Nutritional Status, Body Composition, and Psychosocial Outcomes Among Individuals with Advanced Head and Neck Cancers: A Prospective Investigation in An Outpatient Setting

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DEDICATION

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ABSTRACT

Malnutrition among individuals with head and neck cancer (HNC) is of particular concern, with up to 40% - 57% with a compromised nutritional status even before beginning their treatment. Within the US, the prevalence of malnutrition has not been well-documented due to a lack of consensus on its definition and diagnosing markers. Therefore, the primary aim of this prospective natural history pilot study was to estimate the prevalence of malnutrition among individuals with HNC (n = 19) during and up to 3 months after treatment using the new Consensus malnutrition definition. The scored Patient-Generated Subjective Global Assessment (PG-SGA) was used as the reference standard to evaluate the sensitivity and specificity of the Consensus framework in defining malnutrition. Another aim of this research was to investigate the utility of raw bioimpedance parameters such as 50 kHz phase angle (PA) and 200 kHz/5 kHz impedance ratio (IR) to identify individuals with malnutrition, and to evaluate how bioimpedance markers relate to functional status outcomes. Finally, this research also assessed how malnutrition relates to quality of life (QoL) and self-efficacy perceptions among individuals with HNC.

Results indicate that individuals with HNC are malnourished even before treatment initiation. Using the Consensus framework, 67% of our participants were malnourished before treatment; and the prevalence of malnutrition consistently increased during treatment and the post-treatment period. When compared to our reference standard PG-SGA, the Consensus criteria identified malnutrition with overall good sensitivity (95%) and specificity (43%).

Bioimpedance markers PA and IR were useful in identifying individuals who were at increased risk for malnutrition and/or impaired functional status. From a psychosocial perspective, compared with well-nourished participants, malnourished individuals scored significantly lower in the global QoL and cognitive function scales and significantly higher in the disease- and treatment-related symptom scales and items.

In the future, if clinicians are trained to assess malnutrition diagnostic markers before individuals with cancer undergo aggressive treatments, nutritional interventions could be initiated at an earlier time and loss in weight and/or lean tissue can be prevented. Early detection of malnutrition could also help with patient-specific intervention strategies aimed to improve overall health-related QoL outcomes.

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CHAPTER 1: INTRODUCTION

Malnutrition is commonly identified by unintended loss of body weight and has been associated with increased morbidity such as impaired wound healing, increased post-operative complications, and reduced quality of life. Malnutrition among individuals with head and neck cancer (HNC) is of particular concern, and depending on the parameters used for its identification, it is estimated that 50 - 70% are malnourished and 25% - 57% have impaired nutrition status at the time of diagnosis.[1] Poor nutrition may result in treatment delays and/or interruptions and increased hospital admissions, which further increases costs and compromises the quality of care to the patient.[2,3]

Within the US, there is a paucity of data regarding the effect of nutritional care during the course of HNC treatment, and the lack of a consensus definition of malnutrition has made early identification and diagnosis of malnutrition a challenge. Recently, the Academy of Nutrition and Dietetics in conjunction with the American Society for Parenteral and Enteral Nutrition have published a joint consensus regarding identification of adult malnutrition.[3] If malnutrition is appropriately diagnosed at an earlier stage of treatment, the clinical team can take the necessary steps to address the condition early, which could positively influence patient health, decrease length of stay, and reduce costs. Therefore, ***the primary aim in conducting this prospective pilot study was to estimate the prevalence of malnutrition among individuals with HNC during and up to 3 months after treatment using the new consensus definition.***

Routine assessment of body composition is important for identification of individuals with HNC who might be at risk for malnutrition due to progressive

losses of lean muscle mass. Lean tissue depletion has been associated with reduced functional status, higher infections, and lengthier stay in hospital among those who are malnourished.[4–7] Changes in body composition have not been sufficiently investigated in the HNC setting during and after treatment. Additionally, without body composition assessment, it is not possible to discern whether any gain in body weight is due to a gain in muscle mass or is simply due to fat accumulation or fluid retention. Simple anthropometric measures such as body weight and body mass index are not sensitive to changes in body composition.[7,8] Clearly, the diagnosis of malnutrition may be improved by incorporating feasible body composition measures such as those provided by bioimpedance devices that can be used to assess changes in lean muscle mass over time. Therefore, ***the second aim of this research was to investigate whether clinicians can potentially use raw bioimpedance parameters such as 50 kHz phase angle and 200 kHz/5 kHz impedance ratio to identify individuals with malnutrition, and to evaluate how bioimpedance markers relate to functional status outcomes.***

HNC-related symptoms and intensive treatment regimens can negatively affect the basic functions of living such as speech, respiration, hearing, eating, chewing, and swallowing.[8,9] Health-related quality of life is therefore an important parameter to assess among individuals with HNC at various time points during and after treatment. Cancer diagnosis and treatment can also negatively affect individuals' self-efficacy to cope with illness-related stress and threaten their psychosocial well-being and quality of life.[10] However, limited research has

investigated the relation between malnutrition and quality of life or coping self-efficacy in the HNC setting. Therefore, ***the <u>third aim</u> for this research was to assess how malnutrition relates to quality of life and self-efficacy perceptions among individuals with HNC.***

In the following chapters, this dissertation addresses these three aims. Chapter 2 provides a literature review on the background information relevant to these aims; part I addresses nutrition-related and psychosocial aspects of HNC, and part II reviews bioimpedance techniques for bed-side assessment. Chapter 3 addresses the first 2 aims of the study, identifying the prevalence of malnutrition among individuals with HNC and investigating the utility of bioimpedance parameters for the assessment of malnutrition. Chapter 4 addresses the third aim, evaluating whether quality of life and coping self-efficacy relate to malnutrition and further investigates the association between the quality of life and functional status outcomes. Lastly, Chapter 5 provides overall conclusions and suggestions for future directions.

CHAPTER 2: LITERATURE REVIEW – PART I

Head and Neck Cancer (HNC) Malnutrition: An Overview

Malnutrition is highly prevalent among individuals with HNC, with up to 40% - 57% having a compromised nutritional status even before beginning their treatment.[1,11] Previously, HNC malnutrition has been associated with poor survival outcomes and increased morbidity including post-surgical complications, risk of infections, impaired wound healing and recovery, declining quality of life (QoL) and functional status, and poor disease prognosis.[1,8,11–15] Lethargy, loss of appetite, anxiety, and depression, as well as surgery-, chemotherapy-, and radiotherapy-related side-effects (e.g., difficulty chewing, pain while swallowing, mouth sores) are some of the key factors contributing to inadequate dietary intake, resulting in unintended weight loss and loss of fat and muscle mass.[1,8] From the health care perspective, malnutrition is associated with frequent treatment interruptions and increased hospital readmissions and length of stay, further adding to costs related to patient care.[2,3]

Malnutrition: An Etiology-Based Definition is Needed

Although malnutrition in the United States (US) has been recognized as a significant clinical problem, a lack of standardization in defining, diagnosing, and documenting malnutrition has made addressing this issue a continuous challenge for clinicians.[3,16] The 2012 Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition Consensus Statement on adult malnutrition has noted the necessity for a uniform definition, and has suggested the use of two or more of the following six markers for diagnosis: insufficient energy intake, weight loss, loss of muscle mass, loss of subcutaneous fat,

localized or general fluid accumulation, and diminished functional status as measured by hand grip strength.[3] Additionally, it is important to screen all patients in order to identify those at risk for malnutrition through the administration of appropriate screening tools. Although nutrition screening is used to identify risk of malnutrition based on readily accessible information upon admission, nutrition assessment involves more in-depth evaluation to diagnose malnutrition utilizing the aforementioned parameters.[17] Early detection of malnutrition through timely screening, and subsequent assessment and intervention has been shown to improve QoL and tolerance to treatment.[16,17] Nevertheless, the efficacy of early nutritional screening in identifying those at risk for malnutrition has not yet been examined among individuals with HNC.

In *inpatient* clinical facilities, the Joint Commission mandates that all newly admitted patients undergo screening for malnutrition within 24 hours of admission, and then patients that are identified as high risk undergo a complete nutrition assessment by a Registered Dietitian Nutritionist within a time-frame specified by the individual facility.[17] While *outpatient* clinical facilities are not mandated to routinely screen individuals with HNC for the risk of malnutrition, in those that do, there is significant variation in the screening parameters used. Similarly, clinicians may use different assessment parameters to diagnose malnutrition, which heretofore has not had a clear consensus-driven definition; this has resulted in a wide range of reported HNC malnutrition prevalence (ranging from 19% to 70%).[1,3,16] Therefore, an important first step to more accurately estimate the prevalence of malnutrition among individuals with HNC is

to implement the malnutrition definition and guidelines from the recent Consensus Statement. In addition, the efficacy of incorporating screening tools to identify those at-risk for malnutrition (especially during the pre-treatment period) at outpatient clinical facilities also needs to be examined.

Malnutrition and Functional Status Markers

Hand grip Strength

Hand grip strength is a simple, non-invasive marker of muscle strength and functional status that has been used among the hospitalized elderly, general surgery, and among individuals with HNC.[8,18] Impaired grip strength correlates with decreased muscle function[18] and losses of total body protein,[19] and is associated with immediate postoperative complications and poor nutritional status among individuals with cancer.[18,20,21] Additionally, chronic inflammation, skeletal muscle catabolism, and poor nutritional intake and sedentary behavior during HNC treatment often results in loss of protein and lean muscle mass stores.[8,20] Although research has shown that disease-related malnutrition results in impaired muscle function and strength, such data are limited in individuals with HNC, especially during the course of their treatment.

Five-times-sit-to-stand-test

Five-times-sit-to-stand-test (FTSST) is another measure for assessing functional status, and it involves recording the quickest time required by a participant to rise and sit down five times from a chair.[22] Yielding high reliability and validity, the FTSST has been used to assess lower extremity muscle strength and balancing function among the frail elderly, and individuals with

Parkinson's disease, arthritis, stroke, prostate cancer, cerebral palsy, spinal cord injury, and chronic obstructive pulmonary disease.[22–28] Higher FTSST time is associated with impaired muscle function and strength, poor balance, and a higher risk for falls among the elderly.[22,24,27] To date, the reliability of FTSST has not been tested among individuals with HNC who usually undergo losses in muscle mass and strength during treatment. Such data will provide valuable information for clinicians who could easily incorporate a feasible and quick to administer measure such as the FTSST to assess functional status and muscle function during various phases in treatment.

Psychosocial Measures

Quality of Life (QoL)

Head and neck cancer-related symptoms and intensive treatment regimens can negatively affect the basic functions of living such as speech, respiration, hearing, eating, chewing, and swallowing.[8,9] Among individuals with advanced disease, issues with facial disfigurement, general appearance, and communication affect social interaction and activities of daily living, which may lead to isolation and depressive symptoms, also influencing adherence to treatment and recovery.[9,29–31] Health-related quality of life is therefore an important parameter to assess among individuals with HNC at various time points during and after treatment. Such data provide valuable information about treatment-related symptoms, and physical, psychological, and social functioning, and further help to identify individuals in need of clinical and therapeutic interventions.[8,30]

Although prospective studies have assessed QoL among individuals with HNC during various treatment and post-treatment time points,[9,29–31] limited data are available on how QoL relates to malnutrition and associated symptoms. HNC research investigating the effect of nutritional symptoms (including malnutrition) on QOL has mostly been conducted elsewhere (Italy, The Netherlands, Portugal),[32–35] and such data are lacking in the US.

Coping Self-efficacy

Self-efficacy theory suggests that the greater a person's self-confidence to execute a course of action (e.g., coping with cancer pain), the higher the probability that the desired goal (e.g., to improve QoL) will be attained.[36] Coping self-efficacy is a form of self-efficacy that refers to people's beliefs in their ability to negotiate particular stressors or obstacles.[37] Such beliefs affect how people perceive and react to adverse life events and conditions, and favorable coping self-efficacy perceptions help people to draw effectively on social support and persist at problem-solving when faced with difficult situations.

Cancer diagnosis and treatment can negatively affect patients' self-efficacy to cope with illness-related stress and threaten their psychosocial well-being and QoL.[10] Previous oncology research has indicated that individuals with higher self-efficacy report better health-related QoL, may live longer, feel less depressed, participate in treatment decision making, and exhibit fewer illness related symptoms compared to those who are less efficacious in coping.[10,37–40] Therefore, perceptions regarding self-efficacy are important to clinical knowledge so that individuals' cancer-coping strengths and weaknesses may be identified,

and possible psychosocial interventions may be administered in a timely way0. Research investigating self-efficacy perceptions among individuals with HNC is particularly limited, and the current study will delineate the influence of this important psychosocial construct among this patient population.

Malnutrition and Assessment of Lean Tissue

The loss of muscle mass is a defining characteristic for malnutrition and sarcopenia.[3,41] A low skeletal muscle mass has also been associated with treatment-related adverse events among individuals with breast, lung, and renal cancer.[42–45] Therefore, there has been a significant interest in the estimation of lean tissue in the clinical setting. However, limited methods are available for this purpose. Dual-energy X-ray absorptiometry (DXA) measures fat and lean soft tissue mass through X-ray attenuation.[46] DXA scanners are used in a variety of settings including exercise and radiology labs,[46] and as an assessment method, DXA is precise, safe (although it involves minor exposure to radiation), quick to administer, and requires moderate cooperation from the participant.[47,48]However, DXA scanners are relatively expensive, non-portable, and require trained technicians for their operation and maintenance.[49–51] Therefore DXA appears to be a less feasible and/or practical option for lean tissue assessment in the HNC population.

Another method used in the assessment of lean tissue is computerized tomography (CT) scanning.[47] Previously, CT scanning has been reported to be a precise, valid, and accurate method to assess body composition.[44,46,52,53] Although CT scanning is regarded as an accurate measure of body composition

at the tissue-organ level, this method is expensive and requires skilled technicians for operation.[47,54] Additionally, CT scanning is time consuming and exposes individuals to a relatively higher dose of radiation making it unsafe for repeated measurements.[47] CT scanning is thus typically not used clinically as a body composition method. However, many cancer patients (particularly those with gastrointestinal and abdominal cancers) undergo CT scanning for diagnostic purposes and thus, scans can be utilized to assess lean tissue. For example, CT scans were used to assess skeletal muscle mass among individuals with advanced gastrointestinal and lung cancers, and a substantial number of individuals with obesity were found to meet the criteria for sarcopenia.[44,53]

Given the challenges with CT and DXA, there is a growing interest in the use of bioimpedance devices for the assessment of lean tissue at the bed-side.[46,55] Bioimpedance techniques are non-invasive, portable, require little training for operation, and are relatively lower cost alternatives to DXA and CT scanning.[49,54,56,57] A thorough review of the various bioimpedance techniques and their clinical utility to provide whole body estimates of lean tissue for bed-side nutritional assessment is discussed in the following section.

CHAPTER 2: LITERATURE REVIEW – PART II
BIOIMPEDANCE AT THE BEDSIDE: CURRENT APPLICATIONS, LIMITATIONS, AND OPPORTUNITIES*

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Overview

The loss of muscle mass is a defining characteristic of malnutrition and there has been an ongoing interest in the assessment of lean tissue at the bed-side. Globally, bioimpedance techniques have been widely appreciated for their non-invasiveness, safety, ease of use, portability, and relatively low cost compared to other clinically available methods. In this brief update, we review the three primary types of commercially available bioimpedance devices (single- and multiple-frequency and spectroscopy) and differentiate the underlying theory and current applications of each. We also address limitations and potential opportunities for using these devices at the bed-side for clinical assessment. Mixed reports in the validation literature for all bioimpedance approaches have raised questions about absolute accuracy to estimate whole body composition in clinical populations, particularly those with abnormal fluid status and/or body geometry in whom underlying method assumptions may be violated. Careful selection of equations can improve whole body estimates by single- and multiple-frequency techniques, however, not all devices will allow for this approach. Research is increasing on the use of bioimpedance variables including phase angle and impedance ratio as potential markers of nutritional status and/or clinical outcomes; consensus on reference cut-points for interpreting these markers have yet to be established. Novel developments in the bioimpedance spectroscopy approach are allowing for improved fluid management in individuals on dialysis; these have implications for the clinical management of other conditions associated with fluid overload, and may also prove to provide

enhanced whole body estimates of lean tissue through new modeling procedures.

Introduction

The new Consensus malnutrition framework[3] features the loss of muscle mass as one of the key characteristics defining malnutrition. The loss of muscle mass is also a key characteristic of sarcopenia, which is a core defining characteristic of cachexia.[58] From a therapeutic standpoint, lean tissue is an important concept for appropriate drug dosing, given the risk of toxicity with certain drug therapies in individuals with lean tissue depletion.[42,43,45] Furthermore, the current American Society of Parenteral and Enteral Nutrition critical care guidelines recommend that protein delivery in individuals with extreme obesity should be based on ideal body weight;[59] but it is likely that a more effective strategy would be to dose protein on the basis of lean tissue given what we know about the relationship between the two.[60–63] For these reasons, there has been ongoing interest in the assessment of body composition (and in particular lean tissue) at the bed-side. Globally, bioimpedance techniques have been widely appreciated for their non-invasiveness, safety, ease of use, portability, and relatively low cost compared to other clinically available methods (e.g. dual-energy X-ray absorptiometry [DXA]);[56,64] and various applications of bioimpedance across the lifespan were presented in a recent supplement of the European Journal of Clinical Nutrition.[65] There are three primary categories of devices available today, including single-frequency, multiple-frequency, and spectroscopy. Although single-frequency devices were the first to be made

commercially available and are the most abundant in the market place, multiple-frequency and spectroscopy devices are becoming more readily available.

Thorough reviews of the validation literature for whole body composition estimates have been published previously.[55,66] Although many available bioimpedance devices have been shown to be relatively valid for estimating fat-free mass (FFM) and other body composition compartments in healthy normal weight individuals, studies in various clinical populations are much less abundant and tend to yield mixed results regardless of approach. All bioimpedance approaches have been shown to be largely erroneous for whole body composition estimates in individuals with obesity.[67–70] Although refinements in bioimpedance techniques have led to important advancements in the management of individuals on dialysis, the clinical applications for whole body lean tissue assessment require additional development. Validation studies in clinical populations have typically reported good mean-level agreement between bioimpedance and reference methods based on correlation and paired t-test statistics, but poor accuracy at the individual level (i.e. wide limits of agreement by Bland-Altman analysis) raising doubts about the capacity of bioimpedance techniques to accurately quantify whole body compartments. It should be noted that each reference method has a certain amount of inherent error, and it can be argued that the aforementioned statistical techniques utilized to prove validity do not effectively take into account the errors associated with the reference.[71] Furthermore, prediction equations are scaled to a particular reference method and when evaluated against a different reference method can produce error. For

example, a bioimpedance equation that may have been developed for FFM from DXA may produce substantial scaling errors when compared against total body water (TBW) measures generated by deuterium dilution in a different study. Although in many cases the errors in estimates generated from bioimpedance techniques at the individual level probably are truly significant, it is certainly possible that at least some of the time bioimpedance techniques have been unfairly judged to be erroneous due to these limitations inherent to body composition validation studies.

Nevertheless, there remains significant global interest in the applications of bioimpedance techniques for bed-side assessment of nutritional status either through the evaluation and monitoring of whole body lean tissue, or through the interpretation of some bioimpedance derived variable independent of whole body mass or volume. Indeed, given the difficulties associated with the validation of bioimpedance techniques, there is growing interest in new applications of bioimpedance for the clinical setting that go beyond quantifying whole body composition. There are also new developments in the field for whole body fluid volume management in dialysis that hold promise for improving the capacity to estimate whole body lean tissue. In this brief update, we review the three primary types of commercially available bioimpedance devices and differentiate the underlying theory and current applications of each. We also address limitations and potential opportunities for using these devices at the bed-side for clinical assessment.

General Principles of Bioimpedance

The three general categories of bioimpedance devices available commercially include single-frequency, multiple-frequency, and spectroscopy. Regardless of the device, bioimpedance involves the administration of a weak, alternating electrical current at one or more radiofrequencies through leads attached to surface electrodes in order to characterize the conductive and non-conductive tissue and fluid components of the body.[56,72] The applied current flows at various rates depending on the composition of the body, and is well conducted by water and electrolyte-rich tissues such as blood and muscle, and is poorly conducted by fat, bone, and air-filled spaces.[64,72,73] The voltage drop of the current as it passes through the body is detected through the current sensing electrodes and the impedance data are recorded by the bioimpedance device.

Bioimpedance measurements are typically taken in the supine position following standardized protocol.[55,66,73] Electrodes can be attached to the body in several different arrangements. The most common approach for generating whole body composition estimates is the standard tetrapolar arrangement (also termed wrist-ankle), which involves the placement of two electrodes on the hand (one on the bony protuberance that forms the wrist, i.e. between the styloid processes of the ulna and radius, and the other just behind the meta-carpals), and two electrodes on the foot (one on the ankle placed midline between the medial and lateral malleoli, and the other just behind the metatarsals). A less common option utilized by select devices (e.g. the InBody segmental multiple-frequency devices) involves the placement of eight electrodes in a tetrapolar

arrangement on both hands and both feet. Segmental approaches require the placement of electrodes in various arrangements depending on the limb or segment to be measured.[56,72]

Several excellent reviews provide a comprehensive discussion of bioimpedance and the underlying assumptions to available technologies.[56,64,72] However, it is useful to review the core general concepts here. In brief, *impedance* (Z) is the frequency-dependent opposition by the conductor (i.e. the body) to the flow of electric current.[74,75] Geometrically, impedance is the vector composed of two frequency-dependent parameters – *resistance* (R) and *reactance* (Xc).[72,75] Resistance is the opposition to the flow of current when passing through the body.[72,75] Reactance is the delay in conduction caused by cell membranes, tissue interfaces, and non-ionic substances.[64,72,73,75] *Capacitance* is a function of reactance that arises when cell membranes store a portion of the current for a brief time.[56]This temporary storage of charge creates a phase shift or *phase angle* (PA), quantified as the ratio of the arc tangent of reactance to resistance (arc tangent [Xc/R] × [180°/π], expressed in degrees).[64] At very low (or theoretically approaching zero) frequencies, virtually no conduction occurs because a higher cell membrane capacitance permits the current to only pass through (and therefore quantify) the extracellular water (ECW).[66,72] At very high (or theoretically approaching infinity) frequencies, total conduction occurs through cell membranes, thus allowing for the quantification of TBW.[66,72] The difference between the TBW and ECW further determines the intracellular water (ICW) volume which can theoretically be used to estimate

body cell mass (BCM) based on the assumption that cells are comprised of 70% water.[76] Therefore, the potential applications available depend on the nature of the device at hand, including the number and range of frequencies, software capacity, quality of circuit board, and other factors. It is useful to consider the general framework, underlying assumptions, and strengths and limitations for each of the three general approaches for estimating whole body fluid volumes and lean and fat tissue masses.

Bioimpedance for Estimating Whole Body Composition

Single-Frequency Bioelectrical Impedance Analysis (SF-BIA)

SF-BIA using a 50 kHz single-frequency device and wrist-ankle tetrapolar electrode placement is the most widely utilized bioimpedance approach to estimate whole body composition (see Table 1). Most typically, impedance data measured at 50 kHz is used to estimate various body compartments through application to regression-derived equations previously derived from reference data. For example, an equation for predicting TBW would typically be developed by measuring TBW using deuterium dilution as the reference method in a homogeneous sample from a study population. Bioimpedance data obtained from the study sample would then be regressed against TBW reference measures in order to develop an equation that can be used to predict TBW from bioimpedance data. The new equation must then be cross-validated in a separate independent sample of individuals with similar characteristics. Once TBW is predicted from SF-BIA generated impedance data applied to such an equation, then fat-free mass (FFM) can be derived through the assumption that

FFM is constantly hydrated at 73.2%. By this method, fat mass (FM) can then be derived through subtraction of FFM from body weight. Thus, it can be appreciated that SF-BIA inherently is based upon the two- component model of body composition (FM + FFM = Body weight). Alternatively, regression equations have been developed based on other appropriate reference methods for directly predicting FM, FFM, and other compartments from 50 kHz data; these have been well reviewed by Kyle et al.[56] Ideally, an equation that is appropriately matched to the characteristics of an individual should be chosen to provide optimal body composition estimates. However, in the clinical setting there are significant barriers to this approach and underlying assumptions to SF-BIA are frequently violated.

First and foremost, the SF-BIA approach relies on an assumption that the body is a uniform conductor with constant geometry and composition, and resistance (R, ohms) is directly related to the product of specific resistivity (ρ, ohm-cm) and conductor length (L, cm), and indirectly related to conductor cross-sectional area (A, cm^2), such that $R = \rho (L/A)$.[56,64,72] Rearranging these variables allows for the prediction of volume from what has been termed the impedance quotient (L^2/R) or which is essentially $Height^2/R$ (Ht^2/R), with an appropriate adjustment factor (ρ) which accounts for the lack of uniformity in the conductivity of the body. In this way, impedance data can be used to predict the volume (V, cm^3) of TBW as follows: $V = \rho (Ht^2/R)$, also referred to as the 'volume conductor model'.[56,64]

The presumption underlying the whole body SF-BIA approach that the human body is a single, symmetrical cylinder with homogenous composition and uniform cross-sectional area is not physiologically accurate, as the body can be better described by having 5 distinct cylinders (2 arms, 1 trunk, and 2 legs).[73,77] Furthermore, the SF-BIA approach is based on the assumptions that the intra- to extracellular water ratio remains constant, and specific resistivity (ρ) is constant across all tissues of the body so that the bioelectrical current is conducted uniformly.[73] However, ρ is related to factors such as electrolyte concentration (inverse relation) and temperature (direct relation),[66,73,74] and the distribution of fluid between the intra- and extracellular compartments (and consequently the electrical properties) of various tissues varies with disease state and nutritional status.[55] These factors, and the fact that SF-BIA relies solely on the utility of just one frequency makes it highly improbable that it can accurately differentiate between intra- and extracellular water based on static assumptions; the validation literature bears that out.[55,73,78] Indeed, clinicians should be wary of reports generated by SF-BIA devices in their patients that provide values for intra- and extracellular water, BCM, and even bone mass, as they are highly questionable.

