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The Prevalence of Cancer Cachexia Using Different Diagnostic Criteria

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PREVALENCE OF CANCER CACHEXIA USING DIFFERENT DIAGNOSTIC CRITERIA

By

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TABLE OF CONTENTS

ABSTRACT

Cancer cachexia is a wasting syndrome that has been poorly characterized partly due to the lack of an adequate definition. In an attempt to establish diagnostic criteria, a formal consensus process was established, proposing three possible definitions for cancer cachexia: 1. Weight loss >5% over past 6 months (in absence of simple starvation); 2. Body mass index (BMI) <20 kg/m^2 and any degree of weight loss >2%; 3. Sarcopenia (i.e. muscle depletion) defined by lumbar skeletal muscle index determined by computerized tomography (CT) imaging (men <55 cm^2/m^2; woman < 39 cm^2/m^2) and any degree of weight loss >2%. Using baseline data from a clinical trial (n=547 patients with lung cancer), we investigated the use of these different diagnostic criteria and hypothesized that each criterion would result in a similar prevalence of cachexia, consistently identifying individuals across definitions. Demographic characteristics including BMI and history of weight loss were used as well as CT images obtained as part of medical diagnosis. The prevalence of cachexia by each diagnostic criterion described above was approximately 47%, 8% and 41% for criterion 1, 2 and 3, respectively. According to McNemar test, cachexia diagnosis was not consistent among the three classifications: criterion 1 vs. 2, p = <0.0001; criterion 1 vs. 3, p = 0.021, and criterion 2 vs. 3, p =<0.0001. The recently proposed diagnostic criteria for cancer cachexia do not consistently identify individuals as having this condition, which may have potential unfavorable implications to research and clinical practice.

Key words: Cancer, Cachexia, Prevalence

1. LITERATURE REVIEW

1.1 Introduction

Cancer is a term used to group many diseases that are characterized by uncontrolled cell division and development. Normally, the rate of cell growth is balanced with the rate of death. Cancerous cells have damaged DNA that cause an over replication of cells and invasion to other tissues in its proximity (1). In most cancers, these abnormal cells form masses called tumors. Tumors can grow and affect the functioning of circulatory, nervous, and digestive systems.

Cancer is the number two killer in the United States (US), after heart disease. According to the American Cancer Society, "half of all men and one-third of all women in the country will develop cancer during their lifetimes" (1). Throughout the 100 types of cancers that exist, lung cancer is the leading cancer killer in both men and woman in the US (2). Worldwide, lung cancer is diagnosed at approximately 1.61 million cases per year, making it the most prevalent type of cancer. In addition, lung cancer is also the leading cause of cancer deaths at an incidence rate of 1.38 million cases per year (3).

Lung cancer originates from tissues in the lungs and is mainly divided into three main types. These types include small cell lung cancer, non-small cell lung cancer, and lung carcinoid tumor. Within these lung cancer cases, non-small cell lung cancer (NSCLC) is the most common type, accounting for 85% of lung cancers in the US (2). Lung cancer is commonly associated with poor outcomes because once the disease begins to present itself with signs and symptoms hinting toward its diagnosis, it is already advanced enough for extreme curative measures to be taken. Due to the presence of poor physical status, functional decline, or comorbidity, lung cancer patients have especially low survival rates (3). As a result, weight loss, particularly loss of muscle mass, is commonly observed in patients with NSCLC (4).

1.2 Cancer Cachexia

The weight loss associated with NSCLC often culminates in cancer cachexia. Cachexia has generally been conceived as the process of severe wasting and weakness of the body due to a chronic illness. The prevalence of cachexia in chronic diseases is currently growing and should be seriously considered. In particular, the prevalence and adverse effects of cancer cachexia are very high, at both an incidence and mortality rate of 80% in advanced cancer (5). When

comparing the occurrence between men and woman, men were notably more afflicted by loss of skeletal muscle mass (6).

