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Muscle radiodensity and mortality in patients with colorectal cancer

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Abstract

Background—Low skeletal muscle radiodensity (SMD) is related to higher mortality in several cancers but the association with colorectal cancer (CRC) prognosis is unclear.

Methods—This observational study included 3,262 men and women from the Kaiser Permanente Northern California population diagnosed from 2006–2011 with stages I–III CRC. We evaluated hazard ratios for all-cause and CRC-specific mortality of low SMD, assessed by computed tomography using optimal stratification, relative to patients with normal SMD. We also evaluated the cross-classification of categories of low vs. normal SMD and muscle mass (MM), with outcomes.

Results—Median follow-up was 6.9 years. Optimal stratification cutpoints for SMD were 32.5 in women and 35.5 in men. In multivariate-adjusted analyses, compared to those with normal SMD levels, CRC patients with low SMD showed higher overall (hazard ratio [HR]=1.61, 95% confidence interval [CI]:1.36–1.90) and CRC-specific (HR=1.74, 95% CI:1.38–2.21) mortality. Patients with low SMD and low MM (i.e., sarcopenia) had the highest overall (HR=2.02, 95% CI: 1.65–2.47) and CRC-specific (HR=2.54, 95% CI: 1.91–3.37) mortality rates.

Conclusion—In patients with CRC, those with low SMD had elevated risks of disease-specific and overall mortality, independent of MM or adiposity. Clinical practice should incorporate body composition measures into the evaluation of CRC patient health status.

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The authors report no conflicts of interest.

Keywords

Body composition; muscle radiodensity; muscle radiodensity; myosteatosis; muscle; adiposity; colorectal cancer; survival; mortality

Introduction

Colorectal cancer (CRC) is the fourth most common cancer diagnosed and the second leading cause of cancer-related mortality in the United States each year[1]. An increasing number of investigations have examined associations between markers of body composition, including skeletal muscle radiodensity (SMD), i.e., the radiodensity of skeletal muscle measured by computerized tomography (CT) and cancer prognosis. Sarcopenia (low muscle mass) and myosteatosis, i.e., the fatty infiltration into muscle which governs SMD, are normal by-products of aging, the latter related to higher levels of body fat, but are exacerbated by disease and cancer treatments[2–6] and thus are common in cancer patients[7,8]. Several studies have found that low SMD is associated with poorer cancer prognosis generally[9] and more specifically in patients with lung[10], breast[11], pancreatic[10,12], and ovarian[13] cancers. The influence of SMD in CRC patients is, however, unclear.

Findings have been highly mixed. Boer noted no association of either psoas or abdominal SMD and survival in 91 patients with resectable colon cancer[14] though Blauwhoff-Buskermolen and colleagues reported a significant association of abdominal SMD and overall survival in 67 metastatic colorectal cancer patients but only after multiple adjustment[15]. By contrast, in 322 patients with primary operable colorectal cancer, McSorley and colleagues found a significant association between SMD and disease-specific survival in univariate analysis but no significant association after multiple adjustment[16]. Malietzis et al. reported nonsignificant, elevated associations between low abdominal SMD and overall and disease-specific survival in 805 CRC patients[17] whereas Sabel and colleagues found significant associations of psoas-area SMD and both disease-specific and overall survival in 302 colon cancer patients[18]. Because low SMD has been related to higher systemic inflammatory response[16,19], metabolic dysregulation[20,21], and post-surgical complications[14], we would expect low SMD to be related to poorer CRC prognosis. However, associations in previous studies, while suggestive, are equivocal due in large part to small study size. Furthermore, as indicated, methods of body composition assessment differed across studies impeding direct comparison.

Therefore, using computed tomography (CT) scans, collected as a routine part of clinical care to help diagnose CRC patients, as well as electronic medical record (EMR) data within the Kaiser Permanente Northern California (KPNC) population, we evaluated body composition and examined the effect of SMD on overall and CRC-specific mortality in 3,262 stage I–III CRC patients diagnosed at KPNC from 2006–2011. We used CT scans assessed at the L3 vertebra because of the high correlation of L3 with whole body values[22]. We further considered the combined influence of low SMD and low MM on CRC outcomes.

