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Screening for low muscularity in colorectal cancer patients: a valid, clinic-friendly approach that predicts mortality

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Abstract

Background Low skeletal muscle quantified using computed tomography (CT) scans is associated with morbidity and mortality among cancer patients. However, existing methods to assess skeletal muscle from CT are time-consuming, expensive, and require training. Clinic-friendly tools to screen for low skeletal muscle in cancer patients are urgently needed.

Methods We included 807 scans from non-metastatic colorectal cancer patients. With the digital ruler available in most radiological software, we implemented an abbreviated method to assess skeletal muscle area at the third lumbar vertebra (L3), which consisted of assessing the height and width of the psoas and paraspinal muscles and computing their combined 'linear area' in centimetres squared (cm^2). A subset of CT scans was assessed twice by two analysts to compute intra-rater and inter-rater reliability. We derived cut-points for 'low' linear area using optimal stratification and then calculated the sensitivity and specificity of these cut-points relative to standard methods (total L3 cross-sectional area assessed with Slice-O-Matic research software). We further evaluated the association of low linear area with death from any cause after colorectal cancer diagnosis in Cox proportional hazards models adjusting for demographics, smoking, body mass index category, and tumour characteristics.

Results The linear area was highly correlated with total cross-sectional area assessed using standard methods [$r = 0.92$; 95% confidence interval (CI): 0.91, 0.93] overall and within subgroups defined by age, sex, and body mass index group. Intra-rater and inter-rater reliability were equally high (both intra-class correlations = 0.98). Cut-points for low linear area were sensitive (0.75; 95% CI: 0.70, 0.80) and specific (0.77; 95% CI: 0.73, 0.80) for identifying low skeletal muscle relative to the standard of total L3 cross-sectional area. The hazard ratio and 95% CI for death associated with a low linear area were hazard ratio = 1.66; 95% CI: 1.22, 2.25.

Conclusions Clinic-friendly methods that assess linear area from CT scans are an accurate screening tool to identify low skeletal muscle among non-metastatic colorectal cancer patients. These linear measures are associated with mortality after colorectal cancer, suggesting they could be clinically useful both to improve prognostication and to provide a practical screening tool to identify cancer patients who require nutrition or exercise intervention.

Keywords Sarcopenia; Muscle mass; Cancer; Screening

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Introduction

Low skeletal muscle mass is common among cancer patients[1,2] and predicts surgical complications,[3–9] treatment toxicity,[10–14] poor quality of life, and reduced survival.[9,15–17] This accumulating evidence has prompted oncologists to identify skeletal muscle mass as an important biomarker for numerous adverse outcomes in cancer patients.[18] Despite

the prognostic value of this information and availability of diagnostic images from which muscle mass can be precisely quantified, muscle mass is rarely assessed in early stage cancer or used in clinical decision-making. This is, in part, due to a lack of time-efficient, clinic-friendly assessment tools that screen for low muscle and associate with cancer outcomes.

As previously reviewed,[19,20] there are many ways to assess skeletal muscle—from dilution methods to imaging modalities—in clinical settings. In oncology research,[21,22] computerized tomography (CT) has emerged as a common reference method because CT scans are a routine part of diagnosis and surveillance in many cancers. The standard method to evaluate muscle mass is manual analysis of the total cross-sectional area of all muscle groups at the level of the third lumbar vertebra (L3), which is highly correlated (r = 0.90) with whole body muscle volumes.[23] While the standard method provides an accurate estimates of muscle area, it has limited potential for clinical translation due to time (~10 min by a trained operator with anatomical knowledge), expense (~$4000 per software licence), and logistics (image analysis is conducted in research software, which is not easily integrated into clinical workflows). Automated image analysis methods exist but are only beginning to be validated and are not typically available in the clinical setting through existing radiologic software. We conjecture that these factors represent barriers to the integration of body composition assessment from CT scans into clinical practice.

Abbreviated methods to screen for low muscle from routine CT imaging have been proposed in intensive care and trauma populations,[24] and to a limited extent in cancer patients, where results have been mixed.[25,26] One recently proposed method[27] allows the user to quickly assess patient muscularity using the combined area of the psoas and paraspinal muscles computed from linear measurements that take $<$2 min per patient. Not only is this 'linear measures method' method simple, reproducible, and efficient, it can be implemented using the digital ruler found in most radiological software, facilitating integration into existing clinical workflows. In the derivation cohort, the linear area at L3 calculated using this method was highly correlated (r = 0.86) with the standard of 'total cross-sectional area' assessed using research software.[27] While the linear measures method shows promise for clinical translation, its validity among diverse groups of cancer patients is unknown: the derivation cohort was a small group of intensive care patients (n = 145) who were $\geq$65 years old and primarily of European descent. The previous study also did not assess whether patient muscularity assessed using this method associated with mortality outcomes.

