To investigate the nutritional status, including body composition, of oncology patients attending an outpatient clinic at Groote Schuur hospital: a cross-sectional study

by

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DECLARATION

I, …*Megan Blacker*…, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Abstract

Background

There is an increase in cancer prevalence globally with an increase in cancer mortality in South Africa. Malnutrition, cancer cachexia and sarcopenia are conditions commonly experienced by people with cancer. Not only is there a deterioration of nutritional status, but these conditions are also known to have negative clinical and patient outcomes that include a decreased quality of life and functional status, increased hospital length of stay, increased treatment toxicity, reduced efficacy of anticancer treatments and an association with depression.

Even though there is a greater understanding of the aetiology of cancer cachexia over recent decades, there has not been a global adoption of a definition and a framework for identification of cancer cachexia. Therefore, there is no standardisation of research to compare results related to prevalence and multimodal interventions which hampers implementation of awareness and identification of and treatment for cancer cachexia. The Global Leadership Initiative on Malnutrition (GLIM) identifies and classifies malnutrition across different health care settings. Recently suggested cancer guidelines identified cancer cachexia using amended GLIM diagnostic criteria. With sarcopenia identification, there have been American, Asian and European formulated guidelines with variation in the diagnostic criteria used. This makes it challenging for other countries not represented to create awareness and identification of sarcopenia in different healthcare settings.

Gold standard methods in body composition, namely computer tomography (CT) and magnetic resonance imaging (MRI), and reference standard methods, namely dual energy X-ray absorptiometry (DEXA) have highlighted the common phenotypic component of reduced muscle mass in malnutrition, cancer cachexia and sarcopenia, with a plethora of reference populations used and cutoff points determined for different representations of muscle mass. This variety in research has added to the challenges of identifying reduced muscle mass, particularly in resource limited healthcare settings that do not have access to expensive CT, MRI and DEXA scans and relevant reference populations. Therefore, there is a need to identify alternative methods to identify reduced muscle mass earlier in the cancer journey that need to be cheap, accessible, easy to use within the South African health setting. These alternative methods will be helpful in the identification of malnutrition, sarcopenia and cancer cachexia.

Aims

The first aim was to investigate body composition, with particular focus on muscle mass, using DEXA as the reference standard in this sample of cancer patients, in relation to nutritional status indicators and alternative muscle mass markers.

The second aim was to investigate malnutrition in cancer outpatients according to Global Leadership Initiative on Malnutrition (GLIM) using different approaches, including technical (DEXA) and clinical approaches to determine muscle mass.

The third aim was to investigate sarcopenia in cancer outpatients according to the newest diagnostic guidelines from the European Working Group on Sarcopenia in Older People (EWGSOP) using muscle mass determined from DEXA (reference standard) and alternative muscle mass markers.

The fourth aim was to investigate cancer cachexia using different diagnostic frameworks and the associations with nutritional status indicators in cancer outpatients.

Method

The study followed a quantitative, cross-sectional design where data were collected over 2 days and twenty-eight eligible cancer patients were recruited through consecutive sampling from colorectal, head and neck, ear, nose and throat oncology outpatient clinics at Groote Schuur Hospital (GSH). A two-phase questionnaire was developed for the purposes of this study where sociodemographic, clinical and cancer related data, biochemistry, physical activity, dietetics related data, a twenty-four-hour recall and semi-quantitative food frequency questionnaire information were collected. On the second data collection day, handgrip strength (HGS), nutrition risk screening-2002 (NRS-2002), patient generated subjective global assessment (PG-SGA), a second a twenty-four-hour recall, alternative muscle mass markers [mid upper arm circumference (MUAC), calf circumference (CC), corrected arm muscle area (cAMA), estimated appendicular skeletal muscle (est ASM), global physical examination (GPE)] and DEXA measurements were collected.

Results

There is a high prevalence of reduced muscle mass (82.1%) as determined by our reference standard, DEXA, expressed as ASM. From the six alternative muscle mass markers, calf circumference performed best across the different statistical tests in comparison to the reference standard, DEXA. Calf circumference demonstrated fair agreement related to Cohen's kappa, overall fair for sensitivity (73.9%) / specificity (80%) and a percentage agreement of 78.6%. Our results suggest that calf circumference may be used to screen cancer patients to determine those without RMM as the specificity was 80% i.e., only 20% of participants without RMM will be incorrectly categorised.

None of our nutritional status indicators can be used as proxies for detecting reduced muscle mass. BMI, scored NRS-2002 and scored PG-SGA were statistically significant in participants identified with reduced muscle mass.

Our study confirmed that malnutrition is prevalent in this cancer population ranging from 75.0% to 92.9% depending on the muscle mass assessment method and Global Leadership Initiative on Malnutrition (GLIM) approach used. Out of the six alternative muscle mass markers and not having muscle mass phenotype, calf circumference demonstrated good agreement related to Cohen's kappa, overall fair for sensitivity (73.9%) / specificity (80%) and a percentage agreement of 92.9% suggesting that it may be used as an alternative muscle mass phenotype in the GLIM diagnostic criterium for reduced muscle mass.

We found a prevalence of sarcopenia from 7.4% to 18.5%, depending on the muscle mass method used Of the five alternative muscle mass markers, calf circumference agreed perfectly and had 100% sensitivity and specificity.

We found that the diagnosis and classification of cancer cachexia varied depending on the diagnostic models used. We used two diagnostic models to identify pre-cachexia and found a range of 17.9% to 28.6%. We used four diagnostic models to identify cancer cachexia and found a range from 45.8% to 82.1%. None of the three diagnostic cancer cachexia frameworks performed well when compared to the most recent cancer cachexia framework adapted from GLIM. In addition, none of our nutritional status indicators performed well across all the different tests when compared to the recent cancer cachexia framework. Therefore, suggesting that our routine use of nutritional status indicators within practice, may not be sufficiently sensitive, specific and agree with our reference framework to diagnose cancer cachexia. Only handgrip strength and albumin are significantly different in the cancer cachexia group.

In conclusion, despite our limitation regarding small sample size, calf circumference may be a possible alternative muscle mass marker to screen for reduced muscle mass, may be used as a proxy in the GLIM diagnostic criteria and for sarcopenia diagnosis. As cancer cachexia is recognized as a multifactorial and multi-organ syndrome, all diagnostic components may need to be present, therefore simplistic commonly used clinical and practical approaches may not be adequate to detect cancer cachexia early in the cancer patient's journey.

ACKNOWLEDGEMENTS

Desmond Tutu (amongst others) once wisely said that “There is only one way to eat an elephant: a bite at a time.”

Throughout this research journey, I have encountered remarkable people, both strangers, family, colleagues, friends that have had a role to play with each step that I took. Thank you for the invaluable part that you played, both intentionally and unintentionally, whether it was only the one step, a few steps or the entire journey.

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ABBREVIATIONS

ADP	Air displacement plethysmograph
AgRP	Agouti gene-related protein (AgRP)
Alb	Albumin
ALM	Appendicular lean muscle
ALMT	Appendicular lean muscle tissue
aPG-SGA	Abridged patient generated subjective global assessment
ASMI	Appendicular skeletal muscle mass index
ASM	Appendicular skeletal mass
AT	Adipose tissue
AUC	Area under the curve
BC	Body composition
BD	Body density
BF	Body fat
BIA	Bio-electrical impedance analysis
BM	Body mass
BMC	Bone mineral content
BMI	Body mass index
BMN	Bone mineral
BV	Body volume
BW	Body weight
CART	Cocaine and amphetamine regulated transcript
CASCO	Cachexia score
CCx	Cancer cachexia
cAMA	Corrected arm muscle area

CC	Calf circumference
CHF	Congestive heart failure
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CSA	Cross sectional area
CT	Computerised tomography
DAEK	Dietary Assessment and Education Kit
DEXA	Dual energy X-ray absorptiometry
DNA	Deoxy ribose nucleic acid
Dsp	Dessert spoon
ECOG	Eastern Cooperative Oncology Group
EL	Essential lipid
ENT	Ear, nose and throat
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
ESPEN	European Society for Clinical Nutrition and Metabolism
EWGSOP	European Working Group on Sarcopenia in Older People
FAACT	Functional assessment of anorexia / cachexia therapy
FFDM	Fat free dry mass
FFM	Fat free mass
FFMI	Fat free mass index
FFQ	Food frequency questionnaire
FM	Fat mass
GI	Gastrointestinal
GLIM	Global Leadership Initiative for Malnutrition

GLY	Glycogen
GPAQ	Global physical assessment questionnaire
GPE	Global physical examination
GSH	Groote Schuur Hospital
GTT	Glucose tolerance test
Hb	Haemoglobin
HGS	Handgrip strength
HR	Hazard ratio
HUAC	Hounsfield unites average calculation
ICC	intraclass coefficient
IL-1	Interleukin-1
IL-6	Interleukn-6
ISAK	International Society for the advancement of Kinathropometry
ISCD	International Society for Clinical Densitometry
K	Kappa Cohen’s test
KPS	Karnofsky performance status
L3	Lumbar vertebrae three
LLR	Leukocyte / lymphocyte ratio
LM	Lean mass
LMQ	Low muscle quantity
LT	Lean tissue
OS	Overall survival
MAMC	Mid arm muscle circumference
MC	Mineral content
MET	Metabolic equivalents
MetT	Metabolic tissue

mGPS	Modified Glascow Prognostic score
MM	Muscle mass
MRI	Magnetic resonance imaging
MV	Muscle volume
NA	Not applicable
NAA	Neutron activation analysis
NCCTG	North Central Cancer Treatment Group
NEL	Non-essential lipid
NFPE	Nutrition focused physical examination
NHANES	National Health and Nutrition Examination Survey
NLR	Neutrophil / lymphocyte ratio
NPγ	Neuropeptide γ
NRS-2002	Nutritional risk screening 2002
PFS	Progression free survival
PG-SGA	Patient generated subjective global assessment
PMI	Psoas muscle index
POMC	Proopiomelanocortin
PTHrP	Parathyroid hormone related protein
QLQ	Quality of life question
QOL	Quality of life
RMM	Reduced muscle mass
ROS	Reactive oxygen species
SAFBDG	South African food based dietary guidelines
SAFQT	South African food quantity tables
SARC-F	Sarcopenia questionnaire
Se	Sensitivity

SFT	Skinfold thickness
SGA	Subjective Global Assessment
SIR	Systemic inflammatory response
SNAQ	Simplified Nutrition Assessment Questionnaire
SM	Soft tissue mineral
SMI	Skeletal muscle index
SMM	Skeletal muscle mass
Spe	Specificity
SSISA	Sports Science Institute of South Africa
Tbsp	Tablespoon
TBW	Total body water
TG	Triglycerides
TNF	Tumour necrosis factor
Tsp	Teaspoon
UCP1	Uncoupling protein 1
US	Ultrasound
UWW	Underwater weighing
WB	Whole body
WCC	White cell count
WHO	World Health Organisation
WL	Weight loss

CHAPTER 1: INTRODUCTION

1.1 Introduction

The Global Burden of Disease reported 23.6 million cases and 10 million deaths related to cancer in 2019 (Global Burden of Disease Collaborative Network, 2020). Statistics SA (2023) reported that in 2018, cancer related mortality was about 10%, fourth highest after circulatory conditions, infectious diseases and external causes. Over a ten-year period, all-cause mortality has decreased but cancer related mortality has increased by 29.3% (Statistics SA, 2023a). Oesophageal, gastric and colorectal cancers are ranked high amongst cancers that cause the greatest number of deaths in some Sub-Saharan African countries (Ogundipe et al., 2018). The Western and Northern Cape provinces have the highest cancer mortality rates with oesophageal cancer accounting for the most cancer related deaths in the Eastern Cape (Made et al., 2017).

Malnutrition, cachexia and sarcopenia are commonly experienced by cancer patients and negatively impact nutritional status and prognosis through decreased quality of life and functional status, increased hospital length of stay, increased treatment toxicity, reduced efficacy of anticancer treatments and associated with depression (Bossi et al., 2021; Dewys et al., 1980; Leandro-Merhi & Aquino, 2017; LeBlanc et al., 2015; Nipp et al., 2017; Pan et al., 2013; Prado et al., 2016; Pressoir et al., 2010). The prevalence of malnutrition in cancer patients varies from 10% to 60% globally (Inagaki et al., 1974; Pan et al., 2013; Pressoir et al., 2010) and is dependent on age, cancer type and cancer staging (Wie et al., 2010). Sixty to eighty percent of patients with advanced disease experience cancer cachexia (von Haehling & Anker, 2012) and 10% of these patients die from it (Inagaki et al., 1974). Sarcopenia prevalence in cancer patients varies between 20% to 70% dependent on tumour type and definition used (Ryan et al., 2016). In addition, sarcopenia is found in 38.6% of cancer patients even before receiving treatment (Pamoukdjian et al., 2018).

It is well established that unintentional weight loss of more than 5% predicts reduced survival (Dewys et al., 1980). Even smaller losses of weight of 2.4%, regardless of performance status, tumour location and staging, independently predicts mortality (Martin et al., 2015). Unintentional weight loss is a common component of malnutrition, cachexia and sarcopenia. With the high prevalence of these three similar but distinct conditions, there are many barriers to identification and treatment: lack of awareness of health care professionals of the changes in nutritional status of cancer patients (Caccialanza et al., 2016; Caccialanza et al., 2020; Farkas et al., 2013; Muscaritoli et al., 2019; Muscaritoli et al., 2016); adoption of global standardisation of definitions; the lack of standardised diagnostic criteria of these conditions (Ryan et al., 2016); lack of sufficient, robust evidence that nutritional intervention in cancer patients has impact on clinical and patient outcomes (Arends et al., 2023; Muscaritoli et al., 2019).

There has been a movement to unify the understanding of malnutrition and nutrition related care processes (Cederholm et al., 2017; Schneider & Correia, 2020). Malnutrition i.e., undernutrition can be defined as “a state resulting from lack of intake or uptake of nutrition that leads to altered body

composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease" (Sobotka, 2012). Recently, different types of malnutrition have been defined namely starvation-related malnutrition, chronic disease-related malnutrition (with or without inflammation) and acute / injury related-malnutrition (Cederholm & Jensen, 2017; White et al., 2012) and diagnostic criteria proposed by the Global Leadership Initiative on Malnutrition (GLIM) (Cederholm et al., 2018). Specific cancer clinical guidelines for diagnosis and treatment (Arends et al., 2021; Muscaritoli et al., 2019; Muscaritoli et al., 2021) have been updated and published. These guidelines include the recommendation of early screening to detect nutritionally at-risk patients followed by assessment of nutritional status as early detection may allow timely multi-modal treatment for improved impact on clinical outcomes (Avancini et al., 2021; Muscaritoli et al., 2021). It is proposed that the metabolic nutrition care pathway runs alongside cancer treatment pathway (Muscaritoli et al., 2019).

As with malnutrition, cancer cachexia identification has been lacking due to disparities in the definition and diagnosis of cancer cachexia with no globally accepted treatment guidelines for cancer cachexia (Sadeghi et al., 2018). Fearon et al., (2011) describes cancer cachexia as "a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass, with or without loss of fat mass, that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment" (Fearon et al., 2011). This commonly cited definition in the literature reflects the multifactorial nature of cancer cachexia that includes cytokine / neuroendocrine driven changes in food intake, energy expenditure, adipocyte lipolysis and hepatic / skeletal muscle protein synthesis and degradation (Fearon et al., 2012). Because of the complexity of cancer cachexia, nutritional support cannot be the sole mode of treatment (Arends et al., 2017a; Sadeghi et al., 2018). Other multi-modal treatments include pharmacotherapy, exercise (Arends et al., 2017a) and psychological support to improve management of cancer patients (Avancini et al., 2021). In addition, early detection of nutritional issues may allow timely multi-modal treatment for positive impact on clinical outcomes to allow nutritional support to have the greatest benefit (Aapro et al., 2014; Martin et al., 2015). However, further research is needed to determine effective nutritional and other supportive interventions in the cancer population (Paccagnella et al., 2010).

The definition by Fearon et al., (2011) has been widely adopted. However, the diagnostic criteria are not easily implemented in clinical practice and cancer cachexia stages not always distinguishable (Blum et al., 2014). Therefore, more recent research has attempted to define, diagnose and classify cancer cachexia (Arends et al., 2021; Argiles et al., 2017; Blum et al., 2014; Martin et al., 2021; Martin et al., 2015; Vigano et al., 2017; Wiegert et al., 2021; Zhou et al., 2018). As there is no global adoption of specific diagnostic cancer cachexia criteria, currently comparing studies, standardising treatment and diagnosing cancer cachexia in clinical practice is challenging (Avancini et al., 2021; Caccialanza et al., 2016; Muscaritoli et al., 2021)

Cancer guidelines recommend early screening to detect nutritionally at-risk patients followed by assessment of nutritional status (Arends et al., 2021; Mueller et al., 2011; Muscaritoli et al., 2021). Nutritional status is “an individual’s health condition as it is influenced by nutrient intake and utilisation of nutrients” as defined by Todhunter et al. (1970). Nutritional status assessment is a systematic, rigorous approach to identify nutritional issues so that nutritional intervention can be implemented and monitored to maintain or improve an individuals’ health condition. (Mueller et al., 2011). There is no gold standard assessment tool to determine nutritional status (Du et al., 2017; Silva et al., 2019; Teigen et al., 2017). Different guidelines recommend different components being assessed, e.g., dietary intake, medical history, physical activity, biochemical and clinical parameters, socio-economic background (Cederholm & Jensen, 2017) and body composition (Arends et al., 2017b; Arends et al., 2021; Thompson et al., 2017; White et al., 2012). There are a range of tools that are validated and reliable that may assist with the assessment of nutritional status (Thoresen et al., 2013) namely, patient generated subjective global assessment (PG-SGA), subjective global assessment (SGA) and mini nutritional assessment (MNA). To determine who receives a nutritional assessment, screening tools have been developed and validated to identify patients that are at risk of malnutrition e.g., Nutrition Risk Screening 2002 (NRS-2002), malnutrition universal screening tool (MUST) and malnutrition screening tool (MST) (Arends et al., 2021; Castillo-Martínez et al., 2018; Cederholm & Jensen, 2017; Isenring & Elia, 2015). As no validated screening and assessment tools exist for cancer cachexia, nutrition risk screening and assessment tools traditionally used for malnutrition are used in practice.

In the last decade, there has been a focus on encompassing body composition, particularly muscle mass as a component of nutritional assessment as it impacts patient outcomes. This includes impact on quality of life, physical activity levels, survival, post-surgical complications, effectiveness of anti-cancer treatment and mortality (Ferrão et al., 2020; Jeffery et al., 2019; Malietzis et al., 2016; Ryan et al., 2019). Referrals for nutritional intervention based on weight loss alone, is impractical and counter-productive (Arends et al., 2017). This is even more relevant with increasing overweight and obesity trends as clinical observation of weight loss is not always evident even when there is loss of skeletal muscle mass (Martin et al., 2013; Pressoir et al., 2010). Changes in or loss of muscle mass and functional status need to be identified earlier before patients develop cancer cachexia, (Bruggeman et al., 2016), even before detectable changes in weight (Guinan et al., 2018). Furthermore, reduced muscle mass is one of the diagnostic criteria for malnutrition and sarcopenia (Arends et al., 2021; Cederholm et al., 2019; Cruz-Jentoft et al., 2019; Fearon et al., 2011; Muscaritoli et al., 2021) and can be used to predict prognosis (Cespedes Feliciano & Chen, 2018; Martin et al., 2013).

Muscle mass assessment in the clinical setting is not routinely implemented (Teigen et al., 2017). Unfortunately, with some cancer research, loss of muscle mass has been incorrectly referred to as sarcopenia (Fearon et al., 2011; Ni Bhuachalla et al., 2018; Srdic et al., 2016). However, sarcopenia is

recognized as a separate clinical nutrition concept to malnutrition (Cederholm et al., 2017). In addition, recent guidelines have recommended the assessment of sarcopenia after diagnosing malnutrition, both in general and cancer specific patients (Arends et al., 2017; Compher et al., 2022).

Sarcopenia has been defined as “a muscle disease (muscle failure) rooted in adverse muscle changes that accrue across a lifetime.” Muscle weakness is identified as the main characteristic of sarcopenia, either detected using handgrip strength or the chair stand test. Confirmation of sarcopenia diagnosis is then based on skeletal muscle mass or skeletal muscle quality (Cruz-Jentoft et al., 2019). Sarcopenia has been categorised as primary sarcopenia if it occurs due to ageing process or secondary sarcopenia if it occurs due to pathogenic processes (Cederholm et al., 2017).

There exists a variety of methods to quantify and interpret and categorise reduced muscle mass (Kuriyan, 2018; Smith et al., 2023; Teigen et al., 2017; Watanabe et al., 2022). Technical methods like computer tomography (CT) are precise and highly accurate, yet together with dual-energy X-ray absorptiometry (DEXA) are expensive and need technical expertise (Bazzocchi et al., 2016; Smith-Ryan et al., 2017). Furthermore, technical methods are not readily available to be used in all clinical practice settings (Ceniccola et al., 2019). Therefore, alternative markers of muscle mass have been suggested when there is no access to technical body composition methods together with no comparable reference population and cut-off points to categorise low muscle mass (Cederholm et al., 2018; Compher et al., 2022; Cruz-Jentoft et al., 2019). Alternative markers of muscle mass are therefore important in the South African context where health care access is not equitable for all its population.

1.2 Motivation for study

There is scant nutrition related research of South African cancer patients despite the increase in prevalence and mortality. With the recent publications of guidelines related to the diagnosis of malnutrition by using GLIM diagnostic criteria (Cederholm et al., 2019), sarcopenia (Cruz-Jentoft et al., 2019) and cancer cachexia (Arends et al., 2021), this research is timeous.

With associated negative outcomes of reduced muscle mass, malnutrition, sarcopenia and cancer cachexia, early identification of any of these conditions leads to early multi-modal intervention, with nutritional support as the cornerstone. There has been research on increased muscle mass linked to positive clinical outcomes (Lønbro et al., 2013; Paccagnella et al., 2010). With maintained or increased muscle mass in cancer patients, there may be impact on treatment tolerance and efficacy (Davis & Panikkar, 2019; Hilmi et al., 2019) but more randomsied controlled trials are needed (Davis & Panikkar, 2019; Hilmi et al., 2019; Peterson & Mozer, 2017). Some evidence exists of individualised nutritional intervention to meet requirements of protein and energy intake of identified cancer patients at nutritional risk provides positive outcomes on mortality (Bargetzi et al., 2021; De Waele et al., 2015).

To the best of our knowledge, we did not find research within South Africa that described the nutritional status of cancer outpatients that included body composition using the reference standard dual energy X-ray absorptiometry (DEXA). With a greater focus on body composition, particularly muscle mass, as part of nutritional status assessment, the need to investigate alternative markers of muscle mass that are quick, easily accessible and cheap is essential within South Africa's resource limited healthcare system. We investigated the use of several alternative muscle mass markers in comparison to the reference standard DEXA. These included mid upper arm circumference (MUAC), calf circumference (CC), estimated appendicular skeletal muscle (est ASM), corrected arm muscle area (cAMA), and using global physical examination to determine muscle deficit.

There is limited research globally regarding diagnosing malnutrition and sarcopenia using cheaper, accessible and easy methods to measure muscle mass in cancer patients. One other South African study by LaGrange et al., (2021) investigated the usability of mid upper arm circumference as an alternative muscle mass marker as part of GLIM diagnostic criteria in adult inpatients.

Cancer cachexia is still a poorly defined and managed multi-factorial syndrome. To the best of our knowledge, we did not find South African research focused on investigating different diagnostic frameworks of cachexia in comparison to the recent guidelines published by the European Society of Medical Oncologists (ESMO) and associations of cancer cachexia with nutritional status indicators (Arends et al., 2021).

In summary, the purpose of our research is to build on the body of evidence investigating indicators of nutritional status that will best reflect changes in body composition for early identification of patients that may potentially benefit from multi-model intervention. These nutritional indicators need to be cheap, accessible, easy to use within limited health resource settings.

1.3 Aims and objectives

The broad aim of this research is the investigation of the nutritional status, including body composition (using dual energy X-ray absorptiometry; DEXA), malnutrition, sarcopenia and cancer cachexia of a sample of patients attending the oncology clinic at Groote Schuur Hospital (GSH).

The broad aim encompasses four specific aims with the formulation of specific and general objectives as follows:

Aim 1: Investigation of body composition, with a particular focus on muscle mass, using DEXA as the reference standard in this sample of cancer patients, in relation to nutritional status indicators and alternative muscle mass markers

Specific objectives:

- Examine and describe the following indicators of body composition using DEXA and anthropometry
    - DEXA: muscle mass, body fat mass, percentage fat mass, fat mass index, appendicular skeletal muscle (ASM), appendicular skeletal muscle index (ASMI), appendicular lean muscle index (ALMI), appendicular skeletal muscle standardised by BMI (ASM/BMI).
    - Anthropometry (skinfold measurements): percentage body fat and bone free arm muscle area
- Determine the representation of muscle mass from DEXA to use within the study as the reference standard.
- Investigate the associations and effect sizes between body composition as measured by DEXA with various indicators of nutritional status.
- Investigate the associations and effect sizes between body composition as measured by DEXA with treatment interventions received by participants.
- Examine the sensitivities, specificities, Cohen's ƙ and percentage agreements of some nutritional status indicators [BMI, nutrition screening risk 2002 (NRS-2002), patient generated subjective global assessment (PG-SGA), handgrip strength (HGS)].
- Examine the sensitivities, specificities, Cohen's ƙ and percentage agreements of muscle mass markers [mid upper arm circumference (MUAC), calf circumference and adjusted calf circumference, estimated ASM from calf circumference, corrected arm muscle area (cAMA) and global physical examination (GPE; worksheet 4 of PG-SGA)] compared with DEXA for screening reduced muscle mass.
- Identify nutritional status indicators that are most sensitive as a proxy for assessing body composition (using DEXA as the reference standard).

Aim 2: Investigated malnutrition in cancer outpatients according to Global Leadership Initiative on Malnutrition (GLIM) using different approaches, including technical (DEXA) and clinical approaches to determine muscle mass

Specific objectives:

- Describe the individual variables that make up components of both the phenotypic and aetiologic criteria of GLIM.
- Classify the number of patients diagnosed with malnutrition according to GLIM using:
    - different approaches for the aetiologic criteria disease burden or inflammation,
    - DEXA (technical approach and reference standard) to assess muscle mass to identify reduced skeletal muscle as part of the phenotypic criteria,
    - clinical approaches to assess muscle mass as part of the phenotypic criteria i.e., mid upper arm circumference (MUAC), calf circumference, adjusted calf circumference, corrected arm muscle area (cAMA), estimated appendicular skeletal muscle (ASM) from calf circumference

and global physical examination (GPE) from the patient generated subjective global assessment tool worksheet 4 (PG-SGA); this includes a malnutrition diagnosis using GLIM without the reduced muscle mass component,

- Examine the sensitivities, specificities, Cohen's ƙ and percentage agreements without using reduced muscle mass component and using MUAC, calf circumference, adjusted calf circumference, cAMA, estimated ASM from calf circumference and GPE in the phenotypic criteria for GLIM when compared with GLIM using DEXA.
- Identify clinical approaches to assess muscle mass that are most sensitive as a proxy for identifying malnutrition based on GLIM.
- Describe the participants that were diagnosed as malnourished according to different GLIM approaches and PG-SGA that were identified not at nutritional risk according to NRS-2002 tool.

Aim 3: Investigate sarcopenia in cancer outpatients according to the newest diagnostic guidelines from the European Working Group on Sarcopenia in Older People (EWGSOP) using muscle mass determined from DEXA (reference standard) and alternative muscle mass markers

Specific objectives:

- Classify the number of patients with sarcopenia using muscle mass as measured by DEXA.
- Classify the number of patients with sarcopenia using alternative markers of muscle mass that includes MUAC, calf circumference, adjusted calf circumference, cAMA, GPE.
- Examine the sensitivities, specificities, Cohen's ƙ and percentage agreements using alternative markers of muscle mass compared with using DEXA (reference standard) in sarcopenia diagnosis.
- Identify alternative markers of muscle mass that are most sensitive as a proxy for assessing muscle mass for the diagnosis of sarcopenia.

Aim 4: Investigate cancer cachexia using different diagnostic frameworks and the associations with nutritional status indicators in cancer outpatients

Specific objectives:

- Describe the variables and criteria used in the different cancer cachexia diagnostic frameworks.
- Classify and categorise the number of patients with cancer cachexia using different diagnostic frameworks.
- Examine the sensitivities, specificities, Cohen's ƙ and percentage agreements of the various cancer cachexia diagnostic frameworks compared with the most recent diagnostic framework from the European Society of Medical Oncologists (ESMO).

- Examine the sensitivities, specificities, Cohen's ƙ and percentage agreements of selected nutritional status indicators compared with the most recent diagnostic model from the European Society of Medical Oncologists (ESMO).
- Investigate the association between cancer cachexia and nutritional status indicators and socio-economic factors.

Additional objectives of this study were to:

- Describe general characteristics, socio-economic and health related variables of participants.
- Describe current and past cancer risk factors.
- Assess inflammation (C-reactive protein and albumin) of participants.
- Assess muscle strength using handgrip strength (HGS).
- Assess and describe physical activity.
- Assess and describe dietary intake and dietary requirement.
- Categorise participants into meeting energy (>25kcal/kg) and protein requirements (>1g/kg).
- Describe the nutritional support received by patients (including dietary interventions, awaiting intervention, use of prescribed or over the counter oral nutrition supplements).
- Assess PG-SGA and NRS-2002.
- Assess and interpret BMI, percentage weight loss, MUAC and calf circumference.

1.4 Outline of thesis

Chapter 2 presents the literature review related to cancer patients and nutritional status with a focus on three areas namely, 1) cancer cachexia, 2) measures and estimates of body composition and 3) nutrition screening and assessment tools commonly used in clinical practice. The first area covers definitions and diagnoses and classifications of cancer cachexia. The second area describes body composition and technical methods of measuring body composition with a focus on DEXA. In addition, alternative clinical approaches to estimate body composition are presented with consideration of methodology, interpretation, validation, associations with cancer related / general nutritional factors. The third area presents various nutritional screening and assessment tools that includes its use and interpretation, validation, limitations and advantages of these tools. Chapter 3 reports the materials and methods used for the entire research project whilst chapter 4 presents all the results that includes the four main aims of this Master's project, namely body composition, malnutrition, sarcopenia and cancer cachexia.

The discussion is found in chapter 5 and the conclusion, recommendations, strengths and limitations found in chapter 6. The bibliography is in chapter 7 presented in the APA 7th style, followed by all the appendices.

1.5 Contribution by candidate

The Master's candidate was responsible for the following contributions:

- Conceptualised research project together with main supervisor.
- Crafted and refined proposal, ethics clearance and research grants with the guidance and support of main supervisor.
- Co-ordinated with staff both at GSH and SSISA to develop the logistics around collection of data.
- Organised and managed equipment and tools needed for data collection through support of main supervisor.
- Recruited, trained and managed field workers to assist candidate in collection of data.
- Creation of participant report for consultants at the clinic and simplified report, together with relevant dietetic information provided to participants.
- Liaison and engagement with oncologists at GSH when participants needed to be referred to dietetic services.
- Inputting, cleaning and analysis of data with the support of main supervisor, statistician and attendance of biostatistics course.
- Calculation and interpretation of data that included physical activity, anthropometry, DEXA variables, energy and protein requirements, categorising foods into groups, determining portions for food frequency questionnaire.
- Compilation and revision of all chapters with guidance and support from main supervisor.

CHAPTER 2: LITERATURE REVIEW

This literature review will discuss and critique three major areas related to cancer cachexia, namely definitions and diagnoses of cancer cachexia; body composition indicators as well as nutritional screening and assessment tools for nutritional status assessment. The identification, classification and treatment of cancer cachexia remains challenging (Arends et al., 2023); (Baracos et al., 2022). Therefore, part one will focus on the multiple definitions and diagnoses of cancer cachexia that exist.

Cancer cachexia is mainly defined by measuring muscularity by analysis of body composition using expensive radiological measuring equipment like computer tomography scans, magnetic resonance imaging and dual energy X-ray absorptiometry (Heymsfield et al., 2014). Part two of the literature review will focus on indicators of body composition as this is an emerging field to best identify sensitive alternatives of body composition without needing sophisticated imaging equipment.

The evolving definition of cancer cachexia reflects the improved understanding of the aetiology (Schmidt et al., 2018). The complex pathophysiology of cancer cachexia implies that a single treatment option is not feasible but rather requires multimodal management plans (Argilés et al., 2017; Aversa et al., 2017; Maddocks et al., 2016; Muscaritoli et al., 2011). To effectively treat cancer patients, early screening and assessment for cancer cachexia has recently been suggested (Arends et al., 2021). There are presently no validated screening and assessment tools for cancer cachexia (Muscaritoli et al., 2014). However, Blum and Strasser (2011) suggest the use of nutritional screening and assessment tools that exist (Blum 2011). Part three of the literature review will discuss nutritional screening and nutritional assessment tools.

2.1 Cancer cachexia

2.1.1 Introduction

The term cachexia originates from the Greek words “kakos” and “hexis” meaning “bad condition.” Cachexia has not only been observed in cancer but also in many other medical conditions, namely chronic heart failure, chronic obstructive pulmonary disease and sepsis. Cachexia is recognised as a public health concern because it is estimated that nine million people with chronic medical conditions have cachexia(Farkas et al., 2013) while cancer cachexia is prevalent in 50% to 80% of cancer patients (Ryan et al., 2016). Therefore, there has been a realisation over the past decade that a standardised definition was needed, together with diagnostic criteria (Evans et al., 2008) and degree of severity or classification of cachexia (Fearon et al., 2011).

2.1.2 Definition of cachexia

In the past 20 years, several definitions for cachexia, both general and specific to cancer have been proposed (Table 2.1). Two international consensus definitions for the diagnosis of cachexia have been proposed, one specifically for cancer cachexia (Fearon et al., 2011) and one for cachexia in adults and children, but not specifically related to cancer only (Evans et al., 2008). Fearon et al., (2011) proposed

the cancer specific cachexia definition as it was felt that the diagnostic criteria needed to be cancer specific. In addition, countries like Italy, Germany, Sweden and the United Kingdom under the banner of the European Society for Clinical Nutrition and Metabolism (ESPEN) have also developed a definition for cancer cachexia (Table 2.1) (Bozzetti & Mariani, 2009). More recently, there have been additional cachexia definitions. The European Society for Medical Oncology (ESMO) utilised the Global Leadership Initiative on Malnutrition (GLIM) diagnostic framework for malnutrition (Cederholm et al., 2019) to define cancer cachexia (Arends et al., 2021). Furthermore, the Asian working group has a cachexia definition as previous definitions do not account for the difference in body composition of the Asian population (Arai et al., 2023).

The definition of cachexia has evolved as the pathophysiological processes involved in the development of cachexia are better understood (Fearon et al., 2012). To diagnose cachexia, the definition has to be standardised, widely accepted and recognised by researchers together with clinical practitioners (Berardi et al., 2021). This standardised consensus definition for cancer cachexia may aide an earlier diagnosis that may potentially change the timing or the efficacy of the intervention (Arends et al., 2017b). However, further research is needed to elucidate the role of cachexia as a multiorgan disorder (Sayers et al., 2023), not only the manifestation of reduced skeletal muscle. It is recognised that skeletal muscle cross talk happens with various other organs, namely adipose tissue, the gut, brain, liver, heart, central nervous system and bone (Berardi et al., 2021; Schmidt et al., 2018).

Three definitions agree, as summarized in Table 2.1, that general and cancer cachexia is a complex or multifactorial syndrome (Bozzetti & Mariani, 2009; Evans et al., 2008; Fearon et al., 2011). All five definitions either have weight loss (Arai et al., 2023; Bozzetti & Mariani, 2009), or muscle mass loss (Fearon et al., 2011) or both (Arends et al., 2021; Evans et al., 2008) as defining components of cachexia.

There is mostly agreement that metabolic disturbances such as insulin resistance and changes in protein and energy metabolism occur that impact on weight loss. Furthermore, metabolic disturbances can impact poor nutrient intake, that may in part be due to anorexia, is a common attributable factor to general and cancer specific cachexia (Arai et al., 2023; Bozzetti & Mariani, 2009; Evans et al., 2008; Fearon et al., 2011).

The differences in the definitions of general and cancer cachexia are seen in the inclusion or exclusion of the following factors: inflammation, nutritional support, early satiety, together with the impact on functional status. Interestingly, Fearon et al. (2011) has not included inflammation to define cancer cachexia. It is known that inflammation may be partly responsible for hypercatabolism. As hypercatabolism is a variable component of cachexia, Fearon et al. (2011) argue that patients can be cachexic without marked systemic inflammation. It appears that all the other definitions, particularly the more recent ones (Arai et al., 2023; Arends et al., 2021), have included inflammation as part of the definition. Interestingly, Jensen et al., (2010) defines disease related malnutrition as having chronic

inflammation with mild to moderate severity, which is distinct from starvation related malnutrition (Jensen et al., 2010); this infers cachexia which may explain Arends et al., (2021) suggestion of using the GLIM criteria to define cancer cachexia.

Only two definitions for cancer cachexia have included the point that conventional nutritional support may not be sufficient to reverse cancer cachexia and the impact on functional status. With treatment of cancer cachexia, one of the measurable outcomes of impact may be the functional status of the patient hence the inclusion in the cancer cachexia specific definitions (Bozzetti & Mariani, 2009; Fearon et al., 2011).

Bozzetti et al. (2009) has uniquely included early satiety in the definition as an associated factor of cancer cachexia. This may be because of an investigation by the same author, using early satiety as part of the clinical diagnosis to attempt a classification of cancer cachexia (Bozzetti & Mariani, 2009). Despite early satiety being recognised in early management of poor oral intake because of upper gastrointestinal dysmotility, Fearon et al. (2011) has not included early satiety in their cancer cachexia definition. Unsurprisingly, the two non-cancer specific cachexia definitions refer to illness or chronic disease as part of the definitions. Arai et al., (2023) go as far to define the type of chronic diseases that are associated with cachexia.

Despite some differences in the definition, there is agreement that cachexia, whether general or cancer specific, is a complexed, multi-factorial syndrome with loss of weight and / or muscle mass associated with metabolic disturbances and an impact on nutrient intake. Even though the definition by Fearon et al. (2011) of cancer cachexia has generally been widely cited by many cancer researchers, a universally accepted, clearly defined and clinically relevant definition is still lacking (Roeland, 2022). Dunne (2017) maintains that a uniformed approach to diagnosing and classifying cachexia is expected in the next decade (Dunne et al., 2017).

Table 2.1 Definitions of cachexia

Author and date		Definition
Evans et al., 2008	International consensus statement of general cachexia	"Cachexia is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders). Anorexia, inflammation, insulin resistance and increased muscle protein breakdown are frequently associated with wasting disease. Wasting disease is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption and hyperthyroidism and is associated with increased morbidity."
Bozzetti et al., 2009	European Society of Parenteral and Enteral Nutrition	"Cancer cachexia is a complex syndrome characterized by a chronic, progressive, involuntary weight loss which is poorly or only partially responsive to standard nutritional support and it is often associated with anorexia, early satiety and asthenia. It is usually attributable to two main components: a decreased nutrient intake and metabolic alterations due to the activation of systemic proinflammatory processes."
Fearon et al., 2011	International consensus statement of cancer cachexia	"Cancer cachexia is defined as a multifactorial syndrome characterised by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. The pathophysiology is characterised by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism."
Arends et al., 2021	European Society Medical Oncology Clinical practice guidelines	"A disease-related subtype of malnutrition identified by malnutrition screening, at least one phenotypical criterion of weight loss, low BMI or reduced muscle mass and systemic inflammation"
Arai et al., 2023	Consensus report from Asian working group for cachexia	"A metabolic imbalance related to chronic diseases that are associated with weight loss, inflammatory conditions, and/or anorexia. Chronic diseases include cancer, CHF, COPD, CKD, rheumatoid arthritis, other collagen diseases, Chronic respiratory failure, chronic liver failure, progressive worsening or uncontrolled chronic infections."

BMI – body mass index; CHF – congestive heart failure; COPD – chronic obstructive pulmonary disease; CKD – chronic kidney disease

2.1.3 Pathophysiology of cancer cachexia

The main pathophysiology of cancer cachexia involves the systemic inflammatory response (SIR). Both the cancer cells and the host produce inflammatory cytokines, namely interleukin-1 (IL-1), interleukn-6 (IL-6), tumour necrosis factor α (TNFα). This SIR is sustained via neuroendocrine metabolism, haematological changes and the production of acute phase proteins. Organs like the brain, heart, gut, liver, bone muscle and adipose tissue are involved, hence cancer cachexia being recognised recently as a multiorgan disorder (Sayers et al., 2023). Refer to Figure 2.1 for the visual representation of the pathophysiology of cancer cachexia.

A central sign of cancer cachexia is weight, muscle and fat mass loss. Various proteins, produced both by cancer cells and the hosts inflammatory response, mediate the reduction in protein synthesis with an increase in degradation, leading to muscle mass loss. In addition, there is the conversion of white to brown adipose tissue with an increase in heat production, equating to lost energy (Sayers et al., 2023).

Anorexia, a common symptom of cancer cachexia, has multiple aetiologies. It is not only caused by malabsorption related to tumour location or anti-cancer treatment or psychological factors like depression and anxiety, but also the neuroendocrine system (Nishikawa et al., 2021). Appetite control centres include the hypothalamus, pituitary gland and adrenal gland. Neuropeptide γ (NPγ) and agouti gene-related protein (AgRP) increases appetite whereas proopiomelanocortin (POMC) and cocaine and amphetamine regulated transcript (CART) decreases appetite. Chronic inflammation, as seen in cancer cachexia, causes neurons to activate POMC and CART and deactivate NPγ and AgRP thereby increasing symptoms of anorexia (Sayers et al., 2023). Gut microbiota of patients with cancer cachexia, have been found to have influence over appetite and inflammation (Sayers et al., 2023). Nutritional requirements are not met due to anorexia impacting oral intake and ultimately the deterioration of nutritional status. The anorexia impact is expansive, not only causing weight loss and fatigue, but also impacting on physical performance and quality of life (Nishikawa et al., 2021).

As depicted in Figure 2.1, metabolic disturbance is an early sign as seen in insulin resistance and impaired glucose tolerance (Fearon et al., 2011) through cancer cells depletion of glycogen and the systemic inflammatory response impacting on glycogenesis which further influences the decline in muscle and fat tissue. Cancer cells produce proliferin 1 that increases lipolysis but reduces lipogenesis. Cancer cells also produce parathyroid hormone related protein (PTHrP) that causes hypercalcaemia through calcium reabsorption via the kidneys and bone. In addition, PTHrP influences the brown adipocytes to produce uncoupling protein 1 (UCP1) that converts energy into heat (Sayers et al., 2023). See Figure 2.1.

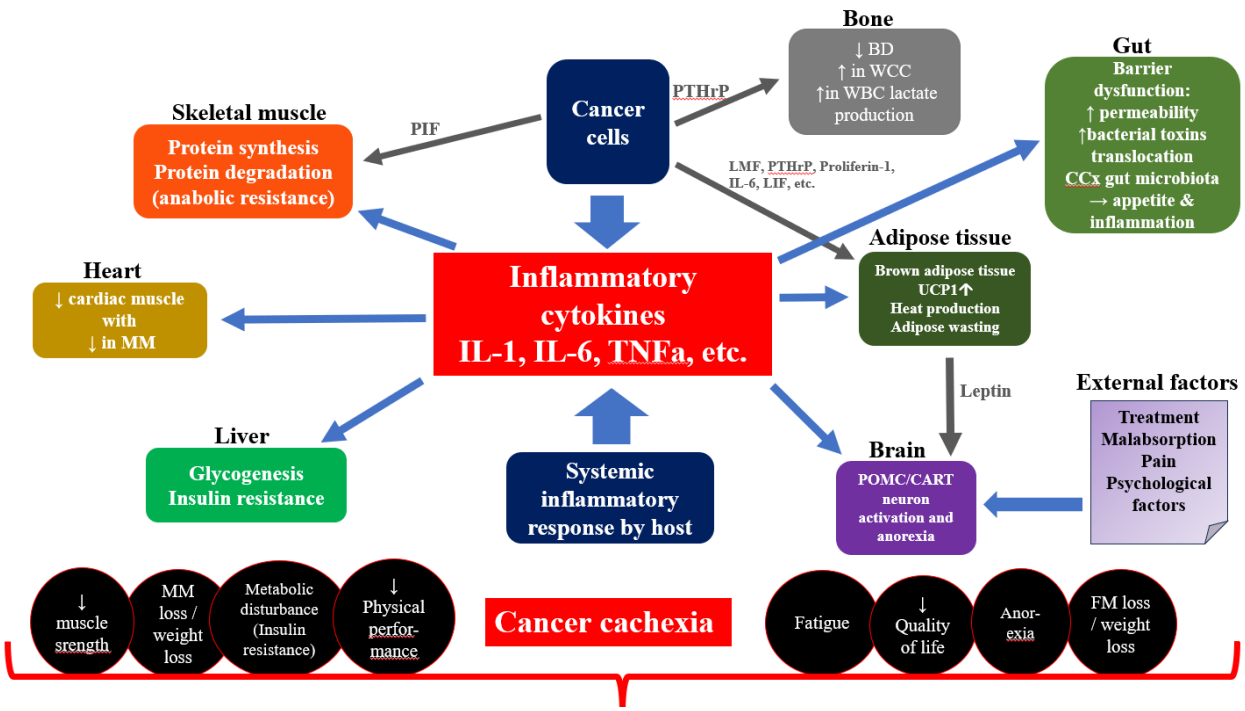


Figure 2.1 Pathophysiology of cancer cachexia

Adapted from Nishikawa et al., (2021) using creative commons license (Creative Commons). Components added were the bone, heart, gut, other factors that could cause anorexia and the black circles that indicate signs and symptoms of cancer cachexia; (Fearon et al., 2012; Sayers et al., 2023)

Interleukin-1 (IL-1), interleukn-6 (IL-6), tumour necrosis factor α (TNFα); NPγ - Neuropeptide γ; AgRP - agouti gene-related protein; POMC – proopiomelanocortin; CART - cocaine and amphetamine regulated transcript; PTHrP - parathyroid hormone related protein; UCP1 - uncoupling protein 1; MM – muscle mass; LIF – leukin inhibiting factor; PIF – proteolysis inducing factor; BD – bone density WCC – white cell count; WBC – white blood cell; CCx – cancer cachexia

2.1.4 Diagnosis and classification of cachexia and pre-cachexia

In addition to qualitative definitions of general and cancer cachexia, it has been recognised that the diagnosis and classification of cachexia needs to be quantitative and clinically practical. Table 2.2 represents the diagnostic criteria of general, cancer cachexia and pre-cachexia. Variables such as weight loss, BMI, reduced muscle strength, fatigue, anorexia, early satiety, loss of muscle mass, abnormal biochemistry, physical performance and quality of life are used in the different diagnostic criteria.

