.16-2.90)	0.010	1.01 (0.27)	2.76 (1.63-4.67)	<0.001
25.0 to 27.9	571 (17.9)	-0.13 (0.17)	0.88 (0.63-1.23)	0.458	0.20 (0.17)	1.22 (0.87-1.71)	0.243	0.51 (0.25)	1.67 (1.03-2.70)	0.037	0.10 (0.31)	1.11 (0.61-2.02)	0.737
≥28.0	467 (14.7)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
MNA MLR model[3]		**Multivariable MLR Analysis**											
Variables in model	**N (%)**	**WL 2.5-5.9% N= 534 (22.7%)**			**WL 6.0-10.9% N= 537 (22.8%)**			**WL 11.0-14.9% N= 211 (9.0%)**			**WL >=15.0% N= 211 (9.0%)**		
		β (SE)	**OR (95% CI)**	**P-Value**	**β (SE)**	**OR (95% CI)**	**P-Value**	**β (SE)**	**OR (95% CI)**	**P-Value**	**β (SE)**	**OR (95% CI)**	**P-Value**
Current Food Intake													
severely decreased	267 (11.4)	0.77 (0.29)	2.17 (1.24-3.80)	0.007	1.93 (0.26)	6.87 (4.12-11.46)	<0.001	2.28 (0.31)	9.73 (5.33-17.75)	<0.001	3.29 (0.32)	26.86 (14.29-50.49)	<0.001
moderately decreased	1000 (42.4)	1.32 (0.13)	3.74 (2.89-4.83)	<0001	2.00 (0.14)	7.38 (5.57-9.78)	<0.001	1.787 (0.20)	5.94 (3.99-8.86)	<0.001	1.95 (0.25)	7.05 (4.29-11.60)	<0.001

no decrease	1090 (46.2)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
Cancer Diagnosis													
respiratory	364 (15.4)	0.48 (022)	1.62 (1.05-2.50)	0.029	0.63 (0.25)	1.87 (1.16-3.04)	0.011	0.75 (0.38)	2.12 (1.00-4.48)	0.051	0.74 (0.42)	2.10 (0.92-4.82)	0.079
other	292 (12.4)	0.29 (0.23)	1.34 (0.85-2.10)	0.204	0.43 (0.26)	1.54 (0.92-2.56)	0.100	0.96 (0.38)	2.62 (1.24-5.53)	0.012	0.85 (0.42)	2.35 (1.03-5.35)	0.042
genitourinary	433 (18.4)	0.42 (0.20)	1.51 (1.03-2.23)	0.037	0.66 (0.23)	1.93 (1.24-3.01)	0.004	0.70 (0.36)	2.02 (0.99-4.13)	0.053	0.67 (0.40)	1.96 (0.89-4.31)	0.092
upper GI	384 (16.3)	1.08 (0.24)	2.94 (1.83-4.73)	<0.001	1.60 (0.26)	4.95 (2.99-8.20)	<0.001	2.42 (0.36)	11..24 (5.53-22.86)	<0.001	2.55 (0.39)	12.75 (5.90-27.53)	<0.001
lower GI	403 (17.1)	0.88 (0.22)	2.40 (1.57-3.66)	<0.001	1.54 (0.24)	4.67 (2.94-7.42)	<0.001	2.03 (0.35)	7.62 (3.83-15.15)	<0.001	1.93 (0.39)	6.87 (3.19-14.82)	<0.001
breast	481 (20.4)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
MNA Section C: Mobility													
bed or chair bound	225 (9.5)	0.09 (0.25)	1.09 (0.66-1.79)	0.734	0.30 (0.25)	1.34 (0.83-2.18)	0.232	0.25 (0.24)	2.13 (1.20-3.77)	0.010	1.08 (0.30)	2.94 (1.64-5.27)	<0.001
able to get out of bed/chair but does not go out	417 (17.7)	0.23 (0.17)	1.26 (0.90-1.77)	0.179	0.40 (0.18)	1.49 (1.06-2.11)	0.023	0.76 (0.29)	1.28 (0.81-2.03)	0.287	0.37 (0.25)	1.44 (0.88-2.36)	0.145
goes out	1715 (72.8)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
Cancer Stage													
stage 4	1420 (60.2)	0.48 (0.16)	1.62 (1.19-2.21)	0.002	1.05 (0.18)	2.86 (1.99-4.10)	<0.001	1.02 (0.27)	2.77 (1.62-4.74)	<0.001	1.10 (0.32)	3.01 (1.61-5.61)	0.001
stage 3	423 (17.9)	0.69 (0.18)	2.00 (1.40-2.87)	<0.001	0.75 (0.22)	2.11 (1.37-3.25)	0.001	0.77 (0.33)	2.16 (1.14-4.08)	0.018	0.92 (0.38)	2.51 (1.20-5.23)	0.014

