

The deterioration of muscle mass and radiodensity is prognostic of poor survival in stage I–III colorectal cancer: a population-based cohort study (C-SCANS)

Justin C. Brown^{1*}, Bette J. Caan², Jeffrey A. Meyerhardt¹, Erin Weltzien², Jingjie Xiao³, Elizabeth M. Cespedes Feliciano², Candyce H. Kroenke², Adrienne Castillo², Marilyn L. Kwan² & Carla M. Prado³

¹Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, ²Division of Research, Kaiser Permanente Northern California, Oakland, CA, USA,

³Department of Agricultural Food and Nutritional Science, University of Alberta, Edmonton, AB, Canada

Abstract

Background Muscle abnormalities such as low muscle mass and low muscle radiodensity are well known risk factors for unfavourable cancer prognosis. However, little is known in regard to the degree and impact of longitudinal changes in muscle mass and radiodensity within the context of cancer. Here, we explore the relationship between muscle wasting and mortality in a large population-based study of patients with non-metastatic colorectal cancer (CRC).

Methods A total of 1924 patients with stage I–III CRC who underwent surgical resection in the Kaiser Permanente Northern California Health System were included. Muscle mass and radiodensity were quantified using computed tomography images obtained at diagnosis and after approximately 14 months. Cox proportional-hazards models were used to estimate hazard ratios for all-cause mortality.

Results The hazard ratio for all-cause mortality among patients with the largest deterioration in muscle mass (≥ 2 SD; $\geq 11.4\%$ loss from baseline), as compared with those who remained stable (± 1 SD; $0.0 \pm 5.7\%$) was 2.15 [95% confidence interval (CI): 1.59–2.92; $P < 0.001$]. The hazard ratio for all-cause mortality among patients who experienced the largest deterioration in muscle radiodensity (≥ 2 SD; $\geq 20.2\%$ loss from baseline), as compared with those who remained stable (± 1 SD; $0.0 \pm 10.1\%$) was 1.61 (95% CI: 1.20–2.15; $P = 0.002$).

Conclusions In patients with stage I–III CRC, muscle wasting is a risk factor for mortality, independent of change in body mass and other body composition parameters.

Keywords Body composition; Survival; Adiposity; Body mass; Prognosis

Received: 16 February 2018; Revised: 10 March 2018; Accepted: 21 March 2018

*Correspondence to: Justin C. Brown, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA. Email: justinc_brown@dfci.harvard.edu

Introduction

Skeletal muscle represents 40% of body mass, constituting the largest organ in non-obese humans.¹ Skeletal muscle secretes hundreds of myokine peptides that influence insulin sensitivity, inflammation, immune function, adipose tissue oxidation, and whole-body metabolism.² Moreover, skeletal muscle serves as a central determinant of physical strength and the ability to complete activities of daily living.³ Muscle wasting is characterized by the progressive deterioration of

muscle mass or radiodensity (a novel radiologic measure of lipid contained within muscle).^{4,5} The causes of these muscle abnormalities are multifactorial, including metabolic alterations that promote a catabolic state, physical inactivity, nutritional deficiency, and cancer therapy.⁶

Low muscle mass, measured at a solitary time point, is associated with inferior survival in patients with colorectal cancer (CRC).⁷ Two studies in stage IV CRC (metastatic spread to distant organs) measured longitudinal changes in muscle mass during chemotherapy and concluded that muscle

wasting was associated with a two-fold to four-fold increase in the risk of mortality.^{8,9} However, muscle wasting is often overt in stage IV CRC, occurring concurrently with weight loss and the depletion of adiposity.^{10,11} Overt muscle wasting may be refractory to therapeutic intervention.¹² Conversely, in stage I–III CRC, muscle wasting may be occult,¹³ occurring independently of weight loss^{14–16} and the depletion of adiposity.¹⁷ Identifying occult loss of muscle mass may offer the opportunity for timely provision of therapeutic intervention and improve patient management when utilized as a prognostic measure.

It is not known if muscle wasting is a risk factor for mortality in patients with stage I–III CRC who have received cancer therapy with curative intent. If muscle wasting is a risk factor for mortality in this population, the serial measurement of muscle mass or radiodensity may hold promise as an objective measure to inform prognostic decision making and offer a therapeutic target to guide intervention development.¹⁸ The utility of automated methods to quantify muscle wasting for large-scale screening are being explored.¹⁹ To this end, we conducted a population-based retrospective cohort study to examine the relationship between changes in muscle mass and radiodensity with all-cause and cancer-specific mortality in 1924 patients with stage I–III CRC.

