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Comparative Analysis Between Computed Tomography and Surrogate Methods to Detect Low Muscle Mass Among Colorectal Cancer Patients

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Abstract

Background: We aimed to evaluate the agreement between computed tomography (CT) and surrogate methods applied in clinical practice for the assessment of low muscle mass. In addition, we assessed the association between different muscle-assessment methods and nutrition status, as well as the prognostic value of low muscle mass on survival in patients with colorectal cancer (CRC). *Methods:* This is a cohort including 188 CRC patients with 17 months' follow-up (interquartile range: 12–23 months) for mortality. Low muscle mass was evaluated by corrected mid-upper arm muscle area (AMAc) and calf circumference, skeletal muscle mass by bioelectrical impedance analysis (BIA), muscle deficit by physical examination with the Patient-Generated Subjective Global Assessment (PG-SGA), and lumbar muscle cross-sectional area by CT (reference method). *Results:* The prevalence of low muscle mass ranged from 9.6% to 54.3% according to the method used. The physical examination had the highest κ coefficient compared with CT. Low muscularity was associated with the presence of malnutrition, lower body fat, and low phase angle. The Cox regression models—adjusted for age, sex, and treatment 3 months before study inclusion—showed that severe muscle loss measured by BIA and CT and low muscle mass measured by PG-SGA predicted higher mortality rates. *Conclusions:* Compared with CT, the physical examination had the best agreement to assess low muscle mass. Low muscle mass assessed by PG-SGA, BIA, and CT showed similar prognostic values for survival. (*JPEN J Parenter Enteral Nutr.* 2020;44:1328–1337)

Clinical Relevancy Statement

Low muscle mass is highly prevalent in patients with cancer and should be evaluated in clinical practice by methods that enable adequate assessment. Computed tomography (CT) is a gold-standard method that has been opportunistically used to assess muscle mass. In this study, we showed that the physical examination to assess muscle mass, which can be easily used in hospitalized and outpatients, had the best agreement with CT. In addition, low muscle mass assessed by Patient-Generated Subjective Global Assessment, bioelectrical impedance analysis, and CT showed similar prognostic values. Our results emphasize the importance of screening for low muscle mass and shows that physical examination is a feasible option to be used for this end in clinical practice.

Introduction

Low muscle mass is a common feature of patients with cancer, with an estimated prevalence varying from 5% to 89% depending on the method and cutoff applied.[1,2] The etiology of low muscle mass in patients with cancer is multifactorial and is mainly caused by a negative energy balance due to an inhibition of protein synthesis and an increase of protein degradation.[3] The factors contributing to a negative energy balance in patients with cancer include tumor-related mechanisms, host response to tumor, anticancer treatment, reduced protein intake, and physical inactivity.[3] Of note, as shown in recent studies in patients with cancer, low muscle mass can also be present in overweight and obese people (sarcopenic obesity),[4-7] and it is associated with shorter

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survival, chemotherapy toxicity, tumor progression, adverse postoperative outcomes, and poor quality of life.[4-6,8-10]

Although muscle-mass assessment appears to be mandatory for patients with cancer, it is not routinely performed. Among the suitable methods for muscle-mass assessment in clinical practice, the anthropometric measurements and bioelectrical impedance analysis (BIA) stand out because of characteristics such as being portable, noninvasive, and inexpensive. However, these methods have limited applicability in obese patients and in individuals with edema.[11] Similarly, the Patient-Generated Subjective Global Assessment (PG-SGA) is another method currently applied to assess nutrition status in patients with cancer.[12] As the PG-SGA includes the assessment of muscle deficit by physical exam, it could be implemented in the clinical setting to assess muscle mass in these patients.

In parallel, computed tomography (CT) is considered a gold-standard method for evaluating body composition.[13] Recently, the level of the third lumbar vertebra (L3) from CT scan has been validated as the standard landmark to assess body composition in patients with cancer[14] and has been used to assess muscle mass in some studies in oncological and non-oncological individuals.[15-18] Although the CT scan of the abdomen includes the scan of the L3 and is routinely used for diagnosis and follow-up in colorectal cancer (CRC) patients, its high cost, the need for training, and the exposure to radiation dose limit the use of CT to research purposes. Of note, the revised sarcopenia consensus from the European Working Group on Sarcopenia in Older People (EWGSOP)[19] recommended the use of CT from L3 for the assessment of muscle mass. Therefore, considering the importance of assessing muscle mass in patients with cancer, we aimed to evaluate the agreement, sensitivity, and specificity between CT and surrogate methods applied in the clinical setting to diagnose low muscle mass in a sample of patients with CRC; to explore the association between different muscle-assessment methods for the diagnosis of low muscle mass with nutrition status and body composition; and to test which method has the best prognostic value to predict overall survival.

Materials and Methods

Subjects and Study Design

This study included patients with CRC recruited between April 2015 and June 2016 at the outpatient clinic of the Cancer Hospital Unit I of the National Cancer Institute José Alencar Gomes da Silva (INCA, Rio de Janeiro, Brazil). Those who met eligibility criteria and were scheduled for abdominal CT scan at the L3 region as part of routine care were invited to participate. Inclusion criteria comprised age higher than 18 years and Eastern Cooperative Oncology Group performance status below 3. Subjects with physical deformity unable to carry out physical tests, pacemaker, congestive heart failure, chronic kidney disease, liver cirrhosis, anal canal cancer, synchronous CRC, or >1 cancer type were not included in the study. From 204 patients initially invited to participate in the study, 188 were eligible to participate (Figure 1). The study was approved by the local Research Ethical Committee (protocol number 38992014.5.0000.5274), and written informed consent was obtained from each subject before inclusion. The study adhered to the Declaration of Helsinki.