METHODS

Study Population

The study population consisted of all patients ages 18–80 years from KPNC diagnosed from 2006–2011 with stage I–III invasive CRC whose cancer was confirmed by computed tomography (CT), who received surgery, and for whom an electronic weight and height were available at diagnosis. Study participants have been previously described[23]. Case ascertainment began in 2006, one year after weights routinely became available in the EMR. A third of the Northern California population are KP members; members represent the underlying population except at socioeconomic extremes[24]. 49.9% of study participants were female and 50.1% male. A waiver of written informed consent was obtained and the study was approved by the KPNC and University of Alberta institutional review boards.

Data Collection

Body composition assessment and CT image analysis—Body composition was measured from CT scans (96% contrast vs. non-contrast images) taken within four months of diagnosis and prior to treatment with (neoadjuvant or adjuvant) chemotherapy or radiation (median = 0.2 months, range from −2.0 to 3.8 months); 82% of CT scans occurred prior to surgery. Using SliceOmatic Software version 5.0 (TomoVision, Montreal, Quebec, Canada), a single, trained researcher (JX) quantified the cross-sectional area of muscle and adipose in centimeters squared (cm^2) at the third lumbar vertebra (L3), a vertebral landmark previously validated and utilized in studies of cancer patients[25]. Single-slice abdominal cross-sectional areas at the L3 vertebra have been strongly correlated with whole body volumes of muscle and adipose tissue[22]. Skeletal muscle areas included rectus abdominus, erector spinae muscles, quadratus lumborum, psoas, and internal, transverse and external oblique muscle groups. Using pre-established thresholds of Hounsfield units[26,27], we assessed MM, and adipose tissue was segmented to distinguish visceral (intra-abdominal) adipose tissue (VAT), subcutaneous adipose tissue (SAT) and intramuscular adipose tissue (IMAT). SMD was assessed as mean Hounsfield units across muscle area measured at the L3 vertebra. The coefficient of variation for paired observations for SMD was 0.7%.

Clinical variables and endpoints—KPNC Cancer Registry data and the EMR were reviewed for information on prognostic factors, including disease stage, tumor characteristics, surgical procedures, and treatment (chemotherapy, radiation therapy). Data on overall and CRC-specific mortality were obtained from the KPNC computerized mortality file, which is comprised of data from the California State Department of Vital Statistics, U.S. Social Security Administration, and KPNC utilization data sources. Colorectal cancer death was attributed to persons if CRC was listed as a cause of death on the death certificate.

Other covariate data—EMR data were accessed for information on numerous potential confounding variables including sociodemographic variables (self-reported race is included in the EMR) and smoking status. The Charlson-Deyo index[28] was used to measure comorbidity. Height and weight were measured by a medical assistant at each medical visit. Partitioned BMI was computed in kilograms per height in meter squared removing

kilograms of muscle and adipose from the measure of weight; partitioned BMI thus included body weight due to organ, bone, and water weight and was analyzed continuously. BMI closest to the CT scan (median=0.0 months) was used in analyses.

Statistical analysis

We examined covariate distributions by low vs. normal SMD, evaluating differences using $\chi 2$ tests. Cox proportional hazards regression was used to examine associations between SMD at the time of diagnosis, and all-cause and CRC-specific mortality. Follow-up time was computed in years from the date of diagnosis.

We initially evaluated tertiles and quartiles of SMD with outcomes. We also explored possible nonlinear relationships between SMD and survival, nonparametrically, and by sex, with restricted cubic splines[29], a technique enabling specification of a relationship between two variables when the function is nonlinear. Tests for nonlinearity used the likelihood ratio test, comparing the model with the linear term to one with linear and cubic spline terms. Because each of these analyses provided strong evidence of a threshold effect of SMD with outcomes, we used optimal stratification[30,31] to generate sex-specific cutpoints to distinguish patients at higher mortality risk. All subsequent analyses used the dichotomous (low vs. normal) SMD variable. We defined patients to have low SMD if values fell below the cutpoints and normal SMD if patient values were greater than or equal to computed cutpoints.

We evaluated time to failure using Kaplan-Meier curves, comparing survival in patients with low and normal SMD using log-rank tests. We subsequently compared Cox models controlling for age, race, sex, to those adjusted additionally for stage, grade, cancer site (distal colon, proximal colon, and rectal), treatment, partitioned BMI, and smoking. Models were further adjusted for tertiles of VAT and SAT. We specifically did not include IMAT in adjustment to avoid collinearity since SMD levels are governed by IMAT levels.