Table 2.2 Diagnostic criteria for general and cancer cachexia and pre-cachexia

Author and year	**Evans 2008**	**Bozzetti et al., 2009**	**Muscaritoli et al., 2010**	**Fearon et al., 2011**	**Argiles 2011**
Study design	Consensus report for general cachexia	Database of prospective mainly Italian multicentre oncology patients	Consensus report for general pre-cachexia	A consensus report for general cancer cachexia	Italian & Spanish collaboration regarding scoring system for cancer cachexia stages
Weight loss	≥ 5% in 3 – 6 months; if %WL not known, BMI to be used (see BMI) + 3 out of 5 criteria below	< 10% = pre-cachexia > 10% of usual BW = cachexia (no time frame) + ≥1 out of 3 criteria below	unintentional ≤ 5% of usual BW during the last 6 months + both criteria below	Involuntary >5% over 6 months OR any degree of WL >2% + see BMI and body composition	32% of CASCO: <5%; ≥5% = mild; ≥10% = moderate; ≥15% = severe; ≥20% = terminal
Anorexia	Suggested tools: Limited food intake= total caloric intake <20 kcal/kg body weight/d; <70% of usual food intake or poor appetite; SNAQ	4-point score (1 = no; 2 = mild; 3 = moderate; 4 = severe)	Suggested tools: visual analogue scales, specific questionnaires and/or reduced nutrient intake <70% estimated needs; section AC/S-12 of the FAACT questionnaire; NCCTG Anorexia/Cachexia questionnaire	X	15% of CASCO: Recommended tool - SNAQ
Abnormal biochemistry	increased inflammatory markers (CRP + IL-6) or Anaemia (low Hb) or low Alb	X	Pre-cachexia: chronic / recurrent systemic inflammatory response (raised CRP)	X	20% of CASCO: Inflammation (CRP + IL6); metabolic disturbances [Alb + pre-Alb + lactate (reflects acidosis) + TG + Hb + urea (reflects nitrogen catabolism) + Oxidative stress: ROS + GTT] immunosuppression (IL2 + Peripheral lymphocytes)

Author and year	Evans 2008	Bozzetti et al., 2009	Muscaritoli et al., 2010	Fearon et al., 2011	Argiles 2011
Physical Performance Status	X	X	X	Refractory cachexia only: ECOG score 3 – 4	15% of CASCO: 5 questions from EORTC QLQ-C30
Body composition	anthropometry (MUAMC); DEXA (ASMI)	X	X	Order of preference: CT or MRI (lumbar SMI), DEXA (ASMI), anthropometry (MUAMA), BIA (whole body FFMI without bone)	8% of CASCO: BIA or DEXA (preferred)
BMI	If %WL unknown, BMI < 20	X	X	BMI < 20	X
Reduced Muscle strength	handgrip strength	X	X	X	X
Fatigue	No tool suggested	4-point score (1 = no ;2 = mild; 3 = moderate; 4 = severe)	X	X	X
QOL	X	X	X	X	QOL questionnaire (25 questions from EORTC QLQ-C30)
Early satiety	X	4-point score (1 = no ;2 = mild; 3 = moderate; 4 = severe)	X	X	X

Table 2.2 continued: Diagnostic criteria for general and cancer cachexia and pre-cachexia

Author and year	Blum et al., (2014)	Argiles 2017	Vigano 2017	Zhou 2018	Arends et al., (2021)
Study design	Cross-sectional study design from 6 European countries and Australia and Canada	Observational prospective case-control study of Italian patient base	Retrospective study of Canadian gastrointestinal & lung cancer	prospective study of advanced Chinese cancer patients for scoring cancer cachexia stages	Clinical practice guidelines: European Society for Medical Oncology
Weight loss	>1kg and <5% WL = pre-cachexia; >5%WL in 6 mo or >2% WL + see BMI	As for Argiles 2011 but mini-CASCO score	≤ 5% = pre-cachexia + 1 – 2 criteria (see below); > 5% in 6 mo = cachexia + 1-2 criteria (See below)	Score 0-3: Within 6 mo, weight stable or gain or ≤5% or >5% and ≤15% or >15% WL	> 5% in 6 months or see BMI or body composition + see abnormal biochemistry
Anorexia	X	Recommended tool: SNAQ	≥ 1 point for abridged PG-SGA part 2	Score 0-2 for appetite loss (most severe)	X
Abnormal biochemistry	X	Inflammation (Hb + CRP); metabolic disturbances (Alb); Immunosuppression (Absolute lymphocyte count)	Raised CRP or low Hb or low Alb or raised WCC	Score 0-2 where Hb, Alb, WCC measured	Chronic systemic inflammation depicted by mGPS (requires CRP and albumin)
Physical Performance Status	X	2 questions from EORTC QLQ-C30	>2 for aPG-SGA part 4 (equates to >50% of time in bed; based on ECOG)	Score 0-2 for ECOG	X
Body composition	X	BIA or DEXA or CT	X	X	Anthropometry or BIA or DEXA or CT
BMI	<20 with >2%WL	X	X	X	<20
Reduced Muscle strength	X	X	X	Score 0-3 for SARC-F	X
Fatigue	X	X	X	X	X
QOL	X	10 questions from EORTC QLQ-C30	X	X	X
Early satiety	X	X	X	X	X

BMI – body mass index; BW – body weight; WL – weight loss; CASCO – cachexia score; SNAQ - Simplified Nutrition Assessment Questionnaire; FAACT - Functional Assessment of anorexia / cachexia therapy; NCCTG - North Central Cancer Treatment Group; EORTC - European Organization for Research and Treatment of Cancer QLQ-C30; ECOG - Eastern Cooperative Oncology Group; SARC-F - Sarcopenia questionnaire; CRP – C-reactive protein; IL – interleukin; Hb – haemoglobin; Alb – albumin; TG – triglycerides; ROS – reactive oxygen species; GTT – glucose tolerance test; MUAMC – mid upper arm muscle circumference; DEXA – dual X-ray absorptiometry; ASMI – appendicular skeletal muscle index; CT –

computed tomography; MRI – magnetic resonance imagery; SMI – skeletal muscle index; FFMI – fat free mass index; BIA – bio-electrical impedance; WCC – white cell count; mGPS – modified Glascow Prognostic score; aPG-SGA – abridged patient generated subjective global score

As seen in Table 2.2, over the past 2 decades there have been four global consensuses for the diagnosis of general cachexia (Evans et al., 2008), general pre-cachexia (Blum et al., 2014; Muscaritoli et al., 2010) and cancer cachexia (Blum et al., 2014; Fearon et al., 2011). In addition, one Chinese (Zhou et al., 2018), one Canadian (Vigano et al., 2017) and four European groups have formulated cancer cachexic specific diagnostic criteria (Arends et al., 2021; Argiles et al., 2017; Argiles et al., 2011; Blum et al., 2014) with Bozzetti et al. (2009) being the first to classify cancer cachexia into pre-cachexia and cachexia. In addition, there are only two research groups that utilised a scoring system to classify cancer cachexia (Argiles et al., 2017; Argiles et al., 2011; Zhou et al., 2018). Out of ten publications, half have validated the diagnostic and classification criteria themselves according to nutritional (Arends et al., 2021; Bozzetti & Mariani, 2009; Vigano et al., 2017), clinical (Arends et al., 2021; Bozzetti & Mariani, 2009; Vigano et al., 2017; Zhou et al., 2018) and functional aspects (Arends et al., 2021; Argiles et al., 2017; Bozzetti & Mariani, 2009; Vigano et al., 2017; Zhou et al., 2018).

There are ten diagnostic criteria that span across some or all the diagnostic frameworks, with weight loss being included by all research groups, followed by anorexia and abnormal biochemistry being criteria in 70% of the tools. Both physical performance status and body composition were used by half of the researchers, with Fearon et al., (2011) only using performance status for determining refractory cachexia. Two fifths of the tools included BMI; while reduced muscle strength, fatigue and quality of life were criteria in 20% of the tools; early satiety was incorporated by one group of researchers (Table 2.2). More information on these diagnostic criteria attributes is provided in the following paragraphs.

Weight loss and BMI

Weight loss is a universal criterion for diagnosis, but the cutoff percentage and time frame for significant weight loss is arbitrary. Fearon et al. (2011) suggested that the percentage weight loss should be linked to clinically significant patient outcomes like survival and functional status. As depicted in Table 2.2, most researchers used the cutoff of 5% weight loss over three to six months with only two specifying involuntary or unintentional weight loss (Fearon et al., 2011; Muscaritoli et al., 2010). Bozzetti et al. (2009) used 10% weight loss based on the same cutoff as the SGA nutritional assessment tool to distinguish between pre-cachexia and cachexia. This may be as a result of Detsky et al., (1987) who presents <5% weight loss over 6 months to be small, 5% to 10% weight loss to be potentially significant and >10% weight loss to be definitely significant weight loss. It needs to be noted that, together with absolute weight loss percentage, the rate of weight loss and pattern of weight loss is also important (Detsky et al., 1987). Blum et al., (2014) was the only research group presented in Table 2.2 that classified patients as pre-cachexic with >1kg and <5% weight loss. However, these researchers concluded that weight loss and BMI were insufficient to distinguish pre-cachexia patients, rather inflammation and appetite components may be helpful to add to the framework (Blum et al., 2014).

Martin et al., (2015) investigated percentage weight loss and BMI linked to survival of cancer patients and found that weight loss as little as 2.4% was independently associated with reduced survival. This infers

waiting for a higher arbitrary weight loss percentage to meet diagnostic criteria to be counter intuitive to start early multimodal intervention (Martin et al., 2015). Fearon et al., (2011) and Blum et al., (2014) stipulate >2% weight loss and BMI < 20kg/m^2 to meet diagnostic criteria for cancer cachexia. This may be problematic for patients that are overweight and obese when taking the research by Martin et al., (2015) into account. The researchers that classified cachexia by using a cachexia score, also further classified percentage weight loss by as much as >20% (Argiles et al., 2017; Argiles et al., 2011; Zhou et al., 2018). The cachexia scores, or CASCO, devised by these research groups were developed to determine different stages of cachexia, inclusive of pre-cachexia to better treat and provide a prognosis for patients. CASCO classifies cancer cachexia into mild, moderate and severe (Argiles et al., 2017; Argiles et al., 2011) in contrast to Zhou et al. (2018) that classifies patients into no cachexia, pre-cachexia, cachexia and refractory cachexia. Time frames related to percentage weight loss varies from 3, 6 and 12 months with only Bozzetti et al. (2009) not defining time. Evans et al. (2008) distinctly report that if percentage weight loss cannot be calculated, a body mass index (BMI) of < 20 kg/m^2 as part of the cachexic diagnosis can be used. Interestingly, the researchers were not in agreement regarding the BMI cutoff of 20 kg/m^2 as alternatives ranged from 18.5 kg/m^2 to 22 kg/m^2 and suggested further research was needed (Evans et al., 2008). Fearon et al. (2011) maintain that a weight loss of >2% together with a BMI of < 20 kg/m^2 would diagnose the presence of cachexia.

In the context of South Africa, it is challenging to calculate percentage weight loss as most of the population do not know their usual weight, despite being able to confirm that weight loss has taken place. Therefore, percentage weight loss can only be calculated if previous weights have been documented in medical folders. In addition, La Grange et al., (2021) noted that because of limited funding within the South African health care environment, equipment needed to measure weight and height were not available or maintained thereby hampering the calculation of BMI (La Grange et al., 2021). Therefore, documentation of weight is not a standard procedure across medical facilities, thereby making the universal criterion of weight loss challenging to quantify across all patients initially presenting with cancer whether related to their usual weight or a specified time frame. However, percentage weight loss is far more practical to calculate in the clinical setting than body composition.

Anorexia (loss of appetite)

Anorexia is accepted as a frequent symptom as used by 70% of the researchers in table 2.2. It is characteristic of general and cancer cachexia but can be experienced with depression, certain medications, and part of the natural ageing process amongst other reasons. As seen in Table 2.2, there is no agreement on how to measure anorexia. Evans et al. (2008) and Muscaritoli et al., (2010) both make several suggestions on tools that may be used, whereas the other research groups prescribe the anorexia tool to be used. These different tools to measure anorexia are varied in their application from needing a trained health professional to calculate caloric intake (Evans et al., 2008; Muscaritoli et al., 2010) to completion of several suggested questionnaires. These questionnaires include the following: Simplified Nutrition Assessment Questionnaire (SNAQ) consisting of 4 questions (Argiles et al., 2017;

Evans et al., 2008) or only 2 questions that are scored (Argiles et al., 2017; Argiles et al., 2011; Evans et al., 2008); Functional Assessment of anorexia / cachexia therapy (FAACT) and North Central Cancer Treatment Group (NCCTG) anorexia / cachexia questionnaires (Muscaritoli et al., 2010) have 12 and 15 questions respectively that are related to appetite and symptoms that assess qualitative and quantitative anorexia information; abridged-PG-SGA (Vigano et al., 2017) where ≥ 1 point can be scored for anorexia affecting amount and type of oral intake; lastly asking questions that are scored (Bozzetti & Mariani, 2009; Zhou et al., 2018) that simply rely on the subjectivity of the patient.

Abnormal biochemistry

Seventy percent of research groups have included abnormal biochemistry as diagnostic criteria for either general or cancer cachexia or pre-cachexia. Abnormal biochemistry for the diagnosis of cachexia is divided into markers of inflammation (such as CRP, interleukin-6, haemoglobin, albumin), metabolic disturbances (such as albumin, pre-albumin, lactate, haemoglobin, urea) and immunosuppression (such as interleukin-2, peripheral lymphocytes, absolute lymphocyte count. The only blood result that Muscaritoli et al., (2010) included was CRP for inflammation to be detected in pre-cachexia. Haemoglobin and albumin appear in both the inflammatory and metabolic disturbance categories as multiple reasons exist for developing anaemia and hypoalbuminaemia. Evans et al. (2008) included inflammatory and metabolic without immunosuppressive markers. Argiles et al. (2011 and 2017), Vigano et al. (2017) and Zhou et al. (2018) include immunosuppression as it may be detected even before weight loss begins, together with inflammatory and metabolic markers. Arends et al., (2021) uses modified Glascow prognostic score (mGPS) to detect inflammation, the most validated inflammatory prognostic score (McMillan, 2013).

Three groups did not include biochemistry in their diagnostic criteria (Blum et al., 2014; Bozzetti & Mariani, 2009; Fearon et al., 2011). Bozzetti et al. (2009) intentionally excluded blood results as they deemed it clinically impractical for a bedside diagnostic assessment. In addition, certain facilities do not have the expertise to process certain results (e.g., interleukin 6, pre-albumin) and some of these tests are costly. Furthermore, patients may have to wait up to 2 to 3 hours to complete the tests i.e., the glucose tolerance test and results may not always be processed and accessible on the same day. As previously mentioned, Fearon et al. (2011) had not included inflammation in their definition as they explain that cachexia can exist with or without noticeable systemic inflammation. They argue that despite relevance of metabolic changes during the pre-cachexic phase (e.g., impaired glucose intolerance), no blood results are needed as they are costly and impractical (Fearon et al., 2011). Lastly Blum et al., (2014) intentionally only included weight loss and BMI in their diagnostic tool, as easily measured if not always readily available and they have validated the tool against inflammation.

Molecular biomarkers, not only blood biochemistry but including biomarkers taken from urine, tumours, muscle biopsies and patient's DNA, may be promising in the future but to date, only CRP is measured routinely and related to prognosis (Bruggeman et al., 2016). Furthermore, CRP has been linked to quality

of life independently from performance status (Bruggeman et al., 2016). However, blood biochemistry may not be feasible diagnostic criteria in all health care settings as demonstrated in a public government hospital in South Africa as only 43% of inpatients had documented CRP results in their medical folders (La Grange et al., 2021).

Physical performance

Being diagnosed with general and cancer cachexia undoubtedly impacts on the patient's physical performance but is only included as a diagnostic tool by half of the cancer specific research groups (Argiles et al., 2017; Argiles et al., 2011; Fearon et al., 2011; Vigano et al., 2017; Zhou et al., 2018), either being assessed by Eastern Cooperative Oncology Group (ECOG) score or using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 (Table 2.2). Both these tools have been validated (Dolan et al., 2020) for independently impacting on quality of life and survival. ECOG has 0 – 4 stages with stage 0 being fully active through to stage 4 being bedridden with full dependency for activities of daily living (Oken et al., 1982). EORTC QLQ-C30 is divided into nine multi-item scales further divided into three categories namely functional, symptoms and global health (Aaronson et al., 1993). The functional scales contain physical roles, emotional, cognitive and social, where Argiles et al. (2011) used five and Argiles et al. (2017) used only two questions related to physical function.

Body composition

A review by Bruggeman et al. (2016) states that determining body composition and functional status is more important than weight loss to detect cancer cachexia early, despite not being used routinely in clinical practice to diagnose cancer cachexia. Only half of the research groups have included muscle mass as a diagnostic category for cancer cachexia (Table 2.2). There are several reasons for this. Even though DEXA (dual energy X-ray absorptiometry), CT (computer tomography) and MRI (magnetic resonance imaging) are powerful imaging tools for assessing body composition, they are costly, not available or accessible to all facilities and generally used in research (Kuriyan, 2018). Therefore, the consensus reports for diagnosis of general (Evans et al., 2008) and cancer cachexia (Fearon et al., 2011), included alternative anthropometric measurements, namely mid upper arm circumference (MUAC) together with triceps skinfold thickness (TSF) for the calculation of mid arm muscle circumference (MAMC) or arm muscle area (AMA) as it is inexpensive, mobile and easily performed at the bedside. The accuracy of these methods has been questioned (please see section 2.2.8 for details).

Interpretation of body composition, particularly muscle mass must be approached cautiously as more research is needed in different ways muscle mass is expressed, the determination of reference values and cutoff points for populations that should be related to patients' outcomes, especially low to middle income countries (Kuriyan, 2018). It may be argued that with increasing levels of obesity in a population, determining body composition is essential, as loss of muscle mass can take place at any BMI and body weight, but often unnoticed in the obese (Prado et al., 2016).

In the absence of access to technical tools and reference standards to interpret the muscle mass measurements, guidance was offered by Compher et al., (2022) to estimate reduced muscle mass using clinical approaches when using the GLIM framework. This is particularly important within limited resource health settings. Part of this GLIM framework is used by Arends et al., (2021) in their cancer cachexia diagnostic tool. A recent review by Prado et al., (2022), emphasises the importance of muscle health which includes not only muscle mass, but also muscle quality (fatty deposits within muscle tissue) and muscle function. Muscle health, not only muscle mass, has an impact on immune function and clinical outcomes (Prado et al., 2022).

Fatigue and Muscle strength

Loss of muscle mass, together with anaemia, directly impacts muscle strength and fatigue (Evans et al., 2008). As seen in Table 2.2, muscle strength has been included in the diagnostic criteria by Evans et al., (2008) and Zhou et al., (2018) and respectively measured by handgrip strength or using a sarcopenia questionnaire (SARC-F). SARC-F is a simplistic tool used for screening of sarcopenia which has been validated for assessing muscle function (Zhou et al., 2018). Fatigue has only been used by the older research groups (Bozzetti & Mariani, 2009; Evans et al., 2008) perhaps because there is no objective measurement to quantify fatigue despite it directly impacting on quality of life and predicts short term survival.

Quality of Life

Quality of life is only used by Argiles et al., (2011; 2017) as part of the diagnostic criteria for cancer cachexia. These authors felt that quality of life is important to consider as it is impacted by weight changes, performance status and metabolic alterations. The EORTC QLQ-C30 has been used to assess quality of life where either 5 or 2 questions from EORTC QLQ-C30 were used respectively by Argiles et al., (2011) and Argiles et al., (2017).

Early satiety

Early satiety was only included by Bozzetti et al., (2009) as a diagnostic component of cachexia. Despite early satiety being a less frequently associated characteristic of cachexia, it is partly responsible for weight loss and usually reflects gut dysmotility complications. Quantifying early satiety is based on a scoring system of 1 to 4 based on the patient's experience.

Concluding remarks

As demonstrated above, differences exist in the number of variables identified by the various research groups. In addition, there are also differences in the number of criteria that need to be met to diagnose and classify cachexia. Muscaritoli et al., (2010), Argiles et al., (2011 and 2017) and Zhou et al., (2018) consider all criteria to be met for a diagnosis to be made with being classified as asymptomatic pre-cachexia, symptomatic pre-cachexia, asymptomatic cachexia, symptomatic cachexia; mild, moderate, and severe cancer cachexia and pre-cachexia, cachexia and refractory cachexia, respectively. Evans et al., (2008) uses weight loss and three out of their other five criteria; Bozzetti et al., (2009) requires only

one out of three of the criteria to be met whereas Fearon et al., (2011) offers a combination of weight loss, BMI and loss of muscle mass for the diagnosis and classification of cachexia. Arends et al., (2021) defining criterion is inflammation with one phenotype criterion needed. Blum et al., (2014) needs only weight loss criterion to be met or a combination of weight loss and BMI. Vigano et al., (2017) uniquely classifies pre-cachexia and diagnoses cachexia when 2 or 3 criteria are met and classifies refractory cachexia when 3 or 4 criteria are met.

With the lack of a standardised approach to diagnosing and classifying cancer cachexia, comparisons of heterogenous and even homogeneous cancer groups regarding prevalence of cancer cachexia and classifying cachexia stages, are difficult. As cancer cachexia is a multifactorial syndrome and multiorgan disorder, further research is needed to better understand this complex condition (Sayers et al., 2023). At present, to correctly diagnose cancer cachexia, it has been suggested to assess nutritional status, muscle mass and function together with body composition analysis and estimate quality of life (Arends et al., 2021; Berardi et al., 2021).

There is lack of a global approach to assess nutritional status as there is no one tool that assesses nutritional status completely (Du et al., 2017; Silva et al., 2019; Teigen et al., 2017) with different guidelines recommending different components being assessed, e.g., weight loss history, food intake, body composition, functional assessment using different tools. In the last decade, not only including cancer patients but all patients, there has been a focus on encompassing body composition, particularly the muscle mass component in both the diagnosis of malnutrition and assessment of nutritional status (Arends et al., 2021; Cederholm et al., 2018; Fearon et al., 2011; Muscaritoli et al., 2021; White et al., 2012).

2.2 Body composition and muscle strength

2.2.1 Introduction

Commonly, cancer patients experience cancer cachexia, malnutrition and sarcopenia, three distinct conditions that share reduced muscle mass as a diagnostic criterion. All cancer cachexic patients are malnourished, but not all malnourished cancer patients are cachexic (Muscaritoli et al., 2010). In addition to muscle mass, muscle strength and muscle quality are important components that make up muscle health, that impacts clinical outcomes, not only in cancer but in other conditions, most recently COVID 19 (Prado et al., 2022).

Reduced muscle strength is associated with cancer (Evans et al., 2008; Zhou et al., 2018) and is a characteristic of sarcopenia (Cruz-Jentoft et al., 2019; Studenski et al., 2014) and frailty (Fried et al., 2001). The term sarcopenia was coined in 1988 (Rosenberg, 1997) and is described as a muscle disease where there are changes in muscle that develop generally in older adults (primary sarcopenia) but also in younger adults. These changes in muscle are attributed to reduced muscle strength, muscle mass and muscle quality which impacts on physical performance, in turn impacting on the severity of sarcopenia (Cruz-Jentoft et al., 2019).

Both sarcopenia and frailty are described as nutrition-related conditions that are complexed and have pathological frameworks (Cederholm et al., 2017). Frailty is an age-related clinical condition that increases vulnerability to internal and external stressors; frailty impacts on independence and disability and is influenced by modifiable life-style factors (Goede, 2023). There are two accepted gold standard methods to identify frailty, the “Rockwood frailty index” and “Fried frailty criteria” (Goede, 2023). The Rockwood frailty index is impractical to perform in clinical settings as the number of deficits as a ratio of the 70 pre-defined deficits that include signs from physical examination and impairment of activities needs to be assessed. The “Fried frailty criteria” involves presence of three out of five diagnostic criteria that have been suggested: weight loss; exhaustion (fatigue); low physical activity; slowness (e.g. reduced gait speed); and weakness (e.g. low grip strength) (Fried et al., 2001). Therefore, low muscle strength as well as fatigue are factors that relate to these clinical yet distinct conditions of frailty, sarcopenia and cachexia, especially in elderly cancer patients where it impacts on mortality, anti-cancer treatment tolerance and post-operative complications (Goede, 2023; Vigano et al., 2017).

Another shared characteristic by both sarcopenia and cachexia is inflammation, together with loss of and impaired regeneration of muscle mass and negative protein and energy stores (Peixoto da Silva et al., 2020). Even with the natural ageing process, there is sub-clinical chronic inflammation found. Therefore, with frailty found with cancer, the disease itself and anti-cancer treatment can exacerbate frailty in already vulnerable elderly patients (Goede, 2023).

The most recent recommendations for nutritional status assessment indicate that components of muscle mass and fat must be included to describe body composition (Arends et al., 2017b; Arends et al., 2021).

It has been well established that body composition has an impact on patient outcomes (Kazemi-Bajestani et al., 2016; Prado et al., 2023) and can be used to predict prognosis (Cespedes Feliciano & Chen, 2018; Martin et al., 2013; Prado et al., 2016). Despite this, nutritional status assessment that includes body composition in the clinical setting is not routinely implemented (Teigen et al., 2017). This review chapter Sections 2.2.2 through to section 2.2.12 presents the following themes related to body composition: description of body composition; methods that are currently used to measure body composition, focusing on DEXA; the tools that are used to estimate body composition namely skinfolds, HGS, other anthropometry and any other methods, particularly in the cancer population.

2.2.2 Body composition description

The field of body composition can be viewed in 3 parts, namely how it is classified methods and techniques used; how various factors (genetics, environmental, biological) impact on body composition (Bazzocchi et al., 2016). For research purposes, body composition is classified and organised into 5 levels namely atomic, molecular, cellular, tissue organ, and whole body. Methods to determine body composition assess two, three, four or multiple body compartments.

In clinical practice, body composition usually describes lean mass, adipose tissue distribution and its impact on health (Mazzoccoli, 2016; Sheean et al., 2020). The weighing scale for one compartment, that is total body mass, is commonly used but does not provide body composition information. However, unless body mass is presented in relation to height, that is body mass index, a proxy for body composition, can one interpret body mass linked to health and disease (Holmes & Racette, 2021). DEXA, the three-compartment method, is also commonly used in clinical practice and has been recognised as the current reference method for body composition (Barone et al., 2022). With the multiple compartment model, the major elements in the body are analysed, for example carbon, oxygen, nitrogen, calcium, phosphorous. Even though validation of other methods for measuring body composition is made through the multicompartment model, it is not readily used in clinical practice. It is expensive with a lack of appropriate facilities that can perform these measurements and increased exposure to radiation for participants (Kuriyan, 2018). Table 2.3 depicts the different compartments assessed in body composition and related methods.

Table 2.3 Compartments assessed in body composition

Number of compartments	Method	Component
1 compartment	Weighing scale	BM
2 compartments	Hydrodensitometry; ADP; hydrometry; UWW	FM + FFM
3 compartments	DEXA	FM + FFM + MC
4 compartments	Combination of methods	FM + TBW + Met T + MC
Multiple compartments	NAA	EL + NEL + TBW + Met T (protein) + GLY + SM + BM

BM – body mass; ADP - air displacement plethysmography; UWW – underwater weighing; FM – fat mass; FFM – fat free mass; MC – mineral content; TBW – total body water; DEXA – dual energy X-ray absorptiometry; Met T – metabolic tissue; NAA - Neutron activation analysis; EL – essential lipid; NEL – non-essential lipid; GLY – glycogen; SM – soft tissue mineral; BM – bone mineral

2.2.3 Body composition components

Figure 2.2 presents the visual representation of how body composition components are arranged (Buckinx et al., 2018). Lean body mass, comprising 81% of total body weight, is the fat free component that includes bone, tendons, connective tissue, skin and organs. Appendicular skeletal muscle mass (ASM) is the focal area for cancer cachexia and sarcopenia research. It is the largest component of body composition making up 75% of total body muscle mass that includes only the legs and arms without the bone., The other 25% of total body muscle mass is the muscle mass, without bone, found in the torso, head and neck (Buckinx et al., 2018). Adipose tissue is formed by connective tissues (adipocytes, collagenous and elastic fibres), fibroblasts and capillaries, and comprises of 80% fat mass (Sheean et al., 2020).

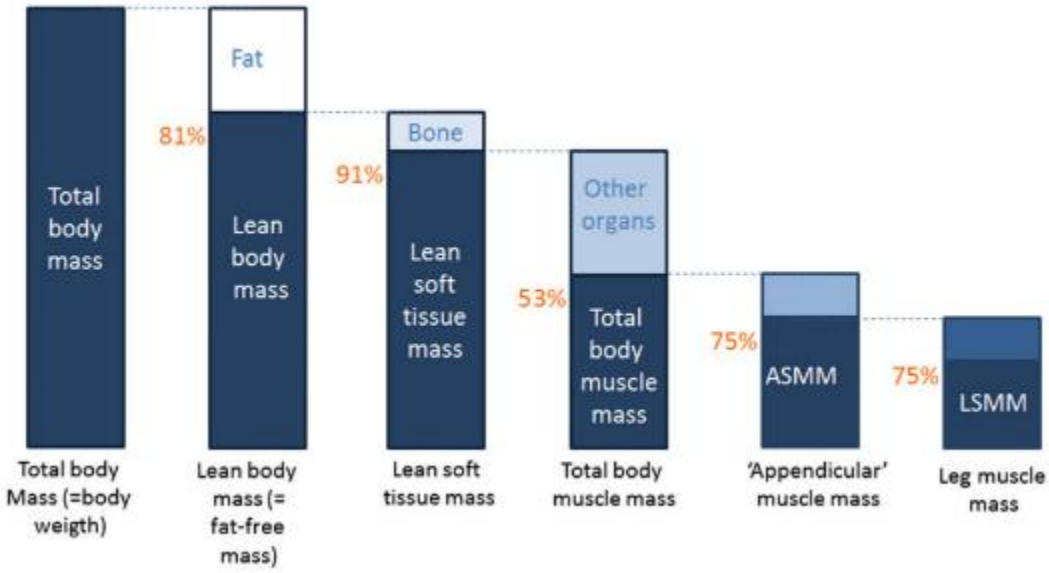


Figure 2.2 Visual representation of body composition components (Buckinx et al., 2018)

2.2.4 Body composition methods

There are various methods, each with its own strengths and limitations, that can be used to measure body composition. When selecting a body composition assessment method, many factors need to be considered, namely the clinical or research setting, the comfort of the patient, expense involved, availability of equipment, accessibility and expertise needed. Therefore, no consensus has been reached for one method being the best technique (Buckinx et al., 2018). Body composition methods include laboratory and imaging techniques.

Laboratory methods (Table 2.4) that use the two-compartment model, which comprises fat mass (FM) and fat free mass (FFM), are hydrodensitrometry or underwater weighing (UWW), air displacement plethysmography and isotope dilution method (Kuriyan, 2018). In the two-compartment model, assumption is made that body density for FFM (bone, muscle and water) is the same for all regardless of age, fitness level or ethnicity. Body density is used to calculate percentage body fat (Cambridge Biomedical Research Centre). For research settings, these techniques are acceptable but for clinical settings, mainly due to cost and patient discomfort, these techniques are never used (Holmes & Racette, 2021; Kuriyan, 2018).

Table 2.4 Laboratory techniques for body composition

Two compartment method	**Hydrodensitrometry or underwater weighing**	**Air displacement plethysmography**	**Isotope dilution method (hydrometry)**
Basic explanation of technique	Measures displacement of water; lung volume accounted for; muscle and bone are denser than water	Chamber measures the association between pressure and volume, thereby calculates BV	TBW estimated when the isotope's concentration and volume known; natural amount of isotope measured in body fluids (blood, urine or saliva), then remeasured after 2 to 3 hours
What is measured	BV accurately measured and used to estimate BD and % BF	Total BF and LT can be calculated from BV	FFM can be estimated from TBW
Disadvantage	Time consuming; Participant discomfort; Participant cooperation needed; High cost; Technical expertise needed; Expensive equipment used; accuracy impacted by consumption of food and carbonated drinks; fluid losses through exercise	High cost; Large space needed for equipment; Large amounts of body hair may impact accuracy	High cost due to isotope, equipmemt, analysis; Technical expertise needed for results; tiresome preparation of isotope (usually deuterium); Measurement consistency influenced by fluid type measured, isotopic equilibrium time, correction for dilution space and analysis method for isotope measurement
Advantage	Accurate; validated;	Easy to use as automated; low participant burden	Accurate

(Cambridge Biomedical Research Centre; Di Sebastiano & Mourtzakis, 2012; Holmes & Racette, 2021; Kuriyan, 2018)
BV – body volume; TBW – total body water; BD – body density; BF – body fat; LT – lean tissue; FFM – fat free mass

Fortunately, with technological advancements in the medical field, there are other body composition measuring techniques that may be used in research and clinical practice. Table 2.5 refers to these body composition measurement techniques, namely CT, MRI, DEXA, BIA and ultrasound (US). All are imaging techniques excluding BIA, with CT and MRI being accepted as the gold standard reference techniques at tissue level (Smith & Madden, 2016).

CT, MRI and US can assess adipose tissue and muscle mass. CT and MRI can measure visceral and subcutaneous adipose tissue as well as inter- and intra-muscular adiposity (Smith & Madden, 2016), ongoing research is still needed to better understand the use of US in measuring muscle mass and muscle quality (Bauer et al., 2019). Both DEXA and BIA measure FFM and FM. In addition, DEXA is accepted as the gold standard technique to determine bone mineral density and discerns lean mass from FFM (Kuriyan, 2018).

There is a lack of standardised units of measurement and measurement areas with the use of terminology being inconsistent across researchers and clinicians (Sheean et al., 2020). This makes it

challenging to compare different technologies and agree on a reference standard for measuring muscle mass (Buckinx et al., 2018).

Decisions to apply techniques for body composition assessments are based largely on advantages and disadvantages within various contexts (Ceniccola et al., 2019); (Table 2.5). There is always a need to implement low-cost diagnostic technologies at the bedside of the patient (Ceniccola et al., 2019). BIA and US scans are the only two portable techniques available, in addition to being inexpensive. Costly CT and MRI scans are routine diagnostic tools for some oncology patients (Daly et al., 2018). Because of CT scans' high radiation dose, it is never requested specifically for measuring body composition in cancer patients. Therefore, many researchers have used CT scans retrospectively to determine body composition (Teigen et al., 2017). There is no gold standard that accounts for all requirements for assessing body composition. Considering the advantages and disadvantages, DEXA may be used as reference standard for measuring body composition and muscle mass for research and clinical practice (Buckinx et al., 2018; Ceniccola et al., 2019).

Ideally, body composition interpretation using different techniques needs to be in the relevant context i.e., clinical setting within the cancer population against a reference standard where it can be used diagnostically, prognostically and in a monitoring capacity for intervention purposes (Table 2.5). More recent research is focusing on Hounsfield units average calculation (HUAC) that determines muscle quality – investigating relationship to mortality, morbidity, nutritional risk assessment, predicting surgical outcomes (Price & Earthman, 2019).

In summary, for clinicians to use body composition techniques appropriately, there needs to be ubiquitous understanding of terminology across research and clinical settings; the development of various cutoff points will enable clinicians to diagnose and categorise patients in a standardised way e.g., inadequate or excess fat mass or lean mass; research needs to include healthy controls so that comparisons can be made across techniques (Sheean et al., 2020).

Table 2.5 Body composition measurement techniques used within research and some clinical settings

Technique	CT	MRI	DEXA	BIA	US
Basic explanation of technique	X-ray beam rotates around whole body or area creating multiple cross-sectional images based on different tissue densities; Pixels make up images called Hounsfield units that reflect tissue attenuation and radiation attenuation	Body protons all align whilst absorbing the energy from the radiofrequency waves emitted from the scanner; once the waves are switched off, the energy is released from the protons and absorbed by the radiofrequency signal creating images	Imaging technique measures the difference in tissue attenuation of the 2 different energy X-ray beams; affected by tissue composition and thickness	Electrolytes and water within tissues are less resistant to an electrical current than fat within adipose tissues; impedance and / or reactance and capacitance are measured and used within equations to calculate BC measurements that are population based	US probes, called transducers, emit sound waves; these are reflected back to the transducer when there are boundaries within tissues, creating electric signals that are sent back to the scanner to create 2D images
Body compartments being assessed	SMM AT	SMM AT	FFM = LM without BMC LM FM	FFM FM	SMM AT
Muscle mass measurement	Usually L3 SMI = CSA divided by height squared	Usually L3 SMI	appendicular skeletal LM = SMM of limbs	WB FFMI without bone	Muscle quantity and quality without intermuscular adipose tissue; assessment of soft tissue structures
Advantages	High quantitative and qualitative accuracy; High image resolution; Able to determine tissue quality; Validated cutoff values (Price 2019)	No radiation exposure; Modern scanners can accommodate obese individuals; Cutoff points pertaining to muscle now emerging	Rapid; Low dose radiation; Non-invasive and quick; Differentiates fat, lean and bone tissue; Possibility of obtaining regional measures; Well tolerated for repeated measures; High precision and accuracy	Portable; Low cost; Non-invasive and quick; Safe for repeated measures; Easy to operate; precisely measures resistance and reactance	Portable; Low cost; Non-invasive and highly accessible; Satisfactory reliability intra- and interrater; Safe for repeated measures; assess longitudinal changes in muscles

Technique	CT	MRI	DEXA	BIA	US
Limitations	Not portable; High cost; Weight and size limits; Expertise for image analysis; not readily available; Various measurement methods, machines and software packages; high radiation exposure	Not portable; High cost; Weight and size limits; Expertise for image analysis; not readily available; Various measurement methods, machines and software packages; individuals with ferromagnetic implanted devices unable to undergo scan; lack of universally agreed cut offs for adiposity that take account of differences in age, sex and ethnicity (Smith & Madden, 2016)	Not portable; Costly; Weight and size limits; Expertise needed to operate; not readily available; Variability of instrument; Body thickness and hydration status may influence measurements; Cannot measure individual muscles, rather estimates WB MM; Cannot distinguish different fat types (visceral, subcutaneous, and intramuscular); equations used based on assumptions; Contraindicated in pregnancy	Indirect method; Limited by hydration status; Specific equation needed for each population; Variability of equipment, operators and individual factors affect results; large individual errors for predicting MM; no BIA specific equations validated for extreme BMI	standardised measurement protocols lacking; lack of cutoff points for diagnoses; limited by excessive oedema
Associations of measurements	Abdominal L3 SM CSA correlates well with WB SM estimates by DEXA in cancer (Price 2019); SMI cutoff points correlates with morbidity and mortality in cancer populations (Price et al., 2019)		Reasonably valid method to assess regional and total FM in a wide group of adult clinical patients (Sheean 2020); Appendicular LM is correlated with CT and MRI measures of skeletal MV in health populations (Buckinx 2018); No studies explored validity of DXA for LM ax in any clinical population (Sheean et al., 2020)	High reliability when measuring appendicular LM between using same operator and assessing 2 different individuals; Low agreement when compared to DEXA measurement of appendicular LM	When compared to DEXA, CT, and MRI, US is a reliable and valid tool for the assessment of muscle size in healthy population (Price 2019) and older adults (based on large muscles); no data to support its validity in specific patient populations (Sheean et al., 2020)

CT - computer tomography ; MRI - magnetic resonance imaging; DEXA - dual X-ray absorptiometry; BIA - bio-electrical impedance analysis; BC – body composition; US – ultrasound; SMM – skeletal muscle mass; AT – adipose tissue; FFM – fat free mass; BMC - bone mineral content; LM – lean mass; FM – fat mass; L3 SMI - lumbar vertebrae 3 skeletal muscle index; WB = whole body; FFMI – fat free mass index; MM – muscle mass; MV – muscle volume; Ax - assessment

2.2.5 Dual energy X-ray absorptiometry (DEXA), reference standard used to measure body composition

Introduction

DEXA is an imaging technique first used in clinical practice in 1987 (Sawicki et al., 2021) and is the gold standard for measuring bone mineral density but has, over the past 30 years, grown in technology to be used in three component body composition analysis (Shepherd et al., 2017). Body composition is measured through the attenuation of high and low energy X-rays as they travel through various tissues, namely bone mineral content (BMC), and soft tissue divided into lean and fat tissue (Bazzocchi et al., 2016). DEXA will be discussed in relation to methodology, interpretation, validity and its value in cancer populations.

Methodology

The International Society for Clinical Densitometry (ISCD) have recommended standardised protocols to reduce error in measurements. This includes daily calibrations of DEXA machines and ensuring the technician's skill (Hangartner et al., 2013). The correct placement of the patient is essential where head is placed 3cm lower than the top horizontal line, with body central and arms and legs not touching, without any patient movement during measurements (Hangartner et al., 2013; Libber et al., 2012). To limit variability and detect actual body composition changes, hydration status, meals and physical activity should be defined as fluid status and intestine and stomach contents can impact both fat mass and lean mass measurements (Bazzocchi et al., 2016).

Interpretation of results

There are various makes of DEXA scans (Hologic, GE Lunar) that previously used their own equations to calculate fat and lean mass. Since 2009, scans' software has been standardised to use the National Health and Nutrition Examination Survey (NHANES) reference population (Shepherd et al., 2017) to interpret measurements. However, there is uncertainty about the generalisability of any reference population.

ISCD recommends the following parameters to be reported for body composition: bone mineral density, bone mineral content, total mass, total lean mass (that may also include bone free), total fat mass, and percent fat mass (Petak et al., 2013). Optional muscle mass parameters can be calculated from these suggested reported parameters and include appendicular lean mass (ALM), appendicular lean muscle index (ALMI), and fat mass index (FMI) where Studenski et al., (2014) recommends adjusting muscle mass to BMI. Interpretation of results have included using Z scores, percentiles and cutoff points according to different representative reference populations (Baumgartner et al., 1998; Clark et al., 2016; Gould et al., 2014; Kelly et al., 2009; Studenski et al., 2014).

Within cancer research related to cachexia, sarcopenia and malnutrition, less information is available regarding measuring and interpreting fat mass, which is understandable as fat mass is not a determining

factor for these conditions. One of the recommendations of the ISCD is to measure the fat mass of patients with muscle weakness and physical impairment (Bazzocchi et al., 2016; Sheean et al., 2020). Newer DEXA technology can determine visceral adipose tissue, subcutaneous adipose tissue and the ratio of android to gynoid fat mass as fat distribution is more helpful than total fat mass in clinical health (Bazzocchi et al., 2016). Kelly et al., (2009) provides interpretation of fat mass, fat mass index and percentage fat mass using the 1999 to 2004 NHANES population where percentiles were derived from calculated z scores, then categorised into under fat, average fat, over fat and excess fat.

With variability in types of DEXA machines, technician skill, using different parameters and interpretation of body composition depending on the accessibility to representative reference populations, makes interpretation challenging and difficulty exists in comparing measurements, particularly in the cancer population.

Validity of using DEXA to measure body composition in cancer patients

The validity of using DEXA for body composition analysis in healthy populations is well demonstrated when compared to MRI and CT imaging. However, a most recent systematic review in 2020 investigated the validity of using DEXA in clinical populations (Sheean et al., 2020). Using DEXA to determine fat mass in adult patients is valid.

However, there was insufficient research to recommend using DEXA for lean mass analysis in clinical populations as no research group assessed validity, including sensitivity and specificity parameters (Sheean et al., 2020). Despite this lack of research, the major research groups involved in diagnostic criteria for sarcopenia have used DEXA as a tool to determine muscle mass (Cruz-Jentoft et al., 2019; Studenski et al., 2014) However, when focusing on cancer research, there is a larger body of evidence that uses CT and MRI scans to determine body composition as, for some cancers, these imagining techniques are used for diagnostic and cancer categorisation purposes (Brown et al., 2018). Whereas CT and MRI scans are now seen as the gold standard for the analysis of body composition, DEXA is the reference standard used in both research and clinical settings when available (Kuriyan, 2018).

DEXA measured body composition in cancer patients and associations

There has been limited research investigating the relationship of muscle mass as measured by DEXA on morbidity and mortality in cancer patients as compared to research using CT scans to investigate associations of muscle mass with clinical and patient centred outcomes. Focusing on DEXA related studies, associations of reduced muscle mass with overall survival, physical activity, function and inflammation are considered in this section (Table 2.6).

When considering overall survival and reduced muscle mass, results are not in agreement. Research that focused on homogenous cancer populations, found a positive association between muscle mass and overall survival (Chambard et al., 2018; Limpawattana et al., 2018). Interestingly, Tenuta et al., (2021) who focused on advanced non-small cell lung cancer, did not find an association of muscle mass with

overall survival, but did find an association with progression free survival. A secondary analysis revealed that patients with low muscle mass that only received first line treatment, as opposed to second- and third-line treatment, demonstrated an association with overall survival. This may be because of less confounding factors impacting survival in patients that received first line treatment over a shorter time (Tenuta et al., 2021). Wallengren et al. (2013) did not find an association in their heterogenous advanced cancer group. A review by Wiegert et al. (2020), included metastatic incurable cancer research using a variety of methods to measure muscle quantity [including the former two research groups mentioned (Chambard et al., 2018; Wallengren et al., 2013)]. This systematic review found that evidence was too scant to associate low muscle mass with overall survival (Wiegert et al., 2020). These discrepancies in the literature may be related to cancer heterogeneity, muscle mass variables and reference population cutoff points used in relation to the research population and measure of muscle mass at one time point only, rather than longitudinally.

A statistically significant association was found with low muscle mass and physical activity and function (Table 2.6). However, Anderson et al. (2019) found that ALM predicted physical function in gastro-intestinal and gastro-urinary cancer patients in all physical activity measures excluding handgrip strength and hip extension one repetition maximum test (compared to other measures like stair climb power, chest press, lateral pull, upper back, knee flexion and extension tests); (Anderson et al., 2020). Despite Jeffery et al. (2019) using ASMI as a muscle mass parameter and measuring physical activity with an accelerometer in incurable malignant pleural mesothelioma patients, the results were comparable. Interestingly, patients that had low ASMI, did not self-report lower fatigue and physical functioning levels. Further research is warranted to determine whether increasing muscle mass translates to improving participation in physical activity as there may be compensatory mechanisms to reduce activity with low muscle mass (Jeffery et al., 2019).

Research investigating low muscle mass and inflammation found statistical association across homogenous and heterogenous cancer populations (Table 2.6). Wallengren et al., (2015) concludes that CRP may be a useful marker in the catabolism of cancer cachexia. (Chambard et al., 2018) found that loss of muscle mass was particularly greater during the last 12 to 24 months of life in patients with raised CRP. These results are not surprising as any trauma or diseased state elicits an inflammatory response that causes weight loss which impacts body composition differently than weight loss caused by starvation (Laviano et al., 2015). Despite this knowledge being ubiquitous, intervention to ameliorate the impact of inflammation upon body composition and drive positive patient outcomes has remained challenging, therefore research continues (Arends et al., 2021; Avancini et al., 2021).

Considering the literature that focused on measuring muscle mass using DEXA in cancer patients, low muscle mass has an impact on patients' morbidity and mortality. However, comparing studies remain challenging. Reasons include the heterogenous nature of cancer, from cancer type and stage to treatment options; muscle mass parameters and reference populations with cutoff points used; differing

methods used to measure associated factors; types of studies in terms of prospective, retrospective, cross-sectional or longitudinal research; quality of research that may include limited recruitment numbers, statistical methods, not accounting for confounding factors. Therefore, standardisation of cancer research is essential to screen, diagnose and holistically treat cancer patients with cancer cachexia to positively impact patients' clinical outcomes and mortality.

Conclusions

There is no one method to measure muscle mass in cancer patients that is suitable for all health care settings. However, DEXA can be used as a reference standard in research and clinical practice to assess lean tissue considering the limitations of using DEXA, lack of standardisation of equations, calibration materials across different manufacturers algorithms and body regions (Buckinx et al., 2018). Within resource limited health care settings like South Africa, using DEXA to measure body composition alone, is not feasible and therefore alternative methods are needed within the cancer population.

Table 2.6 Summary of research using DEXA to measure body composition presenting associations of lean body mass with cancer factors

Factor	Reference	Study population	DEXA variable	Cutoff points & reference population used	Relationship with LBM variable	Relationship details
Overall survival	Tenuta 2021	Advanced non-small cell lung cancer (n=47)	ASMI	Cruz-Jentoft et al. 2019: <7.0 kg/m2 for males and < 5.5 kg/m2 for females (rounded up to <6 kg/m^2 in article); Gould 2014	No Yes for PFS	NA ↓ ASMI ↓ PFS
	Chambard et al. 2018	Metastatic lung adenocarcinoma (n=64)	ASMI (in article term used was ALM/ht^2)	Fearon et al. 2011: 7.26 kg/m2 for males and <5.45 kg/m2 for females; Baumgartner et al. (1998)	Yes	↓ ASMI ↓ OS
	Wallengren et al. 2013	Advanced heterogenous cancer (n=405)	ASMI	Fearon et al. 2011: 7.26 kg/m2 for males and <5.45 kg/m2 for females; Baumgartner et al. (1998)	No	NA
	Limpawattana et al. (2018)	Biliary tract cancer (n=75)	ASM	ASM <19kg	Yes	↓ ASM ↓ OS
Physical activity	Jeffery et al. 2019	Incurable Malignant pleural mesothelioma (n=52)	ASMI	Fearon et al. 2011 7.26 kg/m2 for males and <5.45 kg/m2 for females	Yes	↓ ASMI ↓ physical activity
Physical function	Anderson et al. (2020)	Gastro-intestinal and gastro-urinary cancer (males only n=28 with CC, n=28 cancer without CC; n=19 controls)	ASMI & ALM	Fearon et al. 2011 <7.26 kg/m2 for males; Baumgartner et al. (1998)	Yes	↓ ASM ↓ physical function

Factor	Reference	Study population	DEXA variable	Cutoff points & reference population used		Relationship with LBM variable
Inflammation	Tenuta 2021	Advanced non-small cell lung cancer (n=47)	ASMI	Cruz-Jentoft et al. 2019: <7.0 kg/m2 for males and < 5.5 kg/m2 for females (rounded up to <6 kg/m^2 in article); Gould 2014	Yes (for most markers)	↓ ASMI ↑ WCC ↑ neutrophils, ↑ NLR, ↑ LLR, ↑ CRP ↑ fibrinogen ↑ Interleukin-6 (No relationship with TGF-α, TNF- α, transferrin, ferritin, ESR)
	Chambard et al. 2018	Palliative lung adenocarcinoma (n=64)	ASMI (in article term used was ALM/ht^2)	Fearon et al. 2011 7.26 kg/m2 for males and <5.45 kg/m2 for females; Baumgartner et al. (1998)	Yes	↓ ASMI ↑ CRP
	Wallengren et al. 2015	Palliative cancer patients (n=471)	ASMI (called ALMT in article i.e. with bone)	Fearon et al. 2011 7.26 kg/m2 for males and <5.45 kg/m2 for females; Baumgartner et al. (1998)	Yes	↓ ASMI ↑ CRP

DEXA – dual energy X-ray absorptiometry; ASMI - appendicular skeletal muscle mass index; PFS: progression free survival; NA: not applicable; ASM: appendicular skeletal mass; OS - overall survival; ALM – appendicular lean muscle; NLR: neutrophil/lymphocyte ratio; LLR: leukocyte/lymphocyte ratio; WCC: white cell count; CRP: c-reactive protein; TGF-α: tumour growth factor; TNF- α: tumour necrosis factor; ALMT: appendicular lean muscle tissue

2.2.6 Alternative methods to estimate body composition

Introduction

With recommendations to analyse body composition as part of nutritional status assessment, malnutrition (Cederholm et al., 2019), sarcopenia (Cruz-Jentoft et al., 2019) and cancer cachexia diagnoses (Arends et al., 2021; Fearon et al., 2011), alternative methods of estimating muscle mass are essential in health care settings with limited resources and access to more technical methods like CT scans, MRI and DEXA. Anthropometry, an alternative method, determines body size and proportions by weighing, taking length, measuring limb circumferences, bone dimensions and skinfold thickness (Lee, 2013). In addition to anthropometry, other methods like estimating appendicular skeletal muscle from calf circumference and global physical examination will be discussed in relation to methodology, interpretation, validity, advantages, limitations and its value in cancer populations. Table 2.7 presents the equipment used, advantages and limitations of the various methods discussed.

