



Measuring cachexia—diagnostic criteria

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Abstract: Cancer cachexia is characterized by the loss of lean body mass with or without the loss of fat and is associated with increased susceptibility to treatment related toxicities, decreased quality of life, functional impairment, and increased cancer-related mortality. Uncontrolled symptoms which impair nutritional intake, metabolic derangements including elevated energy expenditure and increased catabolism, and chronic inflammation contribute to the development of cancer cachexia. Weight loss in cancer patients is not readily reversible by conventional nutritional support. The definition of cachexia and sarcopenia are evolving with time, as well as the assessment of weight loss in cancer patients. Clinicians should assess all cancer patients regardless of history of weight loss for risk for malnutrition at presentation and periodically throughout the trajectory of illness—pre-cachectic, cachexia, and refractory cachexia stage. For cancer patients with weight loss, assessments of BMI and percentage weight loss, symptoms which impact nutritional intake, quality of life, physical function, biological markers, energy expenditure, and body composition are ideally needed in order to measure cachexia and implement therapeutic interventions.

Keywords: Cancer cachexia; body composition; sarcopenia; malnutrition

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Introduction

Cachexia is derived from the Greek word *kakos*, meaning “bad things” and *hexus*, meaning “state of being” and describes a wasting syndrome found in chronically ill patients such as cancer. Cancer cachexia is characterized by the loss of lean body mass with or without the loss of fat leading to increased susceptibility to treatment related toxicities, decreased quality of life (QOL), functional impairment, and increased cancer-related mortality (1).

Uncontrolled symptoms decreasing caloric intake, metabolic derangements including elevated energy expenditure and increased catabolism, and chronic inflammation contribute to the development of cancer cachexia. Weight loss in cancer patients is unfortunately not readily reversible with adequate caloric intake and pharmacological interventions targeting underlying metabolic derangements and chronic inflammation are being currently investigated. The following review article will highlight the historical evolution of the definition of

cancer cachexia and approaches to assess for malnutrition and weight loss in cancer patients.

Defining cancer cachexia

Cancer results in roughly 8.2 million deaths per year worldwide (2) and complications of cachexia are frequently associated with pancreatic, esophageal, gastric, hepatic, colorectal and pulmonary malignancies as well as other malignancies. Frequency of cachexia increases with advanced disease stage and more common in cancers that compromise ingestion, digestion, and absorption of nutrients.

The WHO statistics identify >600 million adults as obese (BMI of $>30 \text{ kg/m}^2$) (3). Historically, a BMI $<18.5 \text{ kg/m}^2$ was accepted as a marker of being cachectic, but the current obesity epidemic in developed countries, 50% in some (4), results in a shift in the populations' BMI upward complicating attempts to characterize and diagnose cachexia in cancer patients. In obese individuals, decrease in lean body mass, muscle loss, can go undetected resulting in

sarcopenic obesity (5).

Over the years, various definitions have been proposed by researchers to define cancer cachexia and have evolved with time. Historically, involuntary weight loss of >10% has been used to define cancer cachexia (6). Obesity, complications of edema, and increasing mass due to cancer burden may underestimate the frequency of cachexia if weight alone is used to screen for cachexia (7).

In 2007, an expert panel formed at the Cachexia Consensus Conference proposed the following (8):

“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 cachexia. Cachexia is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption, and hyperthyroidism, and is associated with increased morbidity.”

In 2008, an alternative definition was proposed for cancer cachexia and included weight loss with or without the loss of fat with the presence of an additional three of the following criteria: decreased muscle strength, reduced muscle mass, anorexia, symptoms of fatigue, or biochemical abnormalities including anemia, evidence of inflammation, or low albumin (9).

In 2011, an international group of experts provided the following definition of cancer cachexia: *“a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that can be partially but not entirely reversed by conventional nutritional support”* (1). This definition highlighted the loss of skeletal muscle mass associated with cancer cachexia and its complications including increased chemotherapy toxicity and mortality (10).

The same group proposed three consecutive stages to characterize cancer cachexia: pre-cachexia, cachexia, and refractory cachexia (1) and proposed five domains to assess including food intake, catabolic derangements, functional and psychosocial impact, and assessments of body composition including stores of adipose tissue and muscle mass. In addition, the group recommended grading the severity of weight loss using BMI and degree of weight loss.

A preliminary study in cancer patients supported the proposed three-level staging system with respect to symptom burden, QOL, tolerability for chemotherapy, and mortality; however, patients in the pre-cachectic and cachexia group behaved in a similar manner (11). In

a study assessing weight loss specifically at the time of diagnosis, researchers reported that survival coincided with three consecutive stages with pre-cachectic patients having intermediate survival compared with patients with no weight loss who had improved mortality and cachectic patients with the worst survival outcomes (12). A difference in survival in pre-cachectic patients was not noted until 1 year after cancer diagnosis.