For a long time, cachexia has been associated with poorer outcomes in cancer patients, however the exact mechanisms that contribute to this condition are still not completely understood. Cancer cachexia is a dynamic process of involuntary catabolism and it has been recently described 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. Its pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism" (7).*

Cachexia therefore emphasizes weight loss deriving from skeletal muscle, not necessarily involving adipose tissue loss. Although the common phenotype of cachectic patients is low body weight, it is also possible that obese individuals may present with cancer cachexia (8). Human body composition is variable among individuals, as proportions of lean and adipose tissue exist in different amounts independent of body weight or body mass index (BMI, kg/m^2). Regardless of body weight, severe muscle wasting observed with cancer cachexia, also known as sarcopenia, is a strong prognostic indicator of poorer health outcomes (9).

During cancer, an individual may experience loss of appetite, early satiety and nausea, which leads to low caloric intake (7, 10). In addition, catabolism, or breakdown of the cells/tissues of the body, is intensified by an increased metabolic rate and inflammation (7). Consequently, conventional nutritional support (oral, enteral or parental nutrition) is insufficient to promote anabolic potential and homeostasis (11). To compensate for the ongoing negative energy balance, skeletal muscle may be broken down to yield energy and nutrients to the growing tumor and accelerated metabolism (12). This muscle wasting causes systemic inflammation (13), which is associated with low albumin levels and high C-reactive protein concentrations (4).

Cancer cachexia is linked to reduced performance status and quality of life (7). This syndrome is also associated with a reduced immunity to anticancer therapy, leading to a higher risk of chemotherapy toxicity and hence, dose- reductions, treatment delay or termination (9). Reducing or terminating anticancer therapy allows cancer to progress faster, therefore cancer cachexia-related muscle depletion has also been associated with shorter time to tumor progression (14), longer length of hospital stay (14) and shorter survival (8).

Due to the complexity of this multifactorial syndrome, there is no standard treatment that is widely accepted. In view of the multidimensional aspect of cancer cachexia, cachexia management should derive from a combination of interventions, addressing the multiple pathways related to this syndrome. Studies have shown that a multimodal approach to treatment provides better outcomes than a single agent (13).

Similar to other diseases and syndromes, diagnosing and treating individuals earlier in the disease trajectory can diminish cancer cachexia complications. As cancer patients experience a decrease in appetite (leading to reduced food intake) and increased energy expenditure, it is essential for therapy to target this problem with nutritional support and appetite agents (15). Anti-inflammatory drugs are an important therapeutic component to treat inflammation-related metabolic abnormalities from systematic stress (13, 15).

In addition to nutrient supplementation and pharmaceuticals, resistance exercise is also beneficial for patients that are experiencing a reduced functional status (15) and having trouble performing activities of daily living. Resistance rather than endurance exercise has been the preferred mode of treatment for patients with cancer because it prompts oxidative metabolic adaptations (16) and significantly stimulates protein synthesis (17, 18). Resistance training results in increases in strength and muscle fiber cross-sectional area by thickening the myofibrillar proteins myosin and actin (17, 18). Additionally, studies are underway to investigate the effect of a home-based self-assistance exercise program involving both resistance and aerobic exercise as part of a multimodal treatment for cancer cachexia (19).

In despite of the above-mentioned evidence, current clinical practice does not emphasize management of unintended weight loss and severe muscle wasting in cancer patients; therefore, this represents an unfulfilled need that should be addressed in this patient population. Although hundreds of publications have addressed cancer cachexia, the exact definition of this syndrome is debatable and the variability of classification criteria has limited the ability to compare results of individual clinical trials. Consequently, the lack of a standard definition is a limitation to advance our knowledge on cancer cachexia, along with its routine clinical management, trial design, education, and policymaking.

In an attempt to establish diagnostic criteria, a formal consensus process was created, proposing a classification system for cancer cachexia. Although practical, the proposed

classifications have not been systematically applied and evaluated, which limits its applicability in clinical settings.

2. RESEARCH OBJECTIVES AND HYPOTHESIS

Using data from a randomized control trial (RCT), this study investigated the prevalence of cachexia using definitions recently proposed by the International Consensus Group (7). We **hypothesized** that the three proposed diagnostic criterions will provide similar prevalence of cachexia and will consistently identify individuals regardless of the definition used.

3. MATERIALS AND METHODS

3.1 Study Population and Data Collection

We used baseline data (i.e. pre-intervention) from a Phase III, randomized, placebo controlled study of Enobosarm® (Ostarine; GTx-024), a novel oral selective androgen receptor modulator with tissue-selective anabolic and androgenic pharmacologic activity under investigation for anabolic potential and its benefits in patients with NSCLC (20). This study was approved by the Florida State University Institutional Review Board (secondary analysis of the primary study).