Table 2.8 presents the validity of alternative markers of muscle mass to a reference standard or predicting clinical outcomes (survival / mortality) in cancer populations. For clinical practice, good validity is needed in comparison to the reference standard for muscle mass markers to be considered as alternatives in all circumstances related to cancer patients. A variety of different statistical tests, namely sensitivity, specificity, area under the curve, Cohen's kappa (construct and criterion validity), hazard or odds ratio for predictive validity based on clinical outcomes are needed (Van Bokhorst-de van der Schueren et al., 2014) to holistically make clinical decisions to utilise these alternative muscle mass markers.

2.2.7 Skinfold thickness (SFT)

Introduction

Measuring skinfold thickness is a popular method within clinical settings as part of the nutritional assessment. It measures the thickness of the double layer of skin and subcutaneous fat at various specified sites, thereby estimating body composition. In overnutrition, estimating body fat assists in determining the nature of obesity and is associated with non-communicable diseases. In undernutrition, estimating protein and fat reserves assists in our understanding of its impact upon morbidity and mortality (Lee, 2013).

Method

To improve the reliability of skinfold thickness measurements, standardised protocols to identify anatomical sites and perform measurements are essential amongst researchers and clinicians. The protocol as described by Lee (2013) was used in the current research and a detailed description can be found in chapter three, methods, section 3.4.8.

Madden & Smith (2016) reports the various textbooks that describe the location of the anatomical sites, together with pictures provided in the open access NHANES manual (Madden & Smith, 2016). There are other protocols that exist with slight variations with regards to the approach to conducting measurements: European protocols measure the left had side of the body; North America and Canada measure the right side of body; clinicians who subscribe to the International Society for the Advancement of Kinanthropometry (ISAK) guidelines, conduct all measurements on the right-hand side. In practice, there is no significant difference in left or right measurements, however, being consistent and standardised in methodology is expected (Lee, 2013).

Other differences in guidelines exist: one either has to pinch on the anatomical site (ISAK guidelines) or pinch 1cm proximal to the anatomical site (Lee, 2013); placing the calipers 1cm away from the pinch (ISAK guidelines) or on the identified site (Lee, 2013); dial needs to be read two seconds after the measurer releases the callipers (ISAK guidelines) or four seconds after (Lee, 2013). Determining the timing of when to read the dial accounts for the compressibility of the skin and adipose tissue. This has the most impact on the accuracy of the measurements. Even with standardisation of technique, there is variability with the skin and adipose tissue with different individuals and within individuals at different sites (Lee, 2013).

Table 2.7 Alternative markers of muscle mass

Alternative methods	Skinfolds	cAMA & MAMC	MUAC	Calf circumference	Estimated ASM equations	Global physical examination
References	Lee (2013)	Lee (2013)	Lee (2013)	Gonzalez et al., (2019)	[a]Baumgartner et al., (1998) [b]Santos et al., (2019)	Jager-Wittenaar & Ottery (2017)
Equipment	Callipers Brands: Lange mainly used in North America; Harpenden and Holtain mostly used in UK and Europe	Non-stretchable tape + calipers	Non-stretchable tape	Non-stretchable tape	Non-stretchable tape + equation	Observation and examination
Advantages	Inexpensive, mobile, easy & quick to perform	Universally applicable, non-invasive, inexpensive, mobile and easily performed at the bedside; useful in patients with oedema	Universally applicable, non-invasive, inexpensive, mobile and easily performed at the bedside; useful in patients with oedema	Universally applicable, non-invasive, inexpensive, mobile and easily performed at the bedside, standing or lying, left or right leg	Inexpensive, mobile and easily performed at the bedside	Universally applicable, non-invasive, inexpensive, mobile and easily performed at the bedside
Limitations	Assessor skill, type of calipers & equations used impacts measurement accuracy; cannot measure intra-abdominal fat, so more useful in lean individuals; fat compressibility & skin thickness variation impacts accuracy	cAMA overestimates muscle in obese; as for TSF	Includes bone; crude tool to detect early body composition changes	Affected by peripheral oedema and obesity	Both equations need to be validated within the population measured	Requires assessor experience to improved perception of difficulty

cAMA – corrected arm muscle area; MAMC – mid arm muscle circumference; MUAC – mid upper arm circumference; ASM – appendicular skeletal muscle

[a] Baumgartner et al., (1998): ASM (kg) = 0.2487(weight) + 0.0483(height) 0.1584(hip circumference) + 0.0732(grip strength) + 2.5843(sex) + 5.8828 [R2 = 0.91, standard error of estimation (SEE) = 1.58 kg]

[b] Santos et al., (2019):ASM (kg) =−10.427 + (calf circumference × 0.768) − (age × 0.029) + (sex × 7.523) + (white × 0 or black × 2.203 or Mexican American ×−0.540 or other ×−0.402) where male = 1 and female = 0

Table 2.8 Validity of alternative markers of muscle mass to reference standard or predicting clinical outcomes (survival / mortality) in cancer populations

Reference	Study design	Population	Alternative / estimate tools	Reference tool	Validity[a]
Lidoriki et al., (2019)	Cross-sectional study	108 Oesophageal & gastric cancer admission for surgery	MUAC	CT L3 SMI for RMM	Fair correlation
			AMA		Fair correlation
			CC		Fair correlation
Jones et al., (2020)	Comparison study	100 CRC inpatients for surgery	MAMC	CT L3	Poor Se (38%) & Spe (88%) Poor K agreement
Gort van Dijk et al., (2021)	Cross-sectional study	49 oesophageal & gastric cancer	MAMC	CT CSA & PMI	Poor ICC with CT PMI (no correlation with CT CSA) Poor Se (30%) and Spe (86%)
Souza et al., (2020)	Cohort	188 CRC pts	cAMA	CT SMI	Poor Se (27%) & Spe (94%) Poor K agreement Poor HR
			CC		Poor Se (49%) & Spe (86%) Poor K agreement Poor HR
			GPE		Fair Se (79%) & Spe (81%) Fair K agreement Poor HR
Sousa et al., (2020)	Prospective cohort	250 pts any tumour with CT scan	CC	CT SMI	Good HR for CC but not CT
Sousa et al., (2022)	Cross-sectional study	219 Ca pts with CT scans	CC	CT SMI	Total: fair Se (66%) & Spe (55%), poor K agreement, 65% accuracy, fair AUC Fair Se & Spe for males, females < 60 years & ≥60 years Poor K agreement for all but <60 years have fair K agreement Fair AUC for all but females have good AUC

MUAC – mid upper arm circumference; cAMA – corrected arm muscle circumference; CC – calf circumference; CT L3 SMI – computer tomography lumber 3 skeletal muscle index; RMM – reduced muscle mass; CRC – colorectal caner; MAMC – mid arm muscle circumference; Se – sensitivity; Spe – specificity; K – kappa Cohen; ICC – intraclass coefficient; HR – hazard ratio; CSA – cross sectional area; PMI – psoas muscle index; GPE = global physical examination; AUC – area under the curve

[a]As per Van Bokhorst-de van der Schueren et al., (2014) interpretation

Interpretation

Percentage body fat cannot be estimated using a single skinfold site as no equations exist and there is a lack of agreement regarding which site to use. However, the triceps skinfold is the most used single site to compare an individual's measurement to the reference population (Lee, 2013).

In children to young adults, the sum of triceps and subscapular skinfolds can be used to determine percentage body fat. However, to maintain modesty, the skinfold from the medial calf can be used instead of the sub-scapular measurement (Lee, 2013). In addition, Frischanco et al., (2008) developed percentile tables for both males and females aged two to 90 years for the sum of the triceps and subscapular skinfolds. It was determined that sums of measurements >85th percentile denoted excess fat as linked to greater risk for hypertension and hypercholesterolaemia (Lee, 2013).

Different equations exist where three or more anatomical sites are measured to estimate body density, followed by percentage body fat. Equations can be population specific, based on gender and different ages but more recently, generalisable equations have been developed that can be used for any population but are age and gender specific (Madden &Smith, 2016). The most popular equations that are used in clinical practice are those developed by Durnin and Womersley (1974) for body density. Thereafter, percentage body fat is calculated using one of two equations, Brozek or Siri (Lee, 2013).

There are various methods of interpretation for percentage body fat. For children <18 years of age, the sum of biceps, triceps, subscapular and supra-iliac crest can be calculated, and percentage fat can be determined from a table developed by Westrate and Deurenberg (1989). For adults older than 18 years, after calculating percentage body fat, interpretation can be made as follows: using a table developed by Nieman (2003) body fat percentage can be classified as unhealthy (too low or too high), acceptable (lower end or upper end); using a table developed by National Institute of Health / World Health Organisation, body fat percentage can be classified as under fat, healthy, over fat and obese (World Health Organisation, 2000).

Validity

Totosy et al., (2020) tested and retested the reliability (consistency) and validity (accuracy) of using seven skinfold sites using Lang callipers to estimate percentage body fat compared to determining percentage body fat using air displacement plethysmography (ADP). ADP has been validated against three compartment models, namely DEXA and MRI, and four compartment models. Despite the excellent intraclass correlation coefficient and good inter-rater reliability, estimating percentage body fat using callipers for repeated measurements was highly inconsistent and demonstrated poor validity against ADP (Totosy de Zepetnek et al., 2021). Reliability of skinfold measurements can be improved through technician training using standardised protocols and monitoring (Madden & Smith, 2016).

Triceps skinfold measurement as an independent prognostic value is not clear from existing research (Madden & Smith, 2016). However, one cancer related research found that in lung cancer patients that

were malnourished as determined by GLIM together with reduced TSF, in comparison to those that were malnourished with normal SFT, had better predicted prognosis (Yin et al., 2022).

Associations related to skinfold measurement in cancer research within 5 years

Despite triceps skinfolds being easily accessible to measure both in ambulatory patients and those that are bedbound (Jensen 1981), limited cancer research was found.

Reduced quality of life and reduced performance status was significantly associated with lung cancer patients diagnosed with malnutrition via GLIM and had reduced TSF in comparison to malnourished patients with a normal TSF (Yin et al., 2022); (Table 2.9). In another study considering cancer cachexia as determined by Fearon et al., (2011) diagnostic criteria, reduced TSF was significantly associated with 1 year survival, not MAMC nor calf circumference (Ge et al., 2021); (Table 2.9). Interestingly, a study by Silva et al., (2022), investigated hepatocellular carcinoma patients and found that TSF was not statistically different in malnourished patients but was negatively correlated to the Child-Pugh score, prognostic tool for liver disease. Both Yin et al., (2022) and Ge et al., (2021) determined the optimal cutoff points for TSF within the studies population, which appear to yield associations. As there are limited studies that investigated skinfold measurements, no definitive conclusions may be drawn from the clinical usefulness of skinfold measurements, particularly TSF in the heterogenous cancer population.

Conclusions

Using skinfold thickness measurements within clinical practice may be helpful when there is no access to technical methods of body composition assessment. However, one needs to consider the limitations and the need for specialised training, standardisation and monitoring of skinfold techniques when interpreting individual results. There are other anthropometric measurements that may be useful, either separately or in combination with skinfold measurements.

2.2.8 Mid upper arm circumference (MUAC)

Introduction

Mid upper arm circumference (MUAC) is part of anthropometry that incorporates limb circumference, thus accounting for both bone, fat and muscle compartments. It was designed as a quick nutritional screening tool where cutoffs were established at <22cm for women and <23cm for men to identify patients at risk of chronic energy deficiency (James et al., 1994). In addition, as MUAC has a high correlation with BMI, it can be used to estimate BMI. Furthermore, with TSF measurement, corrected arm muscle area can be calculated (Madden & Smith, 2016).

Method

The method used in this research is described in detail in Chapter3, section 3.4.8. The right arm is used as per Lee (2013) protocol but as there is little difference in measuring the left or right arm, any arm may be measured (Elia, 2003). In clinical practice, being consistent with individual measurements is key.

There is slight discrepancy in methods: Lee (2013) describes the mid-point as being between the acromion process of the scapula and inferior margin of the olecranon process of the ulna; Elia (2003) describes the mid-point as between the tip of the acromium process and tip of the olecranon.

Interpretation

Interpretation of MUAC varies, where, within the South Africa context, the WHO (1995) is generally used in clinical practice: in males < 23cm and in females <22cm indicates malnutrition. In the United States, using their relevant population data, slightly higher cut offs denote a BMI <18.5kg/m2 for males and females (Flegal & Graubard, 2009).

Validity of MUAC to measure body composition in cancer patients

MUAC is not validated as a prognostic tool in different populations as results are inconsistent (Madden & Smith, 2016). Within cancer research, MUAC demonstrated fair correlation with CT scan in patients admitted for surgery (Lidoriki et al., 2019); (Table 2.8). In addition, MUAC was used as an alternative measure of reduced muscle mass as part of GLIM diagnostic criteria, however, it could not predict 6-month mortality (Contreras-Bolívar et al., 2019).

Associations related to MUAC within cancer populations (research within 5 years)

Two research articles were found that included MUAC. No significant difference was found in diagnosing malnutrition using MUAC or PG-SGA in a small group of hepatocellular carcinoma patients (Silva et al., 2019), most likely because high prevalence of malnutrition. MUAC was statistically associated with malnutrition as per GLIM but not associated with higher mortality in haematological cancer patients (Yilmaz et al., 2020); (Table 2.9).

Conclusions

As it was designed as a screening tool, and measures bone, fat and muscle mass, MUAC appears to be a crude tool as a marker for body composition as may only be helpful in extreme conditions of malnutrition with cutoff points related to low BMI. In cancer patients that are obese, MUAC may not be sensitive enough to identify loss of muscle mass with minimal weight loss and normal or elevated BMI.

2.2.9 Corrected arm muscle area (cAMA) and mid arm muscle circumference (MAMC)

Introduction

Mid arm muscle circumference and arm muscle area can be calculated to estimate fat free mass or lean mass by measuring MUAC and TSF. Within cancer research and clinical practice, both cAMA and MAMC appear to be used as alternatives to measuring muscle mass in the absence of technical methods like DEXA, CT and MRI scans (Madden & Smith, 2016). However, cAMA is a preferred nutritional index as it changes more in response to development, growth or undernutrition than MAMC changes (Lee, 2013).

Method

In 1974, Frisancho devised an equation that incorporates TSF and MUAC measurements to calculate MAMC (Frisancho, 1974); using the MAMC, Gurney and Jelliffe (1973) developed an equation that calculated arm muscle area (Gurney & Jelliffe, 1973). Heymsfield et al., (1982) compared its accuracy to computer axial tomography of the arm muscle area and found an over estimation of muscle mass due to the equation being based on certain assumptions. Some of these include the arm muscle being circular and the area of the arm bone. An amended equation was developed to account for these assumptions and was found to be directly associated with total body muscle, despite demonstrating a 7–8% average error rate per person (Heymsfield et al., 1982). Please refer to Chapter3, section 3.4.8. for the method used in this research.

Interpretation

Both MAMC and cAMA can be interpreted using population standards or comparing serial measurements in an individual (Madden & Smith, 2016). As there are no international population standards, the United States population standards are used, with a few other smaller data sets that are available for MAMC. More recently, Frisancho et al., (2008) developed percentile tables from the 5th to the 95th percentile for males and females aged two – 90 years for AMA, corrected AMA for those older than 18 years. Identifying the gender, age and AMA measurement using the tables, allows the percentile to be determined. This is then interpreted using a table that categorises the range of percentiles into descriptors that range from wasted through to high muscle (Frisancho, 2008).

Validity of MAMC and cAMA to measure body composition in cancer patients

The standard and corrected AMA equations have not been validated in the elderly population and overestimates AMA in obese individuals (Heymsfield et al., 1982).

The limited cancer related research investigating the validity of AMA and / or MAMC against CT as a standard for body composition, found poor overall sensitivity and specificity, poor agreement (Gort-van Dijk et al., 2021; Jones et al., 2020) and poor hazard ratio (Souza et al., 2020). Despite limitations with the measurement accuracy, the interpretation of the MAMC or AMA varied with two using elderly standard

populations (Gort-van Dijk et al., 2021; Souza et al., 2020) and the third using an America standard population for UK patients. A study that used correlation coefficients found fair correlation between AMA and CT scan skeletal muscle index (Lidoriki et al., 2019), perhaps highlighting the need for relevant reference populations or international standards (Table 2.8).

Associations related to MAMC and cAMA within cancer populations (research within 5 years)

Wiegert et al., (2021) identified AMA, BMI and percentage weight loss through hierarchical cluster analysis and determined cutoff points that discriminated stages of cancer cachexia and differences in body composition, quality of life and overall survival. When comparing cancer cachexic patients using Fearon et al., (2011) diagnostic criteria, MAMC was not significantly associated with one year survival (Ge et al., 2021). In contrast, in colorectal cancer patients taking reduced muscle mass into account via CT scans, cAMA was significantly associated with reduced survival and malnutrition (Souza et al., 2020). cAMA representing the reduced muscle mass component of sarcopenia, was also significantly associated with malnutrition in palliative care cancer patients (da Silva et al., 2019). It was found in hepatocellular carcinoma patients that MAMC was able to diagnose malnutrition without significantly different results in comparison to PG-SGA (Silva et al., 2019).

Conclusions

From the limited cancer research, cAMA may be a better nutritional index and muscle mass marker than MAMC as it accounts for only the muscle mass without the bone and fat components (Lee, 2013). As with other alternative muscle mass markers, the limitations need to be considered, particularly the methodology related to clinician training and interpretation of measurements.

2.2.10 Calf circumference

Introduction

Calf circumference is another limb circumference measurement of anthropometry and is gaining interest as an alternative muscle mass marker, particularly as most of the skeletal muscle is found in the lower limbs and more indicative of total body muscle mass (Madden & Smith, 2016). Calf circumference is an easy measurement to perform in resource limited settings (Gonzalez et al., 2021).

Method

The method used in this research has been described in Chapter3, section 3.4.8. The usefulness of measuring calf circumference is that it can be performed upon standing, in supine position, left or right leg and across the widest circumference of the calf (Madden & Smith, 2016). Being consistent within clinical practice is important to maintain accuracy and standardisation of methods. The intra- and interrater variability is similar to MUAC and less than measuring TSF (Madden & Smith, 2016).

Interpretation

Calf circumference measurements can either be compared to population standards presented as percentiles (Madden & Smith, 2016) or categorised as low when using cutoff points determined either as one or two standard deviations compared to a healthy young reference population (Gonzalez et al., 2021; Rolland et al., 2003). Ideally, interpretation is best when using a relevant refence population. Gonzalez et al., (2021) cutoff points of 33cm and 34cm for females and males, were used respectively.

Validity of calf circumference to measure body composition in cancer patients

Gonzalez et al., (2021) found a strong correlation of calf circumference with DEXA appendicular lean muscle index using data from the National Health and Nutrition Examination Survey (NHANES) 1999 to 2006.

Validation of calf circumference against technical approaches in cancer patients, mainly includes CT scans yields mixed results. Lidoriki et al., (2019) demonstrated fair correlation in gastrointestinal and oesophageal patients. One article found good predictive validity as calf circumference could independently predict death in patients with confirmed tumours, not CT scans (Sousa et al., 2020). A possible explanation is that the cutoff points for calf circumference were population specific unlike the CT skeletal muscle index determined from the cross-sectional area of lumber vertebra three (Sousa et al., 2020). Two other articles found that calf circumference ranged from poor to fair validity against CT scans (Sousa et al., 2022; Souza et al., 2020). To confidently recommend calf circumference as an alternative marker for muscle mass in cancer patients, further research needs to be conducted that is multi-centred across the globe with standardised approaches to reference standards and interpretation, considering the heterogeneity of cancer patients and the myriad factors that may confound the results (Table 2.8).

Associations related to calf circumference within cancer populations (research within 5 years)

Most cancer research appears to investigate calf circumference and its association with mortality or survival, with results that are not unanimous. Both Ge et al., (2021) and Yilmaz et al., (2020) found no association with one year survival in cancer cachexic patients when adjusted for confounding factors nor an association with increased mortality in haematological cancer patients, respectively (Table 2.9). Yilmaz et al., (2020), for their Turkish patients used one cutoff point for both males and females i.e., 31cm without a reference cited in the paper. This may have been obtained from Rolland et al., (2003) that determined cutoff point in elderly community French women for sarcopenia, therefore not appropriate for their population.

Both Da Silva et al., (2019) and De Sousa et al., (2022) found associations with reduced survival in advanced palliative cancer patients and ability to predict survival in gastrointestinal and colorectal patients, respectively. Interestingly, in these Brazilian populations, the cutoff points were determined from young adult population from the same location (Table 2.9). Developing cutoff points from relevant young populations was recommended by Cruz-Jentoft et al., (2019) in their European consensus recommendations for sarcopenia.

Statistical association of calf circumference was found with malnutrition (as per PG-SGA) and nutritional risk (as per NRS-2002) in colorectal and gastrointestinal and older gastrointestinal cancer patients (da Silva et al., 2019; Qiu et al., 2023). However, it was found that when adjustments for confounding factors were made, calf circumference was not an independent risk factor for nutritional risk as was CT determined skeletal muscle mass and handgrip strength (Qiu et al., 2023); (Table 2.9). Relevant cutoff points were used for this research, but one could consider the use of NRS-2002 in elderly cancer populations as a screening tool for nutritional risk. Refer to Chapter 2, section 2.3 for further information on screening tools.

Conclusions

With the heterogeneity of the cancer population, the different reference populations and cutoff points used in research, drawing conclusions of whether calf circumference can be used as a muscle mass marker is challenging. However, most research demonstrated high specificity of calf circumference implying that it may be used to screen patients to identify those without reduced muscle mass (Table 2.8).

2.2.11 Equations that estimated appendicular skeletal muscle (ASM)

Introduction

There are several equations that have been developed to estimate ASM, in a variety of health conditions that compare to different reference standards, namely CT, MRI, BIA and DEXA (Abdalla et al., 2023). Our focus is on two equations developed against DEXA, of which there are a total of 122 equations that exist globally (Abdalla et al., 2023).

Baumgartner et al., (1998) used a subsample comprising of an elderly population to develop and cross-validate the estimated ASM equation against DEXA ASM. He further tested the equation in another healthy elderly group of volunteers to test accuracy (Baumgartner et al., 1998). More recently, Santos et al., (2019) developed an equation from the NHANES 1999 to 2006 sample that incorporated adults from 18 years and older representing a variety of ethnicities. Both researchers caution the use of these equations without first validating it in different settings (Baumgartner et al., 1998; Santos et al., 2019). Interestingly, in the supporting guidelines for the assessment of muscle mass for GLIM diagnostic criteria, the equation from Santos et al., (2019) was cited (Compher et al., 2022).

Method

Both equations are simple to calculate if standardisation exists around measuring the different anthropometrical variables that are needed. Baumgartner et al., (1998) equation requires the measurements of weight in kilogrammes, height and hip circumference in centimetres and grip strength in kilogrammes with methodologies used stated clearly in their research. The advantage of Santos et al.,

(2019) equation is that only calf circumference is required to be measured in centimetres with age, gender and ethnicity needed. Refer to chapter 3, section 3.4.8 for method used in this research.

Interpretation

For the Baumgartner et al., (1998) equation, ASM in relation to height squared is needed for interpretation. Their recommendation is based on the calculation of cutoff points that are -2 standard deviations less than the Rosetta study reference population of young healthy adult values of ASMI (females <5.45kg/m^2; males <7.26kg/m^2 denoting low ASMI). For the Santos et al., (2019) equation, interpretation was not discussed in the article as it was used to estimate ASM only. However, Landi et al., (2022) used a large Italian population that were older than 80 years where cutoff points were determined at the 25th percentile for the estimated ASM values (females <19.62kg; males <11.07kg denoting low estimated ASM). No other studies were found that used Santos et al., (2019) equation with interpretation.

Validity of equations that estimate ASM in cancer patients

Santos et al., (2019) equation that incorporated calf circumference, gender, age and ethnicity had a high Lin's concordance correlation coefficient >0.9 against DEXA and accounted for 90% of the DEXA measured ASM variation. Landi et al., (2022) found that ten-year survival in community dwelling elderly population was predicted by low estimated ASM. No research conducted in the cancer population was found that validated the two equations.

Associations related to equations that estimate ASM within cancer populations (research within 5 years)

The only research found that incorporated estimated ASM was Da Silva et al., (2019) that used estimated ASM to calculate ASMI and incorporate the value into the sarcopenic diagnostic criteria, namely low estimated ASMI and low HGS. Sarcopenia was statistically associated with malnutrition, hypoalbuminaemia and >5% weight loss in 6 months (da Silva et al., 2019); (Table 2.9).

Conclusions

As equations that estimate ASM are generally validated in specific populations, there is a call for equations that estimate ASM to be determined and validated for populations based in Africa and Antarctica (Abdalla et al., 2023). There is scant research based in cancer populations and it may be warranted to explore the Santos et al., (2019) equation further as it is only reliant on one anthropometrical value, calf circumference. In addition, with the new GLIM guidelines and recommendations for alternative muscle mass markers, there is further reason to investigate calf circumference in equations that estimate ASM together with interpretation through validated cutoff points.

2.2.12 Global physical examination

Introduction

Nutrition focused physical examination includes the subjective examination for nutritional deficiency signs and assessment of muscle, fat and fluid status as part of the competencies for practising dietitians as determined by the Health Professions Council of South Africa (Health Professions Council of South Africa, 2022). For our purposes, we are focusing only on the assessment of muscle, fat and fluid status.

It has been recognised that malnutrition can change the physical appearance of a patient and therefore Detsky et al., (1987) developed the Subjective Global Assessment nutritional tool that incorporated a subjective examination of muscle, fat and fluid status of an individual. Thereafter, the PG-SGA incorporated part of the SGA as worksheet 4, the physical assessment section (Ottery, 1996), referred to as global physical examination (GPE). Interestingly, dietitians reported that after a single training using the PG-SGA, their comprehensibility improved to an acceptable level, but not their perceived level of difficulty to perform the GPE part of PG-SGA (Sealy et al., 2018). Please refer to chapter 2, section 3 for further information related to both SGA and PG-SGA.

Method

There are three components of the GPE, namely muscle status, fat status and fluid status. As for worksheet 4 of PG-SGA, examination of muscle status includes the following: prominence of the clavicles; flattening of the interosseus muscles in the area between the thumb and index finger; muscles of the quadriceps. Examination of fat status includes the following: orbital fat pads and pinching the TSF between the assessor's thumb and index finger to determine subjective thickness. Examination of fluid status accounts for peripheral or ankle oedema and / or sacral oedema, particularly if patients sit mostly with legs elevated (Ottery, 2001).

Interpretation

Interpretation of the GPE involves categorising each of the three components into categories that range from 0, 1, 2 and 3, defined as none, mild, moderate and severe, respectively. After each category has been defined, a global assessment is made in terms of no deficit to severe deficit, with muscle deficit taking preference. It is noted that nutritional deficit will impact upper body more than lower limbs; whereas immobility with impact lower limbs more than upper body (Ottery, 2001).

Validity of GPE to measure body composition in cancer patients

The Academy for Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition advocate for a nutrition focused physical examination (NFPE), and recent review focused on the validation of NFPE against the SGA with sensitivity ranging from 80-94% and specificity ranging from 43-99% (Hummell & Cummings, 2022).

When considering cancer research, Souza et al., (2020), found fair overall sensitivity (79%) and specificity (81%), fair agreement (K – 0.48) and poor hazard ratio of 1.9 when compared to CT scans. However, GPE performed better than the other alternative muscle mass methods, namely cAMA and calf circumference (Table 2.8).

Associations related to GPE within cancer populations

Limited research was found related to cancer research. Reduced muscle mass identified by both GPE and CT scans, were significantly associated with reduced survival in a cohort of colorectal cancer patients (Souza et al., 2020); (Table 2.9).

Conclusions

The performance of physical examination appears to be easy to implement in any clinical setting, depending on the training and practice needs of the assessors to standardise methodology and agreement within inter and intra-rater abilities. Much more research is needed within the cancer population to determine the validity and associations of GPE as an alternative muscle mass marker, particularly as GLIM has suggested its use in their guideline (Compher et al., 2022). No research was found that used GPE to identify RMM as part of the sarcopenic diagnostic guidelines nor cancer cachexia guidelines.

In summary, the use of alternative muscle mass markers that are available in clinical practice, need to consider their limitations, their specific use and interpretation within cancer populations, their validation and associations to assess nutritional status and diagnose cancer cachexia, sarcopenia and malnutrition. In addition, ideally, alternative muscle mass markers need to be able to identify the early loss of muscle mass so that multimodal intervention can take place timeously. A review by Almada-Correia et al., (2019) found that of the 41 studies that investigated nutritional status assessment of head and neck cancer patients, only two included anthropometrical measurements. As nutritional status changes, the changes detected by anthropometric measurements occur slowly, so may not be helpful in the early detection of malnutrition. It appears that more research is needed within the cancer population considering the many confounding factors that impact muscle mass. Albeit the limited research, calf circumference, GPE and equations that can estimate ASM using calf circumference appear to hold promise for the future.

Table 2.9 Alternative markers of muscle mass and associations in cancer populations (research within 5 years)

Reference	Study design and purpose	Population and numbers	Alternative / estimate tools	Other varianbles	Associations	Predictions
Yin et al., 2022	Observational cohort	2672 lung cancer patients	TSF	GLIM using CC as RMM	Malnourished as per GLIM + ↓TSF vs N TSF is significantly associated with ↓QOL & ↓physical performance	GLIM diagnosed malnutrition + ↓TSF better predicts prognosis
Silva et al., 2019	Cross-sectional study	43 HCC patients	TSF MUAC MAMC BMI	PG-SGA	All results excluding BMI, are not statistically different to PG-SGA for malnutrition diagnosis	
Ge et al., 2021	Nested case control study to predict 1 year survival	262 with CCx; 262 without CCx patients	TSF MAMC CC	CCx using Fearon et al. framework where RMM was identified by AMA	Only TSF significant association with 1 year survival	
Yilmaz et al.,2020	Cross-sectional study	120 hospitalised haematological cancer patients	MUAC CC	At risk patients that are malnourished via GLIM (RMM from FFMI via BIA)	Not associated with higher mortality	

Reference	Study design and purpose	Population and numbers	Alternative / estimate tools	Other varianbles	Associations	Predictions
Wiegert et al., 2021	Prospective cohort	Advanced palliative care: 882 in development group; 443 in validation group	AMA + BMI + %WL identified via hierarchical cluster analysis, determined cutoff points & best combinations for CCx staging	BC, QOL and overall survival	Successfully discriminates between different CCx stages and BC, QOL, OS	
Da Silva 2019	Observation & prospective	334 advanced palliative patients	AMA Sarco CC Sarco [a] ASMI Sarco	PG-SGA SF, albumin, >5%WL in 6 months	All significantly associated with ↑PG-SGA SF score, ↓ albumin, > 5%WL in 6 months; lower survival	
Souza et al., 2020	Cohort	188 CRC patients	cAMA CC GPE	CT for RMM	All 3 associated with significantly ↓BMI, ↑ malnutrition, ↓%BF (but within N range), ↓survival	
De Sousa et al., 2022	Prospective cohort	178 GI and CRC patients	CC HGS BMI	PG-SGA for malnutrition		CC & PG-SGA independent predictors of mortality
Qiu et al., 2023	Observational comparative study	170 hospitalised GI cancer in older patients	CC HGS BMI CT L3 SMI for sarcopenia (Asian guidelines)	NRS-2002 to determine nutritional risk	All associated with nutritional risk, but with multivariate regression analysis, CC was not an independent RF for nutritional risk, like other variables	

TSF – triceps skinfold; GLIM – global leadership initiative on malnutrition; CC – calf circumference; RMM – reduced muscle mass; QOL – quality of life; HCC – hepatocellular carcinoma; MUAC – mid upper arm circumference; MAMC – mid arm muscle circumference; BMI – body mass index; PG-SGA – patient generated subjective global assessment; CCx – cancer cachexia; AMA – arm muscle area; FFMI – fat free mass index; BIA – bioelectrical impedance analysis; WL – weight loss; BC – body composition; QOL – quality of life; OS – overall survival; Sarco – sarcopenia; ASMI – appendicular skeletal muscle index; PG-SGA SF - patient generated subjective global assessment short form; cAMA – corrected arm muscle area; GPE – global physical examination; CT – computer tomography; GI -gastrointestinal; CRC – colorectal; HGS – handgrip strength; L3 – lumar 3; SMI – skeletal muscle index; NRS-2002 – nutritional screening risk 2002

[a] Baumgartner equation that utilizes body weight, height, hip circumference, and handgrip strength (HGS)

2.2.13 Handgrip strength (HGS)

Introduction

Muscle strength declines with age and is impacted upon by different medical conditions. As weak muscle strength influences clinical outcome, there are a variety of tests that are used in both clinical and research settings (Bohannon, 2019). Some of these tests include manual muscle testing, a subjective test manually performed by the tester; field testing that includes the individual's own body weight e.g. sit to stand or heel raise tests; handheld dynamometry where the tester holds the dynamometer against the individual's body part being measured for strength; HGS where the dynamometer is held by the individual and measures grip strength (Bohannon, 2019); the gold standard measurement, isokinetic dynamometry, utilises expensive computerised equipment to measure muscle strength (Stark et al., 2011). Measuring muscle strength through HGS, in the clinical setting has both clinical and prognostic value (Bohannon, 2015). HGS will be discussed in relation to methodology, interpretation, validity and its value in healthy populations and those with medical conditions.

Method

The method to measure grip strength varies across studies making it difficult to compare the summary of results. The lack of a standardised approach relates to using different dynamometers, measuring only the dominant hand or both hands, the number of measurements taken and representing the mean or highest value (Roberts et al., 2011). Within the last decade, there has been an attempt by Roberts et al. (2011) to describe a standardised approach to measure HGS. The subject sits in a chair where forearms rest on the arms of chair, with wrists in neutral position and thumbs point upwards. A Jamar handheld dynamometer is used where measurement starts in the right hand, subject squeezes as hard as possible till reading is at its highest. Thereafter, the left hand is measured, followed by alternate hand measures till a total of six measurements are completed with the highest measurement being recorded (Roberts et al., 2011). This method has been accepted by the European Working Group on Sarcopenia in Older People (EWGSOP) in the latest global consensus definition and diagnosis of sarcopenia (Cruz-Jentoft et al., 2019).

Interpretation of HGS measurements

To determine clinical relevance, the HGS value of the individual needs to be compared to healthy normalised reference population data. The comparison can be in relation to the norms of a comparable individual for gender and age or T-scores from young healthy adults (Bohannon, 2015). HGS normative data can be stratified further by considering associated factors namely weight, height, self-rated health and functional disability (Bohannon, 2015). A large normative data set with 60 803 observations from 49 964 participants from 12 British studies across the life span determined that the peak mean for grip strength of males was 51.9 (standard deviation of 9.9) kg and females was 31.4 (standard deviation of 6.1) kg at age 32 years (Dodds et al., 2014). Dodds et al., (2014) determined cutoff points at -2 standard

deviations equating to 19kg for females and 32kg for males; -2.5 standard deviations equating to 16kg for females and 27kg for males. EWGSOP guidelines suggest using the cutoff points less than -2.5 standard deviations as determined by Dodds et al., (2014); (Cruz-Jentoft et al., 2019). In comparison, a large American study that pooled data from 9 studies investigating the elderly living within their communities, developed a cut point of <26kg and <16kg for males and females respectively to identify weakness (Studenski et al., 2014).

Large normative population data sets exist for European and United States populations (Alley et al., 2014; Dodds et al., 2014). However, it has been suggested that these data sets with cutoff points for low muscle strength should not be used in developing countries as the mean values were lower compared to Europe, North America, Japan and Australia, higher income countries. South America, Asia and Africa will need to propose region specific cutoff points (Dodds et al., 2016). Only recently, reference data sets for low to middle income countries, with a representation from non-Caucasian populations with wide geographical and socio-economically diverse backgrounds have been developed (Leong et al., 2016). This data has been presented as the median HGS in kilogrammes of 25th to 75th percentiles stratified according to age, gender and geographical location namely South Asia, China, Malaysia, Persia, Arabia, Africa, Latin America and Europe (Leong et al., 2016). This may be unhelpful to categorise weak HGS as below 25th percentile indicates that a quarter of the population falls below.

Comparison of South African individual measurements to these representative data sets should be interpreted with caution as South Africa is a diverse country with reference to ethnicity, geographical location and socio-economic backgrounds. A national survey of 3 840 community dwelling adults older than 50 years from rural and urban areas and varied ethnic backgrounds was conducted in South Africa. For men with a mean age of 61 years, the mean overall handgrip strength was 37.9 kgs. For women with a mean age of 62 years, the mean overall handgrip strength was 31.5 kgs (Ramlagan et al., 2014). There is a lack of representative normative data in South Africa for the interpretation of muscle weakness.

In addition to comparing results to different reference data sets, the expression of HGS needs to be considered, namely in absolute terms (in kilogrammes) or relative to height, weight, fat-free mass, BMI, fat-free mass index and fat-free mass, or as z-scores. Ho et al., (2019) found no difference in results when HGS was expressed in a variety of ways when investigating the association of HGS to all-cause mortality (Ho et al., 2019). Despite the limitation related to lack of relevant reference population data sets for the South African context, HGS is associated with diverse clinical outcomes (McGrath et al., 2020).

Validity of HGS in general and in cancer patients

A recent systematic review with meta-analysis by Bobos et al., (2020) investigated the quality of HGS measurements within healthy populations and those with medical histories. Weak to moderate correlation was found when HGS was compared to patient reported outcome measures or tests, namely 50m run test. However, when HGS was compared with computerised or other instruments, a very strong correlation was found between HGS and the instruments (Bobos & MacDermid, 2020).

Considering reliability of HGS measurement both in healthy participants and patients with a variety of medical conditions, namely musculoskeletal, neurological and systemic conditions, the intraclass correlation coefficients (ICC) of 0.92 – 0.96, indicating excellent reliability (Bobos & MacDermid, 2020).

In the elderly population, the test-retest reliability of HGS was systematically reviewed and an ICC of between 0.41 to 1.00 was found, with 90% of the studies having ICC of >0.8, indicating good to excellent reliability (Bohannon, 2017). However, when investigating absolute reliability that accounts for minimum detectable change, the percentage change ranged from 14.5% to 98.5%. This indicates that the percentage change in HGS over time in elderly population has to be large for the tester to be confident that real change in muscle strength has occurred (Bohannon, 2017).

Within patients with cancer, a review of the literature regarding instruments and their measurement properties related to muscle strength revealed that good quality research is lacking (Granger et al., 2013). Only one out of three articles focusing on muscle strength, looked specifically at the accuracy (validity) and consistency (reliability) of HGS in cancer patients (Granger et al., 2013). The percentage coefficient of variation (%CV) of the Jamar dynamometer and the Biodex handgrip attachment were 6.3 and 16.7, respectively. In conclusion, the Jamar dynamometer showed more consistency of measurement to detect change over time than the Biodex handgrip attachment in advanced cancer patients (Trutschnigg et al., 2008).

Studies related to HGS and associations

There have been investigations of HGS in epidemiological and intervention studies in healthy adult populations and those with a variety of medical conditions (Norman et al., 2011). These studies have investigated the value of HGS in both clinical and prognostic scenarios (Table 2.10).

A meta-analysis of 42 epidemiological studies by Wu et al., (2017), that included about three million participants, concluded that HGS is a predictor of all-cause mortality and cardio-vascular disease (Wu et al., 2017). This agrees with a large UK based study and an elderly Korean population-based study (Celis-Morales et al., 2018; Kim et al., 2019).

With a focus on cancer, both the Korean study and meta-analysis by Wu et al., (2017) found no association between HGS and cancer risk and mortality (Kim et al., 2019; Wu et al., 2017). Furthermore, a large Brazilian meta-analysis study showed a barely significant association of higher HGS with lower mortality risk from cancer mortality (García-Hermoso et al., 2018). In contrast, when cancer types were selected, the UK based prospective study found that lower HGS was associated with greater mortality from colorectal cancer, lung cancer and breast cancer. They, however, found no association of HGS with prostate cancer mortality (Celis-Morales et al., 2018); (Table 2.10). A more recent systematic review of 48 studies that included over 3 million participants determined that HGS has a dose response to cancer related mortality, that is a U-shaped curve with risk reduction between 16-33kg (López-Bueno et al., 2022).

When investigating HGS and its relationship with survival specifically in cancer patients, the results are contradictory. In patients with advanced cancer, high muscle strength was associated with prolonged overall survival (Versteeg et al., 2018) and HGS independently predicted survival (Kilgour et al., 2013). More recently it was demonstrated that HGS was significantly associated with the modified Glascow Prognostic Score (mGPS), a validated tool for survival that measures the systemic inflammatory response (Dolan et al., 2020). In contrast, patients with breast and gastro-intestinal cancer about to receive adjuvant treatment did not find a significant association of HGS with survival (Mauricio et al., 2016); (Table 2.10).

Comparing results across studies investigating HGS in cancer patients and its association with overall survival must take into consideration the age and gender of participants, type and stage of cancer.

HGS is commonly used as a marker of nutritional status (Norman et al., 2011) as there may be association with different nutritional assessment tools but poor validity exists for HGS against these different tools. With no gold standard tool to assess nutritional status and cancer cachexia being described as a multifactorial syndrome (Fearon et al., 2011), investigating HGS and its association to nutritional status in cancer patients has yielded conflicting results (Table 2.10). Several studies did find an association between HGS and PG-SGA, that includes non-resectable lung cancer patients (Barata et al., 2017), advanced gastrointestinal cancer patients (Ozorio et al., 2017) and heterogenous cancer patients (Pereira et al., 2020).

Validity of HGS against PG-SGA in gastric and colorectal cancer patients yielded poor Kappa agreement and fair overall sensitivity and specificity as per van Bokhorst-de van der Schueren et al., (2014) interpretation for clinical practice. This indicates that it cannot be used to diagnose malnutrition (de Sousa et al., 2022). A retrospective multi-centre observational study of 11 314 cancer in-patients found weak or no correlation between HGS and PG-SGA, thereby indicating high misdiagnosis and missed diagnosis (Hu et al., 2018). A possible explanation may be the complexed clinical nature of cancer where patients may experience chronic anaemia, fatigue, pain, anorexia and poor assimilation and absorption of food due to the tumour or anti-cancer treatment. This in turn leads to a poor quality of life and reduced functional status that impacts on HGS due to reduced or limited activity. In addition, cancer is a progressive disease that presents ongoing problems for patients (Hu et al., 2018).

Other domains are used in the assessment of malnutrition apart from PG-SGA. This implies that the association between malnutrition and HGS may be modified. HGS has a positive correlation with weight and mid-upper arm circumference (Hu et al., 2018). Body mass index / weight loss grades (BMI/WL) have been shown to have prognostic value and impact on quality of life (Martin et al., 2015). However, Dolan et al. (2020) found no association between BMI/WL and HGS. Pereira et al., (2020) found poor validation of HGS as all correlation coefficients were below 0.4 for cAMA, MUAC, BMI and SFT (Table 2.10).

An observational, prospective study of a heterogenous group of cancer patients, compared nutritional risk, as measured by NRS-2002 and low muscle strength, as indicated by being in the lowest tertile of HGS, to length of hospital stay (Mendes et al., 2014). It was found that the hazard ratio for a low HGS and nutritional risk was 0.33 and 0.55, respectively. This indicates that having a low HGS related to a 3-fold decrease in probability of being discharged alive and was more strongly associated than NRS-2002 to length of hospital stay (Mendes et al., 2014). When considering head and neck cancer patients, NRS-2002 correlation with HGS for males was -0.323 (P= 0.22) indicating a weak negative association and for women correlation was -0.703 (p = 0.003) indicating a strong negative correlation. Therefore, NRS-2002 has an overall moderate correlation to HGS (Orell-Kotikangas et al., 2015).

The relationship between HGS and body composition through different reference methods within the cancer population has been researched (Table 2.10). HGS was independently associated with low skeletal muscle density as measured by CT scans, (Dolan et al., 2020). Low skeletal muscle density, also known as myosteatosis, refers to the increased deposits of fat within muscle tissue. A recent meta-analysis and systematic review has found that cancer patients with myosteatosis have shorter overall survival (Aleixo et al., 2020). In overweight and obese advanced lung and colorectal cancer patients, when using DEXA to measure muscle mass, only males identified with low SMI had a significantly lower average HGS, perhaps as females were very low in numbers (Prado et al., 2013). When considering phase angle derived from BIA for body composition analysis, it was found that a low phase angle in elderly cancer patients was associated with a low HGS (Norman et al., 2015). Specifically, in advanced gastrointestinal cancer patients, phase angle and HGS showed a fair correlation of r = 0.5 (Ozorio et al., 2017). Interestingly, phase angle predicted a 1-year mortality, but low HGS did not significantly predict survival (Norman et al., 2015).

The Global Leadership Initiative of Malnutrition (GLIM), the most recent proposed diagnostic criteria for malnutrition, has suggested that HGS be used as a surrogate measure for reduced muscle mass (Cederholm et al., 2019). However, newer guidelines suggest using HGS not as a marker of muscle mass but rather muscle function (Compher et al., 2022; Prado et al., 2022). Research in Australian oncology out-patients compared GLIM criteria with and without adding HGS component, using a HGS cut off at the 10th percentile, to PG-SGA. With adding HGS to GLIM criteria sensitivity, specificity and Kappa coefficient were 19%, 96% and 0.183 indicating poor agreement, respectively (De Groot et al., 2020).

The Academy of Nutrition and Dietetics recommends using HGS as part of the nutritional assessment to determine functional decline as reduced functional status is one out of the six characteristics of malnutrition (White et al., 2012). Within epidemiological studies of healthy adult populations, reduced HGS is a predictor of increased risk of functional impairment and disability (Norman et al., 2015). . It is established that cancer cachexia impacts on functional status (Fearon et al., 2011) which is assessed by Eastern Cooperative Oncology Group score (ECOG) or Karnofsky Performance Status (KPS) widely used by Oncologists (Azam et al., 2019). In advanced gastrointestinal and lung cancer patients both admitted

into hospital or visiting clinics, when comparing HGS <10th or > 50th percentile, low HGS was independently associated with poor performance status as measured by ECOG (Kilgour et al., 2013). In addition, a large group of Chinese inpatients with heterogenous cancer diagnoses, HGS was positively correlated with KPS and the physical function domain designed by the European Organization for Research and Treatment of Cancer (EORTC) for quality of life assessment (Hu et al., 2018). Furthermore, a United States longitudinal study on ambulatory older women diagnosed with breast cancer found that HGS was highly predictive of functional decline, with a sensitivity of 67% and specificity of 77%, when evaluated by self-reported activities of daily living (Owusu et al., 2017).

Classifying mostly advanced cancer patients into three cancer cachexia stages as defined by Fearon et al. (2011), showed that both males and females with refractory cancer cachexia had a lower HGS. Furthermore, those patients without cancer cachexia or pre-cachexia showed a significantly different HGS measurement when compared to those with cancer cachexia or refractory cachexia (Ozorio et al., 2017).

Low HGS in neuroendocrine tumour patients was associated with nutrition impact symptoms of nausea, vomiting, stomach-ache and a dry mouth but not poor appetite and early satiety. Interestingly, poor appetite and satiety was only associated with nutritional risk, as screened by NRS-2002, and impaired functional status (Borre et al., 2018).

When considering HGS and its association to blood results in cancer patients, there is agreement. Research has found that HGS is positively associated with albumin, prealbumin and haemoglobin levels (Hu et al., 2018) (Kilgour et al., 2013).

Post-operative complications in cancer patients are exacerbated with loss of muscle mass. In 188 oesophageal cancer patients undergoing oesophagectomy, low HGS was independently predictive for only male patients older than 70 years for post-operative complications, mainly pneumonia (Sato et al., 2018). These results may be impacted upon by small numbers. In contrast, 322 oesophageal cancer patients demonstrated significant association of reduced HGS with increase postoperative complications, specifically cardio and pulmonary conditions (Hagens et al., 2020).

Advantages

When considering measuring muscle strength, HGS has excellent clinimetric properties. Using a dynamometer is a simplistic, non-invasive, portable and inexpensive tool used to measure HGS in the clinical setting, both at the patient's bedside or out-patients' clinic (Bohannon, 2019).

HGS was found to be feasible and acceptable when used in clinical practice by ambulatory digestive cancer patients receiving chemotherapy. These patients found HGS to be unrestrictive and easy to perform. Furthermore, medical staff found it undisruptive to routine clinical practice (Ordan et al., 2018).

