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Cancer cachexia: Comparing diagnostic criteria in patients with incurable cancer

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ABSTRACT

Objectives: Cancer cachexia (CC) is a multifactorial syndrome that is associated with worse outcomes. Several criteria for its diagnosis have been suggested, but notable disparities exist. This study compared different diagnostic criteria for CC in patients with incurable cancer who are in palliative care.
Methods: A prospective cohort study was conducted at the National Cancer Institute in Brazil. Patients were classified by three CC diagnostic criteria, and comparisons between clinical, nutritional, and functional variables were verified according to the CC stage identified. Kaplan-Meier survival curves and Cox regression were used for the survival analysis. Concordance statistics were used to test the prognostic predictive accuracy of the criteria.
Results: The prevalence of cachexia in the 1384 patients included in the study varied from 13.8% to 53.9% according to the classification criteria used. All criteria distinguished noncachectic patients from other categories according to the majority of the domains studied. However, the results were inconsistent in distinguishing patients with intermediate cachexia (mainly precachexia) from noncachectic and cachectic patients. Patients with cachexia or refractory cachexia faced a higher risk of 90-d mortality. The criteria described by Vigano et al. were found to be better at distinguishing the stages of CC regarding overall survival (hazard ratio increases according to CC severity: 1.87 to 2.87; concordance statistic: 0.74).
Conclusions: Our results demonstrate the disparities in existing CC diagnostic criteria and their inability to discriminate intermediate stages. Vigano et al.'s criteria is/was the most effective in predicting the prognosis. The development of new diagnostic criteria to improve CC classification requires future exploration.

Introduction

Cancer cachexia (CC) describes a complex, multifactorial, pathophysiological syndrome that results from a variety of host–tumor interactions that have yet to be comprehended [1–3]. CC affects 50% to 80% of patients with advanced disease [1,42], and its consequences are devastating because CC negatively affects physical function, quality of life, and overall survival [4,42,5].

The development of CC varies according to the nature, stage, and site of the tumor, as well as interindividual variations (e.g., genetic predisposition, initial body composition, physical activity, food intake, and comorbidities) [6]. Cachectic patients are usually characterized by weight loss (WL), muscle wasting, anorexia, and inflammation [3,4,5]. The classification of CC stages is essential for diagnosis, treatment, and prognosis, but challenging in clinical practice because of CC's heterogeneous, pathophysiological, and clinical features [2,7].

Several systems have been proposed to assess CC in two or more stages [2,3,7–10]. However, disparities exist in the diagnostic criteria to classify CC stages in clinical settings [7–9]. When data are accrued using disparate sets of criteria, comparisons are difficult. The contradictions of data between studies may be attributed to nonhomogeneous patient groups, different sample sizes, and assessments of different parameters and cutoff points to define its stages [9–14]. Another issue is the lack of international consensus on what objective criteria should be used to define refractory cachexia (RCa), hindering any meaningful advancement in clinical practice for the classification of these patients [2].

CC staging is important to identify associated phenotypes and thereby enable the interdisciplinary team to provide effective symptom management, nutritional intervention, and specialized supportive care. Given that overall survival is usually limited in incurable cancers, the methods used in a CC diagnosis should be

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related to prognosis, enabling a better standardization of criteria for care. Its predictive prognostic capacity makes the method potentially valuable in planning the nutritional care of patients referred to palliative care services. The aims of the present study were to compare the definition of CC according to three different criteria and determine its clinical relevance in patients with incurable cancer in palliative care.

Methods

Patients and data collection

The study participants were enrolled in a prospective cohort at the palliative care unit of the José Alencar Gomes da Silva National Cancer Institute in Brazil. All consecutive advanced cancer inpatients and outpatients who had their first consultation at the palliative care unit between July 2016 and March 2020 were evaluated at this attendance by trained researchers. The patients had generalized malignant disease or advanced local tumor growth and were not receiving any antineoplastic treatment with curative intent. The eligibility criteria were incurable cancer, both sexes, age ≥20 y, and Karnofsky performance status (KPS) ≥30%. The KPS scores, ranging from 0 (death) to 100 (full function) were assigned according to patient-reported physical function.

The institute's ethics committee (protocol number 1.407.458, 2016) approved the study, and each patient gave written informed consent before participating in the study. Clinical data were collected from electronic medical records, including primary tumor site, extent of metastatic disease, previous antitumor treatment, and date of death.

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 at Pt.Global.org. The PG-SGA SF consists of a four-part questionnaire based on patient-reported history of weight change (box 1 – maximum score of 5), food intake (box 2 – maximum score of 4), presence of nutrition impact symptoms (box 3 – maximum score of 24), and performance status (box 4 – maximum score of 3). The higher the score, the higher the patient's nutritional risk, and cutoff point ≥9 indicates a critical need for nutrition intervention and/or symptom management [15].