Materials and methods

Study population and design

This was a retrospective cohort study. The cohort—Colorectal, Sarcopenia, Cancer And Near-term Survival (C-SCANS)—was derived from the Kaiser Permanente Northern California (KPNC) cancer registry, with ascertainment of all patients diagnosed with stage I–III invasive CRC between the years of 2006 and 2011, aged 18–80 years, who underwent surgical resection for CRC. Inclusion criteria for this analysis required that patients had baseline computed tomography (CT) images within 4 months of diagnosis and before the administration of any post-operative therapy ($n = 3262$) and follow-up CT images 9–27 months after diagnosis ($n = 1924$). Patients with CT images at baseline and follow-up ($n = 1924$) were younger (61 ± 11 vs. 65 ± 11 years; $P < 0.001$), more likely to have a primary rectal cancer (32.2% vs. 24.5%; $P = 0.002$), and less likely to have stage I cancer (18.9% vs. 46.0%; $P < 0.001$) compared with patients with CT images only at baseline ($n = 1338$). KPNC patients are characteristic of the underlying California population, with the exception at socio-economic extremes.²⁰ A waiver of written informed consent was obtained by the study investigators, and this study was approved by the KPNC and University of Alberta institutional review boards.

Measures of body composition

Muscle wasting was operationalized using muscle cross-sectional area (i.e. muscle mass) and muscle radiodensity. Body composition was measured using contrast-enhanced CT images originally collected for clinical purposes (e.g. initial staging and surveillance of recurrent CRC) with sliceomatic software (V5.0, TomoVision, Montreal, Canada).²¹ A single-slice transverse CT image at the third lumbar vertebra was used, as tissue cross-sectional areas at this lumbar region correlate with whole-body tissue volume.²² Tissues were demarcated with a semi-automated procedure using Hounsfield Unit (HU) thresholds of -29 to 150 for muscle (including the rectus abdominus, erector spinae, quadratus lumborum, psoas, and internal, transversus and external oblique muscle groups), -150 to -50 for visceral adipose tissue, and -190 to -30 for subcutaneous adipose tissue.¹¹ Cross-sectional areas were calculated for each tissue compartment by summing tissue pixels and multiplying by the pixel surface area. Muscle radiodensity quantifies the average radiation attenuation rate (HU) and is a radiologic measure of the extent of lipid contained within muscle.⁵ A randomly selected subsample of 50 CT images were analysed by two investigators blinded to outcome, and the remaining CT images were analysed by a single trained investigator blinded to outcome. The inter-investigator coefficients of variation for muscle mass and radiodensity were 1.2% and 0.7%, respectively. The test–retest reliability for muscle mass and radiodensity using CT images are 4.7% and 5.0%, respectively.²³

Study outcomes

The primary study outcome was all-cause mortality, defined as the time from the follow-up CT image to death from any cause. The secondary study outcome was CRC-specific mortality, defined as the time from the follow-up CT image to death attributable to CRC. Deaths were identified from the California state death registry, National Death Index using Social Security Administration data, and KPNC electronic mortality files through 31 December 2016. Deaths were classified as CRC-specific if CRC was documented as an underlying or contributing cause of death on the death certificate through 31 January 2015.

Covariates

The KPNC electronic medical record was used to obtain baseline information on age, sex, race/ethnicity, smoking history, and comorbid conditions using the Charlson comorbidity index.²⁴ Repeated measures of body mass that corresponded with the timing of baseline and follow-up CT image acquisition were obtained from the electronic medical record. A

$\geq 5\%$ threshold was used to define clinically important weight loss.¹⁵ The KPNC cancer registry was used to obtain information on the anatomical site of cancer, cancer stage,²⁵ grade of differentiation, and the administration of chemotherapy and radiation.

Statistical analysis

The relationships between muscle wasting and risks of outcomes were nonlinear and evaluated using categorical parameterization. We calculated the standard deviation (SD) of relative changes in muscle mass and radiodensity for patients in the 5th to 95th percentiles; five categories were derived: (i) stable (defined as no change ± 1 SD from baseline); (ii) moderate gain (defined as ≥ 1 to < 2 SD of gain from baseline); (iii) moderate loss (defined as ≥ 1 to < 2 SD of loss from baseline); (iv) large gain (defined as ≥ 2 SD of gain from baseline); (v) large loss (defined as ≥ 2 SD of loss from baseline). Cox proportional-hazards models were used to estimate the hazard ratio (HR) and 95% confidence interval (CI) of muscle wasting and risk of outcomes. Proportionality of hazards was confirmed with visual inspection of log–log plots.²⁶

Four models were estimated. Model 1 was adjusted for age, sex, race, site of cancer, cancer stage, chemotherapy, radiation, smoking history, Charlson comorbidity index, time interval between CT images, and baseline muscle mass (or radiodensity). Model 2 adjusted for Model 1 and for $\geq 5\%$ weight loss between CT images. Model 3 adjusted for Model 1, and muscle radiodensity (or mass), and visceral and subcutaneous adipose tissue. Model 4 adjusted for Model 1, $\geq 5\%$ weight loss between CT images, muscle radiodensity (or mass), visceral and subcutaneous adipose tissue. Pre-specified subgroups examined were sex (male vs. female) and primary cancer site (colon vs. rectal). A statistical interaction term was added to the Cox proportional-hazards regression model to determine if the relationship between muscle wasting and risk of outcomes differed between subgroups. Exploratory analyses excluded patients with cancer recurrence occurring between the baseline and follow-up CT image (inclusive). Sensitivity analyses were conducted to quantify the strength that an unmeasured confounder must have to explain the observed associations.²⁷ $P < 0.05$ (two-sided) was considered to indicate statistical significance.