Even the generation of TBW by SF-BIA in clinical populations is potentially erroneous due to the assumption that 50 kHz is a high enough frequency to overcome membrane capacitance to completely quantify both intra- and extracellular water. Studies have demonstrated that in certain disease states, much higher frequencies are required in order to fully quantify TBW.[79,80] At

50kHz frequency, the method is actually measuring the weighted sum of ECW and ICW resistivities, and not TBW – therefore it estimates TBW without distinguishing between or measuring the individual ECW and ICW volumes.[56,73] In addition, FFM is typically derived from TBW following the assumption that FFM is constantly hydrated at 73.2%;[77] the hydration of FFM has been demonstrated to be significantly higher in individuals with obesity[81,82] and fluid overload.[83,84] Indeed, predictions of FFM have been reported to be overestimated in cardiac and renal settings, where ECW volume expansion is common.[55,73] This has also been shown among advanced lung and gastrointestinal cancer patients, where FFM was overestimated with wide limits of agreement (1.88±7.66 kg) between a SF-BIA device (TBF-300A, Tanita) and DXA (Lunar Prodigy Advance, GE Healthcare).[48]

Finally, it is important to remember that the SF-BIA approach generates whole body volumes and masses by using statistically-derived, population-specific equations (typically height-, weight-, age-, gender-, and ethnicity-specific) that have mostly been validated among healthy and normal-weight individuals under highly controlled conditions.[55,56] Obtaining optimal results for whole body compartments even in healthy people depends on the selection of an appropriate prediction equation. In reality, many devices do not specify the equation programmed into their software, considering that information to be proprietary, and clinicians rarely have the time or inclination to search the literature to find an equation appropriate to the individual being measured. Furthermore, some devices do not provide the raw impedance data (i.e. resistance, reactance,

impedance, phase angle), thus making it impossible to recalculate body composition compartments using an appropriate equation. This critique can also be made of many multiple-frequency devices.

There is a growing body of literature investigating the utility of 50 kHz derived bioimpedance data to either enhance nutrition assessment or independently predict nutritional status and/or clinical outcomes, without relying on predictions of whole body volumes or masses.[46,85] Specifically, phase angle can be compared to population-specific reference values.[86–89] 50 kHz data can also be used to generate fat-free mass index (FFMI), a height corrected index of FFM that can be calculated by a standardized equation and compared to reference data.[90] Another parameter that can be generated from 50 kHz data is derived from a graphical procedure called bioelectrical impedance vector analysis (BIVA); this method involves the plotting of resistance and reactance standardized for height to create a vector that can then be compared to gender- and race-specific reference values from healthy population samples.[91,92] The use of BIA data in this way is theoretically advantageous in situations where bioimpedance assumptions are not valid to estimate body composition. The BIVA method presents some logistical challenges for clinical application given that few devices are programmed with software appropriate to calculate it. BIVA has been reviewed elsewhere;[55,85] PA and FFMI will be further discussed in a subsequent section.

Multiple-Frequency BIA (MF-BIA)

Similar to SF-BIA, the most commonly applied MF-BIA approach for the determination of whole body masses and volumes involves the measurement of impedance using the wrist-ankle tetrapolar electrode placement, and then applying the data obtained at two or more frequencies to regression-derived population-specific prediction equations.[56,66] Although a bioimpedance spectroscopy (BIS) device can be used to generate data that can be applied to MF-BIA prediction equations, it is most common to take this approach using an actual MF-BIA device. Typically, MF-BIA devices apply the current at one very low frequency (e.g. 5 kHz) and several higher frequencies (e.g. 50, 100, 200, 500 kHz; see Table 1). Thus, theoretically, MF-BIA is able to differentiate between the ECW and ICW compartments, as at lower frequencies, impedance to current flow determines the ECW, while at higher frequencies the impedance quantifies the TBW; ICW can be derived by subtracting ECW from TBW.[56,73] This represents one potential advantage of MF-BIA over SF-BIA approaches, although the efficacy of selecting one specific high frequency to completely quantify TBW across all clinical populations is somewhat questionable, particularly in those with fluid overload. A number of validation studies of various equations to predict whole body composition in healthy and clinical populations can be found in the literature and have been reviewed previously.[56] The same challenges described for the SF-BIA validation literature are evident in the MF-BIA validation literature, typically with good population-level agreement but large individual variability being reported. Furthermore, with the exception of the assumption regarding the

static ratio of intra- to extracellular water, the same underlying assumptions inherent to SF-BIA hold true for MF-BIA, thus potentially limiting its applications for whole body composition assessments in clinical populations.[46]

Although it was first explored using a 50 kHz SF-BIA device,[93] there has been increasing interest in the use of segmental measurements with MF-BIA to potentially produce more accurate whole body composition estimates.[94] Unlike whole body wrist-ankle bioimpedance measurements that relate Ht^2/R to estimate TBW based on the volume conductor model (as discussed previously), segmental BIA recognizes the body as having 5 distinct cylinders with different resistivities over which impedances are measured separately.[95] One of the criticisms that can be made of whole body wrist-ankle measurements is that the trunk contributes very little to whole body resistance (~10%) but comprises a substantial conductor volume (~50%).[56,72,96] Further, the assumption is made that any changes in fluid volume or adiposity within the trunk will have a minor influence on whole body measurements. These assumptions are quite likely violated in obesity and conditions associated with fluid overload (e.g. heart or liver failure).[55] Thus, segmental measurements have been purported to provide more accurate whole body estimates. However, in order to get to whole body estimates from segmental measurements, the bioimpedance data obtained from limb and trunk measurements must still be applied to regression-derived prediction equations developed from reference data, and have been shown to be erroneous in individuals with obesity and, as has been observed with all other bioimpedance approaches, the errors tend to increase with increasing

adiposity.[96] The true potential advantage of segmental measurements is most likely to be evidenced in determining fluid shifts and distribution in individuals with fluid overload and those on dialysis.[94] These applications will be discussed later on.

Similar to the discussion regarding the use of SF-BIA devices to generate 50 kHz PA and FFMI as potential parameters of nutritional status and/or clinical outcomes, there is growing interest in the application of an MF-BIA generated parameter, namely the ratio of impedance at 200 kHz to impedance at 5 kHz as a potential indicator of nutritional status[97,98] and fluid overload.[99–101] The advantage of an MF-BIA device over a SF-BIA device is that it can be used to generate all of these aforementioned parameters; these will be further discussed in subsequent sections.

Bioimpedance Spectroscopy (BIS)

The BIS approach for whole body measurements differs fundamentally from SF-BIA and MF-BIA. BIS devices have been commercially available since 1990 when Xitron Technologies (San Diego, CA) introduced the first one onto the market (4000B). Although Xitron is no longer manufacturing BIS devices, they were pioneering in this field and now there are several companies producing them worldwide. These devices typically measure impedance at a minimum of 50 frequencies over a spectrum of frequencies from very low to ~1000 kHz (see Table 1). Most commercially available BIS devices are programmed with modeling software that generates volumes through Cole modeling and subsequently applies the generated terms to modified versions of mixture

equations first developed by Xitron. Generally speaking, the software fits the impedance data (i.e. resistance and reactance) to the Cole model,[102] a mathematical model shown to best describe this kind of physiologic data. With this procedure, non-linear least-squares curve fitting yields an interrupted semicircle (or impedance locus) that generates Cole model variables which can then be applied to equations to generate fluid volumes.[72] Cole model terms include R_0 (or R_e, resistance associated with ECW), R_∞ (sum of ECW and ICW resistances), C_m (cell membrane capacitance), and exponent α (accounts for distribution affects such as cell size and shape).[72] Cole model term R_i (resistance associated with ICW) can further be computed with R_∞ and R_e or R_0 variables using the following equation: $1/R_i = 1/R_\infty - 1/R_e$. [64,72] Characteristic frequency (fc), which is the frequency at which the effects of cell membrane capacitance are maximum is also calculated with the C_m, R_e, and R_i terms as follows: $1/(2\pi C_m [R_e + R_i])$,[72] and is represented graphically as the point of maximal reactance in the Cole plot (i.e. the top middle point of the semicircle). Ideally, the data around fc are weighted to provide the best overall fit for the model.[72] With this approach, ECW and ICW volumes are generated by applying Cole model terms to equations developed based on Hanai mixture theory which describes how electrical properties of tissues are modified by mixture effects of conducting (water, electrolytes, lean tissue) and non-conducting (bone, fat) components of the body.[72,103] Theoretically, at zero frequency (with resistance R_0), no conduction occurs and impedance (Z) is a function of ECW, i.e., $Z = R_0 = R_e$.[72] At infinite frequency (with resistance R_∞), pure conduction occurs and impedance is

a function of TBW, i.e., $Z = R_{\infty}$.[72] These concepts have been thoroughly reviewed elsewhere[80,104] and the Xitron mixture theory based BIS equations have been published previously.[103,105]

In general, BIS has several theoretical advantages over SF-BIA and MF-BIA in that it measures impedance over an entire range of frequencies, and does not depend upon population-specific prediction equations to generate whole body volumes and masses. The BIS approach is the only one that allows for the possibility of computing (through mathematical modeling) the characteristic frequency (fc), that changes with shifts in fluid compartments and cell membranes; and by measuring impedance up to very high frequencies, ensures that the characteristic frequency is reached, allowing for complete quantification of TBW. In addition, separate specific resistivity constants (derived from dilution references) for each of the fluid compartments (by gender) are applied to the volume equations; thus, the BIS mixture equation approach does not assume that ECW and ICW are uniformly distributed.[72] Therefore, this technique theoretically provides a more direct and individualized measure of ECW, ICW, and TBW compartments, compared to SF-BIA and MF-BIA approaches, which has potential advantages particularly in patient populations with altered fluid homeostasis.[66,72]

However, there are several underlying assumptions to the original Xitron mixture equation approach that potentially introduce error to the volume estimates. There are several constants applied to the equations. Fixed (although separate) values for specific resistivity of the ECW and ICW compartments, and

constants for body density and shape are utilized in the equations. It is assumed that these constants are appropriate across the range of body composition; this is unlikely to hold true, particularly in individuals with excessive adiposity, and those with fluid imbalance associated with injury and disease. Indeed it has been well-documented that overestimation errors in TBW and FFM produced by the Xitron BIS equations increase with increasing adiposity[67,69,70] and much of this error is attributed to the impact that adipose tissue can have on the specific resistivity of ICW.[72,103] This limitation has been partially addressed by modifying the Xitron mixture equations with an adjustment for body mass index (BMI, kg/m^2).[103]

Moissl et al[103] introduced a BIS approach termed as body composition spectroscopy (BCS), that involves the correction of the Xitron mixture equations for BMI, a surrogate for adiposity. The BCS approach was shown to improve volume estimates in individuals at the extremes of BMI. The BMI correction improved the standard error of the estimate for ICW by 24% for all subjects and by as much as 48% for the 24 subjects at BMIs < 20 and > 30.[103] That said, the BCS approach is still associated with significant error in whole body estimates, particularly at the individual level. In the Moissl study, wide limits of agreement were observed in all fluid compartment estimates. Interestingly, in malnourished individuals with advanced cancer, the BCS approach was shown to reduce the underestimation of errors in FFM generated using BIS by 35% (Hydra 4200, Xitron Technologies) compared to DXA (Lunar DPX-L and Lunar Prodigy, GE

Healthcare); however, again substantial variability at the individual level was observed.[106]

As stated previously for SF-BIA and MF-BIA, numerous validation studies in various healthy and clinical populations have been published on BIS (predominantly the original Xitron mixture equation approach), with similar findings of good mean level but poor individual level agreement between reference methods and BIS; much of the literature has been reviewed previously.[56,66] Thus, although adjustment for BMI is an important advance for BIS, particularly in settings with extreme BMIs, further refinements are needed before it can be relied upon to accurately assess whole body masses and fluid volumes in the clinical setting. Nevertheless, the application of BIS (and MF-BIA) approaches for the monitoring of fluid status in individuals on dialysis is an active and growing area. Developments in the BIS technology for managing fluid balance are particularly promising, and will be discussed later. In addition, because BIS devices measure impedance data over the range of frequencies, they can easily be used to generate bioimpedance variables of interest including the 50 kHz PA and FFMI and the impedance ratio at 200/5 kHz (and potentially derivations unique to BIS, e.g. ratio of impedance at infinity/zero). These novel applications will be discussed next.

Table 2-1: Selected Commercially Available Bioimpedance Devices (listed alphabetically by the device manufacturer)[a].

Manufacturer	Device	Method	Price Range[b]	Frequencies Measured
BIOSPACE, Inc. Cerritos, California, USA	InBody770	S-MF-BIA	$15,000 - $ 20,000	1, 5, 50, 250, 500, and 1000 kHz
	InBody720	S-MF-BIA	$15,000 - $ 20,000	1, 5, 50, 250, 500, and 1000 kHz
	InBody570	S-MF-BIA	$5,000 - $10,000	5, 50, and 500 kHz
	InBody370	S-MF-BIA	$5,000 - $10,000	5, 50, and 250 kHz
	InBody230	S-MF-BIA	$5,000 - $10,000	20 and 100 kHz
Bodystat Ltd Douglas, UK	Bodystat 1500	SF-BIA	$500 - $1,500	50 kHz
	Bodystat 1500 MDD	MF-BIA	$1,500 - $5,000	5 and 50 kHz
	QuadScan 4000	MF-BIA	$5,000 - $10,000	5, 50, 100, and 200 kHz
	BBis~MultiScan 5000	BIS	$10,000 - $15,000	50 frequencies from 5 to 1000 kHz

Manufacturer	Device	Method	Price Range[b]	Frequencies Measured
Data Input Pöcking, Germany	Nutribox	SF-BIA	$1,500 - $5,000	50 kHz
	Nutriguard-MS	MF-BIA	$1,500 - $5,000	5, 50, and 100 kHz
Fresenius Kabi AG Bad Homburg, Germany	BodyScout[c]	BIS	NA	50 frequencies from 5 to 1000 kHz
Fresenius Medical Care Bad Homburg, Germany	Body Composition Monitor[c]	BIS	NA	50 frequencies from 5 to 1000 kHz
ImpediMed Carlsbad, California, USA	DF50	SF-BIA	$1,500 - $5,000	50 kHz
	SFB7	BIS	$15,000 - $20,000	256 frequencies between 4 and 1000 kHz
	Hydra 4200 (Xitron Technologies)[d]	BIS	NA	50 frequencies from 5 to 1000 kHz

Manufacturer	Device	Method	Price Range[b]	Frequencies Measured
	Xitron 4000B (Xitron Technologies)[d]	BIS	NA	50 frequencies from 5 to 1000 kHz
Maltron International Ltd Essex, UK	BF-900	SF-BIA	<$500	50 kHz
	BIOSCAN 920-II	MF-BIA	$10,000 - $15,000	5, 50, 100, and 200 kHz
RJL Systems, Inc. Clinton Township, Michigan, USA	Quantum II	SF-BIA	$1,500 - $5,000	50 kHz
	Quantum III	SF-BIA	$1,500 - $5,000	50 kHz
	Quantum IV	SF-BIA	$1,500 - $5,000	50 kHz
	Quantum X	SF-BIA	$1,500 - $5,000	50 kHz
	Quantum Desktop	SF-BIA	$5,000 - $10,000	50 kHz
	MC-780U	MF-BIA	$5,000 - $10,000	5, 50, and 250 kHz

Manufacturer	Device	Method	Price Range[b]	Frequencies Measured
Tanita Corporation of America, Inc. Arlington Heights, Illinois, USA	SC-331S	SF-BIA	$1,500 - $5,000	50 kHz
	BC-418	S-SF-BIA	$5,000 - $10,000	50 kHz
	SC-240	SF-BIA	$500 - $1,500	50 kHz
	SC-240IM	SF-BIA	$5,000 - $10,000	50 kHz
	TBF-410GS	SF-BIA	$1,500 - $5,000	50 kHz
	TBF-310GS	SF-BIA	$1,500 - $5,000	50 kHz
	TBF-300A	SF-BIA	$1,500 - $5,000	50 kHz
	TBF-300WA	SF-BIA	$1,500 - $5,000	50 kHz
	BF-350	SF-BIA	$500 - $1,500	50 kHz
Valhalla Scientific, Inc.	G61-S	SF-BIA	$1,500 - $5,000	50 kHz

Manufacturer	Device	Method	Price Range[b]	Frequencies Measured
Poway, California, USA	G62-S	SF-BIA	$1,500 - $5,000	50 kHz
	G63-S	SF-BIA	$1,500 - $5,000	50 kHz
	G6 Duo	SF-BIA	$1,500 - $5,000	50 kHz
	BCS-1	SF-BIA	$1,500 - $5,000	50 kHz
	BCS-2	SF-BIA	$1,500 - $5,000	50 kHz
	BCS-3	SF-BIA	$1,500 - $5,000	50 kHz

Abbreviations: S-MF-BIA, Segmental Multiple-Frequency Bioelectrical Impedance Analysis; kHz, kilohertz; SF-BIA, Single-Frequency Bioelectrical Impedance Analysis; MF-BIA, Multiple-Frequency Bioelectrical Impedance Analysis; BIS, Bioimpedance Spectroscopy; S-SF-BIA, Segmental Single-Frequency Bioelectrical Impedance Analysis; NA, Not Applicable.

[a]This is not a complete list, and represents devices for which the pricing and other information was most readily available. Due to space constraints, we have not attempted to identify which devices provide raw data and/or the prediction equations used in their devices. Clinicians are advised to take these issues into consideration and obtain up to date information on the technical capacities before purchasing any bioimpedance device.

[b] Approximations based on the current retail price of the devices as of October 2014.

[c] Device not currently commercially available in the US as of October 2014.

[d]Device no longer commercially available in the US as of October 2014.

Novel Applications: Use of Bioimpedance Data for Clinical Assessment

Due to the questionable validity of bioimpedance approaches for the assessment of whole body composition estimates in clinical populations, there is growing interest in the utility of the raw bioimpedance data for its potential to contribute to bed-side assessment of nutritional status and/or clinical outcomes. Bioimpedance-derived parameters (including 50 kHz measured PA, 50 kHz FFMI, and 200/5 kHz impedance ratio) have been investigated as potential prognostic indicators of mortality, disease severity, morbidity, hydration status, and malnutrition.[46,85] The use of such data is mostly independent of regression equations (except for FFMI) and may be potentially useful in situations where assumptions for whole body composition estimates are likely to be violated.

Phase Angle (PA)

Phase angle (PA) is the ratio of the arc tangent of reactance to resistance, and is purported to relate to important cellular characteristics, including membrane capacitance, integrity, and permeability, as well as overall size and hydration.[107,108] Although PA can be calculated at any frequency, the PA measured at 50 kHz has been the primary clinical parameter of interest due to the wide availability and predominance of SF-BIA devices. Moving forward, we will use “PA” to indicate PA measured at 50 kHz. A higher PA indicates a proportionally greater reactance for a given resistance, which has been interpreted to suggest more intact cell membranes and higher BCM.[85,109] On the other hand, a lower PA has been interpreted to indicate cell loss and decreased

cell integrity and BCM.[109] Clinically, a low PA has been studied as a prognostic indicator of disease and/or nutritional risk in HIV infection,[110,111] cirrhosis,[112] hemodialysis,[113] cancer,[107,114–116] chronic heart failure[117] and geriatric settings,[118] where cell membrane integrity is likely to be compromised and fluid-based alterations are common.[85,108,116] Additionally, a low pre-operative PA has been shown to be associated with poor nutritional and clinical outcomes among individuals undergoing cardiac[119] and gastrointestinal[120–122] surgeries. In one of the more recent reports, Kyle et al[108] observed that when compared with healthy controls, hospitalized patients had a lower PA (<5.0° in men, <4.6° in women, using a SF-BIA device [RJL-101, RJL Systems; no longer commercially available]) that was significantly associated with lower FFM and a higher percentage of body fat. Additionally, patients at moderate and severe nutritional risk (identified by Nutritional Risk Screening [NRS-2002] and Subjective Global Assessment [SGA]) were more likely to have low PA than healthy controls.[108] In this study, hospital length of stay (LOS) and non-survival were also associated with a lower PA.[108]

In a series of other investigations, Gupta and colleagues[107,114–116] reported that PA measured by a SF-BIA device (BIA-101Q, RJL Systems; no longer commercially available) was an independent prognostic indicator in individuals with advanced pancreatic (stage IV), advanced lung (stages IIIb and IV), advanced colorectal (stages II and IV), and breast cancer (stages I – IV). For example, using the nutrition assessment tool SGA, this research team identified

various PA cut-points to identify well-nourished or malnourished individuals with advanced colorectal cancer.[115] Individuals classified as malnourished by the SGA had a significantly lower median PA score than well-nourished individuals (5.18° vs. 6.12°, p=0.005), and a modest but significant correlation was found between the SGA and PA scores (r=0.33, p=0.004).[115]

The primary challenge of using PA for clinical assessment is the lack of consensus on cut-points to be used to identify malnutrition (or poor clinical outcomes). Although several investigators around the globe have generated reference values for PA based on large population samples including healthy Swiss,[123] German,[87,88] and American[86] adults, notable differences have been observed. It is not entirely clear whether these differences are solely population dependent or if differences among devices used are contributory. It has been observed[86] that PA reference values generated by the RJL-101 device from healthy US adults were higher than those generated for healthy Swiss adults using various devices including the RJL-101 and 109 (SF-BIA devices no longer commercially available) and the Xitron Technologies 4000B (a BIS device no longer commercially available),[123] even after adjusting for BMI and percent fat mass. Although the use of different devices could have introduced some variation in these results, a more likely explanation is the ethnicity-specific differences in relative leg length, frame size, and body build.[55] Therefore, standardized population-specific reference data are likely to be necessary for optimal interpretation and application. For example, among individuals with cancer

(mostly with gastrointestinal tumors), Norman et al[89] evaluated PA measured by a MF-BIA device (Nutriguard M, Data Input; no longer commercially available) using the age-, sex-, and BMI-stratified data that was previously generated for the healthy German population.[87] In this way, a standardized PA value was generated for each patient. Individuals with a standardized PA value below the 5th percentile exhibited impaired nutritional and functional status, diminished quality-of-life, higher LOS, and a significantly higher 6-month mortality risk when compared to individuals with PA values above the 5th percentile.[89]

Additional research on the applications of standardized PA data for clinical assessment is vitally needed. It is unclear whether adjustments can be made to align reference data generated from different populations using different devices. Furthermore, additional research is needed to see if standardized PA can be used to identify muscle loss as one of the diagnostic markers of malnutrition.[3] With additional research in this area, it is certainly possible that standardized PA might prove to be a useful index of nutritional status in the clinical setting; however, its use as an assessment tool is limited by the lack of clear and consistent reference cut-points.

Impedance Ratio (IR)

Another bioimpedance parameter that has been proposed as a potential indicator of nutritional status and/or clinical outcomes is the ratio of impedance measured at 200 kHz to impedance measured at 5 kHz. This has been termed “impedance ratio” (IR) or “prediction marker” (introduced as such by Bodystat®)

and will be designated in this discussion as IR. With impedance measurements at high (200 kHz) and low (5 kHz) frequencies, the IR parameter has been suggested to reflect the ratio of ECW/TBW fluid distribution. There are a limited number of published studies that have investigated the clinical utility of IR. Although normal reference cut-points have not yet been established as they have for PA, IR values ≤ 0.78 in males and ≤ 0.82 in females have been observed in healthy individuals.[98] IR values approaching 1.0 suggest that the two measured impedances are approaching each other in value; higher IR values have been associated with post-operative edema,[99] worsening renal[100] and cardiac[101] function, and poor nutritional status.[97,98]

Several studies have evaluated IR as a surrogate marker for clinical outcomes associated with fluid overload. Among 38 individuals undergoing major abdominal surgery, pre-operative IR measured by a MF-BIA device (QuadScan 4000, Bodystat) was significantly higher in the 20 participants who developed post-operative edema compared to individuals who did not develop edema later on (0.81±0.03 versus 0.78±0.02; p=0.015).[99] In another observation, an IR value of >0.85 (QuadScan 4000) was found to be an independent predictor of worsening renal function among 80 patients hospitalized with decompensated heart failure.[100] Similarly, among 243 individuals with chronic heart failure, gender-adjusted IR values (QuadScan 4000) were significantly higher (e.g. 0.85 vs 0.82 for females; 0.83 vs 0.80 for males) and gender-adjusted PA values were significantly lower (e.g. 4.2 vs 5.1 for females; 4.9 vs 5.7 for males) in the Class

III-IV New York Heart Association (NYHA) functional classification group (indicative of more severe cardiac symptoms) compared to Class I-II NYHA group (less severe cardiac symptoms).[101] These findings suggest that whole body MF-BIA derived IR may be useful in identifying individuals who already have or are at risk for developing fluid overload, which carries risk for poor clinical outcomes.