Anthropometric measurements

Anthropometric measurements were taken using standardized protocols [16]. Weight was obtained using a calibrated portable Wiso (Brazil) digital scale, model 905, with 180 kg capacity. For patients who were unable to stand, an in-bed scale system (Stryker Go Bed II) was used. Height was measured using a wall-mounted tape stadiometer. When this could not be used, knee height was measured with the knee and ankle joints flexed at 90° using a measuring tape or anthropometer and then used to calculate height according to the formulas described by Chumlea et al. [17]. Body mass index (BMI) was calculated using weight (kg) and height (m), and expressed as kg/m^2. Low BMI was set at <20 kg/m^2 [2].

Triceps skinfold thickness (TSF; mm) was assessed at the midpoint of the dominant arm ascertained by holding a measuring tape between the shoulder (acromion) and elbow (olecranon), with the arm bent at 90°. TSF was measured three times with a skinfold caliper (Lange, Cambridge Scientific Industries). Arm circumference (cm) was determined at the same point as TSF using a nonstretchable measuring tape. Mid-upper-arm muscle area (MUAMA; cm^2) was calculated from TSF and arm circumference, from which muscle mass was determined using the equation proposed by Heymsfield et al. [18]. Low muscle mass was set at MUAMA <32 cm^2 for male and <18 cm^2 for female [2].

Muscle strength

Muscle strength was assessed by handgrip strength using a Jamar hydraulic hand dynamometer (Baseline, Fabrication Enterprises, Inc., Elmsord). Subjects were instructed to self-adjust the dynamometer to fit their hand size comfortably to obtain their best performance. Patients were then instructed to grip the dynamometer with maximum strength in response to a voice command. Three trials were performed on both sides with a 1-min rest period in between the trials of each hand. Maximum strength was defined as the highest of the six measurements. Handgrip strength values were defined as low muscle strength if they were lower than the 10th percentile (<P10) based on data from the Brazilian population, broken down by sex, age group, and arm side [19].

Fatigue and loss of appetite

Fatigue and loss of appetite were assessed using the Edmonton Symptom Assessment System (ESAS). ESAS a validated patient-reported tool to measure symptom severity and is widely used in palliative cancer populations [20]. Patients self-report the intensity of symptoms on a numerical scale ranging from 0 (no symptoms) to 10 (worst possible symptoms). A cutoff of >3 (0–3 vs >3–10) was set for moderate-to-severe symptoms [21].

Laboratory assessments

Routine blood analyses were performed on the day of enrollment at the palliative care unit. A single intravenous blood sample was collected to analyze the serum albumin and C-reactive protein (CRP) and a complete blood count. The serum values were used to determine the neutrophil-to-lymphocyte ratio [22]. The modified Glasgow Prognostic Score was classified as 2 for albumin <3.5 mg/dL and CRP ≥10 mg/L, 1 for albumin ≥3.5 mg/dL and CRP ≥10 mg/L, and 0 for CRP <10 mg/L [23].

Cachexia criteria

Patients were classified according to three previously described CC diagnostic criteria. According to Wallengren et al. [9], patients were classified into two groups: Noncachectic (NCa) and cachectic (Ca), using %WL + fatigue (ESAS) + CRP. Based on Blum et al. [9], patients were classified into four stages, NCa, precachectic (PCa), Ca, or RCa, using combinations of weight change + BMI. Finally, following Vigano et al. [10], patients were classified into NCa, PCa, Ca, or RCa based on a combination of abnormal biochemistry (CRP, leukocytes, albumin, or hemoglobin), %WL, decreased food intake, and/or decreased performance status (assessed by PG-SGA SF; Table 1).

Table 1
Criteria for cancer cachexia diagnosis as described by Wallengren et al. [8], Blum et al. [9], and Vigano et al. [10] and their translation to our study methods

Criteria for diagnosis of cancer cachexia			
Wallengren et al.	Blum et al.	Vigano et al.	Translation to our study methods
Ca: WL >2% + fatigue >3 + CRP >10 mg/L	PCa: WL >1 kg, but WL <5% in the last 6 mo; Ca: WL >5% in the last 6 mo or WL >2% in the last 6 mo + BMI <20 kg/m^2; RCa: WL >15% in the last 6 mo + BMI <23 kg/m^2; or WL >20% in the last 6 mo + BMI <27 kg/m^2	PCa: Abnormal biochemistry and/or decreased food intake and/or WL ≤5% in the last 6 mo; Ca: Abnormal biochemistry, and/or WL >5% in the last 6 mo and/or decreased food intake; RCa: Abnormal biochemistry, WL >5% in the last 6 mo and decreased activity/functioning; or WL >5% in the last 6 mo + decreased food intake + decreased activity/functioning; or Albumin <2.5 g/dL + decreased activity/functioning	WL in the last 6 mo: PG-SGA SF box 1 Fatigue: ESAS (1–10 scale) Decreased food intake: PG-SGA SF box 2 score ≥1 Abnormal biochemistry: CRP >10 mg/L or WBC >11,000/L or Albumin <3.2 g/dL or Hg <11 g/dL (female) or <12 g/dL (male) Decreased activity / functioning: PG-SGA SF box 4 score >2

BMI, body mass index; Ca, cachectic; CRP, C-reactive protein; ESAS, Edmonton symptom assessment system; Hg, hemoglobin; PCa, precachectic; PG-SGA SF, Patient-Generated Subjective Global Assessment Short Form; RCa, refractory cachectic; WBC, white blood cells; WL, weight loss

Survival

Overall survival was defined as the time interval, in days, between the date of recruitment and the date of death from any cause. All patients were followed prospectively until the date of censoring (90 d) or date of death, whichever came first.