Results

Characteristics of the study cohort

The average age of 1924 patients was 61 ± 11 years (range: 19–80; *Table 1*). Baseline CT images were obtained within

Table 1 Baseline characteristics of the study population

Characteristic	(n = 1924)
Age, years	61.1 \pm 11.4
Sex	
Male	973 (50.6%)
Female	951 (49.4%)
Race/ethnicity	
White	1215 (63.2%)
Black	140 (7.3%)
Asian	319 (16.6%)
Hispanic	234 (12.2%)
Other	14 (0.7%)
Site of cancer	
Colon	1305 (67.8%)
Rectal	619 (32.2%)
Cancer stage	
I	363 (18.9%)
II	595 (30.9%)
III	966 (50.2%)
Treatment	
Chemotherapy	1345 (69.9%)
Radiation	397 (20.6%)
Smoking history	
Never	923 (48.0%)
Former	757 (39.4%)
Current	241 (12.5%)
Charlson comorbidity index	
0	1220 (63.4%)
1–2	546 (28.4%)
≥ 3	158 (8.2%)
Body composition measures ^a	
Muscle area, cm ²	137.3 [111.4–167.4]
Muscle radiodensity, HU	40.6 [33.6–46.9]
Visceral adipose area, cm ²	135.8 [68.0–217.2]
Subcutaneous adipose area, cm ²	184.7 [132.6–270.9]

Values are mean \pm standard deviation or count (percentage) unless otherwise noted.

^aValues are median [interquartile, 25–75% range].

a median of 6 days (interquartile range: 0–12) after biopsy-proven diagnosis of CRC. Follow-up CT images were obtained 14.3 months (interquartile range: 12.3–17.1) after baseline CT image acquisition. Between baseline and follow-up CT image acquisition, 478 (24.8%) of patients experienced $\geq 5\%$ weight loss. The median duration of observation, starting at the time of follow-up CT imaging, was 6.8 years (interquartile range: 5.3–8.4). We observed 519 deaths; 297 (57%) attributable to CRC. Muscle mass and radiodensity, stratified by magnitude of change, are described (*Table S1*).

Muscle mass

Among the full cohort, the average change in muscle mass was $+0.1 \pm 5.7\%$. The HR for all-cause mortality in patients with large deteriorations in muscle mass (≥ 2 SD; $\geq 11.4\%$ loss from baseline), as compared with those who remained stable (± 1 SD; $0.0 \pm 5.7\%$) was 2.15 (95% CI: 1.59–2.92; $P < 0.001$; *Table 2*). The HR for all-cause mortality in patients with moderate deteriorations in muscle mass (≥ 1 to < 2 SD; ≥ 5.7 to $< 11.4\%$ loss from baseline), as compared with those

Table 2 Associations between change in muscle mass with all-cause and cancer-specific mortality

	No. Risk/No. Events ^a	Rate ^b	Model 1 ^c			Model 2 ^d			Model 3 ^e			Model 4 ^f		
			HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P		
All-cause mortality														
Large loss: ≥ 2 SD	135/66	12.4	2.66 (2.00, 3.24)	<0.001	2.18 (1.61, 2.95)	<0.001	2.61 (1.96, 3.47)	<0.001	2.15 (1.59, 2.92)	<0.001	2.15 (1.59, 2.92)	<0.001	2.15 (1.59, 2.92)	<0.001
Moderate Loss: ≥ 1 to <2 SD	250/93	7.7	1.87 (1.46, 2.38)	<0.001	1.61 (1.24, 2.07)	<0.001	1.88 (1.47, 2.39)	<0.001	1.62 (1.26, 2.09)	<0.001	1.62 (1.26, 2.09)	<0.001	1.62 (1.26, 2.09)	<0.001
Stable: ± 1 SD	1141/260	4.1	1.00—ref	—	1.00—ref	—	1.00—ref	—	1.00—ref	—	1.00—ref	—	1.00—ref	—
Moderate gain: ≥ 1 to <2 SD	264/58	3.9	0.92 (0.69, 1.23)	0.593	0.94 (0.70, 1.25)	0.663	0.89 (0.67, 1.19)	0.443	0.91 (0.68, 1.21)	0.508	0.91 (0.68, 1.21)	0.508	0.91 (0.68, 1.21)	0.508
Large gain: ≥ 2 SD	134/42	5.5	1.04 (0.75, 1.46)	0.799	1.07 (0.76, 1.49)	0.707	1.01 (0.72, 1.42)	0.940	1.04 (0.74, 1.46)	0.815	1.04 (0.74, 1.46)	0.815	1.04 (0.74, 1.46)	0.815
Cancer-specific mortality														
Large loss: ≥ 2 SD	126/45	8.4	3.43 (2.40, 4.89)	<0.001	2.76 (1.88, 4.07)	<0.001	3.42 (2.40, 4.89)	<0.001	2.76 (1.88, 4.06)	<0.001	2.76 (1.88, 4.06)	<0.001	2.76 (1.88, 4.06)	<0.001
Moderate loss: ≥ 1 to <2 SD	228/53	4.4	1.79 (1.30, 2.47)	<0.001	1.54 (1.10, 2.16)	0.013	1.80 (1.31, 2.49)	<0.001	1.54 (1.10, 2.17)	0.012	1.54 (1.10, 2.17)	0.012	1.54 (1.10, 2.17)	0.012
Stable: ± 1 SD	1078/148	2.3	1.00—ref	—	1.00—ref	—	1.00—ref	—	1.00—ref	—	1.00—ref	—	1.00—ref	—
Moderate gain: ≥ 1 to <2 SD	246/29	1.9	0.78 (0.52, 1.16)	0.215	0.79 (0.53, 1.18)	0.254	0.76 (0.51, 1.14)	0.181	0.78 (0.52, 1.16)	0.222	0.78 (0.52, 1.16)	0.222	0.78 (0.52, 1.16)	0.222
Large gain: ≥ 2 SD	119/22	2.9	1.03 (0.65, 1.63)	0.885	1.06 (0.67, 1.68)	0.796	1.03 (0.65, 1.63)	0.910	1.06 (0.67, 1.68)	0.794	1.06 (0.67, 1.68)	0.794	1.06 (0.67, 1.68)	0.794