Limitations

A scoping review was performed to determine HGS use within long term care homes for elderly when being nutritionally screened and assessed. Even though The Academy for Nutrition and Dietetics recommends functional status to be assessed via HGS, it was found that very few dietitians use HGS in practice (Whiting et al., 2016).

Despite a standardised approach to measuring HGS being presented almost a decade ago, different methods of measuring HGS is still being used in recent research (Roberts et al., 2011).

Within the South African context, normative data with cutoffs defining muscle weakness is needed to reflect age, gender, ethnicity, geographical location of our entire population for HGS to be used in the clinical setting. Despite the large study from low to middle income countries including non-Caucasian participants' normative HGS data (Leong et al., 2016), it cannot be used to compare individual HGS results as the data is not in a format that can be used to interpret muscle weakness.

Conclusion

Please refer to Table 2.10 for the summary of the relationship between HGS and factors in cancer patients specifically.

HGS and mortality association within cancer populations, are not conclusive but studies suggest that advanced cancer patients and perhaps specific cancer types have a positive association with HGS. The association may be true over the short term for sicker specific cancer patients which may have an impact on determining management plans, that is palliative or active treatment.

The cancer patient population is composed of heterogenous group with different types of cancers at different stages that have vastly varied management plans that may all impact nutritional status. In addition, there is no standardised approach to determine low muscle strength across reference populations. HGS is therefore a general marker of malnutrition in cancer patients but cannot be universally used as a single tool of nutritional assessment or screening.

With regards to functional status and certain biochemistry measures, the association with HGS is straight forward. However, there is a lack of research investigating the relationship of HGS and factors like cancer cachexia, nutritional impact symptoms and post-operative complications.

Identifying and treating cancer cachexia is still a challenge. Intervention trials have struggled to show a direct impact on outcome measures, particularly muscle strength as measured by HGS. With a direct increase in muscle mass, muscle strength has not demonstrated an increase (Crawford, 2019). It is suggested that this may be because the relationship between muscle mass and muscle function remains unclear, with variable methodologies, interpretations, patient differences (Ramage & Skipworth, 2018). Therefore, in conclusion, there is agreement with McGrath et al., (2020) that HGS is an overall indicator of health status and cannot be used as a stand-alone tool to directly assess nutritional status and risk and

monitor functional status. Further studies are needed in the cancer population that use standardised methodologies, interpretations and homogenous patient populations to further elucidate HGS's practical use in the clinical setting.

Table 2.10 Associations between HGS and factors in cancer patients

Factor	Relationship to HGS	Details of relationship	Study population	Author
Mortality risk from cancer	No		Healthy	Garcia-Hermoso et al., 2018; Kim et al., 2019; Wu et al., 2017
Mortality risk from lung, colorectal and breast cancer	Yes	↓ HGS ↑ mortality	Healthy	Celis-Morales et al., 2018
Mortality risk from prostate cancer	No		Healthy	Celis-Morales et al., 2018
Mortality association	Yes	↓ HGS ↑ mortality	Gastric and CRC	De Sousa et al., 2022
Survival association	Yes	↓ HGS ↑ mortality	Advanced GI and lung cancer	Kilgour et al., 2013
	Yes	↓ HGS ↑ mortality	Advanced heterogenous cancer (mainly GI and lung cancer)	Dolan et al., 2020
	Yes	↑HGS ↑ overall survival	Advanced elderly breast, CRC, prostate cancer	Versteeg et al., 2018
	No		Breast and GI cancer	Mauricio, Ribeiro, & Correia, 2016
Nutritional status and screening				
PG-SGA	Yes	↓ HGS ↑malnutrition	Lung cancer	Barata et al., 2017
PG-SGA	Yes	↓ HGS ↑malnutrition	Advanced GI cancer	Ozorio, Barao, & Forones, 2017
PG-SGA	Yes	↑HGS ↓malnutrition	Heterogenous cancer	Pereira 2020
PG-SGA	No		Heterogenous cancer	
Weight	Yes	↑ HGS ↑ weight	Heterogenous cancer	Hu et al., 2018
MUAC	Yes	↑HGS ↑ MUAC	Heterogenous cancer	
MUAC	Yes	↑HGS ↑ MUAC	Heterogenous cancer	Pereira 2020
BMI/WL ratio	No		Advanced heterogenous cancer	Dolan et al., 2020
NRS-2002	Yes	↓ HGS ↑ nutritional risk	Head and neck cancer	Orell-Kotikangas et al., 2015

Factor	Relationship to HGS	Details of relationship	Study population	Author
Body composition				
Skeletal muscle density (SMD)	Yes	↓ HGS ↓ SMD	Advanced heterogenous cancer	Dolan e tal., 2020
Muscle mass (DEXA)	Yes	↓ HGS ↓ muscle mass	Overweight and obese lung cancer	Prado et al., 2013
Muscle mass (BIA)	Yes	↓ HGS ↓ muscle mass	Elderly heterogenous cancer	Norman et al., 2015
Muscle mass (BIA)	Yes	↓ HGS ↓ muscle mass	Advanced GI cancer	Ozorio, Barao, & Forones, 2017
Functional status				
ECOG	Yes	↓ HGS ↓ functional status	Advance gastrointestinal and lung cancer	Kilgour et al., 2013
KPS	Yes	↓ HGS ↓ functional status	Heterogenous cancer	Hu et al., 2018
Self-reported	Yes	predictive	Female breast cancer	Owusu et al., 2017
Cancer stages	Yes	↓ HGS associated with cancer cachexia and refractory cancer cachexia	Advanced heterogenous cancer	Ozorio, Barao, & Forones, 2017
Nutrition impact symptoms	Yes	Nausea, vomiting, stomach-ache and dry mouth	Neuroendocrine cancer	Borre et al., 2018
	No	Appetite and early satiety		
Biochemistry	Yes	Pre-albumin, albumin, haemoglobin	Heterogenous cancer; Oesophageal cancer	Hu et al., 2018; Kilgour e tal., 2013
Post-operative complications	Yes but	Predictive only for > 70-year-old males	Oesophageal cancer	Sato et al., 2018
	Yes	↓ HGS ↑ cardiac and pulmonary complications	Oesophageal cancer	Hagens et al., 2020

HGS – handgrip strength; CRC – colorectal cancer; GI – gastrointestinal; MUAC – mid upper arm circumference; cAMA – corrected arm circumference; BMI – body mass index; SFT – skinfold thickness; WL – weight loss; SMD – skeletal muscle density; DEXA – dual energy X-ray absorptiometry; BIA – bioelectrical impedance; NRS-2002 – nutritional risk screening 2002; ECOG – Eastern Cooperative Oncology group; KPS – Karnofsky performance status

Chapter 2.3 Nutrition screening tools and assessment tools for nutritional status assessment

2.3.1 Introduction to nutritional screening and assessment tools

The identification of malnutrition and assessment of nutritional status within the cancer population is not a routine practice globally despite the high prevalence and negative impact of malnutrition on clinical and patient outcomes. To identify malnutrition and risk of malnutrition, including cancer cachexia, nutritional risk screening has been recommended by nutritional guidelines, both general (Cederholm et al., 2019) and cancer specific (Arends et al., 2017b; Arends et al., 2021). Screening should be performed on all cancer patients as this increases malnutrition awareness and allows early identification and intervention (Arends et al., 2021).

Screening tools should have the following characteristics: be cheap, easy, and quick to perform either by the patient or any health care worker; be convenient without calculations or blood samples to be taken or anthropometry to be performed or uses readily available data; without needing in-depth clinical examination; be valid and reproducible within a heterogeneous adult patient population (Ferguson et al., 1999). At present, there is no agreement regarding the best screening tool for patients with cancer (Isenring & Elia, 2015; van Bokhorst-de van der Schueren et al., 2014).

After screening, those at high risk should have an assessment of their nutritional status to determine the cause and severity of metabolic and nutritional disturbances (Arends et al., 2017b). In addition to this, Arends et al., (2021) recommend the categories for cancer cachexia assessment and the parameters that make up each category together with recommended tools. Our focus at present is the nutritional status category where there is no gold standard method, rather several parameters are identified as important to assess (Arends et al., 2021). Many nutritional assessment tools have been developed to support the full nutritional status assessment by a dietitian or nutritionist. As for screening tools, assessment tools have been developed for different population ages, medical conditions and settings. Yet, there is no agreement on a standardized approach (van Bokhorst-de van der Schueren et al., 2014), apart from recommendations made by the various nutritional guidelines (Arends et al., 2017a; Arends et al., 2021; Kondrup, 2003). Unlike screening tools, nutritional assessment tools require more time to complete, and may be more costly as certain tests may be necessary and training needed as expertise required to identify multiple criteria. Nutritional screening and assessment require health care systems to have policies in place to link it to nutritional care plans and multi-modal therapy, particularly in cancer patients. Table 2.11 presents details, validation, advantages and limitations of the most common screening and assessment tools in chronological order. Table 2.12 presents the components of each screening and assessment tool discussed.

Subjective global assessment (SGA)

SGA is an assessment tool developed using subjective measures like medical history and physical examination against objective measures that included anthropometry and biochemical tests. In addition, SGA was developed to predict clinical postoperative outcomes that include length of hospital stay, antibiotic use and infection incidence (Detsky et al., 1987).

Training of clinicians (reported as doctors and nurses) is needed to perform the clinical examination and percentage weight loss calculation for implementation in clinical settings. Patients are categorised as well nourished, moderately malnourished or severely malnourished based on subjective weighting of components per individual case (Detsky et al., 1987).

Mini-nutritional assessment (MNA)

MNA is an assessment tool that contains 18 subjective and objective components to identify elderly patients at malnutrition risk. With training to correctly measure MUAC and calf circumference, together with taking subjective judgements, all health care professionals can perform MNA in less than 15 minutes. The components are scored and added with interpretation as follows: score ≥ 24 = well nourished; score 17-23.5 = at risk; score < 17 = malnourished (Guigoz et al., 1996). ESPEN recommends MNA to be used as a screening tool in the institutionalized elderly (Kondrup, 2003).

Malnutrition screening tool (MST)

MST is a screening tool that identifies nutritional risk where it demonstrated good validity against SGA (Isenring & Elia, 2015). All health care professionals, administrative staff, patients and their families can easily complete the MST as it is meant to be performed within 24 hours of hospital admission. There are 3 questions where a score of 0 – 5 can be attained. A score ≥2 identifies a patient at risk; 0-1 does not identify risk of malnutrition, however, weekly rescreening is expected until discharge (Ferguson et al., 1999).

Mini-nutritional assessment short form (MNA-SF)

The MNA-SF was developed as a screening tool to be used when MNA cannot be used e.g., limited time available. The time consuming and subjective items were removed from the MNA, leaving only 6 items. It therefore takes 3 minutes instead of 15 minutes with the MNA. The score can be interpretated as follows: 12–14 equates to normal nutrition status; 8-11 equates to a patient being at nutritional risk; 0-7 equates to being malnourished (Rubenstein et al., 2001).

Patient generated subjective global assessment (PG-SGA)

The PG-SGA was developed as a modification of the SGA where it is four tools in one tool: nutritional screening tool, assessment tool, interventional triage and monitoring tool for interventional success. The PG-SGA's triaging system includes nutritional, pharmacologic, exercise and other interventions. This enables early identification, prevention and treatment of malnutrition in patients at risk.

Boxes 1 – 4 are completed by the patient, this section is referred to as the PG-SGA Short Form. The rest of the PG-SGA can be completed by health care staff that would require training to perform the physical examination.

The assessment part of PG-SGA has 3 global assessment categories, namely stage A, B and C that equates to being well-nourished, moderately malnourished and severely malnourished, respectively. The nutritional triage score recommendations are as follows: 0-1 means "no intervention required at this time". Re-assessment on routine and regular basis during treatment; 2-3 means "patient and family education by dietitian, nurse, or other clinician with pharmacologic intervention as indicated by nutrition impact symptoms and lab values as appropriate"; 4-8 means "intervention required by dietitian, in conjunction with nurse or physician as indicated by symptoms"; > 9 indicates a "critical need for improved symptom management and/or nutrient intervention options" (Jager-Wittenaar & Ottery, 2017).

Nutrition Risk Screening – 2002 (NRS-2002)

NRS-2002 is different to the other screening tools as it was developed not only to identify nutritionally at-risk patients but also to identify those that would benefit from nutritional support.

It is easily implemented within a hospital setting by nurses and / or doctors who need minimal training to use the tool. If weight and height are difficult to measure to calculate BMI, then MUAC can be measured. It is a suggestion that if <25cm, then BMI likely to be <20.5. The tool consists of a two-step process that allows efficiency of time as only those patients that indicate 'yes' to any of the 4 questions will need to undergo the full screening.

The score of NRS-2002 ranges from 0-6, where a score <3 indicates no nutritional risk unless the patient may develop a score of ≥3 over a short time e.g., after major surgery. In these cases, a nutrition care plan should be implemented as soon as possible. It is recommended to re-screen patients weekly to detect any changes in nutritional risk. The patients that score ≥3, indicating nutritional risk, will need an assessment to determine nutritional intervention (Kondrup et al., 2003). ESPEN recommends using NRS-2002 for nutritional screening in hospitals (Kondrup, 2003).

Malnutrition Universal Screening Tool (MUST)

MUST was developed to identify any adult that is malnourished or at risk of malnutrition in any setting. It has been largely implemented within the United Kingdom's health care system where health care professionals need minimal training to effectively use the tool. Its readily available charts to calculate and interpret BMI or alternative measures when weight and height not available limits use of time.

A score of 0 indicates low nutritional risk; a score of 1 indicates medium risk; a score ≥2 indicates high risk of malnutrition where the patient will be referred for further nutritional support or local policy followed. Interestingly, when medium risk is indicated, documentation of food intake for 3 days is recommended. This allows a decision to be made to refer the patient for further assessment or requires routine follow-up screening. The time frame of follow-up screening is dependent on the health care setting e.g., in hospitals, weekly screening is recommended (Elia, 2003). ESPEN recommends MUST to be implemented in community settings (Kondrup, 2003).

Short Nutritional Assessment Questionnaire (SNAQ)

SNAQ was developed to implement within a hospital setting very easily without taking extra time for nursing staff to complete. It is mainly completed on admission to hospitals in the Netherlands. The three questions are scored and a score of 0-1 classifies a patient as well nourished; a score of 2 indicates moderately malnourished where the patient requires nutritional intervention; a score ≥3 indicates that a patient is severely malnourished where intervention by a dietitian is required (Kruizenga et al., 2005).

Global leadership initiative in malnutrition (GLIM)

The main aim of developing GLIM was to standardize the approach to malnutrition diagnosis and develop a global consensus on the criteria required for the identification and grading of malnutrition. GLIM is easily applied by all health care professionals where modest training is required.

GLIM recommends screening first using any validated tool, where only the nutritionally at-risk patients are further assessed using GLIM. At present, there is no consensus regarding how best to measure and define reduced muscle mass. GLIM recommends the use of dual-energy absorptiometry or other validated body composition measures such as bioelectrical impedance, ultrasound, computed tomography or magnetic resonance imaging. In settings where these tools are unavailable, physical examination or anthropometric measures of calf or arm muscle circumference are recommended as alternative measures. Ideally, reference standards for muscle mass should be gender and race specific, however, further research is warranted to establish general reference standards to further standardise approaches and interpretations (Cederholm et al., 2019).

At least one phenotypic criterion and one etiologic criterion is needed to identify malnutrition. GLIM was developed to grade malnutrition as stage 1, indicating moderate malnutrition and stage 2 indicating severe malnutrition. This grading is based off the phenotypic criteria. The aetiologic criteria may be used to guide intervention and anticipated outcomes (Cederholm et al., 2019).

Components and validation of screening and assessment tools

The components of the screening and assessment tools are mainly varied across aetiologic, phenotypic criteria and symptoms. It can be clearly seen that weight loss, reduced food intake, and inflammation or disease burden are major determinants across the different tools, even though the specific details per component varies (Table 2.12).

The systematic review by van Bokhurst-de van der Schueren et al., (2014) considered research that included screening and assessment tools for adults and elderly within the hospital setting. Barring GLIM and PG-SGA, they concluded that there were no screening nor assessment tools that performed consistently well in relation to construct or criterion validity and predictive validity for nutrition related outcomes. The screening tools that are quick to preform, lack sensitivity to correctly identify patients at nutritional risk. The only tool that demonstrated fair to good construct validity was MUST when compared against acceptable reference standards. The other tools all performed more poorly than MUST.

Considering predictive validity, SGA, NRS-2002 and MUST performed fair to good regarding some or all clinical outcomes namely, length of hospital stay, complications and mortality (van Bokhorst-de van der Schueren et al., 2014).

As GLIM is a new tool, more research is being conducted to determine its construct validity and predictive validity. The most recent review has found that GLIM could predict worse clinical outcomes within the cancer population (Brown et al., 2023). Interestingly, the different methods of measuring muscle mass did not impact the predictive ability of GLIM, unlike the aetiologic criteria, namely inflammation and oral intake.

As malnutrition, sarcopenia and cachexia share some diagnostic components, a systematic review by Miller et al., (2018) investigated the validity of screening tools in cancer patients for each of these conditions. They determined the following: the three-minute nutrition score scored >80% sensitivity and specificity against the SGA; the Strength, Assistance with walking, Rise from a chair, Climb stairs, and Falls (SARC-F) tool and the Short Portable Sarcopenia Measure (SPSM) performed well against Baumgartner et al., (1998) definition of sarcopenia (Baumgartner et al., 1998) but SARC-F displayed low sensitivity and SPSM sensitivity and specificity had not been tested; the cachexia score by Argiles et al., (2017) was found to be the only validated cachexia tool against the consensus definition by Fearon et al., 2011 (Miller et al., 2018). Miller et al., (2018) concluded that there was not one singular screening tool to identify risk for all three conditions simultaneously. As all cachexic patients are malnourished, but not all malnourished patients cachexic, it suggests that screening for malnutrition is a first step, followed by assessment of malnutrition, then cachexia and sarcopenia.

In conclusion, there is no global standardized approach to screening or assessment tools being used within a clinical setting. Importantly, regardless of which tool is utilized within practice, screening and assessment of at-risk patients are essential to detect early in the patient's cancer journey those that may

benefit from nutritional intervention, particularly multi-modal therapy in the case of cancer cachexic patients. The context of the clinical setting needs to be considered in terms of staff abilities and availability, access to tools, tests, nutritional supplements and other supportive services.

Table 2.11 Screening and assessment tools for nutritional status assessment of cancer patients

Tools	Original purpose (what, who and where)	Validity	Advantages	Limitations
SGA (Detsky et al., 1987)	Type: Assessment tool For: malnutrition Population: surgical patients Setting: hospital	High interrater reliability (Detsky et al., 1987) Construct / criterion validity[a] – inconclusive as compared against inappropriate reference tools (pre-albumin, NRS-2002) Predictive validity[a] – fair to good in over half of studies; improved performance of SGA when confounding factors that impact outcomes were controlled	As subjective, clinicians could note pattern of WL not just an absolute amount	Physical examination may not be adequately sensitive to detect changes in NS over a short period; calculation of %WL
MNA (Guigoz et al., 1996)	Type: assessment tool For: risk of malnutrition Population: elderly Setting: hospital and nursing homes	Construct / criterion validity[a] – inconsistent results Predictive validity[a] – in the elderly population, no evidence exists for clinical outcomes	Detailed dietary intake component compared to other tools; only tool that accounts for neuropsychological issues e.g., dementia	Patients may not be capable to complete self-assessment section; takes longer to complete; requires more skill to complete; EN / PN fed patients not accounted for
MST (Ferguson et al., 1999)	Type: screening tool For: risk of malnutrition Population: adult (medical & surgical) Setting: hospital (on admission)	High interrater reliability (Ferguson et al., 1999) Construct / criterion validity[a] – fair against nutritional assessment & anthropometry Predictive validity[a] – poor in predicting clinical outcome	Quick & easy; can be completed by administrative staff or patients	Limiting in non-communicative patients

Tools	Original purpose (what, who and where)	Validity	Advantages	Limitations
MNA-SF (Rubenstein et al., 2001)	Type: screening tool For: risk of malnutrition Population: elderly Setting: hospital & community dwelling	Construct / criterion validity[a] – validated against the MNA, therefore incorporation bias; can be substituted for MNA but has reduced sensitivity Predictive validity[a] – limited adult studies	Quicker to complete than MNA	BMI still needs to be calculated from measured weight and height
PG-SGA (Bauer, Capra, & Ferguson, 2002; Jager-Wittenaar & Ottery, 2017)	Type: Assessment and screening tool For: malnutrition and risk of malnutrition Population: cancer patients Setting: hospital	Construct / criterion validity – 98% sensitivity & 82% specificity at predicting SGA classification (Bauer et al., 2002) Predictive validity – cancer research consistently found associations with mortality, overall survival and LOS (Jager-Wittenaar & Ottery, 2017)	Evaluation is dynamic, not static process e.g., acute weight change considered; aides workflow for practitioners as partly completed by patients; unique inclusion of nutrition impact symptoms	Critical need for validated language translations of the PG-SGA; %WL needs to be calculated
NRS-2002 (Kondrup et al., 2003)	Type: screening tool For: risk of malnutrition Population: adult Setting: hospital and community	Construct / criterion validity[a] – inconsistent validity in hospitalised patients; no research found related to identifying patients that would benefit from nutritional intervention Predictive validity[a] – fair to good for mortality, LOS, complications	First initial screening, only if yes, then actual screening; considers the impact of age on NS	BMI and %WL needs to be calculated; food intake details not always available irt RQ but can use nurses' documentation of oral intake on ward level
MUST (Elia, 2003)	Type: screening tool for malnutrition risk Population: all patient groups Setting: all health care	Construct / criterion validity[a] – fair validity different subgroups of hospitalised patients Predictive validity – fair for LOS & mortality but more research needed in elderly	Score linked to nutritional management guidelines & local policy; facilitates continuity of care as developed to be used across different setting	BMI calculation: surrogate measures when weight & height not easily obtained but more training then needed

Tools	Original purpose (what, who and where)	Validity	Advantages	Limitations
SNAQ (Kruizenga et al., 2005)	Type: screening tool For: nutritional risk Population: surgical, oncology and medical adult patients Setting: hospital	Construct / criterion validity[a] – fair validity to screen in-patients against nutritional assessment Predictive validity[a] – no documentation in systematic review	Quick & easy; less than 5 minutes to complete; no calculating; includes a treatment plan based on the screening score	Same as MST above Original validation – not against acceptable reference standard
GLIM (Cederholm e tal., 2019)	Type: assessment tool For: diagnosis and severity grading of malnutrition Population: Adult Setting: diverse clinical settings	Predictive validity - consistently predictive of worse clinical outcomes; predictive ability not changed with different RMM approaches; varying predictive ability for survival with variation in aetiologic criteria assessment (Brown et al., 2023)	First global consensus diagnostic criteria recommendations	Methodological approaches differ regarding MM criteria and aetiologic criteria

SGA – Subjective Global Assessment; WL – weight loss; NS – nutritional status; MNA – mini-nutritional assessment; EN – enteral nutrition; PN – parenteral nutrition; MST – malnutrition screening tool; MNA -SF - mini-nutritional assessment short form; PG-SA – patient generated Subjective Global Assessment; NRS-2002 – nutrition risk screening; BMI = body mass index; RQ – requirement; MUST = malnutrition universal screening tool; SNAQ – short nutritional assessment questionnaire; GLIM – global leadership initiative on malnutrition

[a]Van Bokhorst-de van der Schueren et al., (2014) systematic review of tools in hospital settings used very specific reference standards i.e., nutritional assessment by professional, SGA and MNA, nutritional assessment & anthropometry; clinical outcomes included length of hospital stay, complications and mortality

Table 2.12 Components of screening tools and assessment tools

Tools	Phenotype						Aetiology		Nutrition impact symptoms	Other
	Weight loss	BMI	MM	FM	Oedema / ascites	Mobility / function	Reduced food intake	Inflammation / Dx burden		
SGA (Detsky et al., 1987)	X		X	X	X	X	X	X	X	
MNA (Guigoz et al., 1996)	X	X				X	X	X		X[a]
MST (Ferguson et al., 1999)	X						X			
MNA-SF (Rubenstein et al., 2001)	X	X				X	X	X		X[b]
PG-SGA Jager-Wittenaar & Ottery, 2017)	X		X	X	X	X	X	X	X	X[c]
NRS-2002 (Kondrup et al., 2003)	X	X					X	X		
MUST (Elia, 2003)	X	X						X		
SNAQ (Kruizenga et al., 2005)	X								X	X[d]
GLIM (Cederholm e tal., 2019)	X	X	X				X	X		

SGA – Subjective Global Assessment; MST – malnutrition screening tool; MNA -SF - mini-nutritional assessment short form; PG-SA – patient generated Subjective Global Assessment; NRS-2002 – nutrition risk screening; MUST = malnutrition universal screening tool; SNAQ – short nutritional assessment questionnaire; GLIM – global leadership initiative on malnutrition

[a] anthropometry (calf circumference; mid upper arm circumference); neuropsychological issues, pressure sores, no. of prescribed drugs, self-assessment in terms of nutrition and overall health

[b] neuropsychological issues

[c] metabolic demand (fever duration and temperature; use of corticosteroids)

[d] use of oral nutritional supplements or tube feeding in the last month

CHAPTER 3: MATERIALS AND METHODS

3.1 Study design and participants

The study followed a quantitative, cross-sectional design where data were collected over 2 days, not more than 2 weeks apart. Phase 1 data collection took place on the day of recruitment at Groote Schuur Hospital (GSH) oncology outpatient clinic and phase 2 data collection took place at Sports Science Institute of South Africa (SISSA) as the dual energy X-ray absorptiometry (DEXA) machine was located there and to limit respondent burden on the day of recruitment.

A cross-sectional design for this research was chosen as it allows the determination of prevalence of specific outcomes, in our case reduced muscle mass, malnutrition, sarcopenia and cancer cachexia. In addition, cross-sectional design also allows the assessment of associated factors, in our research this included a variety of nutritional related factors that are widely assessed in clinical dietetic practice. As our data only reflect a snapshot in time, there is no loss to follow up and therefore cheaper to conduct than a longitudinal study. However, this means that no inference of causality can be made, and one needs to be aware of prevalence-incidence bias, namely under-representation of certain risk or associated factors (Levin, 2006). For this research, it relates to under-representation of patients that may be severely malnourished or have refractory cachexia or severe sarcopenia.

The recruited participants attended the colorectal, head and neck, ear, nose and throat oncology outpatient clinics at Groote Schuur Hospital (GSH), Cape Town, South Africa. These clinics were selected as these cancers represent a group of patients that are most usually nutritionally compromised. In addition, greater number of deaths exist from oesophageal cancer and colorectal cancer in Sub-Saharan Africa. GSH is one of three tertiary level hospitals that receive specialist referrals from other hospitals within the Western Cape Province. The service provided at these oncology outpatient clinics include the first clinical assessment and follow ups by the multidisciplinary team that consists of oncologists, radiologists, potentially a social worker, dietitian or physiotherapist for treatment or management options. Patients also attend these clinics to receive chemotherapy and can access care when required by them. As the oncology outpatient clinics service the wider metropole area of the Western Cape, its patients are representative of the surrounding area's population that are not reliant on medical aid, rather on government accessed health care services.

3.2 Selection criteria

Twenty-eight eligible cancer participants were recruited through consecutive sampling from the ear, nose and throat (ENT), head and neck and colorectal cancer (CRC) clinics at GSH. Medical folders were screened by fieldworkers to assess which patients met the inclusion criteria of age older than 18 years and younger than 70 years; diagnosis of cancer either being actively treated or palliative management of symptoms. Patients were excluded if they were pregnant or lactating; any co-morbid conditions that affected handgrip strength (HGS) namely arthritis, muscular dystrophy and strokes; patients that lived

outside the Cape Town metropolitan i.e., more than 70km from GSH; performance status as measured by Eastern cooperative oncology group (ECOG) score ≥ 3.

Eligible patients were approached, provided with verbal and written study information and invited to participate in the study. After signed consent was received, phase one data collection took place in a designated room within the outpatient clinic and phase two data collection took place at SSISA after agreed date and time.

3.3 Sample size estimation

"OpenEpi" (Dean AG) was used to determine the sample size required to assess the muscle mass and nutritional status of the patients. According to Jeffery et al. (2019), 54% had muscle mass loss as determined by DEXA and 38% were classified as malnourished according to PG-SGA. Using an unlimited population size, a confidence level of 95%, confidence limit of 10% and a design effect of 1, a sample size of 96 was calculated (Jeffery et al., 2019).

Recruitment started in March 2020 where 3 participants consented, but, due to COVID19, data collection was suspended till March 2021. Recruitment restarted from March 2021 to July 2021, thereafter data collection was suspended due to COVID19. Data collection restarted September to November 2021 with a total of thirty-nine adults who consented, of which 11 withdrew due to feeling poorly before data collection was completed. All participants gave written consent (Appendix A). The COVID-19 pandemic, poor health status of patients and exposure to the same patients attending the clinics resulted in low recruitment numbers.

Data were anonymized and stored electronically with data access only to researcher and supervisors. Participants received a monetary incentive to compensate for traveling costs to SISSA for the phase two data collection. In addition, oncology consultants received a summary of nutritional status of participants and, if required, the researcher requested referral to nutrition and dietetic services at GSH. Furthermore, participants received written and verbal general nutrition and dietetic information as relevant.

3.4 Ethical approval and participant consent

Ethics approval was received from the University of Cape Town, Faculty of Health Sciences, Human Research Ethics committee (UCT-FHS-HREC), reference number 763/2018 (Appendix B). In addition, institutional approval was received from the Chief executive officer of GSH, the Head of the Nutrition and Dietetics Department and the Head of the Department of Radiation Medicine at GSH. The research was performed in accordance with the principles of the declaration of Helsinki (World Medical Association, 2013), Good Clinical Practice (Department of Health, 2020) and the laws of South Africa. After verbal and written information was presented to the eligible patient, those that were informed and willing to participate, signed the consent form with the understanding that it was voluntary and they could withdraw from the study at any point, without providing reasons.

3.5 Data collection and assessments

All fieldworkers were qualified and registered dietitians with the Health Professionals Council of South Africa. They were trained by the researcher to complete the questionnaire in a standardised way with measurements collected according to strict protocols as stipulated in the methodology.

3.5.1 Questionnaire

A two-phase questionnaire was developed for the purposes of this study and was reviewed by experts in the field before being piloted. The questionnaire was piloted on 3 patients and refined to cover core research concepts. After recruitment, a field worker collected phase 1 and phase 2 data. Refer to Figure 3.1 for details.

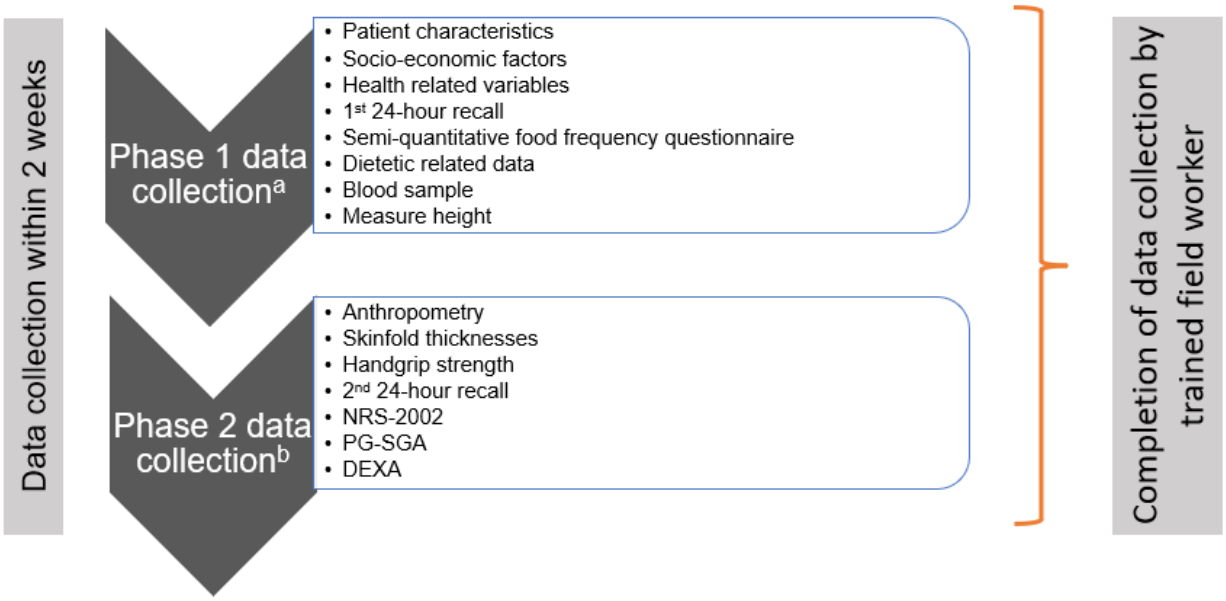


Figure 3.1 Data collection phase one and phase two

[a] Phase 1 data collection at Groote Schuur Hospital oncology outpatient clinics

[b] Phase 2 data collection at Sport Science Institute of South Africa

3.5.2 Participants' characteristics, socio-economic data and health related variables

Medical notes were accessed for gender, age and health related variables, which included the type, stage, date of diagnosis and management of cancer; anti-cancer treatment received (chemotherapy, radiotherapy and surgery) and time frame; additional co-morbidities; prescribed medication for symptoms; reason for clinic visit and documented past weights for calculation of percentage weight loss. Interviewer

questionnaire included questions on marital status, employment and grant status, type of living structure, number of adults and children younger than 18 years living with participant and highest education level achieved; cancer risk factors namely, smoking, intake of alcohol and drugs; past weights if nil documented in medical notes.

3.5.3 Biochemistry

Blood was drawn by a registered nurse that followed the usual hospital protocol. It was analysed for albumin and CRP levels by National Health Laboratory Services (NHLS). Elevated CRP of >10mg/l was the cutoff used as cancer research commonly uses CRP as an inflammatory marker. Hypoalbuminaemia was identified when albumin was <35g/l (Read et al., 2006).

3.5.4 Handgrip strength (HGS)

HGS was measured using the Takei dynamometer and the manufacturers' instructions were followed for taking measurements. The grip width was adjusted if needed before measurements were taken so that the index finger's second joint was at a right angle when the dynamometer's handle was held. Participants stood, holding dynamometer in the right hand, with dial facing outwards and asked to squeeze as hard as possible for three seconds. This process was repeated for the left hand, followed by right, then left again for a total of four measurements where the mean value of the highest values was displayed and then documented. Interpretation of results was as per Cruz-Jentoft et al. (2019) cutoff points for weak grip strength of 27kg for males and 16kg for females. In addition, percentiles as presented by Dodds et al., (2014) were also accounted for, namely <10th, between 10th and 25th and >25th percentiles.

3.5.5 Physical activity

Physical activity was measured using the global physical activity questionnaire (GPAQ) recommended by WHO (World Health Organisation, 2021). The questionnaire consists of 18 questions and it measures physical activity in three domains i.e., activity at work (moderate- or vigorous-intensity), activity related to traveling (walking or cycling), recreational activity (moderate- or vigorous-intensity) and sedentary behaviour. Questions are skipped if not relevant to the participant. For activities in each domain, the number of days in a week and minutes spent performing the activity were documented. WHO recommends 150 minutes per week of moderate activity and 75 minutes per week of vigorous activity for health purposes. When considering physical activity, duration and intensity are accounted for, therefore total physical activity was calculated in metabolic equivalents (MET) and presented as minutes/week. 1 MET equates to 1kcal/kg/hour of sitting quietly; 4 MET equates to 4kcal/kg/hour for moderate and 8kcal/kg/hour for vigorous activities. MET for GPAQ was calculated by multiplying the number of days with minutes and 4 for moderate and 8 for vigorous activities. If <600 MET calculated, then GPAQ indicates inadequate physical activity i.e., not meeting the WHO recommended physical activity minutes per week recommendation (World Health Organisation).

They were further divided into moderately and highly active if MET minutes per week were between 600 to 2,999 and ≥3000, respectively (Singh & Purohit, 2011).

3.5.6 Dietary information

A twenty-four-hour recall using the multiple pass method was performed on recruitment day and the day the DEXA scan was taken to determine macronutrient intakes (Moshfegh et al., 2008). Food amounts eaten were estimated based on standardised kitchen tools or models or pictures of portion sizes from Dietary Assessment and Education Kit (DAEK) (Steyn & Senekal, 2004a) Household measures of portion size of foods were converted into grammes using part of the renal food exchange list (National Department of Health Directorate: Nutrition, 2018), DAEK quantity manual (Steyn & Senekal, 2004a) or South African food quantity tables (SAFQT); (Wolmarans et al., 2009). Analyses of these food items were performed using the software programme, FoodFinder (*FoodFinder: Dietary Analysis Software*, 2020). The analyses included total energy intake measured as kilojoules and macronutrients measured in grammes and presented as percentages of total energy. Total energy intake was converted to kcal/kg/day and total grammes of protein was converted to g/kg/day for each individual participant. This was to determine whether participants were meeting requirements of energy of >25kcal/kg/day and protein of >1g/kg/day (Muscaritoli et al., 2021).

A semi-quantified food frequency questionnaire (FFQ) was completed for each participant consisting of 59 items or grouped items (Appendix C). Although the FFQ was not validated for this study population, a rigorous process was followed for its development. Firstly, the chosen food items from the FFQ were selected from the food frequency questionnaire in the Dietary Assessment and Education Kit (DAEK) visual cards (Steyn & Senekal, 2004b). The DAEK was developed, adapted and researched for local South African diets. The selection was based on foods that may impact cancer risk and ascertain nutritional value, particularly protein intake. The selection was reviewed by dietitians in academia and with practical experience with patients with cancer.

The DAEK visual cards were shown to participants who had to place it in one of 2 piles: foods eaten within the previous month and foods not eaten in the last month. Each food item or grouped item had a standard portion size based on the renal food exchange list (National Department of Health Directorate: Nutrition, 2018) or SAFQT. Participants had to indicate how many portion sizes were eaten at a time, then indicate how frequently those items were eaten, either per day, per week or per month. Each food item for each participant was converted into grammes per day (via food exchange list, DAEK manual or SAFQT) and placed into fifteen food categories (Table 3.1). The portions eaten per day were combined in the specific food categories. These food categories were then compared to the South African food based dietary guidelines (SAFBDG);(Vorster et al., 2013).

Table 3.1: Food items from food frequency questionnaire (FFQ)[a] grouped into food categories

Food category	Food items
Animal Protein	Beef, lamb, pork (with or without fat) 1 matchbox (FFQ1)
	Lean or regular mince 1 Tbsn (FFQ2)
	Chicken eaten with or without skin 1 matchbox (FFQ6 1)
	Fish tinned, grilled, smoked, baked 1.5 matchboxes (FFQ7)
	Eggs (fried, boiled, poached, scrambled) large (FFQ8)
	Organ meats (liver or kidney) 1 matchbox (FFQ9)
Processed protein	Bacon 2 x rashers (FFQ3)
	Vienna (standard size 42g) / polony or ham (2 thin slices) / Tinned meat (1 rounded dessert spoon) (FFQ4)
	Boerewors / sausage / pork bangers (thick x 5cm) (FFQ5)
	Hard cheese 1 matchbox (FFQ17)
	Biltong / Droe wors 30g (FFQ 33)
Dairy	Milk in cereal, tea, coffee, drink 1 cup (FFQ10)
	Sour milk/ amasi or buttermilk 1 cup (FFQ11)
	Yoghurt sweetened or unsweetened 3 heaped Dsp (FFQ14)
	Flavoured milk ½ standard size carton (FFQ15)
	Drinking yoghurt 100ml (FFQ16)
Other Dairy	Coffee creamer 8 tsp (FFQ12)
	Condensed milk spoons 3 tsp (FFQ13)
Plant protein	Beans, split peas, lentils, chickpeas, soy, soya mince ½ cup (FFQ22)
	Peanut butter 1 Dsp (FFQ34)
Starchy cereals, grains, potato	Bread 1 slice or ½ roll (FFQ28)
	Breakfast cereals e.g. Flakes, All bran ½ cup / 1 Weetabix / Pronutro or Muesli ¼ cup / Futurelife 2 Tsp (FFQ9)
	Cooked porridge e.g. ½ cup soft maize, mageau, maltabella, oats / ¼ cup stiff maize (FFQ20)
	Pasta, rice, barley ½ cup / samp 1/3 cup (FFQ21)
	Potato roast, boiled 1 medium / mash ½ cup (FFQ23)
Other starchy snacks	Instant soup 1 packet
	Popcorn 2.5cups
Fruit	Medium fruit x1 / small fruit e.g. plums x2 / Banana 1 small / Grapes x8 / Melon cubed 1 cup / Fruit salad ½ cup (FFQ25)
	Dried fruit equivalent to fresh fruit 1 portion (FFQ27)
Vegetables	Any raw vegetables or salad 1 cup (FFQ28)
	Any cooked vegetables ½ cup (FFQ29)
	Starchy veg e.g., butternut ¼ cup / corn or sweet potato 1 dessert spoon (FFQ30)
Oils and fats	Margarine or butter on bread, vegetables etc. 1 tsp (FFQ31)
	Oil in cooking 1 tsp (FFQ 32)
	Avocado pear ¼ medium (FFQ26)
	Nuts mixed dough model = $^{1}/_{3}$ cup (FFQ35)

Food category	Food items
High fat starchy snacks	Crisps small packet (FFQ37)
	Pies standard (FFQ38)
	Samosas small standard (FFQ39)
	Fried chips 1/3 cup (FFQ42)
	Vetkoek / fat cakes 1 medium (FFQ47)
	Roti side plate size (FFQ48)
	instant noodles 1 packet (FFQ24)
Take-aways	Fried chicken 1 matchbox (FFQ41)
	Fried fish (FFQ43) 1½ matchboxes
	Pizza 1/8 30cm (FFQ44)
	Gatsby 30cm/4 (FFQ45)
	Burger with roll standard (FFQ46)
Baked goods / frozen dairy / chocolates	Cake 1 matchbox = ½ slice (FFQ55)
	Sweet biscuits x 2 (FFQ55)
	Doughnuts / koeksisters 1 small (FFQ56) Eclairsx1 (FFQ56)
	Ice-cream ½ cup (FFQ56)
	Chocolate 2 blocks (FFQ51)
Added sugar	Sugar 3 tsp (FFQ49)
Sugary products	Jam / syrup / honey 3 tsp (FFQ50)
	Sweets 5 hardboiled (FFQ52)
	Jelly / instant puddings ½ cup (FFQ53)
	Gassy Cool drinks ½ cup (FFQ57)
	Fruit juice ½ cup (FFQ58)
	Cooldrinks made with water½ cup (FFQ59)

Tbsp – tablespoon; Dsp – desert spoon; tsp = teaspoon; FFQ – food frequency questionnaire

[a] Refer to appendix B for FFQ

Data on vitamin, mineral and herbal supplements were collected. Information regarding dietetic service referral was included in addition to any oral nutritional supplements (ONS) prescribed or bought over the counter.

3.5.7 Nutritional risk and assessment

The nutritional risk screening-2002 (NRS-2002) tool was developed by Kondrup et al., (2003) to be used as a screening tool to identify patients who are at nutritional risk and may benefit from nutrition intervention (Kondrup et al., 2003). ESPEN recommends NRS-2002 to be used in hospital settings (Kondrup, 2003) and it has been validated against randomized controlled trials consisting of inpatients and outpatients that determined outcome based on length of hospital stay, rates of infections and complications and accelerated mobility (Kondrup et al., 2003). Test-retest reliability was found to be excellent amongst surgical and medical inpatients (Bolayir et al., 2019). The tool consists of an initial screening section and a final screening section. If answered yes to any of the initial screening sections' questions related to BMI, weight loss over 3 months, dietary intake and illness severity, then the final screening section was completed. The final screening section quantifies weight loss, BMI or dietary

intake and severity of illness. A participant who scored ≥3 was identified as being at risk of malnutrition by the NRS-2002 screening tool (Appendix D).

The patient-generated subjective global assessment (PG-SGA) was developed by Ottery et al, (1996) to be used as a triage, screening and an assessment tool in a hospital setting for all patients despite it being developed using oncology patients. It has been validated against Subjective Global Assessment (SGA) tool (Bauer et al., 2002) and its predictive validity (Jager-Wittenaar & Ottery, 2017) and test-retest reliability has been confirmed in cancer patients (Nitichai, 2017). The first section consists of weight details (box 1), food intake (box 2), symptoms affecting oral intake (box 3), activity, and function (box 4). The second section includes disease information (worksheet 2), metabolic demand (worksheet 3), and completion of a physical examination (worksheet 4); (Appendix D). Each part is scored, and the additive score determines nutritional triage recommendations. Zero to 1 score indicated no present intervention required, 2 – 3 score indicated patient and family education around symptoms, 4 – 8 score indicated Dietitian and physician input, ≥ 9 score indicated a critical need for symptom control and nutrient intervention options (Jager-Wittenaar & Ottery, 2017). Participants were nutritionally categorised as well nourished (stage A), moderately malnourished or suspected malnutrition (stage B), or severely malnourished (stage C) (Ottery, 1996).

3.5.8 Anthropometric measurements and calculations for clinical methods

Weight

Weight was measured when DEXA was performed. The participant stood on a Seca 813 electronic scale, placed on a flat surface with feet apart, shoes and heavy clothing removed. Weight was recorded once the digit display settled to the nearest 100g (Lee, 2013). From medical notes or participant recall, past weights and dates were recorded. Significant percentage weight losses of >5% in 1 month or >10% in 6 months were calculated as follows: [(weight at 1 or 6 months ago minus current weight) divided by weight at 1 or 6 months ago] X 100. If previous weight was unknown, questions regarding change of clothing size, jewellery not fitting or needing to adjust belt size was determined. If answered yes to these questions, expert opinion suggests that significant weight loss has occurred.

Height

Height was measured using a Seca stadiometer placed on a flat surface. After shoes and any headgear were removed, the participant stood with feet together on the base of the stadiometer. The participant's head was placed in the Frankfurt plane and their feet, calves, buttocks, upper back and the back of the head were in contact with the stadiometer. The measurement was recorded to the nearest 1cm after inspiration (Lee, 2013). All other anthropometry was completed on the same day as DEXA was performed.

Body Mass Index (BMI)

Body mass index (BMI) was calculated as weight (kg) divided by height (m^2) squared and interpreted according to Table 3.2 (World Health Organisation, 2004).

Table 3.2 World Health Organisation BMI categories

Reference	Anthropometry	Value	Interpretation
WHO (2004)	BMI (kg/m^2)	<18.50	Underweight
		<16.00	Severe thinness
		16.00 - 16.99	Moderate thinness
		17.00 - 18.49	Mild thinness
		18.50 - 24.99	Normal weight range
		≥25.00	Overweight
		25.00 - 29.99	Pre-obese
		≥30.00	Obese
		30.00 - 34.99	Obese class I
		35.00 - 39.99	Obese class II
		≥40.00	Obese class III

WHO – World Health Organisation; BMI – body mass index

Mid upper arm circumference (MUAC)

MUAC was measured using a non-stretchable measuring tape to the nearest millimetre using the right upper arm (Lee, 2013). The mid-point of the lateral side of the right arm was measured whilst the arm was bent in a 90º angle at the elbow, between the acromion process of the scapula and inferior margin of the olecranon process of the ulna. The measurement was taken when the right arm was elongated directly next to the body to relax the muscle with the palm facing the thigh. A participant was categorised as malnourished when females and males had <22cm and <23cm MUAC measurements, respectively (James et al., 1994).

Calf circumference

Calf circumference was measured using a non-stretchable measuring tape to the nearest millimetre using the right leg across the widest circumference (Madden & Smith, 2016) and interpreted using Gonzalez et al., (2021) cutoff points of 33cm and 34cm for females and males, respectively. Adjustments were made for BMIs <18.5kg/m^2, 25-29.9 kg/m^2, 30-39.9 kg/m^2, ≥40 kg/m^2 of +4cm, -3cm, -7cm and -12cm, respectively (Gonzalez et al., 2021); (Table 3.3).

Skinfold thickness

Four skinfold sites were measured using the Harpenden calipers on the right side of the participant's body. The triceps, bicep, subscapular and iliac crest skinfold sites were identified as per Lee and Nieman's textbook (2013). The skinfold was held between the field worker's left thumb and index finger, 1cm proximal to the identified site. The calipers were held perpendicular to the long axis of the site with

the dial facing upwards and placed 1cm distal from the skinfold. After releasing the lever arm of the calipers, the researcher read the measurement after 2 seconds to the nearest millimetre. A second reading was performed 15 seconds apart without the researcher releasing the skinfold. An average of the two measurements was recorded.