Study Protocol

After consenting to participate, patients received instructions to fast for 6 hours before the CT scan (water-soluble oral contrast and medication were allowed). Before the CT scan, all participants had the PG-SGA, anthropometric measurements, BIA, and muscle function assessed by the same trained dietitian. Blood samples were then scheduled to be collected under fasting conditions not later than 30 days after the CT scan. Clinical data were collected from medical records such as age, sex, previous and current treatment, comorbidities, performance status, tumor site, and stage. When all patients concluded the CT scan, the same trained dietitian analyzed the CT images over a period of 3 months to minimize intra-observer bias.

Muscle-Mass Assessment

Five muscle-assessment methods were used to diagnose low muscle mass according to the cutoffs shown in Table 1. The measurements tested were corrected mid-upper arm muscle area (AMAc), calf circumference, and skeletal muscle mass (SMM) from BIA;[20] physical examination of muscle mass deficit from PG-SGA; and muscle cross-sectional area from CT scans. For SMM assessed by BIA and CT, 2 degrees of severity, moderate and severe muscle loss, were evaluated (Table 1). Patients were then classified as low–muscle-mass group and adequate–muscle-mass group.

Corrected mid-upper arm muscle area. AMAc was calculated according to the equation AMAc (cm^2) = (mid-upper arm circumference [cm] − 0.314 × triceps skinfold thickness [mm])$^2/4\pi$, corrected by sex (−10 for men and −6.5 for women, respectively).[25] Mid-upper arm circumference was measured at the midpoint of the nondominant upper arm between the acromion process and the olecranon process. The triceps skinfold thickness was measured at the same point using a Lange caliper (Cambridge Scientific Industries, Inc).

Calf circumference. Calf circumference was measured with the subject in the sitting position, feet 20 cm apart, on the right side at the point of greatest circumference.

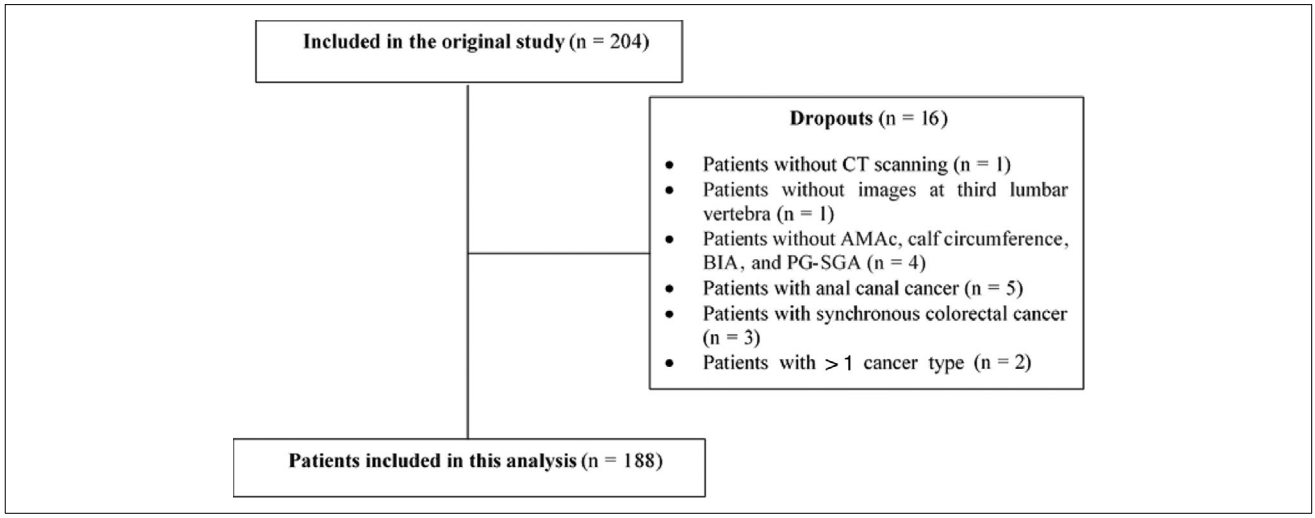

Figure 1. Flow chart of study inclusion and exclusion. AMAc, corrected mid-upper arm muscle circumference; BIA, bioelectrical impedance analysis; CT, computed tomography; PG-SGA, Patient-Generated Subjective Global Assessment.

Table 1. Low Muscle Mass According to Different Methods and Cutoffs.

Methods	Cutoff	Reference
AMAc		
Male	<21.4 cm^2	21
Female	<21.6 cm^2	
Calf circumference		
Male	<34 cm	22
Female	<33 cm	
SMI—BIA		
Male: moderate/severe	$>8.50 \leq 10.75/\leq 8.50$ kg/m^2	23
Female: moderate/severe	$>5.75 \leq 6.75/\leq 5.75$ kg/m^2	
MM PG-SGA	Muscle mass deficit: +1, +2, or +3	12
SMI—CT		
Male: moderate/severe	$>41.6 \leq 44.7/\leq 41.6$ cm^2/m^2	24
Female: moderate/severe	$>32 \leq 32.8/\leq 32$ cm^2/m^2	

Cutoff values of muscle mass at L3 level for CT scans are based on SMI 10th percentile for moderate muscle loss and SMI fifth percentile for severe muscle loss values from healthy Caucasian population.[24]
AMAc, corrected mid-upper arm muscle circumference; BIA, bioelectrical impedance analysis; CT, computed tomography; L3, third lumbar vertebra; MM PG-SGA, muscle mass assessed by Patient-Generated Subjective Global Assessment; SMI, skeletal muscle index.