CI, confidence interval; HR, hazard ratio; SD, standard deviation. SD for muscle area: 5.7%.

^aThe number of patients included in the analysis of colorectal cancer-specific mortality was 1797 because the follow-up for colorectal cancer-specific mortality ended on 31 January 2015.

^bRate per 100 person-years.

^cModel 1 is adjusted for age, sex, race, site of cancer, cancer stage, chemotherapy, radiation, smoking history, Charlson comorbidity index, time interval between CT imaging, and baseline muscle area.

^dModel 2 is adjusted for Model 1 and $\geq 5\%$ weight loss between CT imaging.

^eModel 3 is adjusted for Model 1, muscle radiodensity, visceral adipose tissue area, and subcutaneous adipose tissue area.

^fModel 4 is adjusted for Model 1, $\geq 5\%$ weight loss between CT imaging, muscle radiodensity, visceral adipose tissue area, and subcutaneous adipose tissue area.

who remained stable was 1.62 (95% CI: 1.26–2.09; $P < 0.001$). These associations were independent of change in body mass, muscle radiodensity, visceral and subcutaneous adipose tissue. The above-described associations were similar or stronger in magnitude when CRC-specific mortality was examined. Large deteriorations in muscle mass were associated with an increased risk of all-cause mortality in both patients who did and did not experience disease recurrence between CT imaging (Table S2).

Sex did not modify the relationship between change in muscle mass and risk of all-cause mortality (P for interaction = 0.911; Table S3). Cancer site modified the relationship between change in muscle mass and risk of all-cause mortality, such that the deterioration of muscle mass was a stronger risk factor in primary colon vs. rectal cancer (P for interaction = 0.048; Table S4). Baseline muscle mass did not modify the relationship between change in muscle mass and risk of all-cause mortality (P for interaction = 0.523; data not shown). Correlates of change in muscle mass included primary rectal cancer (vs. primary colon cancer; $\beta = -3.06$; $P < 0.001$); stage II disease (vs. stage I disease; $\beta = 1.71$; $P = 0.003$); and radiation therapy (vs. no radiation therapy; $\beta = -1.74$; $P = 0.01$; Table S5).

Muscle radiodensity

Among the full cohort, the average change in muscle radiodensity was $-0.7 \pm 10.1\%$. The HR for all-cause mortality in patients with large deteriorations in muscle radiodensity (≥ 2 SD; $\geq 20.2\%$ loss from baseline), as compared with those who remained stable (± 1 SD; $0.0 \pm 10.1\%$) was 1.61 (95% CI: 1.20–2.15; $P = 0.002$; Table 3). This association was independent of change in body mass, muscle mass, visceral and subcutaneous adipose tissue. The above-described association was stronger in magnitude when CRC-specific mortality was examined. Large deteriorations in muscle radiodensity were associated with an increased risk of all-cause and cancer-specific mortality in patients who did experience disease recurrence between CT imaging.

Sex and cancer site did not modify the relationship between changes in muscle radiodensity and risk of all-cause mortality (P for interaction = 0.693 and P for interaction = 0.392, respectively). Baseline muscle radiodensity did not modify the relationship between change in muscle radiodensity and risk of all-cause mortality (P for interaction = 0.512; data not shown). Correlates of change in muscle radiodensity included primary rectal cancer (vs. primary colon cancer; $\beta = -2.56$; $P = 0.02$); stage II disease (vs. stage I disease; $\beta = 2.16$; $P = 0.05$); stage III disease (vs. stage I disease; $\beta = 3.10$; $P = 0.02$) and ≥ 3 comorbid conditions (vs. zero comorbid conditions; $\beta = 3.06$; $P = 0.03$).