Body fat percentage

The body fat percentage was calculated as follows (Lee, 2013)

1. Calculate the log of the sum of the 4 skinfolds in mm (triceps, bicep, subscapular and ileac crest)
2. Calculate body density from the body density equations in Appendix E
3. Calculate percentage body fat = (495/body density) – 450
4. Calculate the fat mass (kg) = body mass (kg) X %body fat
5. Calculate fat free mass (kg) = body mass (kg) – fat mass (kg)
6. Classification of % body fat will be according to the World Health Organisation (WHO) BMI guidelines (Appendix E) (World Health Organisation, 2004)

Bone free corrected arm muscle area (cAMA)

The bone free AMA, also called corrected AMA (cAMA) was derived from the triceps skinfold (TSF) and the MUAC using the formula for the cAMA in cm² for males and females (Lee, 2013).

cAMA for females = $\frac{[MUAC-(\pi\ x\ TSF)]^2}{4\ \pi} - 6.5$

cAMA for males = $\frac{[MUAC-(\pi\ x\ TSF)]^2}{4\ \pi} - 10$

Note that both MUAC and TSF must be expressed as centimetres in the equation. Interpretation of cAMA was from Frisancho (1990) percentile tables in the textbook by Lee (2013) where wasted was equivalent to <5th percentile (Appendix E); (Table 3.3).

All the anthropometric measurements reported above are presented as clinical methods in Table 3.3.

Estimated appendicular skeletal muscle (est ASM)

Estimated appendicular skeletal muscle was calculated using the following equation:
ASM (kg) =−10.427 + (calf circumference × 0.768) − (age × 0.029) + (sex × 7.523) + (white × 0 or black × 2.203 or Mexican American ×−0.540 or other ×−0.402) (Santos et al., 2019). For all our participants, we used zero value for ethnicity. Cutoff points used for males and females were <19.62kg and <11.02kg, respectively (Landi et al., 2017); (Table 3.3).

3.5.9 Global physical examination (GPE)

The global physical examination is worksheet 4 of PG-SGA where muscle, fat and fluid status are examined. For muscle status, clavicles, interosseous muscles and thigh muscles are examined; for fat deficit, the orbital fat pads and triceps skinfold are examined; for fluid stats, oedema is checked for in sacral and lower limb areas. These components are scored subjectively as 0, 1, 2, 3 equating to no deficit, mild, moderate and severe deficit, respectively and assigned a global score. Thereafter a total numerical score is calculated with muscle status impacting the score the most and can range from 0 – 3 (Table 3.3).

Table: 3.3 Clinical and technical methods to assess muscle mass and strength, cutoff points, interpretation and reference populations

Methods	Variable	Cutoff points		Interpretation	Reference	Reference population used
		Male	Female			
Clinical	MUAC (cm)	<23cm	<22cm	Malnourished	Ferro-Luzzi et al., (1996)	James et al., (1994)
	CC & Adj CC (cm)	<34cm	<33cm	Low	Gonzalez et al., (2011)	NHANES survey 1999-2006
	cAMA (cm^2)	<5th percentile	<5th percentile	Wasted	Lee and Niemans (2013)	Frisancho et al., (1990)
	Estimated ASM	<19.62kg	<11.02kg	Low	Santos et al., (2019)	Landi et al., (2017)
	GPE	Score ≥1 wk/t 4	Score ≥1 wk/t 4	Deficit	Ottery et al., (1996)	Not applicable
Technical	ASM (kg)	<20kg	<15kg	LMQ	Cruz-Jentoft et al., (2019)	Studenski et al., (2014)
	ASMI 1 (kg/m^2)	<7kg/$m^{2;}$	<6kg/ m^2	LMQ	Cruz-Jentoft et al., (2019)	Gould et al., (2014)
	ASMI 2 (kg/m^2)	<7.26kg/m^2	<5.45 kg/m^2	Sarcopenia[a]	Fearon et al., (2011)	Baumgartner et al., (1998)
	ASM/BMI	<0.789	<0.512	LLM	Studenski et al., (2014)	Studenski et al., (2014)
	ALMI (kg/m^2)	<5th percentile	<5th percentile	Low	Kelly et al., (2009)	NHANES survey 1999-2004
Strength	HGS (kg)	<27kg	<16kg	Weak	Cruz-Jentoft et al. (2019)	Dodds et al., (2014)

ASM – appendicular skeletal muscle; LMQ – low muscle quantity; ASMI – appendicular skeletal muscle mass index (ASM/height in m^2); ASM/BMI - appendicular skeletal muscle divided by BMI; LLM - low lean mass; ALMI – appendicular lean muscle mass index (ALM/height in m^2); NHANES – National Health and Nutrition Examination Survey; MUAC – mid upper arm circumference; CC – calf circumference; Adj CC – adjusted calf circumference; cAMA – corrected arm muscle area; GPE – global physical examination; wk/t 4 – worksheet 4 (from PG-SGA); HGS – handgrip strength

[a] Sarcopenia in some cancer research refers to reduced muscle mass only, not the most recent definition from Cruz-Jentoft et al., (2019)

3.5.10 Dual energy X-ray absorptiometry (DEXA)

A Hologic brand DEXA machine was operated by radiographers who followed best practice guidelines (Hangartner et al., 2013). From the DEXA scan, variables that were measured are listed in Table 3.4. From these measured variables, different representations of muscle mass were calculated and interpreted according to reference populations and cutoff points as presented in Table 3.3. The representation (or unit of measure) of muscle mass that was used as the reference standard in this research was appendicular skeletal muscle (ASM) as determined by investigating the strongest overall relationship between all the muscle mass representations. This is found in results section 4.10, table 4.12.

The subtotal fat mass index (FMI) was calculated using subtotal fat mass divided by height squared in metres. The 1999 to 2004 National Health and Nutrition Examination Survey (NHANES) population derived percentiles from calculated Z scores were used for the interpretation of subtotal FMI and %FM. The interpretations were as follows: <5th percentile – under fat; 5th to 25th percentile – below average; 25th to 75th percentile – average; 75th to 95th percentile – above average; 95th to 97th percentile – excess fat. For categorical data, any variables <5th percentile were under fat and all other variables >5th percentile were 'not under fat.' (Kelly et al., 2009).

Table 3.4 Measured and calculated DEXA variables

DEXA variables measured	**Body location**	**DEXA variables calculated**	**Calculations**	**Explanation**
Subtotal FM (kg)	Total FM without head	FMI[a] kg/m^2	Subtotal FM / Ht in metres squared	Head creates artefact
Subtotal % fat				
BMC (g)	R arm + L arm R leg + L leg	FFSM arms (kg)	[(R arm lean + L arm lean) – sum arm BMC]/1000	Without FM and bone
Lean mass (g)	R arm + L arm R leg + L leg	FFSM legs (kg)	[(R leg lean + L leg lean) – sum leg BMC]/1000	Without FM and bone
		ASM (kg)	FFSM arms + FFSM legs	Without FM and bone
		ASMI (kg/m^2)	ASM / Ht in metres squared	Without FM and bone, standardized to height
		ALM (kg)	(R arm + L arm + R leg + L leg)/1000	Without FM but includes bone

DEXA – dual energy X-ray absorptiometry; FM – fat mass; FMI – fat mass index; Ht – height; BMC – bone mineral content; R – right; L – left; FFSM – fat free skeletal mass; ASM – appendicular skeletal muscle; ASMI - appendicular skeletal muscle index; ALM – appendicular lean mass

3.5.11 Global leadership initiative on malnutrition (GLIM)

Since the Global leadership initiative on Malnutrition (GLIM) guidance was published (Cederholm et al., 2019), there has been research related to the variety of approaches of the consensus criteria for the application of GLIM. The performance and agreement of these varied GLIM approaches have been compared to reference methods for assessing nutritional status (SGA, PG-SGA, NRS-2002, MNA) or to technical methods to determine reduced muscle mass criterium in GLIM. The aim of our study was to determine the prevalence of malnutrition using GLIM and whether alternative cheaper methods of assessing muscle mass could be used in place of the reference standard, DEXA.

The GLIM research group has published guidance on measuring muscle mass (Compher et al., 2022) using technical methods that include CT scans, BIA, ultrasound, DEXA and clinical methods. Their suggestion is that any technical method used to assess muscle mass needs to have expertise to interpret measurements and a relevant reference population with ethnic-specific cutoff points. When this is not possible, alternative markers of muscle mass can be used that are accessible, quick and can be measured accurately in a variety of health settings

The GLIM proposes a two-step approach: identify nutritionally at-risk patients, then perform GLIM consensus criteria. We applied the GLIM approach to all the participants, including those that were found not to be nutritionally at risk to determine prevalence of malnutrition. GLIM consensus criteria are composed of phenotypic and aetiologic criteria where only one criterion from each is needed for malnutrition diagnosis (Table 3.5).

Table 3.5 Global leadership initiative on malnutrition phenotypic and aetiologic criteria

Phenotypic criteria[g]			**Aetiologic criteria**[g]	
Percentage weight loss	*Low body mass index (kg/m2)*	*Reduced muscle mass*[a]	*Reduced food intake or assimilation*[b,c]	*Inflammation*[d,e,f]
>5% within past 6 months	<20 if < 70 years, Asia: <18.5	Reduced by validated body composition measuring techniques[a]	50% of ER > 1 week,	Acute disease/injury[d,f]
or >10% beyond 6 months	or <22 if >70 years Asia: or <20 if >70 years		or any reduction for >2 weeks	or chronic disease-related[e,f]
			or any chronic GI condition that adversely impacts food assimilation or absorption[b,c]	

From Cederholm et al., 2019

GI - gastro-intestinal, ER - energy requirements

[a] Technical body composition techniques see Figure 3.2

[b] GI symptoms that can impair food intake or absorption e.g., dysphagia, nausea, vomiting, diarrhoea, constipation or abdominal pain.

[c] Reduced assimilation of food/nutrients e.g., chronic diarrhoea, eosophageal strictures, high ostomy output. In our research, PG-SGA box 3 was used to determine the impact on food intake and assimilation.

[d] Acute disease/injury-related e.g., severe inflammation (major infection, burns, trauma or closed head injury) or mild to moderate inflammation other disease/injury-related conditions.

[e] Chronic disease-related inflammation is likely to be associated with malignant disease, chronic obstructive pulmonary disease, congestive heart failure, chronic renal disease or any disease with chronic or recurrent inflammation.

[f] C-reactive protein may be used as a supportive laboratory measure.

[g] Requires at least 1 phenotypic criterion and 1 etiologic criterion for diagnosis of malnutrition

Different GLIM approaches were used within both the phenotypic and aetiologic criteria. For reduced muscle mass there were 2 approaches, one technical using DEXA (the reference standard) and the other, clinical. The clinical approach included using MUAC, cAMA, calf circumference, adjusted calf circumference, estimated ASM, and global physical examination, all alternative markers of muscle mass as per the guidance suggested by GLIM (Compher et al., 2022); (Figure 3.2). Table 3.3 presents the alternative muscle mass methods, reference populations used and interpretations for these. For the aetiologic criterion of inflammation there were two approaches i.e., the diagnosis of cancer was considered as fulfilling the criterion and having raised CRP in the alternative approach. The reduced food intake or assimilation criteria were met as follows: 50% less energy requirements were fulfilled when the energy per kilogramme was less than half of 25kcal/kg i.e., 12.5kcal/kg; box 2 of PG-SGA was used to

determine reduced intake for >2 weeks; box 3 of PG-SGA was used to determine nutrition impact symptoms impact on food intake or assimilation (Appendix D).

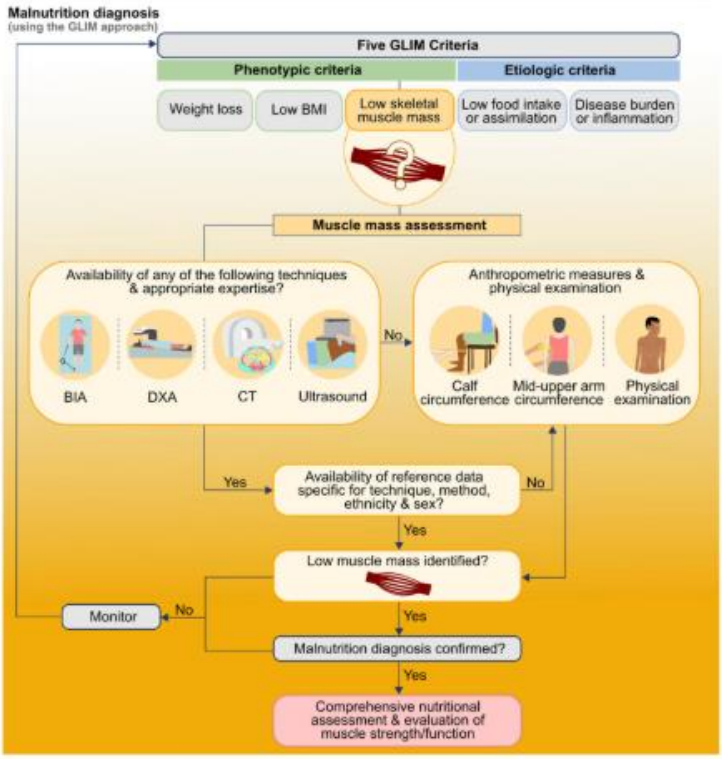


Figure 3.2: Flow chart for GLIM consensus criteria including technical and clinical approaches for muscle mass assessment

From Compher et al., 2022

BIA - bioelectrical impedance analysis; BMI - body mass index; CT - computerized tomography; DXA - dual-energy x-ray absorptiometry; GLIM - Global Leadership Initiative on Malnutrition

3.5.12 Sarcopenia

The sarcopenic diagnostic criteria used was from the European Working Group on Sarcopenia in Older People (EWGSOP 2): weak grip strength indicates that sarcopenia is probable; a reduced muscle mass confirms the diagnosis (Cruz-Jentoft et al., 2019). DEXA, the reference standard, was used to measure muscle mass. Alternative markers of reduced muscle mass used were MUAC, cAMA, calf circumference, adjusted calf circumference, and global physical examination (worksheet 4 of PG-SGA); (Table 3.3).

3.5.13 Cancer cachexia

Four cancer cachexia frameworks from different research groups were used, namely Arends et al. (2021), Blum et al. (2014), Fearon et al. (2011) and Vigano et al. (2017) to diagnose pre-cachexia, cachexia and refractory cachexia (Table 3.6). For each of the frameworks, only 1 diagnostic variable needs to be met to fulfill the diagnosis. The reference cancer cachexia diagnostic framework used was from Arends et al., (2021) as the most updated guideline; DEXA presented by ASM was used for the RMM variable in Arends et al., (2021) diagnostic framework; DEXA presented by ASMI was used for the RMM as per Fearon et al., (2011). The percentage weight loss was calculated from the available weights and dates documented in medical notes.

Table 3.6 Diagnostic parameters of different cancer cachexia frameworks

Diagnosis	Diagnostic variables	Reference			
		Arends et al. (2021)	Fearon et al. (2011)	Vigano et al. (2017)	Blum et al. (1014)
Cancer pre-cachexia	>1kg & ≤5% WL in 6 months				✓
	>1kg & ≤5% WL in 6 months + CRP≥10mg/l			✓	
	>1kg & ≤5% WL in 6 months + PG-SGA box 2≥1			✓	
	>1kg & ≤5% WL in 6 months + CRP≥10mg/l + PG-SGA box 2≥1			✓	
	CRP≥10mg/l + PG-SGA box 2≥1			✓	
Cancer cachexia	>5% WL in 6 months		✓		✓
	>5% WL in 6 months + PG-SGA box 2≥1			✓	
	>5% WL in 6 months + CRP≥10mg/l	✓		✓	
	>5% WL in 6 months + CRP≥10mg/l + PG-SGA box 2≥1			✓	
	>2% WL in 6 months + <20kg/m^2 BMI		✓		✓
	>2% WL in 6 months + Low MM		✓		
	CRP≥10mg/l + <20kg/m^2 BMI	✓			
	CRP≥10mg/l + Low MM	✓			
Refractory cancer cachexia	>15% in 6 months + <23kg/m^2 BMI				✓
	>20% in 6 months + <27kg/m^2 BMI				✓

WL – weight loss; CRP – C-reactive protein; PG-SGA – patient generated subjective global assessment; BMI – body mass index; MM – muscle mass

3.6 Statistical analyses

Statistical analysis was performed using Statistica version 14.0.1.25. Continuous data were checked for normality using Kolmogorov Smirnov and Shapiro Wilk tests; all continuous data were found to be non-normal. Descriptive data were shown as median and interquartile ranges for continuous variables and percentages for categorical variables. The nutritional status indicators and treatment interventions between low and acceptable muscle mass groups and between cachexic and non-cachexic groups were evaluated using Mann Whitney U and Fisher exact tests as appropriate.

Sensitivities and specificities, Cohen's kappa (ƙ) and percentage agreement were calculated for the following data: alternative muscle mass markers against DEXA; sarcopenia diagnoses using alternative muscle markers against DEXA; GLIM diagnoses using different muscle mass markers against technical approach using DEXA; different cancer cachexia frameworks. Sensitivity and specificity were interpreted as follows (overall interpretation took both variables into account): poor if sensitivity or specificity was <50%; fair if sensitivity or specificity was <80% and both >50%; good if sensitivity and specificity >80% (van Bokhorst-de van der Schueren et al., 2014).

Cohen's ƙ coefficients were calculated and agreement categories for interpretation are as follows: < 0.4 as poor agreement, 0.4 – 0.6 as fair agreement; >0.6 as good agreement (van Bokhorst-de van der Schueren et al., 2014). In addition, percentage agreement was performed as Cohen's ƙ is unreliable for small numbers as the confidence intervals would be wide (McHugh, 2012). Percentage agreement of ≥90% was deemed acceptable as higher agreement is needed when clinical decisions need to be made as based upon expert opinion.

Statistical significance is indicated by a p-value < 0.05. Effect size was calculated using Phi for Fisher exact tests and Cohen's r for Mann Whitney U tests to determine the overall power calculation. Phi and Cohen's r interpretation are as follows: ≥0.2-0.49 minimal effect; ≥0.5-0.79 moderate effect; ≥0.8 strong effect (Ferguson, 2009).

CHAPTER 4: RESULTS

4.1 Participant characteristics and socio-economic data

Out of the 28 participants that consented and completed the study, 57.1% were males (Table 4.1). The median and interquartile range (IQR) for age of the total sample was 56.0 (46.0–63.5) years. Just under a third of participants were married and all lived with other adults; the majority (64.3%) lived with children under the age of 18 years. Most participants were retired (35.7%) and 21.4% were employed. A state grant was received by 57.1%. One participant lived in an informal settlement, while the rest lived in a house or flat. The highest median (IQR) school grade completed was 10.5 (8.0-12.0) with 21.4% of participants only completed primary school and only 46.4% completed high school. Five of the participants that completed high school enrolled in tertiary education and 3 completed post national senior certificates; 1 completed a national diploma; 1 completed a degree (Table 4.1).

Table 4.1 General characteristics and socio-economic data (n=28)

Categories	Components	Variables	Results
General characteristics	Gender	Male, n (%)	16 (57.1)
		Female, n (%)	12 (42.9)
	Age	Years, median (IQR)	56.0 (46.0-63.5)
	Marital status	Married, n (%)	9 (32.1)
		Divorced / single / widowed / separated, n (%)	19 (67.8)
Socio-economic	Live with others	Live with other adults, n (%)	28 (100.0)
		No. of adults per participant, median (IQR)	3.0 (2.0-4.0)
		Live with children, n (%)	18 (64.3)
		No. of children per participant, median (IQR)	2.0 (0.0-2.0)
	Employment status	Employed, n (%)	6 (21.4)
		Retired, n (%)	10 (35.7)
		Too sick to work, n (%)	8 (28.6)
		Unemployed not looking, n (%)	4 (14.3)
	Grant	Receiving grant, n (%)	16 (57.1)
		No grant received, n (%)	11 (39.3)
		Grant being processed, n (%)	1 (3.6)
	Living conditions	House / flat, n (%)	27 (96.4%)
		Informal settlement, n (%)	1 (3.6%)
	Education	Highest grade obtained, median (IQR)	10.5 (8.0-12.0)
		Primary school, n (%)	6 (21.4)
		Incomplete high school, n (%)	9 (32.1)
		Complete high school, n (%)	13 (46.4)
		Post NSC certificate / degree / national diploma, n (%)	5 (17.9)

IQR – interquartile range; NSC – national senior certificate

4.2 Health related variables

Half of the participants were recruited from the colorectal clinic, while the remainder were recruited from the head and neck (32.1%) or ear, nose and throat (17.9%) clinics (Table 4.2). Participants were diagnosed with cancer a median (IQR) of 5.0 (2.0-11.0) months ago. Metastases were confirmed in 42.9% (n=12) of participants with the liver (n=5) and lungs (n=3) being the most common sites of metastases. Just over two fifths of participants had palliation as a management plan, with 17.9% of participants actively being treated (Table 4.2).

About three fifths of participants received surgery, over two fifths received radiotherapy and chemotherapy was received by one fifth (Table 4.2). Just under a third of participants were receiving chemotherapy during data collection. One anti-cancer treatment was received by most participants, followed closely by 43.0% who received 2 treatments. The median (IQR) time elapsed since recent treatment was 1.0 (0.0-2.0) month ago.

Prescribed medications, for cancer related symptoms or treatment related side effects, were varied with analgesics being prescribed for over half of participants, followed by laxatives by over a third, and mouth medication, anti-emetics and proton pump inhibitors each being prescribed for over one fifth of participants (Table 4.2). Six participants had no documented prescribed medications for symptoms.

The reasons for attending the cancer clinics at the time of data collection were varied, with almost a third attending to receive chemotherapy and just over half of participants stating ‘other’ reasons. Of the 15 participants that stated other reasons for attending the clinic, a quarter attended follow up related to biopsy, CT scan and post-treatment results (Table 4.2).

Table 4.2 Cancer related data (n=28)

Categories	Components	Variables	Results
Cancer related data	Cancer clinic	Ear, nose, throat, n (%)	5 (17.9)
		Head and neck, n (%)	9 (32.1)
		Colo-rectal, n (%)	14 (50.0)
	Documented diagnosis date[a]	Months ago, median (IQR)	5.0 (2.0-11.0)
	Metastases	Yes, n (%)	12 (42.9)
		No, n (%)	9 (32.1)
		Not evaluated, n (%)	3 (10.7)
		Not documented in notes, n (%)	4 (14.3)
Cancer related treatment	Treatment received[b]	Radiation received, n (%)	12 (42.9)
		Chemotherapy received, n (%)	6 (21.4)
		Receiving chemotherapy, n (%)	9 (32.1)
		Planned chemotherapy, n (%)	3 (10.7)
		Cancer related surgery, n (%)	17 (60.7)
	Time since treatment received (in months)	Radiation, median (IQR)	2.5 (1.0-4.5)
		Chemotherapy, median (IQR)	2.0 (1.0-4.0)
		Surgery, median (IQR)	4.0 (3.0-10.0)
	Number of treatment types received	One, n (%)	13 (46.4)
		Two, n (%)	12 (42.9)
		Three, n (%)	3 (10.7)
	Time since treatment received (in months)	Most recent treatment, median (IQR)	1.0 (0.0-2.0)
	Cancer management	Receiving treatment, n (%)	5 (17.9)
		Receiving palliation, n (%)	12 (42.9)
		Not documented, n (%)	11 (39.3)
Medication data	Prescribed medication[b]	Analgesics, n (%)	15 (53.6)
		Laxatives, n (%)	10 (35.7)
		Mineral supplement, n (%)	2 (7.1)
		Mouthwash / medication, n (%)	6 (21.4)
		Anti-emetics, n (%)	6 (21.4)
		Proton pump inhibitors, n (%)	6 (21.4)
		Cream for dry skin, n (%)	5 17.9)
		Anti-diarrhoea medication, n (%)	3 (10.7)
Clinic data	Reasons for clinic appointment	Initial appointment, n (%)	2 (7.1)
		Treatment completion, n (%)	1 (3.6)
		Treatment interruption by participant, n (%)	1 (3.6)
		Chemotherapy, n (%)	9 (32.1)
	Other appointment reasons	Assessment, n (%)	1 (3.6)
		Decision, n (%)	4 (14.3)
		Follow up[c], n (%)	7 (28.0)
		Routine follow up[d], n (%)	3 (10.7)

IQR – interquartile range; BKA – below knee amputation

[a] missing data n=3

[b] Only 'Yes' responses presented

[c] Follow-up includes receiving results for biopsy, CT scan and post-treatment interventions

[d] Routine follow up incudes weekly or monthly appointments related to pain control or wound dressing

Half of participants were diagnosed with co-morbidities, with the majority (39.3%) being diagnosed with hypertension (Table 4.3). Almost a third of participants had a variety of other co-morbidities diagnosed, with previous tuberculosis being the most common (Table 4.3).

Table 4.3 Non-cancer related co-morbidities

Categories	**Variables**	Classification	**Results, n (%)**
Non-cancer related conditions	Co-morbidities	Yes, n (%)	14 (50.0)
		No, n (%)	14 (50.0)
	Type of co-morbidities	Hypertension, n (%)	11 (39.3)
		Hypercholesterolaemia, n (%)	2 (7.1)
		Diabetes Mellitus, n (%)	3 (10.7)
		Other[a] co-morbidities, n (%)	9 (32.1)

[a] Other co-morbidities included: previous tuberculosis, chronic obstructive pulmonary disease, human immune-compromised virus, asthma, hypothyroidism, post-TB bronchiectasis, Crohn's disease, below knee amputation

4.3 Risk factors

Participants that currently smoked were 39.3% with a median (IQR) of 5.0 (2.0-6.0) cigarettes smoked daily. Ex-smokers (28.6%) smoked about three times more cigarettes than current smokers (Table 4.4). About 70% of our participants currently smoke or smoked in the past.

Alcohol was consumed by 17.9% of participants with 3 participants drinking beer and three drinking wine. Four out of the five were males; one male drank 21.05 exchanges of alcohol per week; the only female drank 0.25 alcohol exchanges per week (Table 4.4). Participants that admitted to using drugs were just over one fifth of participants where four participants smoked cannabis a median (IQR) of 2.3 (0.5-3.8) times per day (Table 4.4).

Table 4.4 Risk factors (n=28)

Categories	Variables	Category	Results
Cigarettes	Smokes cigarettes	Yes, n (%)	11 (39.3)
		No, n (%)	17 (60.7)
		No. of cigarettes smoked per day, median (IQR)	5.0 (2.0-6.0)
	Ex-smoker	Yes, n (%)	8 (28.6)
		No, n (%)	9 (32.1)
		No. of cigarettes smoked per day, median (IQR)	15.0 (4.8-20.0)
		Smoked years ago, median (IQR)	2.0 (0.5-5.0)
Alcohol	Drinks alcohol	Yes, n (%)	5 (17.9)
		No, n (%)	23 (82.1)
	Amount of alcohol	Spirits 25ml in week (n=1), median (IQR)	4.0 (4.0-4.0)
	consumed	Wine 120ml in week (n=3), median (IQR)	1.75 (0.25-12.5)
		Beer 340ml in week (n=3), median (IQR)	14.0 (7.0-19.3)
Drugs	Uses drugs	Yes, n (%)	6 (21.4)
		No, n (%)	22 (78.6)
	Type of drugs used	Cannabis (smokes), n (%)	4 (14.3)
		Cannabis oil, n (%)	2 (7.1)
		Cannabis tea, n (%)	1 (3.6)
		Heroin, n (%)	1 (3.6)

4.4 Biochemistry

Out of the 24 participants that had biochemistry results, the median (IQR) CRP value was 9.0mg/l (3.0-29.0) and albumin was 40.0g/l (37.5-44.5). Only two participants (8.3%) were hypoalbuminaemic (albumin < 35g/l) and eleven (39.3%) had elevated CRP levels > 10mg/l.

4.5 Handgrip strength

The median (IQR) for males and females for grip strength was 31.9 (25.8-42.0) kg and 21.1 (18.6-23.9) kg, respectively. When using percentiles from Dodds et al. (2014), the grip strength of 48.1% (n=13), 22.2% (n=6) and 26.6% (n=8) of participants were below the10th, between 10th and 25th and above the 25th percentiles, respectively. When categorizing participants using the cutoff points of 27kg and 16kg for males and females respectively (Cruz-Jentoft et al. 2019), a weak grip strength was found in 18.5% (n=5) of participants.

4.6 Physical activity

Of 28 participants, just over half were inactive, 28.6% were moderately active while 17.9% were classified as highly active (Table 4.5). One participant's occupation involved vigorous activity while 35.7% had work that required them to be moderately active. Despite half of participants travelling by walking or cycling, the median (IQR) METS for travel activity was 240.0 (120.0-300.0). None of the participants engaged in vigorous physical activity during leisure time, while 28.6% did moderate physical activity during leisure

time. (Table 4.5). The median (IQR) METS per week for the total group was 480.0 (0.0-1800.0), indicating inactivity (results not in table).

Table 4.5 Global physical activity questionnaire

Activity	**n**	**%**	**METS** median (IQR)	**Days**	**Minutes**
Inactive	15	53.6	0.0 (0.0-240.0)		
Moderately active	8	28.6	1200.0 (940.0-1800.0)		
Highly active	5	17.9	5880.0 (5160.0-7020.0)		
Vigorous work	1	3.6	3360.0 (3360.0-3360.0)	7.0 (7.0-7.0)	60.0 (60.0-60.0)
Moderate work	10	35.7	1320.0 (960.0-3000.0)	3.8 (2.0-5.0)	120.0 (60.0-180.0)
Travel	14	50.0	240.0 (120.0-300.0)	2.25 (2.0-7.0)	17.5 (10.0-30.0)
Vigorous leisure	0	0.0	0.0	0.0	0.0
Moderate leisure	8	28.6	720 (150.0-1470.0)	2.0 (1.0-4.5)	52.5 (37.5-90.0)

METS – metabolic equivalents per week

4.7 Dietary information

4.7.1 Food frequency questionnaire

From the semi-quantified food frequency questionnaire (FFQ), participants ate the equivalent of just under 2 [1.8 (0.7-3.2)] matchboxes of animal protein per day. Processed protein was eaten 0.7 (0.2-1.3) servings a day. Participants consumed 0.8 (0.4-1.9) servings of dairy. Plant protein, including legumes and peanut butter, was eaten 0.2 (0.0-0.6) times per day, equating to a total of 1.2 times per week. Only 0.4 (0.0-1.5) and 0.5 (0.0-1.2) servings of fruit and vegetables respectively, were eaten daily. This is a combined total intake of about 1 serving daily (Table 4.6).

High fat starchy snacks, takeaways, baked goods, frozen dairy, chocolates were not eaten regularly. Sugary products were consumed 0.7 (0.1-1.9) times per day. Added sugar was taken the equivalent of 5 teaspoons daily [1.7 (0.0-3.3)] (Table 4.6).

Table 4.6 Food categories expressed as portions eaten per day

Food categories	Median (IQR) of portions per day	Examples of equivalent household amounts
Animal protein	1.8 (0.7-3.2)	Under 2 matchboxes
Processed protein	0.7 (0.2-1.3)	
Dairy	0.8 (0.4-1.9)	About 200ml
Other dairy	0.0 (0.0-0.1)	
Plant protein	0.2 (0.0-0.6)	
Starchy cereals, grains, potato	4.0 (2.7-6.1)	2 x 250ml cups of cereal
Other starchy snacks	0.0 (0.0-0.2)	
Fruit	0.4 (0.0-1.5)	Under half medium fruit e.g., apple
Vegetables	0.5 (0.0-1.2)	¼ cooked vegetables
Oils and Fats	2.1 (0.7-4.1)	Over 2 teaspoons oil
High fat starchy snacks	0.4 (0.1-0.9)	
Take-aways	0.1 (0.0-0.3)	
Baked goods Frozen dairy Choco	0.3 (0.0-0.8)	
Sugary products	0.7 (0.1-1.9)	
Added sugar	1.7 (0.0-3.3)	5 teaspoons

4.7.2 Twenty-four-hour recalls

The macronutrient intake was as follows: the median (IQR) total energy intake was 5669.5 (4767.5-8383.0) kJ; median (IQR) protein intake was 47.2 (35.1-72.5) g; median (IQR) lipid intake was 36.5 (26.7-69.8) g; and the median (IQR) carbohydrate intake 190.5 (153.4-264.7) g. The macronutrient percentages of total energy are presented by Figure 4.1.

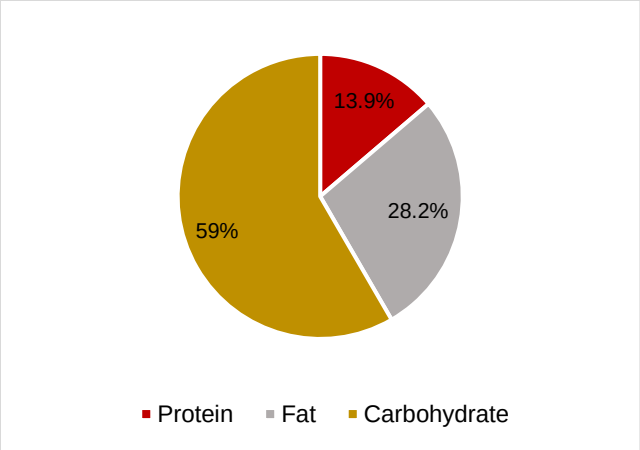
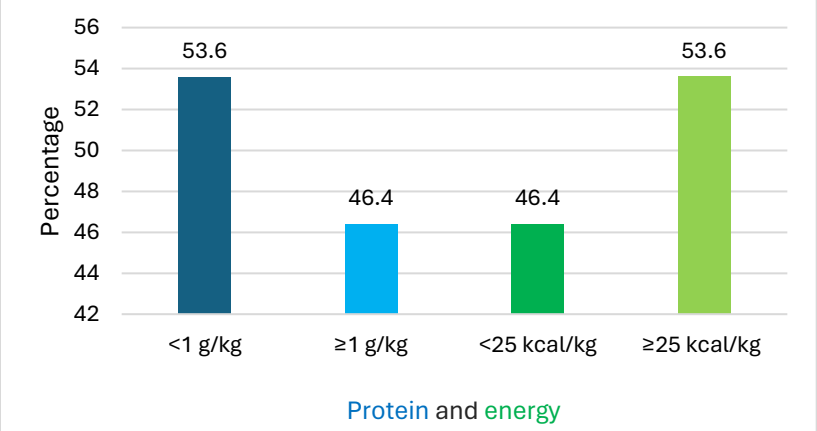


Figure 4.1 Macronutrient percentages of total energy

When considering requirements per kilogramme per day according to recent nutritional cancer guidelines, 46.4% of participants did not meet minimum energy requirements and 53.6% did not meet minimum protein requirements (Graph 4.1).



Graph 4.1: Percentage of participants meeting energy and protein requirements as per ESPEN practical guidelines
ESPEN – European society for clinical nutrition and metabolism as per Muscaritoli et al. (2021)

4.7.3 Supplements

Over the counter vitamins and minerals were consumed by just over a third of participants. B-complex vitamins, complete multivitamins and single minerals (potassium, calcium, magnesium) were each taken by 10.7% of participants (Table 4.7).

4.7.4 Dietary information

Most participants (62.3%) were referred to a Dietitian, with almost all already seen. Twelve out of the 13 that were not referred wanted to see a dietitian (Table 4.7). Reasons they wanted to be referred to a dietitian were categorized according to themes, namely nutritional assessment (9.5%, n=2), nutritional

needs (14.3%, n=3), nutritional impact symptoms (28.7%, n=6) and nutritional information 47.6% (n=10). 'Eating healthily' was the main reason stated in the nutritional information theme together with 'increasing appetite or oral intake' in the nutritional impact symptoms' theme.

Oral nutrition supplements (ONS) were taken by 50% of participants and one participant admitted to not taking a prescribed ONS due to disliking the taste (Table 4.7). There were six different ONS products used by the participants, with Ensure being the most popular (28.6%) and two participants used it enterally as a sole source of nutrition. Philani porridge was taken a median (IQR) of 1.0 (1.0-2.0) portion, the most frequently throughout the day (Table 4.7).

Table 4.7 Dietary information (n=28)

Dietary information	Dietary components	Categories	Results
Supplements	Taken	Yes, n (%)	10 (35.7)
		No, n (%)	18 (64.3)
	Types	Potent antioxidant, n (%)	1 (3.6)
		Vitamin B complex, n (%)	3 (10.7)
		Complete multi-vitamin, n (%)	3 (10.7)
		Single vitamins, n (%)	2 (7.1)
		Single minerals, n (%)	3 (10.7)
		Cod liver oil, n (%)	1 (3.6)
		Fruit extracts, n (%)	2 (7.1)
		Herbal extracts, n (%)	0 (0.0)
Dietetic service	Dietitian referral	Yes, n (%)	15 (62.3)
		No, n (%)	13 (46.4)
	Referred and seen (n=15)	Yes, n (%)	12 (80.0)
		No, n (%)	3 (20.0)
	Not referred and want to	Yes, n (%)	12 (92.3)
	see Dietitian (n=13)	No, n (%)	1 (7.7)
Oral nutritional	Received	Yes, n (%)	14 (50.0)
supplements		No, n (%)	13 (46.4)
	Prescribed but not taken	n (%)	1 (3.6)
	Types of ONS	Ensure, n (%)	8 (28.6)
		Jikijela porridge, n (%)	3 (10.7)
		Philani porridge, n (%)	3 (10.7)
		Clicks supplement, n (%)	1 (3.6)
		Izika drink, n (%)	1 (3.6)
		Izika porridge, n (%)	1 (3.6)
	Amount of ONS consumed		
	Ensure	P; F/day, median (IQR)	1.0 (1.0-2.0); 1.8 (1.0-4.8)
	Jikijela porridge	P; F/day, median (IQR)	1.0 (1.0-1.0); 1.3 (1.0-1.5)
	Philani porridge	P; F/day, median (IQR)	1.0 (1.0-2.0); 3.0 (2.0-3.0)
	Clicks supplement	P; F/day, median (IQR)	1.0 (1.0-1.0); 1.0 (1.0-1.0)
	Izika drink	P; F/day, median (IQR)	1.0 (1.0-1.0); 1.0 (1.0-1.0)
	Izika porridge	P; F/day, median (IQR)	1.0 (1.0-1.0); 1.0 (1.0-1.0)

P – portions at a given time; F/day – frequency per day

4.8 Nutritional screening

Just over two thirds of participants were classified as 'nutritionally at risk' using the NRS-2002 screening tool. Of the four questions that make up the initial screening section of NRS-2002, 60.7% had a BMI<20 and 75% of participants indicated that they have lost weight in the last 3 months. Only 14.3% (n=4) of participants indicated 'no' for all the initial screening questions and therefore it was not necessary to conduct the final screening (Table 4.8).

Twenty-four participants progressed to completion of the final screening questions of the NRS-2002. The next set of questions on the screening tool is made up of impaired nutritional status information and disease severity, of which 62.5% of participants scored in the severe category and 100.0% scored in the mild category section, respectively. As no adults older than or equal to 70 years were recruited, no age adjusted score was needed (Table 4.8).

Table 4.8 Nutrition risk screening-2002 tool

Category	Sections	Components of sections	Results
NRS-2002	Score	Total, median (IQR)	3.5 (2.0-4.0)
	Nutritionally at risk	Yes, n (%)	19 (67.9)
		No, n (%)	9 (32.1)
Initial screening (n=28)	Score	Yes, n (%)	24 (85.7)
		No, n (%)	4 (14.3)
	BMI < 20kg/m^2	Yes, n (%)	17 (60.7)
		No, n (%)	11 (39.3)
	Weight loss in last 3 months	Yes, n (%)	21 (75.0)
		No, n (%)	7 (25.0)
Final screening (n=24)	Reduced intake in last week	Yes, n (%)	14 (50.0)
		No, n (%)	14 (50.0)
	Severe illness	Yes, n (%)	0 (0.0)
		No, n (%)	28 (100.0)
	Impaired nutritional status score	Total, median (IQR)	3.0 (2.0-3.0)
		Absent: score 0, n (%)	2 (8.3)
		Mild: score 1, n (%)	3 (12.5)
		Moderate: score 2, n (%)	4 (16.7)
		Severe: score 3, n (%)	15 (62.5)
	Disease severity score	Cancer score, median (IQR)	1.0 (1.0-1.0)

IQR – interquartile range

4.9 Nutritional assessment

According to the PG-SGA, 92.9% of participants were categorised as malnourished and the nutritional triage recommendations indicated that 71.4% of participants had a critical need for improved symptom management and/or nutrient intervention options (Table 4.9).

Table 4.9 Patient-generated subjective global assessment (PG-SGA)

Category	Sections	Components of sections	Results
Global assessment	Nutritional status categories	Stage A: Well nourished, n (%)	2 (7.1)
		Stage B: Moderately malnourished, n (%)	18 (64.3)
		Stage C: Severely malnourished, n (%)	8 (28.6)
Nutritional triage	PG-SGA total score	Total score, median (IQR)	12.0 (8.0-18.5)
	Intervention categories	Score 0-1: no intervention, n (%)	0 (0.0)
		Score 2-3: patient & family education, n (%)	1 (3.6)
		Score 4-8: requires intervention, n (%)	7 (25.0)
		Score ≥9: critical need for intervention, n (%)	20 (71.4)

IQR – interquartile range; PG-SGA – patient-generated subjective global assessment

PG-SGA has four boxes and four worksheets. Half of the participants lost weight in the previous two weeks (Box 1). Of the half that lost weight, a quarter of participants lost 3-4.9% and a quarter lost 5-9.9% (worksheet 1). The majority (46.4%) of participants reported “less than normal amount” of food intake in the past month (Box 2); (Table 4.10).

The top four nutritional impact symptoms experienced by the participants were feeling fatigued (60.7%), not having an appetite (46.4%), having a dry mouth (42.9%) and feeling full (42.9%); (Box3). Most participants (60.7%) described their activity level as ‘fairly normal’ (Box 4); (Table 4.10).

Worksheet 2 refers to diseases that relate to nutritional requirements and all participants scored 1 for cancer, without any other diseases being scored. Five participants were older than 65 and scored an extra point. For metabolic demand in worksheet 3, all participants scored zero.

Worksheet 4 involves a physical examination of muscle, fat and fluid status. The total numerical score, taking all 3 components into account, indicates a mild overall global deficit in 39.3% of participants. Most participants had mild muscle and a mild fat deficit without fluid accumulation (Table 4.10).

Table 4.10 Patient-generated subjective global assessment (PG-SGA) as per categories

Category	Sections	Components of sections	Results
Box 1 (weight)	During the past 2 weeks, my weight has	Decreased, n (%)	14 (50.0)
		Not changed, n (%)	8 (28.6)
		Increased, n (%)	6 (21.4)
	Amount of weight loss in past 2 weeks	Score 0; 0-1.9% WL, n (%)	11 (39.3)
		Score 1; 2-2.9% WL, n (%)	1 (3.6)
		Score 2; 3-4.9% WL, n (%)	7 (25.0)
		Score 3; 5-9.9% WL, n (%)	7 (25.0)
		Score 4; ≥10% WL, n (%)	2 (7.1)
Box 2 (food intake)	Compared to normal intake, I would rate my food intake over the past month as	Unchanged intake, n (%)	8 (21.4)
		More intake, n (%)	3 (10.7)
		Less intake, n (%)	1 (3.6)
		Less than normal amount, n (%)	13 (46.4)
		Little solid food, n (%)	2 (7.1)
		Only liquids, n (%)	1 (3.6)
		Enteral nutrition, n (%)	2 (7.1)
Box 3 (symptoms)	Problems that have kept me from eating enough over the past 2 weeks	No problem eating, n (%)	6 (21.4)
		No appetite, n (%)	13 (46 .4)
		Nausea, n (%)	10 (35.7)
		Constipation, n (%)	8 (28.6)
		Mouth sores, n (%)	4 (14.3)
		Funny taste, n (%)	11 (39.3)
		Problem swallowing, n (%)	6 (21.4)
		Pain, n (%)	11 (39.3)
		Diarrhoea, n (%)	6 (21.4)
		Vomiting, n (%)	3 (10.7)
		Dry mouth, n (%)	12 (42.9)
		Bothersome smells, n (%)	7 (25.0)
		Feeling full, n (%)	12 (42.9)
		Fatigue, n (%)	17 (60.7)
		Other reasons, n (%)	11 (39.3)
Box 4 (activities and function)	Over the past month, I would rate my activity as	Normal, n (%)	3 (10.7)
		Fairly normal, n (%)	17 (60.7)
		bed / chair < half day, n (%)	6 (21.4)
		bed / chair most of day, n (%)	2 (7.1)

Category	Sections	Components of sections	Results
Worksheet 4	Global overall rating	No deficit, n (%)	7 (25.0)
(physical exam)		Mild deficit, n (%)	11 (39.3)
		Moderate deficit, n (%)	8 (28.6)
		Severe deficit, n (%)	2 (7.1)
	Muscle status rating		
		No deficit, n (%)	7 (25.0)
		Mild deficit, n (%)	11 (39.3)
		Moderate deficit, n (%)	8 (28.6)
		Severe deficit, n (%)	2 (7.1)
	Fat deficit rating		
		No deficit, n (%)	17 (60.7)
		Mild deficit, n (%)	7 (25.0)
		Moderate deficit, n (%)	2 (7.1)
		Severe deficit, n (%)	2 (7.1)
	Fluid status rating		
		No accumulation, n (%)	24 (85.7)
		Mild accumulation, n (%)	1 (3.6)
		Moderate accumulation, n (%)	2 (7.1)
		Severe accumulation, n (%)	1 (3.6)

IQR – interquartile range; PG-SGA – patient-generated subjective global assessment

4.10 Anthropometry, dual energy X-ray absorptiometry and body composition

The median (IQR) BMI was 20.4 (18.0-23.2) kg/m^2 and 57.1% were classified as having a normal range BMI (Table 4.6). Fifty percent of participants experienced more than 10% weight loss over 6 months whereas 39.1% experienced 5% weight loss over 1 month. Most weights used in calculations for weight loss over time were derived from documented weights in medical notes (Table 4.11).

Table 4.11 also presents the median and IQR for MUAC, calf circumference, adjusted calf circumference, corrected arm muscle area, percentage body fat, fat mass index and percentage fat mass for males and females.

Table 4.11 Anthropometry, DEXA and body composition

Method	Variable	Category	Results
Anthropometry	BMI (kg/m^2)	Median (IQR)	20.4 (18.0-23.2)
	BMI categories	Moderate thinness, n (%)	3 (10.7)
		Mild thinness, n (%)	6 (21.4)
		Normal range, n (%)	16 (57.1)
		Pre-obese, n (%)	2 (7.1)
		Obese, n (%)	1 (3.6)
	Height (m)	Median (IQR)	1.6 (1.6-1.7)
	Present weight (kg)	Median (IQR)	61.2 (47.8-65.3)
	Usual weight (kg)	Median (IQR) (n=26[a]),	68.8 (62.5-85.0)
	Diff in months from present weight and usual weight	Median (IQR)	10.0 (5.5-24.0)
	%WL in 1 month	Median (IQR), (n=23[a])	3.8 (0.7-8.7)
	>5% WL in 1 month	n (%)	9 (39.1)
	≤5% WL in 1 month	n (%)	14 (60.9)
		Documented in medical notes, n (%)	19 (82.6)
		Reported by patient, n (%)	4 (17.4)
	%WL in 6 months	Median (IQR); (n=18[a])	9.5 (-3.3-12.9)
	>10%WL in 6 months	Significant WL[c], n (%)	9 (50.0)
	≤10%WL in 6 months	n (%)	9 (50.0)
		Documented in medical notes, n (%)	13 (72.2)
		Reported by patient, n (%)	5 (27.8)
	MUAC (cm)	Males, median (IQR)	27.4 (25.0-29.1)
		Females, median (IQR)	25.9 (24.6-30.3)
	CC (cm)	Males, median (IQR)	32.0 (30.0-35.8)
		Females, median (IQR)	32.2 (30.2-34.2)
	Adjusted CC (cm)	Males, median (IQR)	32.6 (31.3-35.7)
		Females, median (IQR)	33.6 (32.8-34.4)
TSFT & MUAC calculation	cAMA (cm^2)	Males, median (IQR)	34.1 (27.5-41.9)
		Females, median (IQR)	29.8 (25.3-36.6)
4 x SFT calculation	Percentage body fat	Males, median (IQR)	18.3 (13.7-24.6)
		Females[a], median (IQR)	29.8 (28.3-35.8)
DEXA: fat mass	FMI	Males, median (IQR)	4.6 (3.6-5.9)
		Females, median (IQR)	6.8 (5.3-8.1)
	%FM	Males, median (IQR)	23.8 (21.4-30.1)
		Females, median (IQR)	37.1 (32.8-42.9)

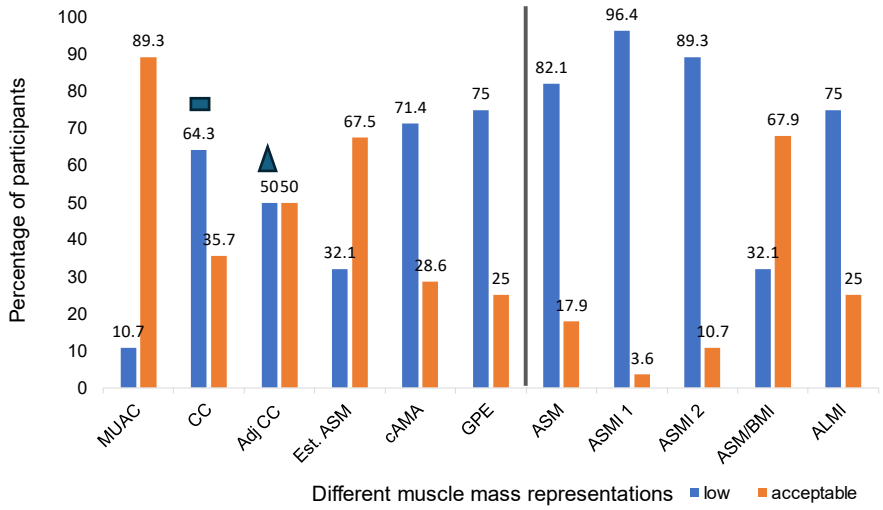
DEXA – dual energy X-ray absorptiometry; IQL – interquartile rang; BMI – body mass index; diff – difference; WL – weight loss;; MUAC – mid upper arm circumference; CC – calf circumference; TSFT – tricep skinfold thickness; SFT – skinfold thickness; cAMA – corrected arm muscle area; FMI – fat mass index (height in metres squared); %FM – percentage fat mass

[a] missing data = 5

[b] ≥5% WL in 1 month

[c] ≥10% WL in 6 months

Graph 4.2 presents the low and acceptable categories of alternatives for muscle mass (MM) and the reference method, DEXA with MM presented by different units of measure. For the alternative muscle mass estimates, only 10.7% of participants were categorised as malnourished when their MUAC was below the designated cutoff. When participants scored 1 to 3 indicating mild, moderate or severe deficit, the global physical examination categorised 75% of participants with overall global deficit. Using DEXA to measure MM and categorise reduced MM using 5 different representations (units of measure) and cutoff points, yielded varying results from 32% to 96%: almost all participants (96.4%) were categorised with RMM according to appendicular skeletal muscle index (ASMI) as per Cruz-Jentoft et al. (2019); the least number of participants (32.1%) were categorised with RMM according to appendicular skeletal muscle adjusted by BMI (ASM/BMI) (Graph 4.2).