Other lines of investigation have evaluated IR as a potential marker for malnutrition. In one limited analysis of 316 hospitalized patients with IR values between 0.75 – 1.0 on admission measured using a BIS device (Hydra 4200S, Xitron Technologies; no longer commercially available), 27% of whom were malnourished, a higher IR was associated with greater risk for malnutrition (defined as weight loss > 5% in 1 month or >10% in 6 months and/or BMI <18.5) and longer length of stay in the hospital.[97] Specifically, for each 0.10 increase in IR above 0.75 at admission, the odds ratio of severe malnutrition was 5.8 (95% Confidence Interval [CI], 2.7 – 12.5; $p<0.001$) and LOS increased by 4.2±1.7 days ($p=0.013$). Similar but less robust findings were observed for PA; for each 1.0 unit decrease in PA at admission, the odds ratio of severe malnutrition was 2.0 (95% CI, 1.2 – 3.6; $p=0.011$) and LOS increased by 2.3±1.2 days ($p=0.056$).[97] In a similar observation among 109 individuals with gastrointestinal disorders, IR and PA (Xitron 4000B BIS device for IR, RJL BIA 101 SF-BIA device for PA) were evaluated for their ability to identify individuals with malnutrition assessed by neutron activation analysis derived total body protein

measurements.[98] In this report, a higher IR (high IR defined as values >0.82 for females, and >0.78 for males, from 151 healthy volunteers) was associated with a 4.15-fold higher odds of being malnourished, whereas the odds ratio for a lower PA was 1.55.[98] Additionally, from a total of 71 identified malnourished individuals, 56 were detected by IR, compared to 16 individuals identified by PA; each 0.10 increase in IR and each unit decrease in PA was associated with a 4.64-fold and a 1.55 fold increased odds of malnutrition, respectively.[98]

The limited research conducted to date seems to suggest that IR and PA may have clinical utility for identifying malnutrition at the bed-side; however, additional research is needed to better identify standardized cut-points and to validate those cut-points in terms of current malnutrition criteria[3] and ideally, against reference methods for lean tissue (i.e. to establish if clinicians can use PA and/or IR to identify individuals with muscle loss in addition to identifying individuals with overall malnutrition).

Fat-Free Mass Index (FFMI)

Kyle et al[90,124] have proposed the use of FFMI, calculated as the ratio between FFM calculated from their published 50 kHz bioimpedance equation[123] and height (kg/m^2), as a standardized, height-independent nutrition assessment method. Although FFMI is not in the same category as PA and impedance ratio (because it requires the use of a prediction equation for FFM), it has similarly been studied for its potential to predict nutritional status and/or clinical outcomes. The interest in FFMI has arisen in part due to the challenges described earlier for

generating whole body FFM estimates by bioimpedance. Furthermore, from a theoretical perspective, it is challenging to interpret the absolute values of FFM in kilograms (kg) measured by any technique, as estimates increase with height and decrease with body weight, age, illness, and gender differences.[90,123,124] This group has published normative data for FFMI developed from measurements in healthy Swiss adults[90] and FFMI cutoff values for various BMI categories have also been reported in this population.[124]

Several studies have investigated the clinical utility of FFMI. In a prospective observational study involving 325 cardiac surgery patients in the Netherlands, pre-operative FFMI calculated from the 50 kHz data generated by a BIS device (BodyScout, Fresenius Kabi; not currently commercially available in the US) was evaluated for various post-operative outcomes.[125] A low FFMI value was set at ≤14.6 kg/m^2 in women and ≤16.7 kg/m^2 in men using previously published normative Swiss population data.[124] It was reported that a low pre-operative FFMI was independently associated with a higher occurrence of post-operative infections and longer LOS in the intensive care unit.[125] More recently, among 123 pre-operative abdominal surgery patients in the Netherlands, FFMI estimates generated by two different devices were compared (BF-906, Maltron International Ltd [a SF-BIA device] and BodyScout [a BIS device]).[126] In this study, the BIS device identified a larger proportion of patients with lower FFMI (47%) compared to the SF-BIA device (16%) ($p<0.001$).[126] Limits of agreement between the two devices indicated that the SF-BIA device overestimated the

values compared to the BIS device for both FFM (4.93±6.22 kg) and FFMI (1.66± 2.25 kg/m^2).[126] These results point to the challenges inherent in applying FFMI as an indicator of nutritional status when potentially using a different device from that used to generate reference cut-points. As mentioned for PA and IR, additional research is needed to determine how FFMI might be utilized as a tool for nutritional assessment in the clinical setting.

Use of Bioimpedance Techniques for Evaluation of Lymphedema and Fluid Management in Dialysis

Beyond its potential role in nutrition assessment, there has been substantial interest from the medical community in the application of bioimpedance for the assessment of various aspects of clinical care including wound healing,[127] neuromuscular disease progression,[128,129] cardiac output monitoring,[130–133] and conditions associated with expanded ECW.[134–136] The reader is referred to the excellent review by Lukaski[64] for a more complete description of these novel applications of bioimpedance. Here, we will discuss the two most prominent examples of the application of bioimpedance for assessment of conditions associated with expanded ECW: the evaluation of lymphedema and the management of fluid balance in individuals on dialysis.

Evaluation of Lymphedema

Lymphedema is the swelling that occurs when protein-rich lymph fluid accumulates in the interstitial space,[137] resulting from damaged or blocked lymphatic vessels that inhibit the drainage of fluid from tissues. This

subcutaneous accumulation of lymph fluid is associated with the expansion of ECW.[138] Secondary lymphedema of one or both arms or legs is a debilitating consequence of cancer or its treatment that is particularly prevalent among individuals with breast, uterine, ovarian, and prostate carcinomas, and lymphomas or melanomas.[137] Although incurable, early detection through regular monitoring is one of the best ways to promptly manage lymphedema.[137,138]

There has been significant interest in the application of segmental BIS to monitor and detect early stages of lymphedema particularly among individuals with breast cancer. Much of the early work in this area involved the application of a BIS device to generate an inter-limb ratio of resistance values for an affected limb compared to an unaffected limb.[138–143] In brief, the BIS device is used to generate Cole model terms and the resistance at zero kHz (R_0) for the unaffected limb is divided by the R_0 for the affected limb. Among women diagnosed with unilateral arm lymphedema post breast-cancer treatment, Ward et al[144] used the aforementioned ratio method to generate the ECW/ICW ratio and volume of the affected arm using a BIS device (SFB7, ImpediMed). The mean arm ECW/ICW ratio was 1.5:1 among those with lymphedema, compared to values between 0.85:1 and 1:1 in the group without lymphedema.[144] When compared with the reference method perometry (which provides more direct measures of limb volume), BIS showed proportional increases in arm size and strong correlations were noted between the two measures for ECW, ICW, and TBW compartments (r=0.80–0.90).[144] In a further evaluation of this technique among women with

lymphedema and those with no history of lymphedema, Czerniec et al[139] reported that when compared with perometry-derived volume data, segmental BIS using the SFB7 device detected mild localized lymphedema; however, it should be noted that the limits of agreement between the two methods varied from 8.5% for the upper arm segment to16.6% for the forearm segment, with increases in bias with the severity of lymphedema.[139] The authors have asserted that because BIS is sensitive to changes in the ECW volume, the method is able to detect mild localized lymphedema better than perometry. However, evaluation of the absolute accuracy of BIS-guided limb volume estimations is difficult to achieve due to limitations inherent to perometry and other reference methods and the lack of segment-specific normative data for limbs. Regardless, this segmental BIS approach appears to hold promise for the early detection of lymphedema in its latent stages and therefore merits additional research.

Fluid Management in Dialysis

Overhydration characterized by expansion of the ECW is common among individuals on dialysis,[72] and bioimpedance techniques have been investigated for monitoring hydration status and adjusting dialysis treatment goals. The primary target of interest is the estimation of ‘dry weight’, which has been defined as the lowest tolerable post-dialysis weight at which the patient is as close as possible to a normal hydration state without experiencing symptoms associated with either overhydration or underhydration.[145,146] Dry weight is technically achieved through the removal of excess water during dialysis.[146] Estimates of dry

weight are further used to calculate the ultrafiltration rate, or the rate at which the fluid is removed during the course of dialysis. Clinical assessment of dry weight is critical because an overestimation of dry weight could result in inadequate ultrafiltration and hypervolemia and its associated symptoms including arterial hypertension, left ventricular dilatation, and left ventricular hypertrophy.[145,146] An underestimation of dry weight, on the other hand, could result in excessive ultrafiltration and hypovolemia, which could lead to hypotension, arrhythmias, reduced compliance to treatment, and an increased risk of vascular thrombosis.[146,147] The clinical estimation of dry weight has been mostly through trial and error methods that involve parameters such as physical examination, changes in blood pressure or respiration rate, or presence of edema, without actually quantifying changes in fluid volume.[146,147] Thus bioimpedance techniques have been explored for their ability to estimate dry weight in individuals on dialysis.

Segmental Measurements

One approach that has been studied is the use of continuous segmental BIS measurements of the calf during hemodialysis. The assumption underlying this approach is that due to gravity effects, the calf would be the last section of the body from which excess ECW is likely to be removed and thus it has been identified as an ideal region to target for measurement given that the relative fluid volume of excess ECW would be expected to be higher in the calf region compared with the arms or trunk.[145,148] By this approach, the dry weight is

identified when the ECW volume in the calf does not decrease further, despite ongoing ultrafiltration. Hence this method identifies the time-point during dialysis at which an individual is assumed to be at his/her dry weight, and thus ultrafiltration should be stopped.[145,148] One of the limitations of this method is that it does not provide a whole body target volume to be removed at the initiation of dialysis, because the dry weight is identified during ongoing dialysis and the excess fluid removed at the whole body level is not quantified.[149]

In a derivation of this approach, Zhou and colleagues[147] used a MF-BIA device (QuadScan, Bodystat) to generate the IR from a segmental measurement of the calf to estimate dry weight in individuals on hemodialysis. Age-stratified calf impedance ratio values were obtained from healthy controls and set as target impedance ratios. In this study, calf IR was measured 30 minutes after the completion of a mid-week dialysis session, and dry weight was incrementally decreased at each subsequent dialysis session (or on a weekly basis) until the target calf IR was reached or symptoms of hypovolemia occurred. Achievement of target calf IR values in this study was associated with a significant reduction of blood pressure and use of antihypertensive medications.[147]

Wrist-Ankle Measurements

Significant recent advancements in the BIS technology provide a novel and promising approach to the fluid management of individuals on dialysis with potential ramifications for other clinical populations. These developments involve the refinement of the whole body wrist-ankle BIS approach to incorporate a new

model of body composition.[83] Essentially, the BMI-corrected mixture equations described earlier as the BCS approach[103] are used to generate ECW and ICW volumes that are then applied to model equations proposed by Chamney et al[83] that attempt to differentiate excess fluid from normally hydrated tissue. In this 3-compartmental model of body composition, the body is delineated into normally hydrated adipose tissue mass (NH_AT), normally hydrated lean tissue mass (NH_LT), and excess fluid mass (ExF).[83]

This new approach has been evaluated in several studies. Wizemann et al[150] used the Body Composition Monitor BIS device (Fresenius Medical Care; not currently commercially available in the US), which incorporates the aforementioned approach into its software based on previous work,[83,151] to estimate overhydration and predict mortality among 269 chronic HD patients during a follow-up period of 3.5 years. The device software is programmed with expected normal values for ECW for a given body weight and composition based on healthy population data; absolute fluid overload is determined by the difference between the normal expected ECW and the actual measured ECW. The relative fluid overload is expressed as the ratio between the absolute fluid overload and the ECW. Wizemann et al[150] reported that the pre-dialysis relative fluid overload was an independent predictor of mortality, with a hazard ratio (HR) of 2.1 (95% CI, 1.39 - 3.18; p=0.003). In a similar study among 529 individuals on peritoneal dialysis, the Body Composition Monitor-derived relative fluid overload

was also found to be an independent predictor of mortality (HR=2.09, 95% CI,1.19 - 2.82; p<0.001).[152]

Recently in a prospective randomized trial, Body Composition Monitor-derived ECW, ICW, and TBW volumes were used to adjust dry weight and prescribe ultrafiltration goals for HD patients over a period of 2.5 years.[153] A total of 131 patients were randomized into the 'bioimpedance group' (n=62), where target dry weight was prescribed based on the read-outs from the BIS device, and the 'control group' (n=69), where dry weight was determined based on the blood pressure value, presence of edema, and other physical parameters.[153] Compared to the control group, all-cause mortality, arterial stiffness, blood pressure, and relative fluid overload were significantly lower in patients who received the BIS-guided dry weight adjustment.[153]

Taken together, these study results are strongly supportive of the application of BIS, in particular the approach incorporated into the Body Composition Monitor software, for the clinical assessment of dry weight in individuals undergoing dialysis. Additional research investigating outcomes including morbidity and mortality in individuals with dialysis being managed with this approach is certainly warranted. Furthermore, the apparent effectiveness of this new 3 compartment model BIS approach in the fluid management of individuals on dialysis carries great potential for application to other clinical conditions associated with fluid overload including heart and other organ failure, sepsis, trauma, and other critical illness. Moreover, the ability to differentiate

between excess fluid and this model's concept of normally hydrated lean tissue holds promise, particularly if it can be refined to provide meaningful estimates of lean tissue for nutritional assessment purposes. Additional research is definitely warranted.

Summary and Conclusions

In this update, we have reviewed the three primary categories of bioimpedance techniques in terms of underlying assumptions, strengths, and limitations in order to orient clinicians to the differences between approaches, and the potential opportunities for their application in the clinical setting. The global interest in these techniques to provide whole body estimates of lean tissue for bed-side nutritional assessment has led to substantial validation research efforts to provide proof of their accuracy and reliability, with mixed results. Predominant reports of large variability in individual estimates by bioimpedance and reference techniques have led to a general mistrust of bioimpedance methods to quantify whole body composition in clinical populations, particularly those with abnormal body geometry and fluid balance. Reliance on statistical methods that may not adequately account for errors in reference techniques and cross-validation of SF-BIA and MF-BIA equations originally developed from one reference method by comparison to a different reference method are just two of the limitations in the validation literature that may contribute to the inconsistencies regarding validity across studies. Thus, it remains somewhat unclear if any bioimpedance technique can be proven to provide sufficiently

meaningful whole body lean tissue estimates at the individual bed-side to appropriately identify individuals with malnutrition and/or to effectively monitor lean tissue changes in response to nutritional interventions. The new developments in BIS technology that are being applied in individuals on dialysis hold promise; the improvements in the ability of BIS devices to quantify excess fluid in these patients using new models of body composition could lead to further refinements for the assessment of lean tissue in other clinical populations.

The SF-BIA and MF-BIA approaches for whole body lean tissue assessment are likely to remain somewhat limited for use in the clinical setting. Although clinicians might optimize accuracy in whole body estimates generated by a particular SF-BIA or MF-BIA device by choosing an appropriate equation from the literature that matches the characteristics of their particular patient, it is not very practical to expect this to happen in the clinical setting. Many bioimpedance devices have a “black box” approach where programmed equations are kept as proprietary information so clinicians have no idea of what equation is being used. Furthermore, some devices do not provide the raw bioimpedance data, and thus clinicians have no way to recalculate their own estimates of body composition, even if they are able to find the time to identify an appropriate prediction equation. Taken together, these concerns have led to the pursuit of using raw bioimpedance data for the evaluation of nutritional status and/or clinical outcomes independent of whole body composition estimates. Although these applications appear promising, they are limited by the lack of

consensus on reference cut-points. From the literature on PA and FFMI, it appears that there may be potentially important population- and device-specific differences in reference values; the ongoing turnover of devices in the market place is a significant consideration. Moreover, these applications require further study to determine if they can be used to accurately identify individuals with malnutrition and/or monitor response to nutritional interventions. There is clearly a need for additional research investigating the applications of bioimpedance for clinical assessment of malnutrition and response to nutritional interventions. Two specific questions that merit further investigation are:

- Can the application of PA and/or IR be sufficiently refined (i.e. with clear cut-points) to be useful for the diagnosis of sarcopenia (with and without the presence of obesity) and malnutrition in clinical settings?
- Can BIS derived “normally hydrated lean tissue mass” as generated from the new BIS models being applied in dialysis be used to effectively identify malnutrition and evaluate responses to nutritional interventions at the bed-side?

Obtaining answers to these questions will likely require the design of rigorous clinical trials that incorporate appropriate reference techniques and solid statistical design, and the cooperation of the bioimpedance manufacturing industry.

Overall Summary and Current Study

In summary, although malnutrition has been recognized as a significant clinical problem among individuals with HNC, its prevalence has not been well-documented due to a lack of consensus on definition and diagnosis. Malnutrition and a delay in the administration of nutritional intervention are associated with negative clinical outcomes including poor QoL and functional status, hospital readmissions, and increased infectious complications. This is particularly relevant among individuals with HNC, who, if not already malnourished at the time of diagnosis, frequently become malnourished as a result of treatment-induced weight loss, loss of appetite, taste changes, and reduced oral intake. Studies investigating the applications of bioimpedance for the clinical assessment of malnutrition are limited among individuals with HNC. Further, the relationship between psychosocial measures such as the QoL and self-efficacy and nutritional outcomes also warrants additional research in this patient population.

The following chapters will address these notable gaps in HNC related research. Chapter 3 estimates the prevalence of malnutrition among individuals with HNC during and up to 3 months after treatment, testing the hypothesis that the prevalence of malnutrition will be higher at the completion of treatment when compared to the start of treatment and the later post-treatment period. Chapter 3 also investigates the utility of raw bioimpedance parameters such as the 50 kHz phase angle and 200 kHz/5kHz impedance ratio to identify individuals with malnutrition, testing the hypothesis that malnourished individuals will exhibit

lower phase angle and higher impedance ratio when compared to those who are well-nourished. Chapter 4 evaluates whether malnutrition relates to QoL and coping self-efficacy among individuals with HNC before and after treatment completion, testing the hypothesis that malnourished individuals will report having a lower QoL and self-efficacy scores when compared to those who are well-malnourished. Finally, Chapter 5 provides an overall conclusion and suggestions for future directions.

CHAPTER 3: NUTRITIONAL STATUS AND BODY COMPOSITION AMONG INDIVIDUALS WITH ADVANCED HEAD AND NECK CANCER: A PROSPECTIVE INVESTIGATION IN AN OUTPATIENT SETTING.

Introduction

Malnutrition, generally defined as a decline in lean body mass with functional impairment at the molecular, physiologic, and/or motor levels,[3] is highly prevalent among individuals with head and neck cancer (HNC), with up to 40% – 57% with a compromised nutritional status even before beginning their treatment.[1,11] Malnutrition has been associated with poor survival outcomes, post-surgical complications, risk of infections, impaired wound healing and recovery, declining quality of life and functional status, and poor disease prognosis.[1,8,11–15] From the health care perspective, malnutrition is associated with frequent treatment interruptions and increased hospital readmissions and length of stay, further adding to patient and hospital care related costs.[2,3]

Although malnutrition has been recognized as a significant clinical problem in the HNC population, its prevalence has not been well-documented in the US due to a lack of consensus on malnutrition diagnosis and definition. Standardized protocols for screening, assessment, and intervention for malnutrition in this population are lacking, due in large part to a paucity of data. The 2012 Academy of Nutrition and Dietetics (the Academy) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Consensus Statement on adult malnutrition has suggested the use of two or more of the following six markers for diagnosis: insufficient energy intake, unintended weight loss, loss of muscle mass, loss of subcutaneous fat, localized or general fluid accumulation, and diminished functional status as measured by hand grip strength.[3] The

efficacy of the new Consensus framework in identifying those at risk for malnutrition has not been examined among individuals with HNC in an outpatient setting. Therefore using the new malnutrition diagnosis, the purpose of this prospective, natural history pilot study is to identify the prevalence of malnutrition among individuals with HNC at one outpatient clinic during and up to 3 months after treatment completion. We used the scored Patient-Generated Subjective Global Assessment (PG-SGA) as the reference standard to evaluate the sensitivity and specificity of the Consensus framework in defining malnutrition.

Knowing that the loss of muscle mass is one of the defining characteristics of the new malnutrition framework, there has been a growing interest in the use of body composition techniques to assess lean tissue at the bedside. For this purpose, bioimpedance techniques have been widely appreciated for their non-invasiveness, safety, ease of use, and portability, and as lower cost alternatives for lean tissue assessment.[154] Although the utility of raw bioimpedance data in the bedside assessment of nutrition status has been emerging in the research literature,[55,154] these data have not been validated in terms of the recent malnutrition criteria. Therefore we also investigated whether clinicians can potentially use the bioimpedance parameters such as phase angle and impedance ratio to identify individuals with overall malnutrition, and how bioimpedance markers relate to functional status outcomes.

Methods

Study Participants and Time-points

This study included 19 individuals with head and neck cancer intending to undergo treatment with concurrent chemoradiotherapy (CRT) at the Masonic Cancer Clinic and Radiation Oncology Clinic at the University of Minnesota Medical Center, Fairview. All participants classified themselves as Caucasian. Specifically, individuals ≥ 18 years of age with pathologically confirmed squamous cell cancers of the oral cavity, oropharynx, hypopharynx, larynx and maxillary sinuses were included in the study. Individuals with pacemakers or other similar internally placed biomedical devices were excluded as it is not recommended that these individuals undergo testing by bioimpedance devices.

Beginning December 2013 through March 2015, data were collected during routine care when individuals were attending the clinics for their CRT appointments and post-treatment follow-up visits. The five time-points of this study were as follows (see Figure 3-1): **Time 1 (T1)**, within 7 days prior to starting the CRT; **Time 2 (T2)**, 3.5 weeks (about midpoint) into treatment ± 1 week; **Time 3 (T3)**, during the last week of treatment; **Time 4 (T4)**, follow-up, 1 month after the completion of treatment ± 14 days; and **Time 5 (T5)**, follow-up, 3 months after the completion of treatment ± 1 month. The time-points for this study were established in order to evaluate and assess any changes in nutrition-related parameters during and after treatment completion. Overall, 85 independent study visits were completed and each visit lasted up to 1.5 hours in

duration. Five participants missed one study visit, one individual missed two visits, while another missed three visits. Reasons for absence were changes in the treatment plan for four individuals, death in two cases, and declining to participate in one case. The Institutional Review Board and the Cancer Protocol Review Committee (Masonic Cancer Center) at the University of Minnesota (UMN) approved this study. Study data were entered and managed using the REDCap electronic data capture tools hosted at the UMN.[155]

Anthropometric Procedures

Anthropometric data were collected by a researcher trained in recording height, weight, skinfolds and arm circumference measurements. Using standard protocols,[156] height was recorded to the nearest 0.1 cm and body weight to the nearest 0.1 kg. Body Mass Index (BMI) was calculated by dividing the participant's weight in kilograms by the squared value of their height in meters: [weight (kg)/ (height (m))^2]. BMI was categorized based on the National Heart, Lung, and Blood Institute's classification (National Institutes of Health, 2015). Percent weight loss was calculated as [(Usual Body Weight – Actual Body Weight)/ Usual Body Weight] * 100. Using the cut-points identified in the Consensus criteria,[3] ***unintended weight loss*** was used to assess the severity of malnutrition as follows: weight loss of > 5% in the past month or >10% in the past 6 months was a marker for severe malnutrition; weight loss of 5% in the past month or 10% in the past 6 months was a marker for nonsevere (moderate) malnutrition.

Triceps skinfold thickness (TSF) was measured to the nearest 0.1 mm and mid-upper-arm circumference (MUAC) was measured to the nearest 0.1 cm.[156] Three sequential measurements were recorded for TSF and MUAC, and the average of the three values were used for analysis.

Nutrition-focused Physical Exam

Three out of the six Consensus markers were evaluated through the nutrition-focused physical exam. Using the physical assessment guidelines provided by Malone and Hamilton,[157] a nutrition-focused physical exam was conducted by one researcher at each time point to assess the presence of ***muscle and/or subcutaneous fat loss and fluid accumulation***. At one time towards the beginning and once towards the end of the study, another researcher independently conducted the physical exam, and inter-observer agreement was noted in the overall subjective ratings between the two researchers.

Dietary Intake: 24-hour Dietary Recall and 3-day Food Records

A researcher with experience in collecting dietary recalls conducted the 24-hour recall at each of the five time points. A four stage, multiple-pass interviewing technique was used, that included 1) obtaining a complete list of foods and beverages consumed; 2) detailed description of each item including cooking methods and brand names; 3) collecting estimates of the amounts and portion sizes of the items consumed, and 4) reviewing the information to ensure that all items were entered correctly.[158]

Starting at Time 1, participants were given an orientation by the researcher on how to keep accurate dietary records, including reading nutrition labels, using measurement aids, estimating portion sizes, and reporting mixed dishes (Appendix B). Individuals were asked to bring the 3-day dietary records to their next clinic appointment beginning Time 2 through Time 5. Diet records were reviewed with the participants during each follow-up visit. Dietary intake data were collected and analyzed using the Nutrition Data System for Research software (2014) developed by the Nutrition Coordinating Center, UMN, Minneapolis, MN. The 24-hour dietary recall and the 3-day food records were analyzed in order to estimate an average 3 - 4 day intake for calories and protein.