BIA for SMM. BIA was determined using the Janssen equation[20]: SMM (kg) = (([height centimeter]^2/resistance $\times$ 0.401) + (sex [0 for female and 1 for male] $\times$ 3.825) + (age years $\times$ [−0.071])) + 5.102. A tetrapolar device model Quantum II (RJL Systems, Detroit, MI, USA) with an electrical current of 800 μA at 50 kHz was used to assess resistance (R) and reactance (Xc) with the participants under 6 hours of fast. All patients remained in the supine position for 5 minutes before the BIA measurement was performed, with legs apart and arms not touching the torso. Four electrodes were placed on the right side of the body at the wrist, hand, ankle, and foot. The SMM was normalized by height squared and reported as skeletal muscle index (SMI) (kg/m^2). Phase angle was calculated with the following equation: phase angle (degrees) = arctan (Xc/R) $\times$ (180/π).

Physical examination of muscle mass deficit. Low muscle mass was investigated through visual inspection and palpation of muscles, with loss of bulk and tone in the sites of temple, clavicle, shoulder, scapula, thigh, calf, and interosseous muscle indicating muscle depletion. The degree of muscle depletion was rated as 0 (normal), +1 (mild), +2 (moderate), or +3 (severe).[12]

CT for skeletal muscle area. CT was assessed with the Slice-O-Matic software 5.0 (Tomovision, Montreal, Quebec, Canada) using routine CT scans conducted for

diagnostic/follow-up purposes. One image from L3 was assessed for skeletal muscle using Hounsfield unit (HU) thresholds −29 to +150 HU.[14] Skeletal muscle area was normalized by height squared and reported as lumbar SMI (cm^2/m^2).

Measurement of Muscle Strength and Physical Performance

Muscle strength was measured using a Jamar hydraulic hand dynamometer (Sammons Preston, Chicago, IL, USA). Everyone sat in a chair and the upper limb was placed alongside the body with the elbow at a 90° angle. The participant was instructed to use the maximum strength in each measurement. Three measurements were determined for each hand, and the maximum strength was used.

Physical performance was assessed by gait speed test. The subject was instructed to walk through a predetermined 4.6-m straight path while the time was measured. The test was applied twice, and the lower of the 2 measurements was used.

Nutrition Assessment

Body weight (kg) was assessed using a platform-type mechanical scale (Filizola, São Paulo, Brazil) with a maximum capacity of 150 kg and height (cm) by a vertical stadiometer 200 cm long. Body mass index (BMI) was calculated. The percentage of total body fat (%BF) was assessed by BIA based on the predictive equation provided from the manufacturer's software. Obesity was defined according to sex- and age-specific %BF cutoff points for the healthy population.[26] In addition, each patient was classified as well nourished (PG-SGA A) and malnourished (PG-SGA B and C).[12]

Laboratorial Measurements

Serum dosages of albumin (green bromocresol) and high-sensitivity C-reactive protein (hsCRP) (turbidimetric method) were measured by specific kits from Roche using a COBAS 311 analyzer (Roche Diagnostics, Mannheim, Germany) according to laboratory routine.

Overall Survival

Survival data were obtained from the electronic medical record up to 1 year after the last patient had been included (median: 17 months; interquartile range [IQR]: 12–23 months). Survival time was defined as time from inclusion in the study until death and recorded as number of months. Patients were censored at the last visit date or at the data when follow-up for survival was concluded (June 2017), whichever occurred first, if they had no death information or if they were still alive.

Statistical Analyses

Continuous variables were summarized as mean and standard deviation or median and IQR, depending on normality distribution (assessed by Shapiro-Wilk test). Categorical variables were summarized as the absolute frequencies and their corresponding percentages. To assess differences among nutrition status, body composition, and physical function according to the presence of low muscle mass based on different muscle-assessment methods, *t*-test and Mann-Whitney test were used depending on its normality distribution, and χ^2 test was used for categorical variables. The agreement between CT and the surrogate methods was evaluated by κ test. The agreement according to κ value can be interpreted as follows: 0.20 poor, 0.21–0.60 moderate, 0.61–0.80 good, and 0.81–1.00 very good.[27] The sensitivity and specificity of the methods were assessed through a cross-reference table. For the survival analysis, the SMM assessed by BIA and CT was tested as moderate and severe muscle loss groups as described in Table 1. Kaplan-Meier survival curves for different muscle-mass assessments were then performed. Univariate Cox regression models between survival and clinical variables that can influence survival (such as performance status, tumor stage, and cancer treatment in the 3 months before enrollment) were evaluated. Because of collinearity between the latter 3 variables, the variable with the highest hazard ratio (HR) will be used in multivariate Cox regression model, in addition to age and sex (variables well known to influence muscle mass) to test associations between overall survival and low–muscle-mass groups assessed by different methods. Harrell's C-statistic test was calculated to identify which method showed the best predictive accuracy for survival (the higher the C-statistic value, the better the model's accuracy). Statistical significance was defined as $P < .05$. SPSS 20.0 was used for the statistical analyses, except for C statistics, for which STATA 15.0 was used.

Results

This study included 188 patients; 52% had colon cancer, 40% rectal cancer, and 8% rectosigmoid cancer; most were males (n = 108; 57%) with a mean age of 61 ± 11.4 years and mean BMI of 27.1 ± 5.4 kg/m^2 and with 32% (n = 60) of the patients having malnutrition, according to the PG-SGA. Cancer stage III–IV was observed in 147 (78%) patients, and 58% (n = 108) had performance status 1 and 2. Most of the patients (n = 118; 63%) were not receiving cancer treatment (chemotherapy, radiotherapy, or surgery) in the 3 months before enrollment in the study, whereas 70 patients (27%) were receiving treatment, either chemotherapy or radiotherapy. The median time between the tumor diagnosis and the CT scan was 26 months (IQR: 13–46 months). Regarding comorbidities, hypertension and