We simultaneously evaluated associations of SMD and MM to determine independent effects of muscle components on survival. To consider the influence of body phenotypes on outcomes, we further evaluated the cross-classification of dichotomous SMD with normal vs. low MM (i.e., sarcopenia, the definition based on our previous work[32]) with the reference category including those with both normal SMD and normal MM.

Finally, we conducted analyses of SMD and outcomes stratified by sex, age (<64 vs. ≥64 years), race, stage, BMI (18.5–<25 25–<30, 30+ kg/m^2), comorbidity, treatment status, and CRC site. Heterogeneity in associations in stratified analyses were examined via introduction of cross-product terms for the dichotomous SMD variable and stratification variables in regression models with evaluation of significance by likelihood ratio $\chi 2$ tests. We conducted tests of proportionality with variable by time interactions. Tests of statistical significance were two-sided. Significant results denote p-values≤0.05.

RESULTS

Of the 3,262 CRC patients, 879 died with 451 deaths from CRC. Follow-up ranged from 0–10.9 years, with a median 6.9 years follow-up.

Baseline characteristics

Examining covariates, age, adiposity, BMI, comorbidity, and smoking were inversely related and MM was directly related to SMD. Whites and Hispanics had lower SMD than Blacks or Asians/Pacific Islanders. Proximal cancers were more common among those with low SMD and rectal cancers were more common in those with high SMD. Patients with low SMD were less likely to receive radiation or chemotherapy. Sex and stage were unrelated to SMD (Table 1).

Categorization of SMD

As indicated, analyses of SMD categories (Table 2) as well as spline analysis (Figure 1) each showed that associations between SMD and all-cause, as well as CRC-specific mortality, were best characterized as a threshold effect. Using optimal stratification[30,31], sex-specific cutpoints were 32.5 in women and 35.5 in men.

SMD, all-cause and CRC-specific mortality

The Kaplan-Meier curve (Figure 2) showed that patients with low SMD had worse overall survival than those with normal SMD (log rank $p<0.0001$). In models adjusted for age, sex, and race, low SMD was associated with elevated risks of CRC-specific and overall mortality. Multivariable-adjusted results were qualitatively similar. Compared to those with normal SMD, CRC patients with low SMD showed higher overall (hazard ratio [HR]=1.61, 95% confidence interval [CI]:1.36–1.90) and CRC-specific (HR=1.74, 95% CI:1.38–2.21) mortality (Table 2).

Cross-classification of SMD and MM

Evident in analyses with simultaneous adjustment for SMD and MM, low SMD and sarcopenia (low MM) were each independently associated with higher overall and CRC-specific mortality. In analyses of the cross-classification of SMD and MM, the highest mortality risks were seen in those with both low SMD and sarcopenia compared with the reference (normal SMD/normal MM), true in both men and women (Table 3), consistent with an additive, rather than multiplicative, effect (p-value, test for interaction=0.30).

Stratified analyses

We noted a stronger association between low SMD and mortality in patients less than vs. greater than or equal to 64 years of age (p-value, test for interaction=0.04). We noted a slightly weaker association in stage II vs. stage I and III patients (p-interaction=0.09). There was little evidence of effect modification by sex (Table 4) or other variables (data not shown).

With stratification on grade, stage, and treatment with chemotherapy, proportional hazards assumptions were met.

DISCUSSION

Consistent with hypotheses, CRC patients with low SMD at diagnosis had worse overall and CRC-specific prognosis compared to those with normal SMD. Patients with both low SMD and sarcopenia had the highest overall and CRC-specific mortality risks. These findings, in the largest CRC cohort to date with data on body composition, provide support that low SMD, as well as phenotypes based on combinations of SMD and MM, are important prognostic factors in CRC patients.

Our results clarify and represent an advance over findings from previous studies of SMD and prognosis in patients with CRC[14–18]. Findings in previous studies, ranging from 67 to 805 patients, have suggested a possible relationship but they have been inconclusive due largely to insufficient power. In fact, in the largest previous study to examine SMD and CRC prognosis, Malietzis et al. found no significant association between myosteatosis (low SMD) and overall or CRC-specific survival[17] (N=805) even though risks appeared elevated among patients with low SMD. Our findings confirm, and provide strong support for, an association of low SMD with both overall and CRC-specific mortality. The stronger association in younger patients in this population further suggests that low SMD may better differentiate CRC mortality risk in younger vs. older patients given that SMD levels decline with age.