Sensitivity analyses

The minimum strength of association, on the HR scale, independent of all other variables, that an unmeasured confounder must have with muscle wasting and mortality to fully explain away the observed associations would be 2.78 and 2.14 for large and moderate deteriorations in muscle mass, respectively, and 2.13 for large deteriorations in muscle radiodensity.

Discussion

In this large population-based cohort study, we demonstrated that longitudinal declines in muscle mass and radiodensity are a risk factor for all-cause and CRC-specific mortality in patients with stage I–III CRC. The observed associations were independent of recurrent disease and changes in body mass and other body composition parameters including visceral and subcutaneous adipose tissue. Extrapolated from the abdomen to the whole body, moderate and large deteriorations in muscle mass are consistent with losses of 1.8 ± 0.6 and 4.4 ± 1.9 kg of skeletal muscle, respectively.²²

Among 215 patients receiving first-line chemotherapy for metastatic CRC, a $>5\%$ deterioration in muscle mass over 4 months was associated with a 2.1-fold higher risk of mortality.⁹ A $\geq 9\%$ deterioration over 3 months was associated with a four-fold increase in the risk of mortality in a cohort of 67 patients receiving first-line and second-line chemotherapy for metastatic CRC.⁸ In our study, over 14 months we observed small overall changes in muscle mass ($+0.1 \pm 5.7\%$) and muscle radiodensity ($-0.7 \pm 10.1\%$). This is in contrast to patients with stage metastatic CRC, such that over 14 months it is estimated that patients lose, on average, 28.5% and 17.3% in muscle mass and muscle radiodensity, respectively.⁸ In a cohort of 1803 healthy older adults, each $\approx 4\%$ decline in thigh muscle mass over 4 years was associated with a 20% increase in the risk of death, independent of weight loss and changes in adiposity.²⁸

At the time of diagnosis, 30–60% of patients with CRC may have a low muscle mass or low muscle radiodensity.^{8,29} Low muscle mass and low muscle radiodensity at diagnosis are risk factors for mortality.^{8,29} Our analyses demonstrated that, independent of muscle mass or radiodensity at diagnosis, muscle wasting within the first 9–27 months after diagnosis was a risk factor for mortality. In subgroup interaction analyses, the prognostic importance of muscle wasting did not vary by baseline muscle mass or radiodensity. This suggests that muscle wasting may be deleterious among all patients, regardless of their body composition at diagnosis. The identified associations were independent of weight loss, suggesting that monitoring changes in body mass may be insufficient to promptly identify occult muscle wasting. CT

Table 3 Associations between change in muscle radiodensity with all-cause and cancer-specific mortality

	No. Risk/No. Events ^a	Rate ^b	Model 1 ^c			Model 2 ^d			Model 3 ^e			Model 4 ^f		
			HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P		
All-cause mortality														
Large loss: ≥ 2 SD	149/58	8.3	1.54 (1.15, 2.06)	0.004	1.55 (1.16, 2.07)	0.003	1.58 (1.18, 2.12)	0.002	1.61 (1.20, 2.15)	0.002	1.61 (1.20, 2.15)	0.002	1.61 (1.20, 2.15)	0.002
Moderate loss: ≥ 1 to <2 SD	281/78	5.1	1.07 (0.83, 1.37)	0.614	1.08 (0.84, 1.39)	0.546	1.08 (0.84, 1.39)	0.545	1.09 (0.84, 1.40)	0.545	1.09 (0.84, 1.40)	0.511	1.09 (0.84, 1.40)	0.511
Stable: ± 1 SD	1147/280	4.5	1.00—ref	—	1.00—ref	—	1.00—ref	—	1.00—ref	—	1.00—ref	—	1.00—ref	—
Moderate gain: ≥ 1 to <2 SD	222/57	4.6	0.85 (0.64, 1.14)	0.280	0.81 (0.61, 1.09)	0.163	0.84 (0.63, 1.13)	0.248	0.80 (0.60, 1.07)	0.248	0.80 (0.60, 1.07)	0.134	0.80 (0.60, 1.07)	0.134
Large gain: ≥ 2 SD	125/46	6.9	1.01 (0.72, 1.42)	0.963	0.92 (0.65, 1.30)	0.642	0.98 (0.70, 1.38)	0.906	0.89 (0.63, 1.25)	0.906	0.89 (0.63, 1.25)	0.495	0.89 (0.63, 1.25)	0.495
Cancer-specific mortality														
Large loss: ≥ 2 SD	133/31	4.4	1.63 (1.10, 2.42)	0.015	1.66 (1.12, 2.46)	0.012	1.71 (1.15, 2.54)	0.008	1.77 (1.19, 2.63)	0.008	1.77 (1.19, 2.63)	0.005	1.77 (1.19, 2.63)	0.005
Moderate loss: ≥ 1 to <2 SD	266/48	3.2	1.18 (0.85, 1.63)	0.320	1.20 (0.87, 1.66)	0.271	1.21 (0.87, 1.67)	0.258	1.22 (0.88, 1.69)	0.258	1.22 (0.88, 1.69)	0.231	1.22 (0.88, 1.69)	0.231
Stable: ± 1 SD	1075/160	2.6	1.00—ref	—	1.00—ref	—	1.00—ref	—	1.00—ref	—	1.00—ref	—	1.00—ref	—
Moderate gain: ≥ 1 to <2 SD	208/33	2.7	0.94 (0.64, 1.38)	0.750	0.90 (0.61, 1.32)	0.580	0.93 (0.63, 1.36)	0.707	0.88 (0.60, 1.30)	0.707	0.88 (0.60, 1.30)	0.521	0.88 (0.60, 1.30)	0.521
Large gain: ≥ 2 SD	115/25	3.7	1.16 (0.73, 1.83)	0.522	1.03 (0.65, 1.63)	0.896	1.11 (0.70, 1.76)	0.652	0.97 (0.61, 1.55)	0.652	0.97 (0.61, 1.55)	0.909	0.97 (0.61, 1.55)	0.909