Sample size estimation

Based on a sample size calculation, at least 346 patients should be included in the study to have 80% power, with an absolute error of 5% and 5% significance level to detect differences in the prevalence of CC in patients with cancer in the order of 13.8% to 53.9%. In addition, at least 104 patients would have to be classified at each stage of CC to detect up to 1.8-fold differences in risk of death.

Statistical analysis

The statistical analyses were performed using Stata, version 13.1 (Stata Corp., College Station, TX). The Kolmogorov-Smirnov test was performed to assess distribution symmetry. Descriptive statistics (count/frequency [%], mean ± standard deviation, or median/interquartile range) were used as appropriate to describe patient characteristics.

An independent sample *t* test was applied to the continuous variables and a χ^2 test was used for the categorical variables. The Mann-Whitney U test was used to compare the medians between the two groups. Comparisons between the four CC groups were performed using a one-way analysis of variance for continuous variables or Kruskal-Wallis for nonnormally distributed variables, followed by the Bonferroni post hoc test.

Kaplan-Meier's method was used to estimate the probability of overall survival, and log-rank tests were used to compare pairwise differences between stages according to the CC diagnostic criteria. A Cox proportional hazards model (estimated hazard ratio [HR] and 95% confidence interval [CI]) adjusted for confounding factors (age, sex, primary tumor site, KPS ≤40%, and current medical status [inpatient or outpatient]) was used to predict mortality per CC stage. The NCa group was used as a reference category.

Concordance statistics (c-statistics) were used to test the predictive prognostic accuracy of the diagnostic criteria to discriminate - overall survival (alive vs death). For the c-statistic, a value of 0.5 indicates that there is no discrimination, whereas a value of 1.0 indicates perfect discrimination between the expected and observed events (i.e., death) [24]. Statistical significance was set at $P < 0.05$.

Table 2
Descriptive characteristics of patients with incurable cancer (n = 1384)

Variables	n (%)
Age (y)	61.7 (± 13.4)*
Age <65 y	781 (56.4)
Sex	
Female	780 (56.4)
Male	604 (43.6)
Race/skin color	
White	595 (43.0)
Black	229 (16.5)
Others	560 (40.5)
Tumor type	
Gastrointestinal tract	445 (32.2)
Gynecology	229 (16.6)
Head/neck†	241(14.5)
Lung	141 (10.2)
Breast	144(10.4)
Skin	60 (4.3)
Bones and soft tissues	47 (3.4)
Leukemia, lymphomas, myeloma	17 (1.2)
Others‡	100 (7.2)
Cancer stage	
Locally advanced	204 (14.7)
Metastatic	1180 (85.3)
Site of metastasis (yes)	
Lymph nodes	679 (49.1)
Lung	444 (32.1)
Liver	337 (24.3)
Bone	245 (17.7)
Current medical status	
Inpatient	328 (23.7)
Outpatient	1056 (76.3)

*Mean/standard deviation.
†Oral and nasal cavity, pharynx, larynx, salivary glands, paranasal sinuses, eyes, and thyroid.
‡Central nervous system, kidney and urinary tract, male genital organs, peritoneum, mediastinum, and unrecognized site.

Results

A total of 1,384 consecutive patients were included in this study. The mean age was 61.7 y (±13.4 y), and the majority of patients were female (56.4%). The gastrointestinal tract was the most frequent location of the primary tumor (32.2%), followed by the gynecologic area (16.0%) and head and neck (13.9%). The cancer stage for the sample was predominantly metastatic distant disease (85.3%), and the main sites of metastases were the lymph nodes (49.1%), lungs (32.1%), and liver (24.3%). Most patients were outpatients (76.3%; Table 2).

The prevalence of patients classified as cachectic varied from 13.8% to 53.9% depending on the diagnostic criteria. Using Wallengren et al.'s definition, 13.8% of patients were Ca and 86.2% were NCa. Using Blum et al.'s, 53.9% of the population were classified as Ca, 12.3% as PCa, 26.1% as RCa, and 9.7% as NCa. Finally, when using Viagno et al.'s diagnostic criteria, 17.3% were classified as Ca, 20.8% as PCa, 53.3% as RCa, and 8.2% as NCa (Table 3). The overlaps between the Ca patients classified by the different methods are shown in Figure 1. The absence of concordance between the results obtained by the different diagnostic criteria is notable. Only 28 patients (3.1%) were classified as Ca by all three definitions, and 33 patients (2.4%) did not meet the criteria of any of the methods (data not shown).