Before it can be used in oncology practice, a practical screening tool to identify low muscle (such as the linear measures method described in this paper) needs to be validated relative to standard analysis among cancer patients. To be useful for improving prognostication, such a screening tool would produce measures of skeletal muscle that are associated with clinical outcomes such as mortality after diagnosis. In the present study, we applied the linear measures method among an ethnically and racially diverse group of 807 non-metastatic colorectal cancer patients. The muscle area of these patients was previously quantified using standard analysis of total L3 cross-sectional area and found to be associated with surgical complications, treatment-related toxicities,[28] and premature mortality.[15] If shown to be valid, the linear measures method has high potential for integration into existing clinical workflows as a tool to screen cancer patients for low muscle, improve prognostication, and target supportive interventions like nutrition and physiotherapy.

Materials and methods

Study population

Our study population was derived from patients in the 'C-SCANS' (Sarcopenia, Colorectal cancer, And Near-term Survival) cohort, described in detail elsewhere.[15,29] C-SCANS included all Kaiser Permanente Northern California patients diagnosed from 2006–11 with American Joint Committee on Cancer stage I–III colon cancer that had a surgical resection and an abdominal CT scan within 4 months of diagnosis and before any chemotherapy or radiation (median, 0.25 months; range $-$2.0 to 3.8 months). The study sample (n = 825) was drawn from subjects in the C-SCANS parent cohort. We selected 125 patients from each of the minority racial/ethnic groups (Black/African American, Latino/Hispanic, and Asian/Pacific Islander) and the remaining 450 from among the non-Hispanic White patients. Our sampling scheme used frequency matching of each racial/ethnic group on the variables age, sex, body mass index (BMI), and stage. Frequency matching ensures that each racial/ethnic group has the same distributions over categorical levels of potential confounders.[30] The variables were categorized as age, in quartiles, sex as dichotomous, BMI [in kilograms divided by height in metres squared (kg/m^2)] as $<$18.5, 18.5–$<$25, 25–$<$30, 30–$<$35, or 35+ kg/m^2, and stage as I, II, or III. We applied frequency matching to each racial/ethnic group to match the distributions in the C-SCANS parent cohort.

Covariates

We selected the height and weight closest to the CT scan measured by medical assistants (within 6 months of diagnosis) and computed and categorized BMI as described above. We reviewed the Kaiser Permanente Northern California electronic medical record and Cancer Registry for demographics (e.g. age, race/ethnicity, and sex), smoking status, and disease characteristics (tumour site, stage, grade, and receipt of chemotherapy or radiation).

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Standard analysis of skeletal muscle mass

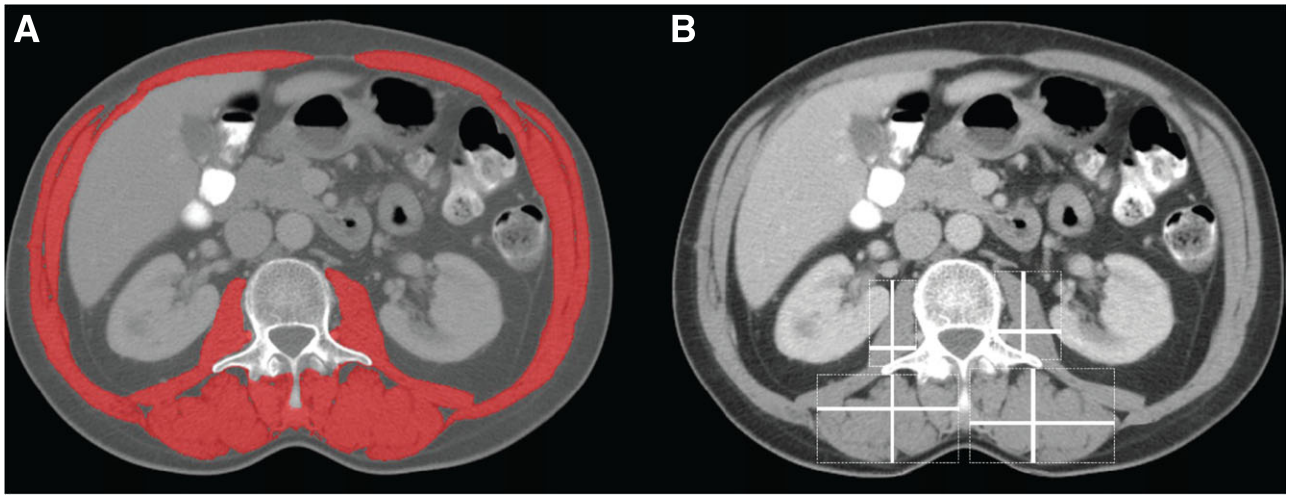
As part of the C-SCANS study, muscle was quantified using standard analysis from an axial CT scan that had been taken before chemotherapy or radiation, if received, and archived within the electronic medical record. The median time from diagnosis to scan in this study sample was 6 days (range: −2 to 4 months; 79% pre-surgical). A single, trained researcher with anatomical knowledge selected the L3 and analysed the total cross-sectional area of muscle in centimetres squared (cm^2) according to tissue-specific Hounsfield units ranges using Slice-O-Matic Software version 5.0 (Tomovision, Quebec, Canada).[31] We computed the skeletal muscle index as the total cross-sectional area in centimetres squared scaled to height in metres squared. Figure 1A shows the CT scans of an example patient in this cohort with the total cross-sectional muscle area analysed using standard analysis implemented in Slice-O-Matic.