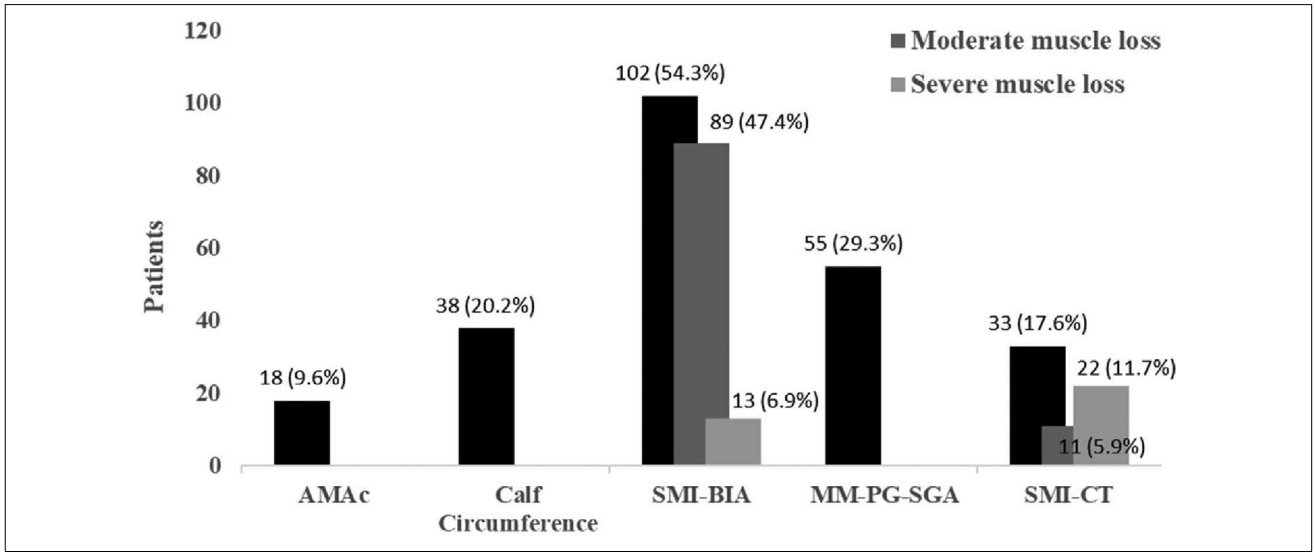

Figure 2. Low muscle mass prevalence according to different muscle-assessment methods (n = 188). AMAc, corrected mid-upper arm muscle circumference; BIA, bioelectrical impedance analysis; CT, computed tomography; MM-PG-SGA, muscle mass assessed by Patient-Generated Subjective Global Assessment; SMI, skeletal muscle index.

diabetes were the most frequent (n = 90, 48% and n = 38, 20%; respectively). The prevalence of low muscle mass varied from 9.6% to 54.3% depending on the method applied to assess muscle mass (Figure 2).

As can be seen in Table 2, the κ coefficients were indicative of moderate agreement, and the specificity was higher than the sensitivity (except for BIA). Although showing lower sensitivity than BIA, the physical examination had the highest κ coefficient and positive predictive value among all methods.

For all methods applied to assess muscle mass, the patients in the low–muscle-mass group had significantly lower BMI, higher prevalence of malnutrition, lower phase angle, and lower %BF (Table 3). Handgrip strength was lower in the group with low muscle mass when assessed by AMAc, calf circumference, and BIA. Gait speed was also lower when assessed by AMAc, calf circumference, and physical exam. Interestingly, in the groups with low muscle mass, %BF was within the normal values and not indicating malnutrition. Similarly, serum albumin levels were within the normal range (>3.5 g/dL) (Table 3).

After 17 months (IQR: 12–23) of follow-up, there were 52 (28%) deaths. According to Kaplan-Meier survival analysis, patients with low muscle mass had significantly lower survival for all methods (Figure 3). The unadjusted Cox regression model showed that tumor stages II–IV as compared with I and II (HR: 3.65; 95% CI, 1.32–10.13; $P = 0.01$), performance status 1 and 2 as compared with 0 (HR: 3.24; 95% CI, 1.67–6.32; $P < .01$), and receiving cancer treatment in the previous 3 months as compared with not receiving treatment (HR: 3.99; 95% CI, 2.25–7.01; $P < .01$) were significantly associated with worse survival, with the last one showing the highest HR. The multivariate Cox regression model adjusted by sex, age, and treatment in the 3 months

Table 2. Agreement Between Muscle Mass Evaluated by Computed Tomography and Methods Applied in Clinical Practice (n = 188).

Method	κ Test (r; P)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
AMAc	0.26 (<.01)	27.3	94.2	50	85.9
Calf circumference	0.32 (<.01)	48.5	85.8	42.1	88.7
SMI-BIA	0.26 (<.01)	93.9	54.2	30.4	97.7
MM PG-SGA	0.48 (<.01)	78.8	81.3	47.3	94.7

AMAc, corrected mid-upper arm muscle circumference; BIA, bioelectrical impedance analysis; MM PG-SGA, muscle mass assessed by Patient-Generated Subjective Global Assessment; SMI, skeletal muscle index.

Table 3. Differences in Nutrition Status, Body Composition, and Physical Function Between Muscle-Mass Groups Defined by Different Muscle-Assessment Methods (n = 188).