Patients classified with advanced stages of CC, irrespective of the criteria, were different from NCa patients according to the majority of the domains studied (Table 3). Patients classified as Ca by Wallengren et al. were statistically different in all analyzed variables except for MUAMA. However, for the criteria with four CC stages (i.e., Blum et al. and Vigano et al.), the PCa classifications were inconsistent in nearly all domains, failing clearly distinguish from NCa and Ca. For example, PCa compared with Ca according to Blum et al.'s criteria showed no statistical differences for KPS, BMI, CRP, albumin, leukocytes, MUAMA, or HGS (in female). Per Vigano et al.'s definition, the only statistical differences between PCa and Ca were for BMI, WL, and modified Glasgow Prognostic Score (Table 3).

The median overall survival for all patients studied was 53 d (interquartile range, 20–90 d; Table 4). When the Wallengren et al. diagnostic criteria were used, a significant difference was identified in overall survival according to the severity of the stage of CC, with the following medians: 64 d versus 16 d ($P < 0.001$). The same applied when the Vigano et al. criteria were used: 90 d versus 76 d versus 66 d versus 39 d, respectively ($P < 0.001$, except for PCa vs Ca, when $P = 0.113$). When the Blum et al. criteria were used, median overall survival was 80 d versus 77 d versus 53 d versus 45 d, respectively. In this case, no statistical differences were found between NCa and PCa ($P = 0.213$) or between Ca and RCa ($P = 0.125$; Fig. 2).

Our results show that the risk of mortality was the highest in the later stages of CC, irrespective of the diagnostic criteria used. Specifically, patients classified as Ca per the Wallengren et al. criteria (HR: 2.21; 95% CI, 1.86–2.62) and as RCa per the Blum et al. (HR: 1.72; 95% CI, 1.32–2.24) and Vigano et al. criteria (HR: 2.87; 95% CI, 2.01–4.10) were at a significantly higher risk of death within 90 d. However, PCa (HR: 1.07; 95% CI, 0.79–1.46; $P = 0.644$) and Ca (HR: 1.27; 95% CI, 0.99–1.63; $P = 0.054$) as defined by Blum et al. were not significantly associated with mortality. Finally, Vigano et al.'s criteria demonstrated good predictive discrimination of the model of survival for the CC stages (c-statistic: 0.74; 95% CI, 0.71–0.79; Table 4).

Table 3
Differences between cancer cachexia stages as defined by different diagnostic criteria