Clinic-friendly linear measurements

A prior publication by Avrutin *et al*. describes the development and internal validation of the clinic-friendly linear measures method, including a detailed step-by-step protocol in Supporting Information.[27] Figure 1B shows a CT image assessed using the clinic-friendly linear measurements method. As health care systems have transitioned from film to digital imaging, radiologists throughout North American now use a variety of Picture Archiving and Communication Systems (PACS) and Digital Imaging and Communications in Medicine viewers to interpret diagnostic images, including CT scans. While the vendor varies, each includes a ruler tool that can be used to administer linear measures. We used the digital ruler feature to measure muscle length—corresponding to the widest and longest horizontal and vertical distances, respectively. These two measures were obtained for each of the muscle groups examined [left and right psoas and left and right paraspinal group (the paraspinal group included the erector spinae muscles but not the quadratus lumborum)], resulting in a total of eight measures per scan (Figure 1B). To minimize the inconsistencies between analysts, the orientation of each line remained in the horizontal or vertical direction as the scan appears on the screen, irrespective of the orientation of the patients (i.e. on some scans, the individuals did not appear evenly flat on their backs). A strategy to envision the linear measurement is to consider the line placement not as lines drawn such that their length and width is perfectly within the boundaries of the muscle itself, but rather to draw two lines within which the entirety of the muscle would be enclosed if they were to form a rectangular box, as indicated with dotted guideline on Figure 1B.

The product of the horizontal and vertical measures was calculated for the left and right sides of each muscle group separately, by multiplying the values. We summed the products of the left and right side for each muscle group, which

Figure 1 Assessment methods for total cross-sectional area and linear area. (A) Total cross-sectional area at the third lumber vertebra analysed using research software. (B) Linear measures applied to the right and left psoas and paraspinal groups using the digital ruler in radiological software. (A) Assessed total L3 cross-sectional area using Slice-O-Matic research software. (B) Applied the eight linear measures to the L3 using the digital ruler native to most radiological software. To minimize the inconsistencies between analysts, the orientation of each line remained in the horizontal or vertical direction as the scan appears on the screen, irrespective of the orientation of the patients (i.e. on some scans, the individuals did not appear evenly flat on their backs). A strategy to envision the linear measurement is to consider the line placement not as lines drawn such that their length and width is perfectly within the boundaries of the muscle itself, but rather to draw two lines within which the entirety of the muscle would be enclosed if they were to form a rectangular box, as indicated with dotted guideline on Figure 1B. A detailed step-by-step protocol is included in Supporting Information to the original Avrutin *et al*. publication that established this method.



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resulted in (i) the linear area of the psoas muscles, (ii) the linear area of the paraspinal muscles, and (iii) their combined linear area (the sum of the psoas and paraspinal muscle linear areas). The index values were calculated by dividing the sums of (i) to (iii) by height squared. The length and width measures are relative to the size of the patient on the scan and unaffected by image magnification or screen resolution. We analysed the linear areas treated in their native units (cm^2) as well as scaled to height in metres squared for derivation of cut-points and for comparison with the skeletal muscle index derived from the total cross-sectional area measured using the standard approach.

Statistical analysis

Descriptive statistics for the patients included in this validation are shown in Table 1. We computed the coefficient of variation (CV%) and the intra-class correlation to assess intra-rater and inter-rater reliability on the subset of 25 scans that each of the two raters evaluated twice, several weeks apart. We calculated the Pearson correlation coefficients between the linear area (clinic-friendly linear measures method) and the total cross-sectional area (standard). To assess the prognostic value of the linear measures, we evaluated their association with overall survival in Cox proportional hazards models adjusting for smoking, race/ethnicity, stage, grade, receipt of chemotherapy or radiation, cancer site (colon or rectum), sex, age, and BMI category. Different measures of muscularity are on different scales. Thus, to compare the magnitude of the associations of muscle assessed using each of the methods with overall mortality after colorectal cancer diagnosis, we standardized the linear and total cross-sectional areas to the normal distribution and report mortality associations per standard deviation (SD). To derive sex-specific cut-points for low muscle from the linear area that identified patients with increased risk of death, we used optimal stratification, a method commonly employed in the oncology literature to derive cut-points for continuous exposures.[15,17,32] For each candidate cut-point, the log-rank statistic testing the between group difference in overall survival was computed, and the cut-point with the maximum absolute value of the log-rank statistic was chosen.[32] We then calculated the sensitivity and specificity of these linear area cut-points for identifying low muscle relative to previously published cut-points based on total cross-sectional area from the C-SCANS cohort (<52 cm^2/m^2 and <38 cm^2/m^2 for normal or overweight men and women, respectively, and <54 cm^2/m^2 and <47 cm^2/m^2 for obese men and women, respectively).[15] As there are no universally accepted cut-points for low muscle mass from CT and the appropriate binary cut-points are debated in the oncology literature,[33] we also presented results with the linear measures as continuous and categorical in tertiles to represent the dose–response relationship with mortality and enable comparison with other studies which selected different cut-points. We compared the overall survival probabilities of patients above vs. below the linear area cut-points for low muscle using Kaplan–Meier curves (Figure 2). Using multivariable-adjusted Cox proportional hazards models, we report the risk of death from any cause associated with the continuous and categorical linear measures. Because the results for the psoas and paraspinal muscle areas were similar, we report on the results for their combined areas in the text and tables and the results for each muscle group separately in the supplement. We performed all analyses using SAS 9.3 (SAS Institute, Inc., Cary, North Carolina).