Estimated energy requirements were calculated as 25 kcal/kg ideal body weight for obese individuals; 30 kcal/kg actual body weight for overweight, and 35 kcal/kg actual body weight for normal weight individuals.[159] ***Percent energy intake*** was calculated as follows: (Recent intake/Estimated intake)*100, and intake ≤ 75% of estimated energy requirement for ≥ 1 month was the marker for severe malnutrition and < 75% of estimated energy requirement for ≥ 1 month was considered as a marker for nonsevere (moderate) malnutrition.[3]

Scored Patient-Generated Subjective Global Assessment (PG-SGA)

Nutritional status was also assessed using the features of the PG-SGA, which included information on medical history that was completed by the participant; features include weight change, changes in dietary intake, nutritional and gastrointestinal symptoms, and functional capacity (Appendix C).[160] The

study researcher completed the remainder of the form that included other disease-related information and its relation to the patient's nutritional requirements and estimated level of metabolic stress. Additionally, a thorough nutrition-focused physical exam was conducted that subjectively evaluated changes in fat, muscle, and fluid status.[160]

Based on the overall subjective ranking for nutritional and functional status, individuals were rated as being well nourished or anabolic (SGA-A); moderately malnourished or suspected of malnutrition (SGA-B); or severely malnourished (SGA-C). Additionally, a total numerical score was calculated from history, disease condition, metabolic demand, and physical examination components of the PG-SGA tool. Per this scoring process, a score ≥ 9 indicated a critical need for improved symptom management and nutrient intervention.[161]

Figure 3-1: An outline depicting various study time points and measures.

	Time 1 (Within 7 days prior to starting CRT)	Time 2 (3.5 weeks into treatment ± 1 week)	Time 3 (During the last week of treatment)	Time 4 (Follow-up, 1 month post treatment ± 14 days)	Time 5 (Follow-up, 3 months post treatment ± 1 month)
MEASURES					
Anthropometrics					
Height	X				
Weight	X	X	X	X	X
Triceps skinfold	X	X	X	X	X
Mid-upper-arm circumference	X	X	X	X	X
Body composition					
Bioimpedance	X	X	X	X	X
Scored Patient-Generated Subjective Global Assessment (PG-SGA)	X	X	X	X	X
Dietary intake data					
24-hr dietary recall	X	X	X	X	X
3-day dietary records		X	X	X	X
Functional status					
Hand grip strength	X	X	X	X	X
Five-times-sit-to-stand-test	X	X	X	X	X
Psychosocial measures					
Quality of life	X			X	X
Self-efficacy	X			X	X

Functional Status

Hand grip strength

Hand grip strength was measured in both hands using a Grip-D dynamometer (Takei Scientific Instruments Co. Ltd., Japan). Participants were asked to sit comfortably with the shoulder adducted and forearm neutrally rotated, elbow flexed to 90°.[162] The dominant hand was tested first, and three successive measurements were taken for each hand.[162] The time between the trials was about 15 seconds, and an average measurement for both hands was used for analysis. ***Measurably reduced grip strength*** was defined as the value below the average for specific age and gender as supplied by the device manufacturer.

Five-times-sit-to-stand-test

Participants were asked to sit on a slightly padded armless chair with their feet flat on the floor and the back upright against the back rest of the chair.[22] Next, they were asked to fold their upper limbs across the chest and to stand up all the way and sit down landing firmly, as fast as possible, 5 times without using their arms. Using a stop watch, the test timing began on the command “go” (participant sitting), and ceased on landing after the fifth stand up.[22] The sit-to-stand time was recorded to the nearest 0.10 seconds. Individuals with sit-to-stand-test time exceeding 11.4 seconds in the 50 - 69 year age group and 12.6 seconds in the 70 - 79 year group were considered having worse than average functional performance.[163]

Bioimpedance Analysis (BIA)

Changes in lean body mass were assessed by bioimpedance analysis at each of the five time points using a multiple-frequency device (QuadScan 4000, Bodystat Ltd, Douglas, UK). After the participant assumed a supine position, four electrodes were placed in the standard tetrapolar arrangement, which involved the placement of two electrodes on the hand (one on the bony protuberance that forms the wrist, i.e. between the styloid processes of the ulna and radius, and the other just behind the metacarpals), and two electrodes on the foot (one on the ankle placed midline between the medial and lateral malleoli, and the other just behind the metatarsals).[55,66] Two measurements were taken at 5 and 10 minutes, we have utilized the 10 minute BIA data for our analysis.[164] The two primary BIA variables of interest were phase angle (PA), quantified as the ratio of the arc tangent of reactance to resistance (arc tangent [Xc/R] × [180°/π], measured at 50 kHz and expressed in degrees); and Impedance Ratio (IR) as the ratio of impedance measured at 200 kHz to impedance measured at 5 kHz.[154]

Reference values for PA were taken from data generated among the American adult population,[86] and PA value below the 5th percentile was used as an indicator of malnutrition. Additionally, standardized phase angle (SPA) was calculated as [(Observed PA – Mean PA)/Standard Deviation (SD)], where mean and SD were taken from the reference values.[89] A SPA < -1.65 represented the 10th percentile and was used as a cutoff to indicate malnutrition.[165] Although reference cut-points have not yet been established as they have for PA, IR

values > 0.78 in males and > 0.82 in females were used as cutoffs for malnutrition.[98]

Statistical Analysis

The data were analyzed using the SAS software, Version 9.4 (Copyright © 2013 SAS Institute Inc., Cary, NC, USA). Descriptive statistics were used to calculate frequencies, means and standard deviation. One-way repeated measures ANOVA was performed to assess changes in total PG-SGA score, anthropometric, bioimpedance, functional status, and dietary intake data over time. A post-hoc analysis with Bonferroni's adjustment was done for multiple pairwise comparisons over time. A contingency table was used to determine the sensitivity, specificity, and predictive values. Fisher's exact test was used to test the differences between the PG-SGA and Consensus ratings at each time-point. Independent samples t-test assessed differences for mean PA and IR between the Consensus identified malnourished and well-nourished individuals (or PG-SGA score 0-8 vs. ≥ 9 categories). Simple logistic regression was used to analyze the BIA related predictors of malnutrition as defined by the Consensus or the PG-SGA criteria [with either the Consensus or the PG-SGA as binary outcome variables (0 = not-malnourished, 1 = malnourished)]. Pearson's correlation examined the association between variables. Significance level was set at $P \leq 0.05$. Figures were constructed using the GraphPad Prism version 6.07 for Windows, GraphPad Software, La Jolla California USA.

Results

Baseline Characteristics

Of the19 participants, 18 were male and 1 female; the mean age was 59 ± 7 years (Table 3-1). The mean BMI was 29 ± 5 kg/m^2; 26% were normal weight, 32% overweight, and 42% were categorized as being obese. Fifteen (79%) participants were diagnosed with Stage IV cancer and four (21%) had Stage III disease. Most tumors were localized at the oropharynx (58%), followed by the oral cavity (16%), larynx (11%) and maxillary sinuses (11%), and paranasal sinuses (5%). Thirteen individuals had undergone a tumor resection surgery prior to starting their treatment. About 74% were either current or former smokers and 63% were either current or former alcohol consumers. Only 2 participants had a history of smokeless tobacco intake.

Consensus Diagnostic Criteria

Frequency of individuals meeting the malnutrition diagnostic markers as outlined by the Consensus is shown in Table 3-2 and Figure 3-2. Seventy-eight percent were identified as having reduced grip strength at baseline, while 100% had reduced strength during the post-treatment period (T4 and T5). At T3 and T4, 88% indicated a loss in muscle mass and up to 94% showed loss in subcutaneous fat in this period. At T1 39% and at T3 82% exhibited unintended weight loss.

Table 3-3 shows the number of characteristic markers met at each time point. Two or more of the 6 characteristics were evident, indicating a diagnosis of

malnutrition in 67% at T1, 94% at T3, and by all participants during the post-treatment period. Of the total 84 observations, 76 (90%) met 2 or more of the 6 characteristic markers. Nine met 5 markers (and of these, all 9 were rated PG-SGA-B or -C) and 35 met 4 markers (with 34 rated as PG-SGA-B or -C and one -A). Additional comparison of the two diagnostic approaches will be thoroughly presented in a subsequent section.

PG-SGA Score and Nutrition Impact Symptoms

The frequency of obtaining a higher PG-SGA score (≥ 9, indicating a critical need for improved symptom management and nutrient intervention) and the most commonly reported nutrition impact symptoms (NIS) are shown in Table 3-4. At baseline, 39% scored ≥ 9 in the PG-SGA (score range 2 – 16), while at T3, all individuals had a higher score (range 11 – 26). At T4, 81% (range 5 – 20) and at T5, 93% (range 3 – 17) had higher PG-SGA scores (Table 3-4). Overall, individuals scoring ≥ 9 in the PG-SGA had undergone 11% weight loss in the past 6 months and 8% loss in the previous 3 months.

Problems with eating and swallowing, taste changes, pain, no appetite, mouth sores, dry mouth, and nausea were the most commonly reported NIS during and after treatment (Table 3-4, Figure 3-3). At baseline, 58% reported problems with eating and 28% had problems swallowing. During treatment (T2 and T3), all participants had problems with eating, and up to 82% reported having pain and swallowing issues. At T2, 63% had taste alterations and 47% reported having mouth sores and no appetite. At T4, 94% reported problems with

eating, 63% problem swallowing, 56% had taste changes, and up to 38% reported pain, mouth sores, and appetite loss. At T5, 86% had problems with eating, 50% problem swallowing, and 43% reported changes in their taste.

Table 3-1: Baseline demographic and clinical characteristics of participants (n = 19).

Age (years ± SD)	59 ± 7	
	n	**%**
Gender		
Male	18	95
Female	1	5
Body weight (kg ± SD)	89 ± 21	
Height (cm ± SD)	179 ± 9	
Body mass index (kg/m^2 ± SD)	29 ± 5	
Normal (18.5–24.9)	5	26
Overweight (25.0–29.9)	6	32
Obesity Class I (30.0–34.9)	4	21
Obesity Class II (35.0–39.9)	4	21
TNM Staging†		
Stage III	4	21
Stage IVA	13	68
Stage IVB	1	5
Stage IVC	1	5
Primary tumor localization		
Oropharynx	11	58
Oral cavity	3	16
Larynx	2	11
Maxillary sinuses	2	11
Paranasal sinuses	1	5
Surgical resection*	13	68
Tobacco and Alcohol Status		
Smoking		
Current	3	16
Former	11	58
None	5	26
Alcohol		

Current	9	47
Former	3	16
None	7	37

† Created and updated by the American Joint Committee on Cancer and the International Union Against Cancer. TNM system is based on the size and/or extent of the primary tumor (T), the amount of spread to nearby lymph nodes (N), and the presence of metastasis (M).[166]
*Participants who underwent tumor resection surgery prior to the initiation of chemotherapy and radiation therapy.

Table 3-2: Frequency (n,%) of individuals meeting the malnutrition diagnostic markers as outlined by the Consensus criteria during each time-point.†

	Time 1	**Time 2**	**Time 3**	**Time 4**	**Time 5**
Characteristic markers	**n = 18**	**n = 19**	**n = 17**	**n = 16**	**n = 14**
Inadequate energy intake	5 (28)	9 (47)	3 (18)	2 (13)	8 (57)
Weight loss	7 (39)	12 (63)	14 (82)	10 (63)	12 (86)
Loss of muscle mass	10 (56)	13 (68)	15 (88)	14 (88)	12 (86)
Loss of subcutaneous fat	9 (50)	13 (68)	15 (88)	15 (94)	6 (43)
Reduced hand grip strength	14 (78)	15 (79)	15 (88)	16 (100)	14 (100)
Five-times-sit-to-stand-test*	12 (67)	9 (47)	9 (53)	8 (50)	9 (64)
Edema	0	0	0	2 (13)	1 (7)

† Per the Consensus criteria, five-times-sit-to-stand-test (FTSST) is not the usual recommendation for assessing reduced functional status; and is included in this table to allow for comparisons with reduced hand grip strength.

***** Individuals with an inability to perform FTSST due to muscle weakness or excess body weight making it difficult to perform the test are included in this count (excluding individuals who declined to perform the test due to reasons such as surgery in leg, and pain, fever, nausea, drowsiness, and tiredness due to ongoing treatment.).

Figure 3-2: Number of participants meeting the malnutrition diagnostic markers as outlined by the Consensus criteria during each time-point.

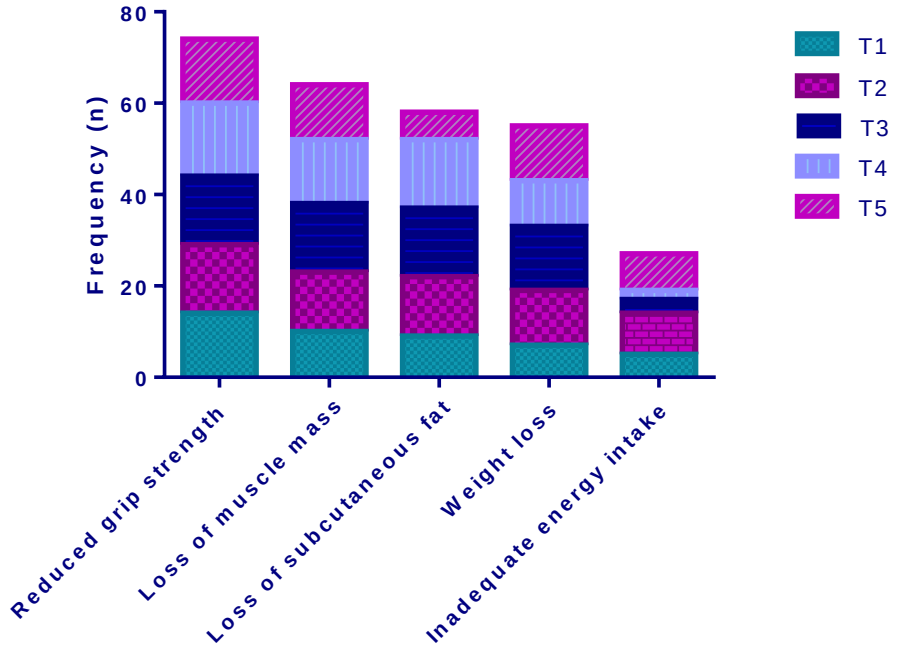


Table 3-3: Number of Consensus characteristic markers met at each time point.

Number of markers	Time 1	Time 2	Time 3	Time 4	Time 5	Total
	n=18	n=19	n=17	n=16	n=14	
0	1	0	0	0	0	1
1	5	1	1	0	0	7
2	2	4	1	2	0	9
3	5	5	5	2	6	23
4	4	7	7	11	6	35
5	1	2	3	1	2	9
2 or more met†, n (%)	12 (67)	18 (95)	16 (94)	16 (100)	14 (100)	76 (90)

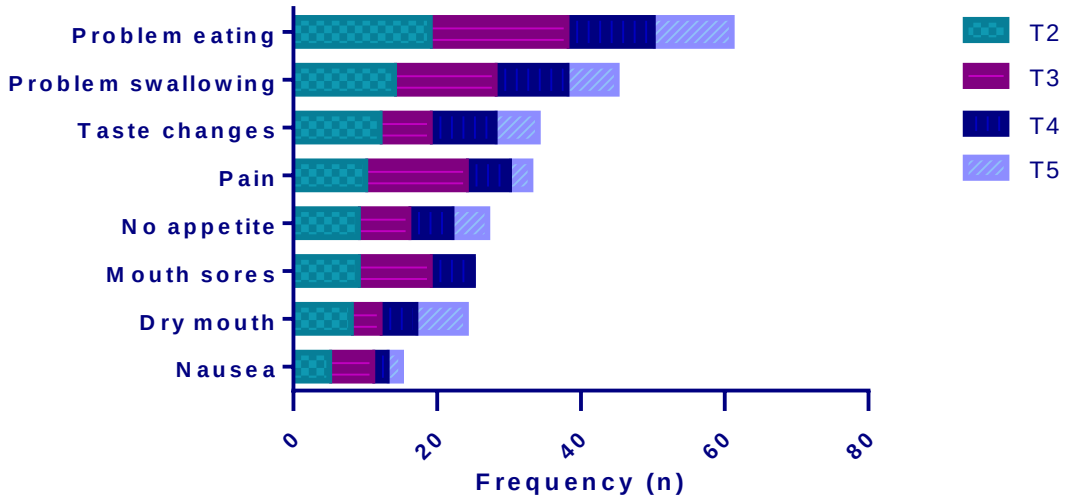
† Per the Consensus criteria, meeting at least 2 out of the 6 characteristic markers indicates a diagnosis of malnutrition.

Table 3-4: Frequency (n,%) of PG-SGA score ≥ 9 and most commonly reported nutrition impact symptoms across time.

	Time 1	Time 2	Time 3	Time 4	Time 5
	n = 19	n = 19	n = 17	n = 16	n = 14
PG-SGA score ≥ 9	7 (39)	18 (95)	17 (100)	13 (81)	13 (93)
Nutritional impact symptoms*					
No problem eating	8 (42)	0	0	1 (6)	2 (14)
Problem swallowing	5 (28)	14 (74)	14 (82)	10 (63)	7 (50)
Taste changes	2 (11)	12 (63)	7 (41)	9 (56)	6 (43)
Pain	3 (17)	10 (53)	14 (82)	6 (38)	3 (21)
No appetite	2 (11)	9 (47)	7 (41)	6 (38)	5 (36)
Mouth sores	0	9 (47)	10 (59)	6 (38)	0
Dry mouth	3 (17)	8 (42)	4 (23)	5 (31)	7 (50)
Nausea	0	5 (26)	6 (35)	2 (13)	2 (14)

*Participants could select multiple symptoms in the PG-SGA form.
Abbreviation: PG-SGA, Patient-Generated Subjective Global Assessment

Figure 3-3: Frequency of commonly reported nutrition impact symptoms in the PG-SGA during and after treatment.



Abbreviation: PG-SGA, Patient-Generated Subjective Global Assessment

Comparison of the Consensus Diagnostic Criteria with the PG-SGA

The frequency of PG-SGA ratings and the Consensus criteria is presented in Table 3-5. At each time point, no significant differences in ratings were found between the two measures (Fisher's exact test $P > 0.05$). At T1, the PG-SGA rated 13 (68%), while the Consensus diagnosed 12 (67%) individuals with malnutrition. From T2 through T4, only one participant was found well-nourished by the PG-SGA, while the Consensus found 2 well-nourished individuals in this period. At T5, the PG-SGA rated 13 (93%) while the Consensus criteria rated 14 (100%) individuals with malnutrition. Significant differences were found between the mean PG-SGA scores for the three categories of Consensus criteria ($P < 0.0001$) (Figure 3-4).

Of the total 84 observations, 72 (86%) were correctly classified by the Consensus criteria as being malnourished (true positives) and 3 (4%) were correctly classified as well-nourished (true negatives) (Table 3-6). Four (5%) observations were misclassified by the Consensus as being malnourished (false positives), and 5 (6%) were misclassified as well-nourished (false negatives). The sensitivity of the Consensus criteria was 94% with a positive predictive value of 95%; specificity was 43% with a negative predictive value of 37%.

Table 3-5: Nutritional status ratings by PG-SGA and the Consensus diagnostic criteria across time.

	Time 1	Time 2	Time 3	Time 4	Time 5
Scored PG-SGA Global Assessment	**n=19**	**n=19**	**n=17**	**n=16**	**n=14**
Well-nourished (SGA-A)	6 (32)	0	0	0	1 (7)
Moderate or suspected malnutrition (SGA-B)	11 (58)	16 (84)	9 (53)	12 (75)	10 (71)
Severely malnourished (SGA-C)	2 (11)	3 (16)	8 (47)	4 (25)	3 (21)
Consensus Diagnosis	**n=18***	**n=19**	**n=17**	**n=16**	**n=14**
Well-nourished	6 (33)	1 (5)	1 (6)	0	0
Nonsevere (Moderate) Malnutrition	11 (61)	12 (63)	12 (71)	16 (100)	7 (50)
Severe Malnutrition	1 (6)	6 (32)	4 (23)	0	7 (50)

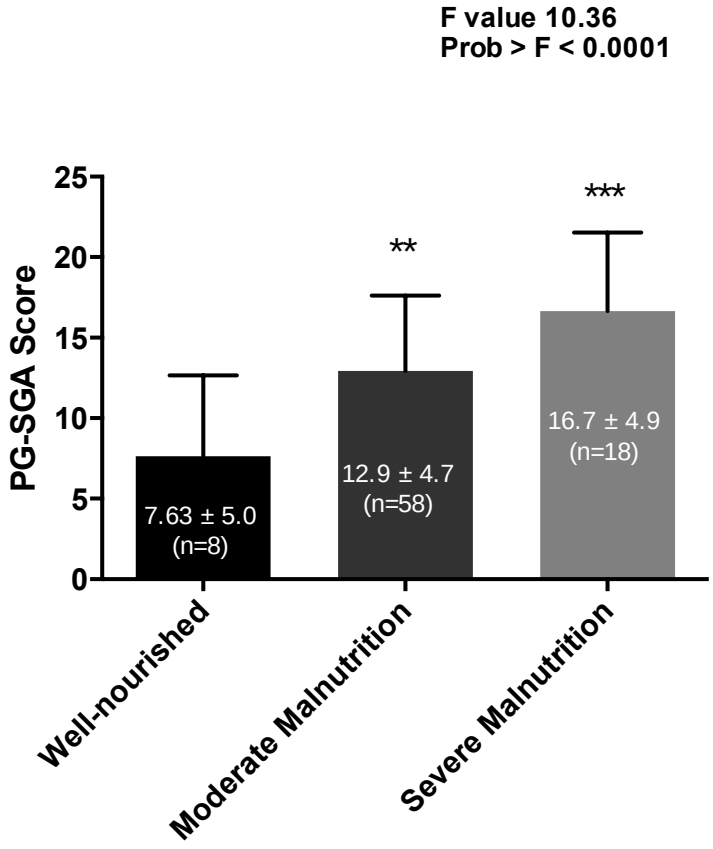
*Missing, n=1
Abbreviation: PG-SGA, Patient-Generated Subjective Global Assessment

Table 3-6: Sensitivity and specificity of the Consensus diagnostic criteria (over all observations including all time-points, n = 84).

	PG-SGA Malnourished (B or C)	PG-SGA Well-nourished (A)
Consensus Malnourished	72 (86%) True positive*	4 (5%) False positive
Consensus Well-nourished	5 (6%) False negative	3 (4%) True negative†

***Sensitivity**, or the ability of the Consensus to correctly identify individuals with malnutrition was 94%. **Positive predictive value**, or the likelihood that individuals with Consensus diagnosed malnutrition were truly malnourished was 95%.
†**Specificity**, or the ability of the Consensus to correctly identify individuals with no malnutrition was 43%. **Negative predictive value**, or the likelihood that individuals with Consensus categorized well-nourished were truly not malnourished, was 37%.
Abbreviation: PG-SGA, Patient-Generated Subjective Global Assessment

Figure 3-4: Overall comparison of the PG-SGA scores according to the Consensus diagnostic criteria (over all observations including all time-points, n = 84).



*** P < 0.001 compared to well-nourished, P < 0.01 compared to moderate malnutrition.
** P = 0.01 compared to well-nourished.
Values are means ± standard deviation.
Abbreviation: PG-SGA, Patient-Generated Subjective Global Assessment

Changes in the PG-SGA Score, Anthropometric, BIA, and Functional Status Markers

Compared to the baseline, a significant increase in the total PG-SGA score was noted from T2 through T5 (Table 3-8). Significant decreases in the absolute body weight and BMI were observed between T1 and the other time-points (P ≤ 0.0001) (Table 3-8, Figure 3-5). At T1, 71% of all participants had lost

some weight. At T3, mean weight loss of 11% over the past 3 months was observed (Figure 3-5). The PG-SGA score was significantly correlated with BMI ($r = -0.23$, $P = 0.032$) and percent weight loss 6 months ago ($r = 0.34$, $P = 0.004$). The correlation between hand grip strength and the PG-SGA score did not reach statistical significance ($r = -0.19$, $P = 0.085$).

No changes in the TSF measurements were observed over time, while mean MUAC significantly decreased from mid-treatment (T2) to the post-treatment period (T4 and T5) ($P \leq 0.001$). No significant differences were found in the mean TSF ($P = 0.337$) or MUAC ($P = 0.807$) measurements between the Consensus identified malnourished and well-nourished individuals.

Mean PA significantly decreased from baseline to the end of treatment (T1 - T3) and post-treatment period (T1 - T4, T1- T5) ($P < 0.05$). A significant increase in the mean IR was observed from baseline to the end of treatment (T1 – T3) ($P <0.05$) and post-treatment periods (T1 – T4, T1 – T5) ($P \leq 0.01$).

Hand grip strength decreased between the baseline and one month post-treatment period (T1 - T4) ($P < 0.01$). Hand grip strength was significantly correlated with sit-to-stand-test time ($r = - 0.37$, $P = 0.002$). Although the sit-to-stand time increased from T1 through T3, this change was not found to be significant.

Changes in Dietary Intake and Nutrition Support (NS)

Significantly fewer calories and protein (gm/kg body weight) were consumed during treatment (T2) compared to the post-treatment period (T4) ($P < 0.01$) (Table 3-9). At the end of treatment, 15 of 17 participants (88%) were using enteral NS, and 75% of the total calories and 80% of the total protein intake was provided through NS. One month post-treatment, 12 of 16 individuals (75%) were on enteral feedings, and 66% of the total caloric and 68% of the total protein needs were met through NS.