		Wallengren et al. [9]		Blum et al. [9]				Vigano et al. [10]			
	n	NCa (n = 1193; 86.2%)	Ca (n = 191; 13.8%)	NCa (n = 135; 9.7%)	PCa (n = 170; 12.3%)	Ca (n = 746; 53.9%)	RCa (n = 272; 26.1%)	NCa (n = 114; 8.2%)	PCa (n = 288; 20.8%)	Ca (n = 244; 17.6%)	RCa (n = 738; 53.3%)
KPS (%)*	**1384** 50 (40–60)	50 (40–60)‖	40 (30–50)	50 (40–70)‖	50 (40–60)	40 (40–50)	50 (40–50)	70 (50–80)§,¶	50 (40–60)	60 (50–60)	50 (40–50)
BMI (kg/m²)†	**992** 22.4 (5.4)	22.6 (5.4)‖	21.5 (4.7)	23.5 (6.2)¶	23.7 (5.3)¶	24.4 (5.4)¶	19.3 (3.0)	24.7 (5.9)‖,¶	23.8 (5.2)‖,¶	22.3 (5.0)	21.6 (5.2)
WL 6 mo (%)*	**1384** 11.1 (4.3–20.0)	10.4 (3.7–19.4)‖	16.0 (8.7–22.6)	0.5 (0–2.4)§,‖,¶	3.2 (2.2–4.1)‖,¶	10.9 (7.2–16.1)¶	23.8 (19.3–29.5)	3.8 (0–10.4)§,‖,¶	8.8 (2.4–17.3)‖,¶	14.1 (8.8–21.3)¶	16.3 (10.0–23.5)
MUAMA (cm²)†											
Male	**579** 30.4 (12.0)	30.7 (10.8)	30.9 (12.4)	33.8 (14.3)‖,¶	32.7 (12.5)‖,¶	29.5 (10.9)¶	25.1 (9.0)	33.4 (12.7)¶	33.8 (12.4)¶	32.7 (12.9)¶	27.4 (11.0)
Female	**707** 28.3 (11.6)	29.2 (11.1)	24.9 (9.7)	29.5 (12.0)¶	29.9 (10.7)¶	29.9 (12.5)¶	22.5 (9.0)	34.1 (14.3)§,‖,¶	29.1 (10.5)¶	30.6 (12.3)¶	25.0(10.3)
HGS (kg)†											
Male	**471** 24.3 (9.2)	25.4 (9.7)‖	21.4 (9.5)	29.6 (9.6)‖,¶	28.6 (11.0)‖,¶	24.0 (9.6)	23.5 (7.4)	29.6 (10.8)¶	26.5 (11.0)¶	27.8 (8.2)¶	21.5 (8.3)
Female	**581** 15.7 (6.9)	18.5 (5.9)‖	14.4 (6.6)	15.1 (6.9)¶	13.2 (6.2)¶	14.3 (6.0)¶	12.3 (6.0)	21.2 (7.5)§,¶	16.4 (6.3)¶	18.7 (5.6)¶	13.2 (6.0)
PG-SGA SF (score)†	**1384** 14.9 (6.6)	14.3 (6.6)‖	18.7 (6.0)	12.0 (6.5)‖,¶	12.6 (6.2)‖,¶	15.3 (6.6)	16.3 (6.4)	7.7 (5.2)§,‖,¶	12.9 (6.1)¶	13.4 (5.7)¶	17.3 (6.2)
CRP (mg/L)*	**1307** 5.5 (1.9–11.4)	4.3 (1.5–8.3)‖	16.3 (13.3–23.4)	3.4 (0.8–8.4)‖	4.1 (1.1–8.9)	6.1 (2.0–12.1)	5.7 (2.9–12.1)	0.9 (0.3–2.0)§,‖,¶	4.9 (1.7–9.8)¶	5.5 (2.2–11.2)¶	7.0 (3.2–13.2)
Alb (g/dL)*	**1318** 3.4 (2.8–3.9)	3.5 (2.9–4.0)‖	2.9 (2.4–3.3)	3.7 (3.0–4.2)‖,¶	3.5 (3.0–4.1)	3.4 (2.8–3.9)	3.3 (2.7–3.8)	4.2 (3.9–4.4)§,‖,¶	3.6 (3.0–4.0)¶	3.5 (2.9–4.0)¶	3.1 (2.6–3.7)
Hg (g/dL)*	**1375** 10.1 (8.7–11.7)	10.3 (8.8–11.9)e	9.1 (7.9–10.3)	10.8 (8.7–12.4)‖,¶	10.8 (8.8–12.1)‖,¶	10.0 (8.7–11.4)	9.8 (8.5–11.5)	12.7 (12.0–13.2)§,‖,¶	10.2 (8.7–11.8)¶	10.0 (8.8–11.2)	9.6 (8.4–11.1)
WBC (10^3L)*	**1375** 9 (6.7–12.7)	8.7 (6.5–12.2)‖	11.8 (8.6–17.3)	7.9 (6.2–10.9)‖,¶	8.3 (6.3–12.1)¶	9.1 (6.7–12.8)	9.9 (7.2–13.7)	7.5 (5.9–8.3)§,‖,¶	8.5 (6.3-–12.5)¶	9.0 (6.512.0)¶	9.9 (7.2–14.1)
NRL*	**1375** 6 (3–11)	5.0 (3.0–10.0)‖	9.0 (5.5–16.0)	4.6 (3.0–9.7)‖,¶	4.7 (2.7–9.1)‖,¶	5.7 (3.4–11.2)	6.2 (3.9–11.9)	3.3 (2.4–5.3)§,‖,¶	4.8 (3.1–9.7)¶	5.5 (3.5–10.4)¶	6.8 (3.9–12.5)
mGPS 1 + 2 (%)‡	**1271** 354 (27.8)	180 (16.4)‖	174 (98.9)	24 (19.8)‖,¶	29 (19.6)‖,¶	205 (29.9)¶	96 (30.4)	0§,‖,¶	53 (21.5)‖,¶	64 (28.6)¶	237 (34.5)
Fatigue*,#	**1367** 3 (0–6)	2 (0–5)‖	7 (5–9)	0 (3–6)§,‖,¶	2 (0–6)‖,¶	3 (0–6)¶	4 (1–7)	0 (0–3)§,‖,¶	2 (0–6)¶	3 (0–6)¶	5 (0–7)
Loss of appetite*,#	**1367** 2 (0–8)	0 (0–7)‖	5 (0–10)	0 (0–5)‖,¶	0 (0–7)‖,¶	2 (0–8)¶	3 (0–8)	0 (0–1)¶	1 (0–7)¶	1 (0–7)¶	4 (0–8)

Alb, albumin; BMI, body mass index; Ca, cachexia; CRP, C-reactive protein; ESAS, Edmonton symptom assessment system; Hg, hemoglobin; HGS, handgrip strength; KPS, Karnofsky performance status; mGPS, modified Glasgow prognostic score; MUAMA, mid upper-arm muscle area; NCa, noncachexia; NLR, neutrophil-to-lymphocyte ratio; P10, 10th percentile; PCa, precachexia; PG-SGA SF, Patient-Generated Subjective Global Assessment Short Form; RCa, refractory cachexia; WBC, white blood cell; WL, weight loss

*Median; interquartile range; Mann-Whitney U or Kruskal-Wallis, as appropriate.

