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ORIGINAL SCIENTIFIC REPORT

Change in Skeletal Muscle Following Resection of Stage I–III Colorectal Cancer is Predictive of Poor Survival: A Cohort Study

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Abstract

Background Sarcopenia at time of diagnosis predicts worse survival outcomes. It is currently unknown how changes in muscle mass over time interact with sarcopenia in colorectal patients treated with curative intent. Objectives of this study were to quantify sarcopenia and skeletal muscle loss from time of diagnosis to end of surveillance and determine its effect on survival outcomes after completion of 2 years of surveillance.

Methods Retrospective cohort study of stage I–III colorectal cancer patients from 2007–2009, who underwent resection and had preoperative and 2-year surveillance computed tomography scans, without recurrence during that time. Body composition analysis was done at both time points to determine lumbar skeletal muscle index, radiodensity and adiposity. Change over time was standardized as a percentage per year. Cox proportional hazard regression modeling was used for survival analysis.

Results Of 667 patients included, median survival from surgery was 7.96 years, with 75 recurrences occurring after 2 years. On average patients lost muscle mass (−0.415%/year; CI −0.789, −0.042) and radiodensity (−5.76 HU/year; CI −6.74, −4.80), but gained total adipose tissue (7.06%/year; CI 4.34, 9.79). Patients with sarcopenia at diagnosis (HR 1.80; CI 1.13, 2.85) or muscle loss over time (HR 1.55; CI 1.01, 2.37) had worse overall survival, with significantly worse joint effect (HR 2.73; CI 1.32, 5.65).

Conclusions Sarcopenia at diagnosis combined with ongoing skeletal muscle loss over time resulted in significantly worse survival. Patients with these features who are recurrence-free at 2 years are more likely to have a non-colorectal cancer cause of death.

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Introduction

Computed tomography (CT)-derived body composition parameters are novel prognostic factors [1–4]. Sarcopenia and myosteatosis have been associated with poor overall, recurrence-free and cancer-specific survival (OS, RFS, CSS) in colorectal cancer (CRC) [1, 2, 4, 5]. Visceral, subcutaneous and total adipose tissues (VAT, SAT, TAT) have unclear effects on survival [2, 6, 7] and have traditionally been quantified at a single point in time [8–12].

Surveillance is aimed at early diagnosis of recurrence, with guidelines suggesting annual CT for 2–5 years. Currently, there are no well-described risk factors to predict recurrence beyond 2 years. Quantifying body composition from surveillance CT scans may provide an opportunistic modality to predict survival and recurrence outcomes. While serial measurements have been previously reported, there is a lack of studies exploring relationships between longitudinal muscle change and survival in CRC patients treated with curative intent [13–17].

The primary aim of this study was to evaluate whether loss of skeletal muscle over time, particularly in the presence of pre-existing sarcopenia, is related to long-term survival outcomes in stage I–III CRC. It was hypothesized that sarcopenic patients with ongoing muscle losses would have worse OS, RFS and CSS after completion of 2-year surveillance and may represent novel prognostic factors.

Methods and materials

Cohort and endpoints

A retrospective cohort of stage I–III CRC patients was identified from the Alberta Cancer Board database as undergoing surgical resection and being seen in a comprehensive cancer clinic from January 2007 to December 2009. Exclusion criteria included no preoperative or 2-year CT scan, recurrence or death prior to 2 years and unenhanced CT scan at 1 time point [2, 18].

Primary endpoints were disease recurrence, OS, RFS and CSS. All endpoints were measured from date of operation. Date of death or last contact, cause of death, American Joint Committee on Cancer 6th edition stage, and disease recurrence were obtained from the Alberta Cancer Board database. All other data, including tumor/patient characteristics and surgical procedure, were obtained from electronic medical records. This study was approved by the Health Research Ethics Board of Alberta Cancer Committee. STROBE guidelines were followed for reporting of observational studies [19].