Graph 4.2: Percentage participants categorised according to different muscle mass estimates and DEXA representations

Left of grey line represents the muscle mass estimates: circumferences include MUAC, CC and adj CC; Est ASM derived from equation that uses CC; triceps and MUAC used to calculate cAMA; GPE derived from worksheet 4 from PG-SGA
Right of the line represents the DEXA representations (see Table 3.3 for further details of cutoff points used)

MUAC – mid upper arm circumference; CC – calf circumference; Adj CC – adjusted calf circumference; Est. ASM – estimated appendicular skeletal muscle; cAMA – corrected arm muscle area; ASM – appendicular skeletal muscle; ASMI1 – appendicular skeletal muscle mass index (ASM/height in m^2) as per Cruz-Jentoft et al., (2019); ASMI2 – appendicular skeletal muscle mass index (ASM/height in m^2) as per Fearon et al., (2011); ASM/BMI - appendicular skeletal muscle divided by BMI; ALMI – appendicular lean muscle mass index (ALM/height in m^2); CC – severely low 46.4% / moderately low 17.9%; Adj CC– severely low 28.6% / moderately low 21.4%

Table 4.12 presents five different units of measure for muscle mass. A participant was categorised as having RMM for that specific MM unit of measure according to the specific cutoff used. A quarter of participants were identified with RMM by all 5 units of measure with an additional 43% identified by 4 units of measure. ASM/BMI identified 1 participant with RMM when no other MM units of measure did; this participant was the only one classified as obese. ASMI as per Cruz-Jentoft et al., (2019) identified 1 participant with RMM when no other MM units of measure did; this participant had a height of 1.65m and BMI 24.9kg/m^2.

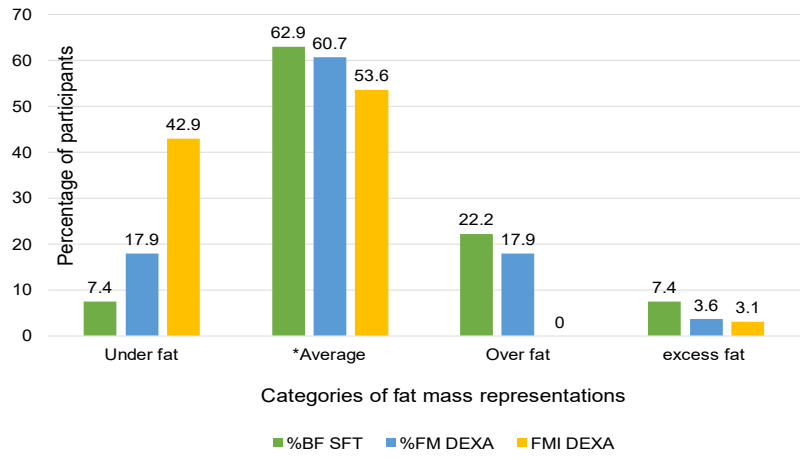
DEXA MM represented as ASM was chosen as the unit of measure for MM for the rest of the research objectives. Our reference standard is therefore referred to as DEXA hereafter. The reason for this choice is that ASM was recommended by Cruz Jentoft et al., (2019) where the cutoff points were developed from a study by Studenski et al., (2014) that used a large cohort from 9 diverse sources (including African American, Puerto Rican, Norway, Italy). Most cancer research uses muscle mass measures derived from CT scans rather than DEXA, our only available tool in this research.

Table 4.12 Reduced muscle mass in participants presented by different units of measure as calculated from DEXA variables

	Muscle mass					
Participants	ASM	ASMI (Cruz-Jentoft et al)	ASMI (Fearon et al)	ASM/BMI	ALMI	No. of low MM representations
2	✓	✓	✓	✓	✓	5
4	✓	✓	✓	✓	✓	5
10	✓	✓	✓	✓	✓	5
13	✓	✓	✓	✓	✓	5
15	✓	✓	✓	✓	✓	5
18	✓	✓	✓	✓	✓	5
25	✓	✓	✓	✓	✓	5
1	✓	✓	✓	X	✓	4
8	✓	✓	✓	X	✓	4
3	✓	✓	✓	X	✓	4
11	✓	✓	✓	X	✓	4
5	✓	✓	✓	X	✓	4
6	✓	✓	✓	X	✓	4
17	✓	✓	✓	X	✓	4
21	✓	✓	✓	X	✓	4
22	✓	✓	✓	X	✓	4
23	✓	✓	✓	X	✓	4
14	✓	✓	✓	X	✓	4
12	✓	✓	✓	✓	X	4
26	✓	✓	✓	X	X	3
27	✓	✓	✓	X	X	3
28	✓	✓	✓	X	X	3
20	✓	✓	✓	X	X	3
7	X	✓	✓	X	✓	3
19	X	✓	✓	X	✓	3
24	X	✓	X	X	✓	2
9	X	✓	X	X	X	1
16	X	X	X	✓	X	1
	23	27	25	8	21	

ASM – appendicular skeletal muscle; ASMI1 – appendicular skeletal muscle mass index (ASM/height in m^2) as per Cruz-Jentoft et al., (2019); ASMI2 – appendicular skeletal muscle mass index (ASM/height in m^2) as per Fearon et al., (2011); ASM/BMI - appendicular skeletal muscle divided by BMI; ALMI – appendicular lean muscle mass index (ALM/height in m^2)

Most participants were categorised into the average fat mass group by skinfold and DEXA methods. Forty-three percent of participants were categorised as under fat and none as overfat according to the FMI (Graph 4.3).



Graph 4.3: Percentage participants categorised according to different fat mass estimates from skinfold thicknesses and representations from DEXA

%BF SFT – percentage body fat from skinfold thickness; %FM DEXA – percentage body fat via dual energy x-ray absorptiometry; FMI DEXA – fat mass index via dual energy x-ray absorptiometry

%FM DEXA had categories 'below average' of 46.4% (n=13) and 'average' of 14.3% (n=4) that were collapsed into 'average' category

%FMI DEXA had categories 'below average' of 42.9% (n=12) and 'average' of 10.7% (n=3) that were collapsed into 'average' category

Participants classified with a low DEXA MM had a significantly lower BMI, MUAC, calf circumference and percentage body fat compared to participants with an acceptable DEXA MM (Table 4.13). There were no significant differences between the DEXA low and acceptable MM groups for percentage weight loss over one or six months, adjusted calf circumference, est ASM, cAMA, handgrip strength and the categories of these variables. Participants with a low DEXA MM also had a significantly higher NRS-2002 score and PG-SGA score. No significant associations were found between the low and acceptable DEXA MM groups for categorical data, excluding calf circumference, for nutritional status indicators and DEXA-ASM (Table 4.13). MUAC, calf circumference and albumin were close to or reached moderate effect size. For the Mann Whitney U tests the overall power was 0.29 (minimal) from an average effect size of 0.27 (minimal); for the Fisher exact tests the overall power was 0.17 from an average effect size of 0.19 (small).

Table 4.13 Associations between reduced and acceptable muscle mass DEXA groups and nutritional status indicators

Nutritional status indicators	Categories	DEXA low MM (n=23)	DEXA acceptable MM (n=5)	p-value[a]	Effect size[b]
Anthropometry	BMI in kg/m^2, median (IQR)	20.2 (17.7-22.3)	24.5 (22.3-27.2)	0.026	0.42
BMI	<18.5kg/m^2, n (%)	9 (39.1)	0 (0.0)	0.144	0.32
	≥18.5kg/m^2, n (%)	14 (60.9)	5 (100.0)		
>5% WL in 1 month	Yes, n (%)	10 (43.5)	0 (0.0)	0.128	0.35
	No, n (%)	13 (56.5)	5 (100.0)		
>10% WL in 6 months	Yes, n (%)	9 (39.1)	1 (20)	0.626	0.15
	No, n (%)	14 (60.9)	4 (80)		
MUAC	In cm, median (IQR)	26.0 (24.0-28.5)	30.6 (30.4-35.6)	0.004	0.60
	Malnourished, n (%)	3 (13.0)	0 (0.0)	1.00	0.16
	Not malnourished, n (%)	20 (87.0)	5 (100.0)		
CC	In cm, median (IQR)	31.7 (29.4-33.4)	36.0 (35.5-37.4)	0.011	0.48
	Low, n (%)	17 (79.3)	1 (20.0)	0.041	0.33
	Acceptable, n (%)	6 (26.1)	4 (80.0)		
Adjusted CC	In cm, median (IQR)	33.0 (31.6-34.3)	34.4 (32.5-35.5)	0.294	0.22
	Low, n (%)	12 (52.2)	2 (40.0)	1.00	0.09
	Acceptable, n (%)	11 (47.8)	3 (60.0)		
Est ASM	In kg, median (IQR)	17.6 (12.9-20.2)	18.5 (17.2-22.6)	0.436	0.15
	Low, n (%)	9 (39.1)	0 (0.0)	0.144	0.22
	Acceptable, n (%)	14 (60.9)	5 (100.0)		
cAMA	In cm^2, median (IQR)	31.4 (27.0-39.0)	37.0 (28.9-42.5)	0.509	0.14
	Wasted, n (%)	17 (73.9)	3 (60.0)	0.606	0.15
	Not wasted, n (%)	6 (26.1)	2 (40.0)		
Percentage body fat (n=27)	%BF, median (IQR)	24.3 (16.6-28.3)	35.2 (28.6-41.2)	0.049	0.39
	Under fat, n (%)	2 (9.1)	0 (0.0)	1.000	0.13
	Not under fat, n (%)	20 (90.9)	5 (100.0)		
HGS (n=27)	HGS in kg, median (IQR)	24.9 (21.4-31.9)	24.3 (20.7-39.5)	0.779	0.06
	Weak handgrip, n (%)	5 (22.7)	0 (0.0)	0.547	0.23
	Not weak handgrip, n (%)	17 (77.3)	5 (100.0)		
Screening & assessment					
NRS-2002	score, median (IQR)	4 (2 – 4)	2.0 (0.0-3.0)	0.031	0.41
	Nutritionally at risk, n (%)	17 (73.9)	2 (40.0)	0.290	0.28
	Not at risk, n (%)	6 (26.1)	3 (60.0)		
PG-SGA	score, median (IQR)	13 (9 – 20)	6.0 (6.0-11.0)	0.019	0.44
	Malnourished, n (%)	22 (95.7)	4 (80.0)	0.331	0.23
	Not malnourished, n (%)	1 (4.4)	1 (20.0)		
	Box 3 NIS score, median (IQR)	7.0 (4.0-10.0)	3.0 (2.0-6.0)	0.093	0.32
	Box 4 ECOG score, median (IQR)	1.0 (1.0-2.0)	1.0 (1.0-1.0)	0.529	0.12
	Wk/t 4, median (IQR)	1.0 (0.0-2.0)	1.0 (1.0-1.0)	0.697	0.07
	Deficit, n (%)	17 (73.9)	4 (80.0)		0.05
	No deficit, n (%)	6 (26.1)	1 (20.0)	1.000	

Nutritional status indicators	Categories	DEXA low MM (n=23)	DEXA acceptable MM (n=5)	p-value[a]	Effect size[b]
Biochemistry	CRP, median (IQR)	8.5 (3.0-29.5)	9.0 (7.0-19.0)	0.938	0.02
	Elevated, n (%)	10 (50.0)	1 (25.0)	0.596	0.19
	Within range, n (%)	10 (50.0)	3 (75.0)		
	Albumin, median (IQR)	39.0 (37.0-45.0)	42.0 (41.5-43.0)	0.314	0.60
	Hypoalbuminaemia, n (%)	2 (10.0)	0 (0.0)	1.000	0.13
	Within range, n (%)	18 (90.0)	4 (100.0)		
Dietary	Total energy in kJ, median (IQR)	5609.0 (4374.0-7580.0)	7946.0 (5694.0-9271.0)	0.178	0.28
	Kcal/kg, median (IQR)	25.7 (18.0-36.2)	28.6 (17.6-33.0)	0.905	0.02
	<25kcal/kg, n (%)	10 (43.5)	2 (40.0)	1.000	0.03
	≥25kcal/kg, n (%)	13 (56.5)	3 (60.0)		
	Total protein in g, median (IQR)	46.5 (26.4-72.4)	75.1 (74.2-80.8)	0.159	0.29
	Protein in g/kg, median (IQR)	0.9 (0.5-1.4)	1.1 (0.7-1.2)	0.857	0.04
	<1g/kg, n (%)	12 (52.2)	2 (40.0)	1.000	0.09
	≥1g/kg, n (%)	11 (47.8)	3 (60.0)		
Physical activity	MET minutes/week, median (IQR)	280.0 (0.0-1680.0)	960.0 (920.0-5160.0)	0.242	0.24
	Inactive, n (%)	14 (60.9)	1 (20.0)	0.153	0.31
	Active, n (%)	9 (39.1)	3 (80.0)		
Treatment None	Yes, n (%)	21 (91.3)	5 (100.0)		
	No, n (%)	2 (8.7)	0 (0.0)	1.000	0.13
Chemotherapy	Yes, n (%)	12 (52.2)	3 (60.0)	1.000	0.06
	No, n (%)	11 (47.8)	2 (40.0)		
Time ago received	Months, median (IQR)	0.0 (0.0-2.0); n=11[c]	0.0 (0.0-0.0)	0.276	0.29
Radiotherapy	Yes, n (%)	10 (43.5)	2 (40.0)	1.000	0.03
	No, n (%)	13 (56.5)	3 (60.0)		
Time ago received	Months median (IQR)	4.0 (1.0-5.0)	1.0 (1.0-1.0)	0.334	0.28
Surgery	Yes, n (%)	15 (65.2)	2 (40.0)	0.353	0.20
	No, n (%)	8 (34.8)	3 (60.0)		
Time ago received	Months, median (IQR)	4.0 (3.0-11.0)	2.5 (1.0-4.0)	0.371	0.22
Number of treatments received	Median (IQR)	2.0 (1.0-2.0)	1.0 (1.0-1.0)	0.436	0.15
Time elapsed since recent treatment	Months, median (IQR)	1.0 (0.0-4.0); n=20[c]	0.0 (0.0-1.0)	0.164	0.28

DEXA – dual energy X-ray absorptiometry; MM – muscle mass; IQL – interquartile rang; BMI – body mass index; WL – weight loss; MUAC – mid upper arm circumference; CC – calf circumference; Adj CC – adjusted calf circumference; est ASM – estimated appendicular skeletal muscle; cAMA – corrected arm muscle area; %BF – percentage body fat; HGS – handgrip strength; NRS-2002 – nutritional risk screening 2002; PG-SGA – patient-generated subjective global assessment; NIS – nutrition impact symptoms; ECOG – Eastern cooperative oncology group; CRP – C-reactive protein; MET - metabolic equivalents

[a] p-value statistically significant < 0.05 and Fisher exact or Mann Whitney U tests as appropriate

[b] effect size interpreted as ≥0.2-0.49 minimal effect; ≥0.5-0.79 moderate effect; ≥0.8 strong effect

[c] missing data

The indicator of nutritional status with the highest sensitivity was the PG-SGA, while the BMI, HGS and MUAC had 100% specificity when compared with DEXA RMM...However, the indicators of nutrition status with the best sensitivity and specific for DEXA RMM were the NRS, calf circumference and adjusted CC. Calf circumference performed overall well with fair sensitivity / specificity, fair Cohen's agreement and 78.6% agreement. Despite NRS-2002 and adjusted calf circumference with overall fair sensitivity / specificity both had poor Cohen's agreement. NRS-202 had 71.4% agreement, whereas adjusted calf circumference was much lower. The highest percentage agreement and sensitivity with DEXA RMM was PG-SGA. The highest specificity was MUAC and HGS (Table 4.14).

Table 4.14 Sensitivity, specificity and agreement of indicators of nutritional status and alternative muscle mass markers against DEXA

Variables	**Category**	**Sensitivity %**	**Specificity %**	**Inter-pretation Of Se & Spe[a]**	**Cohen's Kappa (ƙ)**	**Cohen's Agreement[a]**	**Percen-tage agree-ment**	**% agreement interpretation**
Nutritional status indicators								
BMI	<18.5kg/m^2 Underweight	39.1	100.0	Poor	0.187	Poor	50.0	Not acceptable
NRS-2002	At risk	73.9	60.0	Fair	0.258	Poor	71.4	Not acceptable
PG-SGA	Malnourished	95.7	20.0	Poor	0.206	Poor	82.1	Not acceptable
HGS[b]	Weak HGS	21.7	100.0	Poor	0.098	Poor	37.0	Not acceptable
Alternative muscle mass markers								
MUAC	Malnourished	13.0	100.0	Poor	0.051	Poor	28.6	Not acceptable
CC	Low	73.9	80.0	Fair	0.503	Fair	78.6	Not acceptable
Adj CC	Low	52.2	60.0	Fair	0.071	Poor	53.6	Not acceptable
Est ASM	Low	39.1	10.0	Poor	0.187	Poor	50.0	Not acceptable
cAMA	Wasted	73.9	40.0	Poor	0.113	Poor	67.9	Not acceptable
GPE	Global deficit	73.9	20.0	Poor	0.388	Poor	64.3	Not acceptable

DEXA – dual energy X-ray absorptiometry; BMI – body mass index; NRS-2002 – nutritional risk screening 2002; PG-SGA – patient-generated subjective global assessment; HGS – handgrip strength; MUAC – mid upper arm circumference; CC – calf circumference; Adj CC – adjusted calf circumference; Est ASM – estimated appendicular skeletal muscle; cAMA – corrected arm muscle area; GPE – global physical examination from worksheet 4 PG-SGA

[a] according to van Bokhurst-de van der Schueren et al., (2014)

[b] missing data (n=1)

4.11 Global leadership initiative on Malnutrition (GLIM)

Individual variables within each criterion of Global Leadership Initiative for Malnutrition (GLIM) are presented in Table 4.15. The variable 'percentage weight loss', had the most participants at 67.9% having lost >5% weight loss within 6 months. The category of 'intake and absorption or assimilation' had 85.7% of participants that experienced chronic gastrointestinal conditions that impacted food intake (Table 4.15).

Table 4.15 Results of individual variables used in Global Leadership Initiative on Malnutrition

	Criteria	Variables	Yes, n (%)	No, n (%)
Phenotypic Criteria[a]	**% Weight loss**	>5% WL within 6 months	19 (67.9)	9 (32.1)
		>10% WL beyond 6 months	8 (33.3)	16 (66.7)
	BMI	<20kg/m^2	12 (42.9)	16 (57.1)
Aetiologic Criteria	**Intake & absorption / assimilation**	≤50% ER > 1 week[b]	2 (7.1)	26 (92.9)
		Reduced food intake >2 weeks[c]	17 (60.7)	11 (39.3)
		GI condition[d]	24 (85.7)	4 (14.3)
	Inflammation	Chronic disease	28 (100.0)	0 (0.0)
		Elevated CRP[e]	11 (45.8)	13 (54.2)

WL – weight loss; ER – energy requirements; BMI – body mass index; GI - gastrointestinal; DEXA – dual energy X-ray absorptiometry; DEXA – dual energy X-ray absorptiometry; MUAC – mid upper arm circumference; CC – calf circumference; Adj CC – adjusted calf circumference; Est ASM – estimated appendicular skeletal muscle; cAMA – corrected arm muscle area; GPE – global physical examination from worksheet 4 patient generated subjective global assessment; CRP – c-reactive protein

[a] Without the muscle mass criteria (see graph 4.2)

[b] Yes when ≤12.5kcal/kg calculated from kcal/kg derived from 2 x 24-hour recall as ER as recommended to be 25-30kcal/kg;

[c] Used Box 2 PG-SGA ≥1 for yes;

[d] Used box 3 PG-SGA for symptoms impacting intake;

[e] Missing data = 4

Malnutrition diagnosis varied from 75.0% (21) to 92.9% (26) depending on the GLIM approach used. The least participants were diagnosed when the aetiologic criterion for inflammation was raised CRP and the phenotypic criterion for muscle mass was low mid upper arm circumference, global physical examination deficit or no muscle mass component. The most participants were diagnosed when the aetiologic criterion for inflammation was the cancer diagnosis and the phenotypic criterion for muscle mass was low adjusted calf circumference (Table 4.16).

Table 4.16 Malnutrition diagnosis using different approaches of Global Leadership Initiative on Malnutrition

Muscle mass component	**GLIM with cancer fulfilling inflammation criterion**		**GLIM with raised CRP[a] fulfilling inflammation criterion**	
	Malnourished, n (%)	Not malnourished, n (%)	Malnourished, n (%)	Not malnourished, n (%)
Without RMM	22 (78.6)	6 (21.4)	18 (75.0)	6 (25.0)
With low ASM	25 (89.3)	3 (10.7)	21 (87.5)	3 (12.5)
With MUAC	22 (78.6)	6 (21.4)	18 (75.0)	6 (25.0)
With low CC	25 (89.3)	3 (10.7)	18 (78.0)	6 (25.0)
With low adj CC	26 (92.9)	2 (7.1)	21 (87.5)	3 (12.5)
With low est. ASM	22 (78.6)	6 (21.4)	19 (79.2)	5 (20.8)
With cAMA	25 (89.3)	3 (10.7)	21 (87.5)	3 (12.5)
With GPE	25 (89.3)	3 (10.7)	18 (75.0)	6 (25.0)

GLIM - Global Leadership Initiative on Malnutrition; CRP – c-reactive protein; RMM – reduced muscle mass; ASM – appendicular skeletal muscle MUAC – mid upper arm circumference; CC – calf circumference; Adj CC – adjusted calf circumference; Est ASM – estimated appendicular skeletal muscle; cAMA – corrected arm muscle area; GPE – global physical examination from worksheet 4 patient generated subjective global assessment

[a] missing data = 4

As the diagnosis of malnutrition is made if only one criterion out of each phenotypic and aetiologic criteria is fulfilled, adding the reduced muscle mass component yielded varying additional participants. Using GLIM with cancer fulfilling the inflammation criterion, low MUAC and low estimated ASM did not add any extra participants that fulfilled the reduced muscle mass phenotypic criterion. However, when low adjusted calf circumference was used, it added an additional 4 participants. Using GLIM with raised CRP fulfilling the inflammation criterion, low MUAC, low calf circumference and global physical deficit did not add any additional participants that fulfilled the reduced muscle mass phenotypic criterion. Three more participants were identified as malnourished when low ASM, low adjusted calf circumference and low cAMA were used to fulfil the reduced muscle mass criterion (Table 4.17).

The comparator or reference standard used (GLIM DEXA) was GLIM where aetiologic criterion of inflammation was met by 100% of participants when cancer is interpreted as a chronic disease and RMM was identified by low ASM. The highest overall sensitivity (96.4%) / specificity (66.7%) for GLIM with calf circumference is interpreted as fair with good Cohen's and percentage agreement. GLIM with MUAC, estimated ASM, and without muscle mass component demonstrated good Cohen's agreement with GLM DEXA, the reference standard. All the alternative muscle mass markers had percentage agreement higher than 85% (Table 4.17)

Table 4.17 Sensitivity, specificity and agreement of Global Leadership Initiative on Malnutrition diagnosis using alternative muscle mass markers

Alternative markers of MM[a]	Sensitivity %	Specificity %	Interpre-tation of Se & Spe[a]	Cohen's Kappa (ƙ)	Cohen's agreement[b]	Percentage agreement	Interpretation of percentage agreement
Without RMM	88.0	0.0	Poor	0.611	Good	89.3	Not acceptable
MUAC	88.0	0.0	Poor	0.611	Good	89.3	Not acceptable
CC	96.4	66.7	Fair	0.677	Good	92.9	Not acceptable
Adjusted CC	96.0	33.3	Poor	0.343	Poor	89.3	Not acceptable
Est ASM	88.0	0.0	Poor	0.611	Good	89.3	Not acceptable
cAMA	92.0	33.3	Poor	0.253	Poor	85.7	Not acceptable
GPE	88.0	33.3	Poor	0.253	Poor	85.7	Not acceptable

MM – muscle mass; Se – sensitivity; Spe – specificity; DEXA – dual energy X-ra absorptiometry; RMM – reduced muscle mass; MUAC – mid upper arm circumference; CC – calf circumference; Adj CC – adjusted calf circumference; Est ASM – estimated appendicular skeletal muscle; cAMA – corrected arm muscle area; GPE – global physical examination from worksheet 4 patient generated subjective global assessment

[a] the comparator is DEXA ASM where aetiologic criterion of inflammation was met by 100% of participants when cancer is interpreted as a chronic disease

[b] according to van Bokhurst-de van der Schueren et al., (2014)

The GLIM consensus guidelines suggest that a screening tool that has been validated is used, then assessment is performed on the nutritionally at-risk patients (Cederholm et al., 2019). Our research included all 28 participants. Table 4.18 presents participants that were identified as nutritionally not at-risk by NRS-2002 and diagnosed as malnourished by PG-SGA and the different GLIM approaches.

Out of the nine that were not at-risk, PG-SGA and adjusted calf circumference identified 77.8% as malnourished; GLIM using calf circumference, cAMA and physical examination identified 66.7% as malnourished; GLIM using DEXA-ASM identified 55.6% as malnourished; GLIM using estimated ASM, MUAC and no reduced muscle mass component identified 33.3% as malnourished (Table 4.18).

Table 4.18: Participants not at nutritional risk as per NRS-2002 but diagnosed as malnourished

Participant	PG-SGA	GLIM + low DEXA-ASM	GLIM + no RMM	GLIM + low MUAC	GLIM + low Adj CC	GLIM + low CC	GLIM + est ASM	GLIM + cAMA	GLIM + physical exam
0039	✓	×	×	×	×	×	×	✓	✓
0040	✓	✓	×	×	✓	✓	×	✓	×
0041	×	×	×	×	✓	✓	×	×	✓
0042	✓	✓	✓	✓	✓	✓	✓	✓	✓
0049	✓	×	✓	✓	✓	✓	✓	✓	✓
0051	✓	✓	✓	✓	✓	✓	✓	✓	✓
0053	✓	×	×	×	✓	×	×	✓	×
0055	×	✓	×	×	✓	✓	×	×	×
0071	✓	✓	×	×	×	×	×	×	✓
n=9	7	5	3	3	7	6	3	6	6

✓ indicates malnutrition; × indicates not malnourished

NRS-2002 – nutritional risk screening-2002; PG-SGA – patient generated subjective global assessment; GLIM – global leadership initiative on malnutrition; DEXA – dual energy X-ray absorptiometry; RMM – reduced muscle mass; MUAC – mid upper arm circumference; CC – calf circumference; Adj CC – adjusted calf circumference; Est ASM – estimated appendicular skeletal muscle; cAMA – corrected arm muscle area; GPE – global physical examination from worksheet 4 PG-SGA;

4.12 Sarcopenia

Using DEXA, sarcopenia was identified in 18.5% of participants. Using alternative markers of muscle mass, sarcopenia varied from 7.4% to 18.5%, with MUAC identifying the lowest, calf circumference the most participants (Table 4.19).

Measuring sensitivities and specificities of sarcopenia diagnosis against DEXA-ASM found 100% sensitivity for calf circumference. The specificity was 100% in all alternative muscle mass markers. Cohen's kappa test found perfect agreement with calf circumference, followed by good agreement for cAMA, adjusted calf circumference and global physical examination; percentage agreement was above 90% for all alternative MM markers, excluding MUAC (Table 4.19).

Table 4.19 Sensitivity, specificity and agreement of sarcopenia diagnosis using alternative markers of muscle mass against using DEXA (n=27)[a]

Alternative markers of MM	Sarcopenia n (%)	Sensitivity %	Specificity %	Interpretation of Se & Spe[a]	Cohen's Kappa (ƙ)	Cohen's Agreement[b]	Percentage agreement	% agreement interpretation
MUAC	2 (7.4)	40.0	100.0	Poor	0.521	Fair	88.9	Not acceptable
Adj CC	4 (14.8)	80.0	100.0	Fair	0.867	Good	96.3	Acceptable
CC	5 (18.5)	100.0	100.0	Good	1.000	Perfect	100.0	Acceptable
cAMA	4 (14.8)	80.0	100.0	Fair	0.867	Good	96.3	Acceptable
GPE	3 (11.1)	60.0	100.0	Fair	0.710	Good	92.6	Acceptable

DEXA – dual energy X-ray absorptiometry; MM – muscle mass; Se – sensitivity; Spe – specificity; MUAC – mid upper arm circumference; CC – calf circumference; Adj CC – adjusted calf circumference; cAMA – corrected arm muscle area; GPE – global physical examination from worksheet 4 patient generated subjective global assessment

[a] missing data; n=1

[a] according to van Bokhurst-de van der Schueren et al., (2014)

4.13 Cancer cachexia

The four cancer cachexia models consist of different combinations of the classifications of five components namely, percentage weight loss, BMI, inflammation, food intake and muscle mass (Table 4.20). Under the component, 'Percentage weight loss' the majority (85.7%) of participants experienced >2% weight loss over 6 months with only 7.7% that experienced >20% weight loss over 6 months. Sixty point seven percent reported reduced food intake as indicated by a score ≥1 using Box 2 of PG-SGA. Reduced muscle mass was similar when using ASM or ASMI to categorise participants.

Table 4.20: Variables used in cancer cachexia models grouped into 5 components

Components	Variables	Yes, n (%)	No, n (%)
Percentage weight	>1kg & ≤5% in 6 months	5 (17.9)	23 (84.1)
loss	>2% in 6 months	24 (85.7%)	4 (14.3)
	>5%WL in 6 months	19 (67.9)	9 (32.1)
	>15% in 6 months[a]	6 (23.1)	20 (76.9)
	>20% in 6 months[b]	2 (7.7)	24 (92.3)
BMI	<20kg/m^2	12 (42.9)	16 (57.1)
	<23kg/m^2	20 (71.4)	8 (28.6)
	<27kg/m^2	26 (92.9)	2 (7.1)
Inflammation	CRP≥10mg/l[b]	11 (45.8)	13 (54.2)
Food Intake	PG-SGA box 2≥1	17 (60.7)	11 (39.3)
Muscle mass	Low ASM (kg)	23 (82.1)	5 (17.9)
	Low ASMI (kg/m^2)	25 (89.3)	3 (10.7)

WL – weight loss; BMI – body mass index; CRP – c-reactive protein; PG-SGA – patient generated subjective global assessment; ASM – appendicular skeletal muscle (kg); ASMI - appendicular skeletal muscle index (kg/m^2)
[a] missing data n=2
[b] missing data n=4

Variables are either standalone variables or combined with 1 or 2 others to form the criteria. Table 4.21 presents the results of the individual diagnostic criteria of pre-cachexia, cancer cachexia and refractory cachexia using different diagnostic models. Three criteria in the cancer cachexia category are shared by two diagnostic models (Table 4.21). There is more than one way to make a diagnosis when there is more than one tick within a category for a diagnostic model. Within the pre-cachexia model, a quarter of participants met the CRP ≥10mg/l and PG-SGA box 2≥1 as set out by Vigano et al., (2017). Fearon et al., (2011) diagnostic model identified the most participants (78.6%) as cachexic using >2% WL in 6/12 and RMM ASMI. The least participants (16.7%) identified using >5% WL in 6/12 + [a]CRP≥10mg/l + PG-SGA box 2≥1 as from Vigano et al., (2017) model.

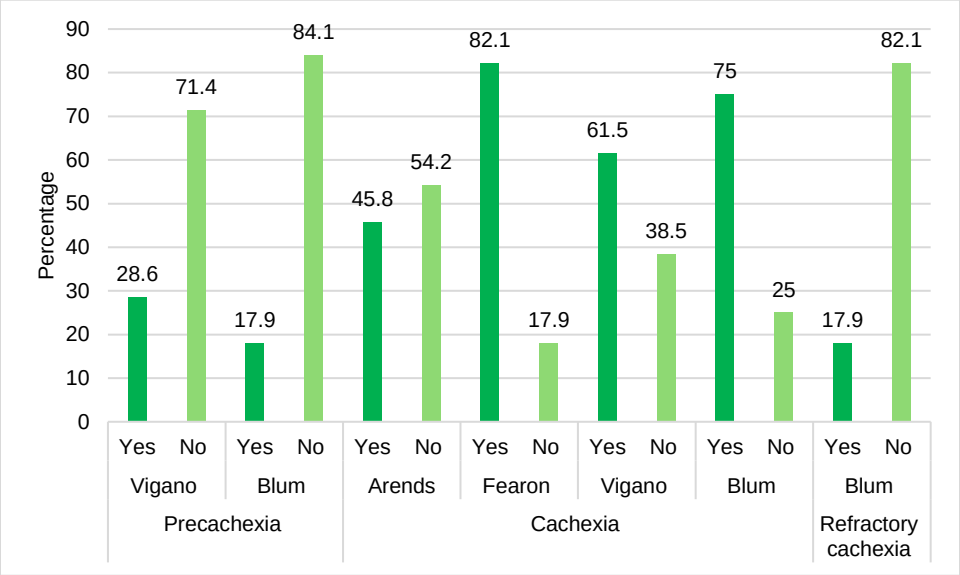
Table 4.21: Diagnostic criteria of pre-, cancer, refractory cachexia using different diagnostic frameworks

Categories	Criteria	Yes	No	Diagnostic models of cachexia			
				Arends et al., (2021)	Fearon et al., (2011)	Vigano et al., (2017)	Blum et al., (2014)
Pre-cachexia	>1kg & ≤5% WL in 6/12, n (%)	5 (17.9)	23 (84.1)				✓
	>1kg & ≤5% WL in 6/12 + CRP[a]≥10mg/l, n (%)	2 (8.3)	24 (91.7)			✓	
	>1kg & ≤5% WL in 6/12 + PG-SGA box 2≥1, n (%)	2 (7.1)	26 (92.9)			✓	
	>1kg & ≤5% WL in 6/12 + CRP[a]≥10mg/l + PG-SGA box 2≥1, n (%)	1 (4.2)	23 (95.8)			✓	
	[a]CRP≥10mg/l + PG-SGA box 2≥1, n (%)	6 (25.0)	18 (75.0)			✓	
Cancer cachexia	>5% WL in 6/12, n (%)	19 (67.9)	9 (32.1)		✓		✓
	>5% WL in 6/12 + PG-SGA box 2≥1, n (%)	13 (46.4)	15 (53.6)			✓	
	>5% WL in 6/12 + CRP[a]≥10mg/l, n (%)	7 (29.2)	17 (70.8)	✓		✓	
	>5% WL in 6/12 + CRP[a]≥10mg/l + PG-SGA box 2≥1, n (%)	4 (16.7)	20 (83.3)			✓	
	>2% WL in 6/12 + <20kg/m^2, n (%)	11 (39.3)	17 (60.7)		✓		✓
	>2% WL in 6/12 + RMM ASM, n (%)	21 (75.0)	7 (25.)				
	OR >2% WL in 6/12 + RMM ASMI, n (%)	22 (78.6)	6 (21.4)		✓		
	CRP[a]≥10mg/l + <20kg/m^2, n (%)	6 (25.0)	18 (75.0)	✓			
	CRP[a]≥10mg/l + Low MM ASM, n (%)	10 (41.7)	14 (58.3)	✓			
Refractory cancer cachexia	>15% WL in 6/12 + <23kg/m^2, n (%)	5 (17.9)	23 (82.1)				✓
	>20% WL in 6/12 + <27kg/m^2, n (%)	1 (3.6)	27 (96.4)				✓

WL – weight loss; 6/12 – 6 months; CRP – C-reactive protein; PG-SGA – patient generated-subjective global assessment; RMM – reduced muscle mass; ASM – appendicular skeletal muscle; ASMI – appendicular skeletal muscle index

[a] missing data n= 4

Pre-cachexia was found in 17.9% (Blum et al. 2014) and 28.6% (Vigano et al. 2017) of participants depending on the diagnostic model used. Only three participants were categorised as pre-cachexic by both Vigano et al. (2017) and Blum et al. (2014). Cancer cachexia was found in 45.8% to 82.1% depending on the diagnostic model used. The same seven participants were categorised as cachexic by all 4 diagnostic models. Five participants were categorised as having refractory cachexia (Graph 4.3).



Graph 4.3: Diagnoses of pre-cachexia, cancer cachexia, refractory cachexia using different frameworks

The sensitivity, specificity and agreement between the reference standard diagnostic model for cancer cachexia (Arends et al. 2021) and the other three diagnostic models as well as various nutritional indicators are summarized in Table 4.22/ Fearon et al. (2011) demonstrated the highest sensitivity at 90.9% and Vigano et al. (2017) demonstrated the highest specificity at 46.1% (Table 4.22). For cancer cachexia, all three diagnostic models poorly agreed with Arends et al., (2021). Common nutritional indicators used in clinical practice were chosen to determine their sensitivity, specificity, and agreement with Arends et al., (2021) cancer cachexia model (Table 4.22). PG-SGA and the components of Box 3 and worksheet 4 had the highest sensitivities at 90.9%; percentage fat mass had 20.0% sensitivity, at the lowest end. PG-SGA and the component Box 3 had 100% specificity while handgrip strength had the lowest specificity at 7.6% (Table 4.17). Good agreement was found with handgrip strength (kappa = 0.638; % agreement = 83%); poor and no agreement was found with all the other nutritional status indicators (Table 4.22).

Table 4.22 Sensitivity, specificity and agreement of cancer cachexia models and nutritional indicators with Arends et al. (2021) model

	Sensitivity %	**Specificity %**	**Interpretation of Se & Spe[a]**	**Cohen's Kappa (k)**	**Cohen's Agreement[a]**	**Percentage agreement**	**% agreement interpretation**
Diagnostic model							
Fearon et al., (2011)	90.9	23.1	Poor	0.132	Poor	54.2	Not acceptable
Vigano et al. (2017)[b]	63.6	46.1	Poor	0.096	Poor	54.2	Not acceptable
Blum et al. (2014)	81.8	30.8	Poor	0.120	Poor	54.2	Not acceptable
Nutritional indicators							
NRS-2002	81.8	61.5	Fair	0.195	Poor	58.3	Not acceptable
PG-SGA	90.9	100.0	Good	-0.084	Poor	41.7	Not acceptable
Box3 PG-SGA	90.9	100.0	Good	-0.084	Poor	41.7	Not acceptable
Wk/t 4 (GPE)	90.9	46.2	Poor	0.356	Poor	66.7	Not acceptable
MUAC	27.3	0.0	Poor	0.289	Poor	66.7	Not acceptable
CC	63.6	61.5	Fair	0.020	Poor	50.0	Not acceptable
Adj CC	27.9	61.5	Poor	-0.343	Poor	33.3	Not acceptable
cAMA	54.5	84.6	Fair	0.220	Poor	33.3	Not acceptable
%FM	20.0	0.0	Poor	-0.289	Poor	65.2	Not acceptable
HGS	70.0	7.6	Poor	0.638	Good	83.0	Not acceptable

Spe – specificity; NRS-2002 – nutritional risk screening 2002; PG-SGA – patient-generated subjective global assessment; Wk/t – worksheet; GPE – global physical examination; MUAC – mid upper arm circumference; CC – calf circumference; Adj CC – adjusted calf circumference; cAMA – corrected arm muscle area; %FM – percentage fat mass; HGS – handgrip strength

[a] according to van Bokhurst-de van der Schueren et al., (2014)

[b] missing data n=2

Participants that were categorized as cachexic or non-cachexic using the diagnostic criteria by Arends et al. (2021) were compared across socio-economic factors, nutritional screening and assessment tools, anthropometry, biochemistry, handgrip strength, dietary parameters and physical activity (Table 4.23 and Table 4.24).

Handgrip strength and albumin levels were significantly lower in the cancer cachexic group, with p-values of 0.038 and 0.003, respectively (Table 4.23). In addition, the cancer cachexia group did demonstrate greater muscle deficit and higher score with worksheet 4 from PG-SGA, lower corrected arm muscle area and lower metabolic equivalent minutes per week. However, these nutritional status indicators did not reach statistical significance (Table 4.23). Furthermore, the cancer cachexia group ingested greater total kilojoules and protein per day and was found to have higher kilocalories of energy per kilogramme and grammes protein per kilogramme daily. No significant differences were found for the categorical data (Table 4.24).

Table 4.23: Comparing participants with and without cancer cachexia in relation to socio-demographic factors and nutritional status indicators of continuous variables (n=24)

	Continuous variables	Cancer cachexia, median (IQR) Yes (n=11)	No (n=13)	p-value[a]
Socio-demographic factors				
Age	Age in years	60.0 (40.0-64.0)	51.0 (45.0-56.0)	0.385
Nutritional status indicators				
NRS-2002	Score	4.0 (3.0-4.0)	3.0 (2.0-4.0)	0.235
PG-SGA	Total score	11.0 (7.0-20.0)	12.0 (11.0-19.0)	0.643
	Box 3 score (symptoms)	5.0 (2.0-8.0)	7.0 (5.0-10.0)	0.224
	Wk/t 4 score	1.0 (1.0-2.0)	1.0 (0.0-1.0)	0.068
cAMA	cAMA in cm^2	27.6 (19.9-48.8)	32.7 (28.9-38.4)	0.487
Fat mass[b]	Fat mass in mm	26.3 (18.6-29.5)	27.5 (18.1-28.6)	0.780
MUAC	MUAC in cm	26.0 (22.0-29.9)	27.2 (25.8-28.5)	0.451
CC	CC in cm	31.9 (29.0-36.0)	32.2 (30.5-33.8)	0.602
Adj CC	CC in cm	34.0 (31.0-35.9)	33.0 (31.7-33.8)	0.297
HGS	HGS in kg	22.6 (18.5-24.3)	27.8 (24.0-39.3)	0.038
Biochemistry	Albumin in g/l	37.0 (37.0-41.0)	42.0 (39.0-45.0)	0.003
24-hour recall	Total energy in KJ	7318.0 (4376.0-10517.0)	5396.0 (4274.0-6966.0)	0.523
	Total protein in g	59.5 (35.7-87.5)	46.5 (26.4-67.8)	0.728
Dietary input	Energy kcal/kg	30.9 (17.2-42.9)	20.7 (17.4-28.6)	0.451
	Protein g/kg	1.1 (0.5-1.6)	0.8 (0.5-1.3)	0.524
Physical activity	MET minutes/week	480.0 (165.0-1260)	900.0 (200.0-5040.0)	0.602

IQL – interquartile rang; NRS-2002 – nutritional risk screening 2002; PG-SGA – patient-generated subjective global assessment Wk/t – worksheet; cAMA – corrected arm muscle area; %FM – percentage fat mass; MUAC – mid upper arm circumference; CC – calf circumference; Adj CC – adjusted calf circumference; HGS – handgrip strength; MET - metabolic equivalents

[a] p-value statistically significant < 0.05 for Mann Whitney U test

[b] missing data (n=1) due to ascites preventing measurement of all 4 skinfold thicknesses

Table 4.24: Comparing participants with and without cancer cachexia in relation to socio-demographic factors and nutritional status indicators of categorical variables (n=24)

	Categorical variables	Cancer cachexia		p-value[a]
		Yes (n=11)	No (n=13)	
Socio-demographic factors				
Gender	Male, n (%)	5 (45.5)	8 (61.5)	0.431
	Female	6 (54.6)	5 (45.5)	
Education	Matriculated: Yes	5 (45.5)	6 (46.2)	1.000
	Matriculated: No	6 (54.6)	7 (53.9)	
Nutritional status indicators				
NRS-2002	At nutritional risk: Yes	9 (81.8)	8 (61.5)	0.386
	At nutritional risk: No	2 (18.2)	5 (38.5)	
PG-SGA	Malnourished: Yes	10 (90.9)	13 (100.0)	0.596
	Malnourished: No	1 (9.1)	0 (0.0)	
	Wk/t 4 deficit: Yes	10 (90.9)	7 (53.9)	0.078
	Wk/t 4 deficit: No	1 (9.1)	6 (46.2)	
cAMA	Wasted: Yes	6 (54.6)	11 (84.6)	0.182
	Wasted: No	5 (45.5)	2 (15.4)	
%FM[b]	Under fat: Yes	2 (20.0)	0 (0.0)	0.178
	Under fat: No	8 (80.0)	13 (100.0)	
MUAC	Malnourished: Yes	3 (27.3)	0 (0.0)	0.082
	Malnourished: No	8 (72.7)	13 (100.0)	
CC	Low: Yes	7 (63.6)	8 (61.5)	1.000
	Low: No	4 (36.4)	5 (38.5)	
Adj CC	Low: Yes	3 (27.3)	8 (61.5)	0.123
	Low: No	8 (72.7)	5 (38.5)	
HGS	Weak: Yes	3 (30.0)	1 (7.7)	0.281
	Weak: No	7 (70.0)	12 (92.2)	
Biochemistry	Hypoalbuminaemia	2 (18.2)	0 (0.0)	0.199
	Normal albumin	9 (81.8)	13 (100.0)	
Energy requirements[c]	<25kcal/kg	5 (45.5)	7 (53.9)	1.000
	≥25kcal/kg	6 (54.6)	6 (46.2)	
Protein requirements[c]	<1g/kg	5 (45.5)	8 (61.5)	0.682
	≥1g/kg	6 (54.6)	5 (38.5)	
Physical activity	Active	5 (45.5)	7 (53.9)	1.000
	Inactive	6 (54.6)	6 (46.2)	

NRS-2002 – nutritional risk screening 2002; PG-SGA – patient-generated subjective global assessment Wk/t – worksheet; cAMA – corrected arm muscle area; %FM – percentage fat mass; MUAC – mid upper arm circumference; CC – calf circumference; Adj CC – adjusted calf circumference; HGS – handgrip strength

[a] p-value statistically significant < 0.05 for Fisher exact test

[b] missing data (n=1) due to ascites preventing measurement of all 4 skinfold thicknesses

[c] requirements as per Muscaritoli et al., (2021)

CHAPTER 5: DISCUSSION

Identifying patients at risk of or with reduced muscle mass (RMM) is important when assessing nutritional status and for the diagnosis of malnutrition, sarcopenia and cancer cachexia. Technical methods are not always readily available within clinical practice. Our aim, therefore, was to determine whether easily accessible, accurate, cheaper alternative tools or indicators regularly used in clinical practice can identify cancer patients with RMM as determined by the reference standard, DEXA and expressed by appendicular skeletal muscle (referred to as DEXA hereafter).

5.1 Alternative muscle mass markers, nutritional status indicators and the reference standard, DEXA (aim 1)

There was a high prevalence of reduced muscle mass (82.1%) as determined by our reference standard, DEXA. Eighty-two percent of participants had reduced muscle mass as determined by DEXA which differed in comparison to Sousa et al., (2022) and Souza et al., (2020) where RMM was 30% and 17.6%, respectively. The majority of their patients were older colorectal cancer patients, where the reference standard was computerized tomography (CT) scans. Despite Souza et al., (2020) cohort being majority in stage 3 and 4, they did not receive any anti-cancer treatment within 3 months of recruitment, unlike our participants whom just under a third were on chemotherapy when recruited and received any treatment a median of 1 (0.0-2.0) month ago. Secondly, 42% of our participants had metastases; Sousa et al., (2022) reported only a quarter of their participants in stage 4. This implies a great impact of anti-cancer treatment and cancer stage upon muscle mass in our research group.

From the six alternative muscle mass markers, calf circumference performed best across the different statistical tests in comparison to DEXA. Calf circumference showed the highest agreement with DEXA (fair agreement with ƙ=0.503), followed by global physical examination (GPE) from PG-SGA, worksheet 4 (poor agreement; ƙ=0.388). Our results are comparable to Souza et al., (2020) who found that, in the colorectal cancer population, GPE to have the highest agreement (ƙ=0.48) with their reference standard, CT scan, followed by calf circumference (ƙ=0.32). Sousa et al., (2022) demonstrated greater agreement of calf circumference in males (ƙ=0.332) and those <60 years (ƙ=0.419) indicating the difference in body composition across gender and age.