Researchers have also developed a cachexia staging score (CSS) for advanced cancer patients consisting of five components in order to clarify the three-level staging system (13):

- (I) Weight loss in 6 months (score range, 0–3);
- (II) A simple SARC-F questionnaire assessing muscle function and sarcopenia (score range, 0–3);
- (III) ECOG performance status (score range, 0–3);
- (IV) Appetite loss (score range, 0–2);
- (V) Abnormal biochemistry (score range, 0–2);
 - (i) Non-cachexia (score 0–2);
 - (ii) Pre-cachexia (score 3–4);
 - (iii) Cachexia (score 5–8);
 - (iv) Refractory cachexia (score 9–12).

The CSS was able to discriminate different cachexia stages according to patient-related outcomes, including body composition, symptom burden, QOL, and survival (13). The Cachexia SCORe (CASCO) which includes five components: body weight loss and composition, inflammation/metabolic disturbances/immunosuppression, physical performance, anorexia, and QOL has also been developed and validated to quantify staging of cachexia in cancer patients (14).

In order to aid clinicians in treating patients with cancer cachexia and facilitate research, a single definition would be ideal. Clinicians need to be aware that cachexia may manifest overtime and signs of early weight loss must be vigilantly screened for throughout the trajectory of illness. In 2017, the European Society of Clinical Nutrition and Metabolism publish evidence-based guidelines for nutritional care and recommended the following (15):

- (I) Screen all patients with cancer for nutritional risk early in the course of their care regardless of body mass index and weight history;
- (II) Expand nutrition-related assessment practices to include measures of anorexia, body composition, inflammatory biomarkers, resting energy expenditure (REE) and physical function;
- (III) Use multimodal nutritional interventions with individualized plans, including care focused

on increasing nutritional intake, lessening inflammation and hypermetabolic stress, and increasing physical activity.

Assessment of cancer cachexia

A careful history, with attention to risk factors and symptoms impacting caloric intake and presence of psychosocial distress, as well as a thoughtful physical examination evaluating evidence of loss of subcutaneous adipose tissue, muscle wasting, edema, ascites, and overall functional status is the initial assessment for cancer patients with weight loss. In addition, integrating systematic screening for risk of weight loss and evidence of malnutrition is critical in cancer patients. Basic components of nutritional screening in cancer patients include assessments of the following domains: measurements of caloric intake and QOL, underlying risk factors and symptoms which impact the development of weight loss, changes in weight and body composition, and biological markers.

QOL and anorexia

Assessing QOL is critical endpoint in cancer patients with cachexia. The functional assessment of anorexia-cachexia therapy (FAACT) scale consists of the functional assessment of cancer therapy general (FACT-G) scale and the anorexia-cachexia subscale (ACS) and is a QOL scale specific for cancer patients with cachexia (16). FAACT scale includes five subscales: 7 items for physical well-being, 6 items for emotional well-being, 7 items for social well-being, 7 items for functional well-being, and 12 items for ACS with each item rated as a five-level scoring system (0–4 points) with a higher sum of all 39-item score equating with a better QOL.

Poor oral intake contributes to the development of cancer cachexia which can be exacerbated by symptoms of anorexia, lack of desire to eat. In advanced cancer patients, a lack of adequate caloric intake to support basal metabolic demands was noted even for patients with high food intake, and patients with high risk of weight loss reported to have decreased frequency of eating, little variety of food groups, and high proportion of liquids (17). The FAACT questionnaire, used mainly in the research setting, is a patient-rated assessment tool to assess symptoms of anorexia, but may be too time consuming (18). In clinical practice, the revised Edmonton Symptom Assessment System assesses lack of appetite with a numeric rating scale is more practical.

Measuring caloric intake

Dietary history prospectively collected is the standard evaluation of caloric and nutrient intake; however, in frail and debilitated advanced cancer patients, it can be too difficult to obtain when conducted over several days and a 3-day collection period is often utilized (19). Alternatively, in the research setting, trained proxies (either a nurse or volunteer) can estimate percentage of food portions consumed which has good correlation with actual caloric intake and superior to a 24-hour dietary recall food questionnaire (20).

Total caloric and macronutrient intake can be obtained with dietary records including type, frequency, and quantity of meals. A dietary history should also include an assessment of symptoms which impact nutritional intake including pain, nausea, vomiting, early satiety, constipation, taste alterations, dental and oral problems, issues of dysphagia, mood abnormalities as well as practical concerns including a patient's ability to obtain, prepare, and afford meals.