The prevalence of cachexia was investigated by the diagnostic criteria proposed by Fearon *et al*. (7), **Table 3.1**. Demographic information, including body weight, height, BMI, and history of weight loss were obtained from study records. For the diagnosis of sarcopenia, skeletal muscle mass was obtained from computerized tomography (CT) images previously conducted as part of medical diagnosis. BMI was calculated as the ratio of weight (kg)/height (m^2) and classified according to the World Health Organization (WHO) categories as follows: <18.5 kg/m^2 as underweight, 18.5-24.9 kg/m^2 as normal range, 25.0-29.9 kg/m^2 as overweight, 30.0-34.9 kg/m^2 as class I obese, 35.0-39.9 kg/m^2 as class II obese, and ≥40.0 kg/m^2 as morbid obese (21). The study's inclusion criteria precluded morbidly obese individuals from participating.

Table 3.1 Diagnostic Criteria for Cancer Cachexia		
1	**2**	**3**
Weight loss >5% over past 6 months (in absence of simple starvation)	BMI <20 kg/m^2 and any ongoing degree of weight loss >2%	Lumbar skeletal muscle index determined by CT imaging that is consistent with sarcopenia (men <55 cm$^{2/}$m^2; woman < 39 cm$^{2/}$m^2) and any degree of weight loss >2%

BMI = body mass index; CT = computerized tomography

3.2 Computerized Tomography (CT) in Analyzing Cancer Cachexia

CT images are an accurate and reliable tool for measuring human body composition (22). Direct visualization of cross-sectional areas of skeletal muscle is possible using CT scans (**Figure 3.1**). Image analysis was performed at the Nutrition, Body Composition and Metabolism Laboratory (PI: Dr. Carla Prado) in the Department of Nutrition, Food and Exercise Sciences, The Florida State University.

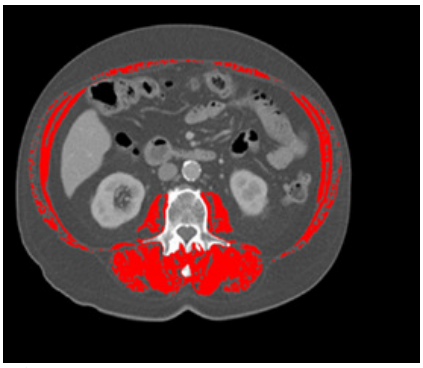


Figure 3.1 The third lumbar vertebrae cross-sectional region of a male patient with cancer cachexia (skeletal muscle).

For the purpose of body composition (i.e. skeletal muscle) analysis, the images of the 3rd lumbar vertebrae (L3) were selected, as tissue areas in single images in this region are significantly correlated to whole-body muscle and adipose tissue masses (23). This field contains psoas, posterior paraspinal muscles as well as the abdominal wall muscles. Tissues were analyzed using Slice-O-Matic V5.0 (Tomovision, Montreal, Canada), which permits specific tissue demarcation using Hounsfield Unit thresholds of –29 to +150 for skeletal muscles (psoas,

erector spinae, quadratus lumborum, transversus abdominus, external and internal obliques, rectus abdominus). Cross-sectional areas (cm^2) were computed for each tissue by summing tissue pixels and multiplying by the pixel surface area. This value was normalized by stature (L3 skeletal muscle index, cm^2/m^2) as is conventional for body composition components. Sarcopenia was defined using the cut-off points for L3 skeletal muscle index of <39 cm^2/m^2 for women and <55 cm^2/m^2 for men as described by Prado *et al.* (8).

3.3 Statistical Analysis

Prevalence's of cachexia defined by three criteria were presented as percentages and compared using Chi-square (χ^2) test or Fisher's exact test, as appropriate. McNemar test was utilized to assess the consistency of individuals identified among the different criteria. This test is commonly used for the analysis of paired dichotomous data (24); and was used here to compare whether two diagnostic criteria classified the same individuals as having cancer cachexia or not. Demographic characteristics of patients with and without cachexia were investigated using independent samples t-Test or Mann-Whitney independent samples test for continuous variables as appropriate, and Chi-square (χ^2) test or Fisher's exact test for categorical variables as appropriate. All tests were two-sided and statistical significance was reported at the $p \leq 0.05$ level. All analyses were conducted using SPSS Statistics (Version 21.0, IBM Corporation, Armonk, NY).