According to McHugh et al (2012) a kappa of >0.6 may be needed for health-related clinical practice decisions but cautions interpretation when numbers are small and suggests performing both kappa and percentage agreements (McHugh, 2012). Our acceptable MM category only consisted of 5 participants, we therefore performed percentage agreement where calf circumference had 78.6% agreement with DEXA.

Our results for calf circumference were overall fair for sensitivity (73.9%) and specificity (80%), as was Sousa et al, (2022) as sensitivity and specificity both >80% has been proposed as indicating good validity by Van Bokhurst et al., (2014). For research purposes, the selection of cutoff points is dependent on specific clinical outcomes. Our results differed from Souza et al., (2020) as their overall results for

sensitivity and specificity can be interpreted as poor. Despite using different comparators, DEXA versus CT, our participants and Sousa et al., (2022) had mixed cancers. Souza et al., (2019) focused on colorectal cancer patients using CT as a comparator.

Sixty-four percent of participants had low calf circumferences. It is well established that in elderly and clinical populations, calf circumference is a marker of muscle mass (Barbosa-Silva et al., 2016; Gonzalez et al., 2021; Prado et al., 2022). Our results are similar to da Silva et al., (2019) but other researchers found lower percentages of participants with low calf circumferences, even though the same cutoff points were used (Sousa et al., 2020; Souza et al., 2020). This could be due to our sample and others (de Silva et al. 2019) had lower median BMIs versus the BMIs reported by Sousa et al, (2020) and Souza et al., (2022), with adiposity impacting calf circumference measurements (Gonzalez et al., 2021).

We demonstrated that global physical examination (GPE; worksheet 4 of PG-SGA) showed poor overall sensitivity (74%) and specificity (20%). Our sensitivity result is similar to Souza et al., (2020) but our specificity is lower. The GPE identified 75% of participants with muscle deficit in comparison to DEXA (82.1%). Our results may be explained by the greater subjective nature of GPE where, despite being trained, we had 4 field workers whereas Souza et al., (2020) had 1 field worker. In addition, our participants categorised in the acceptable MM group were only 5, impacting accuracy of results.

Adjusted calf circumference demonstrating overall fair sensitivity / specificity but poor agreement with DEXA. A possible explanation for poor agreement of adjusted calf circumference with DEXA is that we adjusted circumferences for 9 participants with BMIs < 18kg/m^2 as per Gonzalez et al., (2021) recommendation. This may shift some underweight participants with RMM into the acceptable calf circumference category. Prado et al., (2022) cautions against adjusting calf circumference if participants are underweight and unwell, as Gonzalez et al., (2021) suggestion was only for healthy individuals (Prado et al., 2022).

The corrected arm muscle area (cAMA), estimated ASM, mid upper arm circumference (MUAC) had overall poor sensitivity and specificity and poor agreement with DEXA. Our cAMA results were dissimilar to Souza et al., (2020) as they found fair agreement. This difference with our results may be related to the inter-rater reliability of the field workers' techniques, particularly triceps skinfold thickness (Madden & Smith, 2016). Interestingly, MUAC had 100% specificity meaning that it will identify 100% correctly those without RMM and only correctly identify 13% with RMM. On the other hand, cAMA will correctly identify 74% with RMM.

None of our results indicate good agreement i.e., Cohen's and percentage agreement and overall good sensitivity and specificity. This suggests that in our cohort, calf circumference and GPE cannot be used as proxies for identifying RMM; instead, calf circumference may be used to screen cancer patients to determine those without RMM as the specificity was 80% i.e., only 20% of participants without RMM will

be incorrectly categorised. Our results infer that with a larger sample size, calf circumference may be a good alternative marker of muscle mass.

Patients with reduced muscle mass as per DEXA had significantly lower BMIs, MUAC, calf circumference, percentage body fat, NRS-2002 and PG-SGA scores in comparison to patients with acceptable muscle mass. Of the same variables researched, our results were similar to Souza et al., (2020) apart from their albumin being significantly different. They too did not find statistically significant differences in HGS and CRP. This discrepancy in our albumin results may be explained by only two of our participants having hypoalbuminaemia. Surprisingly, the effect size was 0.6, indicating medium effect.

Investigating nutritional status indicators, all variables demonstrated poor Cohen's agreement. As Cohen's ƙ is not reliable with small numbers in a category, in our case 5 in acceptable MM category, our results are difficult to interpret. However, taking percentage agreement into account, PG-SGA displayed 82.1% agreement with DEXA, followed by NRS-2002 with 71.4% agreement. It is acknowledged that percentage agreement does not account for chance agreement, unlike Cohen's ƙ. Taking all the tests into account, namely sensitivity, specificity, Cohen's ƙ and percentage agreement, NRS-2002 faired the best against DEXA. Increasing the sample size would likely yield greater agreement and improve the tests results.

5.2 Malnutrition in cancer outpatients according to Global Leadership Initiative on Malnutrition (GLIM) using different approaches, including technical (DEXA) and clinical approaches to determine muscle mass (aim 2)

Our study confirmed that malnutrition is prevalent in this cancer population ranging from 75.0% to 92.9% depending on the muscle mass assessment method and Global Leadership Initiative on Malnutrition (GLIM) approach used. This is within the upper end and higher than the global prevalence of malnutrition as diagnosed by GLIM i.e., 11.9% to 88% within varied cancer cohorts comprised of different approaches, MM measurements and interpretation (Matsui et al., 2023; Peng et al., 2022; Xu et al., 2022; Yin et al., 2023). To the best of our knowledge, within sub-Saharan Africa, there is scant research on malnutrition in cancer patients using GLIM criteria (La Grange et al., 2021).

All our comparisons of GLIM using alternative MM markers were with GLIM using DEXA represented by appendicular skeletal muscle mass (ASM) for the MM category and cancer diagnosis meeting the inflammation category, referred to as our comparator. Comparing our research to other cancer research is limited as previous research used other comparators like reference assessment tools that have been previously validated, namely PG-SGA (da Silva Couto et al., 2023; Yin et al., 2021; Zhang et al., 2021) and SGA (Contreras-Bolívar et al., 2019). The only similar research found were in non-cancer patients where GLIM using alternative muscle mass markers were compared to GLIM using other technical

methods, namely BIA and DEXA (MM not represented by ASM) (Ozturk et al., 2022; Sanchez-Rodriguez et al., 2021; Sobestiansky et al., 2021).

We found that GLIM using mid upper arm circumference (MUAC), calf circumference, estimated ASM and not including the muscle mass (MM) category to have good agreement with our comparator, with the highest agreement (ƙ=0.677) demonstrated by GLIM using calf circumference. Adjusted calf circumference, corrected arm muscle area (cAMA) and global physical examination (worksheet 4 in PG-SGA) demonstrated fair agreement. With only 3 participants in the well-nourished category, all seven approaches demonstrated above 85% percentage agreement with GLIM using DEXA.

Ozturk et al., (2022) found near perfect agreement of GLIM using calf circumference, MUAC and no MM category but when compared to BIA skeletal muscle index in general medical inpatients, whether at nutritional risk or not. Interestingly, they used cutoff points from relevant Turkish reference populations for calf circumference and their comparator BIA; GLIM was performed on all participants with clinical judgement supported by CRP results for the inflammatory category (Ozturk et al., 2022). It could thus be argued that if we were to use relevant South African reference population cutoff points for our comparator DEXA and our alternative muscle mass markers, our agreement may improve.

Our sensitivity and specificity results are similar to Sanchez-Rodriguez et al., (2021) for calf circumference only as they found overall fair sensitivity and specificity for MUAC and GLIM without RMM category to have substantial agreement with their comparator, DEXA expressed as fat free mass index or appendicular lean mass index (Sanchez-Rodriguez et al., 2021). They too did not include a screening step before using GLIM. These authors used insulin growth-like growth factor and interleukin-6 as biomarkers for the inflammatory category; whereas we used CRP and their sample size was larger.

Sobestiansky et al., (2021) found high sensitivity and specificity of GLIM using calf circumference when compared to GLIM using DEXA expressed as fat free mass index. They did not use the kappa statistical test but used the correlation coefficient instead. A fair correlation (0.57) was found between calf circumference and fat free mass index (Sobestiansky et al., 2021).

GLIM using estimated ASM to meet the MM category is a method suggested by Compher et al., (2022) in the guidance article for muscle mass assessment methods. There are no suggestions for interpretation of estimated ASM as per the equation developed by Santos et al., (2019) for clinical populations (Compher et al., 2022; Santos et al., 2019). Despite using a cut-off point determined from an Italian elderly population (Landi et al., 2022) and choosing white ethnicity in the equation we found good agreement with our comparator. No GLIM related research was found that used this alternative muscle mass marker. Landi et al., (2022) found the same estimated ASM cut-off points we used to predict 10-year mortality in community dwelling elderly (Landi et al., 2022). In our South African health context, this equation may be helpful in clinical practice as only one anthropometric value (the calf circumference) is

needed, with potential improvement in agreement with our comparator if relevant South African reference populations were used and cut-off points determined.

Our comparator diagnosed 89.3% of participants as malnourished; GLIM using MUAC diagnosed 78.6% of participants as malnourished. This is similar to Contreas-Bolivar et al., (2019) despite their cohort being cancer in-patients with more advanced disease. As we included patients not at nutritional risk as determined by nutritional risk assessment-2002 (NRS-2002), this may have increased our findings together with 100% of participants meeting the inflammation category under aetiologic criteria. This is different to their research as they used the Glascow Prognostic Score (a systemic inflammation-based scoring system) to meet the aetiologic criteria (Contreras-Bolívar et al., 2019).

Focusing on non-cancer research, Ozturk et al., (2022) found 46.7% malnutrition using their comparator, BIA. In addition, they found GLIM using CC and GLIM using MUAC identified 55.9% and 47.5% in-patients as malnourished. Their research suggests that GLIM using MUAC identifies less malnourished participants than their comparator in clinical populations, as do our results.

Within a healthy elderly population, Sanchez-Rodriguez et al. (2021) results found malnutrition in 24.4% with GLIM using DEXA, 13.9% malnourished without a RMM category and 18.8% malnourished with GLIM using either calf circumference or MUAC. This research suggests that GLIM using DEXA identifies more malnourished participants when they are healthy as more ill patients will meet the other categories of percentage weight loss and low BMI.

GLIM using ASM identified 3 additional patients as malnourished in relation to GLIM using no reduced muscle mass, MUAC and estimated ASM as only 1 criterium needs to be met for each phenotypic and aetiologic criteria. This means that all patients with low estimated ASM or low MUAC where already identified by either the percentage weight loss or low BMI categories. When no reduced muscle mass component is used as part of GLIM (including using MUAC and estimated ASM in our cohort), it suggests that patients will be missed as malnourished. This is confirmed by Kiss et al., (2023) who found 10% of cancer patients were missed when there was no reduced muscle mass phenotypic category included. They did however use combinations of only 1 option per category, rather than any criterion to meet the phenotypic and aetiologic criteria (Kiss et al., 2023).

All three of the GLIM approaches discussed above had good sensitivity, i.e., ability to identify malnutrition when present in a patient. Our sensitivity was higher and specificity much lower than previous cancer and non-cancer research using GLIM without reduced muscle mass component (De Groot et al., 2020) and for GLIM using MUAC (Sanchez-Rodriguez et al., 2021), respectively. This may be due to our small sample as only 3 were categorised as well nourished by our comparator, GLIM using ASM. Moreover, our three GLIM approaches were unable to correctly identify those three participants that were not

malnourished. Fortunately, in the healthcare environment, it is more necessary to identify those that are malnourished.

Compher et al., (2022) provides guidelines on using alternative muscle mass markers when there are no technical methods available. There is discrepancy in the article by Compher et al. (2022) as it refers to MUAC and CC as alternative measures to be used as depicted in their GLIM algorithm. However, in the text of their article, they refer to mid arm muscle circumference and arm muscle area, not MUAC. As previously pointed out by Duarte et al., (2022), corrected arm muscle area is a more accurate estimate of muscle mass than mid arm muscle circumference (MAMC) (Duarte et al., 2022; Heymsfield et al., 1982). Our results for sensitivity of GLIM using cAMA was higher and specificity was lower than Munoz Fernandez et al., (2021) even though the same cAMA reference population and interpretation were used. Their population were elderly emergency ward patients with the mini nutritional assessment full form used as a reference standard for older adults (Munoz Fernandez et al., 2021). We did not find any other research to compare our result of fair agreement of GLIM using cAMA with GLIM using ASM.

Poor overall sensitivity (88%) / specificity (33.3%) and poor agreement was also found for GLIM using physical examination (worksheet 4 of PG-SGA) with our comparator. To the best of our ability, we could not trace similar research to ours. Using GLIM with GPE found 81.3% as malnourished. This is a higher prevalence of malnutrition than found by Poulter et al., (2021) and Steer et al., (2020). This may, in part, be because of them identifying malnutrition only in participants identified as at risk by the malnutrition screening tool. This contrasts with our research as we identified malnutrition even in participants that were not at nutritional risk. In addition, their time frames differed regarding percentage weight lost and reduced food intake duration. They used the presence of metastases as a proxy for meeting the inflammation aetiologic criteria with less metastases found than our study (Poulter et al., 2021; Steer et al., 2020). Neither of these studies used a reference standard as comparator for their results.

A variety of approaches to meet the inflammation category is found in the literature as the GLIM guidelines are interpreted differently despite the text that accompanies the diagnostic criteria table (Cederholm et al., 2019). Clinical judgment, raised inflammatory markers, Glascow Prognostic Score, presence of cancer or metastases or even omitting the inflammatory category are some of the different approaches in the literature (Brown et al., 2023). Our results show the difference in the prevalence of malnutrition when using cancer (78.6%-92.9%) or raised CRP (75.0%-87.5%) to meet the inflammatory category. We decided to use GLIM with cancer meeting the inflammatory category as our comparator. Our results relating to associations with malnourished or not malnourished groups, investigating the sensitivity, specificity and agreement of alternative MM markers may be different if our comparator had been GLIM using raised CRP. Brown et al., (2023) demonstrated in their systematic review that the different approaches to meeting the inflammatory category impact the predictive ability of GLIM for survival.

Not at nutritional risk patients (n=9; 32.1%) were included in the GLIM assessment. Our results found higher prevalence of malnutrition when NRS-2002 was omitted before performing GLIM. Our results agree with previous research (Zhang et al., 2021) and may, in part, explain our high malnutrition prevalence in comparison to other GLIM cancer research. Interestingly, the design purpose of NRS-2002 is to identify patients that are at nutritional risk that would benefit from nutritional support, rather than screen patients (van Bokhorst-de van der Schueren et al., 2014). Research has found that using different validated screening tools before GLIM may yield different malnutrition results (Henriksen et al., 2022)

Overall, results suggest better agreement of MUAC, calf circumference and no RMM category when comparators are technical methods, namely DEXA, BIA or CT scans. In addition, results suggest that better agreement exists with alternative muscle mass markers and comparators where reference populations and cut-off points used are relevant to the researched group.

Comparing our research results has been challenging as there is limited research, particularly in cancer. Additional reasons include variation in research methods, comparators, heterogeneity of participants, alternative muscle mass markers that include different methods and interpretation using different reference populations and cutoff points, application of GLIM and whether GLIM was applied only to nutritionally at-risk participants.

5.3 Sarcopenia according to the European Working Group on Sarcopenia in Older People (EWGSOP) using muscle mass determined from DEXA (reference standard) and alternative muscle mass markers (aim 3)

Many cancer patients develop sarcopenia which has direct impact on clinical and patient outcomes. We found a prevalence of sarcopenia from 7.4% to 18.5%, depending on the muscle mass method used. This aligns, in part, with the lower end of global sarcopenia prevalence of 20-70% (Ryan et al., 2016). Comparison of sarcopenia prevalence in cancer patients across studies is difficult due to heterogeneity of cancer, variety of methods and representations of muscle mass measurement, and different reference populations with unique cut-off points. In addition, within earlier cancer research, reduced muscle mass was simply referred to as sarcopenia, without the muscle strength component as per the recent sarcopenia guidelines (Fearon et al., 2011; Ni Bhuachalla et al., 2018; Srdic et al., 2016).

Calf circumference agreed perfectly and had 100% sensitivity and specificity while adjusted calf circumference had good agreement with DEXA for identifying sarcopenia with overall fair sensitivity (80%) / specificity (100%). There is inconsistency in the literature with calf circumference being used as an alternative muscle mass marker. Our adjusted calf circumference results are similar to cancer research by Trussardi et al., (2021) with respect to agreement, despite CT scan being their reference standard. Unsurprisingly, they found higher sarcopenia prevalence as their population was older Brazilian cancer inpatients (Trussardi Fayh & de Sousa, 2021). Other cancer research in palliative patients with advanced

cancer found diagnosing sarcopenia at 53% using calf circumference (da Silva et al., 2019). Our results are similar to the majority of non-cancer research, even though they were conducted in older populations (Kawakami et al., 2015; Kim et al., 2018) or patients with other chronic diseases (Pribadi et al., 2022).

The research that found calf circumference unsuitable as an alternative marker in diagnosing sarcopenia used the same cut-off point for both genders and a much lower cut-off point (Sobestiansky et al., 2021; Sousa-Santos et al., 2021) than our research. This implies that the cut-off point used for calf circumference influences the agreement with the reference standard used when diagnosing sarcopenia using Cruz-Jentoft et al., (2019) guidelines. Furthermore, research that used cut-off points derived from a reference population similar to their research population (da Silva et al., 2019; Trussardi Fayh & de Sousa, 2021) found calf circumference to be a good alternative to the reference standard used. This is also true for research that determined their own cut-off points to be used during their research by using their own populations (Kawakami et al., 2015; Kim et al., 2018; Pribadi et al., 2022).

We chose to use Gonzalez cut-off points for calf circumference as, despite using NHANES USA population, there was a mixed ethnicity in their sample. In addition, we adopted to adjust the calf circumference relative to BMI, as recommended by Gonzalez et al., (2021) as the differences in calf circumference in the different ethnic groups were confounded by adiposity (Gonzalez et al., 2021). None of the other research reported using adjusted calf circumference when comparing agreement to any reference standard for muscle mass in sarcopenia diagnosis.

Corrected arm muscle area (cAMA) also had good agreement diagnosing sarcopenia using DEXA (ASM) with overall fair sensitivity (80%) / specificity (100%). Our results align with the only other cancer research group that investigated using corrected arm muscle area to diagnose sarcopenia. Da Silva et al., (2019) found that using cAMA could predict overall survival in advanced palliative care cancer patients where the prevalence of sarcopenia was double our prevalence of 14.8% (da Silva, Wiegert, Oliveira, & Calixto-Lima, 2019). We found two research groups that used mid arm muscle circumference instead of cAMA. Jones et al., (2020) investigated colorectal cancer patients and Sousa-Santos et al., (2021) researched the elderly, finding poor levels of agreement, using CT scan and DEXA (ASM) as the comparators, respectively (Jones et al., 2020; Sousa-Santos et al., 2021). A possible reason for this difference with our results may be because cAMA is a more accurate muscle mass estimate than mid arm muscle circumference (Heymsfield et al., 1982).

The PG-SGA worksheet 4 physical examination to determine global muscle mass deficit to diagnose sarcopenia had good agreement with DEXA and overall fair sensitivity (60%) and specificity (100%). The PG-SGA worksheet 4 is partly based on the subjective global assessment tool. Pribadi et al., (2022) argued that a subjective global assessment cannot be used as a proxy for muscle mass in patients with inflammatory bowel disease when diagnosing sarcopenia against DEXA (ASMI) as a comparator. No other similar studies could be traced to compare our results with.

The prevalence of sarcopenia was the lowest using mid upper arm circumference (MUAC) with fair agreement and overall poor sensitivity (40%) and specificity (100%). To our best knowledge, we did not find any similar studies to compare our results too. We investigated MUAC as a proxy for muscle mass as it is easy and cost effective to measure within any setting. It is a method designed to screen for malnutrition in emergencies and corresponds to BMI (Ferro-Luzzi & James, 1996). However, it has been well established that BMI is not a good indicator of muscle mass, particularly in obese cancer patients (Prado et al., 2016)

5.4 Cancer cachexia using different diagnostic frameworks and the associations with nutritional status indicators in cancer outpatients (aim 4)

We found that the diagnosis and classification of cancer cachexia varied depending on the diagnostic models used. This is unsurprising as globally the diagnostic criteria have not been agreed upon. This lack of consensus, together with the heterogeneity of cancer, differing sample sizes, methods of assessments or measures and interpretation thereof and study designs, make comparisons within research difficult. This in turn hampers clinical implementation and interventions within practice (Arends et al., 2023).

We used two diagnostic models to identify pre-cachexia and found a prevalence range of 17.9% to 28.6% which is similar to Wiegert et al., (2020) who also applied Blum et al., (2014) and Vigano et al., (2017) diagnostic models. The pre-cachexia diagnostic criteria by Vigano et al., (2017) is largely based on the work by Muscaritoli et al., (2010) but replaced the appetite assessment method, for food intake using PG-SGA box 2 ≥1. Furthermore, Vigano et al., (2017) uses additional abnormal biochemistry (white cell count, haemoglobin, albumin), not only CRP, in keeping with Fearon et al., (2011) definition of pre-cachexia stage (Fearon et al., 2011). Wiegert et al., (2020) reported that Vigano et al., (2017) pre-cachexia diagnostic criteria was significantly associated with an increased risk of death and demonstrated predictive discrimination for survival (Wiegert et al., 2020), unlike when applying the diagnostic criteria of Blum et al., (2014). This could be because Blum et al., (2014) only incorporated weight loss as a component for pre-cachexia while Vigano et al., (2017) had the inflammatory and / or food intake components. It is worth noting that Roeland et al., (2017) demonstrated loss of muscle mass with <5% weight loss which suggests that patients may be missed as pre-cachexic if not presenting with weight loss as, in their research, some gained visceral fat (Roeland et al., 2017). Neither of these diagnostic models accounted for muscle mass reduction (Blum et al., 2014; Vigano et al., 2017).

Six other researchers identified pre-cachexia in 11% to 34% of mostly advanced cancer patients mainly using Muscaritoli et al., (2010) diagnostic criteria with variation in methods used to assess appetite. Only two of these found significant association with quality of life, both with large sample sizes (Antoun et al.,

2019; van der Meij et al., 2013); none found statistically significant association with survival (Antoun et al., 2019; Blum et al., 2014; Ozorio et al., 2017; van der Meij et al., 2013; Wesseltoft-Rao et al., 2015; White et al., 2020), barring Blum et al., (2014) but only when both lack of appetite and raised CRP were fulfilled together with weight loss (Blum et al., 2014).

We used four diagnostic models to identify cancer cachexia and found a range from 45.8% to 82.1%. Using Fearon et al., (2011) diagnostic criteria, identified the highest percentage of cancer cachexia in our cohort. Our results agree with three research groups that also compared Fearon et al., (2011) diagnostic criteria with one or more other models (Vanhoutte et al., 2016; Wallengren et al., 2013; Wesseltoft-Rao et al., 2015). A plausible explanation is that Fearon et al., (2011) model omits aetiologic criteria, limiting the sensitivity and specificity to identify cancer cachexia (Arends et al., 2023). Despite the lack of an aetiologic criteria, two out of these three research groups found significant association with survival and / or quality of life in cancer patients. This may merely reflect that malnutrition is also linked to morbidity and mortality.

Blum et al., (2014) adapted Fearon et al., (2011) diagnostic criteria and removed the muscle mass component, leaving only BMI and percentage weight loss. As cachexia is characterized by reduced muscle mass, it implies that a diagnostic model should include this as a criterion. In our cohort, 7% were additionally identified because of the reduced muscle mass component when comparing Fearon et al., (2011) and Blum et al., (2014). Researchers that used Blum et al., (2014) diagnostic model, found significant association with survival when compared to no cancer cachexia, potentially reflecting the impact of weight loss and low BMI against a background of chronic disease (Blum et al., 2014; Wiegert et al., 2020).

We identified 61.5% of participants with cancer cachexia using Vigano et al., (2017) diagnostic criteria, where previous research found discrepancy in the association with survival (Calixto-Lima et al., 2022; White et al., 2020).

We could not trace any research that focused on Arends et al. (2021) diagnostic criteria, which is based on meeting any 1 out of 3 GLIM's phenotypic criteria and only GLIM's inflammatory criteria of raised CRP for aetiologic criteria. The premise that all cachexic patients are malnourished but not all malnourished patients are cachexia (Muscaritoli et al., 2010) bears fruit when considering Arends et al., (2021) criteria identified 45.8% as cachexic, and malnutrition was identified in 87.5% to 92.9% of our participants using GLIM or PG-SGA, respectively. When comparing the three diagnostic models to Arends et al., (2021), all demonstrated poor sensitivity, specificity, and agreement. This suggests that the inflammatory criterion omitted in Fearon et al., (2011) and Blum et al., (2011) and the muscle mass component omitted in Vigano et al., (2014) and Blum et al., (2011) diagnostic criteria is important in identifying cachexic patients in our research cohort.

We used one diagnostic model to identify refractory cachexia in 17.9% of our participants. The diagnostic criteria using Blum et al., (2014) includes only BMI and percentage weight loss. Research using the same diagnostic criteria, demonstrated a significant association with survival when compared to patients not having cachexia (Blum et al., 2014; Wiegert et al., 2020). Significant association with survival was also found using different diagnostic models with variations in BMI, percentage weight loss and other components like physical activity, biochemistry (Antoun et al., 2019; Ozorio et al., 2017; White et al., 2020).

The GLIM has presented cachexia as a subtype of disease related malnutrition (Cederholm et al., 2019) which is most likely an inflammatory syndrome (McGovern et al., 2022). This is incorporated by Arends et al., (2021) cancer diagnostic criteria (Arends et al., 2021), but there is concern that using GLIM for cancer cachexia diagnosis will omit other unique cachexia information, like identifying pre-cachexia for early intervention (McGovern et al., 2022). Suggestions that quality of life, patient reported symptoms and impaired physical function are diagnostic components that feature minimally in previous research but may add value to future research (Roeland et al., 2020).

We found handgrip strength and albumin significantly different in the cancer cachexia group, identified using Arends et al., (2021) criteria. Most cancer research have used Fearon et al., (2011) diagnostic criteria or adapted versions thereof. Results demonstrate discrepancy regarding associations of HGS with cancer cachexic: our results agree with Ozoria et al., (2017) and Vigano et al., (2017), albeit for their males only; our results disagree with Jager-Wittenaar et al., (2017) even though they too had a small sample size (Jager-Wittenaar et al., 2017; Ozorio et al., 2017; Vigano et al., 2017). Handgrip strength was the only measure that demonstrated good Kappa and percentage agreement with Arends et al., (2021) diagnostic criteria, with poor sensitivity and specificity. To the best of our knowledge, we did not find similar research to compare this result to. Heterogeneity in the research exists across many different aspects: cancer type and stage; cut-off points and reference populations used; cancer cachexia diagnostic models and methods; study designs. Refer to handgrip discussion section, 5.8.

Albumin was significantly lower in our cancer cachexia group as it is a negative acute phase protein and linked to inflammation, of which CRP is a marker and used in our diagnostic criterion. Our research agrees with some researchers (Srdic et al., 2016; van der Meij et al., 2013) that investigated patients with non-small cell lung cancer only, but not other researchers (Ozorio et al., 2017; Solís-Martínez et al., 2022). Discrepancies in research may exist as low albumin and raised CRP is also indicative of infection, therefore not uniquely specific for chronic inflammatory conditions. Albumin has a much longer half-life than CRP, therefore slow to demonstrate any shift. Depending on laboratory techniques, cutoffs for albumin and CRP values may vary in research. Considering the different tools available within clinical practice, we found that PG-SGA and Box 3 of PG-SGA that quantifies symptoms demonstrated good sensitivity and specificity, meaning they both would correctly identify cachexia in 90.9% of patients and correctly identify no cachexia 100% of the time. However, they both demonstrated poor Kappa

agreement and percentage agreement of 41.7% with Arends et al., (2021) diagnostic criteria. These results may be explained by having only 1 participant identified as well-nourished and 1 participant without nutrient impact symptoms. Interestingly, similar research to ours, yet dissimilar with some components, conducted by Song et al., (2022) investigated cancer cachexia as determined by Fearon et al., (2011) diagnostic criteria. When including NRS-2002 first, then GLIM demonstrated good sensitivity and specificity with 91.3% accuracy; without NRS-2002, GLIM demonstrated fair sensitivity and specificity with 67.4% accuracy and PG-SGA fair sensitivity and specificity with 63.1% accuracy to Fearon et al., (2011) diagnostic criteria (Song et al., 2022).

Similar research to ours, yet dissimilar with some components, by Cavalcante Martins et al., (2019), found that PG-SGA could predict cancer cachexia as defined by Fearon et al., (2011) and death in head and neck cancer patients (Cavalcante Martins et al., 2019). Their overall sensitivity and specificity was fair for cancer cachexia with 72% accuracy.

Considering anthropometry, we found that calf circumference and corrected arm muscle area demonstrated fair sensitivity and specificity, poor Kappa agreement and percentage agreement of 50% and 33.3%, respectively with Arends et al., (2021) diagnostic criteria. Research by Ge et al., (2021) investigated anthropometry that would predict survival in patients that were identified as cachexic by Fearon et al., (2011) diagnostic criteria. Triceps skinfold thickness, not calf circumference or mid arm muscle circumference (they did not use cAMA), was associated with 1 year survival and stronger association seen in older than 65-year-old patients (Ge et al., 2021).

None of our nutritional status indicators performed well across all the different tests. PG-SGA and Box 3 are sensitive and specific enough but not in agreement with our cancer cachexic reference framework; handgrip strength is not specific or sensitive enough but has good agreement with the reference framework. Our results suggest that our routine use of nutritional status indicators within practice, may not be sufficiently sensitive, specific and agree with our reference framework to diagnose cancer cachexia. As it is a multifactorial and multi-organ syndrome (Sayers et al., 2023), all diagnostic components may need to be present, therefore simplistic commonly used clinical and practical approaches may not be adequate.

5.5 Patient characteristics, socio-economic data and health related variables

Our cohort was majority males which aligns with the global cancer prevalence being dominant in males. This is different to South Africa's latest cancer statistics where males account for 48.6% of all cancers (Statistics SA, 2023a). However, considering the types of clinics we targeted, more males were recruited from the head and neck cancer clinic. This agrees with research that found males develop more head and neck cancers than females (Jackson et al., 2022; Park et al., 2022).

The median age of our participants was 56.0 (46.0–63.5) years which is younger than South Africa's national average for people diagnosed with cancer (Statistics SA, 2023a). A possible reason for our younger cohort is the exclusion criterion of patients older than 70 years of age.

There is a global increase in cancer prevalence and the burden of cancer, with knowledge that socio-economic factors have a role to play (Kocarnik et al., 2022). Our country faces a large burden of chronic disease, inclusive of cancer, where poorer South Africans experience a worse health outcome (Statistics SA, 2023a). Unemployment was 43.2% in our cohort, higher than the most recent South African unemployment rate of 32.9% (Statistics SA, 2023b). This is unsurprising as most of them were too sick to look for work. This is supported by most participants receiving a grant from the state. The percentage of participants that completed high school was 64.3% (includes those with further certifications, diplomas or degrees), in agreement with South Africa's high school completion rate (Statistics SA, 2019).

Colorectal cancer, the world's third most diagnosed cancer (Sung et al., 2021), may explain the recruitment of half the participants from the colorectal clinic. Most males were recruited from the head and neck clinic in agreement with sex differences found in this cancer type (Park et al., 2022). Our cohort had lower documented metastases than sub-Saharan African patients at presentation (Ngwa et al., 2022), possibly reflecting the recruitment bias in our participants: many patients declined to participate due to their illness.

As cancer is classified as a type of non-communicable disease (NCD), it is unsurprising that most of the co-morbidities found in our participants are NCDs. Our participants presented with similar prevalence of diabetes mellitus and hypertension, but higher prevalence of reported asthma and chronic obstructive pulmonary disease (COPD) as found in the most recent South Africa Health Survey (SADHS, 2016).

Medications for symptom control were prescribed for most of the participants. Guidelines recommend managing nutrition impact symptoms to optimize nutritional intake (Muscaritoli et al., 2021). In our cohort, analgesia for pain control was prescribed for over half of participants, with almost 40% indicating that pain was impacting on their nutritional intake. This is similar to a recent review on overall pain prevalence (Snijders et al., 2023) that appears to have declined over the past decade, most likely due to more focus on pain management.

5.6 Risk factors

Results demonstrated that 70% of our participants smoke or smoked in the past. This high percentage may be expected as smoking is associated with cancer risk, particularly colorectal, mouth and throat cancer (Thanikachalam & Khan, 2019). Our results are higher than the 20% reported for a general South African sample that smoke or smoked in the past (Fagbamigbe et al., 2020). Present alcohol intake was under 20%, another associated risk factor related to cancer. More males were consuming alcohol which aligns with the findings of the South Africa Demographic and Health Survey of 2016 (SADHS,

2016). Five participants used cannabis reportedly to assist with symptoms (not investigated in research officially). Cannabis use for symptom control is not supported by the most recent clinical nutrition cancer guidelines (Muscaritoli et al., 2021).

5.7 Biochemistry

Raised C-reactive protein (CRP) and reduced albumin levels are indexes of systemic inflammation that have impact on clinical outcomes. Under half of participants had increased CRP. Our results are lower than CRP levels in palliative care cancer groups (Cordeiro et al., 2020; Wallengren et al., 2015). Interestingly these researchers found systemic inflammation associated with reduced muscle mass and overall survival. A systematic review by Abbas et al. (2019) found in over 11 000 cancer patients a consistent association between skeletal muscle index (majority of studies used CT scans) and systemic inflammation (Abbass et al., 2019). This contrasted to our results as there was no association found between CRP, albumin levels and reduced muscle mass. Our small sample size, together with different methods for measuring muscle mass and bloods may explain our results.

5.8 Handgrip strength

Assessing muscle strength as part of nutritional assessment is necessary (Arends et al., 2017b) as it is an indicator of general health status (McGrath et al., 2020) and linked to mortality (López-Bueno et al., 2022). We found variation (18.5% to 48.1%) in the prevalence of weak handgrip strength depending on the method of interpretation used because HGS varies across geographical location, ethnicity, age, gender, physical activity, weight and height (Leong et al., 2016). Using the same cut off points as Dolan et al., (2020), our results are lower for weak handgrip strength as their population had advanced cancer and were older. We found no cancer research that used Dodds et al., (2014) percentiles of gender across different ages for HGS interpretation. Instead, more cancer research determined cut off points of handgrip strength using receiver operating characteristic statistics to determine association with different outcomes.

There was no association found between reduced muscle mass and handgrip strength. Our results differed to research conducted in advanced cancer patients (Dolan et al., 2020; Kilgour et al., 2013), oesophageal (Hagens et al., 2020) and gastric cancer patients (Lidoriki et al., 2019) where the reference standard methods for muscle mass, muscle mass expression and interpretation varied. Possible reasons for our results being different are the heterogeneity in the research methods and our small sample size. In addition, the relationship between muscle mass and handgrip strength is complex as metabolic and neurological factors may play a role in developing weak handgrip strength (McGrath et al., 2020; Ramage & Skipworth, 2018).

5.9 Physical activity

Physical inactivity can be both a risk factor in the development of and a consequence of cancer, compounding loss of muscle mass. The European nutrition cancer guidelines recommend 10 to 60 minutes 3 days a week of aerobic activity and suggests resistance training to support muscle strength and mass (Muscaritoli et al., 2021). Most of our participants did not meet the minimum physical activity requirements to maintain health as determined by the global physical activity questionnaire, namely more than 600 metabolic equivalents per day.

This is unsurprising as 60% reported feeling fatigued as determined by PG-SGA. We found no cancer research that used GPAQ, most likely because it was developed by World Health Organisation to assess activity levels of entire countries' populations, rather than smaller cohorts of patients. We found 46.5% of our participants met the minimum physical activity recommendation by GPAQ. This is higher than one study investigating oesophageal cancer patients of similar age to our cohort (Guinan et al., 2018) that found 18% meeting the physical activity requirements as determined by an accelerometer method.

No significant association was found between reduced muscle mass and physical activity. This disagrees with previous cancer research (Guinan et al., 2018; Jeffery et al., 2019). Apart from our small sample size and difference in the physical activity assessment methods, reference body composition method and muscle mass expression, the cancer type also differed to ours.

5.10 Dietary information

It was evident from the semi-quantified food frequency questionnaire that the intakes of dairy, protein, fruit and vegetables were not meeting the South African food based dietary guidelines (SAFBDG). These SAFBDG were developed to simplify communication about energy and nutrient intakes and prevention of non-communicable diseases (Vorster et al., 2013). The SAFBDG's suggests 400-500ml of low-fat milk or yoghurt a day. The participants consumed less than half of the daily recommended servings equivalent to about 200ml milk per day. Animal protein provides high biological value protein, with the recommendation of a palm sized portion, equivalent to approximately 3 matchboxes at least. Participants ate the equivalent of just under 2 matchboxes per day. Plant proteins were eaten 1.2 times per week. Just under a half a serving of fruit and half a serving of vegetables were consumed daily.

The reasons for inadequate intake of dairy, high biological value protein, plant protein, fruit and vegetables are multifactorial. For our cohort of cancer patients, these may be related to the reported side effects of the cancer and treatment, and socio-economic variables. Our participants also had low consumption of sugar, high fat starchy snacks and takeaways. To the best of our knowledge, we did not find any South African cancer research related to SABDG. Despite participants' low intake of certain healthy food components according to SAFBDG, our percentage of macronutrient distribution in terms of total energy is within the acceptable range globally (Venn, 2020). There is no ideal range that promotes overall health, rather varying global ranges that account for diverse dietary patterns across countries.

The median (IQR) total energy intake of 5670 (4767 – 8383)kJ (1350; 1135-1996kcal) as calculated from the two 24 hour recalls was similar to total energy of a mixed cancer group that received conventional nutritional counselling (5368KJ or 1278kcal) but lower than the group that received intense nutritional counselling (6951KJ or 1655kcal) (De Waele et al., 2015). Compared to a head and neck cancer group, our results for both total energy and protein [47.2 (35.1-72.5)g/day] were lower than their 8400KJ (2000kcal) and 85g protein/ day intake at baseline (Arribas et al., 2017), where they were younger and mainly male, despite the majority being in stage 4 cancer. Our lower dietary results agree with the food intake box 2 of PG-SGA where 46.4% of participants reported to have a less than normal intake the past month.

Despite participants' low intake of certain healthy food components according to SAFBDG, our percentage of macronutrient distribution in terms of total energy is within the acceptable global ranges (Venn, 2020). There is no ideal range that promotes overall health, rather varying global ranges that account for diverse dietary patterns across countries.

Total energy and protein intakes were converted to kcal/kg/day and g/kg/day, respectively to determine that about half of our participants were meeting the lower end of the expected range of their nutritional requirements according to the recent European cancer nutrition guidelines of 25-30 kcal/kg of energy and 1-1.5g/kg of protein (Muscaritoli et al., 2021). Our energy intake of 25.6 (17.5-34.8) kcal/kg/day was similar to head and neck cancer patients before treatment but our protein intake of 0.9 (0.5-1.3) g/kg/day was lower (McCurdy et al., 2019). Our lower protein intake may be due to several reasons: different socio-economic characteristics as their research was based in a developed country and the impact of anti-cancer treatment. Our results are concerning as these researchers (McCurdy et al., 2019) and others (Della Valle et al., 2018) suggested that meeting the recommended energy requirements of head and neck cancer patients during treatment may not be sufficient to minimise muscle mass loss.

We found no association between dietary intake and reduced muscle mass. This contrasts with McCurdy et al., (2019) who used skeletal muscle index via CT scan, to measure muscle mass and 3 days of 24-hour recalls. It implies that our small sample size, method of measurement and expression of muscle mass with only 2 days' worth of 24-hour recalls may not be sufficient to detect an association. Unfortunately, only a limited number of cancer studies report on the details of oral intake when assessing nutritional status of head and neck cancer patients, making comparisons difficult (Dechaphunkul et al., 2013).

It is reassuring that over half of our participants were referred to dietetic services taking into account South Africa's challenges with equitable access to health care (Statistics SA, 2023a) and limited healthcare resources. Even in developed countries, Caccialanza et al., (2020) found that the needs of cancer patients were not met in terms of diagnosing malnutrition and implementing clinical nutrition timeously (Caccialanza et al., 2020). Of the 46.4% that were not referred to dietetic services, all apart from 1 participant expressed a need to see a dietitian. Our percentage is higher than outpatients from

Norway who wanted more attention on nutrition and weight loss (Vagnildhaug et al., 2018). It suggests that our participants appear to have a poorer nutritional status and more nutrition-related issues than their out-patients.

Half of our participants received oral nutritional supplements (ONS), with Ensure being the most frequent ONS taken a median of 1.0 (1.0-2.0) portion and 1.8 (1.0-4.8) times per day. We only calculated the nutritional composition of the supplements taken if mentioned in the two 24-hour recalls. A review by Kim et al., (2016) found that ONS provided 400-640 kcal per day, equivalent to about 2-3 portions of Ensure daily. No daily protein as provided by ONS was reported by these researchers (Kim & Sung, 2016). Our results imply that the amount of ONS taken by the majority of participants was lower than ONS amounts in research investigating nutritional impact of ONS on cancer patients. This suggests that, despite half of our participants receiving ONS, it is not adequately taken and insufficiently adds energy and protein to the daily requirements.

5.11 Nutrition risk and assessment

More than two thirds of participants were nutritionally at risk as per NRS-2002. The recent clinical cancer nutrition and GLIM guidelines suggest nutritional screening in clinical situations with any validated screening tool (Cederholm et al., 2019) to assess nutritional status (Muscaritoli et al., 2021) and, ideally, initiate multimodal interventions (Arends et al., 2021). Our results are different to four cancer research groups that used NRS-2002 as a screening tool, where nutritional risk ranged from 28% to 38% in mainly patients with colorectal, lung cancer (Du et al., 2017; Ruan et al., 2022) and head and neck cancer (Hsueh et al., 2021; Orell-Kotikangas et al., 2015). Nutritional risk is higher in our cohort despite these cancer research groups reporting similar or higher prevalence of metastases. Only one study of colorectal cancer patients reports a slightly higher nutritional risk at 76%, with metastases reported 74% to 85% and a slightly older cohort (Ziętarska et al., 2017). Henriksen et al., (2022) used only the 4 questions in the initial screening section – as still predicts morbidity and mortality and easier to use – and found their colorectal patients 37% at nutritional risk (Henriksen et al., 2022). We found 85.7% at risk when only the first screening section was used. Our small sample size, difference in socio-economic circumstances, variety of 3 different cancer types at different points in the cancer trajectory may explain our higher malnutrition prevalence than other cancer related research.

We found a statistically significant association between NRS-2002 score and reduced muscle mass (RMM). Our results are similar to other cancer research mainly focused on gastric cancer that determined RMM using CT scans and investigated post-operative complications (Fang et al., 2021; Shi et al., 2019) but differed from research that found no association with RMM and pre- and post-neoadjuvant therapy. Our lack of association between RMM and NRS-2002 category of nutritionally at risk may be due to our small sample size of heterogenous cancer types at different cancer trajectories.

As derived from using the patient-generated subjective global assessment (PG-SGA), malnutrition, at 92.9%, is extensively found in our patient population. Our prevalence is above the estimation that 40-80% of all cancer patients experience malnutrition. Our cohort of participants are categorised as 64.3% moderately and 28.6% severely malnourished. No other research within the last five years were found that had higher prevalence of moderately (ranging from 12.2% to 41.8%) and severely (ranging from 3% to 11.9%) malnourished patients than our cohort (da Silva Couto et al., 2023; de Sousa et al., 2022; Djordjevic et al., 2022; Wang et al., 2021). The majority of these were advanced CRC and mixed cancer patients of similar age apart from one group (Djordjevic et al., 2022).

Research that reported about a third of participants malnourished (not separating moderately and severely malnourished categories) using PG-SGA, both Orell et al., (2022) and Souza et al., (2020) had participants where the majority had not received any anti-cancer treatment (Orell et al., 2022) yet or no anti-cancer treatment within 3 months of recruitment into the study (Souza et al., 2020). Our participants received anti-cancer treatment a median 1.0 (0.0-2.0) months ago, with 32% on chemotherapy at recruitment. This may partly explain our high malnutrition prevalence as anti-cancer treatment is known to cause malnutrition. In addition, our small sample size, difference in socio-economic circumstances, variety of 3 different cancer types at different points in the cancer trajectory may explain our results.

The PG-SGA allows nutritional triage, where 71.4% of our participants required critical need for improved symptom management and / or nutrient intervention options. To our knowledge, within the last 5 years, only one other research group reported the nutritional triage score. Mendes et al., (2020) reported that 53.9% of their Brazilian in-patients with cancer required critical need; they too reported a high malnutrition prevalence of 82.4% (Mendes et al., 2020). The nutritional triage recommendation informs that all our participants require input regarding their symptom control, which links to their expressed need of having or wanting to see a dietitian.

Very few studies reported on the separate components of PG-SGA. For box 3 of PG-SGA, participants mostly experienced fatigue, followed by loss of appetite, dry mouth and early satiety. Zhang et al., (2021) reported loss of appetite, pain, early satiety and nausea as the most frequent nutrition impact symptoms in patients with advanced stages of colorectal cancer. Our patients may have had their pain and nausea controlled as analgesia and anti-emetics were mostly prescribed. For box 2 of PG-SGA, the majority (46.6%) of participants reported eating less than usual amounts. This ties in with the many identified nutritional impact symptoms and oral intake data barely meeting minimum requirements. For box 4 of PG-SGA, most participants reported being up and about fairly normally. We intentionally recruited participants that mobilised fairly normally as they needed to travel to have DEXA measurements. Most participants (75%) were found to be in global (muscle and fat) deficit as per the physical examination, worksheet 4 of PG-SGA.

We found a statistically significant association between PG-SGA score and reduced muscle mass. This is similar to results from Gao et al., (2022) where 432 Chinese gastrointestinal cancer patients were found

to have significant and negative correlation with increased PG-SGA score and reduced muscle mass, determined by CT scan and expressed as skeletal muscle mass using Chinese reference population (Gao et al., 2022).

There was no statistically significant association between PG-SGA categories and reduced muscle mass. Djordjevic et al., (2022) found similar results with a small sample of 57 colorectal cancer patients that had curative surgery (Djordjevic et al., 2022). Souza et al., (2020) found statistically significant association between PG-SGA categories and reduced muscle mass. They had a bigger sample size of 188 colorectal cancer patients with a similar participant profile to ours but used CT scan expressed as skeletal muscle index as a reference (Souza et al., 2020). Our small sample size can explain our results that are similar to Djordjevic et al., (2022).

5.12 Anthropometric measurements, Dual energy X-ray absorptiometry (DEXA) and body composition

More than a third of participants had significant weight loss of >5% in 1 month and half had significant weight loss >10% in 6 months. Weight loss, even as little as 2.4%, has been related to decreased survival in cancer patients (Martin et al., 2015). The calculations for percentage weight loss were mainly from documented weights in medical notes. However, in our resource limited settings within South Africa, calibrated scales are not always available (La Grange et al., 2021).

Most of our participants had a normal BMI, even though the majority were malnourished, and had reduced muscle mass. BMI is not able to discriminate between fat mass and fat free mass which are necessary components to assess nutritional status to add prognostic information (Madden & Smith, 2016). Our median BMI of 20kg/m^2 is similar to research focused on advanced mixed cancer Brazilian patients, even though they had a slightly older female dominant cohort. Other studies found higher BMI (25.8kg/m2) in English patients with colorectal cancer that were older and were awaiting surgery; BMI of 27kg/m2 in colorectal patients with cancer majority in stages 3 and 4 but 63% did not have any treatment 3 months before recruitment (Souza et al., 2020). As the majority of our participants had two treatments a median on 1 month ago, it infers the impact of anti-cancer treatment upon weight loss and in turn muscle mass loss as supported by previous research (Blauwhoff-Buskermolen et al., 2016; Ferrão et al., 2020). Perhaps not surprising then, that we found a statistically significant association between RMM and the continuous BMI variable, but not BMI <18.5kg/m^2 (likely due to small sample size). Only two studies were found that compared BMI to muscle mass loss. These authors reported significant associations between BMI and muscle mass loss, using CT scans expressed as skeletal muscle index as the reference standard (Lidoriki et al., 2019; Souza et al., 2020). Interestingly, out of our three participants that had BMI ≥ 25kg/m^2, one had RMM.

Two thirds of participants had low calf circumferences. It is well established that in elderly populations, calf circumference is a marker of muscle mass (Barbosa-Silva et al., 2016; Gonzalez et al., 2021). Our results are similar to da Silva et al., (2019) but other researchers found lower percentages of participants with low calf circumferences, even though the same cut-off points were used (Sousa et al., 2020; Souza et al., 2020). Our median BMI is similar to da Silva et al., (2019), with higher BMIs reported by Sousa et al, (2020) and Souza et al., (2020). When we used an adjusted calf circumference according to BMI, only 50% of participants had low calf circumference. This may explain the discrepancy in the results as adiposity is accounted for using adjusted calf circumference (Gonzalez et al., 2021). We had a third of participants with BMI <18.5kg/m2 that had an upward adjustment of calf circumference and 3 with a downward adjustment. As Sousa et al, (2020) and Souza et al., (2020) had cohorts with higher BMIs, they had lower participant percentages meeting the low calf circumference categories. We did not find cancer research reporting the use of adjusted calf circumferences perhaps as Prado et al., (2022) cautions on adjusting calf circumference for unwell patients that are underweight as Gonzalez et al., (2021) research was on a healthy population.