Table 1 Descriptive characteristics of the study sample

	All patients (n = 807)	Normal muscle (n = 486)	Low muscle (n = 321)
	Mean (standard deviation)		
Age, years	61 (11)	58 (11)	65 (11)
	Percentage		
Sex			
Male	50	47	51
Female	50	53	49
Race/Ethnicity			
Non-Hispanic White	54	50	54
Black/African American	15	18	12
Hispanic/Latino	15	18	10
Asian/Pacific Islander	15	13	24
Other			
Body mass index, kg/m^2			
<18.5	4	1	8
18.5–<25	31	24	46
25–<30	33	41	19
30–<35	20	21	17
$> = 35$	12	13	10
Stage			
I	31	30	33
II	30	31	30
III	39	39	38
Grade			
Well-differentiated	8	8	7
Moderately differentiated	76	74	80
Poor/undifferentiated	12	13	9
Unknown	5	5	4
Cancer site			
Proximal colon	42	44	41
Distal colon	28	26	30
Rectum	30	30	29

Percentage may not total to 100% due to rounding.

Results

Table 1 shows descriptive characteristics of our study population of non-metastatic colorectal cancer patients. By design, 15% of the population was Black/African American, 15%

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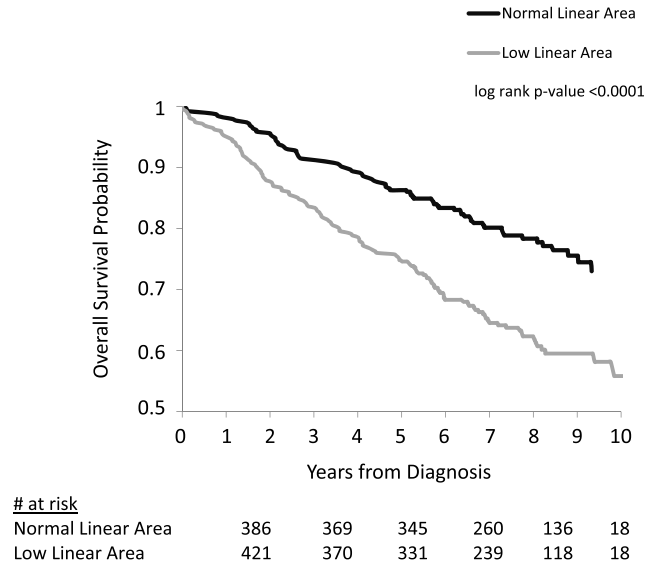
Figure 2 Kaplan–Meier curves for low muscle assessed using linear measures and overall survival. Patient survival by low vs. normal muscle assessed using the combined psoas and paraspinal linear area in centimetres squared.



Hispanic/Latino, and 15% Asian Pacific Islander; the rest were non-Hispanic White. The mean (SD) age at diagnosis was 61 (11) years; half of patients were female and a third were overweight or obese.

Table 2 shows body composition characteristics overall and by sex. Compared with women, men had higher indices of muscle; for example, mean (SD) values for the combined area of the psoas and paraspinal muscles assessed using the clinic-friendly linear measures method were 102 cm^2 for men and 74 cm^2 for women, respectively. Similarly, the mean (SD) values for the total L3 cross-sectional area assessed using standard methods were 169 cm^2 for men and 115 cm^2 for women, respectively.