	AMAc			Calf Circumference			SMI—Janssen's Equation			MM PG-SGA			SMI—CT		
	Muscle Mass			Muscle Mass			Muscle Mass			Muscle Mass			Muscle Mass		
Variable	Low (n = 18)	Adequate (n = 170)	*P*	Low (n = 38)	Adequate (n = 150)	*P*	Low (n = 102)	Adequate (n = 86)	*P*	Low (n = 55)	Adequate (n = 133)	*P*	Low (n = 33)	Adequate (n = 155)	*P*
BMI[a], kg/m^2	21.7 ± 4.9	27.9 ± 5.1	<.01	21.8 ± 3.2	28.7 ± 4.9	<.01	24.8 ± 4.1	30.3 ± 5.2	<.01	21.7 ± 2.4	29.6 ± 4.5	<.01	22.3 ± 3	28.4 ± 5.2	<.01
PG-SGA B/C (n [%])[b]	14 (78%)	46 (27%)	<.01	25 (66%)	35 (23%)	<.01	43 (42%)	17 (20%)	<.01	47 (85%)	13 (10%)	<.01	26 (79%)	34 (22%)	<.01
Serum albumin level, g/dL[a,d]	4.1 ± 0.5	4.4 ± 0.4	0.07	4.1 ± 0.5	4.4 ± 0.3	<.01	4.4 ± 0.4	4.3 ± 0.4	0.7	4.1 ± 0.4	4.4 ± 0.3	<.01	4.2 ± 0.3	4.4 ± 0.4	0.03
hsCRP, mg/dL[c,e]	0.5 (0.3–1.4)	0.4 (0.2–0.9)	0.7	0.4 (0.2–1.7)	0.4 (0.3–0.9)	0.9	0.4 (0.2–1)	0.5 (0.3–0.9)	0.8	0.4 (0.2–1.4)	0.4 (0.3–0.9)	0.5	0.4 (0.3–1.6)	0.4 (0.2–0.9)	0.4
PA (°)[a]	4.9 ± 0.8	5.7 ± 0.9	<.01	4.9 ± 0.9	5.8 ± 0.9	<.01	5.5 ± 1	5.8 ± 0.9	0.047	4.9 ± 0.8	5.9 ± 0.8	<.01	4.9 ± 0.7	5.8 ± 0.9	<.01
Body fat (%)[c]	27 (17–36)	35 (28–42)	0.02	27 (17–36)	35 (28–42)	<.01	30 (23–35)	41 (34–49)	<.01	26 (19–33)	38 (31–47)	<.01	26 (20–33)	36 (30–45)	<.01
HGS, kg[c]	22 (18–29)	30 (24–37)	<.01	25 (18–29)	32 (24–38)	<.01	34 (26–37)	27 (22–32)	<.01	28 (20–35)	30 (24–38)	0.07	32 (26–36)	29 (22–37)	0.5
GS, m/s[a]	0.98 ± 0.18	1.09 ± 0.24	0.02	0.97 ± 0.18	1.11 ± 0.24	<.01	1.11 ± 0.24	1.05 ± 0.24	0.1	1.03 ± 0.24	1.11 ± 0.24	0.047	1.09 ± 0.25	1.08 ± 0.24	0.9

Results are shown as n (%), mean ± standard deviation or median (IQR Q1–Q3).
AMAc, corrected mid-upper arm muscle circumference; BMI, body mass index; CT, computed tomography; GS, gait speed; HGS, handgrip strength; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; MM PG-SGA, muscle mass assessed by Patient-Generated Subjective Global Assessment; PA, phase angle; PG-SGA, Patient-Generated Subjective Global Assessment; SMI, skeletal muscle index.
[a] *t*-test.
[b] χ^2 test.
[c] Mann-Whitney test.
[d] N = 168.
[e] N = 157.