In non-cancer populations[33,34] and in cancer patients[19,35], low SMD promotes higher systemic inflammatory response[16,19] and insulin resistance[20,21]. Inflammation and metabolic derangements stimulate tumor cell proliferation[36,37] and lead to worse cancer survival. Low SMD is also related to higher post-surgical complications[14], which are related to elevated CRC mortality. Though this could be in part to the association with adiposity which has been associated with poorer wound healing[38], the independent association of SMD with mortality, adjusted for adiposity, suggests other mechanisms which remain to be explored[7].

As expected, the combination of both low SMD and sarcopenia predicted elevated mortality in CRC patients, consistent with an additive effect. Sarcopenia has predicted higher mortality in many cancers including CRC patients as seen in our recent study[32]. Sarcopenia has also been related to higher systemic inflammatory response[16,19,35], metabolic dysregulation[39–41], and post-surgical complications[14] and the effects of each of these muscle abnormalities appear to be independent predictors of outcomes in CRC patients.

A study strength was the ability to examine body composition parameters at diagnosis prior to treatment. A great strength was the ability to evaluate associations in a large population-based cohort of 3,262 CRC patients, ensuring sufficient power to examine associations. Other study strengths include a large sample size, data on treatment and comorbidities, and follow-up to 10.9 years.

A study limitation, it is not possible to clearly determine whether low SMD influences or is a consequence of tumor progression though strong associations of SMD at diagnosis and outcomes even in stage I patients in the study provides some credence that the effect may not be entirely explained by reverse causation. A possible concern, most (96%) patients had contrast vs. non-contrast scans; SMD levels may be higher in scans with contrast[42]. This

could lead to a higher numeric value at which the threshold of low SMD is defined. However, this should not influence the relative ranking of SMD in patients and thus should not influence overall associations. We did not have information on optimization of treatment and quality measures such as surgical margins or extensiveness of nodal resection. Another potential limitation was the lack of information on functional status which is often included in assessments of sarcopenia in aging populations though this information is not typically included in assessment of body composition in cancer populations. Other potential concerns are the inclusion of CT scans months from diagnosis or after surgery. However, when we conducted sensitivity analyses restricting analyses to patients with scans ≤ 1 month from diagnosis, or to patients with scans prior to surgery, results were qualitatively similar (data not shown). An additional limitation, as is true in all observational studies, residual confounding is possible though we were able to adjust for a larger set of covariates than most analyses of body composition and cancer outcomes.

In summary, low SMD was associated with elevated all-cause and CRC-specific mortality in a large population of stage I–III CRC patients. Studies are needed to understand the mechanisms underlying these results. Regardless, body composition markers are prognostic of outcomes in CRC patients and should be incorporated into clinical assessments of patient health status.

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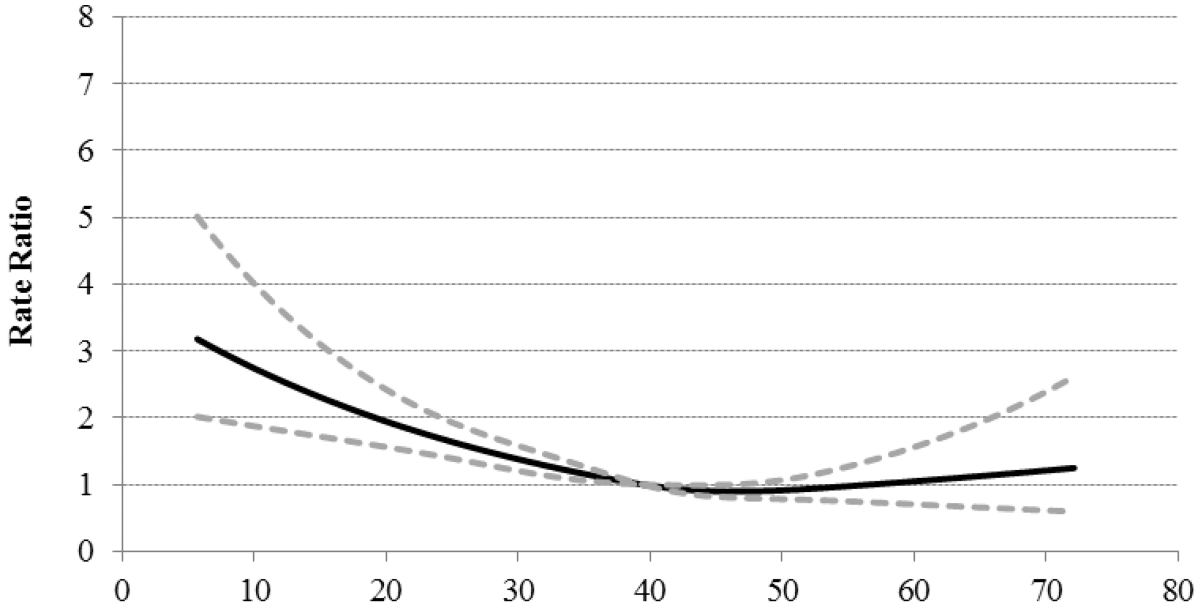