Body composition analysis

CT scans completed pre- and postoperatively (2-years) were identified. A single image from each scan was obtained from the third lumbar level, which correlates with total body muscle and fat [20]. Each image was segmented in MATLAB software for total cross-sectional skeletal muscle area (SMA) and adipose tissue areas [21]. Two blinded individuals (JH and RR) manually edited all scans, as previously described [1, 3]. Skeletal muscle and total adipose tissue (TAT) were normalized by height (m^2) and reported as lumbar skeletal muscle index (SMI, cm^2/m^2) and TAT index (TATI, cm^2/m^2). Mean skeletal muscle radiodensity (SMR) in HU was reported for total cross-sectional SMA. Inter-observer coefficients of variation for measurements of SMA, SMR, VAT and SAT were 1.2, 1.1, 1.3 and 1.2%, respectively.

Definition of body composition parameters and change over time

Optimal stratification is a statistical method used to identify population specific cutoff points from continuous data, based on log-rank statistics and time-to-event outcomes [1, 3, 22, 23]. OS was used as our event outcome for analysis [1]. Thresholds were used to dichotomize SMI, SMR, VAT and TATI. These cutoffs defined sarcopenia, myosteatosis, visceral obesity and elevated total adiposity, respectively.

As time between scans varied, change was measured as percentage change per year (365.25 days) for SMI, VAT, SAT and TAT. Change in SMR was defined by absolute change (HU) per year. Change in body composition variables were divided into tertiles and defined as losing (tertile 1), stable (tertile 2) or gaining (tertile 3). Mean values of change per tertile were assessed to ensure that they represented true loss and gain (±2%), beyond measurement error [15, 24].

Statistical analysis

Group differences were tested using paired Student's *t* test, Fisher's exact test or Kruskal–Wallis test. Patient follow-up began at date of operation and continued until death, loss to follow-up or October 31, 2017. Disease recurrence was defined as first objective evidence on endoscopy/imaging of recurrent disease, as per Response Evaluation Criteria in Solid Tumors [25]. RFS was defined as time from surveillance CT until identification of recurrent disease, loss to follow-up or end of study. OS and CSS were defined as time from surveillance CT until time of death from any cause or secondary to CRC, respectively, or until loss to follow-up or study end.

Univariate and multivariate Cox proportional hazards models were used. Modeling was done with purposeful selection and a priori inclusion of biologically and clinically important covariates, including sex, age, stage, comorbidities (Charlson comorbidity index, CCI), tumor location and high-risk tumor characteristics (lymphovascular/perineural invasion, high grade, adjuvant treatment). Sarcopenia at diagnosis and follow-up were included in multivariate analysis to control for regression to the mean [26, 27]. Hazard ratios (HRs) and 95% confidence intervals (CIs) were obtained, and Schoenfeld residuals showed no evidence of proportional hazards assumption violation. Post-estimation linear combinations were used to determine overlapping effects of sarcopenia and muscle loss, or elevated total adiposity.

SAS software (version 9.3; SAS Institute Inc., Carey, NC) was used for optimal stratification analysis. All other statistical analyses were performed using Stata 15.0 software (College Station, TX: StataCorp LLC). Statistical significance was established with two-sided tests and $p < 0.05$.

Results

Baseline characteristics

From the Alberta Cancer Board database, 1418 patients were identified and 356 did not have a preoperative CT. After applying exclusion criteria, the cohort had 667 patients (Fig. 1). Most patients had stage II/III disease, median OS was 7.96 years, and there were 75 (11.1%) recurrences (Table 1). Prevalence of sarcopenia and myosteatosis prevalence at follow-up was 28.8 and 72.7%, respectively. Patients with recurrence did not differ in age, sex, CCI, stage, tumor location or use of adjuvant chemotherapy. They were more likely to die (64 vs. 19%, $p < 0.001$), with shorter OS (6.47 vs. 8.16 years). Prevalence of sarcopenia, myosteatosis, visceral obesity and elevated TAT did not differ significantly between groups. Comorbid status was not significantly different in patients with disease recurrence or muscle loss over time.

Change in muscle mass, radiodensity and fat mass

On average, SMI (−0.415% change/year) and SMR (−5.77 HU/year) decreased over time. TAT increased over time (+7.06%/year), including VAT (+8.96%/year) and SAT (+7.71%/year).