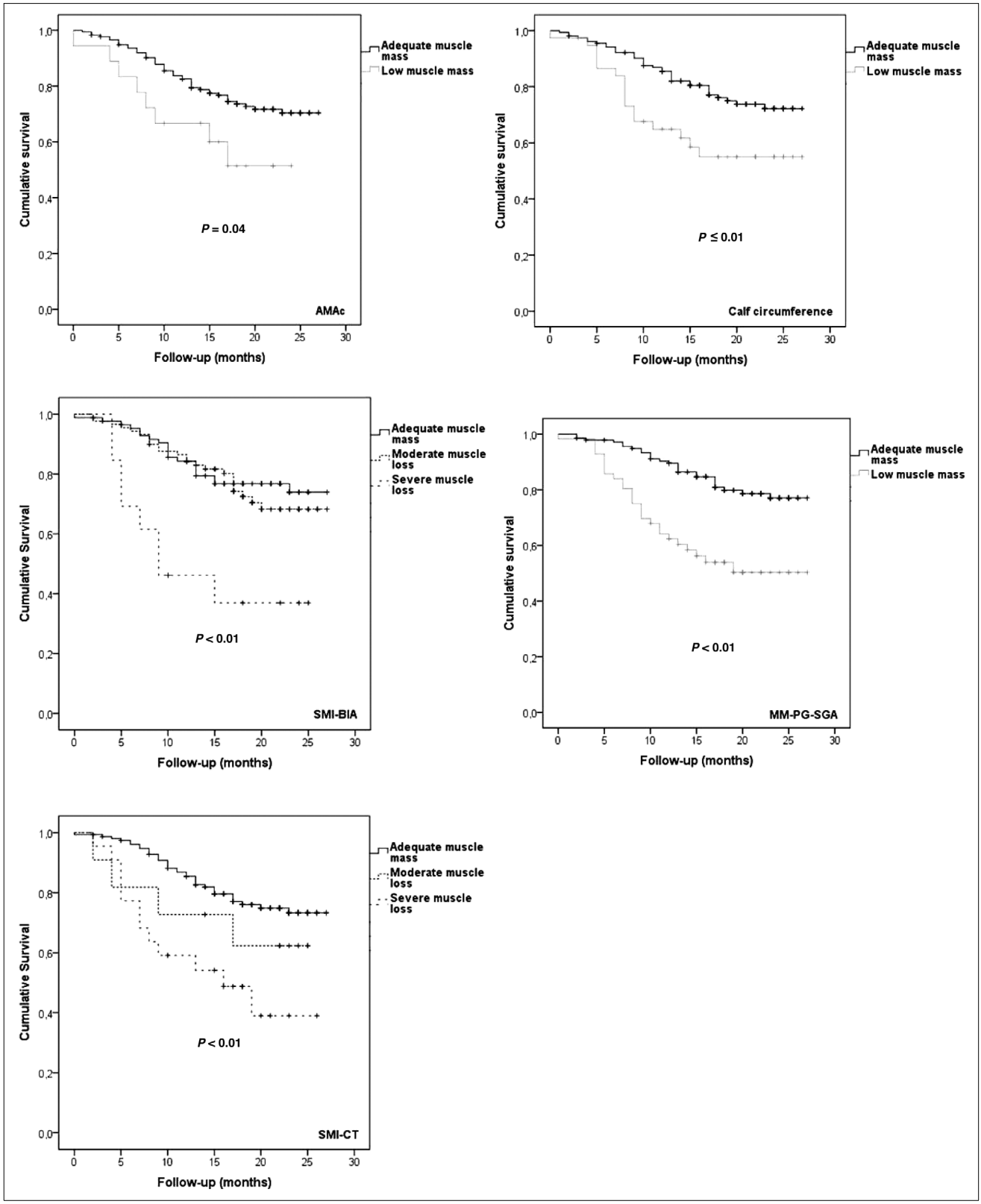

Figure 3. Kaplan-Meier survival curves of different muscle-assessment methods (n = 188). AMAc, corrected mid-upper arm muscle circumference; BIA, bioelectrical impedance analysis; CT, computed tomography; MM-PG-SGA, muscle mass assessed by Patient-Generated Subjective Global Assessment; SMI, skeletal muscle index.

Table 4. Multivariate Cox Regression Analysis of Different Muscle-Assessment Methods (n = 188).

Variable	HR	95% CI	*P*	C Statatistic
Model 1[a]				
Low muscle mass—AMAc	1.74	0.80–3.75	.16	0.68
Model 2[a]				
Low muscle mass—Calf circumference	1.54	0.84–2.85	.16	0.69
Model 3[a]				
Low muscle mass—SMI-BIA				
Moderate muscle loss	0.93	0.47–1.88	.85	0.69
Severe muscle loss	2.46	1.03–5.88	.04	
Model 4[a]				
Low muscle mass—MM PG-SGA	1.90	1.05–3.43	.03	0.71
Model 5[a]				
Low muscle mass—SMI-CT				
Moderate muscle loss	1.07	0.37–3.13	.90	0.70
Severe muscle loss	2.14	1.06–4.31	.03	

AMAc, corrected mid-upper arm muscle circumference; BIA, bioelectrical impedance analysis; CT, computed tomography; HR, hazard ratio; MM PG-SGA, muscle mass assessed by Patient-Generated Subjective Global Assessment; SMI, skeletal muscle index.
[a]Adjusted for age, sex, and cancer treatment in the 3 months prior to enrollment (no or yes). The group with adequate muscle mass was taken as reference for the analysis.

previous to enrollment (no or yes) showed that severe muscle loss assessed by BIA and CT and low muscle mass assessed by the physical exam from PG-SGA remained significantly associated with lower survival and had similar C-statistic values to predict mortality (Table 4).

Discussion

This study aimed to evaluate the agreement between CT and surrogate methods highly applied in the clinical setting for the muscle mass measurements and to assess the prognostic value of low muscle mass for survival in a follow-up of 17 months in a representative group of 188 well-characterized CRC patients. Our main finding was that among all methods tested, low muscle mass assessed by the physical examination from PG-SGA showed the highest κ coefficient and the best agreement with CT, which is considered a reference method.[13] In addition, as expected, the low–muscle-mass groups had a higher proportion of malnourished individuals and lower %BF. Depending on the method applied to assess muscle mass, the groups with low muscle mass had lower handgrip strength and gait speed, denoting lower strength and muscle function. Finally, the Cox regression models adjusted for age, sex, and receiving cancer treatment in the 3 months before study enrollment showed that severe muscle loss (measured by BIA and CT) and low muscle mass (measured by PG-SGA) predicted higher mortality rates than the adequate–muscle-mass groups. These results are aligned with the notion that low muscle mass has a negative impact on outcome, which emphasizes the importance of implementing its assessment by a method that can be easily used in the routine care of cancer patients.

In addition, we observed a wide variation in the prevalence of low muscle mass depending on the method applied, which was similar to that previously reported in patients with varying types of cancer.[1,2] This large variability may be explained not only by different methods applied but also by distinct thresholds used for screening for low muscle mass. Although the EWGSOP recommends using normative data of the study population,[28] researchers have used different cutoff points of the distinct populations to assess low muscle mass, and the results may be difficult to interpret. Therefore, our findings, together with those previously reported, highlight the importance of exploring which method has the best agreement with a reference method. In this regard, we showed that the muscle deficit assessed by the physical examination from the PG-SGA had the best agreement with CT in the slice located at L3, which was shown to reflect the muscle mass of the whole body in healthy individuals[17] and in patients with cancer.[14] We speculate that the good performance of physical examination may result from the fact that it includes the assessment of 7 sites of the body (temple, clavicle, shoulder, scapula, thigh, calf, and interosseous muscle) that are rated according to the clinical judgment of the examiner in +1 (mild), +2 (moderate), and +3 (severe) of muscle deficit. Hence, we hypothesize that it can yield a better overall condition of muscle depletion than other methods, such as calf circumference and AMAc, that restrict the assessment to 1 site of muscle mass. Although the muscle deficit assessed by the physical examination from the PG-SGA had the best agreement with CT, the moderate positive predictive κ value that was found highlighted the importance of adequate training to perform the different assessments used in the study. Preferably, a trained dietitian should perform the physical examination, but other