Nutrition impact risk factors and symptoms

Multiple factors including co-morbidities and symptoms can increase the risk for malnutrition in cancer patients. In general, older age, decreased function, cognitive dysfunction and advanced stage of cancer can contribute to the development of weight loss. Co-morbidities such as compromised organ dysfunction, infectious complications, and symptoms such as dysphagia contribute to the development of cachexia.

Symptoms that impact nutrition, defined as secondary nutrition impact symptoms (S-NIS), have to be treated in order to prevent weight loss. In a study of 151 patients presenting to a cancer cachexia clinic, the median number S-NIS was 3 and early satiety, constipation, depressed mood, and uncontrolled nausea and vomiting were the most common (21). In the same study, it was noted that cancer patients with more S-NIS were significantly more likely to gain weight with treatment emphasizing the importance of assessing and treating S-NIS.

Weight and body composition

Height and weight are reliable and easily obtained by patients and caregivers (22) or measured by healthcare providers in order to calculate the body mass index (BMI kg/m²). In addition, percentage of weight loss can

be determined by change of weight from the baseline premorbid level or over a specified duration of time such as 1, 3, or 6 months. In the literature, various degrees of weight loss, 5%, 10%, or 20% over various intervals and BMI values (BMI <17, <18.5, or <20) have been associated with increased risk of malnutrition. Complications of edema, ascites, or degree of tumor metastasis can cause fluctuations in determining weight changes and BMI, and both measures don't account for changes in a patients' body composition.

Regardless, severity of cancer associated weight loss have been proposed Weight Loss Grading System (WLGS 0, 1, 2, 3, or 4) which factors both percent weight loss and BMI extrapolated from a large population data set and has reported prognostic significance of both values (23).

- ❖ WLGS grade 0—weight-stable patients (weight loss $\pm 2.4\%$) with BMI ≥ 28 kg/m² had the longest survival;
- ❖ WLGS grade 1—BMI 20 to 25 kg/m² and weight loss $\leq 2.4\%$, or BMI ≥ 28 kg/m² and weight loss 2.5% to 6.0% had median survival 14.6 months;
- ❖ WLGS grade 2—BMI 20 to 28 kg/m² and weight loss 2.5% to 6%, or BMI ≥ 28 kg/m² and weight loss 6% to 11% had median survival 10.8 months;
- ❖ WLGS grade 3—BMI ≤ 20 kg/m² and weight loss <6%, or BMI 20 to 28 kg/m² and weight loss 6% to 11%, BMI 22 to >28 kg/m² and weight loss 11% to 15%, or BMI ≥ 28 kg/m² and weight loss $>15\%$ had median survival 7.6 months;
- ❖ WLGS grade 4—BMI ≤ 20 kg/m² and weight loss 6% to 11%, BMI ≤ 22 kg/m² and weight loss 11% to 15%, or BMI ≤ 28 kg/m² and weight loss $>15\%$ had median survival of 4.3 months;
- ❖ In a recent study, the addition of Karnofsky Performance Status, anorexia, and physical and emotional functioning improved the prognostic accuracy of the WLGS (24).

Biological markers

Laboratory data collected during routine clinical care has been incorporated into assessments for risk of malnutrition and focus on markers of an acute-phase response to complications of infection, malignancy or trauma. Elevated C-reactive protein (CRP) has been linked with weight loss and has been confirmed in numerous studies (25,26), and low serum albumin has also been associated with weight loss (27,28). In the literature, cut-off laboratory values associated

with weight loss vary: albumin (<30, <32, or <35 g/L), CRP (>5 or >10 mg/L), and transthyretin (prealbumin) (<110 or <180 mg/L). Laboratory abnormalities associated with malnutrition have been integrated into a calculated score including the Prognostic Inflammation Nutrition Index (PINI) (29) and the Nutritional Risk Index (NRI) (30).

- ❖ $PINI = [CRP (mg/L) \times \alpha 1\text{-acid glycoprotein}] / [albumin (g/L) \times transthyretin (g/L)];$
- ❖ $NRI = 1.519 \times albumin (g/L) + 0.417 \times (current\ weight/usual\ weight \times 100).$

The modified Glasgow Prognostic Score, which is a combination of albumin and CRP, has been validated and reported to correlate with poor nutritional status and weight loss, decrease response to chemotherapy and increased sensitivity to toxicities, and is a useful prognostic scoring tool (31,32). In addition, a high neutrophil/lymphocyte ratio, at baseline and follow-up intervals, has been shown to be associated with progressive disease, weight loss, and decreased survival in cancer patients and may be a surrogate for ongoing inflammation (33). However, inflammation associated cytokines produced in an acute phase response during an illness include interleukin (IL)-6, IL-1b, tumor necrosis factor- α , IL-8, interferon- γ and others have been reported to be poor biomarkers for weight loss in cancer patients as opposed to CRP (34,35).

