Nutrition 90 (2021) 111271

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

New cancer cachexia staging system for use in clinical practice

Emanuelly Varea Maria Wiegert Ph.D. [a,*], Livia Costa de Oliveira Ph.D. [a], Larissa Calixto-Lima Ph.D. [a], Gabriela Villaça Chaves Ph.D. [b], Márcia Soares Silva Lopes Ph.D. [c], Wilza Arantes Ferreira Peres Ph.D. [c]

[a] Palliative Care Unit, National Cancer Institute, Rio de Janeiro, RJ, Brazil
[b] Cancer Hospital II, National Cancer Institute, Rio de Janeiro, RJ, Brazil
[c] Josué de Castro Institute of Nutrition, Federal University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil

ARTICLE INFO

Article History:
Received 18 December 2020
Received in revised form 27 March 2021
Accepted 6 April 2021

Keywords:
Nutritional status
Cancer cachexia criteria
Muscle wasting
Incurable cancer
Quality of life
Survival

ABSTRACT

Objectives: Previous attempts to classify cancer cachexia (CC) have demonstrated limitations regarding stages and diagnostic criteria. This study aims to develop and validate a new staging system for CC in patients with incurable cancer.

Methods: This is an analysis of a database from a prospective cohort study of 1325 patients with advanced cancer referred for palliative care between 2016 and 2020. The cohort was randomly divided into two groups: Development (882 patients) and validation (443 patients) sets. A hierarchical cluster analysis was performed to distinguish different stages of CC in the development set. Next, the optimal cutoff points and ideal combinations of the most important factors associated with the CC groups (clusters) were ascertained. Finally, the relationship between the CC stages determined using the new system and body composition, quality of life, and overall survival was verified with the validation set.

Results: The new system classified CC into three stages: Precachexia (10.8%), cachexia (57.8%), and refractory cachexia (31.4%), based on a combination of percentage weight loss in the past 6 mo (<15 or ≥ 15), body mass index (<21.0, 21.0–26.4, >26.4 kg/m^2), and mid-upper-arm muscle area ($\geq 38.0/\geq 35.5$ or $<38.0/<35.5$ cm^2 in men/women, respectively). The new staging system enabled a clear classification of patients into three CC groups according to the outcomes analyzed. Outcomes of patients with refractory cachexia were significantly worse than those in the other groups.

Conclusions: This study presents a useful, valid system for CC staging in the clinical setting, and is also capable of predicting outcomes, including quality of life and overall survival.

Introduction

Cancer cachexia (CC) is a complex, multifactorial, pathophysiological syndrome resulting from a variety of host–tumor interactions that are still not fully understood [1]. CC contributes to a poor prognosis due to the progressive depletion of the body' energy and protein reserves (e.g., skeletal muscle and adipose tissue), and negatively affects physical function and the quality of life (QoL) of both patients and their caregivers [1–3]. CC could be described as a spectrum that develops to varying degrees. The full spectrum, which not all patients develop, consists of weight loss (WL), muscle wasting, anorexia, and inflammation [1]. Some patients die before they develop advanced CC, while others stabilize with treatment of their primary disease or due to other clinical factors that preclude further progression [4,5].

Current guidelines recommend early recognition of CC, but its diagnosis is complex, not least because of its heterogeneous mechanisms and multiple phenotypes and clinical features [6,7]. One of the barriers to the study of CC is the lack of a commonly accepted definition for use in clinical practice. Several criteria for its diagnosis have been suggested, but there is some disagreement between the systems available in the literature [8–13]. Consequently, the prevalence of CC varies considerably depending on the diagnostic criteria used [9,14–17].

The main diagnostic criteria assess CC in two or more stages [1,8–13]. The two-stage system (i.e., noncachexia [NCa] or cachexia [Ca]) fails to discriminate between different CC phenotypes, making the system less effective for clinical applications [3,9,18]. A four-stage system (i.e., NCa, precachexia [PCa], Ca, and refractory cachexia [RCa]) would be more useful in the clinical

*Corresponding author: Tel.: +55 21 97577 0548; fax: +55 21 32073 700.
E-mail address: manuvarea@gmail.com (E.V.M. Wiegert).

https://doi.org/10.1016/j.nut.2021.111271
0899-9007/

setting, but the current systems fail to distinguish successfully between the different stages, especially transitional and intermediate stages [10,12,15]. In addition, there is disagreement across systems as to what number of CC stages would be optimal, what parameters to use, and what cutoff points to apply, not to mention the fact that these parameters have been determined quite randomly [8–13].

In 2011, an international consensus definition of CC established a classification of the syndrome based on WL, body mass index (BMI), and/or low muscle mass [1]. The classification sets cutoffs for Ca, but only provides for a qualitative classification of other categories, such as PCa and RCa. Capitalizing on the above work, in the study presented herein, we analyze an extended database of patients with incurable cancer to develop and validate a new staging system for CC based on optimal combinations and cutoffs of factors associated with the syndrome.

Methods

Study population, study setting, and data collection

Study participants were enrolled in a prospective cohort at the palliative care unit (PCU) of the National Cancer Institute in Brazil between July 2016 and March 2020. The focus of care in the PCU is symptom-oriented. The study population has been described in more detail elsewhere [16,19,20]. The National Cancer Institute Research Ethics Committee (registration number 1.407.458; 2016) approved the research, and all participants provided written informed consent before participating in the study.

Consecutive eligible inpatients (hospitalized) and outpatients (ambulatory, not including home care) were evaluated during their first visit to the PCU and followed for mortality events after inclusion. The eligibility criteria were incurable cancer (locoregional advanced or metastatic cancer proven by histologic, cytologic, or radiologic evidence); not receiving any antineoplastic treatment with curative intent; age ≥20 y; both sexes; and Karnofsky performance status (KPS) ≥30%. KPS scores (ranging from 0 [death] to 100 [full function]) were assigned according to patient-reported daily physical function [21]. The following data were collected from the electronic records: primary cancer site, metastatic disease, antitumor treatment, and date of death. A routine laboratory analysis was performed on the day of enrollment at the PCU. A single intravenous blood sample was collected to analyze serum albumin, C-reactive protein (CRP), and a complete blood cell count.

Of the 2190 patients who were enrolled in the original cohort, 1325 were included in the present analysis after excluding patients with incomplete data on the variables analyzed and those with a life expectancy of <1 mo (n = 865). Patients were randomly divided into two groups, with 70% of patients (n = 882) forming the development cohort and 30% (n = 443) the validation set. There were no statistical differences between the present study sample and the original cohort in terms of key characteristics (age, sex, primary cancer site, distant metastasis, and most KPS distributions; all $P > 0.050$).