Intra-rater and inter-rater reliability were equally high (ICC = 0.98; 95% CI: 0.96, 0.99), and all CV% were <5% (Table 3). The combined linear area of the psoas and paraspinal areas had a higher correlation with total L3 cross-sectional area (r = 0.92, Table 4 and Figure 3) than when either the psoas (r = 0.84) or the paraspinal muscles (r = 0.86,

Table 2 Body composition characteristics, overall and by sex

	All (n = 807)	Male (n = 406)	Female (n = 401)
	Mean (standard deviation)		
Total adipose and muscle areas at L3 assessed via standard analysis			
Subcutaneous adipose tissue, cm^2	211.2 (126.4)	182.7 (107.4)	240.0 (135.8)
Visceral adipose tissue, cm^2	145.5 (109.5)	190.0 (119.0)	101.0 (75.8)
Intra-muscular adipose tissue, cm^2	12.02 (9.38)	12.24 (9.75)	11.67 (8.76)
Skeletal muscle tissue, cm^2	142.0 (38.6)	168.9 (32.4)	114.6 (20.8)
Skeletal muscle index, cm^2/m^2	49.17 (10.14)	54.65 (9.63)	43.70 (7.38)
Muscle radiodensity, Hounsfield units	40.23 (9.66)	41.59 (8.97)	38.83 (9.98)
Linear measurements			
Combined linear area, cm^2	88.25 (22.49)	102.2 (20.2)	73.83 (14.00)
Psoas linear area, cm^2	23.93 (8.64)	29.43 (7.85)	18.24 (4.85)
Paraspinal linear area, cm^2	64.32 (15.61)	72.81 (14.64)	55.59 (11.20)
Combined linear index, cm^2/m^2	30.62 (5.99)	33.07 (5.96)	28.15 (4.96)
Psoas linear index, cm^2/m^2	8.249 (2.501)	9.523 (2.449)	6.944 (1.776)
Paraspinal linear index, cm^2/m^2	22.37 (4.31)	23.55 (4.29)	21.20 (4.04)

Table 3 Intra-rater and inter-rater reliability of linear measures method

	Intra-rater reliability		Inter-rater reliability	
	ICC (95% CI)	%CV	ICC (95% CI)	%CV
Combined linear area, cm^2	0.98 (0.96, 0.99)	3	0.98 (0.96, 0.99)	3.5

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Table 4 Pearson correlation coefficients overall and by subgroup for combined linear area of L3 muscle groups

	N	Correlation (95% CI)
Overall	807	0.92 (0.91, 0.93)
Age		
<65 years at diagnosis	479	0.94 (0.93, 0.95)
> = 65 years at diagnosis	328	0.88 (0.85, 0.90)
Sex		
Male	406	0.87 (0.84, 0.89)
Female	401	0.83 (0.79, 0.85)
Race/ethnicity		
Non-Hispanic White	435	0.90 (0.88, 0.91)
Black/African American	123	0.94 (0.92, 0.96)
Hispanic/Latino	125	0.93 (0.90, 0.95)
Asian/Pacific Islander	124	0.92 (0.89, 0.95)
Body mass index, kg/m^2		
<18.5	29	0.69 (0.43, 0.84)
18.5– < 25	249	0.90 (0.88, 0.92)
25– < 30	269	0.89 (0.86, 0.91)
30– < 35	160	0.90 (0.86, 0.92)
> = 35	100	0.90 (0.86, 0.93)
Inter-muscular adipose tissue tertile		
Low	269	0.94 (0.93, 0.95)
Middle	269	0.93 (0.91, 0.94)
High	269	0.89 (0.86, 0.91)

Supporting Information Table S2) were examined individually. While the correlations of the combined linear area with total cross-sectional area were strong regardless of the subgroup examined (Table 4), the linear measures had slightly weaker correlations with total cross-sectional area among older vs. younger patients (0.88; 95% CI: 0.85, 0.90 for patients ≥65 years old at diagnosis vs. 0.94; 95% CI: 0.93, 0.95 for patients <65 years old), in underweight vs. heavier patients (0.69; 95% CI: 0.43, 0.84 for BMI <18.5 kg/m^2 vs. 0.90; 95% CI: 0.88, 0.92 for BMI 18.5–<25 kg/m^2), and among patients with high levels of inter-muscular adipose tissue vs. patients with low levels (r = 0.89; 95% CI: 0.86, 0.91 for patients in the highest tertile of inter-muscular fat vs. r = 0.94; 95% CI: 0.93, 0.95 for patients in the lowest tertile).

Over a maximum follow-up of 10.9 years, we observed 237 deaths (133 from colorectal cancer). Considered in native units (cm^2), the linear area exhibited a dose–response relationship with risk of death from any cause across tertiles: compared with patients in the highest tertile of linear area (greatest muscularity), patients in the lowest tertile (lowest muscularity) had a more than two-fold increased risk of death [hazard ratio (HR) = 2.26; 95% CI: 1.52, 3.36], and patients in the middle tertile had a moderately elevated risk of death (HR = 1.47; 95% CI: 1.03, 2.10; Table 5). The strength of the mortality associations for the linear area was similar in magnitude to the association with standard methods that quantify the total cross-sectional area of all muscle groups at L3: a one SD increase in the linear area (22 cm^2) was associated with a 41% reduced risk of death (HR = 0.59; 95% CI: 0.47, 0.74), similar in magnitude to the 43% reduced risk of death for a one SD increase in the total cross-sectional area (39 cm^2): HR = 0.57; 95% CI: 0.43, 0.75 (Table 6).