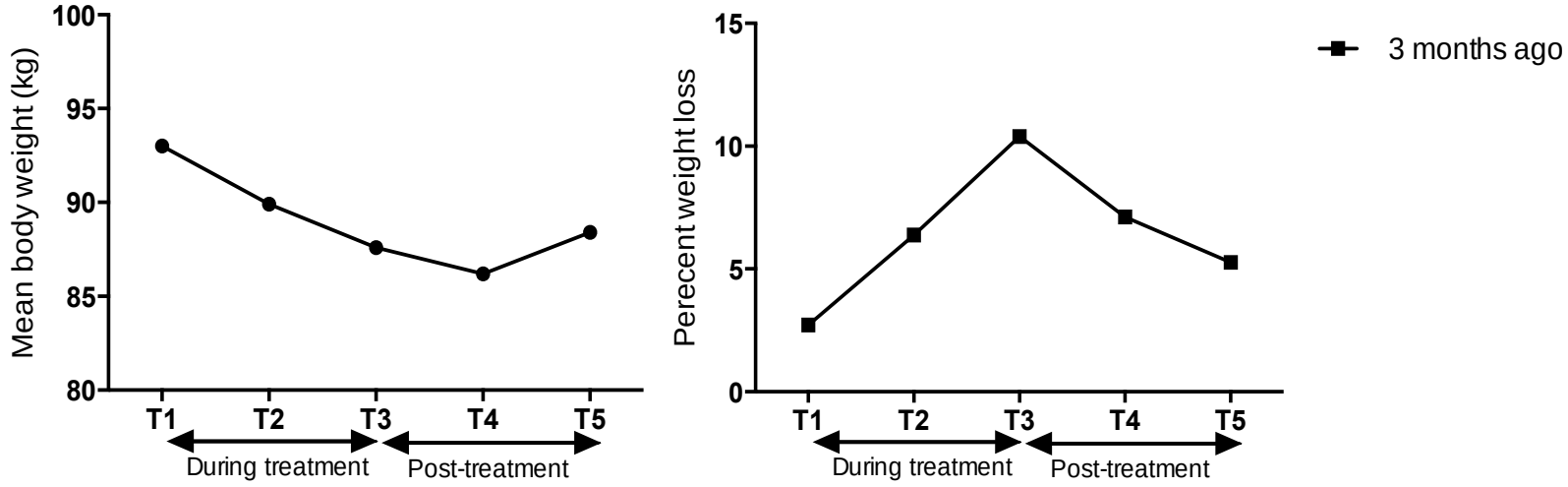
Table 3-7: Anthropometric, bioimpedance, and functional status data across time.

	Time 1	Time 2	Time 3	Time 4	Time 5	P-value[†]
	n = 19	**n = 19**	**n = 17**	**n = 16**	**n = 14**	
Total PG-SGA Score	8 ± 4	15 ± 5	17 ± 5	13 ± 4	12 ± 4	**<0.0001[a]**
Anthropometry						
Body weight (kg)	93 ± 23	90 ± 22	88 ± 21	86 ± 20	88 ± 21	**0.0001[b]**
Body mass index (kg/m^2)	29 ± 5	28 ± 5	27 ± 5	27 ± 4	27 ± 5	**<0.0001[c]**
Triceps skinfolds (mm)	13 ± 6	13 ± 6	12 ± 7	13 ± 7	13 ± 5	0.522
Mid-upper-arm circumference (cm)	30 ± 5	34 ± 4	33 ± 5	29 ± 3	29 ± 3	**0.0001[d]**
Bioimpedance						
Phase angle (50 kHz)	5.56 ± 0.79	5.5 ± 0.9	5.13 ± 0.85	5.0 ± 0.8	5.14 ± 0.71	**0.0023[e]**
Impedance ratio (200 kHz/5 kHz)	0.81 ± 0.02	0.81 ± 0.03	0.82 ± 0.03	0.82 ± 0.03	0.82 ± 0.03	**0.0015[f]**
Functional status						
Hand grip strength (kg)	32 ± 8	32 ± 9	31 ± 8	31 ± 6	30 ± 6	**0.0031[g]**
Five-times-sit-to-stand test (sec)	13 ± 4	13 ± 4	15 ± 7	13 ± 4	13 ± 3	0.1763

Values are means ± standard deviation.
[†]Analyzed by one-way repeated measures ANOVA.
[a-g] Per the Bonferroni post-hoc test, pairwise comparisons (adjusted P values):
[a] $P \leq 0.0001$ for T1 – T2 and T1 – T3; $P < 0.05$ for T1 – T4 and T1 – T5.
[b,c] $P \leq 0.0001$ for T1 – T2, T1 – T3, T1 – T4, and T1 – T5; $P < 0.001$ for T2 – T3, T2 – T4, and T2 – T5; and $P < 0.05$ for T3 – T5.
[d] $P \leq 0.001$ for T2 – T4 and T2 – T5 and $P < 0.05$ for T3 – T5.

[e] P < 0.05 for T1 – T3, T1 – T5, T2 – T3; P < 0.01 for and T1 – T4 and T2 – T4.
[f] P < 0.005 T1 – T4, T2 – T3, and T2 – T4; P < 0.05 for T1 – T3, and T1 – T5.
[g] P < 0.01 for T1 – T4; P < 0.05 for T2 – T4.
Abbreviation: PG-SGA, Patient-Generated Subjective Global Assessment

Figure 3-5: Mean body weight and percent weight loss over the previous 3 months† across time.



†3 months ago body-weights were obtained from medical record review when patients were visiting the clinic and nurses took patients' weights during routine clinic assessment.

Table 3-8: Changes in total caloric and protein intake and Enteral Nutrition Support (ENS) across time.

	Time 1	Time 2	Time 3	Time 4	Time 5	P-value[†]
Total intake (Diet + ENS)	**n = 19**	**n = 19**	**n = 17**	**n = 16**	**n = 14**	
Energy (kcal)	2058 ± 687	1822 ± 293	2150 ± 459	2265 ± 399	1805 ± 582	**0.001[a]**
Energy (kcal/kg)	23 ± 9	21 ± 6	26 ± 8	27 ± 7	22 ± 11	**0.001[b]**
% Estimated energy needs	94 ± 41	84 ± 28	100 ± 35	103 ± 34	76 ± 29	**0.001**
Protein (gm)	85 ± 32	72 ± 17	90 ± 20	94 ± 19	70 ± 20	**0.002[c]**
Protein (gm/kg)	0.9 ± 0.4	0.9 ± 0.3	1.0 ± 0.3	1.1 ± 0.3	0.9 ± 0.3	**0.001[d]**
Enteral nutrition support	**n = 2**	**n = 7**	**n = 15**	**n = 12**	**n = 6**	
Energy (kcal)	208 ± 620	546 ± 749	1630 ± 769	1521 ± 996	587 ± 876	**<.0001[e]**
Protein (gm)	9 ± 28	24 ± 33	72 ± 35	67 ± 44	26 ± 39	**<.0001[f]**
% Energy intake of total	10 ± 28	29 ± 40	75 ± 33	66 ± 42	28 ± 41	**<.0001[g]**
% Estimated energy needs	13 ± 38	27 ± 41	76 ± 47	70 ± 54	25 ± 37	**<.0001[h]**
% Protein intake of total	10 ± 31	31 ± 43	80 ± 33	68 ± 43	30 ± 44	**<.0001[i]**

Values are means ± standard deviation.

[†]Analyzed by one-way repeated measures ANOVA.

[a-i] Per the Bonferroni post-hoc test, pairwise comparisons (adjusted P values):

[a- d] $P \leq 0.01$ for T2 – T4.

[e-i] $P < 0.0001$ for T1 – T3, T1 – T4; and $P \leq 0.001$ for T2 –T3.

Bioimpedance Analysis (BIA): Malnutrition and Functional Status Outcomes

PA was significantly lower among the Consensus categorized malnourished individuals than those who were well-nourished (P = 0.019) (Table 3-9). Individuals with a PG-SGA score ≥ 9 had a lower PA than those with < 9 PG-SGA score (P = 0.023) (Table 3-10). IR was significantly higher among Consensus diagnosed malnourished individuals than those categorized as well-nourished (P = 0.013); and those with PG-SGA score ≥ 9 had a higher IR than those scoring < 9 (P = 0.022).

Overall, 63% were correctly identified by the SPA as being malnourished (true positives) and 5% were correctly classified as well-nourished (true negatives) (Table 3-11). The sensitivity of the SPA was 68% with a positive predictive value of 96%; specificity was 67% with a negative predictive value of 14%. Significant differences in the mean PG-SGA score were found between SPA identified malnourished (14.3 ± 4.7) and well-nourished (11.5 ± 5.6) individuals (P = 0.016). Simple logistic regression showed that SPA was a significant predictor of malnutrition when defined by the Consensus criteria (P = 0.014), but not with the PG-SGA rating criteria (P = 0.133). Similarly, IR was a significant predictor of malnutrition when defined by the Consensus (P = 0.04), but not when using the PG-SGA rating criteria (P = 0.851).

Overall, the PG-SGA score was significantly correlated with PA (r = -0.35, p = 0.002), SPA (r = -0.34, P = 0.002), and IR (r = 0.36, P = 0.001) (see Figure 3-

6 and 3-7). Hand grip strength was correlated with PA (r = 0.48, P < 0.001), SPA (r = 0.35, P = 0.001), and IR (r = -0.47, P < 0.0001) (see Figure 3-8 and 3-9). Sit-to-stand-test time was correlated with IR (r = 0.30, P = 0.014) and PA (r = -0.34, P = 0.005) but not with the SPA (r = -0.19, P = 0.124).

Table 3-9: Phase angle and impedance ratio among the Consensus categorized malnourished and well-nourished individuals.

	Consensus Well-nourished	Consensus Malnourished	P - value
Phase angle	5.9 ± 0.67 (4.5 - 6.6)	5.2 ± 0.84 (3.0 - 7.1)	0.019
Impedance ratio	0.80 ± 0.02 (0.78 - 0.83)	0.82 ± 0.03 (0.75 - 0.89)	0.013

Values are means ± standard deviation (range).

Table 3-10: Phase angle and impedance ratio among the PG-SGA score categories.

	Not at nutrition risk (PG-SGA score 0-8)	At nutrition risk (PG-SGA score ≥ 9)	P - value
Phase angle	5.7 ± 0.77 (4.4 - 7.1)	5.2 ± 0.83 (3.0 - 7.1)	0.023
Impedance ratio	0.80 ± 0.02 (0.76 - 0.85)	0.82 ± 0.03 (0.75 - 0.89)	0.022

Values are means ± standard deviation (range).
Abbreviation: PG-SGA, Patient-Generated Subjective Global Assessment

Table 3-11: Sensitivity and specificity of the SPA over all observations including all time-points (n = 83).

	PG-SGA Malnourished (B or C)	PG-SGA Well-nourished (A)
SPA Malnourished	52 (63%) True positive*	2 (2%) False positive
SPA Well-nourished	25 (30%) False negative	4 (5%) True negative†

*__Sensitivity__, or the ability of the SPA to correctly identify individuals with malnutrition was 68%. **Positive predictive value**, or the likelihood that individuals with SPA identified malnutrition were truly malnourished was 96%.
†__Specificity__, or the ability of the SPA to correctly identify individuals with no malnutrition was 67%. **Negative predictive value**, or the likelihood that individuals who were SPA identified well-nourished were truly not malnourished, was 14%.
Abbreviation: PG-SGA, Patient-Generated Subjective Global Assessment. SPA, Standardized Phase Angle.

Figure 3-6: Pearson's correlation between the PG-SGA score and phase angle over all observations including all time-points (n = 84).

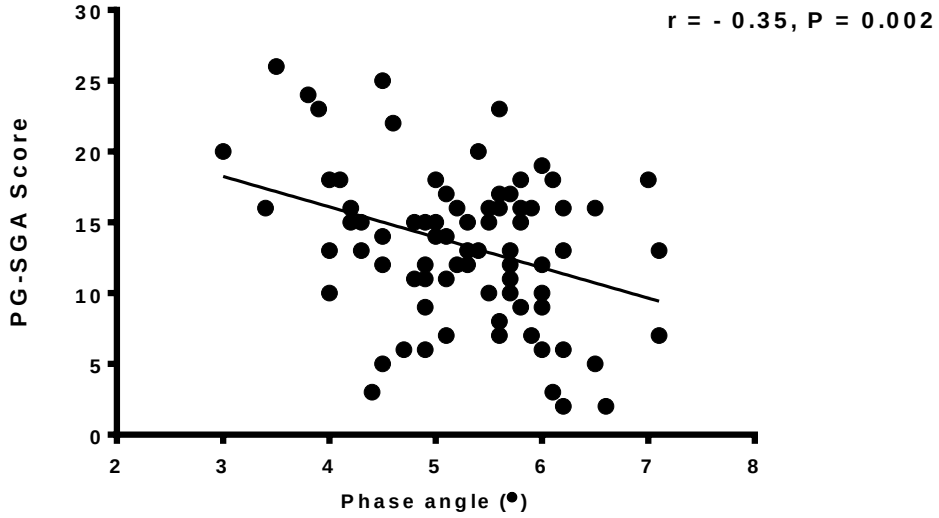


Figure 3-7: Pearson's correlation between the PG-SGA score and impedance ratio over all observations including all time-points (n = 84).

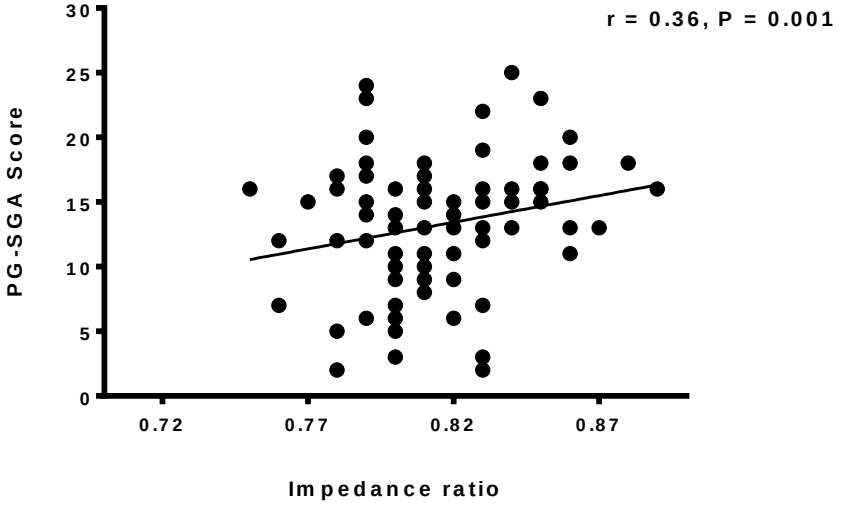


Figure 3-8: Pearson's correlation between the hand grip strength and phase angle over all observations including all time-points (n = 84).

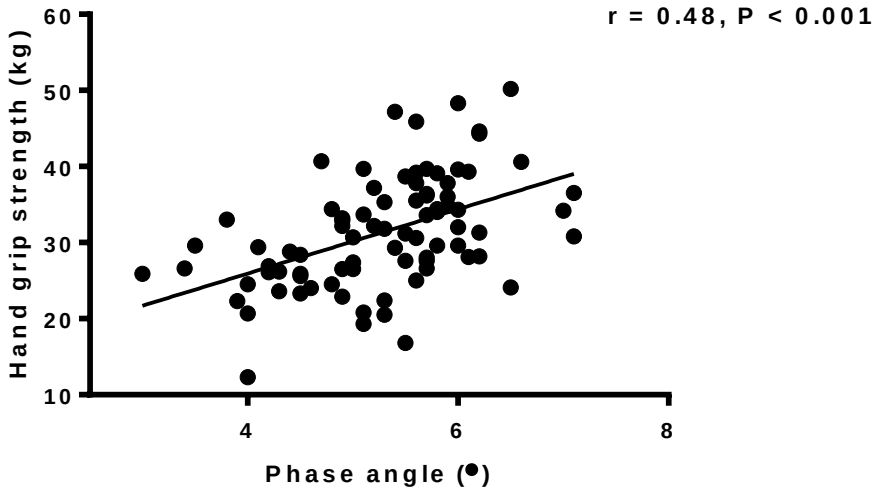
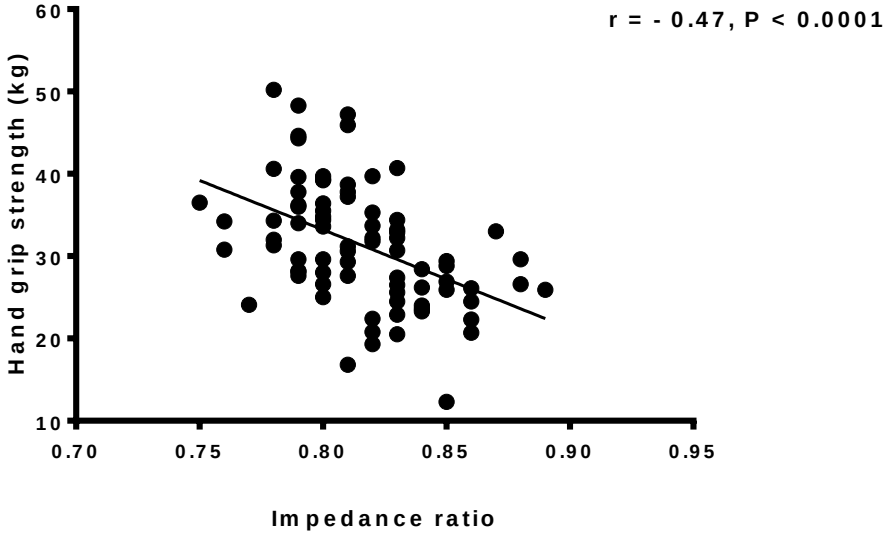


Figure 3-9: Pearson's correlation between the hand grip strength and impedance ratio over all observations including all time-points (n = 84).



Discussion

To our knowledge, this is the first study that has longitudinally investigated nutritional status outcomes among individuals with HNC in an outpatient setting using the recent Academy/A.S.P.E.N. Consensus malnutrition diagnostic criteria. Our results indicate that individuals with HNC are malnourished even before treatment initiation. Using the Consensus criteria, 67% of our participants were malnourished before treatment; and the prevalence of malnutrition consistently increased during treatment and the post-treatment period. Significant weight loss was exhibited by nearly 40% of our participants before treatment; and loss in weight continued up to 3 months after treatment was completed for 86% of the participants. Problems with eating, dry mouth, taste changes, and difficulty swallowing were the commonly reported nutrition impact symptoms even 3 months after treatment completion, likely contributing to inadequate dietary intake and resulting in unintended weight loss and loss of lean tissue. The mean triceps skinfolds (TSF) measurement did not change over time; and while the mean mid-upper-arm circumference (MUAC) decreased after treatment, no changes in MUAC were observed during treatment. Additionally, no differences in the mean TSF or MUAC measurements were found between the Consensus identified malnourished and well-nourished individuals. Therefore, despite significant losses in the absolute body weight and the loss of body fat and muscle mass identified by the nutrition-focused physical exam, anthropometric measures such

as TSF and MUAC seemed less sensitive to identify malnutrition or changes in the lean tissue over time.

Comparing the Two Malnutrition Diagnosis Approaches – Scored PG-SGA and the Consensus Criteria

Our results indicate that compared to our chosen reference standard PG-SGA, the Consensus criteria identified malnutrition with overall good sensitivity (95%) and specificity (43%). A higher sensitivity indicates that the Consensus was correctly categorizing individuals with actual malnutrition; which takes precedence over specificity, or correctly classifying individuals with no malnutrition. Longitudinally, no significant differences between the ratings of these two measures were observed; and both reported increases in the prevalence of malnutrition from the beginning of treatment to up to 3 months after treatment completion. Individuals who met the Consensus definition for malnutrition were more likely to be rated malnourished using the PG-SGA assessment.

That said, some functional differences between the two assessment approaches needs discussion. The PG-SGA calculates an overall numerical score that can possibly be used to cater immediate symptom management and/or nutritional intervention strategies.[161] Statistically speaking, unlike the three Consensus categories (well-nourished, or moderate or severe malnutrition) the PG-SGA score is a continuous variable against which other nutritional parameters can be validated. For instance, we found that individuals with ≥ 9 PG-

SGA score had also lost 11% of their absolute body weight in the past 6 months. Furthermore, about 40% of our participants were in critical need of nutrition intervention before treatment initiation as indicated by a PG-SGA score ≥ 9. Agreeably, significant differences were also observed between the mean PG-SGA scores for the three Consensus categories, and malnourished individuals had a higher score than those categorized as well-nourished.

The PG-SGA also offers the feature of selecting various nutrition impact symptoms (NIS) that affect oral intake. While some researchers have administered the PG-SGA in the HNC setting once; either before or during treatment,[167,168] this longitudinal study gathered NIS data before, during, and after treatment completion. Problems with eating and swallowing, taste changes, pain, and mouth sores were among the most commonly reported NIS during treatment. Usually, most symptoms that affect intake are expected to resolve soon after treatment completion, however we noted that even 3 months after treatment, 86% continued to have problems with eating, and dry mouth, taste changes, and difficulty swallowing were among the commonly reported symptoms. It has been reported that many individuals with HNC become malnourished after treatment as a result of treatment-induced weight loss, loss of appetite, taste changes, and reduced oral intake.[169] Not surprisingly in our study, all participants met the Consensus malnutrition criteria at 1 month and 3 months after treatment completion, suggesting poor nutritional and functional status outcomes months after treatment completion. In the future, knowing the

prevalence of NIS could be useful while considering patient-specific interventions that could potentially help with the timely management of unintended weight loss and reduced dietary intake.[170]

While the PG-SGA calculates a numerical score and specifies symptoms that affect oral intake, its capacity to evaluate dietary and functional status related data is fairly limited. For example, dietary intake and functional status is assessed primarily through two subjective questions in the PG-SGA history section that are self-reported by the participant. On the other hand, the Consensus characteristic for insufficient energy intake is gathered through dietary assessment methodologies such as 24-hour recall, diet history, or in the case of nutrition support (NS), through intake and output records.[157] In our study, at the end of treatment 18% of the participants met the Consensus criterion of inadequate energy intake. Importantly, 15 out of 17 individuals were actively using enteral NS at the end of treatment, and 75% of the total caloric and 80% of the total protein requirements were met through enteral feedings. Earlier, the use of enteral NS in HNC setting has been shown to prevent weight loss, malnutrition, dehydration, and treatment interruptions.[171] A gastrostomy tube was placed in 18 of our participants before treatment initiation, and NS was crucial during and immediately after treatment completion when symptoms such as pain, mouth sores, taste changes, and problems swallowing made oral intake quite challenging. Clearly, the Consensus characteristic for assessing inadequate intake takes a comprehensive approach while gathering oral and/or NS related

data. It is important to note that currently there is a lack of consensus on estimating energy requirements in the HNC patient population, and this study used the kcal/kg body weight method using the European Society for Clinical Nutrition and Metabolism guidelines (2006).[159] For example, using these guidelines we found that at Time 1, 7/19 individuals were meeting their energy needs, but of these, four individuals still experienced moderate to severe weight loss at Time 2. Estimated energy requirements calculated by another method (for example, Mifflin St. Jeor equation) could possibly yield differences in energy estimation and interpretation of the 'insufficient energy intake' marker for the Consensus criteria. Therefore, additional studies are needed for establishing evidence-based nutrient recommendations for the ambulatory oncology patient population.

The Consensus recommends the use of hand grip strength as an objective marker of performance status. Among individuals with HNC, reduced grip strength has been associated with a higher risk for mortality and postoperative complications.[172,173] Moreover, chronic inflammation, skeletal muscle catabolism, poor nutritional intake, and sedentary behavior during HNC treatment often results in loss of protein and lean muscle mass stores.[8,20] Seventy-eight percent of our participants were identified to have reduced grip strength before treatment initiation, and all had reduced strength after treatment completion. Jager-Wittenar et al[169] noted that although grip strength showed improvements 4 months after HNC treatment completion, no improvements in

lean muscle mass were noted as measured by dual-energy X-ray absorptiometry. In our study, the mean grip strength was significantly lower after treatment completion when compared to during treatment, and those with lower grip strength also had a lower PA and higher IR, suggesting that a loss of lean tissue mass was associated with impaired muscle function and strength.

Individuals with a reduced grip strength had higher five-times-sit-to-stand-test (FTSST), and a higher FTSST also correlated with a low PA and higher IR. However, unlike the grip strength test, some individuals declined to perform the FTSST due to various reasons such as muscle weakness, and treatment induced pain, fever, nausea, drowsiness, and tiredness making it difficult to rise and sit down five times from a chair. Therefore based on our observation, FTSST might not be a feasible measure of performance status among individuals actively undergoing chemoradiation treatment.

BIA Parameters and Malnutrition Outcomes

Our results indicated a lower PA and higher IR among individuals with ≥ 9 PG-SGA scores than those with lower scores; suggesting the utility of BIA parameters in detecting poor nutritional status. In the past, limited research has suggested PA[108] and IR[63] to be valid parameters for identifying malnutrition among hospitalized inpatients. Among individuals with advanced colorectal cancer, Gupta and colleagues have found that the subjective global assessment (SGA) classified well-nourished individuals had a significantly higher median PA score (6.12) than those who were malnourished (5.18).[115] We observed similar

findings using the Consensus criteria; malnourished HNC individuals had a lower mean PA (5.2 vs. 5.9) and higher IR (0.82 vs. 0.80) than those classified as well-nourished.

Recent (and limited) observations have indicated that the standardization of phase angle by creating z-scores per the reference values adjusted for age, gender, and BMI, known as the SPA is a more reliable indicator of nutritional and functional status than the absolute PA value.[174] In a heterogeneous sample of individuals with various malignancies (n = 399, including HNC), SPA was found to be an independent predictor for malnutrition, impaired functional status, and six-month survival.[89] Our results indicated that individuals identified as malnourished using the SPA cut-off had significantly lower PG-SGA score than well-nourished ones and overall, the SPA identified malnutrition with good sensitivity (68%) and specificity (67%). We also found that SPA and IR were significant predictors of malnutrition when defined by the Consensus criteria, but not using the PG-SGA criteria. A possible explanation for this observation could be that the Consensus criteria requires a comprehensive assessment of malnutrition with more objective assessment parameters compared to the PG-SGA; and was therefore detected through the BIA.