Anthropometry

Weight (in kg) and height (in m) were measured with patients wearing light clothing and without shoes. Weight was obtained using a calibrated portable Wiso digital scale (model 905; Brazil; 180 kg capacity). For patients unable to stand, an in-bed scale system (Go Bed II; Stryker, Kalamazoo, MI) was used. Height was measured using a tape wall-mounted stadiometer. When the use of a stadiometer was not possible, an anthropometer was used to measure knee height with the knee and ankle joints flexed at 90°, and height was estimated using the Chumlea et al. formulas [22]. Patient-reported weight history in the past 6 mo and percentage WL were calculated as follows: ([current weight − previous weight]/previous weight) × 100. BMI (kg/m^2) was calculated using weight (kg) and height (m^2).

Triceps skinfold thickness (in mm) was assessed at the midpoint of the dominant arm between the shoulder (acromion) and elbow (olecranon) while the person was bending their arm at 90°. Thickness was measured three times with a skinfold caliper (Lange; Cambridge Scientific Industries, Watertown, MA). Arm circumference (in cm) was measured at the same point using a nonstretch measuring tape. Mid-upper-arm muscle area (MUAMA; in cm^2) was calculated from triceps skinfold thickness and arm circumference using the equation proposed by Heymsfield et al. [23]. Calf circumference (in cm) was determined by measuring the largest perimeter (maximum measurement in the plane perpendicular to the longitudinal line of the calf) with the patient sitting with the knees flexed to 90° and feet 20 cm apart.

Nutritional risk

Nutritional risk was evaluated using the Portuguese-validated version of the Patient-Generated Subjective Global Assessment short form (PG-SGA SF) (FD Ottery, 2005, 2006, 2015; available from Ottery at pt-global.org). The PG-SGA SF consists of a four-part questionnaire to obtain a patient-reported history of weight change (score 0–5), food intake (score 0–4), nutrition impact symptoms (score 0–24), and performance status (score 0–3). The sum of the scores (0-36) gives the total score, with higher scores indicating higher nutritional risk.

Fatigue and loss of appetite

Fatigue and loss of appetite were assessed using the Edmonton Symptom Assessment System. This system is a validated patient-reported tool to measure symptom severity, and is widely used in palliative cancer populations [24]. Patients self-report the intensity of their symptoms on a numerical scale from 0 (no symptoms) to 10 (worst possible symptoms). The cutoff value to identify moderate-to-severe symptoms was set at >3 (0–3 vs. ≥4) [25].

Muscle strength

Muscle strength was assessed by handgrip strength (in kg) using a Jamar hydraulic dynamometer (Baseline, Fabrication Enterprises, Inc., Elmsord, NY). Patients were instructed to remain seated and self-adjust the dynamometer to fit comfortably in their hand, elbows flexed to 90°, and forearms in a neutral position to obtain their best performance contractions in response to a voice command. Three trials were performed on each side of the hand with a 1-min rest interval between the trials of each hand [26]. Maximum handgrip strength was defined as the highest value of the six measurements performed with both upper limb sides.

Body composition measures based on computed tomography

The subgroup of patients in the development set who had computed tomography (CT) scans available up to 30 d before recruitment were evaluated. Tissue was analyzed on transverse cross-section CT images at the third lumbar vertebra level using SliceOmatic, version 5.0 (TomoVision, Montreal, Canada), which enables the differentiation of tissues using the following preestablished tissue-specific Hounsfield unit (HU) boundaries: −29 to +150 for the skeletal muscles (psoas, erector spinae, quadratus lumborum, transversus abdominus, internal and external obliques, rectus abdominus); −150 to −50 for visceral adipose tissue; and −190 to −30 for subcutaneous and intermuscular adipose tissue [27]. A selected subsample of 32 images was analyzed by a second investigator. The interobserver coefficient variations of muscle mass and adipose tissue measurements were 0.56% and 0.12%, respectively.

Skeletal muscle index (SMI; in cm^2/m^2) was calculated using the skeletal muscle cross-sectional area (in cm^2) normalized for height squared (in m^2). Similarly, total adipose tissue (TAT) was calculated as the sum of intramuscular, visceral, and subcutaneous adipose tissue, and normalized for height to calculate the TAT index. Sarcopenia was defined as low SMI, and set at ≤34.6 cm^2/m^2 for women and ≤38.3 cm^2/m^2 for men. Low TAT index was set at ≤58.5 cm^2/m^2 for women and ≤41.0 cm^2/m^2 for men, and myosteatosis was defined as low skeletal muscle radiodensity (SMD) and set at ≤26.3 HU for women and ≤28.4 HU for men, all of them defined according to values below the first tertile of the studied sample.

Quality of life

QoL was assessed using the Brazilian Portuguese-language version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative [28]. This tool consists of 15 items, including two multiitem functional scales (physical [items 1–3] and emotional [items 13 and 14]); two multiitem symptom scales (fatigue [items 7 and 11] and pain [items 5 and 12]); five single-item symptom scales (nausea/vomiting [item 9], dyspnea [item 4], insomnia [item 6], appetite loss [item 8], and constipation [item 10]); and one question referring to global QoL (item 15) [29]. In responding to the questionnaire, patients assess each question/item on a numerical scale with four answer categories: 1 (not at all), 2 (a little), 3 (quite a bit), or 4 (very much), except for global QoL (item 15), which is rated with seven answer categories from 1 (very poor) to 7 (excellent).

Survival

Overall survival was calculated as the time interval between the date of recruitment and the date of death from any cause or last follow up. In other words, all included patients were followed prospectively until their date of death, and patients who were alive after the follow-up period (180 d) were censored for the survival analysis.

New cancer cachexia staging system

The new CC staging system was developed in three parts. In the first part, we made a preliminary preselection of the main factors associated with CC (%WL, BMI, muscle mass [by MUAMA]), laboratory markers (CRP and albumin), and signs and symptoms (fatigue and loss of appetite) according to previously described diagnostic criteria [9–12]. Next, we carried out the procedure for the construction of a new CC staging system based on these variables, using the development set. Finally, we assessed the validity of the new staging system by ascertaining the relationship between the CC stages and outcomes in the validation set.