CI, confidence interval; HR, hazard ratio; SD, standard deviation. SD for muscle radiodensity: 10.1%.

^aThe number of patients included in the analysis of colorectal cancer-specific mortality was 1797 because the follow-up for colorectal cancer-specific mortality ended on 31 January 2015.

^bRate per 100 person-years.

^cModel 1 is adjusted for age, sex, race, site of cancer, cancer stage, chemotherapy, radiation, smoking history, Charlson comorbidity index, time interval between CT imaging, and baseline muscle radiodensity.

^dModel 2 is adjusted for Model 1 and $\geq 5\%$ weight loss between CT imaging.

^eModel 3 is adjusted for Model 1, muscle area, visceral adipose tissue area, and subcutaneous adipose tissue area.

^fModel 4 is adjusted for Model 1, $\geq 5\%$ weight loss between CT imaging, muscle area, visceral adipose tissue area, and subcutaneous adipose tissue area.

images of the chest and abdomen is recommended every 6–12 months in patients with stage II and III CRC for the surveillance of recurrent disease.³⁰ If our findings are replicated, it may provide empirical support to the viewpoint that quantifying body composition in routinely collected CT images will add value to patient care.¹⁸ Additional research is necessary to replicate the effect modification of cancer site on the relationship between change in muscle mass and risk of all-cause mortality.

The observation that muscle wasting is associated with mortality may serve as a framework to test the hypothesis that interventions which prevent or retard muscle wasting may offer clinical benefit in this population. In this framework, the measurement of muscle mass and radiodensity may serve as therapeutic targets (i.e. biomarkers) to guide early-phase intervention development. Muscle wasting is characterized by inflammation and oxidative stress, which activate the ubiquitin-proteasome system and apoptosis-inducing proteins, and suppress insulin-like growth factors.^{31,32} Pharmacotherapy development for muscle wasting has just begun to emerge.³³ Participation in physical activity after diagnosis of stage I–III CRC is associated with a 40% relative reduction in the risk of mortality.³⁴ Physical activity, particularly resistance exercise, is efficacious for preserving or improving muscle mass in adults³⁵ and may be synergized when prescribed with nutritional supplementation.³⁶ However, the efficacy of resistance exercise and nutritional supplementation in patients with stage I–III CRC has not yet been established.

The main limitation of this study is that we are unable to comment on the causal relationship between muscle wasting and mortality. There is also the possibility of residual confounding by an unmeasured variable(s). In our sensitivity analyses, this unmeasured variable would need to be moderate in size ($HR \geq 2$) and be completely independent of the variables included in our regression models. Our models were robust to adjustment for changes in body mass and multiple objective measures of body composition. The exclusion of baseline muscle area or radiodensity from our statistical models did not substantively alter the strength of the reported associations. These data were collected for clinical care purposes. The retrospective nature of this study precluded our ability to obtain information on patient behaviours such as physical activity, dietary patterns, intentional weight loss, and other behaviours or health conditions that may influence muscle wasting and the risk of mortality. We did not have information on surgical procedures in this population, such as laparoscopic vs. open resection, length of hospital stay, and post-operative complications. The patients included in this cohort with repeated CT images were younger, more likely to have primary rectal cancers, and less likely to have stage I disease, when compared with those without CT images. These inclusion characteristics reflect historical and contemporary clinical practice recommendations for the use of CT imaging in the initial staging and surveillance of recurrent CRC.³⁰ Our analyses are

applicable to patients who live long enough, or have a clinical justification, to receive follow-up imaging (e.g. surveillance for recurrent disease or presentation of new symptoms).