Taken together, our results indicate that the BIA parameters PA, SPA, and IR might be useful in identifying individuals who are at increased risk for malnutrition, and can possibly be incorporated in the outpatient clinical setting as prognostic indicators of malnutrition. Thus in situations where simple measures

such as body weight and BMI might not be reliable indicators of body composition, the diagnosis of malnutrition may be improved by incorporating feasible bioimpedance measures that can be used to assess changes in lean tissue over time. However, additional research is certainly warranted to investigate the utility of PA and IR in identifying malnutrition using the Consensus framework.

Limitations and Conclusion

This study has some limitations that should be noted. First, the elements of the nutrition-focused physical exam that assess the loss of muscle and fat along with edema are similar to both the Consensus malnutrition diagnostic framework and the PG-SGA tool. Therefore, there is a lack of complete independence between the subjective elements of the two diagnostic approaches, which also makes their comparison difficult. Second, the subjective evaluation of muscle and fat loss is often challenging and is prone to inter-observer error; in this study, the nutrition-focused physical exam was conducted by one researcher and thus inter-observer error was not evaluated. Therefore in clinical practice and research, physical assessment should be conducted by more than one dietitian in order to evaluate reliability and to confirm exam findings. A third limitation is that from a field research perspective it was not feasible in this study to incorporate a reference method such as the DXA or CT imaging for comparisons of subjective evaluation of muscle and fat stores, given the constraints of time, space, and patient burden in the CRT outpatient setting.

Fourth, the validity and interpretation of apparent loss of muscle tissue is further complicated by the possibility that some individuals might have a below normal muscle mass but have not actually lost mass; in these instances erroneous interpretation of low muscle mass as malnutrition could result. Fifth, the longitudinal design of this investigation along with the inclusion of individuals with advanced head and neck cancers made it challenging to recruit and enroll a larger number of participants. Sixth, with most of our participants being males and all Caucasian in descent, our study sample was not heterogeneous in terms of gender and ethnicity and thus the results may not be generalizable. Finally, given that some data were collected during treatment, it is likely that some participants could have felt burdened and did not fully engage with the study procedures during this period. Given these limitations and the single center site for our data collection, additional research with a heterogeneous and larger sample that is conducted in other oncology treatment centers could validate our findings.

Despite these limitations, this study is novel and is the first one to longitudinally incorporate the new Consensus framework in the diagnosis of malnutrition among the vulnerable HNC population. Notably, compared to the PG-SGA, the Consensus criteria involves in-depth data collection and comprehensive nutrition assessment parameters. For clinicians, it is also worth noting that the scoring of the PG-SGA tool and the identification of the 6 Consensus markers require time and training. Nevertheless, if clinicians are

trained to assess malnutrition diagnostic markers before individuals with cancer undergo aggressive treatments, nutritional interventions could be initiated at an earlier time and loss in weight and/or lean tissue can be prevented. As we found, individuals with HNC do not regain their pre-treatment body weight and are at an increased risk for nutritional complications during and after treatment completion. That said, timely screening and early detection of malnutrition is a collaborative effort between dietitians, physicians, nurses, and other members of the healthcare team.[3,157] Therefore, dietitian training is needed to identify the malnutrition diagnostic characteristics, who could then work collaboratively with the physician team for standardization of malnutrition coding practices in medical record documentation. Such practices would help with timely identification of malnutrition and subsequent implementation of intervention strategies.[157]

Based on our results, the use of raw bioimpedance parameters such as PA and IR to identify individuals who are at increased risk for malnutrition and/or impaired functional status seems promising. However, given that this was a small homogenous sample of HNC, additional research is certainly warranted to investigate the broader clinical utility of BIA in detecting malnutrition using the new Consensus framework in other clinical populations. Research is also needed to further validate the Consensus criteria in hospital and ambulatory care settings, and to investigate the impact of early nutrition interventions for malnutrition in cancer.

CHAPTER 4: MALNUTRITION AND ITS ROLE IN QUALITY OF LIFE AND COPING SELF-EFFICACY AMONG INDIVIDUALS WITH ADVANCED HEAD AND NECK CANCER.

Introduction

Malnutrition, generally defined as a decline in lean body mass with functional impairment,[3] is highly prevalent among individuals with HNC, with up to 40% - 57% having a compromised nutritional status even before beginning their treatment.[1,11] Malnutrition in HNC has been associated with poor survival outcomes and increased morbidity including post-surgical complications, risk of infections, impaired wound healing and recovery, and poor functional status.[1,8,11–15] Additionally, HNC disease related symptoms and intensive treatment regimens can negatively affect the basic functions of living such as respiration, speech, hearing, social eating (e.g., enjoying meals with family and friends), chewing, and swallowing.[8,9]

Health-related quality of life (QoL) takes a subjective and multidimensional approach to assessment that translates an individual's experience regarding their psychosocial well-being, functional status, and disease- and treatment-related symptoms.[175,176] Therefore, QoL is an important parameter to assess among individuals with cancer during various phases of their treatment. Importantly, malnutrition has been associated with poor QoL outcomes in cancer, and it has been suggested that management of malnutrition may improve QoL for individuals with cancer and their caregivers and families.[175] However, limited research has investigated the relationship between malnutrition and QOL in the HNC setting; most research has been conducted elsewhere (Italy, The

Netherlands, Sweden, Portugal)[32–35,177] involving participants with various disease stages and treatment modalities and such data are lacking in the US.

Self-efficacy theory posits that the greater an individual's confidence in their ability to execute a course of action, the higher the probability that a desired goal will be attained.[38] Coping self-efficacy is a form of self-efficacy that reflects an individual's belief in their ability to negotiate particular stressors or obstacles in their life.[178] Receiving a cancer diagnosis and undergoing aggressive treatments can negatively affect an individual's self-efficacy to cope with stress and threaten their psychosocial well-being and QoL.[10] Previous oncology research has indicated that those with higher coping self-efficacy report better QoL, may live longer, feel less depressed, participate in treatment decision making, and exhibit fewer illness-related symptoms compared to those who are less efficacious in coping.[10,36–40] To date, research investigating self-efficacy perceptions among individuals with HNC is limited, particularly in the context of nutritional outcomes.

Therefore, the purpose of this study was to evaluate whether QoL and coping self-efficacy relate with malnutrition and to investigate the association between the QoL and functional status outcomes among advanced HNC outpatients. We also assessed longitudinal changes in the QoL and coping self-efficacy perceptions before and up to 3 months after treatment completion.

Methods

Study Participants and Time-points

Nineteen individuals with HNC intending to undergo treatment with chemoradiotherapy (CRT) at the Masonic Cancer Clinic and Radiation Oncology Clinic at the University of Minnesota Medical Center, Fairview were included in this study. Quality of life and self-efficacy measures were administered during the following three time-points: **Time 1 (T1)**, within 7 days prior to starting the CRT; **Time 2 (T2)**, 1 month after the completion of treatment ± 14 days; and **Time 3 (T3)**, 3 months after treatment completion ± 1 month. Information regarding clinical psychological diagnosis was collected through medical record review. Data were collected over a total of 47 independent visits. Four participants missed one visit and 3 missed two visits. Reasons for absence were changes in the treatment plan for three individuals, death in two cases, and declining to participate in another two cases.

Quality of Life and Coping Self-efficacy Assessment

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ): QLQ -C30 and -H&N35

The EORTC QLQ-C30 (version 3.0) consists of one global health status (global QoL) scale and 5 multi-item functional scales that measure physical, role, emotional, cognitive, and social functioning. Three multi-item symptom scales measure fatigue, nausea and vomiting, and pain, and six single-item symptom

scales measure dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties (Appendix D).

Using the standard scoring procedures outlined by the EORTC Quality of Life Group,[179] each scale and single-item was scored from 0 - 100. Higher scores in the global QoL and functional scales imply higher levels of global QoL or functioning; but higher scores in the symptom scales (or single items) indicate higher levels (or worsening) of symptoms.[180]

The EORTC QLQ-C30 was supplemented with the head and neck cancer specific module, QLQ-H&N35[180] in order to assess disease- and treatment-related symptoms common among individuals with HNC. Previously, QLQ-H&N35 has been used among HNC individuals varying in their disease stages and/or treatment modalities.[9,33,181–183] The QLQ-H&N35 module comprises a total of 35 questions incorporating 7 multi-item scales that assess pain, swallowing, sense of taste and smell, speech, social eating, social contact, and sexual function; and 11 single-items that assess other symptoms (see Appendix D).

Since the QLQ-H&N35 questionnaire does not include items that assess chewing-related problems, the following three questions were added to the module:[33] 1) How much difficulty did you experience while eating solid food (like meat/hard bread)? 2) How much difficulty did you experience while eating dry food (like cookies)? 3) How much difficulty did you experience while eating soft food (like soft bread)?

The QLQ-H&N35 items and scales were scored from 0 - 100, and higher scores indicated worsening symptoms.[179,180] The chewing-related symptom scale was also assessed using the EORTC guidelines.[179] The EORTC QLQ-C30 in conjunction with QLQ-H&N35 have been shown to be reliable and valid measures for assessing QoL among individuals with HNC from various countries.[180] As expected, most participants in our study were able to complete the EORTC questionnaires between 10 and 15 minutes.[180]

Cancer Behavior Inventory-Brief Version (CBI-B)

Self-efficacy for coping with cancer was measured using the Cancer Behavior Inventory-Brief Version (CBI-B), a 12-item unidimensional instrument (See Appendix D).[39,40] Specifically, the CBI-B assesses the following areas: 1) participant's beliefs about maintaining independence and a positive attitude; 2) belief in their ability to participate in their medical care; 3) skills important for coping and stress management; and 4) capacity to manage their emotions in difficult situations.[38]

Items are rated on a 9-point scale ranging from 1 (not at all confident) to 9 (totally confident), and the self-efficacy score is calculated as the sum of all 12 items.[38] The CBI-B has been noted to have high internal consistency and concurrent validity among individuals with breast, prostate, colon, and lung cancer.[39,40] Most individuals in our study took about 2 - 5 minutes to complete the CBI-B measure.

Malnutrition and Functional Status Assessment

Malnutrition was assessed using the features of the Scored Patient-Generated Subjective Global Assessment (PG-SGA),[160] and based on their overall subjective ranking for nutritional and functional status, individuals were rated as being well nourished (SGA-A) or malnourished (SGA-B or SGA-C). Additionally, a total numerical PG-SGA score was also calculated; higher scores reflect poor nutritional status and a greater risk for malnutrition.[161,184]

Hand grip strength was used to objectively assess changes in the functional status. Measurements were taken in both hands using a Grip-D dynamometer (Takei Scientific Instruments Co. Ltd., Japan). The dominant hand was tested first, and three successive measurements were taken for each hand.[185] The time between the trials was about 15 seconds, and an average measurement for both hands was used for analysis.

Statistical Analysis

The data were analyzed using the SAS software, Version 9.4 (Copyright © 2013 SAS Institute Inc., Cary, NC, USA). Descriptive statistics were used to calculate frequencies, means and standard deviation. One-way repeated measures ANOVA was performed to assess changes in mean EORTC QLQ-C30, QLQ-H&N35, and self-efficacy scores over time. A post-hoc analysis with Bonferroni's adjustment was done for multiple pairwise comparisons. Independent samples t-test assessed differences in mean EORTC QLQ-C30, QLQ-H&N35, and self-efficacy scores between malnourished and well-nourished

individuals. Guidelines from Osoba and colleagues[186] were also used to determine whether the differences in the mean EORTC QLQ-C30 scores for malnourished and well-nourished individuals were clinically relevant. Accordingly, a difference of 5 -10 points represented little change, 10 - 20 points indicated a moderate change, and > 20 points indicated a large change in the difference.[186,187] Multiple regression analysis was conducted to test the effect of PG-SGA rating, hand grip strength, and age as predictors on the global QoL score (dependent variable). Pearson's correlation was used to examine the association between variables. Significance level was set at $P \leq 0.05$. Figures were constructed using the GraphPad Prism version 6.07 for Windows, GraphPad Software, La Jolla California USA.

Results

Participants' Clinical Psychological Diagnoses

Thirty-two percent were clinically diagnosed with depression or depressive mood disorder, and another 32% with anxiety or anxiety disorder (Table 4-1). Adjustment disorder (21%), altered mental status (11%), insomnia (11%), and grief (5%) were other common psychological diagnoses among our participants.

Table 4-1: Clinical psychological diagnoses among participants (n = 19).†

	n	%
Depression (or Depressive mood disorder)	6	32
Anxiety (or Anxiety disorder)	6	32
Adjustment disorder	4	21
Altered mental status	2	11
Insomnia	2	11
Grief	1	5

†Participants with multiple psychological diagnosis are included in this count.

Longitudinal Changes in Quality of Life and Self-Efficacy Scores

Physical functioning was significantly lower immediately before starting treatment (T1) compared to 1 month post-treatment (T2) (83 ± 26 vs. 86 ± 13, P = 0.007) (Table 4-2). Compared to T1, significantly greater problems with chewing, swallowing, sticky saliva, speech, and social eating, and losses in taste and smell sensations were reported at T2 (Table 4-3, Figure 4-1). When compared to T1, significantly more issues with dry mouth was reported at T2 (P = 0.007) and T3 (P = 0.003) (Table 4-3). Although the mean self-efficacy score decreased from T1 to T2 (101 ± 20 vs 95 ± 27), this change was not significant.

Quality of Life and Self-efficacy in Relation to Malnutrition and Functional Status Assessment

Individuals who were categorized as malnourished per the PG-SGA had significantly lower global QoL score than those who were well-nourished (65 ± 15 vs. 80 ± 19, P = 0.016) (Table 4-4). Cognitive functioning scores were significantly higher among well-nourished individuals than those who were malnourished (98 ± 6 vs. 83 ± 18, P = 0.038). The differences in the mean global QoL and cognitive functioning scores between malnourished and well-nourished participants was 15 points, indicating moderate clinical relevance.

In the EORTC QLQ-C30, malnourished individuals scored significantly higher in the fatigue, pain, and appetite loss symptom scales/item than those who were well-nourished (P < 0.05) (Table 4-4, Figure 4-2). The differences in

the mean fatigue, pain, and appetite loss scores between the malnourished and well-nourished participants was > 20 points, indicating a larger clinical relevance.

For the QLQ-H&N35, when compared to the well-nourished individuals, malnourished participants scored significantly higher in the swallowing, coughing, dry mouth, sticky saliva, and speech problem related scales and items ($P \leq 0.05$) (Table 4-5, Figure 4-3). Malnourished participants had more troubles with chewing and social eating, felt more ill, and reported less enjoyment and/or interest in sex than those who were well-nourished ($P < 0.05$). The use of pain killers, feeding tube, and nutritional supplements was also reportedly higher among malnourished individuals (Table 4-5, Figure 4-3).

The self-efficacy scores as measured by the CBI-B were not different between malnourished and well-nourished individuals (98 ± 21 vs. 105 ± 26, $P = 0.436$).

A significant correlation was noted between the global QoL and the PG-SGA score ($r = -0.37$, $P = 0.012$) but not between the global QoL and the self-efficacy scores ($r = 0.25$, $P = 0.087$). The correlation between the self-efficacy score and the PG-SGA score also did not reach significance ($r= -0.21$, $P = 0.171$). The physical functioning score was correlated with the hand grip strength ($r = 0.62$, $P < 0.0001$) and with the five-times-sit-to-stand test ($r = -0.56$, $P = 0.0002$).

Multiple regression analysis indicated that the PG-SGA rating, hand grip strength, and age were significant predictors of the global QoL score (Table 4-6).

The overall model was also significant (F value = 20.47, P < 0.0001), and 60% of the variance in global QoL score could be predicted from the PG-SGA rating, hand grip strength, and age.

Table 4-2: Changes in the EORTC QLQ-C30[¥] and coping self-efficacy scores across time.*

	Time 1 (n = 19)	Time 2 (n = 15)	Time 3 (n = 13)	P-value[†]
Global Quality of Life	66 ± 17	69 ± 15	65 ± 16	0.725
Functional Scales				
Physical functioning	83 ± 26	86 ± 13	83 ± 21	**0.005[a]**
Role Functioning	66 ± 34	72 ± 26	65 ± 25	0.374
Emotional functioning	79 ± 15	80 ± 12	75 ± 14	0.582
Cognitive functioning	87 ± 16	86 ± 18	82 ± 20	0.133
Social functioning	68 ± 20	73 ± 22	64 ± 21	0.477
Symptom Scales/items				
Fatigue	35 ± 26	40 ± 13	38 ± 20	0.606
Nausea and vomiting	6 ± 13	16 ± 25	14 ± 16	0.170
Pain	32 ± 28	23 ± 24	21 ± 24	0.360
Dyspnea	11 ± 22	13 ± 17	21 ± 26	0.067
Insomnia	33 ± 22	29 ± 25	26 ± 20	0.494
Appetite loss	33 ± 29	47 ± 28	46 ± 29	0.293
Constipation	16 ± 23	20 ± 17	15 ± 17	0.312
Diarrhea	7 ± 18	11 ± 16	10 ± 16	0.534
Financial difficulties	28 ± 28	20 ± 17	21 ± 22	0.402
Coping Self-efficacy	101 ± 20	95 ± 27	100 ± 15	0.746

¥ Higher scores for global quality of life (QoL) and functional scales implies higher levels of global QOL or functioning; but higher scores in the symptom scales (or single items) indicate higher levels (or worsening) of symptoms.

* Values are means ± standard deviation.

†Analyzed by one-way repeated measures ANOVA.

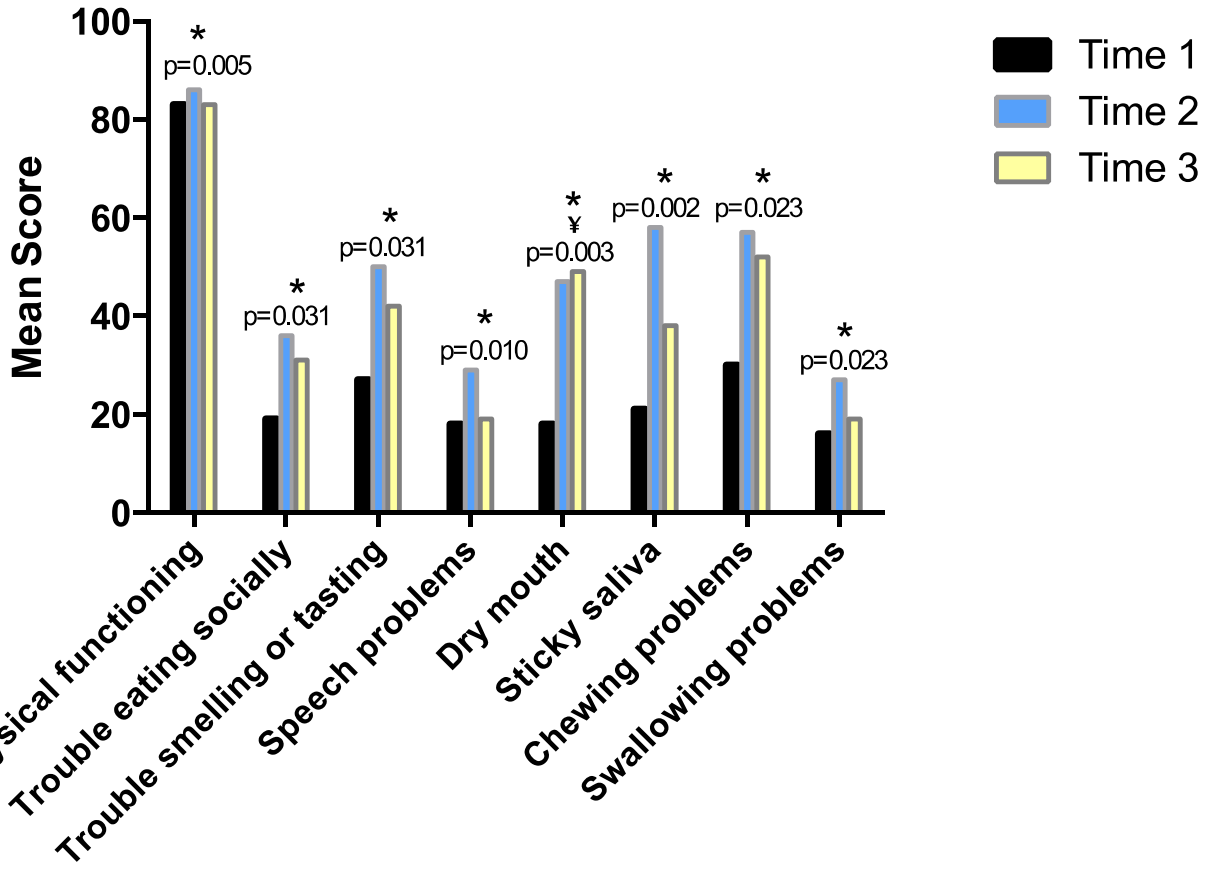
[a] Per the Bonferroni post-hoc test, pairwise comparison significant between Time 1 and Time 2 (P = 0.007 (adjusted)).

Table 4-3: Changes in the QLQ-H&N35 scores* across time.

	Time 1 (n = 19)	Time 2 (n = 15)	Time 3 (n = 13)	P-value†
Pain	25 ± 19	31 ± 17	24 ± 25	0.434
Swallowing problems	16 ± 18	27 ± 27	19 ± 18	**0.023**[a]
Trouble smelling or tasting	27 ± 35	50 ± 28	42 ± 22	**0.031**[a]
Speech problems	18 ± 23	29 ± 27	19 ± 25	**0.010**[a]
Trouble eating socially	19 ± 23	36 ± 25	31 ± 28	**0.031**[a]
Chewing problems¥	30 ± 33	57 ± 27	52 ± 26	**0.023**[a]
Trouble with social contact	9 ± 9	18 ± 22	14 ± 13	0.088
Sex interest and/or enjoyment	22 ± 29	31 ± 33	28 ± 28	0.600
Teeth problems	14 ± 28	5 ± 13	13 ± 29	0.303
Trouble opening mouth wide	21 ± 34	22 ± 27	13 ± 17	0.775
Dry mouth	18 ± 23	47 ± 21	49 ± 22	**0.003**[a,b]
Sticky saliva	21 ± 34	58 ± 29	38 ± 23	**0.002**[a]
Coughing	30 ± 19	40 ± 29	33 ± 27	0.652
Felt ill	14 ± 20	22 ± 21	23 ± 25	0.374
Pain killers	74 ± 45	80 ± 41	62 ± 51	0.695
Nutritional supplements	42 ± 51	73 ± 46	69 ± 48	0.108
Feeding tube	37 ± 50	73 ± 46	38 ± 51	0.063
Weight loss	58 ± 51	33 ± 49	46 ± 52	0.285
Weight gain	0	20 ± 41	23 ± 44	0.070

* Values are means ± standard deviation.
¥ Scale assessing problems with chewing is not included in the QLQ-H&N35.
†Analyzed by one-way repeated measures ANOVA.
[a,b] Per the Bonferroni post-hoc test, pairwise comparisons (adjusted P values):
[a] $P < 0.05$ between T1 and T2.
[b] $P = 0.003$ between T1 and T3.

Figure 4-1: Longitudinal changes in the physical functioning and disease- and treatment-related symptoms.



* Pairwise comparison significant between Time 1 and Time 2
¥ Pairwise comparison significant between Time 1 and Time 3

Table 4-4: EORTC QLQ-C30[¥] and coping self-efficacy scores* for individuals categorized as malnourished (PG-SGA B or C) versus well-nourished (PG-SGA A).

	Malnourished (n = 40)	Well-nourished (n = 7)	P-value[†]
Global Quality of Life	65 ± 15	80 ± 19	**0.016**
Functional Scales			
Physical functioning	83 ± 20	87 ± 27	0.688
Role Functioning	66 ± 29	79 ± 28	0.281
Emotional functioning	77 ± 13	83 ± 19	0.288
Cognitive functioning	83 ± 18	98 ± 6	**0.038**
Social functioning	67 ± 21	76 ± 19	0.286
Symptom Scales/items			
Fatigue	41 ± 19	19 ± 21	**0.008**
Nausea and vomiting	13 ± 19	0	0.077
Pain	29 ± 26	7 ± 13	**0.035**
Dyspnea	14 ± 21	14 ± 26	0.989
Insomnia	31 ± 22	24 ± 25	0.447
Appetite loss	47 ± 27	10 ± 16	**0.001**
Constipation	18 ± 20	14 ± 18	0.692
Diarrhea	11 ± 18	0	0.112
Financial difficulties	25 ± 24	14 ± 18	0.259
Coping Self-efficacy	98 ± 21	105 ± 26	0.436

[¥] Higher scores for global quality of life (QoL) and functional scales implies higher levels of global QOL or functioning; but higher scores in the symptom scales (or single items) indicate higher levels (or worsening) of symptoms.
*Values are means ± standard deviation.
[†]Analyzed by independent samples t-test.

Figure 4-2: A comparison between the mean EORTC QLQ-C30 scores between well-nourished and malnourished individuals.