Statistical analysis

The analysis was performed using Stata 13.1 (Stata Corp., College Station, TX), except for the cluster analysis, which was performed using SPSS Statistics 21.0 (IBM SPSS, Inc., Chicago, IL). Normality of distribution for the quantitative variables was tested using the Kolmogorov–Smirnov test. Normally distributed variables were presented as mean ± standard deviation, and those not distributed normally were presented as median and interquartile range (IQR). Categorical data were demonstrated as numbers of observations (n) and percentages (%). Student's *t* test or the Mann–Whitney U test (for continuous variables) and the ^{2} test (for categorical variables) were used to compare differences between patient characteristics.

Part 1: Data set and cancer cachexia features

The database of the 1325 patients for whom complete data was available on all main factors previously reported in association with CC (%WL, BMI, muscle mass [by MUAMA]), laboratory markers (CRP and albumin), and signs and symptoms (fatigue and loss of appetite) [9–12] was randomly divided into two groups: Development (≈70% of the sample) and validation (≈30% of the sample) sets, using a random selection process (random list generated by STATA).

Part 2: Development of new cancer cachexia staging system

Hierarchical cluster analyses by Ward's minimum-variance method were performed to identify distinct groups of patients who had similar features according to the preselected factors related to CC. For this analysis, squared Euclidian distance was used as a quantitative indicator for the degree of similarity between cases, and data were standardized by the Z-score. The appropriate number of cluster (subgroups) was decided from a combination of visual inspection of the dendrogram and clinical interpretation of groupings. From the cluster analysis, ordinal logistic regression using generalized linear models was performed to identify the explanatory variables associated with the CC group clusters (dependent variable).

Receiver operating characteristic curves were plotted to determine the optimal cutoff points for these significant explanatory variables to discriminate between the CC groups (clusters). The CC staging system was obtained from the estimated coefficient probability (≥70%) of each of the 27 possible combinations of independent variables and cutoffs for the respective CC groups (clusters) given by the adjusted ordinal logistic regression model (Suppl. Table 2). After classifying the combinations within the CC groups, the 27 possibilities were collapsed to simplify the new CC system (Fig. 1).

Part 3: Validity of new cancer cachexia staging system

Patients in the validation set were classified using the new proposed CC classification system, and the relationships between the CC stages and the clinical, inflammatory, and body composition factors, including QoL and OS, were determined. Comparisons between the CC groups were tested for normal distribution by analysis of variance, followed by the Bonferroni post hoc test, and nonnormally distributed variables were tested by the Kruskal–Wallis test. The chi-square test or Fisher's exact test were used for pairwise comparisons of the frequencies of patients' responses of QoL questions/items from the questionnaire Cancer Quality of Life Questionnaire Core 15 Palliative, and compare body composition compartments (SMI, TAT index, and SMD) between the groups.

The survival analysis included the Kaplan–Meier method (comparisons with log-rank tests) and Cox proportional hazards model (estimated hazard ratio [HR] and 95% confidence interval [CI]) adjusted for confounding factors (age, primary tumor site, and inpatient or outpatient). Statistical significance was set at $P < 0.050$.

Results

A total of 1325 patients were included in the study. There were no statistical differences between any of the patient characteristics in the development (n = 882) and validation (n = 443) data sets (Table 1). According to the cluster analysis of the development set, discrimination of the three distinct groups of patients in relation to the features of CC was possible, and were classified as 1 (better), 2 (moderate), and 3 (worse; Suppl. Fig. 1). BMI, %WL in the past 6 mo, and MUAMA (all $P < 0.001$) were significantly associated with the groups identified in the cluster analysis (Table 2).

Table 3 provides the accuracy of the cutoff points for the three factors used to establish the new CC system. MUAMA (area under the receiver operating characteristic curve [AUC]: 0.97; 95% CI, 0.95–0.99), and BMI (AUC: 0.95; 95% CI, 0.93–0.97) showed excellent discrimination for the better group (cluster 1), and %WL in past 6 mo was very accurate in discriminating the worse group (cluster 3), with an AUC of 0.95 (95% CI, 0.94–0.96).

Based on the new CC staging system (Fig. 1), patients in the validation group were classified into PCa (n = 48; 10.8%), Ca (n = 256; 57.8%), and RCa (n = 139; 31.4%) according to the cutoff points and a combination of %WL in the past 6 mo (<15 or ≥15), BMI (<21.0, 21.0–26.4, >26.4 kg/m^2), and muscle mass by MUAMA (≥38.0/≥35.5 for men; <38.0/<35.5 cm^2 for women). In the comparison between the CC stage groups, RCa presented significantly worse values for most features studied (clinical, inflammatory, and nutritional) than the other two groups. In addition, 293 patients (n = 176 female, n = 117 male) in the validation set had CT scans from ≤30 d before enrollment. Sarcopenia (low SMI), low TAT index, and myosteatosis (low SMD) identified according to the sex-specific cutoff points were significantly more prevalent in RCa and Ca than in PCa (all $P < 0.050$; Table 4).

As shown in Figure 2, the increasing severity of CC was significantly related with a poorer QoL. Patients staged as RCa presented a lower percentage to answer a question/item about overall QoL (as assessed by item 15) as excellent (representing a better overall

	BMI >26.4		BMI 21.0-26.4		BMI < 21.0
	MUAMA		MUAMA		
	≥ 38.0 (♂) ≥ 35.5 (♀)	< 38.0 (♂) < 35.5 (♀)	≥ 38.0 (♂) ≥ 35.5 (♀)	< 38.0 (♂) < 35.5 (♀)	
%WL <15.0	**PCa**	**Ca**	**Ca**		**Ca**
%WL ≥15.0	**Ca**		**Ca**	**RCa**	**RCa**

Fig. 1. A new cancer cachexia staging system. %WL, percentage weight loss; MUAMA, mid upper-arm muscle area (cm^2); BMI, body mass index (kg/m^2); PCa: pre-cachexia; Ca: cachexia; RCa: refractory cachexia; ♀, female; ♂, male.