Patients who gained, maintained or lost muscle had average SMIs of 49, 47 or 43 cm^2/m^2, respectively. The mean rate of change of muscle was +4.33, −0.46 and −5.01% SMI/year. Patients who were gaining muscle were on average losing SMR (−2.89 HU/year), but at a rate less than those losing muscle mass (−9.09 HU/year) (Table 2). Patients who received chemotherapy were equally likely to be in the SMI losing or gaining tertiles (51.6 vs. 59.9%, $p = 0.177$). Patients gaining muscle mass had a significantly greater rate of increase in adipose tissue ($p < 0.001$). Those losing muscle were more likely to have a *non-cancer death*, decreased OS and increased prevalence of sarcopenia and myosteatosis at follow-up (Table 1).

Tertiles of SMR change had mean rates of change (HU/year) of +6.11, −6.03 and −17.33 and average HU of 33, 28 and 24 for gaining, stable and losing groups, respectively. Patients losing SMR had fewer deaths (22 vs. 30%, $p = 0.031$), were more likely to have stage III disease and received adjuvant chemotherapy (64 vs. 52%, $p = 0.009$). Patients gaining SMR were less likely to have visceral obesity (43 vs. 58%, $p = 0.009$) or elevated TAT (65 vs. 77%, $p = 0.024$). Patients gaining fat were gaining muscle at a faster rate, while losing SMR (Table 2).

From our cohort, 170 patients were sarcopenia at diagnosis and 199 at follow-up, with 134 (67%) at both time points. In those only sarcopenic at follow-up, 26 (13%) patients developed recurrence and 16 died from CRC. In 134 patients who were sarcopenic at both time points, 19 (14%) developed recurrences and 12 died of CRC. There were 36 patients who were sarcopenic at diagnosis, but not at follow-up. Of these, 4 (11%) patients developed recurrence and all died of their disease.

Survival analysis

In univariate analysis, sarcopenia and loss of skeletal muscle over time were associated with worse OS. Sarcopenia at either time point was associated with worse CSS (Table 3). Neither sarcopenia nor muscle loss predicted worse RFS. In multivariate analysis, sarcopenia at diagnosis (HR 1.80, $p = 0.013$) and skeletal muscle loss (HR = 1.55, $p = 0.044$) were independently predictive of worse OS. Sarcopenia and loss of skeletal muscle trended toward worse RFS and CSS but did not reach significance. Elevated total adiposity was protective in terms of OS (HR 0.66, $p = 0.024$), but not RFS and CSS (Table 3).

Sarcopenia at diagnosis combined with loss of muscle resulted in worse OS (HR = 2.73, $p = 0.007$) and worse RFS (HR 2.71, $p = 0.080$) that neared significance (Table 4). No combinations predicted worse CSS (Table 4). Elevated total adiposity and concurrent sarcopenia at either time point was nonsignificant. Linear combinations of elevated total adiposity and muscle loss over time did not reach significance, but trended toward worse RFS.