Research on leptin and ghrelin has reported to be both negative and positive studies regards to their relationship with weight loss (36,37). Patients with cancer cachexia also been reported to have other metabolic derangements including hyperglycemia, hypertriglyceridemia, and insulin resistance (38). Other endocrine abnormalities that may contribute to cachexia include hypothyroidism, adrenal insufficiency, and hypogonadism in male patients.

Malnutrition screening tools

Nutrition screening tools have been developed which incorporate various risk factors for weight loss; however, there is no universal gold standard screening tool for cancer cachexia. In a study comparing four screening tools for malnutrition, (39) only minor variations between the estimated nutritional risk of patients were noted.

Patient-Generated Subjective Global Assessment (PG-SGA)

The Subjective Global Assessment (SGA) (40) is a validated screening tool for malnutrition in hospitalized patients and the PG-SGA has been adapted for cancer patients (41).

The PG-SGA incorporates questions for patients regarding weight history, caloric intake, functional status and requires additional assessments by healthcare professional including comorbid conditions, fever, and medications such as steroids which impact nutrition as well as detailed physical examination of seven muscle groups, three adipose depots, and evidence of edema at three sites.

Mini Nutritional Assessment (MNA)

The MNA is a validated, rapid—designed to be completed in 10 minutes—screening assessment tool of nutritional status in elderly patients across various settings, outpatient, nursing homes and in hospitals (42). The MNA records information including diet history, weight including BMI (or calf circumference), mid-arm circumference, and nutritional risk factors. Diet history includes questions regarding food and fluid intake, number of meals per day, quantity of protein intake, and ability to eat independently. Information regarding presence of acute illness or psychological distress, cognitive impairment, presence of pressure ulcers, and medications associated with increased risk for malnutrition are incorporated. The score calculated by the MNA categorizes elderly patients with either adequate nutritional status, at risk for malnutrition, or presence of protein-calorie malnutrition.

Malnutrition Universal Screening Tool (MUST)

The MUST incorporates a score for three components including BMI, history of weight loss, and disease comorbidities in combination with a history of no oral intake for greater than 5 days. For frail patients who are unable to stand the combination of ulnar length, demi-span, and knee height replaces height and mid-upper arm circumference is used as an alternative for BMI.

Other nutritional screening tools include the Malnutrition Screening Tool and Nutritional Risk Screening 2002, but only the PG-SGA and the MUST have been validated in cancer patients.

Further assessments of risk for malnutrition in cancer patients can be difficult to implement in frail cancer patients with advanced disease and include detailed dietary history and biological laboratory workup. Fearon *et al.* patients with pancreatic and esophageal malignancies at risk for malnutrition and multiple regression analyses identified the following risk factors for malnutrition: dietary intake <1,500 kcal/day,

elevated serum CRP levels and stage of disease (43,44).

Assessment of energy balance

Total energy expenditure (TEE) comprises of two major components, energy consumed by physical activity and REE. Cancer patients are hypothesized to have decreased energy due to less physical activity but overall increase energy cost due to increased REE attributed to the cancer burden, chronic inflammation, altered body composition, and brown tissue activation (45). Increased energy cost could be calculated by the difference between measured REE and predicted REE (calculated by standard equations such as Harris-Benedict, below) [BMR = basal metabolic rate; W = weight (kg); H = height (cm); A = age (years)]:

- ❖ Male: $BMR \text{ (kcal/day)} = 66.4730 + 13.7516W + 5.0033H - 6.7550A$
- ❖ Female: $BMR \text{ (kcal/day)} = 655.955 + 9.5634W + 1.8496H - 4.6756A$

REE can be measured by indirect calorimetry which can be conducted in various clinical settings. Measuring TEE required specialized equipment and expertise and few research studies in the cancer setting (46,47). Accurate REE measurements allow for dietitians to prevent underfeeding of cancer patients, resulting in cachexia, or overfeeding resulting in hyperglycemia or hepatic dysfunction.

Assessment of body composition

Most commonly used body composition assessments in cancer patients include anthropometric methods (48), bioelectrical impedance analysis (BIA) (49), computed tomography (CT) imaging analysis (50), and dual-energy X-ray absorptiometry (DXA) (51).