healthcare professionals (nurses, physicians, and physiotherapist) can also be trained for this purpose. As there is no need of equipment and the exam takes <10 minutes to be completed, it can be easily implemented in the clinical setting, such as in outpatient clinics and hospitals. However, it should be acknowledged that the physical examination has the disadvantage of not being an objective measurement and, therefore, can be subjected to inter-examiner and intra-examiner variability. In agreement with our results, Raeder et al, in a study with 97 nonmetastatic CRC patients, identified 64% sensitivity and 78% specificity of the physical examination from PG-SGA when compared with fat-free mass estimated by BIA.[29] On the other hand, in a study from our group carried out in nondialyzed chronic kidney disease patients, we failed to show good agreement between CT and the physical examination (κ coefficient in males: 0.32; sensitivity: 40%; specificity: 88%; κ coefficient in female: −0.12; sensitivity: 9%; specificity: 79%).[18] The difference in the results between oncologic and chronic kidney disease patients may be attributed to the characteristics related to the group itself. Patients with chronic kidney disease are known to show fluctuation in hydration status, which is likely not visualized by the physical examination[30] unless it comes as a pronounced edema. In addition, it should also be kept in mind that the results from our study, as well from the previous one in patients with cancer, showed a better specificity than sensitivity of the physical examination to diagnose low muscle mass, suggesting a limited capacity to detect the true cases of low muscle mass. Despite these findings, the physical examination was able to differentiate nutrition status between patients with and without muscle loss.

Also of note, in our findings, the low–muscle-mass group had worse nutrition status than the adequate–muscle-mass group, as depicted by higher prevalence of malnutrition by PG-SGA and lower values of BMI, %BF, and phase angle. However, in all groups with low muscle mass, the mean %BF was not indicative of low values, suggesting that overweight and obesity can occur together with low muscle mass, which is known as obese sarcopenia.[4-7] Similarly, for all methods applied, serum albumin level was indicative of normal values (>3.5 g/dL), even in the low–muscle-mass group, which is aligned with the median hsCRP levels denoting low degree of inflammation. Finally, phase angle, considered a marker of the amount and quality of soft-tissue mass,[31] was able to detect the differences between the group with and without muscle loss.

When we investigated the prognostic outcome of low muscle mass on overall mortality diagnosed by different methods, we found that severe muscle loss (measured by BIA and CT) and low muscle mass (measured by PG-SGA) were able to predict overall mortality in the models adjusted for sex, age, and treatment in the 3 months prior to inclusion the study. Our findings are not in accordance with a previous study[32] in which, among the methods applied to diagnose cachexia in patients with cancer, AMAc had the highest HR compared with the other methods, including CT. The lack of agreement with our results is likely to be explained by the fact that Blauwhoff-Buskermolen et al[32] applied different cutoffs for AMAc and BIA, and CT was assessed L3 and fourth thoracic vertebra (T4), whereas we assessed at L3. Moreover, in our study, the physical examination from PG-SGA, BIA, and CT had similar C-statistic values, suggesting comparable prediction for mortality. We are not aware of studies in patients with cancer testing the prognostic effect of low muscle mass assessed by these methods, especially by physical examination, on overall mortality. But in nondialyzed and dialyzed patients, Carrero et al[33] also showed that mortality was significantly higher in patients having muscle depletion by physical exam, which agrees with our results. Altogether, low muscle mass assessed by the physical examination had the best agreement with CT and, together with BIA and CT, was able to differentiate nutrition status measured by objective measurements.

The strengths of the present study include the measurement of muscle mass by 4 surrogate methods and 1 reference method, all performed by the same trained researcher and in a representative and relatively large sample of CRC patients. Moreover, the reliability of the physical examination for the assessment of low muscle mass has important clinical application, allowing its implementation in routine nutrition screening for patients with high need of nutrition care. The limitations include (1) the lack of a long-term follow-up, which probably explains why only severe muscle loss for BIA and CT was associated with higher mortality in the multivariate Cox adjusted models; (2) the lack of reference values for low muscle mass from Brazilian normative tables, except for calf circumference; and (3) muscle mass from BIA using a nonvalidated equation in our population.

In conclusion, physical examination showed the highest κ coefficient and the best agreement with CT to identify muscle-mass depletion. Groups with low muscle mass had a higher proportion of malnourished individuals and lower values of %BF and phase angle. Severe muscle loss (measured by BIA and CT) and low muscle mass (measured by physical examination) were independent factors of mortality in patients with CRC. Moreover, physical examination from PG-SGA, BIA, and CT had similar predictive results in survival analysis of CRC patients. Future prospective studies are warranted to confirm our findings, and the use of specific equation/cutoffs may show different results.

Statement of Authorship

M. C. Gonzalez and C. M. Avesani contributed to the conception and design of the research; N. C. Souza, R. B. Martucci, N. B. de Pinho, and V. D. Rodrigues contributed to the design of the research; N. C. Souza contributed to the acquisition, analysis, and interpretation of data; M. C. Gonzalez, A. R. Qureshi, and C. M. Avesani contributed to the analysis and

interpretation of data; N. C. Souza, M. C. Gonzalez, and C. M. Avesani drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, read and approved the final manuscript.