stage 1-2	514 (21.8)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
Sex													
female	1207 (51.2)	-0.14 (0.14)	0.87 (0.67-1.14)	0.315	-0.21 (0.14)	0.81 (0.61-1.07)	0.141	-0.13 (0.19)	0.88 (0.61-1.26)	0.482	-0.26 (0.200	0.77 (0.52-1.14)	0.189
male	1150 (48.8)												
Age (years)	2357 (100)	0.01 (0.05)	1.01 (0.92-1.12)	0.782	-0.04 (0.05)	0.96 (0.87-1.07)	0.469	0.126 (0.07)	1.13 (0.98-1.31)	0.091	0.16 (0.08)	1.17 (1.00-1.37)	0.050
BMI Categories (kg/m2)													
<20.0	278 (11.8)	0.66 (0.26)	1.93 (1.15-3.23)	0.012	1.26 (0.27)	3.51 (2.08-5.93)	<0.001	2.45 (0.40)	11.59 (5.31-25.32)	<0.001	3.77 (0.47)	43.47 (17.46-108.24)	<0.001
20.0 to 21.9	337 (14.3)	-0.07 (0.23)	0.93 (0.60-1.46)	0.76	0.78 (0.23)	2.19 (1.40-3.40)	0.001	1.81 (0.37)	6.11 (2.94-12.69)	<0.001	2.59 (0.46)	13.33 (5.45-32.57)	<0.001
22.0 to 24.9	792 (33.6)	0.70 (0.16)	2.014 (1.47-2.77)	<0.001	0.63 (0.19)	1.88 (1.30-2.72)	0.001	1.56 (0.34)	4.74 (2.42-9.25)	<0.001	1.64 (0.44)	5.14 (2.15-12.28)	<0.001
25.0 to 27.9	528 (22.4)	0.20 (0.180	1.22 (0.86-1.73)	0.266	0.59 (0.20)	1.80 (1.22-2.67)	0.003	1.49 (0.35)	4.46 (2.23-8.91)	<0.001	1.38 (0.47)	3.99 (1.60-9.97)	<0.001
≥28.0	422 (17.9)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	

β, beta coefficient; BMI, body mass index; *I*-VVAS, *Ingesta*-verbal/visual analogue scale GI, gastrointestinal; MNA, Mini-Nutrition Assessment; MLR, multinomial logistic regression; N, number; OR, odds ratio; PGSGA, Patient-generated subjective global assessment; PS, performance status; WL, weight loss
*Severely reduced includes the following PG-SGA categories (little solid food, only liquids/oral nutritional supplements, very little of anything)
[1]PG-SGA MLR Model - Reference weight stable (+/- 2.4%) N=1777 (28.8%); Intercept only model: –2 log likelihood (LL)=18682.909, AIC 18690.909;
Final Model: -2LL=16403.448, AIC=16555.448, $\chi 2$=2279.461 (df=72), P<0.001; Pseudo R2 (Nagelkerke) = 0.323; Pearson goodness-of-fit P=0.063
[2]*I*-VVAS MLR Model - Reference weight stable (+/-2.4%) N=928 (21.9%); Intercept only model: -2 LL=9671.159, AIC=9679.159;
Final Model: -2LL=8658.277, AIC=8818.277, $\chi 2$=1012.883 (df=76), P<0.001; Pseudo r2 (Nagelkerke)=0.285; Pearson goodness-of-fit P=0.792
[3]MNA MLR Model - Reference weight stable (±2.4%) N=864 (36.7%); Intercept only model: -2 log likelihood (LL)= 6755.457, AIC 6763.457;
Final Model: -2LL=5533.028, AIC=5677.028, $\chi 2$=1222.429 (df=68), P<0.001; Pseudo R2 (Nagelkerke)=0.427, Pearson goodness-of-fit P=0.198

Appendix V.

Chapter 6 Supplementary Table 1. Univariable multinomial logistic regression (MLR) analysis for the association of selected variables to cancer-associated weight loss.