To derive clinically relevant cut-points for low muscle from the linear measures, we scaled to height (cm^2/m^2) and used optimal stratification to identify sex-specific thresholds for patients with a high mortality risk; these were 31 cm^2/m^2 for men and 28 cm^2/m^2 for women, respectively. These cut-points were sensitive (0.75; 95% CI: 0.70, 0.80) and specific (0.77; 95% CI: 0.73, 0.80) relative to previously published cut-points[15] for low muscle mass derived from the total cross-sectional area (Table 7). As shown in the Kaplan–Meier curves, patients with low muscle identified by these cut-points had worse overall survival, with a median survival time of 6.3 years for patients below the cut-point compared with 7.4 years for patients above the cut-point (Figure 2, log-rank P-value <0.001). The multivariable-adjusted HR (95% CI) for death from any cause following colorectal cancer diagnosis associated with low muscle defined by these linear area cut-points was HR = 1.66; 95% CI: 1.22, 2.25, independent of smoking status, race/ethnicity, stage, grade, receipt of chemotherapy or radiation, cancer site (colon or rectum), sex, age at diagnosis, and BMI category (Table 5).

Figure 3 Comparison of the linear measures method to standard methods. Scatterplot and trend line comparing the combined psoas and paraspinal linear area as a predictor of total L3 cross-sectional area, both in centimetres squared.

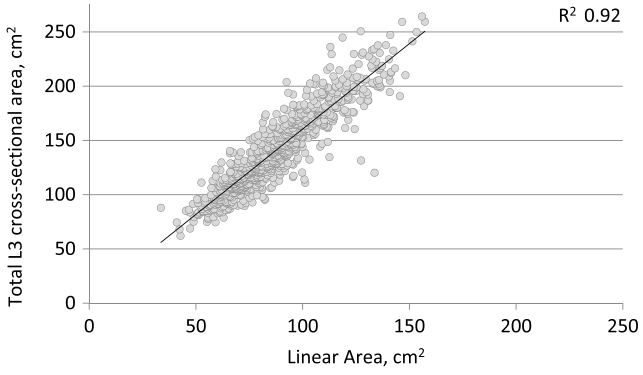

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Table 5 Association of linear measures with overall survival in non-metastatic colorectal cancer

	Hazard ratio for death from any cause[a]	LCI	UCI
Combined linear area, cm^2			
Low tertile	2.26	1.52	3.36
Middle tertile	1.47	1.03	2.10
High tertile	Reference		
Continuous	0.98	0.97	0.99
Combined linear index, cm^2/m^2			
Low tertile	1.52	1.02	2.26
Middle tertile	1.54	1.08	2.18
High tertile	Reference		
Continuous	0.96	0.93	0.99
Binary cut-point	1.66	1.22	2.25

[a]Models adjust for smoking status, race/ethnicity, stage, grade, receipt of chemotherapy or radiation, cancer site (colon or rectum), sex, age at diagnosis, and body mass index category.

Table 6 Association of standardized linear measures with overall survival in non-metastatic colorectal cancer

		Hazard ratio for death from any cause per standard deviation[a]		
	1 SD	Hazard ratio	LCI	UCI
Linear measures				
Combined linear area, cm^2	22	0.59	0.47	0.74
Combined linear index, cm^2/m^2	6	0.77	0.64	0.92
Standard measures				
Muscle total cross-sectional area at L3, cm^2	39	0.57	0.43	0.75
Skeletal muscle index, cm^2/m^2	10	0.80	0.65	0.98

[a]Models adjust for smoking status, race/ethnicity, stage, grade, receipt of chemotherapy or radiation, cancer site (colon or rectum), sex, age at diagnosis, and body mass index category; SD, standard deviation unit.

Table 7 Characteristics of linear measures as a screening tool to identify low muscle mass in non-metastatic colorectal cancer

		Cut-point[a]	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Combined linear index, cm^2/m^2	Men	30.8	0.75 (0.70, 0.80)	0.77 (0.73, 0.80)	0.68 (0.63, 0.73)	0.82 (0.79, 0.86)
	Women	28.0				

[a]Cut-points were selected based on optimal stratification.

Discussion

In this study of 807 non-metastatic colorectal cancer patients, we found that the clinic-friendly linear measures method produced muscle metrics that have high potential for use as a screening tool as they are highly correlated with standard assessments, sensitive (75%) and specific (77%) for identifying low muscle at cancer diagnosis and have strong associations with survival following colorectal cancer diagnosis. Accumulating evidence, including from the C-SCANS cohort from which our study sample was derived,[15] testifies to the importance of skeletal muscle in cancer survival [9,15–17] and to the benefits of building and maintaining muscle throughout the cancer trajectory.[1,34–38] While standard methods for assessing muscle (e.g. total cross-sectional area at L3 from CT scans) are highly accurate, they are impractical for bedside use due to time, expense, and lack of integration with clinical workflows. By contrast, the linear measures method provides a valid and practical tool to identify patients with low muscle within existing radiologic software and existing clinical workflows.