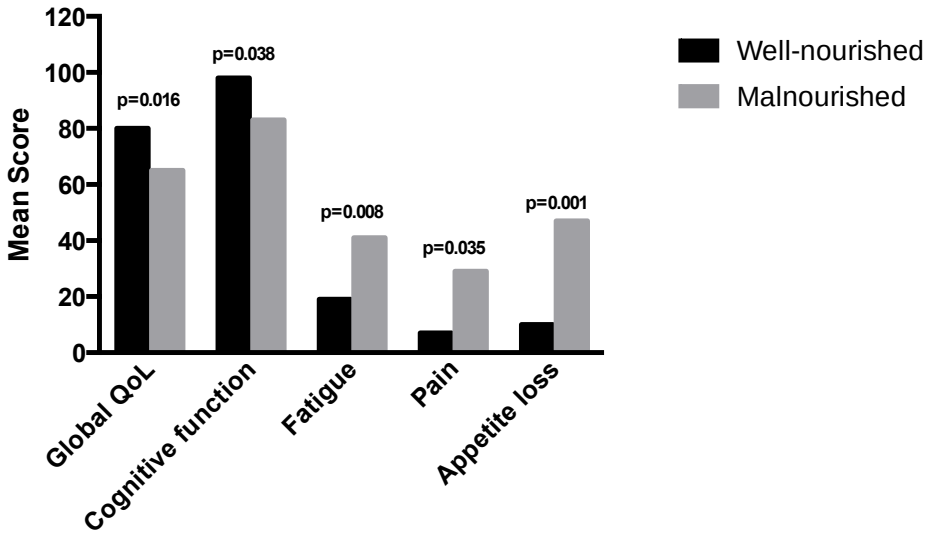
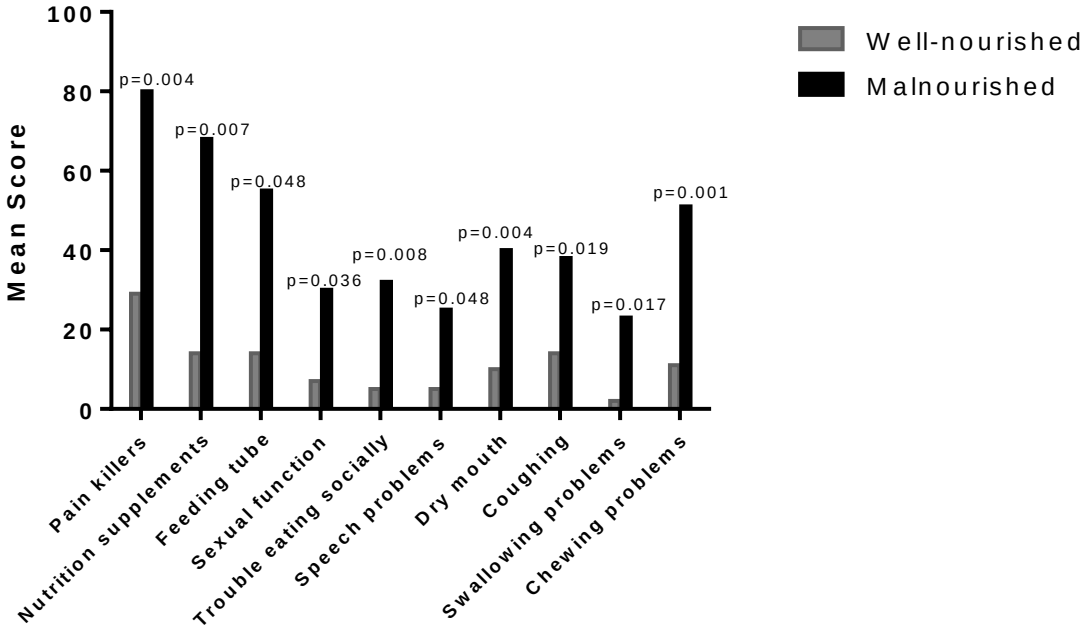


Figure 4-3: A comparison between the mean QLQ-H&N35 scores* between well- nourished and malnourished individuals.



*Scale assessing problems with chewing is not included in the QLQ-H&N35.

Table 4-5: EORTC QLQ-H&N35 scores* for individuals categorized as malnourished (PG-SGA B or C) versus well-nourished (PG-SGA A).

	Malnourished (n=40)	Well-nourished (n=7)	P-value†
Pain	28 ± 21	18 ± 12	0.221
Swallowing	23 ± 22	2 ± 4	**0.017**
Senses problems	40 ± 29	31 ± 41	0.481
Speech problems	25 ± 26	5 ± 9	**0.048**
Trouble with social eating	32 ± 26	5 ± 8	**0.008**
Chewing problems¥	51 ± 28	11 ± 21	**0.001**
Trouble with social contact	15 ± 16	6 ± 6	0.168
Sex interest and/or enjoyment	30 ± 27	7 ± 13	**0.036**
Teeth problems	12 ± 26	5 ± 8	0.464
Trouble opening mouth wide	18 ± 26	24 ± 37	0.633
Dry mouth	40 ± 25	10 ± 16	**0.004**
Sticky saliva	44 ± 29	0	**0.0002**
Coughing	38 ± 24	14 ± 18	**0.019**
Felt ill	23 ± 22	0	**0.001**
Pain killers	80 ± 41	29 ± 49	**0.004**
Nutritional supplements	68 ± 47	14 ± 38	**0.007**
Feeding tube	55 ± 50	14 ± 38	**0.048**
Weight loss	53 ± 51	14 ± 38	0.064
Weight gain	13 ± 34	14 ± 38	0.899

*Values are means ± standard deviation.
†Analyzed by independent samples t-test.
¥Scale assessing problems with chewing is not included in the QLQ-H&N35.

Table 4-6: Significant predictors for global quality of life (or global function) as identified by the multiple regression analysis.

	Beta-coefficients*	95% Confidence Intervals		P-value
Global Quality of Life				
PG-SGA rating†	-0.44	-29.98	-9.54	**0.0003**
Hand grip strength	0.39	0.41	1.51	**0.001**
Age	-0.45	-1.66	-0.53	**0.0003**

* Standardized regression coefficients
†1 = Malnourished (PG-SGA B or C), 0 = Well-nourished (PG-SGA A).

Discussion

This study is novel because it investigated longitudinal quality of life (QoL) and self-efficacy perceptions in the context of malnutrition among individuals with advanced head and neck cancers in an outpatient setting. We found that participants who were categorized as malnourished by the PG-SGA scored significantly lower in the global QoL and cognitive functioning scales than those who were well-nourished, and the mean difference was 15 points, which also suggests clinical relevance based on the guidelines provided by Osoba and colleagues.[186] Limited research has been conducted using the PG-SGA as a diagnostic criteria for malnutrition and investigating its relationship to QoL symptoms in the HNC setting. In a heterogeneous sample of ambulatory patients receiving radiation to the head, neck, abdominal, or rectal area, Isenring et al[184] found a significant correlation between the PG-SGA score and the EORTC global QoL score at baseline and 4 weeks after treatment ($P < 0.001$). Likewise, we reported a significant association between the global Qol score and the PG-SGA score, suggesting a relationship between an impaired QoL and malnutrition.

We also found that malnourished participants scored significantly higher in the disease- and treatment-related symptom scales and items compared to those who were well-nourished. Specific symptoms that impact oral intake such as dry mouth, sticky saliva, coughing, and problems with chewing and swallowing had significantly higher scores for malnourished individuals. A > 20 point difference in the mean appetite loss, pain, and fatigue symptom scales/item was noted

between the malnourished and well-nourished participants; this difference was not only statistically significant but also of higher clinical relevance as per the Osoba et al[186] guidelines.

Other QoL symptoms such as trouble with social eating, feeling more ill, speech problems, and sexual issues were reportedly higher among malnourished participants. Previous research among individuals with HNC has yielded mixed findings while comparing the EORTC scales in relation to malnutrition. In one cross-sectional analysis in Sweden, when compared with the well-nourished participants, those who were malnourished [identified by the weight index (WI) < 0.80, WI= (actual weight/reference weight)] scored poorly in the global QoL and physical and role functioning scales, but these differences were not statistically significant.[188] In the Netherlands, Jager-Wittenaar and colleagues[33] reported that malnourished oral and oropharyngeal cancer participants [identified by ≥ 10% weight loss in 6 months or ≥ 5% loss in 1 month] scored significantly lower in the EORTC physical functioning and fatigue scales when compared with the well-nourished participants, but no other EORTC scale yielded significant differences between the two groups. In a retrospective observation involving individuals with colorectal cancer in the US, malnourished individuals [identified by the subjective global assessment (SGA)[189]] scored worse in the EORTC symptom and functional scales than those who were well-nourished.[187] One reason for such mixed findings while comparing malnourished and well-nourished individuals could be that the choice of nutrition assessment method used for the

identification of malnutrition could possibly yield differences in the EORTC scales' results.

To our knowledge, research investigating QoL outcomes as identified by the PG-SGA assessment tool has not been conducted exclusively among individuals with head and neck cancers. However, reports among individuals with gastric cancers[190] have shown that PG-SGA-identified malnourished individuals score significantly higher in the EORTC symptom scales and lower in the functional scales when compared with the PG-SGA categorized well-nourished individuals. Our study confirms these findings in the advanced HNC patient population, although additional research is certainly needed for additional insights on how QoL outcomes relate to malnutrition.

Longitudinal Changes in the Quality of Life

Interestingly, our participants reported lower physical functioning before treatment initiation than one month after treatment. One reason for low physical function before treatment could be that 68% of our participants had undergone surgical resection immediately before treatment and therefore were not physically active during this period. We found that compared to pre-treatment symptoms, individuals scored significantly higher with regards to problems with chewing, swallowing, sticky saliva, sense of taste and smell, speech, and social eating one month after the completion of treatment. Furthermore, dry mouth was reported as a significant problem even 3 months after the completion of treatment. An observation in Sweden[177] reported that while significant deterioration in the HNC

treatment and disease-related symptoms was observed 3 months after the treatment completion, problems with teeth, sense of taste and smell, and dry mouth persisted even 3 years after the diagnosis. These results suggest that the treatment and disease induced symptoms that negatively affect an individual's quality of life could possibly last years after the completion of treatment, and therefore may require routine follow-up through clinical assessment.

Quality of Life and Functional Status Outcomes

Our results indicated that individuals with higher EORTC physical functioning score had better hand grip strength and took less time to complete the five-times-sit-to-stand test, indicating a strong association between the subjective and objective markers of functional status. It has also been suggested that changes in muscle strength affect functional status and quality of life outcomes.[18] In one observation involving participants with gastric cancers, those categorized as malnourished per the reduced hand grip strength values [grip strength below 85% of the age and sex-adjusted reference] had significantly lower EORTC global QoL scores than well-nourished participants.[190] In our study, besides age, hand grip strength and malnutrition identified by the PG-SGA tool were significant predictors of global QoL score, suggesting that impaired functional status and malnutrition are associated with poor quality of life outcomes. Similar findings have been reported in a mixed sample of individuals with gastrointestinal, head and neck, urinary tract, and gynecologic cancers,

where malnutrition identified by the SGA[189] emerged as an independent determinant for EORTC physical function status.[21]

Self-Efficacy and Its Relation with Malnutrition

In regards to the CBI-B measure, no significant changes in the coping self-efficacy scores were noted over the course of this study. Because statistical significance was not reached, we cannot say for certain that malnourished individuals experienced lower coping self-efficacy compared to those who were well-nourished. Similarly, neither the association between the self-efficacy score and the PG-SGA score ($r = -0.21$) nor the self-efficacy score and global QoL score ($r = 0.25$) reached statistical significance; however, it is interesting to note that they were in the anticipated direction. This suggests that individuals who experienced lower coping self-efficacy could have had poor nutritional status and reported impaired QoL but additional research is warranted to further explore these relationships.

In the past, psychosocial oncology research has not investigated the relationship between self-efficacy and nutritional outcomes. In another area, studies involving heterogeneous cancer sites including HNC have reported that depression is a potential risk factor for lower self-efficacy.[36] Although we did not assess depression in the current study, one-third of our sample was clinically diagnosed with depression or depressive mood disorders; future research could investigate whether depression relates to coping self-efficacy among individuals with HNC. Another investigation found that pre-treatment patient education

regarding upcoming treatment-related expectations, side-effects, and social support may reduce anxiety and increase self-efficacy among individuals receiving radiation therapy.[191] Therefore, while some investigators suggest that oncology patients with higher self-efficacy experience less anxiety and depressive symptoms and cope better with their disease and prognosis,[36,38,39] as we found, the relation between self-efficacy perceptions and other health outcomes including nutritional status still remains unclear and needs additional investigation.

Conclusion and Future Directions

So far, very limited research has been conducted in the US that has explored the association between malnutrition and QoL outcomes among the vulnerable HNC population. Our results suggest that individuals with advanced HNC who were identified as malnourished using the PG-SGA tool have poor quality of life symptoms compared to those who were categorized as well-nourished. Specifically, malnourished participants scored significantly lower in the global QoL and cognitive function scales and significantly higher in the disease- and treatment-related symptom scales and items. Malnutrition and impaired functional status as measured by the hand grip strength were significant predictors of global QoL. No significant differences in the self-efficacy scores were noted over time or between malnourished and well-nourished individuals, although additional research is certainly needed to explore how self-efficacy attitudes relate to nutritional outcomes.

Our results also indicate a need for regular nutritional and psychosocial assessments during various phases of the HNC treatment. About 60% of our participants were diagnosed with depression, anxiety, or related disorders, and malnourished individuals experienced fatigue, speech issues, difficulties with social eating, and also reported impaired cognitive function. Therefore, early detection of malnutrition could help with patient-specific intervention strategies aimed to improve disease- and treatment-related symptoms and health-related QoL. It has also been found that many HNC survivors feel hesitant to discuss their psychosocial well-being with their physicians.[192] Therefore, future clinicians would need to be proactive in assessing individuals' nutritional and psychosocial status through cancer-specific tools such as the PG-SGA and the EORTC questionnaires. Regular assessment would also help with the identification of individuals who may benefit from psychosocial support and rehabilitative services that an oncology treatment center has to offer.

CHAPTER 5: OVERALL CONCLUSIONS AND FUTURE DIRECTIONS

In conclusion, the results from this dissertation research indicate that individuals with HNC are malnourished even before treatment initiation. Using the Consensus criteria, 67% of our participants were malnourished before treatment; and the prevalence of malnutrition consistently increased during treatment and the post-treatment period. When compared to our chosen reference standard PG-SGA, the Consensus criteria identified malnutrition in individuals with HNC with overall good sensitivity (95%) and specificity (43%). Additionally, it was found that the BIA parameters PA and IR might be useful in identifying individuals who are at increased risk for malnutrition and/or impaired functional status. However, given that this was a small homogenous sample of HNC, additional research is certainly warranted to investigate the broader clinical utility of BIA in detecting malnutrition using the new Consensus framework in other clinical populations. Research is also needed to validate the Consensus malnutrition diagnostic framework in hospital and ambulatory care settings.

From a psychosocial perspective, we found that compared with well-nourished participants, malnourished individuals scored significantly lower in the global QoL and cognitive function scales and significantly higher in the disease- and treatment-related symptom scales and items. No significant differences in the self-efficacy scores were noted over time or between malnourished and well-nourished individuals, although additional research is certainly needed for insights on how self-efficacy and quality of life relates to nutritional outcomes.

Taken together, these results suggest a need for regular nutritional and psychosocial assessments during various phases of HNC treatment. In the future, training dietitians to identify the malnutrition diagnostic characteristics and working collaboratively with the physician team for standardization of malnutrition coding practices in medical records are some of the important steps for timely diagnosis of malnutrition. Importantly, if clinicians are trained to assess malnutrition diagnostic markers before individuals with cancer undergo aggressive treatments, nutritional interventions could be initiated at an earlier time and loss in weight and/or lean tissue can be prevented. That said, research is also needed on how early nutrition interventions impact malnutrition in head and neck cancer.

Early detection of malnutrition could also help with the implementation of patient-specific intervention strategies aimed to improve overall health-related QoL. Similarly, timely psychosocial screening can help identify individuals who would benefit from rehabilitative programs and similar support services that are offered at an oncology treatment center. Therefore, future research should focus with the aim of providing evidence-based care in the oncology population and incorporate comprehensive nutritional and psychosocial outcome measures at various time-points during the course of treatment.

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APPENDICES

Appendix A: Consent Form

University of Minnesota, Twin Cities
Department of Food Science and Nutrition

Study Title: Nutritional Status among Individuals with Head and Neck Cancer.

You are invited to participate in a research study that will assess your nutritional status and well-being. You were selected as a possible participant because you have been diagnosed with head and neck cancer, and will be undergoing chemotherapy and radiation therapy. We ask that you read this form and ask any questions that you may have before agreeing to participate in the study.

This study is being conducted by Associate Professor Carrie P. Earthman, PhD, RD, LD and Graduate Research Assistant Urvashi Mulasi, MS, RD of the Department of Food Science and Nutrition, in collaboration with Naomi Fujioka, MD; Gautam Jha, MD; Manish Patel, DO; and Venkatesh Rudrapatna, MD, MPH; head and neck physicians at the Masonic Cancer Clinic and Radiation Oncology Clinic at the University of Minnesota Medical Center, Fairview.

STUDY PURPOSE
The purpose of this study is to examine your nutritional status, including body weight and composition (i.e., muscle and fat), and dietary intake, during and up to 3 months after your treatment. We are also interested in knowing how your diagnosis of cancer and treatment might affect your well-being and the way you feel about your social interactions.

GENERAL OVERVIEW
Once you have provided your informed consent to participate in the study, the study staff will orient you with the general information regarding the study procedures.

We anticipate to enroll about 40 individuals with head and neck cancer. We will collect data during the following five times in your treatment: 1) Within 7 days prior to starting the treatment; 2)About 3.5 weeks (± 1 week) into treatment; 3) During the last week of your treatment; 4) One month (± 14 days) after you complete your treatment; and 5) Three months (± 1 month) after treatment. For the first three times, data will be collected during your routine chemotherapy appointments. For the remaining two times (after treatment is completed), you may be asked to go to the Delaware Clinical Research Unit instead of going to the Masonic Cancer Clinic.

During each visit, it might take up to 2 hours of your time in order for us to collect measurements and for you to answer study questions. If you wish so, you can take a break from the study and participate when you feel you are ready. Let the study staff know if you feel you need a break from study procedures.

Your decision to participate in this study is not necessary for your treatment. Your participation will not affect your standard treatment and care in any manner.

STUDY PROCEDURES

Medical History
During the course of the study, your medical records will be reviewed and you may be asked questions so that we can learn about your medical and health history. Your medical records will also be reviewed for your demographic information including age, education level, ethnicity/race, income, occupation, and number of people in your household.

Anthropometry (body measurements) and Nutritional Assessment
You will be asked to remove your outer clothing, so that you are dressed only in underwear, socks, and a hospital gown during measurements. Your height and body weight will be measured at your first visit, and your body weight will be measured again at each subsequent visit. Height will be measured using a standard stadiometer and body weight will be measured with a stand-on scale. Using a skinfold caliper, we will measure your upper arm skinfold thickness (called triceps skinfold), and your overall arm circumference will also be recorded using a measuring tape (called mid-upper-arm circumference).

At each of the five study time points, a trained staff will perform a nutritional assessment on you, where you will be asked questions about changes in your body weight, dietary intake, appetite, and if you have nausea, vomiting, diarrhea, or constipation. In addition, a brief physical examination will be conducted by the study staff in order to assess any changes in muscle and fat tissue in your arms, shoulders, and legs.

Body Composition by Bioimpedance Spectroscopy
Your muscle and fat tissue, and water in the body will be measured by bioelectrical impedance at each of the five times. Four sticky electrodes will be placed on your right hand and foot after cleaning with alcohol, and then a small bioelectrical current that you will not be able to feel will be sent through wires attached to the electrodes. Several measurements will be made up to 30 minutes after you lie down.

Dietary Intake
At each of the five times, you will be asked what you ate and drank on the previous day; this is called a 24-hour dietary recall. During the dietary recall interview, we will ask you additional questions to estimate the portion sizes, and to know more about the types, brands, and cooking methods of the items consumed.

In the beginning of the study, you will be taught how to measure what you eat and drink. The study staff will also educate you on keeping 3-day food records, which will involve writing down everything that you eat and drink, including dietary supplements, in a food record on 3 assigned days during the week before your next scheduled treatment. One of those 3 days will be the day before your treatment, and you will bring your food record with you on the day of your appointment. The study staff will review your 3-day food records with you and we may ask you additional questions about what you ate and drank. During the week before your next scheduled appointment, the study staff will call to remind you to record your dietary intake and to bring the food record with you at your next appointment.

Functional Status
At each of the five study time points, your muscle strength will be measured using a hand grip dynamometer. Your physical function will also be checked using the five-times-sit-to-stand-test, where you will be asked to rise and sit from an armless chair five times in a row.

Quality of Life and Self-efficacy
You will be asked some questions about your health, symptoms or problems, emotions, sexual life, and social functioning once before you start your treatment, and twice after the completion of treatment.

The 'Quality of life' questionnaire will have general questions about your health, symptoms, mood and emotions, and social life. A specific subset of questions will ask whether you experience any pain, weakness, nausea, vomiting, diarrhea, constipation, lack of appetite, or difficulties with chewing and swallowing. The 'Self-efficacy' (i.e. coping with cancer) questionnaire will ask you about your confidence in maintaining an independent and positive attitude, and emotional management during stressful situations.

RISKS OF STUDY PARTICIPATION
This study has minimal risks, which are described as follows.

You may feel that some of the questions that you are asked about your cancer related symptoms, personal history, emotions, and social life may be stressful or upsetting to answer. You will be asked questions regarding your personal health habits, gastrointestinal symptoms (nausea, vomiting, diarrhea, constipation), appetite, and food intake. You will also be asked questions on how you cope with cancer and beliefs about your personal life satisfaction including sexual activity. Being asked such questions may be considered possible invasion of privacy. If you do not wish to answer a question, you may skip it and go to the next question, or you may stop immediately. If you become upset, please let the study staff know.

Another risk may be loss of confidentiality. Your health record for the study may be reviewed by departments at the University, with appropriate regulatory oversight. Study data will be encrypted according to the current University policy for protection of confidentiality. Every effort will be made to keep your study records confidential but we cannot guarantee it.

Specifically, your medical records will be reviewed for information, including your diagnosis, current and past medical history, laboratory data, medications, smoking and exercise history, alcohol consumption, type of treatment, response to treatment, and ongoing medical notes. Your medical records will also be reviewed for your demographic information including age, education level, ethnicity/race, income, occupation, and number of people in your household. Review of such information may be considered possible invasion of privacy.

BENEFITS OF STUDY PARTICIPATION
There are no benefits to you for participating in this study. This study may not help you, but we hope that the information from this study will help increase awareness among

researchers about how nutritional status impacts care outcomes among individuals with head and neck cancer. We also hope that the results from this study will help improve nutritional management and care strategies for individuals with head and neck cancer.

STUDY COSTS AND PARTICIPANT COMPENSATION
You will not be charged for any of the procedures or materials used in this study. We do not have any compensation for your inconvenience and time spent participating in this study.

RESEARCH RELATED INJURY
In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment, and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to you or your insurance company. If you think that you have suffered a research related injury, let the study staff know right away.

CONFIDENTIALITY
The records of this study will be kept private. All records will be coded and kept in a locked file. In any publications or presentations, we will not include any information that will make it possible to identify you as a subject. Your record for the study may, however, be reviewed by departments at the University, with appropriate regulatory oversight. If you have not been seen before at the University of Minnesota Medical Center, Fairview, a permanent medical record will be created at the hospital under your name. Your study data will be added to your medical record. While confidentiality cannot be guaranteed, it will be protected to the fullest extent possible. Study data will be encrypted according to the current University policy for protection of confidentiality.

PROTECTED HEALTH INFORMATION (PHI)
Your PHI created or received for the purposes of this study is protected under the federal regulation known as HIPAA. Refer to the attached HIPAA authorization for details concerning the use of this information.

VOLUNTARY NATURE OF THE STUDY
Participation in this study is voluntary. Your decision whether or not to participate in this study will not affect your current or future relations with the University of Minnesota, Masonic Cancer Clinic, or the Radiation Oncology Clinic. If you decide to participate, you are free to withdraw at any time without affecting these relationships. Refusal to participate will involve no penalty or decrease in any benefits to which you may be otherwise entitled.

CONTACT INFORMATION AND QUESTIONS
The researchers conducting this study are Associate Professor Carrie P. Earthman, PhD, RD, LD and Graduate Research Assistant Urvashi Mulasi, MS, RD of the Department of Food Science and Nutrition, in collaboration with Naomi Fujioka, MD; Gautam Jha, MD; Manish Patel, DO; and Venkatesh Rudrapatna, MD, MPH; head and neck physicians at the Masonic Cancer Clinic and Radiation Oncology Clinic at the University of Minnesota Medical Center, Fairview.

You may ask any questions you have now, or if you have questions later, you are encouraged to contact Dr. Earthman at 612-624-9278. If you have any questions or

concerns regarding the study and would like to talk to someone other than the researcher(s), you are encouraged to contact the Fairview Research Helpline at telephone number 612-672-7692 or toll free at 866-508-6961. You may also contact this office in writing or in person at *Fairview Research Administration, 2433 Energy Park Drive, St. Paul, MN 55108.*

You will be given a copy of this form to keep for your records.

STATEMENT OF CONSENT
I have read the information provided in this consent form. All of my questions have been answered to my satisfaction. The study's purpose, procedures, and possible risks and benefits have been explained to me. I have been told that my participation is voluntary and if I wish so, I am free to withdraw any time.

By signing below, I consent to participate in the study.