Variables in model	N (%)	WL 2.5-5.9% N= 711 (20.7%)			WL 6.0-10.9% N= 822 (23.9%)			WL 11.0-14.9% N= 390 (11.3%)			WL >=15.0% N= 501 (14.6%)		
		β (SE)	OR (95% CI)	P-Value	β (SE)	OR (95% CI)	P-Value	β (SE)	OR (95% CI)	P-Value	β (SE)	OR (95% CI)	P-Value
CRP Categories													
≥43.0 mg/L	1032 (30.0)	0.41 (0.13)	1.51 (1.18-1.93)	0.001	0.89 (0.12)	2.45 (1.94-3.08)	<0.001	1.12 (0.15)	3.06 (2.30-4.08)	<0.001	1.50 (0.14)	4.46 (3.40-5.86)	<0.001
10.0-42.9 mg/L	1036 (30.1)	0.28 (0.11)	1.32 (1.06-1.66)	0.014	0.42 (0.11)	1.52 (1.22-1.90)	<0.001	0.51 (0.15)	1.67 (1.25-2.23)	0.001	0.80 (0.14)	2.23 (1.69-2.94)	<0.001
<10.0 mg/L	1375 (39.9)		1.0 (ref)									1.0 (ref)	
Current Food Intake													
severely reduced intake (scores 1-4)	686 (19.9)	0.99 (0.16)	2.69 (1.96-3.69)	<0.001	1.66 (0.15)	5.26 (3.91-7.07)	<0.001	2.37 (0.18)	10.73 (7.53-15.29)	<0.001	2.88 (0.17)	17.77 (12.64-24.98)	<0.001
moderately reduced intake (scores 5-9)	1380 (40.1)	0.91 (0.11)	2.49 (2.02)	<0.001	1.28 (0.11)	3.61 (2.93-4.46)	<0.001	1.56 (0.15)	4.77 (3.56-6.68)	<0.001	1.82 (0.15)	6.20 (4.65-8.27)	<0.001
normal (score 10)	1377 (40.0)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
Cancer Diagnosis													
respiratory	786 (22.8)	0.29 (0.17)	1.34 (0.97-1.86)	0.080	-0.09 (0.16)	0.92 (0.67-1.24)	0.573	0.33 (0.22)	1.39 (0.90-2.14)	0.139	0.32 (0.23)	1.38 (0.89-2.15)	0.155
other	353 (10.3)	0.02 (0.20)	1.02 (0.69-1.52)	0.906	-0.24 (0.19)	0.78 (0.54-1.14)	0.198	0.22 (0.26)	1.25 (0.75-2.08)	0.390	0.35 (0.26)	1.43 (0.86-2.37)	0.171
genitourinary	607	0.40	1.50	0.023	0.09	1.09	0.585	0.45	1.58	0.051	0.79	2.20	0.001

	(17.6)	(0.18)	(1.06-2.12)		(0.17)	(0.79-1.52)		(0.23)	(1.00-2.49)		(0.23)	(1.41-3.45)	
upper GI	685 (19.9)	0.60 (0.18)	1.82 (1.27-2.60)	0.001	0.36 (0.17)	1.43 (1.03-1.99)	0.033	1.03 (0.23)	2.81 (1.80-4.37)	<0.001	1.63 (0.22)	5.09 (3.31-7.82)	<0.001
lower GI	276 (8.0)	0.21 (0.22)	1.23 (0.79-1.91)	0.357	0.14 (0.20)	1.15 (0.77-1.71)	0.493	0.69 (0.27)	1.99 (1.18-3.37)	0.010	0.66 (0.28)	1.94 (1.13-3.33)	0.016
head & neck	307 (8.9)	0.32 (0.22)	1.23 (0.79-1.91)	0.153	0.37 (0.20)	1.45 (0.98-2.16)	0.062	0.62 (0.28)	1.87 (1.08-3.22)	0.024	1.33 (0.25)	3.77 (3.29-6.19)	<0.001
breast	429 (12.5)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
ECOG PS													
PS 3-4	570 (16.6)	0.42 (0.16)	1.53 (1.11-2.10)	0.009	0.99 (0.16)	2.68 (1.96-3.66)	<0.001	1.24 (0.21)	3.46 (2.31-5.17)	<0.001	1.89 (0.20)	6.65 (4.47-9.89)	<0.001
PS 2	1058 (30.7)	0.29 (0.14)	1.33 (1.02-1.74)	0.034	0.99 (0.13)	2.68 (2.06-3.49)	<0.001	1.21 (0.18)	3.36 (2.37-4.77)	<0.001	1.72 (0.18)	5.58 (3.89-8.00)	<0.001
PS 1	1081 (31.4)	0.35 (0.13)	1.42 (1.11-1.82)	0.005	0.64 (0.13)	1.90 (1.47-2.46)	<0.001	0.69 (0.18)	1.99 (1.39-2.84)	<0.001	1.08 (0.19)	2.94 (2.03-4.25)	<0.001
PS 0	734 (21.3)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
Cancer Stage													
stage 4	2698 (78.)	0.26 (0.17)	1.29 (0.92-1.82)	0.139	0.45 (0.17)	1.57 (1.12-2.20)	0.010	0.58 (0.24)	1.78 (1.12-2.84)	0.014	0.97 (0.25)	2.65 (1.63-4.29)	<0.001
stage 3	482 (14.0)	0.13 (0.21)	1.14 (0.76-1.71)	0.534	0.21-0.21)	1.23 (0.82-1.84)	0.323	0.32 (0.28)	1.38 (0.80-2.38)	0.253	0.79 (0.28)	2.20 (1.27-3.81)	0.005
stage 1-2	263 (7.6)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
Sex													
male	1873 (54.4)	0.18 (0.10)	1.19 (0.99-1.45)	0.071	0.06 (0.09)	1.06 (0.88-1.28)	0.521	0.30 (0.12)	1.35 (1.07-1.71)	0.012	0.52 (0.11)	1.68 (1.35-2.09)	<0.001