†Mean; ± standard deviation; *t* test or analysis of variance, as appropriate.

‡n: number of observations; %: frequency; ^{2} test.

§Statistically different from precachectic.

‖Statistically different from cachectic.

¶Statistically different from refractory cachectic.

#According to Edmonton Symptom Assessment System (score 0–10).

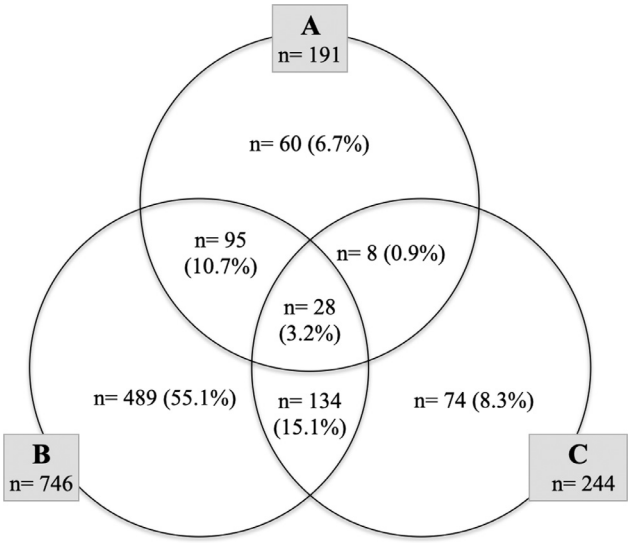

Fig. 1. Overlap between cachexia as defined by (A) Wallengren et al. [8], (B) Blum et al. [9], and (C) Vigano et al. [10] in patients with incurable cancer in palliative care.

Discussion

In the present study, we classified a large sample of patients with incurable cancer in palliative care at a reference center in Brazil by level of severity of CC, using three different published criteria for diagnosis. Irrespective of the criteria adopted, our results showed that patients in late stages of CC were more clearly distinguishable from noncachectic patients with regard to outcome measures. However, there was a lack of clarity in the capacity of the models to discriminate between the transitional/intermediate stages (mainly PCa).

We identified a high prevalence of Ca and RCa in patients with advanced cancer, which is consistent with previous reports [8–10,25,26]. Additionally, as expected, depending on the criteria used, the proportion of Ca patients varied considerably and was the highest when the Blum et al. [9] definition was used compared with other cachexia definitions, which include laboratory markers, dietary intake, fatigue, and/or function [8,10]. Our findings corroborate those by Thoresen et al. [27] who demonstrated that, depending on the criteria, the prevalence of Ca ranged from 22% to 55%, and those by Van der Meij et al. [13] who compared specific and general frameworks to classify CC, finding a prevalence of 18% to 28%, respectively. In another study, Wallengren et al. [8] found an even greater lack of concordance in the results yielded by different diagnostic criteria of CC in patients in palliative care, ranging from 12% to 85%.

Our results showed that patients classified as noncachectic may present some features of cachexia, such as significant WL, higher nutritional risk by PG-SGA SF (score >9), and anemia, but not to the point of fulfilling the criteria for the diagnosis of PCa or Ca. Furthermore, other important aspects concerning the complex relationships between obesity, sarcopenia, and age-related BMI were not considered in the evaluations [28,29]. Our findings indicate that not every patient with advanced disease in palliative care develops cachexia as defined by the methods investigated herein. This is important because concentrated efforts are being made by researchers and clinicians to assess and categorize patients early on, identifying those with a higher risk of developing CC, to enable them to benefit from timely interventions [28].

The results for patients classified as RCa were subpar for most of the factors studied, but those classified as NCa had significantly better results. CC is generally associated with worse outcomes [5,8,10,25], but the results of our study are consistent with those of previous studies [9,10,25], showing consistent difficulties in obtaining a reliable diagnosis of the disease in its early stages, particularly PCa. Furthermore, unlike our study, the studies in question were mostly retrospective, because they enrolled patients at diverse stages of the disease and did not analyze all these factors together, corroborating our hypothesis that existing CC diagnosis criteria need to be improved.