4. RESULTS

4.1 Demographic and Anthropometric Characteristics

A total of 547 patients with NSCLC were included in the study. Patients with missing data required for the diagnostic criteria (e.g. body weight) or poor quality CT images were excluded (n=76). **Table 4.1** shows the characteristics of the study participants. The majority of patients were men (71.1%) with a mean age of 61 ± 8 (range 34-88 years old) and a mean BMI of 24.8 ± 3.9 (range 14-36) kg/m^2. Although most individuals were normal weight (41.7 %), the population consisted of underweight, normal weight, overweight, and obese individuals. Out of the obese subjects, all were classified as obese class I (n=70), except for one subject that was in the class II category.

Over half (54.1%) of the population was sarcopenic, mostly consisting of men (57.1%). Men presented with greater muscularity than women, although women presented with greater BMI. A large percent (75.1%) of the population had experienced an ongoing degree of weight loss of at least 2%. Forty-seven percent of the patients had experienced weight loss greater than 5% in the past six months, **Table 4.1**.

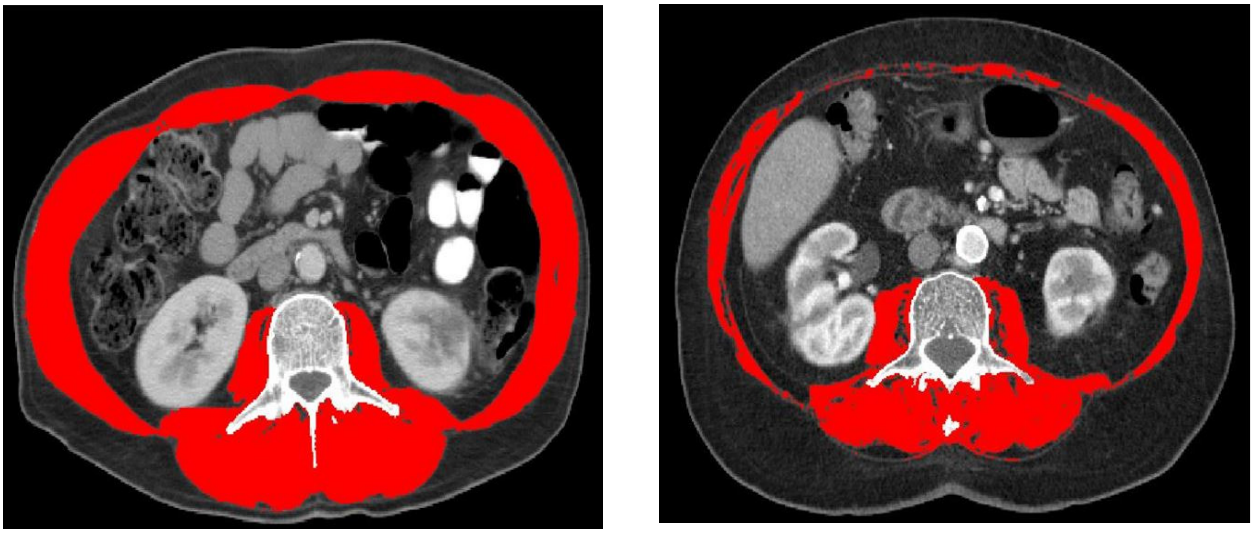
Table 4.1 Overall Characteristics of Cohort