Table 1
Demographic and clinical characteristics of patients in the development and validation sets (N = 1325)

Variables	Development set n = 882		Validation set n = 443		*P*-value
	n		n		
Age (y)*	882	62.4 (13.5)	443	61.7 (13.3)	0.124
Age (y)†					
<65		488 (55.3%)		274 (61.8%)	0.092
≥65		394 (44.7%)		169 (38.2%)	
Sex†	882		443		
Male		404 (45.8%)		180 (40.5%)	0.074
Female		478 (54.2%)		263 (59.5%)	
Primary tumor site†	882		443		
Digestive system		260 (29.4%)		159 (35.9%)	0.074
Gynecological		132 (15.0%)		91 (20.5%)	
Head and neck		166 (18.8%)		32 (7.2%)	
Breast		84 (9.5%)		46 (10.4%)	
Lung		84 (9.55%)		46 (10.4%)	
Others‡		156 (17.7%)		69 (15.5%)	
Cancer stage†	882		443		
Locoregional advanced		255 (28.9%)		90 (20.3%)	0.083
Distant metastasis		627 (71.1%)		353 (79.7%)	
Current health care setting†	882		443		
Inpatient		155 (17.6%)		94 (21.2%)	0.109
Outpatient		727 (82.4%)		349 (78.8%)	
Karnofsky performance status (%)†	882		443		
30		82 (9.3%)		49 (11.1%)	0.653
40		200 (22.7%)		104 (23.5%)	
50		273 (30.9%)		126 (28.4%)	
60		169 (19.1%)		86 (19.4%)	
≥70		158 (18.0%)		78 (17.6%)	
Body mass index (kg/m^2)*	882	22.8 (5.3)	443	22.8 (5.6)	0.940
Weight loss in 6 mo (%)§	882	9.7 (3.0-18.4)	443	9.4 (2.4-18.9)	0.865
Mid-upper-arm muscle area (cm^2)*					
Female	478	28.2 (11.8)	263	27.8 (12.2)	0.658
Male	404	29.2 (11.6)	180	28.8 (9.7)	0.714
C-reactive protein (mg/L)§	874	5.0 (1.4-10.1)	442	5.4 (2.0-10.9)	0.125
Albumin (g/dL)§	878	3.5 (2.9-4.0)	442	3.4 (2.8-3.9)	0.093
Fatigue§	882	4 (0-6)	443	3 (0-6)	0.137
Loss of appetite§	882	2 (0-8)	443	0 (0-6)	0.098
Survival (d)§	882	63 (22-150)	443	56 (23-113)	0.100

n is the number of observations, and % the frequency.
*Mean ± standard deviation; Student' *t* test.
†n; %, χ^2 test.
‡Central nervous system, kidney and urinary tract, male genital organs, peritoneum, mediastinum, and unrecognized site.
§Median; interquartile range - Mann–Whitney U test.

QoL) and highest percentage to answer very poor than the PCa patients. The differences were statistically significant for questions about physical functioning (items 1–3), dyspnea (item 4), insomnia (item 6), fatigue (item 7), pain (item 12), nausea/vomiting (item 9), and appetite loss (item 8), reflecting a higher prevalence of patient responses related to the burden of symptoms in the RCa group.

The median OS for the patients was 75 d (IQR, 31–176 d). Differences in OS were statistically significant according to CC stages (PCa: 123 d [IQR, 65–180 d]; Ca: 89 d [IQR, 38–180 d]; RCa: 46 d [23–100 d]; Fig. 3). In addition, there was a significantly higher risk of death within 180 d in the RCa (HR: 2.90; 95% CI, 1.10–4.01) and Ca (HR: 1.64; 95% CI, 1.15–2.32) groups than in the PCa group, indicating that the proposed new CC staging system predicts 180-d mortality (Table 5).

Table 2
Ordinal logistic regression of factors associated with cancer cachexia groups created according to cluster analysis in the development set (N = 882)

Variables	β coefficient	Standard error	*P*-value
Body mass index (kg/m^2)	−0.428	0.045	< 0.001
Mid-upper-arm muscle area (cm^2)	−0.197	0.018	< 0.001
Weight loss in 6 mo (%)	0.419	0.026	< 0.001
Albumin (g/dL)	0.389	0.559	0.13
C-reactive protein (mg/L)	0.023	0.020	0.24
Fatigue (score)*	0.017	0.039	0.66
Loss of appetite (score)*	0.011	0.034	0.75

n is the number of observations.
*According to Edmonton Symptom Assessment System (score 0–10).

Discussion

This study aimed to determine CC phenotypes from the extensive, robust statistical analysis of data from a homogeneous population diagnosed with incurable cancer receiving care at a PCU. Three distinct groups of CC were distinguished from the factors most commonly described in previous studies to define CC syndrome [9–12]. All analyses were performed with patients randomly grouped into development and validation cohorts, enabling us to validate our results with a separate set of data. Our results demonstrate that the proposed CC system clearly distinguishes patients by patient-centered outcomes, including body composition, QoL, and prognosis. This is the first study to determine a feasible, nonarbitrary number of CC stages and key factors that can easily detect CC, representing an advance in efforts to improve CC classification in clinical practice.

Table 3
Cutoff points and accuracy measurements of independent factors associated with cachexia groups created according to cluster analysis in the development set (N = 882)

Variables	Cluster	Cutoff	Sensitivity (%)	Specificity (%)	AUC	95% CI	*P*-value
MUAMA (cm^2)	1 (better)	≥38.0 ♂	92.3	90.0	0.97	0.95–0.99	< 0.001
		≥35.5 ♀	88.9	86.7	0.94	0.92–0.96	< 0.001
	3 (worse)	<26.5 ♂	72.7	65.6	0.77	0.72–0.82	< 0.001
		<24.0 ♀	71.0	69.3	0.77	0.73–0.81	< 0.001
WL in 6 mo (%)	1 (better)	<6.5	71.0	96.0	0.77	0.73–0.81	< 0.001
	3 (worse)	≥15.0	91.8	87.4	0.95	0.94–0.96	< 0.001
BMI	1 (better)	>26.4	89.5	88.5	0.95	0.93–0.97	< 0.001
(kg/m^2)	3 (worse)	<21.0	76.3	73.6	0.81	0.78–0.84	< 0.001

♀, female; ♂, male; AUC, area under the receiver operator characteristic curve; BMI, body mass index; CI, confidence interval; MUAMA, mid-upper-arm muscle area; WL, weight loss.
n is the number of observations.

In the proposed CC classification, PCa is the first in a three-stage system based on a trajectory format, with the latter two being Ca and RCa. In fact, not every patient with incurable cancer develops later stages of CC [5], but they often experience some degree of involuntary WL and/or loss of appetite or/and impaired function, which is why these patients would be at least at the PCa stage. In the present study population, the prevalence of Ca was 57.8%, and, as expected, the outcomes for the RCa group were significantly worse, and patients in the early stages experienced better results, which is consistent with the findings of previous studies [10,12,16].