We found that percentage fat mass varied depending on the method used. It has been established that DEXA is a validated method for total and regional total fat mass in clinical patients (Sheean et al., 2020). Only two participants were identified as under fat for %FM via skinfold thickness; 5 according to %FM via DEXA; 12 according to FMI via DEXA. Our results suggest, despite following protocols for anthropometric methods and using trained field workers, that using skinfold thickness to determine %FM may be subject to technical error (Kuriyan, 2018; Madden & Smith, 2016) in comparison to reference standard DEXA.

There were no significant differences in percentage fat mass via skinfold thickness in the reduced muscle mass group or the group identified as cachexic. This may be due to only 2 participants being identified as under fat. We could not trace similar research to compare results to. We did not compare %FM and FMI derived from DEXA with RMM nor cachexia groups. Despite the consensus definition of cancer cachexia that includes with or without fat loss, several studies have demonstrated loss of fat mass with anti-cancer treatment with RMM (de Carvalho et al., 2015; Tamandl et al., 2016).

Using our reference standard DEXA, RMM was presented in five different ways with 32% to 96% variation. Most cancer research, when using DEXA as a reference standard, tends to present RMM via ASMI obtained from Baumgartner et al., (1998) who determined cut-off points less than two standard deviations from the mean of a younger and smaller reference population. Cruz-Jentoft et al., (2019) suggests using ASMI cut-off points determined via Gould et al. (2014) where the reference population were largely heterogenous young Caucasian Australians. Cruz-Jentoft et al., (2019) also suggests using ASM cut-off points determined by Studenski et al., (2014) who used a very large diverse ethnic reference population but were older than 65 years.

Studenski et al. (2014) also presented RMM via ASM standardized by BMI. No cancer research was found that represented RMM by ASM/BMI. The reason may be that, for healthy populations standardizing ASM by BMI is acceptable. However, for populations that are unwell with chronic conditions like cancer, this may not identify patients with RMM that are underweight as was found in our cohort.

Kelly et al., (2009) provides z-scores for ALM that are used to determine percentiles where a large reference multi-cultural American population was used that were majority overweight. As ALM includes the bone, no cancer research was found that used this presentation for RMM.

It is suggested that reference data from MM via DEXA may need to be developed accounting for different DEXA machines, for different countries and ethnicities (Cruz-Jentoft et al., 2019). We chose ASM as our representation for RMM as it overlapped most with other presentations of MM when taking each participant into account. Ideally, developing cut-off points for MM from representative reference populations is aspirational for our South African context. As MM correlates with body size, and not only influenced by age, gender, and ethnicity, it may be helpful to standardize MM by height or weight. However, there is no consensus what the best method of standardization should be and whether can be used across different populations, including healthy and unwell (Cruz-Jentoft et al., 2019).

We calculated the effect size for the individual nutritional status indicators and RMM and acceptable MM groups. Of those indicators that were significantly different, BMI, MUAC and calf circumference had medium effect sizes i.e., 0.4 to 0.6. However, albumin had the highest effect size at 0.6, but there were too few participants to detect a statistically significant difference in the 2 groups.

CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

Determining body composition, in particular muscle mass, is important for the assessment of nutritional status and the diagnosis of malnutrition, sarcopenia and cancer cachexia. Our aim was to identify alternative muscle mass markers, commonly used in clinical practice, for assessing reduced muscle mass, using the reference standard, DEXA in patients attending oncology clinics at a large tertiary hospital in Cape Town, South. Out of the six muscle mass methods, we found that calf circumference performed the best overall with fair sensitivity and specificity, fair Cohen's agreement and percent agreement of 79%. However, taking all the statistical tests into account, there is insufficient agreement for calf circumference to be a proxy for reduced muscle mass. It could possibly be used as a screening tool to correctly identify participants with acceptable muscle mass 80% of the time. Our results infer that, if our sample size were larger, calf circumference may have demonstrated better agreement with DEXA. Calf circumference is a simplistic anthropometric measurement that can be easily performed in any clinical setting with minimal training and equipment. Ideally, ethnic specific cut-off points should be considered, both for calf circumference and DEXA measured muscle mass.

Considering the nutritional status indicators routinely used as part of nutritional assessment, our results were difficult to interpret as they do not clearly demonstrate that any could be used as alternatives to identifying reduced muscle mass. With a larger sample size, NRS-2002 may hold the most promise either as a proxy or to screen for reduced muscle mass taking all three tests into account (sensitivity / specificity; Cohens' ƙ; percentage agreement).

There is no gold standard method identified for nutritional status assessment. Most recently, guidelines have suggested the inclusion of body composition assessment, which includes muscle mass. Our different nutritional status indicators that were associated with reduced muscle mass namely BMI, MUAC, calf circumference, percentage body fat through skinfold measurements, NRS-2002, PG-SGA and potentially albumin (as large effect size despite $P < 0.05$), need to be possibly considered as indicators of reduced muscle mass when used in nutritional status assessment.

When identifying malnutrition using GLIM without access to technical methods, calf circumference could possibly be used as a proxy for the phenotypic criteria of reduced muscle mass in our research cohort. As >80% for both sensitivity and specificity could be interpreted as good validity, the 66.7% specificity for calf circumference may be interpreted as 33.3% incorrectly identified as not malnourished; or the 96.4% sensitivity may be interpreted as 3.6% incorrectly being identified as malnourished. Calf circumference performed better than the other clinical approaches, namely corrected arm muscle area, adjusted calf circumference, mid upper arm circumference, estimated ASM and global physical examination. Caution needs to be taken as we acknowledge the different approaches of GLIM that may need to be accounted for. Our research focused on using cancer to meet the aetiologic criteria of inflammation and used DEXA expressed as ASM.

Despite the GLIM recommending step 1 to be nutritional screening, our research demonstrated that patients were being identified as malnourished even when no nutritional risk was indicated. This may infer the need not to nutritionally screen all patients. However, it may also be related to our choice of screening tool used.

Sarcopenia is a distinct condition from malnutrition, with identification of weakness followed by reduced muscle mass needed for its diagnosis. Of the five estimated muscle mass methods, four could possibly be used as alternative markers for identifying reduced muscle mass in our cancer cohort when using the recent sarcopenia diagnostic guidelines. These clinical methods include calf circumference, adjusted calf circumference, corrected arm muscle area, global physical examination. As there is a risk that 40% of patients with sarcopenia may not be correctly diagnosed, caution may be needed when using worksheet 4 of PG-SGA for global physical examination. MUAC is not recommended as an alternative for muscle mass estimates in the diagnosis of sarcopenia.

Cancer cachexia is a multi-factorial syndrome commonly experienced by cancer patients that has negative clinical and patient outcomes. There is still no global consensus on the diagnostic criteria and none of our three diagnostic frameworks agreed with our chosen reference standard for cancer cachexia, as suggested by Arends et al., (2021). This suggests that these frameworks' diagnostic criteria and methods are dissimilar. More research is needed to investigate additional diagnostic criteria that include impact of symptoms, quality of life and impaired physical activity (Arends et al., 2023). There is an understanding that cancer cachexia is a multi-organ disorder involving adipose tissue, brain, heart, liver and gut with inflammation being a central component. Therefore, future research should incorporate multi-organ research to better understand cancer cachexia (Sayers et al., 2023).

There are no clear indications from our results that suggest that any of the common nutritional status indicators can be used to identify cancer cachexia. Only handgrip strength and albumin are significantly different in the cancer cachexia group.

The obvious limitations of this study include our small sample size that produced some small effect sizes. Because of our small cohort, we may have missed significant findings as our research is underpowered at a value of 0.29 for the Mann Whitney U results and 0.19 for the Fisher Exact results. In addition, the heterogenous nature of our cohort that includes different cancer types, cancer stages, management decisions (palliative, curative), different types of treatment, numbers of treatment and timing of treatments has an added impact on our results.

Specific limitations that are relevant to our context are as follows:

- Regional or national normative reference populations do not exist for South Africa, therefore no ideal reference populations exist to compare DEXA muscle mass expressions, handgrip strength, calf circumferences, estimated ASM.

- Our cohort comprised of multiple ethnicities, but we used white ethnicity in Santos et al. (2019) equation for estimating ASM. We did this to be consistent as the DEXA variable for ethnicity that was used consistently when taking measurements was white ethnicity as inputted by the radiographer when operating the DEXA machine.
- We chose DEXA ASM as our comparator throughout our research. However, Wobith et al., (2022) compared BIA and CT MM results using GLIM in cancer patients and found that, despite both methods associated with post operative complications, prevalence, sensitivity and specificity for malnutrition differed depending on the MM method.
- Accuracy of kappa is questionable due to small numbers in the categorised groups.
- Selection bias existed in our cohort as many patients declined participation due to feeling unwell.
- We did not control for any confounding factors that may have impacted muscle mass, namely treatment timing and numbers, cancer stage and type, age, gender.
- Not measuring the change in muscle mass over time is a limitation as our current research is simply a snapshot view of our cohort.
- Our cohort is a small representation of only patients that are under a tertiary hospital's care within a particular region in Western Cape, South Africa and results cannot be translated to different care facilities or regions within South Africa.
- Four different field workers were used to collect data and inter-rater discrepancy could have occurred; however, we did thorough training of field workers to standardise the research.
- Consideration of which screening tool to be used for our research as using NRS-2002 did not identify patients at nutritional risk that were identified as malnourished via PG-SGA.

With considering the general and specific limitations, we do also acknowledge the strengths of our research as follows:

- Our research included a good combination of methods, namely the use of a variety of validated nutrition screening/diagnostic tools, the use of DEXA to compare muscle mass and the inclusion of biochemical indicators
- Registered dietitians that collected the data
- The inclusion of alternative muscle mass markers that are easily implemented within resource limited settings such as an outpatient clinic at a tertiary hospital based in South Africa
- The inclusion of participants from the Cape Town metropolitan area where the availability of data on such resource limited settings are limited

In summary, considering all the different clinical approaches for alternative muscle mass markers, calf circumference potentially may be used to identify reduced muscle mass and as part of the phenotype for reduced muscle mass for GLIM. Handgrip strength is needed as the first step in identifying sarcopenia, followed by the identification of reduced muscle mass where calf circumference could possibly be used as

a proxy instead of technical approaches like DEXA that are not routinely available. Within the context of cancer cachexia, handgrip strength may have potential to be used within the cancer cachexic diagnostic framework. Caution, however, is needed as our sample size is small and further research is warranted to add to the body of research, both within our South African context and further afield in Africa due to the limited research available in this area of oncology.

Despite our limitations and taking our strengths into account, our research has described the body composition of cancer patients attending a tertiary hospital's oncology clinics and we investigated the possibility of cheap, accessible and easily implementable alternatives for muscle mass assessment in clinical practice, that builds on the body of evidence, particularly in low incoming settings of South Africa.

6.2 Recommendations

Recommendations for research

Broadly,

- Within South Africa and perhaps within the Southern African Development Communities, collaborative efforts to define reference populations for DEXA muscle mass expressions, handgrip strength, calf circumferences and estimated ASM would be helpful for more accurate identification of patients rather using reference populations largely from the northern hemisphere.
- As there has been a global call from GLIM (Cederholm et al., 2019) and associated communities (Arends et al., 2023), to standardize research approaches and validate recommended frameworks, particularly across the cancer population, southern Africa needs to heed this call via strong networking and collaborative efforts.
- For cancer cachexia, using the reference framework as suggested by Arends et al., (2021), it may be helpful to determine alternative markers of muscle mass other than technical reference standards as no national or regional reference populations exist in South Africa and access to these methods are mainly only via research.
- Without a gold standard in identifying reduced muscle mass being readily available within research and clinical practice and within malnutrition, sarcopenia and cancer cachexia diagnoses, results should be compared to clinical and patient outcomes e.g. mortality, hospital admissions and length of stay, performance status and quality of life.
- In addition, results may be improved by using cutoff points that were determined from a healthy relevant population. In addition, greater homogeny in type of cancer, stage, and cancer treatment journeys would be ideal for standardisation. Furthermore, analyses of results by separating gender and age as these are confounders for muscle mass.

Recommendations for future research:

- Recruiting a larger sample size across different clinical platforms would improve the quality of our results and highlight significant findings that were undetected in our study due to it being underpowered.
- Using and comparing different expressions of muscle mass as measured by DEXA may be helpful namely ASMI as per Fearon et al., (2011) or ASMI as per Cruz-Jentoft et al., (2019) instead of ASM as there is no standardization in reference to height as taller / bigger people have more muscle mass.
- The addition of BIA to estimate muscle mass as part of the alternative muscle mass markers as it is an additional method that is mobile, more accessible without great need for high expertise in performing and interpreting data.

Recommendations for clinical practice

- As there is a high prevalence of reduced muscle mass, malnutrition and cancer cachexia within our cohort, ideally, it is recommended that all patients are screened as this is not done routinely within the healthcare facility. As limitations to staff capacity are pervasive throughout the public health department, efforts need to be made to implement simple screening tools within different levels of health care.
- Referral to dietetic services based on standardized approach, i.e., identification of at-risk patients through nutritional screening for full nutritional status assessment, that should include body composition assessment.
- As DEXA is not routinely used within our public healthcare system, easily accessible tools should be utilized to screen for or estimate reduced muscle mass. Calf circumference may have the potential to be used for screening for or estimating reduced muscle mass and as an alternative muscle mass marker for sarcopenia and for GLIM identification.
- Risk factors described in our research, namely alcohol consumption, smoking, drugs could potentially be addressed in cancer outpatient clinics as public health educational sessions.
- As albumin is associated with cancer cachexia, and CRP could be used as an inflammatory marker in cancer cachexia diagnostic framework, it may be helpful to routinely check at cancer outpatient visits.
- Handgrip strength could easily be measured as part of routine measurements taken upon visiting cancer outpatient clinic as it is the first step in identifying patients with sarcopenia and potentially to identify cancer cachexia.
- As most participants were physically inactivity, it may be helpful to have group educational sessions related to physical activity, but dependent on cancer stage.

- As there was a lack of fruit and vegetable consumption, together with inadequate protein intake, greater awareness and education needs to be provided within dietetic consultations, dependent upon cancer stage.
- For patients receiving oral nutritional supplements, frequency of taking supplements needs to be monitored and explained, dependent upon cancer stage.
- PG-SGA is a validated screening and assessment tool for cancer patients and implementation could be considered within the cancer outpatient clinic, particularly as it is associated with reduced muscle mass.
- Measuring of height and weight is routinely performed at cancer outpatient clinics. BMI calculation is helpful as associated with reduced muscle mass in our cohort.

Consideration of our clinical practice recommendations needs to be taken with the full understanding of the inherent limitations and constraints that the healthcare system is under with regards to staff capacity, funding, sheer patient numbers, healthcare processes.

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APPENDIX A: CONSENT FORM

Consent form

To investigate the nutritional status, including body composition, of oncology patients attending an outpatient clinic at two tertiary hospitals in Cape Town: A cross-sectional study

Dear Sir/Madam

You are invited to take part in our study. We want to find out more about the risk of malnutrition and body composition of people who have been diagnosed with Cancer. We know that Cancer can cause unintentional weight loss for many reasons. We are using the information obtained to investigate the nutritional status of patients attending the clinic. This may possibly help in the future identification, prevention and management of Cancer related weight loss in a timely fashion in the practical setting of a busy clinic.

This study is being conducted as part of a Masters in Dietetics degree at the University of Cape Town.

You are able to take part in the study if you:

- Are older than 18 years, younger than 70 years
- If you have been diagnosed with head and neck Cancer; near, nose and throat cancer or colorectal cancer.

You are unable to take part in this study if you:

- Are pregnant and breastfeeding
- have a pacemaker
- have severe arthritis, muscular dystrophy and / or had a recent stroke
- live more than 70km from GSH or TBH
- have a performance / functional score ≥ 3

What would be expected of you?

- Today we would like to measure your weight, height and ask you some questions about your dietary intake, physical activity and living conditions. This will take 45 - 60 minutes to complete.
- We would like to include the results of 2 blood tests either from your hospital file (if blood was drawn from you for tests) or we would like to draw about 3ml or 1 teaspoon of blood in the same way as when a sample is taken by your doctor for various tests. This will be done in a sterile way, with sterile equipment, by someone trained in the procedure. The blood will be used to measure markers of inflammation. The sample will be destroyed after being analysed.
- We would like to conduct a non-invasive body composition analysis (i.e. obtain fat free mass) at The Sports Science Institute of South Africa in Newlands (SSISA). The body composition analysis will be arranged at a time that is convenient for you and the researchers. The scan conducted is far less X-rays than a routine X-ray. Thereafter, an arm circumference, 4 skinfold thicknesses, calf circumference, handgrip strength, 24-hour dietary recall will be measured. Lastly, a test where electrodes are placed on 4 parts of your body whilst you lie down will also be conducted to measure your body composition. Your visit will take no longer than 45 - 60 minutes to complete.
- You will receive R150 when you come to SSISA for the body composition analysis.
- You will not be expected to pay for any tests or analysis completed during the research study

<u>Are there any risks or benefits to you taking part in this study?</u>

- There is negligible risk associated with this study as routine blood samples will be drawn by registered nurse and all necessary precautions in terms of drawing, storage and handling of the blood samples will be in place.
- You will receive information regarding your body composition (i.e. muscle mass, fat mass)
- You will receive information on your risk of developing malnutrition. If you have a high risk of developing malnutrition or identified as being malnourished, you will receive nutritional information to help you. The Consultant will receive a report related to the information that was gathered regarding your nutritional risk. You may be advised to see the Dietitian that provides a service at this hospital.

Your confidentiality will be protected at all points in the study. Your name and personal information will not be given to anyone and all study information will be stored on a computer database that can only be accessed and used by study researchers. This study has also been

approved by the UCT, Faculty of Health Sciences, Human Research Ethics Committee (Reference number: 763/2018). This study will be performed in accordance with the principles of the Declaration of Helsinki (2013), Good Clinical Practice (GCP) and the laws of South Africa, meaning it is safe and ethical. You are allowed at any point to withdraw from the study, without providing reason.

For any other information regarding the study, please contact the study supervisor, Dr Janetta Harbron or the master's student, Megan Blacker, on:

Email: janetta.harbron@uct.ac.za Number: 021 406 6769

Email: megan.blacker@uct.ac.za Number: 084 725 4758

You may contact the UCT Human Research Ethics Committee on 021 406 6338 if you have any questions regarding your rights and welfare as a participant on this study.

I, _____(Full name) have read and understood the information provided above and have asked and had answered any further questions I may have had.

By signing this consent form, I voluntarily agree to participate in this study. I understand that I may withdraw at any time without giving reason.

Signature (Participant):_____ Date:_____

APPENDIX B: QUESTIONNAIRE PHASE ONE

<table>
<tr><th colspan="6">PATIENT INFORMATION FROM MEDICAL FILE</th></tr>
<tr><td colspan="3">DATE:</td><td colspan="3">INTERVIEWER NAME:</td></tr>
<tr><td colspan="6">1. Patient details (see medical notes)</td></tr>
<tr><td colspan="6">DOB (dd/mm/yy):</td></tr>
<tr><td>Gender Circle</td><td colspan="2">1. Male</td><td colspan="3">2. Female</td></tr>
<tr><td colspan="6">2. Medical conditions (see medical notes)</td></tr>
<tr><td>1. Type of Ca</td><td colspan="5"></td></tr>
<tr><td>2. Stage of Ca (T / N / M) if available</td><td colspan="5"></td></tr>
<tr><td>3. Management planned / received Circle</td><td colspan="2">1. Treatment</td><td colspan="2">2. Palliative</td><td>3. Unknown</td></tr>
<tr><td>4. Treatment type planned/ received Circle</td><td>1. Radiation</td><td>2. Chemotherapy</td><td colspan="2">3. Surgery (document surgery type)</td><td>4. Nil</td></tr>
<tr><td>5. treatment date (d/m/yyyy) and duration (days)</td><td></td><td></td><td colspan="2"></td><td></td></tr>
<tr><td>6. cancer diagnosis date (1st date seen at LE clinic)</td><td colspan="5"></td></tr>
<tr><td>7. Other co-morbidities circle</td><td colspan="3">1. Hypertension
2. Hypercholesterolaemia
3. Cardiovascular disease
4. Diabetes / insulin resistance
5. Arthritis</td><td colspan="2">6. Other:</td></tr>
<tr><td>8. Chronic medications prescribed (from most recent list in medical file)</td><td colspan="5"></td></tr>
<tr><td rowspan="2">9. Reason for clinic appointment

Circle</td><td colspan="2">1. Initial</td><td>2. completion of treatment</td><td colspan="2">interruption of treatment:
3. self or
4. doctor</td></tr>
<tr><td colspan="2">5. patient request</td><td colspan="2">6. treatment (chemo)</td><td>7. <u>other (provide reason):</u></td></tr>
</table>

				_____	
10. Document <u>any</u> weights in medical notes (include more than 6 months ago; do not ask patient; after interview, copy the dates and weights to questionnaire phase 2 question 1: anthropometry)		Date	Weight	Date	Weight

3. Socio-economic information (ask patient)					
1. Marital status *Circle*	1. Married	2. with partner	3. Divorced	4. single	5. Widowed
2.Employment *Circle*	Employed 1. Part time 2. full time	3. retired	4. student	5. too sick to work	
	6. homemaker	7. Unemployed (looking)	8. Unemployed (not looking)		
3. Receipt of grant *Circle*	1. Yes	2. No			
4. Living conditions *Circle*	1. house	2. flat	3. informal structure		
5. Number of people living with you	Adults ≥ 18 years: _____	children < 18 years: _____			
6. Highest education *Circle*	5. highest grade at school: _____				
	1. certificate post grade 12	*2. degree*	*3. diploma*		
	4. other (provide reason): _____				

4. **Anthropometry**		
1. Height	_____ cm	**At end of data collection:** **If > 18.5 kg/m², then give dietary guidelines for healthy eating** **If < 18.5 kg/m², then give GSH High energy high protein guidelines; GSH recipe for nutritious drinks (use own discretion)**
2. Present Weight	_____ kg	
3. Calculate BMI	_____kg/m²	

5. **Risk factors for cancer**							
1. Do you smoke cigarettes? *Circle*	*1. Yes* *2. No*	If yes, how many cigarettes	per day? _____	per week? _____			
2. Did you smoke? *Circle*	*1. Yes* *2. No*	If yes, how many cigarettes	per day? _____	per week? ____	how long ago did you stop? (Months / years) _____		
3.1 Do you drink alcohol? *Circle*	*1. Yes* *2. No*	If yes, how much (circle all relevant)? tot 25ml glass wine 120ml beer 340ml commercial sorghum beer 3% 500ml)	ml / day? _____ _____ _____ _____	ml / week? _____ _____ _____ _____	ml / month? _____ _____ _____ _____		
3.2 Did you ever drink alcohol? *Circle*	*1. Yes* *2. No*	If yes, gauge past intake (ask about frequency and amount)					

4.1 Do you use any drug substances? *Circle*	*1. Yes 2. No*	If yes, what substances _____	per day? _____	per week? _____	per month? _____
4.2 Did you ever use any drug substances? *Circle*	*1. Yes 2. No*	If yes, gauge past use (ask about frequency and amount)			

6. The next questions are about the time you spend doing different types of physical activities. You need to think about the time that you spend doing both vigorous and moderate activities in a usual week.

- 'vigorous-intensity activities' are activities that require strenuous physical effort and cause large increases in breathing and heart rate. *Refer to the appropriate pictures when asking patient.*
- 'moderate-intensity activities' are activities that require moderate effort and cause small increases in breathing and heart rate. *Refer to the appropriate pictures when asking patient.*

You need to think about all the activities you do at home, at work, travelling from place to place and during you spare time.

Work related Physical Activity (paid or unpaid work outside your own home). If you are unemployed, think about the things that keep you physically active during the day.
When answering the following questions, think back over the past 12 months and consider (think of) a usual week.

1.	Does your work involve vigorous activities that cause large increases in breathing or heart rate, (like heavy lifting, digging, or heavy construction; show pictures) for at least 10 minutes at a time?	*Circle* *1. Yes* ***2.*** *No (Go to question 4)*
2.	In a usual week, how many days do you do vigorous activities as part of your work?	_____ days
3.	On a usual day on which you do vigorous activities, how much time do you spend doing such work?	_____hours _____minutes
4.	Does your work involve moderate-intensity activities that cause small increases in breathing and heart rate (like brisk walking or carrying light loads; show pictures) for at least 10 minutes at a time?	*Circle* *1. Yes* *2. No (Go question 8)*
5.	In a usual week, how many days do you do moderate- intensity activities as part of your work?	_____ days
6.	On a usual day on which you do moderate-intensity activities, how much time do you spend doing such work?	_____hours _____minutes
7.	How long is your usual workday?	_____hours

		_____minutes
Travel-related Physical Activity: Other than activities that you've already mentioned, I would like to ask you about the way you travel to and from places (to work, to shopping, to market, to church, etc.)		
8.	Do you walk or use a bicycle (pedal cycle) for <u>at least 10 minutes</u> at a time to get to and from places?	*Circle* *1. Yes* *2. No (Go to question 11)*
9.	In <u>a usual week</u>, how many days do you walk or cycle for at least 10 minutes to get to and from places?	_____ days
10.	On <u>a usual day</u>, how much time do you spend walking or cycling for travel?	_____hours _____minutes
Non-work Related and Leisure Time Physical Activity: The next questions exclude the work and transport activities you have already mentioned. Now I am going to ask you about activities you do for sport, fitness or recreation in your leisure or spare time.		
11.	Do you do any **<u>vigorous intensity</u>** sport, fitness or recreational activities in your leisure or spare time, that cause large increases in breathing or heart rate (like running or strenuous sports, weightlifting) for <u>at least 10 minutes</u> at a time?	*Circle* *1. Yes* *2. No (Go to question 14)*
12.	In <u>a usual week</u>, how many days do you do <u>vigorous</u> activities as part of your leisure or spare time?	_____ days
13.	How much time do you spend doing this on <u>a usual day?</u>	_____hours _____minutes
14.	Do you do any <u>moderate-intensity</u> sport, fitness or recreational activities in your leisure or spare time that cause small increases in breathing and heart rate (like brisk walking, cycling or swimming) for <u>at least 10 minutes</u> at a time?	*Circle* *1. Yes* **2.** *No (Go to question 17*)
15.	In <u>a usual week</u>, how many days do you do <u>moderate-intensity</u> activities as part of your leisure or spare time?	_____ days
16.	How much time do you spend doing this on <u>a usual day</u>?	_____hours _____minutes
Sitting/Resting Activity: Now I would like to ask you about the time spent sitting or resting, not including sleeping, <u>in the past 7 days</u>. This may include time sitting at your desk, riding in a car or taxi, visiting friends, reading or sitting down to watch television <u>during work hours and spare time</u>**.**		
17.	Over the <u>past 7 days</u>, how much time did you spend sitting or reclining (lying) on a <u>usual WEEKDAY</u> (excluding sleeping)?	_____hours

		_____minutes
18.	Over the <u>past 7 days</u>, how much time did you spend sitting or reclining (lying) on a <u>usual WEEKEND DAY</u> (excluding sleeping)?	_____hours _____minutes

7. Dietary questions: dietary recall (multiple pass method)

Sheet 1: 24-hour dietary recall Summary

Time	Step 1: food and beverage intake during previous 24 hours	Step 2: Forgotten food and beverages

Sheet 2: Recording sheet for information collected in summary of 24-hour dietary recall

Time	Food item (from sheet 1)	Description of food item, preparation	Description of portion size	Serving amount	Food group

Sheet 3: Ask the patient to sort the cards into 2 piles – food items that they have eaten in the past month and food items that they have not eaten in the past month. Ask them how often in the past month they have eaten the food on the cards they have selected – per month, week or day. Briefly record any other comments they mention.

Food item *(circle option/s that are applicable)*		**Frequency**					
		Circle tool used to describe amount eaten	**Amount eaten at a time**	**Daily**	**Weekly**	**Monthly**	**comments**
Red meat							
1	Beef / lamb / pork (with or without fat)	Matchbox					
2	lean / regular mince	1 Tsp					
3	bacon	Rasher x 2					
Processed and tinned meats							
4	Vienna polony / ham Tinned meat	42g standard size 2 thin slices 1 rounded Dsp					
5	Boerewors / sausage / pork bangers	Diameter x length in cm					
6	Chicken eaten with or without skin	matchbox					
7	Fish tinned / grilled / smoked / baked	1 ½ Matchbox					
8	Eggs (fried / boiled / poached / scrambled)	Small Medium Large Extra large					
9	Organ meats (liver / kidney)	Matchbox					
Dairy products							
10	Milk in cereal / tea coffee / drink	1 cup					
11	Sour milk/ amasi or buttermilk	1 cup					
12	Coffee creamer	8 tsp					
13	Condensed milk	spoons					
14	Yoghurt sweetened or unsweetened	3 H Dsp (100ml)					
15	flavoured milk	150ml / half of std size (300ml)					
16	Drinking yoghurt	100ml					
17	Hard cheese	matchbox					
Starchy products							
18	Bread or rolls	Slices x 1 ½ roll					
19	Breakfast cereals e.g Flakes / All bran Weetabix Pronutro Muesli	 ½ cup 1x ¼ cup ¼ cup 2 Tsp					

	Futurelife						
20	Cooked porridge e.g soft maize /mageau /maltabella / oats Stiff maize	½ cup ¼ cup					
21	Pasta / rice barley / samp	½ cup 1/3 cup					
		Circle tool	**Amount eaten at a time**	**Daily**	**Weekly**	**Monthly**	**comments**
22	Beans /split peas / lentils / chickpeas soy / soya mince/	1/2 cup cooked					
23	Potato roast / boiled mash	1 medium ½ cup					
24	Instant soup / instant noodles	1 sachet 1 packet					
All fruit							
25	Medium fruit Small fruit e.g. plums Banana Grapes Melon Fruit salad	any medium 2 X 1 small 8 1 cup cubes ½ cup					
26	Avocado pear	¼ medium					
27	Dried fruit: type	Amount					
All vegetables							
28	Raw veg / salad	1 cup					
29	Cooked veg	½ cup					
30	Butternut Corn / sweet potato	¼ cup 1 Dsp					
Oils and fats							
31	Soft / Brick margarine on butter on bread, vegetables etc.	1 tsp					
32	Oil in cooking	1 tsp					
Spreads and snacks							
33	Biltong Droe wors	handfuls length					
34	Peanut butter	1 Dsp					
35	Peanuts / nuts	Dough model or handfuls					
36	Salty popcorn	1 ½ cups					
37	Crisps						
38	Pies	Diameter and thickness in cm					
39	samoosas	Length of sides in cm					
40	sausage rolls	Length in cm and diameter					
Take out foods		Describe amount					

41	Fried chicken						
42	Fried chips						
43	Fried fish						
44	Pizza						
45	Gatsby						
46	Burger						
47	Vetkoek / fat cakes						
48	Roti						
Sugary foods and drinks							
49	Sugar	tsp					
50	Jam / syrup / honey	tsp					
51	Chocolate	Describe					
52	Sweets	Describe					
53	Jelly / instant puddings	Cup or spoons					
		Circle tool	**Amount eaten at a time**	**Daily**	**Weekly**	**Monthly**	**comments**
54	Ice-cream	Cup or spoons					
55	Cakes Tarts Sweet biscuits	matchbox 2 small					
56	Doughnuts / koeksisters / eclairs	Describe amount					
57	Gassy Cool drinks (excluding lite or SF)	Cup Tall / small Glass 200ml 330ml 440ml 500ml					
58	Fruit juice	Glass					
59	Cooldrinks made with water	Tall / small Glass					

8.Dietetic information				
1. Vitamin and mineral supplement *Circle*	*1. Yes*	*2. No*	If yes, name of product: _____	Amount taken: _____ per day or _____per week
2. Herbal supplement *Circle*	*1. Yes*	*2. No*	If yes, name of product: _____	Amount taken: _____ per day or _____per week
3. Have you been referred to see a Dietitian for Cancer diagnosis				*Circle* *1. Yes* 2. *No*
4.If yes, have you seen the Dietitian for cancer?				*Circle* *1. Yes* *2. No*
5.If no, would you like to see a Dietitian?				*Circle* *1. Yes* *2. No*
6.If yes, reason	_____			

7. Are you receiving any oral nutrition supplements (ONS)?	*Circle* *1. Yes* *2. No*
8.If yes, which ONS? Standard portion (1 carton or 200ml – 250ml) _____	How many standard portions per day? _____ ml

9. Biochemistry Complete NHLS yellow form with patient sticker on plastic sleeve and participant number on test tube. For NHLS, participant code	
1. Albumin 35 – 52g/l	_____
2. CRP < 10mg/l	_____

APPENDIX C: PARTICIPANT QUESTIONNAIRE PHASE TWO

(Request participant to empty bladder before starting)

9. ANTHROPOMETRY DATE:_____ INTERVIEWER NAME:_____		
1.Present weight	_____kg	
2.Usual healthy weight	_____ kg or if unknown, skip to question 5	
3. Is the present weight and usual weight different?	*Circle* *3. Yes* *4. No*	
4.If yes, when did change in weight start?	_____weeks/ months ago	
5. Calculate BMI (use for NRS score, see below)	_____kg/m^2	*If < 18.5 kg/m^2, then give enrichment dietary sheet; if > 18.5 kg/m^2, then give FBDG sheet*
6. Weight 1 month ago (check questionnaire phase 1, if nil documented, ask patient)	_____kg _____date or unknown	Percentage weight loss_____% *Use % weight loss for NRS score (see below)*
7. Weight 2 month ago (check questionnaire phase 1, if nil documented, ask patient)	_____kg _____date or unknown	Percentage weight loss_____% *Use % weight loss for NRS score (see below)*
8. Weight 3 months ago (check questionnaire phase 1, if nil documented, ask patient)	_____kg _____date or unknown	Percentage weight loss_____% *Use % weight loss for NRS score (see below)*
9. Weight 6 months ago (check questionnaire phase 1, if nil documented, ask patient)	_____kg _____date or unknown	Percentage weight loss:_____% *Use this % weight loss for PG-SGA score (see below)*
10. Weight more than 6 months ago (check questionnaire phase 1, if nil documented, ask patient)	_____kg _____date or unknown	Calculate percentage weight loss:_____%
11. If past weight not known, then ask about clothes being too big, jewellery not fitting and / or adjusting belt size within last month.	*Circle* *1. Yes* *2. No*	*Score 3 points for PG-SGA worksheet 1; score 3 points for NRS-2002 under final screening*
12. If Yes, then ask when changes noticed	_____ weeks / months ago or unknown	

10. Nutritional screening **(fill in any relevant information already received from patient; use plate diagram for table 2)**

Nutritional Risk Screening (NRS 2002)

Table 1: Initial screening			
1	Is BMI <20.5	Yes	No
2	Has the patient lost weight in the last 3 months?		
3	Has the patient had a reduced dietary intake in the last week?		
4	Is the patient severely ill? (e.g. in intensive therapy)		
Yes- If answer is yes to any, the screening Table 2 is performed			

(*Turn to next page for table 2)*

Table 2: Final screening			
Impaired nutritional status		**Severity of disease ~ increase in requirements**	
Absent **Score 0**	Normal nutritional status	Absent **Score 0**	Normal nutritional requirements
Mild **Score 1**	Wt loss > 5 % IN 3 MONTHS OR Food intake below 50-75% of normal requirements in preceding week	Mild **Score 1**	Hip fracture, chronic disease patients, in particular with acute complications: cirrhosis, COPD, chronic hemodialysis, diabetes, oncology
Moderate **Score 2**	Wt loss > 5% in 2 months **or** BMI is 18.5-20.5 **+**Impaired general condition or Food intake below 25-60% of normal requirements in preceding week	Moderate **Score 2**	Major abdominal surgery, stroke, severe pneumonia, hemolytic malignancy
Severe **Score 3**	Wt loss > 5% in 1 month (>15% in 3 months) **or** BMI <18.5 **+**Impaired general condition or Food intake below 0-25% of normal requirements in preceding week intake	Severe **Score 3**	Head injury, Bone marrow transplantation, Intensive care patients (APACHE >10)
Total Score =		**+**	
Age adjusted core =		if above ≥ 70 years add 1 to total score	

11.PG-SGA Complete attached form: score_____
(fill in any relevant information already received from patient)

12. Skinfold sites	**1. Bicep (mm)**	**2. Tricep (mm)**	**3. Subscapular (mm)**	**4. Ileac crest (mm)**
Reading 1				
Reading 2				
Average				
5. MUAC (cm)				_____ cm
6. Calf circumference (cm)				_____ cm
13. HGS (kg) Mean value of highest readings from both hands				_____kg

14. BIA	BIA generated number _____	Time of BIA _____	Time of last meal _____
	Circle Yes / No exercise within 12 hours of test Yes / No alcohol taken within 24 hours of test Yes / No tea and / or coffee taken within 24 hours of test Yes / No empty bladder within 30 minutes of test		
15. DEXA	*Circle* Yes / No calcium supplements taken within 24 hours of scan Completed by radiographer – data will be emailed.		

16. 24-hour dietary recall (multiple pass method)

Sheet 1: 24-hour dietary recall Summary

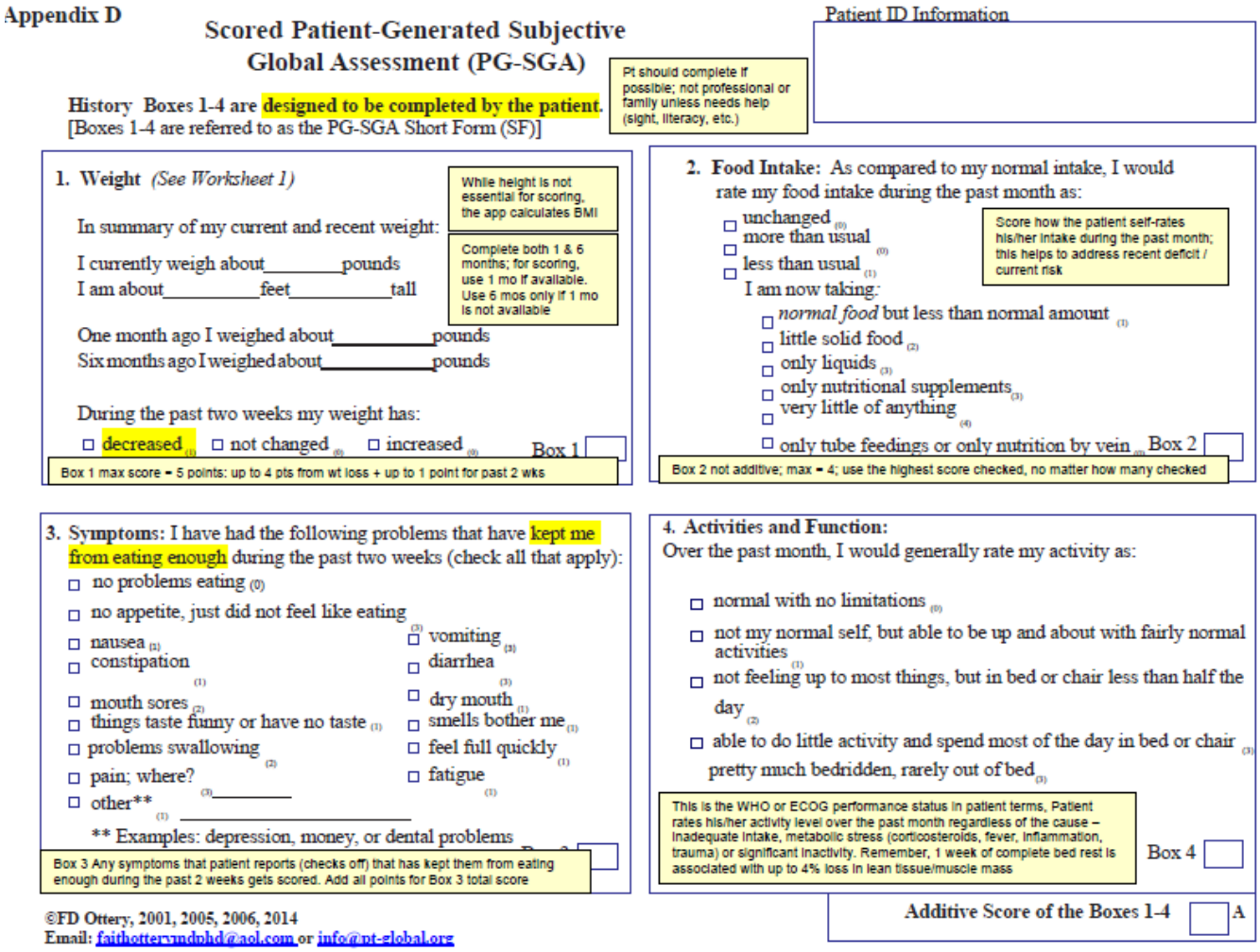
Time	Step 1: food and beverage intake during previous 24 hours	Step 2: Forgotten food and beverages

24-hour dietary recall (multiple pass method)

16.2 Sheet 2: Recording sheet for information collected in summary of 24-hour dietary recall

Time	Food item (from sheet 1)	Description of food item, preparation	Description of portion size	Serving amount	Food group

APPENDIX D: PG-SGA



Appendix D

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

Pt should complete if possible; not professional or family unless needs help (sight, literacy, etc.)

Patient ID Information

History Boxes 1-4 are designed to be completed by the patient.
[Boxes 1-4 are referred to as the PG-SGA Short Form (SF)]

1. Weight *(See Worksheet 1)*

While height is not essential for scoring, the app calculates BMI

In summary of my current and recent weight:

Complete both 1 & 6 months; for scoring, use 1 mo if available. Use 6 mos only if 1 mo is not available

I currently weigh about_____pounds
I am about_____feet_____tall

One month 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) Box 1

Box 1 max score = 5 points: up to 4 pts from wt loss + up to 1 point for past 2 wks

2. Food Intake: As compared to my normal intake, I would rate my food intake during the past month as:

Score how the patient self-rates his/her intake during the past month; this helps to address recent deficit / current risk

☐ unchanged (0)
☐ more than usual (0)
☐ less than usual (1)

I am now taking:

☐ *normal food* but less than normal amount (1)
☐ little solid food (2)
☐ only liquids (3)
☐ only nutritional supplements (3)
☐ very little of anything (4)
☐ only tube feedings or only nutrition by vein (0) Box 2

Box 2 not additive; max = 4; use the highest score checked, no matter how many checked

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 (2)
☐ 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)
☐ fatigue (1)

** Examples: depression, money, or dental problems

Box 3 Any symptoms that patient reports (checks off) that has kept them from eating enough during the past 2 weeks gets scored. Add all points for Box 3 total score

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 or chair less than half the day (2)
☐ able to do little activity and spend most of the day in bed or chair (3)
pretty much bedridden, rarely out of bed (3)

This is the WHO or ECOG performance status in patient terms. Patient rates his/her activity level over the past month regardless of the cause – inadequate intake, metabolic stress (corticosteroids, fever, inflammation, trauma) or significant inactivity. Remember, 1 week of complete bed rest is associated with up to 4% loss in lean tissue/muscle mass

Box 4

Additive Score of the Boxes 1-4 A

Email: faithotteryrndnhd@aol.com or info@pt-global.org

The remainder of this form is to be completed by your doctor, nurse, dietitian, or therapist. Thank you.

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

Worksheet 1 - Scoring Weight (Wt) Loss

To determine score, use 1 month weight data if available. Use 6 month data only if there is no 1 month weight data. Use points below to score weight change and add one extra point if patient has lost weight during the past 2 weeks. Enter total point

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%

Numerical score from Worksheet 1 ☐

Additive Score of the Boxes 1-4 (See Side 1) ☐ A

5. Worksheet 2 - Disease and its relation to nutritional requirements

All relevant diagnoses (specify) _____

Primary disease stage (circle if known or appropriate) I II III IV Other _____

One point each:

☐Cancer ☐AIDS ☐Pulmonary or cardiac cachexia ☐Presence of decubitus, open wound, or fistula
☐Presence of trauma ☐Age greater than 65 years ☐Chronic renal insufficiency

Numerical score from Worksheet 2 ☐ B

6. Work Sheet 3 - Metabolic Demand

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 point

Fever: Score fever intensity or duration, whichever is greater. (99°F= 37.2°C 101°=38.3° and 102° = 38.9°)

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
Corticosteroids	no corticosteroids	low dose (<10mg prednisone equivalents/day)	moderate dose (≥10 and <30mg prednisone equivalents/day)	high dose steroid (≥ 30mg prednisone equivalents/day)

Numerical score from Worksheet 3 ☐ C

Even short term use of corticosteroids can adversely impact protein status and muscle mass

See www.pt-global.org for prednisone equivalents chart and metric and additional language version (as available)

7. Worksheet 4 - Physical Exam

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. Muscle deficit impacts point score more than fat deficit. Definition of categories: 0 = no deficit, 1+ = mild deficit, 2+ = moderate 3+ = severe

Muscle Status:					Fluid Status:				
clavicles (pectoralis & deltoids)	0	1+	2+	3+		0	1+	2+	3+
interosseous muscles	0	1+	2+	3+		0	1+	2+	3+
thigh (quadriceps)	0	1+	2+	3+					
Global muscle status rating	**0**	**1+**	**2+**	**3+**					
orbital fat pads	0	1+	2+	3+					
triceps skin fold	0	1+	2+	3+					
Global fat deficit rating	**0**	**1+**	**2**	**3+**					

These are examples of areas that can/should be considered in determining loss/deficit (or excess fluid). RELAX... One does NOT have to assess all of these to have a global sense for loss or deficit of muscle or fat. Remember the maximum point score for physical exam is only 3 points and you are not likely to be off by more than 1 point...

Numerical score from Worksheet 4 ☐ D

Total PG-SGA score ☐
(Total numerical score of A+B+C+D above)

(See triage recommendations below)

Global PG-SGA rating (A, B, or C) = ☐

Clinician Signature_____RD RN PA MD DO Other_____ Date _____

Worksheet 5 - PG-SGA Global Assessment Categories

Category	Stage A	Stage B	Stage C
Weight	Well nourished No wt loss OR Recent wt gain	Moderately malnourished <5% wt loss in 1 month (or 10% in 6 mos) OR Progressive wt loss	Severely malnourished > 5% wt loss in 1 month (or >10% in 6 mos) OR Progressive 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	Present of nutrition impact symptoms (PG-SGA Box 3)	Present of nutrition impact symptoms (PG-SGA Box 3)
Functioning	No deficit OR Recent improvement	Moderate functional deficit OR Recent deterioration	Severe functional deficit OR recent significant deterioration
Physical Exam	No deficit OR Chronic deficient but tissue recent improvement	Evidence of mild to moderate loss of muscle mass / SQ fat / muscle loss on palpation	Obvious signs of malnutrition (e.g., severe loss muscle, SQ) possible edema)

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.

Triage based on PG-SGA point score

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 lab values as appropriate.
4-8	Requires intervention by dietitian, in conjunction with nurse or physician as indicated by symptoms (Box 3).
≥9	Indicates a critical need for improved symptom management and/or nutrient intervention options.

Worksheet 5 May be helpful to circle relevant statement for each PG-SGA category to visually help identify the overall global assessment

APPENDIX E: ANTHROPOMETRY CALCULATIONS AND INTERPRETATIONS

Reference	Anthropometry	Value	Interpretation			
Frisancho, 1990	cAMA (percentiles)	≤ 5th	Wasted			
		>5th but ≤≤ 15	Below average			
		>15 but ≤ 85th	Average			
		>85th but ≤ 95th	Above average			
		>95th	High muscle			
WHO, 2000	Body fat %		Under fat	Healthy	Over fat	Obese
		Females 20 – 39	<21%	21 -33%	33 – 39%	>39%
		Females 40 – 59	<23%	23 – 34%	34 – 40%	>40%
		Females 60 – 79	<24%	24 – 36%	36 – 42%	>42%
		Males 20 – 39	<8%	8 – 20%	20 – 25%	>25%
		Males 40 – 59	<11%	11 – 22%	22 – 28%	>28%
		Males 60 - 79	<13%	13 – 25%	25 – 30%	>30%

Body Density equations (Lee, 2013)

Age Range (Years)	Equation
Males	
17–19	Body density = 1.1620 − 0.0630 × (log Σ)*
20–29	Body density = 1.1631 − 0.0632 × (log Σ)
30–39	Body density = 1.1422 − 0.0544 × (log Σ)
40–49	Body density = 1.1620 − 0.0700 × (log Σ)
50 +	Body density = 1.1715 − 0.0779 × (log Σ)
Females	
17–19	Body density = 1.1549 − 0.0678 × (log Σ)
20–29	Body density = 1.1599 − 0.0717 × (log Σ)
30–39	Body density = 1.1423 − 0.0632 × (log Σ)
40–49	Body density = 1.1333 − 0.0612 × (log Σ)
50 +	Body density = 1.1339 − 0.0645 × (log Σ)

*log ∑ = sum of the triceps, subscapular, supra-iliac and biceps skinfolds