female	1570 (45.6)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	
Age (years)	3443 (100)	-0.001 (0.004)	0.999 (0.992-1.01)	0.900	-0.002 (0.004)	0.998 (0.991-1.01)	0.654	-0.001 (0.005)	0.999 (0.990-1.01)	0.846	-0.007 (0.004)	0.993 (0.985-1.002)	0.122
BMI Categories (kg/m2)													
<20.0	655 (19.0)	0.65 (0.17)	1.92 (1.37-2.70)		1.16 (0.17)	3.18 (2.29-4.43)	<0.001	2.04 (0.23)	7.67 (4.87-12.09)	<0.001	2.35 (0.19)	10.45 (7.16-15.25)	<0.001
20.0 to 21.9	566 (16.4)	0.43 (0.17)	1.54 (1.11-2.13)		1.05 (0.16)	2.86 (2.10-3.90)	<0.001	1.60 (0.23)	4.94 (3.13-7.78)	<0.001	1.06 (0.21)	2.90 (1.92-4.37)	<0.001
22.0 to 24.9	953 (27.7)	0.50 (0.14)	1.64 (1.25-2.15)		0.69 (0.14)	1.99 (1.51-2.62)	<0.001	1.29 (0.22)	3.63 (2.38-5.53)	<0.001	0..88 (0.19)	2.40 (1.67-3.47)	<0.001
25.0 to 27.9	646 (18.8)	0.18 (0.15)	1.20 (0.89-1.60)	0.229	0.41 (0.15)	1.50 (1.12-2.01)	0.007	0.86 (0.23)	2.36 (1.50-3.71)	<0.001	0.11 (0.22)	1.11 (0.72-1.70)	0.630
≥28.0	643 (18.1)		1.0 (ref)			1.0 (ref)			1.0 (ref)			1.0 (ref)	

β, beta coefficient; BMI, body mass index; CRP, C-reactive protein; MLR, multinomial logistic regression; N, number; OR, odds ratio; PS, performance status; SE, standard error; WL, weight loss

Appendix VI

Chapter 7 Supplementary Table 1. Logistic regression models of the factors associated with extended LOS (model 1), post-operative complications (model 2) for patients in the ERAS implementation group (N=2628)