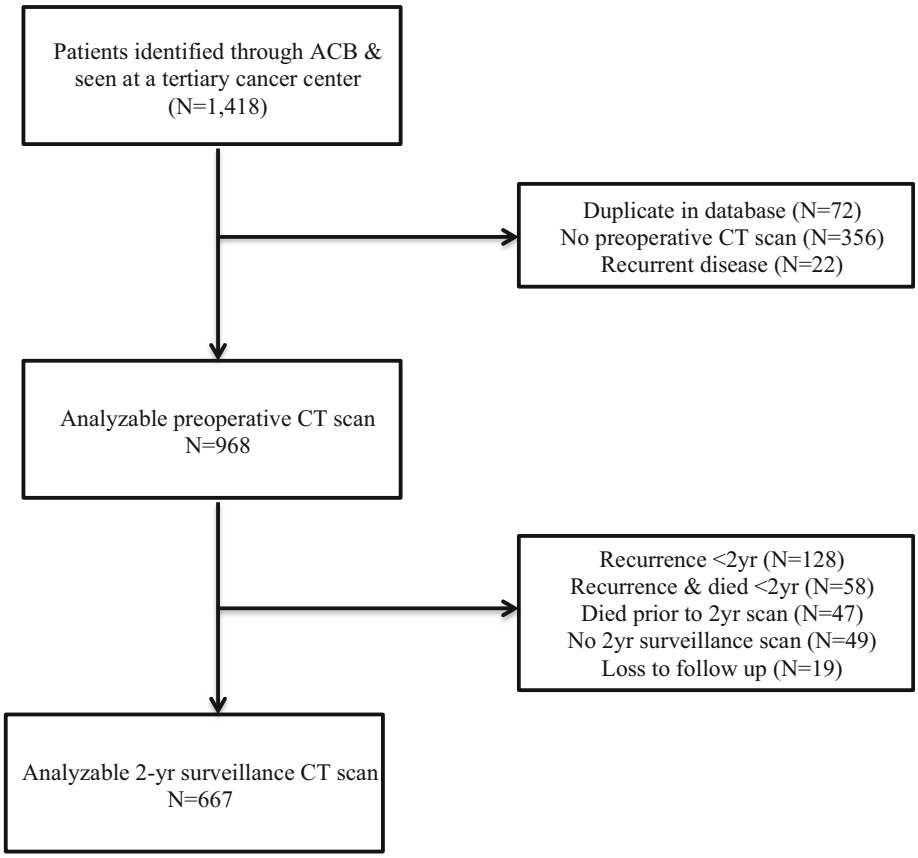

Fig. 1 Flow diagram of patient inclusion to study cohort

Discussion

This study highlights body composition changes from diagnosis to end of surveillance. In this large cohort of CRC patients treated with curative intent, those who completed surveillance without recurrence had significantly worse all-cause mortality if they were sarcopenic at diagnosis and had subsequent muscle loss after surgery. These associations were independent of important clinical and pathological features. This is a novel finding, as previous studies have been limited to use of weight loss or body mass index (BMI) or used non-validated methodology [16, 28–31]. While aging-related muscle loss is expected, pre-existing sarcopenia compounded by accelerated loss of muscle after treatment represents a pathological state associated with poor survival, as demonstrated in this study.

In a recent study, which included a similar cohort of patients, authors identified muscle loss over time in rectal cancer [14]. The current study attempted to build from this by describing change in adipose tissue and relating change in muscle to recurrence and mortality risks after surveillance. This may provide a method of long-term risk stratification for patients who complete post-treatment surveillance.

In healthy adult patients, muscle loss of 1–2% per year is expected [32]. In this cohort, there was a mean loss of 0.5% per year, and there are noticeable differences between tertiles of change (−5.01% vs. +4.33% per year). While surgery and adjuvant chemotherapy are catabolic hits occurring after diagnostic CT, recovery from these effects can be expected within 2 years.[14] Our results suggest there is ability for muscle gain postoperatively. As hypothesized, patients with ongoing losses had significantly worse OS (HR 1.53, CI 1.00, 2.34), which was accentuated by pre-existing sarcopenia (HR 2.73, CI 1.32, 5.65). This suggests that accelerated muscle loss, beyond expected physiological losses, may predict poor OS. This loss is even more important in patients with baseline sarcopenia.

Sarcopenia at diagnosis demonstrated a stronger effect on survival compared to at follow-up. This may be

Table 1 Clinical and pathological characteristics of cohort based on disease recurrence and change in muscle mass and radiodensity