According to international consensus [1], the clinical diagnostic criteria for CC include %WL ≥5 or %WL ≥2 and BMI <20 kg/m^2 or low muscle mass. Like our staging system, the same consensus also recommends classifying the severity of CC into PCa, Ca, and RCa. However, unlike our system, this diagnostic framework does not set specific objective parameters and cutoff points to define PCa and RCa. Since the publication of the international consensus, other proposals for the classification of patients into CC stages have been described, including WL, BMI, sarcopenia, anorexia, decreased functionality, and abnormal laboratory parameters (e.g., high CRP, anemia, or low albumin) [8–13]. However, these criteria of CC

Table 4
Variables of validation group patients classified by new cancer cachexia system into three cachexia stages

Variables	n	Overall	PCa n = 48 (10.8%)	Ca n = 256 (57.8%)	Rca n = 139 (31.4%)
KPS (%) (median; IQR)	443	50 (40-60)	60 (50–70)	50 (40–60)*	50 (40–60)*
BMI (kg/m^2) (mean; ±SD)	443	22.8 (5.6)	32.1 (4.4)	22.8 (4.8)*	19.6 (3.3)*,†
MUAMA (cm^2) (mean; ±SD)	443				
Male	180	28.8 (9.7)	49.2 (7.6)	29.5 (8.4)*	24.1 (6.3)*,†
Female	263	27.8 (12.2)	48.0 (9.7)	26.6 (9.5)*	20.6 (6.6) *,†
Calf circumference (cm) (mean; ±SD)	358				
Male	153	32.4 (3.9)	38.7 (3.1)	32.5 (3.6)*	31.1 (3.2)*
Female	205	34.3 (2.8)	53.2 (7.4)	32.4 (6.7)*	29.1 (3.8)*
WL in 6 mo (%) (median; IQR)	443	9.4 (2.5–18.9)	3.3 (0.5–6.5)	5.8 (0–10.1)*	23.6 (18.4–29.7) *,†
PG-SGA SF (score) (mean; ±SD)	443	14.8 (6.7)	12.6 (6.1)	14.1 (6.6)	16.9 (6.6) *,†
Albumin (g/dL) (median; IQR)	442	3.4 (2.8–3.9)	3.8 (3.1–4.3)	3.4 (2.9–3.9)*	3.1 (2.6–3.6) *,†
C-reactive protein (mg/L) (median; IQR)	442	5.5 (2.0–10.9)	2.5 (0.8–5.0)	5.6 (2.0–10.4)*	6.8 (3.0–13.7)*
White blood cells, 10^3/L (median; IQR)	440	9,200 (7100–13,000)	7750 (6300–11,100)	9100 (7100–12,400)	10,600 (7700–15,010)*,†
Hemoglobin (g/dL) (mean; ±SD)	440	9.8 (2.2)	10.5 (2.2)	9.9 (2.1)	9.2 (2.2)*,†
Fatigue‡ (median; IQR)	443	3 (0–6)	3 (0–5)	3 (0–6)	4 (0–7)
Loss of appetite‡ (median; IQR)	443	0 (0–6)	0 (0–6)	0 (0–7)	1 (0–7)
HGS (kg) (mean; ±SD)	443				
Male	180	27.0 (9.6)	33.5 (12.7)	26.6 (9.2)*	22.6 (7.9)*,†
Female	263	16.4 (6.8)	19.4 (7.3)	16.4 (6.5)*	13.3 (5.9)*,†
Body composition§	293				
Low TAT index (n; %)‖					
Male	117	39 (33.3)	4 (10.2)	12 (38.8)*	23 (59)*,†
Female	175	58 (33.1)	6 (10.3)	23 (39.7)*	29 (50)*,†
Sarcopenia (n; %)¶					
Male	117	39(33.3)	5 (12.8)	13(33.4)*	21(53.8)*,†
Female	175	58 (33.1)	6 (10.4)	22 (37.9)*	30 (51.7)*,†
Myosteatosis (n; %)#					
Male	117	38 (32.5)	6 (12.8)	13 (33.4)*	19 (53.8)*,†
Female	175	58 (33.1)	8 (13.8)	20 (34.5)*	30 (51.7)*,†

BMI, body mass index; Ca, cachexia; HGS, handgrip strength; IQR, interquartile range; KPS: Karnofsky performance status; MUAMA, mid-upper-arm muscle area; PCa, precachexia; PG-SGA SF, Patient-generated Subjective Global Assessment short form; RCa, refractory cachexia; SD, standard deviation; TAT, total adipose tissue; WL, weight loss
n is the number of observations, and % the frequency. Median; IQR – Kruskal–Wallis test. Mean; ±SD – analysis of variance. n; % – χ^2 or Fisher's exact test.
*Statistically different from PCa.
†Statistically different from Ca.
‡According to Edmonton symptom assessment system (score 0–10).
§According to computed tomography.
‖Low TAT index = below 1st tertile (≤58.5 cm^2/m^2 for women and ≤41.0 cm^2/m^2 for men).
¶Sarcopenia defined according to low skeletal muscle index defined as ≤34.6 cm^2/m^2 for women and ≤38.3 cm^2/m^2 for men.
#Myosteatosis defined according to low skeletal muscle radiodensity (≤26.3 Hounsfield unit for women and ≤28.4 Hounsfield unit for men).