References

1. Ryan AM, Power DG, Daly L, Cushen SJ, Ní Bhuachalla Ē, Prado CM. Cancer-associated malnutrition, cachexia and sarcopenia: the skeleton in the hospital closet 40 years later. *Proc Nutr Soc*. 2016;75(2):199-211.
2. Rier HN, Jager A, Sleijfer S, Maier AB, Levin MD. The prevalence and prognostic value of low muscle mass in cancer patients: a review of the literature. *Oncologist*. 2016;21(11):1396-1409.
3. Johns N, Stephens NA, Fearon KC. Muscle wasting in cancer. *Int J Biochem Cell Biol*. 2013;45(10):2215-2229.
4. Prado CM, Lieffers JR, McCargar LJ, 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(7):629-635.
5. Martin L, Birdsell L, Macdonald N, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol*. 2013;31(12):1539-1547.
6. Tan BH, Birdsell LA, Martin L, Baracos VE, Fearon KC. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. *Clin Cancer Res*. 2009;15(22):6973-6979.
7. Caan BJ, Meyerhardt JA, Kroenke CH, et al. Explaining the obesity paradox: the association between body composition and colorectal cancer survival (C-SCANS Study). *Cancer Epidemiol Biomarkers Prev*. 2017;26(7):1008-1015.
8. Prado CM, Baracos VE, McCargar LJ, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. *Clin Cancer Res*. 2009;15(8):2920-2926.
9. Lieffers JR, Bathe OF, Fassbender K, Winget M, Baracos VE. Sarcopenia is associated with postoperative infection and delayed recovery from colorectal cancer resection surgery. *Br J Cancer*. 2012;107(6): 931-936.
10. Morishita S, Kaida K, Tanaka T, et al. Prevalence of sarcopenia and relevance of body composition, physiological function, fatigue, and health-related quality of life in patients before allogeneic hematopoietic stem cell transplantation. *Support Care Cancer*. 2012;20(12):3161-3168.
11. Davies M. Nutritional screening and assessment in cancer-associated malnutrition. *Eur J Oncol Nurs*. 2005;9(suppl 2):S64-S73.
12. Jager-Wittenaar H, Ottery FD. Assessing nutritional status in cancer: role of the patient-generated subjective global assessment. *Curr Opin Clin Nutr Metab Care*. 2017;20(5):322-329.
13. Prado CM, Heymsfield SB. Lean tissue imaging: a new era for nutritional assessment and intervention. *JPEN J Parenter Enteral Nutr*. 2014;38(8):940-953.
14. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab*. 2008;33(5):997-1006.
15. Mauricio SF, Xiao J, Prado CM, Gonzalez MC, Correia M. Different nutritional assessment tools as predictors of postoperative complications in patients undergoing colorectal cancer resection. *Clin Nutr*. 2018;37(5):1505-1511.
16. Feliciano EMC, Kroenke CH, Meyerhardt JA, et al. Association of systemic inflammation and sarcopenia with survival in nonmetastatic colorectal cancer: results from the C SCANS study. *JAMA Oncol*. 2017;3(12):e172319.
17. Shen W, Punyanitya M, Wang Z, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *J Appl Physi*ol (1985). 2004;97(6):2333-2338.
18. Giglio J, Kamimura MA, Souza NC, et al. Muscle mass assessment by computed tomography in chronic kidney disease patients: agreement with surrogate methods. *Eur J Clin Nutr*. 2019;73(1):46-53.
19. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing*. 2019;48(1)16-31.
20. Janssen I, Heymsfield SB, Baumgartner RN, Ross R. Estimation of skeletal muscle mass by bioelectrical impedance analysis. *J Appl Physiol (1985)*. 2000;89(2):465-471.
21. Miller MD, Crotty M, Giles LC, et al. Corrected arm muscle area: an independent predictor of long-term mortality in community-dwelling older adults? *J Am Geriatr Soc*. 2002;50(7):1272-1277.
22. Barbosa-Silva TG, Bielemann RM, Gonzalez MC, Menezes AM. Prevalence of sarcopenia among community-dwelling elderly of a medium-sized South American city: results of the COMO VAI? study. *J Cachexia Sarcopenia Muscle*. 2016;7(2):136-143.
23. Janssen I, Baumgartner RN, Ross R, Rosenberg IH, Roubenoff R. Skeletal muscle cutpoints associated with elevated physical disability risk in older men and women. *Am J Epidemiol*. 2004;159(4):413-421.
24. van der Werf A, Langius JAE, de van der Schueren MAE, et al. Percentiles for skeletal muscle index, area and radiation attenuation based on computed tomography imaging in a healthy Caucasian population. *Eur J Clin Nutr*. 2018;72(2):288-296.
25. 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(4):680-690.
26. Heo M, Faith MS, Pietrobelli A, Heymsfield SB. Percentage of body fat cutoffs by sex, age, and race-ethnicity in the US adult population from NHANES 1999–2004. *Am J Clin Nutr*. 2012;95(3):594-602.
27. Fleiss JL. *The Design and Analysis of Clinical Experiments*. New York: John Wiley Sons Inc; 1986.
28. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on sarcopenia in older people. *Age Ageing*. 2010;39(4):412-423.
29. Raeder H, Henriksen C, Bohn SK, et al. Agreement between PG-SGA category and fat-free mass in colorectal cancer patients. *Clin Nutr ESPEN*. 2018;27:24-31.
30. Carrero JJ, Johansen KL, Lindholm B, Stenvinkel P, Cuppari L, Avesani CM. Screening for muscle wasting and dysfunction in patients with chronic kidney disease. *Kidney Int*. 2016;90(1):53-66.
31. Norman K, Stobaus N, Pirlich M, Bosy-Westphal A. Bioelectrical phase angle and impedance vector analysis–clinical relevance and applicability of impedance parameters. *Clin Nutr*. 2012;31(6):854-861.
32. 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(4):615-622.
33. Carrero JJ, Chmielewski M, Axelsson J, et al. Muscle atrophy, inflammation and clinical outcome in incident and prevalent dialysis patients. *Clin Nutr*. 2008;27(4):557-564.