Characteristic no. (%)	By disease recurrence			By change in muscle[a]			
	Recurrence ($N = 75$)	No recurrence ($N = 592$)	p	SMI losing ($N = 223$)	SMI stable ($N = 222$)	SMI gaining ($N = 222$)	p
Age (years)	65	66	**0.571**	68	68	66	0.355
Sex							
Male	35 (48.0)	357 (60.3)	**0.270**	141 (63.2)	123 (55.4)	128 (57.7)	0.230
Female	40 (52.0)	233 (39.3)		82 (36.7)	99 (44.6)	94 (42.3)	
Charlson comorbidity index							
0	53 (70.1)	369 (62.3)	**0.116**	129 (57.8)	148 (66.7)	144 (64.9)	0.070
1–2	18 (24.7)	188 (31.7)		73 (32.8)	65 (29.3)	69 (31.1)	
≥3	4 (5.2)	35 (5.9)		21 (9.4)	9 (4.0)	9 (4.0)	
Stage							
I	4 (5.3)	56 (9.5)	0.092	20 (9.0)	25 (11.3)	15 (6.8)	0.547
II	39 (52.0)	245 (41.4)		99 (44.4)	91 (41.0)	96 (43.2)	
III	32 (42.7)	291 (49.2)		104 (46.6)	106 (47.7)	111 (50.0)	
Location							
Right	75 (100)	153 (25.8)	0.239	65 (29.2)	82 (36.9)	84 (37.8)	**0.002**
Left	0 (0.0)	188 (31.8)		62 (27.8)	50 (22.5)	76 (34.2)	
Rectal	0 (0.0)	251 (42.4)		96 (43.0)	90 (40.5)	62 (28.0)	
Adjuvant chemo							
No	34 (45.3)	260 (43.9)	1.00	108 (48.4)	93 (41.9)	89 (40.1)	0.177
Yes	41 (54.7)	332 (56.1)		115 (51.6)	129 (58.1)	133 (59.9)	
Recurrences	75 (100)	0 (0.0)	**<0.001**	28 (12.6)	28 (12.6)	19 (8.6)	0.298
Deaths	49 (63.6)	114 (19.0)	**<0.001**	65 (29.2)	47 (21.2)	47 (21.2)	0.079
Survival after follow-up CT (years)	3.69	5.53	**<0.001**	4.84	5.22	5.91	**<0.001**
Sarcopenia[c] at diagnosis	41 (54.7)	303 (51.2)	0.717	52 (23.3)	44 (19.8)	70 (31.5)	**0.015**
Sarcopenia[c] at follow-up	26 (34.7)	173 (29.2)	0.425	105 (47.1)	51 (23.0)	36 (16.2)	**<0.001**
Myosteatosis[c] at diagnosis	47 (62.7)	352 (59.5)	0.714	118 (52.9)	110 (49.6)	120 (54.1)	0.621
Myosteatosis[c] at follow-up	55 (73.3)	437 (73.8)	0.787	179 (80.3)	150 (67.6)	156 (70.3)	**0.006**
Visceral obesity[c] at diagnosis	45 (60.0)	302 (51.0)	0.185	135 (60.5)	110 (49.6)	95 (42.8)	**0.001**
Visceral obesity[c] at follow-up	46 (61.3)	292 (49.3)	0.070	114 (51.1)	112 (50.5)	110 (49.6)	0.952
Elevated total adiposity[c] at diagnosis	51 (68.0)	412 (69.6)	0.697	171 (76.7)	144 (64.9)	142 (64.0)	**0.005**
Elevated total adiposity[c] at follow-up	57 (76.0)	424 (71.6)	0.595	155 (69.5)	161 (72.5)	162 (73.0)	0.690

Significant p values are given in bold

[a]% change in SMI per 1 year

[b]Absolute change in Hounsfield Units per 100 days

[c]Using cohort-specific cutoffs determined from optimal stratification analysis at follow-up CT scan

explained by the CRC's natural history, with most disease recurrences occurring within 2 years. Therefore, even if sarcopenic at follow-up, they may have bypassed a threshold for long-term RFS. Results in this study suggest patients who are sarcopenic at diagnosis and have ongoing losses may have increased recurrence risks, but significantly worse all-cause mortality. These patients may be dying of other causes before their recurrence is identified. It is unknown whether these patients are medically fit to have their recurrence treated with curative intent, and this represents a possible future area of investigation. While current guidelines suggest annual surveillance scans for 5 years, there may be a cohort whose comorbid status would preclude them from aggressive treatment in the

Table 2 Rate of change of muscle and fat parameters based on tertiles of skeletal muscle and adipose tissue change