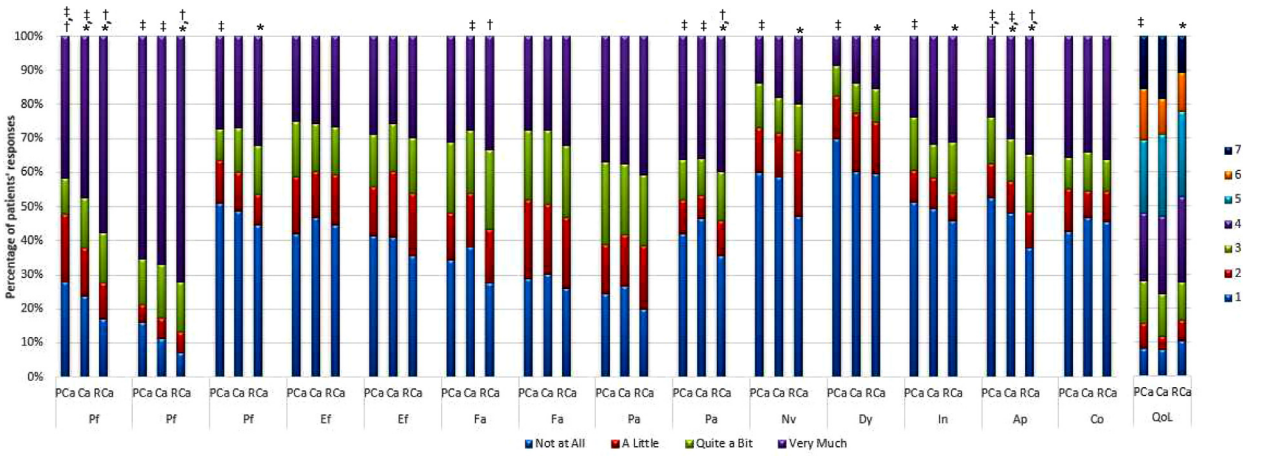

Fig. 2. Baseline responses to the EORTC QLQ C-15-PAL questions 1 to 15 are presented according to percentage of patients' responses to the items/questions. Patients rated each question/item on a numerical scale from 1 (not at all) to 4 (very much) for 1 to 14 and overall QoL was rated from 1 (very poor) to 7 (excellent). QLQ-C15-PAL questions: (1) Do you have any trouble taking a short walk outside the house? (2) Do you need to stay in bed or a chair during the day? (3) Do you need help with eating, dressing, washing yourself, or using the toilet? During the past week: (4) Were you short of breath? (5) Have you had pain? (6) Have you had trouble sleeping? (7) Have you felt weak? (8) Have you lacked appetite? (9) Have you felt nauseated? (10) Have you been constipated? (11) Were you tired? (12) Did pain interfere with your daily activities? (13) Did you feel tense? (14) Did you feel depressed? (15) How would you rate your overall quality of life during the past week? Pf (items 1-3), Ef (items 13,14), Fa (items 7,11), Pa (items 5,12), Nv (item 9), Dy (item 4), In (item 6), Ap (item 8), Co (item 10), and overall QoL (item 15). PCa, precachexia; Ca, cachexia; RCa, refractory cachexia; EORTC QLQ C-15-PAL, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative; QoL, quality of life; Pf, physical functioning; Ef, emotional functioning; Fa, fatigue; Pa, pain; Nv, nausea/vomiting; Dy, dyspnea; In, Insomnia; Ap, appetite loss; Co, constipation. *P* value < 0.05, chi-squared test. *Statistically different from PCa. †Statistically different from Ca. ‡Statistically different from RCa.

have been established on somewhat arbitrary terms that were not derived from the population studied or have not yet been validated.

In this study, a reliable tool was developed based on the evaluation of inexpensive parameters that are easy to measure in routine clinical practice. The main parameters representing the most important features that might indicate the severity of CC were found to be %WL in the past 6 mo, BMI, and low muscle mass by MUAMA. Historically, WL has been the exclusive criterion to classify CC, but with WL alone, distinguishing the effect of CC on body composition compartments is not possible [2,30]. Another point that is still a subject of debate related to WL are the cutoff points [2,11]. Most patients with advanced metastatic cancer have severe WL (≥10% of preillness weight), but neither WL not anorexia alone was found to be capable of defining CC [3]. Fearon et al. [3] described a three-factor profile that included WL, low food intake, and systemic inflammation, which identified patients with both adverse function and prognosis. The comparison based on WL alone failed to show significant differences in terms of function of OS.

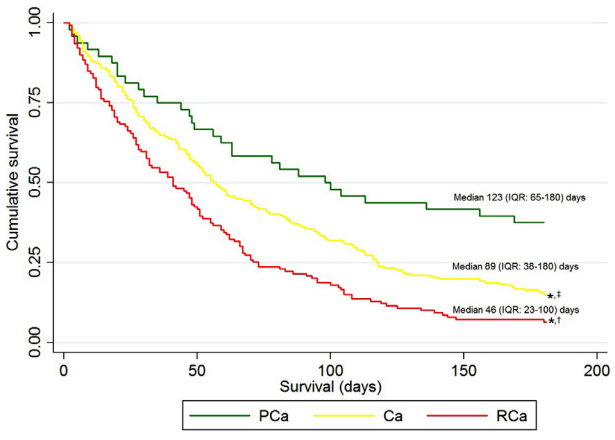

Fig. 3. Kaplan-Meier survival curves and Log-rank test according to cancer cachexia stages in validation group (N = 443). PCa, precachexia; Ca, cachectic; RCa, refractory cachectic; IQR, interquartile range. *Statistically different from PCa. †Statistically different from Ca. ‡Statistically different from RCa.

Low BMI is a traditional phenotypic criterion for malnutrition diagnosis [1,10,31]. However, the BMI levels used to define clinically underweight and cachexia (<18.5, <20, or <21 kg/m^2) are inconsistent [1,18,31,32]. Likewise, some publications [1,18,31] use a single cutoff point to classify subgroups of patients with different degrees of risk. Martin et al. [11] found that BMI adjusted by %WL was associated with the survival of patients with advanced cancer, independently of conventional prognostic factors, including cancer site, stage, and performance status. The researchers argue that the association between BMI and %WL is important because of its representation of the spectrum of these features in contemporary patients with cancer, because overweight/obesity is now prevalent worldwide and the upward shift in body weight makes the definitions of clinically significant %WL increasingly unclear in the cancer context.

Our study is in line with these arguments, because even in patients with incurable cancer, our optimal cutoff points for BMI are considered normal or overweight according to current recommendations for healthy people [32]. Here, we note that the risk of reaching a worse stage of CC in association with any degree of WL is lower for individuals with a higher BMI (i.e., the highest energy reserves) than for individuals with a lower initial BMI. Furthermore, we should not overlook the complex and multifactorial etiologies underlying the cachexia phenotype, irrespective of the body morphology being lean, normal, or obese.

For this reason, body composition can be seen as an important component of cancer, particularly skeletal muscle loss, which is observed as part of the conceptual definition of CC [1,30]. Although routine assessments of muscle mass are encouraged, there is no clear consensus on methodology. Consensual definitions for CC provide different options to measure muscle mass. The order of preference is cross-sectional imaging (CT or magnetic resonance imaging), dual energy x-ray imaging, anthropometric measurements (MUAMA), and bioimpedance analysis (BIA) [1]. CT,

Table 5
Cox proportional regression by new cancer cachexia staging system in validation group (N = 443)

Variables	Univariate		Multivariate*	
	HR (95% CI)	*P*-value	HR[a] (95% CI)	*P*-value
Cachexia stages				
PCa	1.00		1.00	
Ca	0.88 (0.72–1.08)	0.227	1.35 (1.12–1.99)	0.002
RCa	1.62 (1.31–2.01)	< 0.001	1.84 (1.21–2.79)	0.004
Age (y, continuous)	1.02 (1.01–1.06)	0.007	1.02 (1.01–1.06)	0.008
KPS (%, continuous)	0.97 (0.96–0.98)	< 0.001	0.98 (0.97–0.99)	< 0.001
Primary tumor site				
Digestive system	1.62 (1.32–1.87)	0.023	1.34 (1.12–1.69)	0.007
Others	1.00		1.00	
Current health care setting				
Outpatient	1.00		1.00	
Inpatient	2.04 (1.61–2.59)	< 0.001	1.43 (1.09–1.88)	0.009