Adjusted for sex, age, race, stage, grade, site, treatment, smoking, comorbidity, partitioned BMI and muscle/SF/VF in quartiles. Reference is sex-specific median

	p-value
Test for curvature	0.01
Test for overall significance	<0.0001
Test for linear relation	<0.0001

Figure 1.
Restricted Cubic Spline for Muscle Radiodensity and Overall Mortality

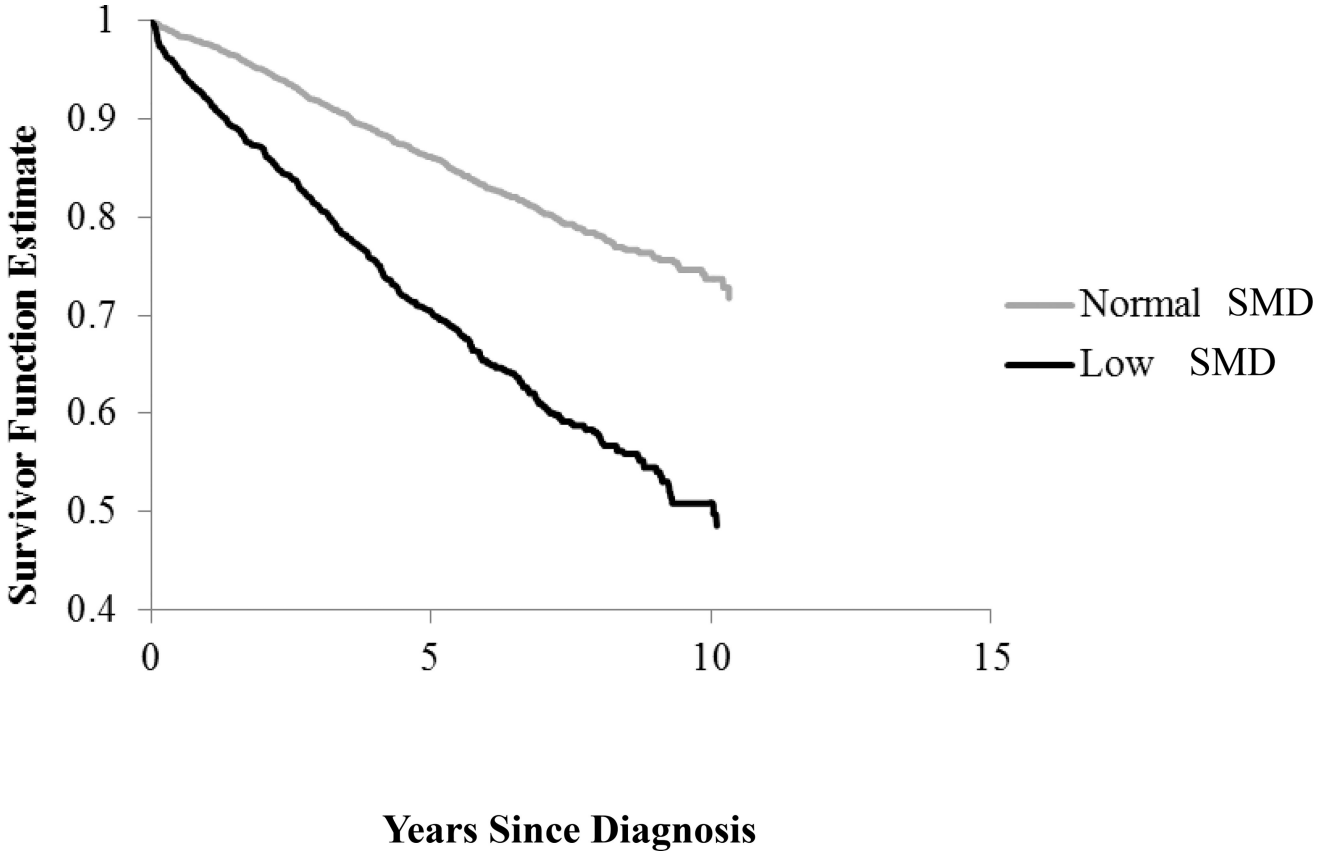

Figure 2.
Kaplan-Meier Curve of Muscle Radiodensity and Overall Mortality

Table 1

Characteristics of CSCANS Cohort, by level of Muscle Radiodensity

			Muscle radiodensity				
	Total n=3,262 N	**Mean SMD**	**N**	**Low n=966 Row%**	**N**	**Normal n=2,296 Row%**	**pvalue**
Overall			27.3 (5.7–35.5)		44.0 (32.5–72.1)		
Gender							
Men	1634	40.6	463	28.3	1171	71.7	0.11
Women	1628	37.5	503	30.9	1125	69.1	
Age at diagnosis							
<50	432	47.9	23	5.3	409	94.7	<0.0001
50–<60	806	42.3	123	15.3	683	84.7	
60–<70	941	38.4	261	27.7	680	72.3	
>=70	1083	33.6	559	51.6	524	48.4	
Race/Ethnicity							
White	2118	37.5	743	35.1	1375	64.9	<0.0001
Black	234	41.5	40	17.1	194	82.9	
Hispanic	365	38.6	118	32.3	247	67.7	
API	520	44.7	59	11.3	461	88.6	
Other	21	38.5	5	23.8	16	76.2	
Stage							
I	979	39.3	279	28.5	700	71.5	0.25
II	1030	38.4	325	31.5	705	68.5	
III	1253	39.4	362	28. 9	891	71.1	
Grade							
Well differentiated	226	38.1	81	35.8	145	64.2	0.02
Moderate	2466	39.1	725	29.4	1741	70.6	
Poor/Undiff	408	38.6	126	30.9	282	69.1	
Unknown	162	41.4	34	21.0	128	79.0	