Our study builds on the work by Avrutin *et al*., which first described the linear measures approach to muscle assessment among elderly patients in intensive care.[27] While smaller studies have taken linear measures of the psoas among colorectal[26] and ovarian cancer[25] patients, ours is the largest study to use the technique developed by Avrutin *et al*. to take linear measures of multiple muscle groups (the psoas and paraspinal) among colorectal cancer patients. In addition, ours is the first to apply the technique with software already in use in clinical practice. Furthermore, we included a relatively large group of patients (n = 807), enabling us to confirm the validity of the method within subgroups defined by age, BMI, and race/ethnicity. We were further able to examine a key limitation of the method, which is that it quantifies the approximate area of the psoas and paraspinal muscles without considering the muscle radiodensity (indicative of lipid deposition into skeletal muscle fibres) or the inter-muscular adipose tissue. Fatty infiltration into skeletal muscle is associated with reduced function[17,39–43] and shorter survival in cancer and in other disease states.[44–46] Importantly, although lower among patients with high levels of inter-muscular

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adiposity vs. with low levels, the correlation of the linear area with the total (lean) cross-sectional area was still relatively high at $r = 0.89$. While quantifying fatty infiltration is important to understand disease pathology, this limitation of the linear measures method does not substantially impact its use in estimating muscle mass and thus is an acceptable limitation for a screening tool that prompts further evaluation.

Two recent studies among cancer patients have evaluated abbreviated methods for assessing skeletal muscle using digital rulers; both have focused on the psoas muscle alone, without quantifying the paraspinal muscle groups as done here.[25,47] The psoas represents only 10% of the total cross-sectional muscle area measurable at L3 and may be an inadequate marker of whole body muscle in cancer patients.[47] Rutten *et al*. found that while their linear method took very little time to implement (<1 min per scan), there was a poor correlation between the psoas linear area (length × width) and the total cross-sectional area ($r = 0.39$) among 150 ovarian cancer patients and no associations with psoas linear area and survival.[25] By contrast, Jones *et al*. found high correlations among 100 colorectal cancer patients between psoas linear area ($r = 0.80$) and total cross-sectional area; these linear measures were associated with complication rates, but Jones *et al*. did not evaluate mortality outcomes.[26]

In our study, the psoas linear area (Supporting Information Tables S1–S4) was highly correlated with the total cross-sectional area ($r = 0.86$) and associated with overall mortality after colorectal cancer diagnosis. A potential reason for the differences between our study and prior studies is the population: we included non-metastatic colorectal cancer patients. Meanwhile, Rutten *et al*. included ovarian cancer patients likely to have advanced tumour spread and reduced performance status.[25] The psoas is a hip flexor muscle indicative of physical fitness; it could be that while the psoas has limited utility in older ovarian cancer patients with advanced illness, the psoas alone is sufficient to represent total cross-sectional area and predict cancer survival in a younger, more mobile populations of non-metastatic patients. Regardless, the combined linear areas of the psoas and paraspinal muscles was even more highly correlated with total cross-sectional area ($r = 0.92$), and thus, we recommend evaluation of both the psoas and the paraspinal muscle groups as the additional linear measurements take little additional time while enhancing validity.

Comparing the linear measures method presented here with methods implemented in prior studies, it is important to distinguish several characteristics that enhance its potential for clinical translation. First, the method we present here calls for the measurement of the full width and height of the psoas and paraspinal muscle groups. Previous work in psoas linear measurements used oblique lines to capture the dimensions of the muscles, but angled orientation may lead to inconsistencies between analysts. In the method we present here, the lines are horizontal and vertical to ensure consistency, which we believe provides a more reliable and suitable screening tool. Second, the linear measures applied in prior studies (and most other CT image analysis research) are implemented using licenced, commercial software (Slice-O-Matic). Meanwhile, the method we present here may be easily completed with the ruler feature included in most PACS systems already in use in clinical care. This also obviates the need for time-consuming set-up steps (downloading the L3 scan into imaging software, adjusting the Hounsfield unit filter settings, etc.) that are performed prior to the actual muscle analysis. The method we present is implemented in PACS and thus does not require downloading the image nor setting filters.

In sum, the linear measures method is a reliable and valid screening tool to identify patients at an early stage in the disease trajectory when they still have robust anabolic potential[48] and declines in muscle mass and loss of functional status may be prevented or effectively treated through exercise and/or nutrition.[1,34–36,49] Early identification is critical because cachexia often coexists with, and is compounded by, pre-existing muscle loss due to ageing.[35] Following cancer diagnosis, several factors exacerbate the risk of muscle loss among cancer patients. These include direct effects of treatment on protein synthesis and degradation, alterations in nutrient intake due to nausea, and changes in energy expenditure due to inactivity or bedrest, all of which accelerate muscle loss in cancer patients. Rapid identification and then treatment of low muscle mass through tailored lifestyle interventions such as resistance training increases patient quality of life and treatment completion[1,34–36] and may also prolong survival.[37,38]

Strengths and limitations

This study has several strengths: first, we examined a practical, clinic-friendly method to assess low muscle mass in cancer patients in a much larger group of 807 patients than prior studies of abbreviated methods, which all had <150 patients. This enabled us to obtain precise estimates of the sensitivity and specificity relative to the standard of total L3 cross-sectional area and to consider the performance of the method among patient subgroups. The index values that are calculated using the linear measures approach, both continuously and as a dichotomous predictor, may be used to identify individuals with a higher risk of mortality.