Anthropometric methods, which incorporate skinfold measurements, body weight, BMI, and body surface, are cost effective and efficient way to assess body composition; however, they are less accurate due to an indirect approach and inability to distinguish amounts of lean muscle mass and fat tissue (50).

Bioelectric impedance analysis also can be used to measure body composition based on the electrical properties of tissues and reflects cellular health. Either using a single 50 kHz frequency or newer multi-frequency analyzers, small currents are passed through both intra- and extracellular fluid to varying degrees depending on tissue characteristics in order to estimate body fat percentage, fat mass, fat-free mass, and total body water with the help of

predictive equations. BIA, unfortunately, has been reported not to be as reliable as DXA for assessing body composition in cancer patients (52); however, BIA can be used to calculate the phase angle which has been reported to predict poor survival in cancer patients (53).

Both DXA and CT imaging both have high precision and specificity for discriminating individual tissue components and are the gold standard for body composition evaluation. DXA scans measure predominantly appendicular muscle while CT scans measure axial skeletal muscle mass. Limitations of DXA include exposure of patients to low levels of radiation and cost, inability to differentiate subsets of adipose tissue into intramuscular, visceral, and subcutaneous and lean body mass into muscle, organ, and tumor, as well as overestimation of lean body mass in settings when changes of >5% hydration status of cancer patients (50).

CT is often used over time to monitor cancer and can be taken advantage of to serve as an assessment tool for body composition. CT imaging can discriminate between adipose tissue, bone, organs and muscle including degree of fatty infiltration by Hounsfield units based on tissue-specific attenuation values using software programs including SliceOmatic (TomoVIsion, Magog, Canada), FatSeg, OsiriX, and ImageJ (54,55). When used to assess for body composition, CT scans are evaluated at a standard skeletal landmark, often the third lumbar vertebra since it strongly correlates with total body skeletal muscle area (56). When precise measurements of body composition such as CT imaging are used in cancer patients, 50–80% of patients were reported to have low lean body mass, a correlate of malnutrition (57). Limitations of CT imaging include exposure to radiation which can be minimized if CT scans used for standard of care in cancer staging are utilized.

Alternative methods to assess gross body composition include hydrodensitometry (underwater weighing) and air displacement plethysmography (Bod Pod) but unable to distinguish regional fat or muscle. Magnetic resonance imaging is a highly accurate method to measure body composition and is comparable to CT imaging without exposing patients to ionizing radiation but is cost prohibitive.

Sarcopenia and sarcopenic obesity

Assessment of body composition is critical in detecting cancer patients with sarcopenia, a reduced quantity of skeletal muscle

in the setting normal or increased adipose tissue. Primary sarcopenia is noted in healthy aging and secondary sarcopenia is associated with physical inactivity, undernutrition and illness such as cancer. In the setting of obesity, loss of skeletal muscle is known as sarcopenic obesity. In non-small cell lung cancer patients, Baracos *et al.* reported that 31% of females and 61% of males had underlying sarcopenia while only a quarter of patients were noted to have weight loss (58). Prado *et al.* has reported that obese cancer patients with sarcopenia have decreased function and increased risk of being bedridden (59), increased mortality (60), and toxicity due to chemotherapy (61).

Due to differences in genders, sex-specific skeletal muscle index cut-off values are adjusted by body height; however, the cut-off values for sarcopenia in cancer patients vary across different ethnicities and body shapes. A recent study conducted in Taiwan reported that Western criteria for sarcopenia results in different diagnosis, more patients diagnosed as sarcopenic, compared with Eastern criteria and recommended that researchers must apply the appropriate sarcopenia criteria for population being studied (62). Both sarcopenia and sarcopenic obesity can be difficult to measure since no clear-cut consensus-based diagnostic criteria have been universally accepted and experts in the field of cachexia argue for a need for consensus diagnostic criteria for sarcopenia in order to facilitate research and treatment (63).

Conclusions

Cancer cachexia is a multifactorial syndrome that impacts QOL, physical function, treatment response, and mortality. The definition of cachexia and sarcopenia are evolving with time, as well as the assessment of weight loss in cancer patients. Clinicians should assess all cancer patients regardless of history of weight loss for risk for malnutrition at presentation and periodically throughout the trajectory of illness—pre-cachectic, cachexia, and refractory cachexia stage. For cancer patients with cachexia, assessments of BMI and percentage weight loss, symptoms which impact nutritional intake, QOL, physical function, biological markers, energy expenditure, and body composition are ideally needed in order to measure cachexia and implement therapeutic interventions.

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Footnote

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