	Total (N=547)	Woman (N=158)	Men (N=389)	
Variables	Mean ± SD (Range)	Mean ± SD (Range)	Mean ± SD (Range)	P-value[a]
Age (y)	61 ± 8 (34-88)	63 ± 8 (45-85)	61 ± 8 (34-88)	0.007
Weight (kg)	70.7 ± 14.0 (37-114.0)	63.6 ± 11.3 (37-90)	73.7 ± 13.9 (39-114)	0.001
Height (m)	1.7 ± 0.1 (1.3-2.0)	1.6 ± 0.07 (1.3-1.8)	1.7 ± 0.07 (1.5-2.0)	0.001
Muscularity (cm^2/m^2)	49.5 ± 8.8 (22.8-74.3)	42.8 ± 6.8 (22.8-67.8)	52.2 ± 8.0 (28.3-74.3)	0.001
BMI (kg/m^2)	24.8 ± 3.9 (14-36)	25.3 ± 4.2 (15-36)	24.6 ± 3.8 (14-33)	0.046
Variables	Percentage	Percentage	Percentage	P-value[a]
BMI Categories: Under Weight	6.2%	5.7%	6.4%	0.196
Normal Weight	41.7 %	38.0%	43.2%	
Overweight	39.1%	38.6%	39.3%	
Obese	13.0%	17.7%	11.1%	
Sarcopenic[b]	54.1%	46.8%	57.1%	<0.001
Weight Loss >2%	75.1 %	79.7%	73.3%	0.249
Weight Loss >5%	47.0%	51.3%	45.2%	0.042

Data are expressed as mean ± SD (range) or percentage.
[a]Independent samples t-Test or Chi-square test, women vs. men.
[b]Cutpoints to defined sarcopenia were used according to Prado *et. al.* (8): Men < 55 cm^2/m^2; woman < 39 $cm^{2/}m^2$, BMI= Body Mass Index

4.2 Sarcopenia

Through the analysis of cross-sectional areas of skeletal muscle in CT images, we were able to clearly identify individuals as sarcopenic or not (**Figure 4.1**). This information completed the evaluation for criterion 3 (any degree of weight loss >2% and sarcopenia). This figure illustrates how patients with similar BMI may present with different body composition phenotypes (i.e. not sarcopenic versus sarcopenic).



Not Sarcopenic
BMI: 22 kg/m^2
Muscularity: 175.3 cm^2

Sarcopenic
BMI: 22 kg/m^2
Muscularity: 85.15 cm^2

Figure 4.1 Comparison of skeletal muscle at the third lumbar vertebrae region between individuals with similar body mass index. Segmented images for ■ skeletal muscle.

4.3 Prevalence of Cancer Cachexia

Figure 4.2 shows the prevalence of cachexia by each diagnostic criterion used. The prevalence of cachexia was approximately 47%, 8% and 41% for criterion 1, 2 and 3 respectively. Diagnostic criterion 1 and 3 diagnosed a similar proportion of individuals, however criterion 2 diagnosed a significantly lower proportion. Additionally, McNemar test showed that cachexia diagnosis was not consistent among the three classifications: criterion 1 vs. 2, $p < 0.0001$; criterion 1 vs. 3, $p = 0.021$, and criterion 2 vs. 3, $p < 0.0001$. Although all three

scenarios were significantly different; criterion 1 vs. 2 and 2 vs. 3 displayed a higher degree of significance, suggesting a greater degree of disagreement.