Factors	Total N	Model 1 Outcome = Extended LOS (> 5 days)					Model 2 Outcome = any complication during primary stay				
		Univariable		Final Multivariable			Univariable		Final Multivariable		
		OR (95% CI)	P-Value	N	OR (95% CI)	P-Value	OR (95% CI)	P-Value	N	OR (95% CI)	P-Value
Nutrition Screen*											
not at nutritional risk	2317	1.0 (ref)		2298	1.0 (ref)		1.0 (ref)		-	-	-
at nutritional risk	311	1.73 (1.36-2.21)	**<0.001**	302	1.40 (1.00-1.96)	**0.052**	1.34 (1.06-1.70)	**0.016**	-	-	-
Sex											
female	1137	1.0 (ref)		1124	1.0 (ref)		1.0 (ref)		1136	1.0 (ref)	
male	1490	1.33 (1.14-1.56)	**<0.001**	1476	1.29 (1.04-1.60)	**0.022**	1.27 (1.09-1.48)	**0.002**	1490	1.26 (1.07-1.49)	**0.006**
Age (years)	2627	1.02 (1.01-1.02)	**<0.001**	2600	1.02 (1.01-1.03)	**<0.001**	1.01 (1.01-1.02)	**0.000**		1.01 (1.01-1.02)	**<0.001**
ASA Class											
1 to 2	1774	1.0 (ref)		1766	1.0 (ref)		1.0 (ref)		1773	1.0 (ref)	
3 to 4	798	1.76 (1.48-2.08)	**<0.001**	779	1.37 (1.08-1.74)	**0.010**	1.50 (1.27-1.78)	**0.000**	798	1.21 (1.01-1.45)	**0.044**
unknown	55	1.04 (0.61-1.79)	0.88	55	0.91 (0.41-2.02)	0.82	0.83 (0.48-1.42)	0.493	55	1.00 (0.54-1.84)	0.992
Cancer Diagnosis											
non-cancer diagnosis	1280	1.0 (ref)		-	-	-	1.0 (ref)		-	-	-
cancer diagnosis	1348	1.49 (1.27-1.73)	**<0.001**	-	-	-	1.21 (1.04-1.41)	**0.014**	-	-	-
Procedure Type											
colon and small bowel procedure	1687	1.0 (ref)		-	-	-	1.0 (ref)		-	-	-
rectal procedure	914	1.98 (1.69-2.33)	**<0.001**	-	-	-	1.37 (1.17-1.61)	**0.000**	-	-	-
Surgical approach											

laparoscopic	1343	1.0 (ref)		1332	1.0 (ref)		1.0 (ref)		1342	1.0 (ref)	
open	930	4.31 (3.60-5.16)	**<0.001**	915	3.13 (2.44-4.03)	**<0.001**	2.47 (2.08-2.93)	**0.000**	929	2.04 (1.68-2.48)	**<0.001**
stoma approach	232	0.83 (0.61-1.12)	0.220	231	1.00 (0.68-1.49)	0.981	0.93 (0.70-1.24)	0.621	232	1.08 (0.80-1.47)	0.609
converted	113	4.03 (2.66-6.10)	**<0.001**	112	2.83 (1.69-4.73)	**<0.001**	2.35 (1.58-3.48)	**0.000**	113	1.81 (1.19-2.75)	**0.005**
unknown	10	0.46 (0.10-2.16)	0.324	10	0.35 (0.05-2.34)	0.279	0.61 (0.16-2.40)	0.487	10	0.60 (0.15-2.41)	0.472
Surgical Complexity											
less complex procedures	1482	1.0 (ref)		1466	1.0 (ref)		1.0 (ref)		1481	1.0 (ref)	
more complex procedures	1146	2.11 (1.80-2.47)	**<0.001**	1134	1.72 (1.37-2.16)	**<0.001**	1.49 (1.28-1.75)	**0.000**	1145	1.18 (0.99-1.41)	**0.059**
Compliance to ERAS Protocol											
>70% (good compliance)	1796	1.0 (ref)		1788	1.0 (ref)		1.0 (ref)		1794	1.0 (ref)	
<70% (low compliance)	832	3.42 (2.87-4.08)	**<0.001**	812	2.57 (2.01-3.29)	**<0.001**	3.05 (2.56-3.62)	**0.000**	832	2.69 (2.23-3.24)	**<0.001**
Complication(s) during primary stay											
no	1327	1.0 (ref)		1326	1.0 (ref)		-	-	-	-	-
yes	1301	16.58 (13.67-20.12)	**<0.001**	1274	17.00 (13.60-21.26)	**<0.001**	-	-	-	-	-
Acute Care Center											
Hospital Site #1	227	1.0 (ref)		223	1.0 (ref)				227	1.0 (ref)	
Hospital Site #2	1089	0.62 (0.47-0.83)	**0.001**	1080	0.54 (0.35-0.82)	**0.004**	0.90 90.68-1.20)	0.483	1088	0.92 (0.67-1.27)	0.609
Hospital Site #3	459	1.19 (0.86-1.65)	0.290	456	2.10 (1.34-3.28)	**0.001**	0.90 (0.66-1.24)	0.528	459	1.10 (0.78-1.55)	0.580
Hospital Site #4	317	0.59 (0.42-0.83)	**0.003**	311	0.83 (0.52-1.34)	0.443	0.50 (0.35-0.71)	<0.001	316	0.49 (0.34-0.71)	**<0.001**
Hospital Site #5	277	0.76 (0.53-1.09)	0.132	273	1.39 (0.84-2.30)	0.197	0.55 (0.38-0.78)	0.001	277	0.62 (0.41-0.91)	**0.016**
Hospital Site #6	259	0.96 (0.67-1.37)	0.814	257	1.02 (0.62-1.67)	0.948	1.01 (0.70-1.44)	0.965	259	1.09 (0.75-1.60)	0.642
Diabetes											
no	2192	1.0 (ref)		-	-	-	1.0 (ref)		-	-	-
yes	432	1.43 (1.16-1.77)	**0.001**	-	-	-	1.34 (1.09-1.65)	**0.006**	-	-	-