However, there are important limitations to this study and to the linear measures method that warrant discussion: there is no accepted 'sentinel muscle' for low muscle mass. We chose the psoas and paraspinal muscles for ease of measurement, but also their functional roles in posture and fitness, and found promising results for their potential use as a screening tool. As discussed earlier, muscle area does not capture morphologic or functional aspects of muscle such as fat infiltration or grip strength, both which are also predictive of cancer outcomes. Further, definitions for low muscle mass from CT in the oncology literature are highly variable,[33]

resulting in variable prevalence. Most authors either define cut-points based on their own study population using ranked categories (e.g. Miyamoto *et al*.[50] defined low muscle mass as the lowest quartile of skeletal muscle index, thus the prevalence was 25% by design) or optimal stratification (e.g. Van Vledder *et al*. defined cut-offs for skeletal muscle index according to where risk of death significantly increased in their study population: 41.10 cm^2/m^2 for women and 43.75 cm^2/m^2 for men,[51] resulting in a low muscle mass prevalence of 19%). Often, authors use previously published cut-points that were originally derived using optimal stratification (e.g. Thoresen[52] used the Prado[53] cut-points for skeletal muscle index, $\leq$38.5 cm^2/m^2 for women and $\leq$52.5 cm^2/m^2 for men, and found a low muscle mass prevalence of 39%). Regardless of the cut-points applied or whether the linear measures were modelled continuously, we found that the linear measures method was valid compared with total L3 cross-sectional area and associated with overall mortality.

The linear measures method is intended for screening: the method was developed to be simple and implemented with minimal training in a consistent and time efficient manner to roughly classify patient risk. It is not a replacement for comprehensive assessment of muscle mass and function in clinical practice nor for standard tools such as Slice-O-Matic used to quantify total L3 cross-sectional area in oncology research. When using our primary definition of low muscle mass, defined using published cut-points from the largest ever study of non-metastatic colorectal cancer patients,[15] the negative predictive value of the linear measures method was 82% [probability that patients who screened as negative (normal muscle mass) using our linear measures screening test truly do not have low muscle mass]. The positive predictive value [probability that patients who screened as positive (low muscle mass) truly have low muscle mass] was 68%. This may be acceptable: while treatment for low muscle mass in early-stage cancer is not standard of care at present, it also does not carry substantial risk of harm to the patient because physical activity, resistance training, and nutritional support are likely to benefit even those patients who do not meet criteria for low muscle mass (the false positives).

Future studies should evaluate a possible learner effect in which the performance of the research assistant or clinician applying the measures improves with practice. Further, it will be important to examine the validity of the linear measures method (and the cut-points chosen to define low muscle mass) in other cancers, later stages, and older ages. In populations with very different demographic characteristics, values of the linear measures lower than a pre-determined percentile of the observed distribution in that cohort could be selected to ensure sufficient sensitivity of the method.

In addition, examination of whether the linear measures method is sensitive to change over time would also be relevant, as muscle loss during cancer treatment has been shown in colorectal and other cancers to be strongly associated with risk of death.[54,55] Because this was a test of the validity of the screening method, we included both pre-surgical and post-surgical scans in this analysis; the validity of the method and associations with mortality were very similar when we restricted to only pre-surgical scans. Tracking change over time and during and after cancer treatment may be important for evaluating interventions to improve muscle mass, but the accuracy of this screening method for quantifying changes in muscle mass must be evaluated before it is used as a tool to measure the efficacy of interventions to prevent muscle loss in cancer patients.

Conclusions

The linear measures method was highly correlated with standard methods, sensitive and specific for identifying low skeletal muscle in cancer patients and associated with mortality among non-metastatic colorectal cancer patients. CT scans are readily available in clinical practice and the linear measures method provides an efficient, low-cost means to utilize these to quantify muscle. The linear measures method is a practical screening tool to identify cancer patients with low muscle for referral to supportive interventions such as exercise and nutrition.

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Ethical guidelines

The authors certify that they comply with the ethical guidelines for authorship and publishing of the *Journal of Cachexia, Sarcopenia and Muscle*.[56]

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 Intra and Inter-rater Reliability
Table S2 Pearson Correlation Coefficients Overall and by Subgroup for Paraspinal and Psoas Muscle Groups
Table S3 Characteristics of Linear Measures as a Screening Tool to Identify Low Muscle Mass in Non-Metastatic Colorectal Cancer
Table S4 Association of Linear Measures with Survival in Non-Metastatic Colorectal Cancer

Conflict of interest

E.M.C.F., E.A., B.J.C., A.B., and M.M. declare no conflicts of interest.

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