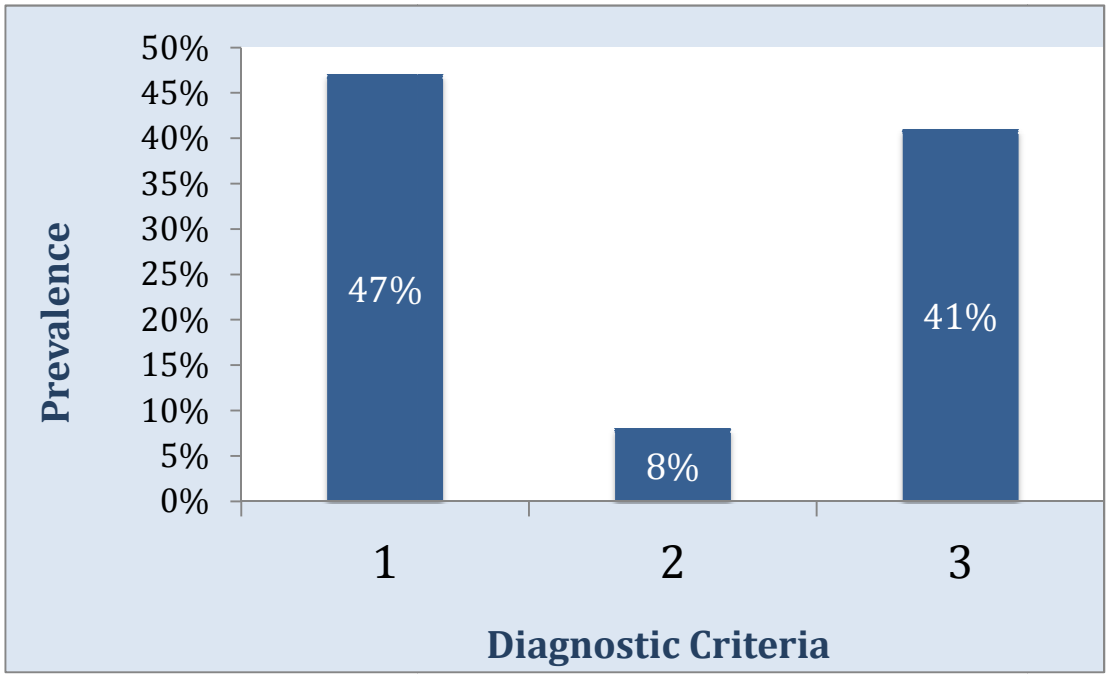


Figure 4.2 Prevalence of cachexia by each diagnostic criterion.
Diagnostic criteria according to Fearon *et al*. (7). 1: Weight loss >5% over past 6 months; 2: BMI <20 kg/m2 and any degree of weight loss >2%; or 3: Skeletal muscle consistent with sarcopenia and any degree of weight loss >2%.

4.4 Prevalence of Cachexia by BMI Categories

Table 4.2 shows the prevalence of cachexia by BMI category for the three definitions. Underweight individuals were mostly identified as having cancer cachexia regardless of the definition used. Since diagnostic criterion 2 includes a BMI of <20 kg/m^2 in addition to the weight loss component, it mostly only identified underweight individuals as having cancer cachexia.

Table 4.2 Prevalence of Cachexia by BMI Categories			
BMI Category [a]	Cachexia 1	Cachexia 2	Cachexia 3
Underweight	67.6%	79.4%	76.5%
Normal Range	61.0%	7.0%	57.9%
Overweight	33.6%	0%	27.6%
Obese	32.4%	0%	12.7%

[a]World Health Organization classification (21): <18.5 kg/m^2 as underweight, 18.5-24.9 kg/m^2 as normal range, 25.0-29.9 kg/m^2 as overweight, 30.0-34.9 kg/m^2 as class I obese, and 35.0-39.9 kg/m^2 as class II obese. Diagnostic criteria according to Fearon *et al*. (7). 1: Weight loss >5% over past 6 months; 2: BMI <20 kg/m2 and any degree of weight loss >2%; or 3: Skeletal muscle consistent with sarcopenia and any degree of weight loss >2%.
BMI= body mass index

5. DISCUSSION

5.1 Review of Hypothesis

The hypothesis was rejected as data analysis demonstrated the exact opposite. The recently proposed diagnostic criteria (7) provided significantly different prevalence of cachexia (47%, 8% and 41%, respectively) and different individuals were identified with each definition used (criterion 1 vs. 2, $p < 0.0001$; criterion 1 vs. 3, $p = 0.021$, and criterion 2 vs. 3, $p < 0.0001$). We concluded that the suggested definitions of cancer cachexia failed to consistently identify individuals as such.

5.2 Discussion of Results

This present study aimed to investigate the consistency of recently proposed cachexia diagnostic criteria. Our results suggest that the classification system proposed by Fearon *et al. (7)* does not consistently identify individuals as having cancer cachexia, a finding of potential impact to clinical and research settings. The diagnosis of cancer cachexia is not only useful for proper identification and understanding of this condition but it is also of outmost importance for proper referral for specialized care, and hence treatment of cachexia. Furthermore, the diagnosis of this condition is useful for establishing entry criteria for cachexia clinical trials (7).

In order for diagnostic criteria to be valuable and applicable it must have high sensitivity and specificity. The studies of Wallengren *et al.* (25) support that cancer cachexia prevalence can be highly variable depending on the definition criterion used. Although the study compared

different diagnostic criteria, it also reported a highly variable prevalence ranging from 6-82% (25).