unknown	4	0.56 (0.05-6.18)	0.636	-	-	-	1.07 (0.15-7.60)	0.946	-	-	-
BMI class											
<18.5 (underweight)	57	0.98 (0.57-1.68)	0.935	-	-	-	1.31 (0.76-2.25)	0.329	-	-	-
18.5-24.9 (normal weight)	789	1.0 (ref)		-	-	-	1.0 (ref)		-	-	-
25.0-29.9 (overweight)	943	1.03 (0.85-1.25)	0.744	-	-	-	1.03 (0.86-1.25)	0.729	-	-	-
≥30.0 (obese)	839	0.95 (0.78-1.15)	0.589	-	-	-	0.96 (0.79-1.16)	0.640	-	-	-
Alcohol use[†]											
No	2378	1.0 (ref)		-	-	-	1.0 (ref)		-	-	-
Yes	219	0.85 (0.64-1.12)	0.237	-	-	-	0.83 (0.63-1.10)	0.191	-	-	-
Stopped because of surgery	5	1.57 (0.26-9.4)	0.623	-	-	-	1.51 (0.25-9.05)	0.652	-	-	-
Unknown	26	1.22 (0.56-2.65)	0.616	-	-	-	1.18 (0.54-2.55)	0.684	-	-	-
Smoker[†]											
no	2160	1.0 (ref)		-	-	-	1.0 (ref)		-	-	-
yes	455	1.09 (0.89-1.34)	0.394	-	-	-	1.04 (0.85-1.280	0.678	-	-	-
unknown	13	2.43 (0.75-7.90)	0.141	-	-	-	1.65 (0.54-5.05)	0.382	-	-	-

ASA, American Society of Anesthesiologists physical status classification; BMI, body mass index; CI, confidence interval; ERAS, Enhanced Recovery After Surgery; LOS, length of hospital stay; N, number; OR, odds ratio

*Nutrition risk was only calculated for the ERAS GRoup and defined as ≥2 on the Malnutrition Screening Tool (MST) or two "yes" answers on the Canadian Nutrition Screening Tool (CNST), patients in the ERAS implementation group whose nutrition screen status was unknown (N=908) were excluded from this analysis

(-) dash indicates variables that were not included in the logistic regression models because they were not significant at univariable or multivariable level

Model 1: Full model (included all variables significant at univariable level) -2 LL = 2196.376, Negelkerke R^2 = 56%, Hosmer & Lemeshow test P= 0.717, Classification = 82%; Fitted Model (retains variables significant at multivariable level) -2LL =2199.019, Negelkerke r^2 = 56%, Hosmer & Lemeshow test P=0.182, Classification = 82%

Model 2: Full model (included all variables significant at univariable level) -2 LL = 3311.719 Negelkerke R^2 = 16%, Hosmer & Lemeshow test P= 0.564, Classification = 65%; Fitted Model (retains variables significant at multivariable level) -2LL = 3316.942 , Negelkerke r^2 = 15%, Hosmer & Lemeshow test P=0.584, Classification = 65%

Appendix VII

Chapter 8. Supplementary Table 1. Simple linear regression models for the effect of sex and age on features of body composition for each study cohort and the aggregated colorectal cancer data