Mean % change per year	Muscle % change tertiles				SMR absolute change tertiles				Total adipose % change tertiles			
	1	2	3	*P*	1	2	3	*P*	1	2	3	*P*
SMI	4.33	−0.46	−5.10	*	0.62	0.12	−1.98	*	1.42	−0.56	−2.10	*
SMR	−2.89	−5.30	−9.09	*	6.11	−6.03	−17.3	*	−8.50	−6.81	−2.01	*
VAT	21.7	5.85	−0.43	*	8.39	9.55	8.94	*	39.4	1.71	−14.1	*
SAT	14.9	6.62	1.63	*	7.13	7.61	8.39	*	25.3	4.67	−6.69	*
TAT	15.9	5.55	−0.18	*	6.64	7.39	7.16	*	28.5	3.06	−10.3	*

*$p < 0.001$

1: Gaining, 2: stable, 3: losing

setting of recurrence. Unfortunately, it is not currently possible to determine whether patients' skeletal muscle loss is secondary to recurrent disease or their comorbid status. It is possible that comorbid status resulting in hospital admissions may be the cause for their accelerated muscle loss and worse OS. Early-stage CRC is not the only condition where sarcopenia predicts worse OS. Sarcopenia predicts OS in end-stage liver disease, lung disease and acutely ill patients in the intensive care unit [33–35]. Montano-Loza et al. showed in 112 cirrhosis patients that patients with sarcopenia had an increased risk of death (HR 2.21 $p = 0.008$) independent of the Model for End-Stage Liver Disease score [35]. Similarly, Moon et al. showed in idiopathic pulmonary fibrosis patients that low muscle mass at the fourth thoracic vertebrae was associated with worse OS [33]. In elderly patients admitted to the ICU, post-trauma sarcopenia was associated with worse survival (32 vs. 14%, $p = 0.018$) [34]. Our study continues this trend in showing that sarcopenia is associated with worse OS. Given the number of diverse medical conditions such as trauma, liver and lung disease that appear to have worse outcomes associated with sarcopenia. We speculate that in these early-stage CRC patients, effects of sarcopenia on other comorbid conditions allowed sarcopenia to predict OS distinct from its effects on CRC outcomes alone.

SMR demonstrated unexpected patterns. Patients with SMR loss had significantly less deaths than those with SMR gain and a clinically nonsignificant decrease in SMI. While counterintuitive, this may be explained by increased incidence of adjuvant chemotherapy. There is evidence that chemotherapy results in reduced SMR and gain of VAT, and this may be predictive of survival [36–41]. Chemotherapy may be causing prolonged systemic inflammation resulting in ongoing SMR loss.

Fat's role as a prognostic marker remains unclear. Elevated total adiposity was predictive of improved OS (HR 0.66, CI 0.46, 0.95), in multivariate analysis. When considered in conjunction with pre-existing sarcopenia, the presence of elevated total adiposity demonstrated a trend toward worse OS and CSS. Conversely, sarcopenia at follow-up combined with elevated adiposity trended toward improved OS. Perhaps toward the end of life adipose tissue may act as a functional reserve, especially in patients with skeletal muscle loss [42]. Regardless, ability to quantify adipose tissues independent of skeletal muscle further diminishes BMI's role as a reliable prognostic factor. CT analysis demonstrates that obese patients with better outcomes also have significantly greater underlying muscle mass, which is likely improving their survival [7]. Studies limited to weight change or BMI are unable to quantify types of weight loss occurring or underlying body composition. Therefore, CT-derived body composition analysis is superior to BMI in prediction of survival for cancer patients.

This study is not free of limitations. It is retrospective in nature, resulting in missing data on performance status and genetic markers. There is risk of selection bias as 25% did not have a preoperative CT. Patients without preoperative CT were more likely to have had stage I disease and tended to be older, but had similar recurrence rates (11.2 vs. 11.7%) While the initial cohort was large, only a subset of patients who were alive without recurrence at their 2-year surveillance CT were considered, limiting patient inclusion. Furthermore, most CRC disease recurrence occurs in the first 2 years, while this study only considered recurrences after that point in time. As this is an observational study, a causal relationship between muscle loss or sarcopenia and survival outcomes cannot be proven. It is possible that sarcopenia solely represents a marker of some other underlying molecular mechanism affecting disease outcome. Despite these limitations, we were still able to collect a large data set with good long-term follow-up. Further randomized trials of physical and nutritional interventions may provide more insight into actual relationships between muscle and survival.