Signature of Subject_____

Date_____

Signature of Person Obtaining Consent_____

Date_____

Appendix B: Case Report Forms

University of Minnesota, Twin Cities
Department of Food Science and Nutrition

Nutritional Status among Individuals with Head and Neck Cancer:

Demographic, Medical, and Anthropometric Data Visit 1

Participant initial and ID :_____ Visit Date (mm/dd/yyyy): _____

Measurement time-point (Circle): T1 T2 T3 T4 T5

Researcher Initial _____

Part I. DEMOGRAPHIC INFORMATION
Age :_____
Gender: Male ☐ Female ☐

Part II. MEDICAL DIAGNOSIS
Tumor localization: Oral Cavity ☐ Oropharynx ☐ Hypopharynx ☐ Maxillary Sinuses ☐ Larynx ☐ (Specify Site: Supraglottis ☐ Glottis ☐ Subglottis ☐) Other: _____
TNM Staging: _____ Stage 0 ☐ Stage I ☐ Stage II ☐ Stage III ☐ Stage IVA ☐ Stage IVB ☐ Stage IVC ☐ Other (specify) _____

Part III. ANTHROPOMETRIC DATA
Height (cm) _____
Current Weight (0.1 kg) _____ month ago: _____ Weight 3 months ago:_____ Weight 6 months ago:_____ Percent weight loss from current weight (identify the time frame):_____ If malnourished based on weight history, identify whether **Nonsevere (moderate) or Severe**_____

Triceps skinfold thickness (0.1mm) (1)_____ (2)_____
(3)_____

Mid-upper-arm circumference (0.1cm) (1)_____ (2)_____

Hand Grip Strength: Dominant hand (R/L): _____

Right (#1): _____kg
Right (#2): _____kg
Right (#3): _____kg

Mean value of the three trials (R): _____kg

Left (#1): _____kg
Left (#2): _____kg
Left (#3): _____kg

Mean value of the three trials (L): _____kg

Five-times-sit-to-stand-test:
Time after landing the fifth stand up _____ seconds

Other notes/observation:

_____
_____
_____
_____
_____
_____

University of Minnesota, Twin Cities
Department of Food Science and Nutrition
Nutritional Status among Individuals with Head and Neck Cancer
Demographic, Medical, and Anthropometric Data Visits 2 - 5

Participant initial and ID # :_____ **Visit Date (mm/dd/yyyy):** _____

Measurement time-point (Circle): T2 T3 T4 T5

Researcher Initial _____

ANTHROPOMETRIC DATA
Current Weight (0.1 kg) _____ Weight 1 month ago: _____ Weight 3 months ago:_____ Weight 6 months ago:_____ Percent weight loss from current weight (identify the time frame):_____ If malnourished based on weight history, identify whether **Nonsevere (moderate) or Severe** _____ _____ **Triceps skinfold thickness (0.1mm)** (1)_____ (2)_____ (3)_____
Mid-upper-arm circumference (0.1cm) (1)_____ (2)_____
Hand Grip Strength: Dominant hand (R/L): _____ Right (#1): _____kg Right (#2): _____kg Right (#3): _____kg Mean value of the three trials (R): _____kg Left (#1): _____kg Left (#2): _____kg Left (#3): _____kg Mean value of the three trials (L): _____kg
Five-times-sit-to-stand-test: Time after landing the fifth stand up _____ seconds

Hand Grip Strength

Participant Initials and ID #:: _____ **Date:** _____

Dominant hand (R/L): _____

Measurement (Circle): T1 T2 T3 T4 T5

Instructions:
Don't press the On/C button while the inner grip is being gripped. Release pressure from the grip as soon as the measurement is over. The device starts measurement when a force of 5 kg is reached and judges the measurement is over when the force decreases below 4 kg.

Hold the device so that the grip meter indicator faces outward. Turn the knob to adjust the grip width so that the second joint of the pointing finger makes a right angle.

1. Press the On/C button.
2. **Measurement position:** Sit comfortably with shoulder adducted and forearm neutrally rotated, elbow flexed to 90°. The forearm and wrist should be in neutral position.
3. Test the dominant hand first.
4. **Verbal instructions:** "I want you to hold the handle like this and squeeze as hard as you can." The examiner demonstrates and then gives the dynamometer to the subject. After the subject is positioned appropriately, the examiner says, "Are you ready? Squeeze as hard as you can." (The dynamometer was lightly held around the readout dial by the examiner to prevent inadvertant dropping). As the subject begins to squeeze. say, "Harder! ... Harder! ... Relax."
5. Take three successive measurements for one hand and then the other hand. (The time between trials was should be about 15 seconds, which is the time needed to read and record each score). The mean of the three trials will be used for data analysis.
6. Turn the instrument off when all measurements are completed.

Right (#1): _____kg
Right (#2): _____kg
Right (#3): _____kg

Left (#1): _____kg
Left (#2): _____kg
Left (#3): _____kg

Mean value of the three trials (R): _____kg
Mean value of the three trials (L): _____kg

Researcher Initials and Signature _____

Five-times-sit-to-stand-test

Subject Initials and ID #: _____ Date: _____

Measurement time-point (Circle): T1 T2 T3 T4 T5

Measurement instructions:

1. Use a slightly padded armless chair with a standard seat height between 40-45 cm.
2. Stabilize the chair, preferably against a wall.
3. Have the patient come forward and sit on the chair seat until their feet are flat on the floor and the back is upright against the back rest of the chair.
4. Have the patient fold the upper limbs across the chest and **sit** with the back against the upright back rest of the chair.
5. Instruct the patient to stand up all the way and sit down once without using the upper limbs.
6. If the patient is able to complete the maneuver without the upper limbs or physical assistance, instruct him or her to stand up all the way and sit down landing firmly, as fast as possible, 5 times without using the arms. Guard the patient as necessary.
7. Using a watch, begin timing on the command "go" and cease timing on landing after the fifth stand up. (i.e., record the time from the command "go" (the patient is sitting) until the patient's back touches the backrest of the chair on the fifth repetition)
8. Abort the test and start all over again if the patient fails to stand up all the way or sit down firmly.

Time after landing the fifth stand up _____ seconds

Researcher Initials _____

Body Composition

Subject Initials and ID #: _____ **Date:** _____

Measurement time-point (Circle): T1 T2 T3 T4 T5

WEIGHT without shoes (kg) _____

HEIGHT without shoes (cm) _____

AGE (years) _____

Record everything that the subject has consumed that morning, including food and beverages, water provided with meds, IV meds, etc. leading up to the measurement.

_____
_____
_____
_____
_____
_____
_____

Have subject void bladder just before you ask them to lie down.

1. Electrode Placement:

a. If possible, the **electrodes should be placed on the right side of the body**, but they may have to be placed on the left side due to logistical considerations. Please indicate on which side of the body the electrodes have been placed:

□ LEFT □ RIGHT

Indicate the circumstances that mandate that the electrodes be placed on the left side:_____
_____

*(Note: All subsequent measurements should be made on the **SAME SIDE** of the body as was used for the first measurement)*

b. Distance measured between the electrodes on hand: _____
(Please measure the distance from the top of the wrist electrode to the top of the metacarpal electrode)

Distance measured between the electrodes on foot: _____
(Please measure the distance from the top of the ankle electrode to the top of the metatarsal electrode)

2. Measurements:

a. TIME laid in supine position:_____

Is the patient lying flat? □ YES □ NO
If supine position is not possible, indicate the position when measurement is being taken_____
(Note: If supine position is not possible, head of bed should be elevated to 30 degrees or less)

If NO, please describe the HOB elevation and/or other details on body position:

_____

_____

b. Measurements:

QuadScan Device (Black lead wire is attached to electrode closest to the heart)	MultiScan Device (Black lead wire is attached to electrode closest to the heart)
4-MIN (Test #_____):	5-MINUTE (Test #_____):
9-MIN (Test #_____):	10-MINUTE (Test #_____):

Researcher Initials:

24-Hour Dietary Recall

Name _____

Visit (Circle): T1 T2 T3 T4 T5

Date: _____ Daily Physical Activity Involvement:_____

Age: _____ Height: _____ Weight: _____

TIME	**Foods/Beverages/Supplements Consumed** *(Include method of preparation, brand names, condiments added, & other details)*	Serving Size	LOCATION

TIME	**Foods/Beverages/Supplements Consumed** *(Include method of preparation, brand names, condiments added, & other details)*	Serving Size	LOCATION

University of Minnesota
Department of Food Science and Nutrition
Nutrition Study

Food Intake Record Booklet

Number of days to Record: 3 days before your next scheduled chemotherapy appointment.
Bring this booklet with you on your next chemotherapy appointment.

Name:_____ **Participant ID:** _____

Recording Day/Days:

_____

_____

_____

Bring with you for next visit on: _____

Questions? Call Study Coordinator Urvashi Mulasi at 952-303-2046

Packet developed using materials from the University of Arizona Nutritional Assessment Laboratory, Dept. of Nutritional Sciences, BEST Study

INSTRUCTIONS FOR RECORDING FOODS, BEVERAGES & SUPPLEMENTS

1. Use brand names and include labels whenever possible. Clean labels can be stapled inside this packet or saved in a bag. **For example: ¼ cup Bumble Bee tuna, packed in water.**

2. Remember to list all additions to foods and beverages, such as cream, sugar, butter, jelly, lemon, salad dressing, artificial sweeteners, catsup, etc. Don't forget ingredients added in food preparation and/or at the table, such as soy sauce, oils, other types of fat, and salt.

3. Describe how foods are prepared. **For example: ½ cup frozen broccoli, steamed.**

4. For multi-vitamin and/or mineral supplements, list the brand, name of the supplement and the amount/dosage in the appropriate columns. **For example: Brand 400IU vitamin E.** If possible, please bring all supplements (vitamin/mineral, herbal etc) with you when you come to the clinic.

5. Use measuring cups or spoons whenever possible. **For example: 1 tsp. Sugar; 1 ½ cups Campbell's cream of tomato soup.**

6. For beverages, indicate if you had ice in the beverage and you may use fluid ounces instead of cups. **For example: 12 oz Pepsi, no ice.**

7. For foods that do not fit in a cup or spoon, use dimensions. **For example: 1 corn tortilla, 6 inches across; 1 piece of cheddar cheese 3"x2"x1"; 1 banana nut muffin 2"x1".** There is a ruler printed on the back page of this booklet to help with measuring foods.

8. For whole pieces of fruit or vegetables, you may use small, medium, or large. Check stickers on fruit for size as well. **For example: 1 small Granny Smith apple.**

9. List each food item, and the amount of each item, in mixed dishes. **For example: 1cup leaf lettuces, 2 ¼" tomato slices, two 2" slices cucumber.**

10. For homemade foods, please give us the recipe. When including recipes, be sure to include how much the recipe yields in cups and your serving size. **For example: Total recipe makes eight 1-cup servings. I had 1 cup.**

Date:_____ **Name:**_____

TIME	Food/Drink	Amount	Notes
For example: 8:15 am	*Yoplait yogurt, plain, made from skim-milk.*	*One 8oz container*	*I have included nutrition fact panel from box (stapled to back page)*

FOOD LABELS

Food labels contain a Nutrition Facts panel with product specific information, including serving size, calories, and nutrient information. **Pay attention to the serving size and number of servings per container.** In the sample label, one serving of yogurt is one 6 oz container. If the food came in a container with two servings and you ate the entire amount, you would double the calories and other nutrients. Pay attention to food labels when keeping your food record. Attach clean labels to this page or feel free to save clean labels in a bag.

Sample label for yogurt:

Nutrition Facts	
Serving Size 6 oz (170 g) Servings Per Container 1	
Amount Per Serving	
Calories 110	Calories from Fat 0
	% Daily Value
Total Fat 0g	
Saturated Fat 0g	
Trans Fat 0g	
Cholesterol less than 5mg	
Sodium 90mg	
Potassium 270mg	
Total Carbohydrate 20g	
Dietary Fiber 0g	
Sugars 15g	
Protein 6g	
Vitamin A 15%	• Calcium 20%
Vitamin D 20%	• Phosphorus 15%
Phosphorus 15%	
Percent daily values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your caloric needs.	

Appendix C: Patient Generated Subjective Global Assessment

Scored Patient-Generated Subjective Global Assessment (PG-SGA)

Patient ID Information

History

1. Weight *(See Table 1 Worksheet)*

In summary of my current and recent weight:

I currently weigh about _____ pounds
I am about _____ feet _____ tall

One months ago I weighed about _____ pounds
Six months ago I weighed about _____ pounds

During the past two weeks my weight has:
☐ decreased (1) ☐ not changed (0) ☐ increased (0) ☐

2. Food Intake: As compared to my normal, I would rate my food intake during the past month as:
☐ unchanged (0)
☐ more than usual
☐ less than usual (1)
I am now taking:
☐ *normal food* but less than normal (1)
☐ little solid food (2)
☐ only liquids (3)
☐ only nutritonal supplements (3)
☐ very little of anything (4)
☐ only tube feedings or only nutrition by vein ☐

3. Symptoms: I have had the following problems that have kept me from eating enough during the past two weeks (check all that apply):
☐ no problems eating (0)
☐ no appetite, just did not feel like eating (3)
☐ nausea (1)
☐ constipation (1)
☐ mouth sores (2)
☐ things taste funny or have no taste (1)
☐ problems swallowing (2)
☐ pain; where? (3)_____
☐ other** (1) _____
☐ vomiting (3)
☐ diarrhea (3)
☐ dry mouth (1)
☐ smells bother me (1)
☐ feel full quickly (1)
** Examples: depression, money, or dental problems ☐

4. Activities and Function: Over the past month, I would generally rate my activity as:
☐ normal with no limitations (0)
☐ not my normal self, but able to be up and about with fairly normal activities (1)
☐ not feeling up to most things, but in bed less than half the day (2)
☐ able to do little activity and spend most of the day in bed or chair (3) ☐

Additive Score of the Boxes 1-4 ☐ **A**

The remainder of this form will be complete by your doctor, nurse, or therapist. Thank you.

5. Disease and its relation to nutritional requirements *(See Table 2)*
All relevant diagnoses (specify) _____
Primary disease stage (circle if known or appropriate) I II III IV Other _____
Age _____
Numerical score from Table 2 ☐ **B**

6. Metabolic Demand *(See Table 3 Worksheet)*
☐ no stress ☐ low stress ☐ moderate stress ☐ high stress
Numerical score from Table 3 ☐ **C**

7. Physical *(See Table 4 Worksheet)*
Numerical score from Table 4 ☐ **D**

Global Assessment *(See Table 5 Worksheet)*
☐ Well-nourished or anabolic (SGA-A)
☐ Moderate or suspected malnutrition (SGA-B)
☐ Severely malnourished (SGA-C)

Total numerical score of boxes A+B+C+D ☐
(See triage recommendations below)

Clinician Signature _____ RD RN PA MD DO Other __ Date _____

Nutritional Triage Recommendations: Additive score is used to define specific nutritional interventions including patient & family education, symptom management including pharmacologic intervention, and appropriate nutrient intervention (food, nutritional supplements, enteral, or parenteral triage). First line nutrition intervention includes optimal symptom management.

0-1	No intervention required at this time. Re-assessment on routine and regular basis during treatment.
2-3	Patient & family education by dietitian, nurse, or other clinician with pharmacologic intervention as indicated by symptom survey (Box 3) and laboratory values as appropriate.
4-8	Requires intervention by dietitian, in conjunction with nurse or physician, as indicated by symptoms survey (Box 3).
≥9	Indicates a critical need for improved symptom management and/or nutrient intervention options.

Tables & Worksheets for PG-SGA Scoring

The PG-SGA numerical score is derived by totaling the scores from boxes A-D of the PG-SGA on the reverse side. Boxes 1-4 are designed to be completed by the patient. The points assigned to items in boxes 1-4 are noted parenthetically after each item. The following worksheets are offered as aids for calcuating scores of sections that are not so marked.

Table 1 - Scoring Weight (wt) Loss

Determined by adding points for subacute and acute wt change. **Subacute:** If information is available about weight loss during past 1 month, add the point score to the points for acute wt change. Only include the wt loss over 6 months if the wt from 1 month is unavailable. **Acute:** refers to wt change during past two weeks. Add 1 point to subacute score if patient lost wt; add no points if patient gained or maintained wt during the past two weeks.

Wt loss in 1 month	Points	Wt loss in 6 months
10% or greater	4	20% or greater
5-9.9%	3	10 -19.9%
3-4.9%	2	6 - 9.9%
2-2.9%	1	2 - 5.9%
0-1.9%	0	0 - 1.9%

Points for Box 1 = Subacute + Acute = ☐ **A**

Table 2 - Scoring criteria for disease &/or condition

Score is derived by adding 1 point for each of the conditions listed below that pertain to the patient.

Category	Points
Cancer	1
AIDS	1
Pulmonary or cardiac cachexia	1
Presence of decubitus, open wound, or fistula	1
Presence of trauma	1
Age greater than 65 years	1

Points for Box 2 = ☐ **B**

Table 3 Worksheet. Scoring Metabolic Stress

Score for metabolic stress is determined by a number of variables known to increase protein & calorie needs. The score is additive so that a patient who has a fever of > 102 degrees (3 points) and is on 10 mg of prednisone chronically (2 points) would have an additive score for this section of 5 points.

Stress	none (0)	low (1)	moderate (2)	high (3)
Fever	no fever	>99 and <101	≥101 and <102	≥102
Fever duration	no fever	<72 hrs	72 hrs	> 72 hrs
Steroids	no steroids	low dose (<10mg prednisone equivalents/day)	moderate dose (≥10 and <30mg prednisone equivalents/day)	high dose steroids (≥30mg prednisone equivalents/day)

Points for Table 3 = ☐ **C**

Table 4 Worksheet - Physical Examination

Physical exam includes a subjective evaluation of 3 aspects of body composition: fat, muscle, & fluid status. Since this is subjective, each aspect of the exam is rated for degree of deficit. Definition of categories: 0 = no deficit, 1+ = mild deficit, 2+ = moderate deficit, 3+ = severe deficit. Degree of muscle deficit takes precedence over fat deficit. Rating of deficit in these categories are *not* additive but a used to clinically assess the degree of deficit (or presence of excess fluid).

Fat Stores:				
orbital fat pads	0	1+	2+	3+
triceps skin fold	0	1+	2+	3+
fat overlying lower ribs	0	1+	2+	3+
Global fat deficit rating	**0**	**1+**	**2+**	**3+**

Muscle Status:				
temples (temporalis muscle)	0	1+	2+	3+
clavicles (pectoralis & deltoids)	0	1+	2+	3+
shoulders (deltoids)	0	1+	2+	3+
interosseous muscles	0	1+	2+	3+
scapula (latissimus dorsi, trapezius, deltoids)	0	1+	2+	3+
thigh (quadriceps)	0	1+	2+	3+
calf (gastrocnemius)	0	1+	2+	3+
Global muscle status rating	**0**	**1+**	**2+**	**3+**

Fluid Status:				
ankle edema	0	1+	2+	3+
sacral edema	0	1+	2+	3+
ascites	0	1+	2+	3+
Global fluid status rating	**0**	**1+**	**2+**	**3+**

Point score for the physical exam is determined by the overall subjective rating of total body deficit; again muscle deficit takes precedence over fat loss or fluid excess.

No deficit	score = 0 points
Mild deficit	score = 1 point
Moderate deficit	score = 2 points
Severe deficit	score = 3 points

Points for Worksheet 4 = ☐ **D**

Table 5 Worksheet PG-SGA Global Assessment Categories

	Stage A	Stage B	Stage C
Category	Well-nourished	Moderately malnourished or suspected malnutrition	Severely malnourished
Weight	No wt loss **or** Recent non-fluid wt gain	~5% wt loss within 1 month (or 10% in 6 months) No wt stabilization or wt gain (i.e., continued wt loss)	a. > 5% loss in 1 month (or >10% loss in 6 months) b. No wt stabilization or wt gain (i.e., continued wt loss)
Nutrient Intake	No deficit **or** Significant recent improvement	Definite decrease in intake	Severe deficit in intake
Nutrition Impact Symptoms	None **or** Significant recent improvement allowing adequate intake	Presence of nutrition impact symptoms (Box 3 of PG-SGA)	Presence of nutrition impact symptoms (Box 3 of PG-SGA)
Functioning	No deficit **or** Significant recent improvement	Moderate functional deficit **or** Recent deterioration	Severe functional deficit **or** recent significant deterioration
Physical Exam	No deficit **or** Chronic deficit but with recent clinical improvement	Evidence of mild to moderate loss of SQ fat &/or muscle mass &/or muscle tone on palpation	Obvious signs of malnutrition (e.g., severe loss of SQ tissues, possible edema)

Global PG-SGA rating (A, B, or C) = ☐

Appendix D: Quality of Life and Self-Efficacy Questionnaires

Visit (Circle): T1 T2 T3 **Participant ID_____**

University of Minnesota, Twin Cities
Department of Food Science and Nutrition
Part A. Quality of Life

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
DURING THE PAST WEEK				
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4

DURING THE PAST WEEK	Not at All	A Little	Quite a Bit	Very Much
16. Have you had diarrhea?	1	2	3	4
17. Were you tired?	1	2	3	4
18. Did pain interfere with your daily activities?	1	2	3	4
19. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
20. Did you feel tense?	1	2	3	4
21. Did you worry?	1	2	3	4
22. Did you feel irritable?	1	2	3	4
23. Did you feel depressed?	1	2	3	4
24. Have you had difficulty remembering things?	1	2	3	4
25. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
27. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4
For the following questions please circle the number between 1 and 7 that best applies to you				
28. How would you rate your overall health during the past week?				
1 2 3 4 5 6 7				
Very poor **Excellent**				
29. How would you rate your overall quality of life during the past week?				
1 2 3 4 5 6 7				
Very poor **Excellent**				

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

DURING THE PAST WEEK	Not at All	A Little	Quite a Bit	Very Much
30. Have you had pain in your mouth?	1	2	3	4
31. Have you had pain in your jaw?	1	2	3	4
32. Have you had soreness in your mouth?	1	2	3	4
33. Have you had a painful throat?	1	2	3	4
34. How much difficulty did you experience while eating solid food (like meat/hard bread)?	1	2	3	4
35. How much difficulty did you experience while eating dry food (like cookies)?	1	2	3	4
36. How much difficulty did you experience while eating soft food (like soft bread)?	1	2	3	4
37. Have you had problems swallowing liquids?	1	2	3	4
38. Have you had problems swallowing pureed food?	1	2	3	4
39. Have you had problems swallowing solid food?	1	2	3	4
40. Have you choked when swallowing?	1	2	3	4
41. Have you had problems with your teeth?	1	2	3	4
42. Have you had problems opening your mouth wide?	1	2	3	4
43. Have you had a dry mouth?	1	2	3	4
44. Have you had sticky saliva?	1	2	3	4
45. Have you had problems with your sense of smell?	1	2	3	4
46. Have you had problems with your sense of taste?	1	2	3	4
47. Have you coughed?	1	2	3	4
48. Have you been hoarse?	1	2	3	4

DURING THE PAST WEEK	Not at All	A Little	Quite a Bit	Very Much
49. Have you felt ill?	1	2	3	4
50. Have you had trouble eating?	1	2	3	4
51. Have you had trouble eating in front of your family?	1	2	3	4
52. Have you had trouble eating in front of other people?	1	2	3	4
53. Have you had trouble enjoying your meals?	1	2	3	4
54. Have you had trouble talking to other people?	1	2	3	4
55. Have you had trouble talking on the telephone?	1	2	3	4
56. Have you had trouble having social contact with your family?	1	2	3	4
57. Have you had trouble having social contact with friends?	1	2	3	4
58. Have you had trouble going out in public?	1	2	3	4
59. Have you had trouble having physical contact with family or friends?	1	2	3	4
60. Have you felt less interest in sex?	1	2	3	4
61. Have you felt less sexual enjoyment?	1	2	3	4
DURING THE PAST WEEK	**No**	**Yes**		
62. Have you used pain-killers?	1	2		
63. Have you taken any nutritional supplements (excluding vitamins)?	1	2		
64. Have you used a feeding tube?	1	2		
65. Have you lost weight?	1	2		
66. Have you gained weight?	1	2		

Part B. Cancer Behavior Inventory-Brief (CBI-B)

This questionnaire contains many things that a person might do when receiving treatment for cancer. We are interested in your judgment of how confident you are that you can accomplish those things. Make sure your ratings accurately reflect your confidence whether or not you have done it in the past. So, your ratings reflect your confidence that you can do these things now (or in the near future). Please read each numbered item. Then rate that item on how confident you are that you can accomplish that behavior. Circle a number on the scale. If you circle a "1" you would be stating that you are not at all confident that you can accomplish that behavior. If you circle a "9" you would be stating that you are totally confident that you can accomplish that behavior. Numbers in the middle of the scale indicate that you are moderately confident that you can accomplish that behavior.Please rate all items. If you are not sure about an item please rate it as best you can.

	NOT AT ALL CONFIDENT			MODERATELY CONFIDENT				TOTALLY CONFIDENT	
1. Maintaining independence	1	2	3	4	5	6	7	8	9
2. Maintaining a positive attitude	1	2	3	4	5	6	7	8	9
3. Maintaining a sense of humor	1	2	3	4	5	6	7	8	9
4. Expressing feelings about cancer	1	2	3	4	5	6	7	8	9
5. Putting things out of my mind at times	1	2	3	4	5	6	7	8	9
6. Maintaining activities (work, home, hobbies, social)	1	2	3	4	5	6	7	8	9
7. Trying to be calm throughout treatments and not allowing scary thoughts to upset me	1	2	3	4	5	6	7	8	9
8. Actively participating in treatment decisions	1	2	3	4	5	6	7	8	9
9. Asking physicians questions	1	2	3	4	5	6	7	8	9
10. Seeking social support	1	2	3	4	5	6	7	8	9
11. Sharing my worries or concerns with others	1	2	3	4	5	6	7	8	9
12. Managing nausea and vomiting (whether or not I have had these problems in the past)	1	2	3	4	5	6	7	8	9
13. Coping with physical challenges	1	2	3	4	5	6	7	8	9
14. Trying to be calm while waiting at least one hour for my appointment	1	2	3	4	5	6	7	8	9