Linear Regression Models	*B*	SE *B*	β	t	P-Value
Skeletal Muscle Index (cm^2/m^2)					
Canada Cohort 1 (N=384)					
Intercept	47.36	2.66		17.82	0.000
Age (years)	-0.28[a]	0.04	-0.31	-7.91	0.000
Sex (male)	11.49[b]	0.81	0.56	14.20	0.000
R^2	0.40				
Canada Cohort 2 (N=961)					
Intercept	43.02	1.67		25.83	0.000
Age (years)	-0.21[a]	0.02	-0.25	-9.88	0.000
Sex (male)	10.95[b]	0.51	0.55	21.40	0.000
R^2	0.37				
UK Cohort 3 (N=755)					
Intercept	44.68	1.85		24.20	0.000
Age (years)	-0.22[a]	0.02	-0.29	-9.39	0.000
Sex (male)	8.73[b]	0.57	0.46	15.19	0.000
R^2	0.30				
Pooled CRC Cohort (N=2100)					
Intercept	44.64	1.13		39.34	0.000
Age (years)	-0.23	0.01	-0.28	-15.79	0.000
Sex (male)	10.24	0.35	0.52	29.24	0.000
R^2	0.35				
Skeletal Muscle Radiodensity (HU)					
Canada Cohort 1 (N=384)					
Intercept	57.85	2.97		19.51	0.000
Age (years)	-0.38[a]	0.04	-0.44	-9.62	0.000
Sex (male)	1.62[b]	0.90	0.08	1.79	0.074
R^2	0.19				
Canada Cohort 2 (N=961)					
Intercept	52.87	1.78		29.71	0.000
Age (years)	-0.34[a]	0.02	-0.44	-15.24	0.000
Sex (male)	1.45[b]	0.55	0.08	2.66	0.008
R^2	0.20				
UK Cohort 3 (N=755)					
Intercept	50.79	1.91		26.61	0.000
Age (years)	-0.37[a]	0.02	-0.49	-15.63	0.000
Sex (male)	2.59[b]	0.59	0.14	4.36	0.000
R^2	0.26				
Pooled CRC Cohort (N=2100)					

Intercept	53.28	1.22		43.77	0.000
Age (years)	-0.36	0.02	-0.46	-23.61	0.000
Sex (male)	1.91	0.38	0.10	5.10	0.000
R^2	0.22				
Visceral Adipose Tissue Index (cm^2/m^2)					
Canada Cohort 1 (N=384)					
Intercept	-3.72	12.53		-0.30	0.767
Age (years)	0.30[a]	0.17	0.09	1.83	0.068
Sex (male)	29.76[b]	3.82	0.37	7.80	0.000
R^2	0.14				
Canada Cohort 2 (N=961)					
Intercept	-12.05	7.53		-1.60	0.110
Age (years)	0.49[a]	0.10	0.15	5.08	0.000
Sex (male)	24.90[c]	2.31	0.33	10.77	0.000
R^2	0.12				
UK Cohort 3 (N=755)					
Intercept	-1.77	7.30		-0.24	0.808
Age (years)	0.26[a]	0.09	0.10	2.86	0.004
Sex (male)	21.84[d]	2.29	0.33	9.53	0.000
R^2	0.12				
Pooled CRC Cohort (N=2100)					
Intercept	-5.68	4.95		-1.15	0.252
Age (years)	0.35	0.06	0.12	5.64	0.000
Sex (male)	24.69	1.53	0.33	16.10	0.000
R^2	0.12				

B = unstandardized beta, slope of the line between predictor and dependent variable

SE = standard error for B

β = standardized beta, values range between 0 to 1 or -1 to 0, indicates the direction and strength of relationship between predictor and dependent variable

R^2 = effect size

[a,b] Skeletal muscle index = no difference between study cohort correlation coefficients for age[a] (P>0.05) or sex[b] (P>0.05), based on Z-test[51]

[a,b]Skeletal muscle attenuation = no difference between study cohort correlation coefficients age[a] (P>0.05) or sex[b] (P>0.05), based on Z-test[51]

Appendix VIII

Chapter 8 Supplementary Table 2. Estimated marginal mean LOS derived from the final adjusted negative binomial regression model for each body composition profile demonstrating the independent effect of the body composition profiles on LOS with or without major post-operative complications.