Chemotherapy *							
No	1559	37.8	537	34.4	1022	65.6	<0.0001

			Muscle radiodensity				
	Total n=3,262 N	**Mean SMD**	**Low n=966 N**	**Low n=966 Row%**	**Normal n=2,296 N**	**Normal n=2,296 Row%**	**pvalue**
Yes	1703	40.2	429	25.2	1274	74.8	
Radiation *							
No	2755	38.5	863	31.3	1892	68.7	<0.0001
Yes	506	42.3	103	20.4	403	79.6	
BMI							
18.5–<25.0	1007	42.3	25	16.0	131	84.0	<0.0001
25.0–<30.0	1164	39.9	176	19.3	736	80.7	
>=30.0	1030	34.6	223	57.9	162	42.1	
Charlson comorbidity score							
0	1770	41.0	380	21.7	1390	78.5	<0.0001
1–2	946	37.0	354	37.4	592	62.6	
>=3	321	32.1	183	57.1	138	43.0	
Missing	225	42.1	49	21.8	176	78.2	
Cancer site							
Proximal	1436	36.9	537	37.4	899	62.6	<0.0001
Distal	879	39.6	233	26.5	646	73.5	
Rectal	947	41.8	196	20.7	751	79.3	
Smoking							
Never	1516	40.7	343	22.6	1173	77.4	<0.0001
Former	1347	37.4	495	36.7	852	63.2	
Current	396	38.5	128	32.3	268	67.7	
Muscle Tertiles							
Low	1086	37.8	381	35.1	705	64.9	<0.0001
Middle	1088	39.5	309	28.4	779	71.6	
High	1088	39.8	276	25.4	812	74.6	
SF Tertiles							
Low	1086	42.8	198	18.2	888	81. 8	<0.0001
Middle	1089	39.3	298	27.4	791	72.6	
High	1087	35.0	470	43.2	617	56.8	

	Total n=3,262 N	Mean SMD	Muscle radiodensity					
			N	Low n=966 Row%	N	Normal n=2,296 Row%	pvalue
VF Tertiles							
Low	1087	44.6	127	11.74	960	88.3	<0.0001
Middle	1087	39.1	293	27.0	794	73.0	
High	1088	33.4	546	50.2	542	49.8	

*
Radiation and chemotherapy could be neoadjuvant or adjuvant.