In this study, men presented with more skeletal muscle depletion (sarcopenia) than woman. This finding has been reported in multiple studies in the past. Harvie *et al*. (6) reported that over the course of chemotherapy, men experienced a decrease in fat free mass and resting energy expenditure that was not seen in woman. Baracos *et al.* (26) also found that a larger percentage of men met the criteria for sarcopenia, compared to women.

Similarly to our study, other studies have also evaluated the prevalence of cancer cachexia using criteria proposed by the International Consensus Group. On a similar fashion, Blum *et al.* (27) evaluated the prevalence of cachexia of several cancer types using 2 of the 3 diagnostic criteria: criterion 1 (weight loss >5% in the past six months) and criterion 2 (any ongoing degree of weight loss >2% + BMI <20 kg/m^2). The study reported the prevalence of cancer cachexia to be approximately 45% and 11.5% for diagnostic criterion 1 and 2, respectively (27). These findings were parallel to our reported prevalence of 47% for criterion 1 and 8% for criterion 2. Both studies showed the tendency of diagnostic criterion 2 to underestimate the prevalence of cancer cachexia. A possible explanation for this is the narrow BMI component of <20 kg/m^2, which directly targets mostly underweight individuals (79.4%) and almost completely excludes other BMI categories. The minority of individuals in this study had a BMI in the underweight category (6.2%), resulting in this underestimation. Blum *et al.* also reported inconsistency of the individuals identified within those two criterions with 88 patients overlapping, leaving 11 that were not classified by both criteria (27).

It is possible that criterion 1 and criterion 2 are inferior to criterion 3, due to a lack of body composition assessment (i.e. sarcopenia). Cachexia has been known to appear regardless of changes in body weight or BMI (28). Many studies have reported a high prevalence of sarcopenia in overweight and obese individuals, in addition to normal ranged and underweight individuals (26, 28, 29).

Therefore, cachexia can be a hidden condition. In fact, sarcopenia may be masked by the presence of obesity (30). Additionally, fluid retention has been shown to disguise the breakdown of skeletal muscle (29) and may lead to failure to identify a cachectic patient if only weight loss is taken into account. It is possible that criterion 3 (any ongoing degree of weight loss >2% + sarcopenia) may lead to a more accurate diagnosis of cancer cachexia. For this reason, more

sophisticated tools may be needed for the diagnosis of cachexia, such as the use of CT scans or other body composition techniques as discussed in Fearon *et al*. (7). Other studies looking into diagnostic criteria for cancer cachexia have also utilized dual energy X-ray absorptiometry for the analysis of body composition (i.e. appendicular skeletal muscularity) (10, 25). In this study, we used highly sophisticated CT scans, which are the preferred method for muscle mass assessment (7). CT scans are a hidden treasure in body composition research (9) and can be readily available from the medical records of cancer patients, because they are constantly being performed for diagnosis and follow-up purposes. Although CT scans cannot be acquired for the sole purpose of body composition analysis due to the amount of radiation, they can be retrieved from the medical records and used for the additional purpose of body composition analysis in oncology settings (9).

It is possible that there are more accurate classifications for cancer cachexia involving the evaluation of additional factor such as symptoms, quality of life, functional measurements, and metabolic profiling. A multifactorial approach to diagnose cancer cachexia would likely provide a more in-depth assessment of nutritional status and overall health in these patient populations (7, 27).

5.3 Limitations and Future Research

This study was composed of a homogenous population, of patients with advanced NSCLC. It is possible that the diagnostic criteria hereby investigated may be more applicable to other cancer types.

A possible limitation has been that weight loss data was self-reported by participants; however, studies have shown this to be a reliable measure in cancer patients. Lin *et al.* (31) reported this measurement to be reasonably accurate, although individuals with a BMI in the normal-range report their weight more precisely.

In the present study, the diagnostic criteria proposed by Fearon *et al.* (7) lead to highly varied prevalence of cancer cachexia. This indicates the remaining need for a classification system with clear cut-off points, which at the same time are cost-effective and easily applied in clinical settings. Having a standard definition will allow improved routine clinical management and lead to early detection and treatment of cancer cachexia. Additionally, a standardized definition would also increase our knowledge and understanding of cancer cachexia, by allowing comparison of results among studies and setting a foundation for future research.

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