The main strength of this study is the large, racially diverse, population-based sample. The use of repeated measures of state-of-the-art body composition is novel in this population and may help to overcome some of the methodologic limitations of prior studies that have examined body composition at a solitary time point.³⁷ The analytic technique using standard deviation thresholds can be applied to regions other than the United States, such as Asia and Europe, to identify patients with significant muscle wasting. All that would be required are the descriptive characteristics (e.g. standard deviations) of changes in body composition for the specific population under study.

In this population-based cohort study, muscle wasting was a risk factor for all-cause and cancer-specific mortality in patients with stage I–III CRC, independent of change in body mass and other body composition parameters. Therapeutic interventions that prevent or retard the magnitude of muscle wasting may offer clinical benefit in this population without needing to produce an increase in muscle mass. These observations stimulate the new hypothesis that objective measures of body composition hold the potential to inform clinical decision making and offer therapeutic targets to guide intervention development in patients with stage I–III CRC.

Acknowledgements

The authors certify that they comply with the ethical guidelines for authorship and publishing of the *Journal of Cachexia, Sarcopenia and Muscle*.³⁸

The research reported in this publication was supported by the National Cancer Institute (K99-CA218603; R25-CA092203; and R01-CA175011).

Online supplementary material

Additional Supporting Information may be found online in the supporting information tab for this article.

Supplementary Table 1. Change in body composition parameters from baseline to follow-up

Supplementary Table 2. Recurrence-stratified associations between change in muscle mass and muscle radiodensity with all-cause and cancer-specific mortality

Supplementary Table 3. Sex-stratified associations between change in muscle mass and muscle radiodensity with all-cause and cancer-specific mortality

Supplementary Table 4. Cancer site-stratified associations between change in muscle mass and muscle radiodensity

with all-cause and cancer-specific mortality

Supplementary Table 5. Multivariable-adjusted marginal means of relative change in muscle mass and muscle radiodensity, by baseline characteristics

Conflict of interest

The authors declare no conflicts of interest.