The current diagnostic criteria show divergences concerning the optimal number of CC stages, which parameters to define them, and which cutoff values should be used for each of these parameters [2,9,10,25,29]. Essentially, the choice of parameters is not consistent, meaning that several parameters used in the classification of CC are still uncertain. For example, WL was the only factor evaluated in all three CC diagnostic criteria studied herein. In fact, WL is a relevant phenotypic characteristic of CC, but what degree of WL (and over what period of time) has the greatest capacity to identify CC and its different stages of development? Unintentional WL of >5% in the previous 6 mo may be a misleading criterion, because equal risk is allocated to WL in excess of 5%, irrespective of its relative severity [12,29]. Another relevant aspect concerns reduced food intake and appetite loss, which are distinct items and cannot be used interchangeably. A multicenter study of patients with incurable cancer emphasized the need to assess both factors when diagnosing CC because, for example, conscious control of eating may sometimes overcome appetite loss [30]. Another

Table 4
Survival analysis - according to different cachexia diagnostic criteria in patients with incurable cancer (n = 1384)

		Deaths/patients (n)	Survival time (days) Median (IQR)	Multivariate analysis HR (95% CI)	*P* value	C-statistic (95% CI)
	Overall	897/1394	53 (20–90)			
Wallengren et al. [9]	NCa	726/1193	64 (25–30)	1		
	Ca	171/191	16 (7–49)	2.21 (1.86–2.62)	< 0.001	0.58 (0.51–0.59)
Blum et al. [10]	NCa	73/135	80 (22–90)	1		
	PCa	95/170	77 (26–90)	1.07 (0.79–1.46)	0.644	0.57 (0.50–0.59)
	Ca	484/746	53 (18–90)	1.27 (0.99–1.63)	0.054	
	RCa	245/272	42 (21–90)	1.72 (1.32–2.24)	< 0.001	
Vigano et al. [11]	NCa	33/114	90 (76–90)	1		
	PCa	164/288	76 (26–90)	1.87 (1.28–2.73)	0.001	0.74 (0.71–0.79)
	Ca	153/244	66 (27–90)	2.39 (1.64–3.49)	< 0.001	
	RCa	547/738	39 (14–90)	2.87 (2.01–4.10)	< 0.001	

C-statistics, concordance statistics; Ca, cachectic; CI, confidence interval; HR, hazard ratio; NCa, noncachectic; PCa, precachectic; RCa, refractory cachectic
Adjusted for age (y), female, primary tumor site (gastrointestinal tract), Karnofsky performance status ≤40%, and current medical status (inpatient or outpatient).

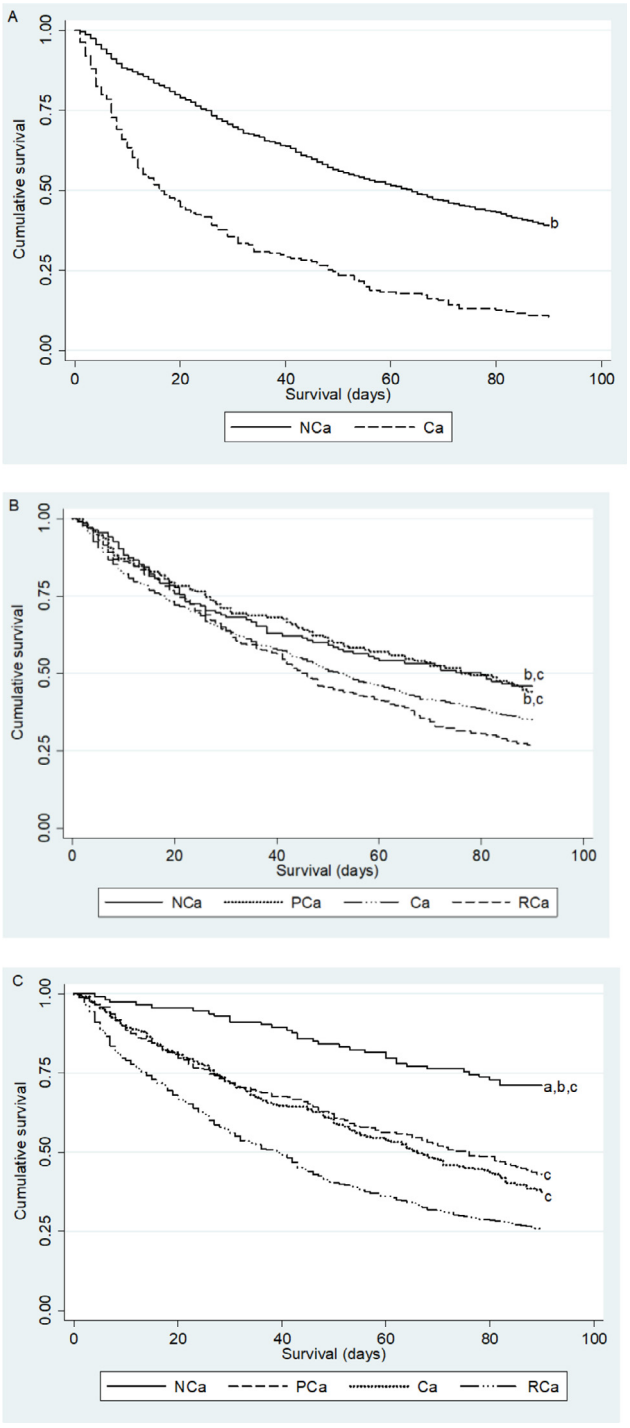

Fig. 2. Kaplan-Meier survival curves for (A) Wallengren et al. [8], (B) Blum et al. [9], and (C) Vigano et al. [10] in patients with incurable cancer in palliative care. Statistically different from (a) precachectic, (b) cachectic; and (c) refractory cachectic

important factor is inflammation, which is an important driver of tumor growth, energy imbalance, and muscle wasting in CC, which not only triggers CC but is related to the occurrence of several symptoms, such as WL, anorexia, reduced energy intake, and functionality [31–33]. However, several cachexia diagnostic criteria do not evaluate any inflammation parameters.