Table 2

Muscle radiodensity and mortality

			Overall Mortality				CRC Mortality		
	SMD Range	**At-risk**	**Events**	**HR**	**Lower bound, 95% CI**	**Upper bound, 95% CI**	**Events**	**HR**	**Lower bound, 95% CI**	**Upper bound, 95% CI**
Low SMD by sex-specific optimal stratification			879				451			
Normal	32.5 – 72.1	2296	481				259			
Low	5.7 – 35.5	966	398	**1.61**	**1.36**	**1.90**	192	**1.74**	**1.38**	**2.21**
Quartiles of SMD										
High	44.4 – 72.1	815	153				93			
Mid-High	37.7 – 47.2	816	177	0.94	0.75	1.18	89	0.94	0.68	1.28
Mid-Low	30.8 – 41.0	816	201	0.95	0.75	1.21	109	1.10	0.79	1.53
Low	5.7 – 34.6	815	348	**1.50**	**1.15**	**1.94**	160	**1.63**	**1.13**	**2.36**
p for trend across quartiles						**0.001**				**0.003**
p for trend (continuous)						**<0.0001**				**0.0001**

"SMD"=skeletal muscle radiodensity (HU); HR=hazard ratio

Models simultaneously adjusted for muscle mass, visceral and subcutaneous adiposity in quartiles

Additionally adjusted for age at diagnosis (continuous), sex (ref=Male), race (ref=White), site (ref=Proximal), stage (ref=I), grade (ref=Well differentiated), chemotherapy (ref=No), radiation (ref=No), smoking history (ref=Never), comorbidity score (ref=0) and partitioned BMI (continuous)

Table 3

Cross-classification of muscle radiodensity (HU) and sarcopenia

		Overall Mortality				CRC Mortality			
	At-risk	**Events**	**HR**	**Lower bound, 95% CI**	**Upper bound, 95% CI**	**Events**	**HR**	**Lower bound, 95% CI**	**Upper bound, 95% CI**
SMD and Sarcopenia									
Normal SMD, no sarcopenia	1482	264		Referent		146	Referent		
Normal SMD, sarcopenia	814	217	**1.30**	**1.07**	**1.57**	113	**1.42**	**1.09**	**1.84**
Low SMD, no sarcopenia	397	142	**1.63**	**1.30**	**2.05**	62	**1.57**	**1.13**	**2.20**
Low SMD, sarcopenia	569	256	**2.02**	**1.65**	**2.47**	130	**2.54**	**1.91**	**3.37**

"SMD"=skeletal muscle radiodensity (HU); HR=hazard ratio

SMD and Sarcopenia model adjusted for visceral and subcutaneous adipose tissue in quartiles

Models additionally adjusted for age at diagnosis (continuous), sex (ref=Male), race (ref=White), site (ref=Proximal), stage (ref=I), grade (ref=well), chemotherapy (ref=No), radiation (ref=No), smoking history (ref=Never), comorbidity score (ref=0) and partitioned BMI (continuous)

Table 4

Muscle radiodensity (HU) and overall mortality, by patient characteristics

	Overall Mortality						
			Normal	Low SMD			
	At-risk	Events		HR	Lower bound, 95% CI	Upper bound, 95% CI	p for interaction
Sex							
Male	1634	469	Referent	**1.57**	**1.25**	**1.97**	0.57
Female	1628	410	Referent	**1.63**	**1.28**	**2.07**	
Age at diagnosis, years							
<64	1627	312	Referent	**2.43**	**1.77**	**3.32**	**0.04**
>=64	1635	567	Referent	**1.57**	**1.30**	**1.90**	
Stage							
I	979	171	Referent	**2.01**	**1.39**	**2.89**	0.09
II	1030	255	Referent	1.28	0.95	1.73	
III	1253	453	Referent	**1.57**	**1.23**	**2.00**	

"SMD"=skeletal muscle radiodensity (HU)

Associations were adjusted for multiple covariates indicated in Tables 2 and 3, except for stratification variables