References

1. Frontera WR, Ochala J. Skeletal muscle: a brief review of structure and function. *Calcif Tissue Int* 2015;**96**:183–195.
2. Pedersen BK, Febbraio MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. *Nat Rev Endocrinol* 2012;**8**:457–465.
3. McLeod M, Breen L, Hamilton DL, Philp A. Live strong and prosper: the importance of skeletal muscle strength for healthy ageing. *Biogerontology* 2016;**17**:497–510.
4. Anker SD, Coats AJ, Morley JE, Rosano G, Bernabei R, von Haehling S, et al. Muscle wasting disease: a proposal for a new disease classification. *J Cachexia Sarcopenia Muscle* 2014;**5**:1–3.
5. Aubrey J, Esfandiari N, Baracos VE, Buteau FA, Frenette J, Putman CT, et al. Measurement of skeletal muscle radiation attenuation and basis of its biological variation. *Acta Physiol (Oxf)* 2014;**210**:489–497.
6. Cohen S, Nathan JA, Goldberg AL. Muscle wasting in disease: molecular mechanisms and promising therapies. *Nat Rev Drug Discov* 2015;**14**:58–74.
7. Shachar SS, Williams GR, Muss HB, Nishijima TF. Prognostic value of sarcopenia in adults with solid tumours: A meta-analysis and systematic review. *Eur J Cancer* 2016;**57**:58–67.
8. Blauwhoff-Buskermolen S, Versteeg KS, de van der Schueren MA, den Braver NR, Berkhof J, Langius JA et al. Loss of muscle mass during chemotherapy is predictive for poor survival of patients with metastatic colorectal cancer. *J Clin Oncol* 2016;**34**(12):1339–1344.
9. Miyamoto Y, Baba Y, Sakamoto Y, Ohuchi M, Tokunaga R, Kurashige J, et al. Negative Impact of Skeletal Muscle Loss after Systemic Chemotherapy in Patients with Unresectable Colorectal Cancer. *PLoS One* 2015;**10**:e0129742, <https://doi.org/10.1371/journal.pone.0129742>.
10. Ebadi M, Mazurak VC. Evidence and mechanisms of fat depletion in cancer. *Forum Nutr* 2014;**6**:5280–5297.
11. Liefers JR, Mourtzakis M, Hall KD, McCargar LJ, Prado CM, Baracos VE. A viscerally driven cachexia syndrome in patients with advanced colorectal cancer: contributions of organ and tumor mass to whole-body energy demands. *Am J Clin Nutr* 2009;**89**:1173–1179.
12. Fearon K, Argiles JM, Baracos VE, Bernabei R, Coats A, Crawford J, et al. Request for regulatory guidance for cancer cachexia intervention trials. *J Cachexia Sarcopenia Muscle* 2015;**6**:272–274.
13. Martin L, Birdsell L, MacDonald N, Reiman T, Clandinin MT, McCargar LJ, 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**:1539–1547.
14. Baade PD, Meng X, Youl PH, Aitken JF, Dunn J, Chambers SK. The impact of body mass index and physical activity on mortality among patients with colorectal cancer in Queensland, Australia. *Cancer Epidemiol Biomarkers Prev* 2011;**20**:1410–1420.
15. Meyerhardt JA, Kroenke CH, Prado CM, Kwan ML, Castillo A, Weltzien E, et al. Association of Weight Change after Colorectal Cancer Diagnosis and Outcomes in the Kaiser Permanente Northern California Population. *Cancer Epidemiol Biomarkers Prev* 2017;**26**:30–37.
16. Vergidis J, Gresham G, Lim HJ, Renouf DJ, Kennecke HF, Ruan JY, et al. Impact of Weight Changes After the Diagnosis of Stage III Colon Cancer on Survival Outcomes. *Clin Colorectal Cancer* 2016;**15**:16–23.
17. Choe EK, Park KJ, Ryoo SB, Moon SH, Oh HK, Han EC. Prognostic Impact of Changes in Adipose Tissue Areas after Colectomy in Colorectal Cancer Patients. *J Korean Med Sci* 2016;**31**:1571–1578.
18. Murray TE, Williams D, Lee MJ. Osteoporosis, obesity, and sarcopenia on abdominal CT: a review of epidemiology, diagnostic criteria, and management strategies for the reporting radiologist. *Abdom Radiol (NY)* 2017;**42**:2376–2386.
19. Popuri K, Cobzas D, Esfandiari N, Baracos V, Jägersand M. Body composition assessment in axial CT images using FEM-based automatic segmentation of skeletal muscle. *IEEE Trans Med Imaging* 2016;**35**:512–520.
20. Gordon N. Similarity of the Kaiser Permanente senior member population in northern California to the non-Kaiser Permanente covered and general population of seniors in northern California: Statistics from the 2009 California Health Interview Survey. Internal Division of Research report. 2012.
21. TomoVision. SliceOmatic. Montreal, Quebec, Canada: TomoVision; 2015.
22. Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge MP, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *J Appl Physiol (1985)* 2004;**97**:2333–2338.
23. Keller A, Gunderson R, Reikeras O, Brox JI. Reliability of computed tomography measurements of paraspinal muscle cross-sectional area and density in patients with chronic low back pain. *Spine (Phila Pa 1976)* 2003;**28**:1455–1460.
24. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994;**47**:1245–1251.
25. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 2010;**17**:1471–1474.
26. Harrell F. *Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis*. Springer; 2015.
27. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med* 2017;**167**:268–274.
28. Santanasto AJ, Goodpaster BH, Kritchevsky SB, Miljkovic I, Satterfield S, Schwartz AV, et al. Body composition remodeling and mortality: the health aging and body composition study. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences* 2016;**72**:513–519.
29. Caan BJ, Meyerhardt JA, Kroenke CH, Alexeeff S, Xiao J, Weltzien E, et al. Explaining the obesity paradox: The association between body composition and colorectal cancer survival. *Cancer Epidemiol Biomarkers Prev* 2017;**26**:1008–1015.
30. Meyerhardt JA, Mangu PB, Flynn PJ, Korde L, Loprinzi CL, Minsky BD, et al. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American Society of Clinical Oncology clinical practice guideline endorsement. *J Clin Oncol* 2013;**31**:4465–4470.
31. Bowen TS, Schuler G, Adams V. Skeletal muscle wasting in cachexia and sarcopenia: molecular pathophysiology and impact of exercise training. *J Cachexia Sarcopenia Muscle* 2015;**6**:197–207.
32. Lenk K, Schuler G, Adams V. Skeletal muscle wasting in cachexia and sarcopenia: molecular pathophysiology and impact of exercise training. *J Cachexia Sarcopenia Muscle* 2010;**1**:9–21.

33. Anderson LJ, Albrecht ED, Garcia JM. Update on Management of Cancer-Related Cachexia. *Curr Oncol Rep* 2017;**19**:3.
34. Schmid D, Leitzmann M. Association between physical activity and mortality among breast cancer and colorectal cancer survivors: a systematic review and meta-analysis. *Ann Oncol* 2014;**25**:1293–1311.
35. Peterson MD, Sen A, Gordon PM. Influence of resistance exercise on lean body mass in aging adults: a meta-analysis. *Med Sci Sports Exerc* 2011;**43**:249–258.
36. Cermak NM, Res PT, de Groot LC, Saris WH, van Loon LJ. Protein supplementation augments the adaptive response of skeletal muscle to resistance-type exercise training: a meta-analysis. *Am J Clin Nutr* 2012;**96**:1454–1464.
37. Vansteelandt S. Asking Too Much of Epidemiologic Studies: The Problem of Collider Bias and the Obesity Paradox. *Epidemiology* 2017;**28**:e47–e49.
38. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2017. *J Cachexia Sarcopenia Muscle* 2017;**8**:1081–1083.