Body composition profiles based on the absence or presence of sarcopenia, myosteatosis, or visceral obesity	**Geographic Region**	**Estimated Marginal Mean LOS (95% CI)**	**Mean Difference (days)**	**P-Value**
no features				
Non-sarcopenic, Non-myosteatotic, Non-viscerally obese	UK	12.21 (11.05-13.49)[a]	3.05	<0.001
	Canada	9.16 (8.26-10.15)[c]		
1 feature				
Sarcopenic	UK	13.80 (12.14-15.69)	3.45	<0.001
	Canada	10.35 (9.03-11.86)		
Viscerally Obese	UK	12.32 (10.51-14.45)	3.08	<0.001
	Canada	9.24 (7.96-10.74)		
Myosteatosis	UK	13.76 (12.36-15.32)	3.44	<0.001
	Canada	10.32 (9.09-11.72)		
2 features				
Sarcopenia + Viscerally Obese	UK	14.00 (7.62-25.71)	3.50	0.005
	Canada	10.50 (5.75-19.18)		
Sarcopenia + Myosteatosis*	UK	15.49 (13.89-17.27)[b]	3.87	<0.001
	Canada	11.62 (10.20-13.23)[d]		
Myosteatosis + Viscerally Obese*	UK	15.28 (13.59-17.17)[b]	3.82	<0.001
	Canada	11.46 (10.16-12.92)[d]		
3 features				
Sarcopenia+ Myosteatosis + Viscerally Obese*	UK	19.24 (15.85-23.36)[b]	4.81	<0.001
	Canada	14.43 (11.84-17.59)[d]		

*profiles identified from negative binomial regression that are significantly (P<0.05) associated with extended LOS (compared to no features) independent of major complications, study cohort, surgical approach, and age

[a,b] Significantly different from no features (Non-sarcopenic, Non-myosteatotic, Non-viscerally obese) from UK

[c,d] Significantly different from no features (Non-sarcopenic, Non-myosteatotic, Non-viscerally obese) from Canada

Appendix IX

Chapter 8. Supplementary Table 3. Factors predictive of major complications (Clavien Dindo Grade ≥3) in colorectal cancer patients undergoing elective surgery.

		Univariable			Multivariable		
Variable	**N**	**Beta**	**OR (95% CI)**	**P-Value**	**Beta**	**OR (95% CI)**	**P-Value**
Pre-surgical Body Composition Profiles							
Sarcopenia+ Myosteatosis + Viscerally Obese	42	0.022	1.02 (0.41-2.57)	0.963			
Sarcopenia + Viscerally Obese	5	-19.389	-	0.999			
Myosteatosis + Viscerally Obese	148	0.121	1.13 (0.65-1.95)	0.664			
Viscerally Obese	90	-0.383	0.68 (0.32-1.45)	0.321			
Sarcopenia + Myosteatosis	189	-0.213	0.81 (0.47-1.39)	0.443			
Sarcopenia	140	-0.465	0.63 (0.33-1.21)	0.162			
Myosteatosis	181	0.35	1.42 (0.87-2.31)	0.160			
None	321						
Sample							
Sample 1	384						
Sample 2	755	-0.046	0.955 (0.669-1.362)	0.798			
Sex							
Female	451						
Male	688	0.972	2.644 (1.7711-3.946)	<0.001	0.881	2.414 (1.610-3.622)	<0.001
Cancer Site							
Colon	731						
Rectum	408	0.803	2.233 (1.588-3.141)	<0.001	0.696	2.005 (1.418-2.836)	<0.001

Surgical Approach							
Laparoscopic	649						
Open	413	0.013	1.013 (0.706-1.454)	0.943			
Converted	77	0.272	1.312 (0.694-2.482)	0.404			
Age (years)	1139	-0.003	0.997 (0.983-1.011)	0.637			
ASA Class (N, %)							
ASA 1	118						
ASA 2	796	-0.102	0.903 (0.519-1.570)	0.717			
ASA 3+4	221	0.042	1.043 (0.554-1.964)	0.897			
AJCC Stage							
I	283						
II	343	-0.126	0.881 (0.568-1.368)	0.574			
III	398	-0.345	0.708 (0.456-1.100)	0.125			
IV	109	-0.521	0.594 (0.295-1.1.95)	0.144			
Diabetes							
no	1028						
yes	105	-0.008	0.992 (0.550-1.791)	0.979			

ASA, American Society of Anesthesiologists; CI, confidence interval; IRR, incident rate ratio; LOS, length of stay; N, number; NS, non-significant OR, odds ratio

*Canadian cohort used American Joint Committee on Cancer (AJCC) version 6, UK cohort used Union for International Cancer Control's (UICC) version 5

†Model = binary logistic regression, dependent variable = major complications (Grade ≥3)