Ca, cachexia; CI, confidence interval; HR, hazard ratio; KPS, Karnofsky performance status; PCa, precachexia; RCa, refractory cachexia.
n is the number of observations.
*Adjusted by age, type of tumor, and current health care setting (inpatient vs. outpatient).

magnetic resonance imaging, and dual energy x-ray imaging are recommended but difficult to include in routine clinical practice. Blauwhoff-Buskermolen et al. [33] found that the prevalence of low muscle mass depended on the type of muscle measurement used (13% with MUAMA; 59% with CT; and 93% with BIA). However, these differences may have little influence on the diagnosis of CC. Additionally, the authors found that patients with CC whose muscle mass was measured by MUAMA had worse OS (HR: 2.00) than those whose mass was measured by CT (HR: 1.64) or BIA (HR: 1.50) [33].

Our study shows that low muscle mass modulates the degree of WL/BMI, as well as evaluates MUAMA cutoff values for low muscle mass, providing results specific for patients with incurable cancer that differ from the consensus position on CC in the literature [1]. Moreover, attention should be paid to the accuracy and practical availability of measurements. For example, MUAMA is easier to use in clinical practice, but can be less accurate due to interrater variability, something that could be minimized by training [34]. Nonetheless, our results demonstrate in a subsample of patients that the prevalence of sarcopenia (low SMI), myosteatosis (low SMD), and low TAT index differed in the three cachexia phenotypes and was significantly higher in later CC stages, emphasizing the validity of our system.

In this study, CRP and albumin were not found to serve as independent factors to identify CC groups. Nevertheless, when comparing RCa and Ca versus NCa patients, significantly higher levels of CRP and lower levels of albumin were found. Although a number of other studies [35,36] have found a relationship between inflammatory markers and CC in patients with cancer and although our study also found that patients in late CC stages had worse levels of inflammatory markers (e.g., CRP and albumin), these markers were not useful to discriminate all stages of CC severity. This corroborates the findings of the European Palliative Care Research Collaborative study, where CRP levels were not a significant item for the classification into any of the three CC groups in patients with palliative cancer [10]

Our results demonstrate that the OS of patients was progressively worse in each respective stage (as measured by the new CC staging method), as was their risk of mortality. Using a four-stage system, Vigano et al. [13] found no statistical discrimination between the PCa and Ca stage for almost all outcomes analyzed, including OS. Blum et al. [10] found a difference in OS only between the NCa and PCa stages according to the survival curves. In addition, no previous study has demonstrated the prognostic significance of risk of death (HR) by their respective methods.

Over the last decade, there has been increasing interest in identifying criteria to define CC. The validity and usefulness of existing CC instruments in patients with cancer is unknown, and the recognition and nutritional management of CC remains unsatisfactory [16,19]. This study provides a plausible new system to stage CC that could be adopted in any clinical setting with the means to determine the parameters it assesses. the system builds on the existing consensus definition [1] to establish cutoff parameters (WL, muscle mass, and BMI) capable of improving the assessment of CC. As suggested in the consensus publication, our work proposes a series of next steps through the exploration of a robust data set, resulting in a clearly defined statistical approach for the development of diagnostic criteria.

Our findings can contribute to guide health care professionals on which criteria to use in a real-life routine in clinical settings to define CC until current diagnostic criteria are improved. The initial phase of CC (PCa) is of particular interest, because its identification could enable the introduction of early nutritional strategies, which could themselves improve clinical outcomes, leaving late-stage (RCa) interventions to focus on symptom control and improvement of QoL [1,14]. In this context, measures should be adequate with the nutritional needs of each patient as part of an individualized and tailored nutritional care plan with the aim of reducing nutritional status impairment and enhancing overall QoL [6].

This study has some limitations. Patient evaluations were conducted at only one cancer center, and no longitudinal information was analyzed except for OS. As is common in many studies in palliative care, the number of missing data was quite high, but there were no statistical differences between the present study sample and the original cohort in terms of main key patient characteristics. Despite this, distinct CC phenotypes were observed in this homogeneous population of patients with cancer at an equivalent stage of disease. Although traditional cluster analysis techniques were used, the robustness and stability of the clusters within the data have not been demonstrated, and consequently may be sensitive to bias. In addition, there is no external validation data set that can show how the results of the clustering could be explained as consistent across different data. Finally, the next steps will be the validation of this CC staging system in other cancer populations in multicenter studies.

Conclusions

Our study presents the use of simple criteria for the classification of CC into three stages based on easily applicable measurements available in routine clinical practice, separating patients with

incurable cancer into distinct CC groups. The new system is valid and successfully discriminates between different CC stages for patient-centered outcomes, including QoL and OS. Future research should validate this staging system in other advanced cancer populations.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.nut.2021.111271.