Previous studies have compared the merits of the two- versus four-stage classification systems [8,11,13,14]. From a purely statistical perspective, a two-stage classification system, or dichotomized groups (NCa vs Ca), is more likely to show significant differences between the groups. However, a system of this kind is unable to discriminate between the different CC phenotypes, which makes the system less efficient for clinical applications. Meanwhile, although a four-stage classification system is considered to have potentially greater clinical utility, the procedures tested herein prove unsuccessful in distinguishing between all stages. Patients with a high Ca risk and those in the early stages of the syndrome could both be classified in the PCa group [10]. In other words, effectively diagnosing CC into four stages using the criteria at disposal is still a challenge. Furthermore, verifying a statistically significant difference between the stages of CC is less challenging than finding the factors or characteristics that are actually clinically significant to adequately define these stages of CC.

Our results found some correspondence between overall survival and stage of CC, irrespective of the diagnostic method used. Patients classified as RCa had the shortest overall survival time, but patients classified as NCa had the longest. In a study by Vigano et al. [10], which was consistent with the study by Wesseltoft-Rao et al. [34], no statistical difference in overall survival was found between patients classified as PCa and Ca. Our results corroborate these findings. However, the Blum et al. [9] study found no difference in the overall survival of patients classified as NCa versus PCa. In our study, no difference in overall survival was found between NCa versus PCa or between Ca versus RCa. In other words, our study confirmed the lack of distinction between PCa and the other groups already identified by previous studies [9,10,33].

The diagnostic criteria suggested by Vigano et al. [10] demonstrate an increased risk of 90 d mortality and a more accurate prognostic prediction according to the severity of CC. Since CC is a negative predictor of mortality in patients with cancer, a shift from Ca to NCa can improve overall survival [35]. In fact, these diagnostic criteria cover more factors associated with CC, such as %WL, decreased food intake, reduced functional capacity, and abnormal laboratory markers, which are important and should be better considered while characterizing a patient with CC.

A study by Prado et al. [36] found that patients with advanced cancer may have the potential for muscle anabolism under specific conditions. In other words, the clinical trajectory of a patient with advanced cancer may extend over a period of months. During this period, nutritional status is challenged by the metabolic disturbances induced by a tumor as well as frequent involuntary WL. However, the windows of opportunity should be exploited to improve these outcomes, and enhance performance status, psychological well-being, and overall quality of life [29,37,38].

This study has some limitations in how the analysis was performed. The study was conducted at one center only, and did not allow for the assessment of temporality between the occurrences of the characteristics evaluated. Furthermore, other criteria for the diagnosis of CC described more recently were not tested [38,39]. Yet, while some original studies have compared cancer-specific with nondisease-specific diagnostic criteria [12,14,15,38], none have compared all three cancer-specific diagnostic criteria that use data available in routine clinical practice, such as our study. In addition only- review articles on this subject have been published recently [39–41] based on other rewiew or opinion publications, whose authors have sought to discuss possible divergences regarding the choice of criteria, features, and CC stages, as well as the cut-off values used.

The development of an effective CC classification system will likely be a long multistage process. The information provided in this study will contribute to the future improvement of the CC classification system to discriminate between the stages of CC and

enable improved intervention strategies. The treatment for CC in the most advanced stages in incurable patients focuses primarily on nutritional advice for symptom control and has to be differentiated from the treatment provided for patients with earlier stage cancer. However, in current practice, CC is not routinely recognized or diagnosed in patients with cancer [12,28]. As such, the effective staging of CC in patients is essential for clinicians to implement effective treatment strategies, and include optimized decision-making for nutritional care. Ours results could help guide clinicians on which criteria to use routinely until CC diagnostic criteria are improved.

Conclusions

Our results demonstrate notable disparities in existing CC diagnostic criteria. The diagnostic criteria based on Vigano et al.'s definition appear to be the most effective in distinguishing between CC stages in their capacity to predict overall survival. The lack of capacity of the diagnostic criteria studied to discriminate adequately between the intermediate stages of CC (mainly PCa) highlights the need to improve the precision of the categories through future studies. The results of this study corroborate the hypothesis that there are currently no simple, effective criteria to define the different stages of CC in clinical practice.

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