References

[1] Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: An international consensus. Lancet Oncol 2011;12:489–95.
[2] Martin L. Diagnostic criteria for cancer cachexia: Data versus dogma. Curr Opin Clin Nutr Metab Care 2016;19:188–98.
[3] Fearon KC, Voss AC, Hustead DS. Definition of cancer cachexia: Effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. Am J Clin Nutr 2006;83:1345–50.
[4] Fearon KCH. Cancer cachexia: Developing multimodal therapy for a multidimensional problem. Eur J Cancer 2008;44:1124–32.
[5] Vagnildhaug OM, Brunelli C, Hjermstad MJ, Strasser F, Baracos V, Wilcock A, et al. A prospective study examining cachexia predictors in patients with incurable cancer. BMC Palliat Care 2019;18:46.
[6] Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr 2016;36:11–48.
[7] Roeland EJ, Bohlke K, Baracos VE, Bruera E, del Fabbro E, Dixon S, et al. Management of Cancer Cachexia: ASCO Guideline. J Clin Oncol 2020;38:2438–53.
[8] Argilés JM, Betancourt A, Guàrdia-Olmos J, Peró-Cebollero M, López-Soriano FJ, Madeddu C, Validation of the CAchexia SCOre (CASCO). Staging cancer patients: The use of miniCASCO as a simplified tool. Front Physiol 2017;8:92.
[9] Wallengren O, Lundholm K, Bosaeus I. Diagnostic criteria of cancer cachexia: Relation to quality of life, exercise capacity and survival in unselected palliative care patients. Support Care Cancer 2013;21:1569–77.
[10] Blum D, Stene GB, Solheim TS, Hjermstad MJ, Baracos VE, Fearon K, et al. Validation of the consensus-definition for cancer cachexia and evaluation of a classification model-A study based on data from an international multicentre project (EPCRC-CSA). Ann Oncol 2014;25:1635–42.
[11] Martin L, Senesse P, Gioulbasanis I, Antoun S, Bozzetti F, Deans C, et al. Diagnostic criteria for the classification of cancer-associated weight loss. J Clin Oncol 2015;33:90–9.
[12] Vigano AAL, Morais JA, Ciutto L, Rosenthall L, di Tomasso J, Khan S, et al. Use of routinely available clinical, nutritional, and functional criteria to classify cachexia in advanced cancer patients. Clin Nutr 2017;36:1378–90.
[13] Zhou T, Wang B, Liu H, Yang K, Thapa S, Zhang H, et al. Development and validation of a clinically applicable score to classify cachexia stages in advanced cancer patients. J Cachexia Sarcopenia Muscle 2018;9:306–14.
[14] Vanhoutte G, Van de Wiel M, Wouters K, Sels M, Bartolomeeussen L, De Keersmaecker S, et al. Cachexia in cancer: What is in the definition? BMJ Open Gastro 2016;3:e000097.
[15] Van der Meij BS, Schoonbeek CP, Smit EF, Muscaritoli M, Van Leeuwen PA, Langius JA. Pre-cachexia and cachexia at diagnosis of stage III non-small-cell lung carcinoma: An exploratory study comparing two consensus-based frameworks. Br J Nutr 2013;109:2231–9.
[16] Wiegert EVM, de Oliveira LC, Calixto-Lima L, Mota e Silva Lopes MSD, Peres WAF. Cancer cachexia: Comparing diagnostic criteria in patients with incurable cancer. Nutrition 2020;79–80:110945.
[17] Van der Werf A, van Bokhorst QNE, de Van der Schueren MAE, Verheul HMW, Langius JAE. Cancer cachexia: Identification by clinical assessment versus international consensus criteria in patients with metastatic colorectal cancer. Nutr Cancer 2018;20:1–8.
[18] Evans WJ, Morley JE, Argiles J, Bales C, Baracos V, Guttridge D, et al. Cachexia: A new definition. Clin Nutr 2008;27:793–9.
[19] Silva GAD, Wiegert EVM, Calixto-Lima L, Oliveira LC. Clinical utility of the modified Glasgow Prognostic Score to classify cachexia in patients with advanced cancer in palliative care. Clin Nutr 2020;39:1587–92.
[20] de Oliveira LC, Abreu GT, Lima LC, Aredes MA, Wiegert EVM. Quality of life and its relation with nutritional status in patients with incurable cancer in palliative care. Support Care Cancer 2020;28:4971–8.
[21] Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: Reliability, validity, and guidelines. J Clin Oncol 1984;2:187–93.
[22] Chumlea WMC, Guo SS, Steinbaugh ML. Prediction of stature from knee height for black and white adults and children with application to mobility impaired or handicapped persons. J Am Diet Assoc 1994;94:1385–8.
[23] Heymsfield SB, McManus C, Smith J, Stevens V, Nixon DW. Anthropometric measurement of muscle mass: Revised equations for calculating bone-free arm muscle area. Am J Clin Nutr 1982;36:680–90.
[24] Paiva CE, Manfredini LL, Paiva BS, Hui D, Bruera E. The Brazilian version of the Edmonton Symptom Assessment System (ESAS) is a feasible, valid and reliable instrument for the measurement of symptoms in advanced cancer patients. PLoS One 2015;10:e0132073.
[25] Oldenmenger WH, de Raaf PJ, de Klerk C, Van der Rijt CC. Cut points on 0–10 numeric rating scales for symptoms included in the Edmonton Symptom Assessment Scale in cancer patients: A systematic review. J Pain Symptom Manage 2013;45:1083–93.
[26] Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, Cooper C, et al. A review of the measurement of grip strength in clinical and epidemiological studies: Towards a standardised approach. Age Ageing 2011;40:423–9.
[27] Prado CM, Lieffers JR, Mccargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol 2008;9:629–35.
[28] Nunes NAH. The quality of life of Brazilian patients in palliative care: Validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 PAL (EORTC QLQ-C15-PAL). Support Care Cancer 2014;22:1595–600.
[29] Groenvold M, Petersen MA, Aaronson NK, Arraras JI, Blazeby JM, Bottomley A, et al. The development of the EORTC QLQ-C15-PAL: A shortened questionnaire for cancer patients in palliative care. Eur J Cancer 2006;42:55–64.
[30] Baracos VE, Mazurak VC, Bhullar AS. Cancer cachexia is defined by an ongoing loss of skeletal muscle mass. Ann Palliat Med 2019;8:3–12.
[31] Cederholm T, Jensen GL, Correia MIT, Gonzalez MC, Fukushima R, Hgashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition – A consensus report from the global clinical nutrition community. Clin Nutr 2019;38:1–9.
[32] World Health Organization, Division of Noncommunicable Diseases. Obesity: Preventing and managing the global epidemic: Report of a WHO consultation on obesity. Geneva, Switzerland: World Health Organization; 2000.
[33] Blauwhoff-Buskermolen S, Langius JAE, Becker A, Verheul HMW, de van der Schueren MAE. The influence of different muscle mass measurements on the diagnosis of cancer cachexia. J Cachexia Sarcopenia Muscle 2017;8:615–22.
[34] Di Sebastiano KM, Mourtzakis M. A critical evaluation of body composition modalities used to assess adipose and skeletal muscle tissue in cancer. Appl Physiol Nutr Metab 2012;37:811–21.
[35] Amano K, Maeda I, Morita T, Baba M, Miura T, Hama T, et al. C-reactive protein, symptoms and activity of daily living in patients with advanced cancer receiving palliative care. J Cachexia, Sarcopenia Muscle 2017;8:457–65.
[36] Srdic D, Plestina S, Sverko-Peternac A, Nikolac N, Simundic AM, Samarzija M. Cancer cachexia, sarcopenia and biochemical markers in patients with advanced non-small cell lung cancer-chemotherapy toxicity and prognostic value. Support Care Cancer 2016;24:4495–502.