Table 3 Survival analysis based on changes in skeletal muscle composition and total adiposity

Variable	Overall survival				Recurrence-free survival				CRC-specific survival			
	Univariate		Multivariate[a]		Univariate		Multivariate[a]		Univariate		Multivariate[a]	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Sarcopenia												
At diagnosis	2.20 (1.60, 3.03)	<0.001	1.80 (1.13, 2.85)	0.013	1.44 (0.88, 2.36)	0.143	1.62 (0.80, 3.29)	0.185	1.67 (1.01, 2.75)	0.044	1.44 (0.69, 2.99)	0.325
At follow-up	2.15 (1.57, 2.94)	<0.001	0.93 (0.58, 1.50)	0.773	1.36 (0.84, 2.20)	0.211	0.86 (0.42, 1.78)	0.685	1.71 (1.05, 2.78)	0.030	1.04 (0.49, 2.19)	0.918
Elevated total adiposity[b]	0.88 (0.63, 1.23)	0.457	0.66 (0.46, 0.95)	0.024	1.07 (0.64, 1.78)	0.802	1.07 (0.63, 1.83)	0.807	1.28 (0.74, 2.25)	0.379	1.01 (0.69, 2.63)	0.980
Change in muscle[c]												
Stable	1.12 (0.74, 1.67)	0.593	1.21 (0.79, 1.86)	0.385	1.57 (0.88, 2.82)	0.128	1.67 (0.92, 3.07)	0.094	1.57 (0.88, 2.82)	0.132	1.58 (0.85, 2.92)	0.145
Losing	1.65 (1.13, 2.39)	0.010	1.55 (1.01, 2.37)	0.044	1.63 (0.91, 2.91)	0.102	1.68 (0.88, 3.24)	0.118	1.51 (0.83, 2.76)	0.180	1.34 (0.69, 2.63)	0.389

[a]Model adjusted for age, sex, disease stage, high risk factors (high grade, lymphovascular invasion), adjuvant treatment,

[b]Elevated total adiposity based on sex-specific optimal stratification cutoffs of total adipose tissue index ($M > 98.3$ cm^2/m^2; $p > 103.6$ cm^2/m^2)

[c]Tertiles of percentage change in skeletal muscle index per year; reference = muscle gaining tertile

Table 4 Linear combinations of sarcopenia and change in skeletal muscle mass over time from multivariate model

Variable	Overall survival[c]				Recurrence-free survival[c]				Cancer-specific survival[c]			
	Sarcopenia at diagnosis		Sarcopenia at follow-up		Sarcopenia at diagnosis		Sarcopenia at follow-up		Sarcopenia at diagnosis		Sarcopenia at follow-up	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Change in muscle mass[a]												
Losing	2.73 (1.32, 5.65)	**0.007**	1.45 (0.89, 2.35)	0.136	2.72 (0.89, 8.35)	0.080	1.45 (0.68, 3.07)	0.332	1.94 (0.62, 6.06)	0.255	1.40 (0.64, 3.04)	0.401
Elevated total adiposity[b]	1.22 (0.68, 2.20)	0.499	0.65 (0.35, 1.21)	0.176	1.72 (0.71, 4.23)	0.230	0.92 (0.36, 2.34)	0.861	1.45 (0.58, 3.65)	0.425	1.05 (0.39, 2.81)	0.927

Significant *p* value is given in bold

[a] Percentage change in skeletal muscle index per year in tertiles; reference = muscle gaining

[b] Sex-specific cutoff based on optimal stratification analysis of total adipose tissue index ($M > 98.3$ cm^2/m^2; $p > 103.6$ cm^2/m^2)

[c] Multivariate model adjusted for age, sex, disease stage, high risk factor (high grade, lymphovascular invasion), tumor location and adjuvant treatment

Conclusion

In patients with resected CRC who survived recurrence-free to their 2-year surveillance CT, the presence of sarcopenia at diagnosis followed by loss of muscle after surgery predicted worse OS. This may represent a novel consideration of skeletal muscle as an indicator for surveillance completion at 2 years, as mortality from a non-CRC cause is high. Patients without muscle loss should be considered for surveillance up to 5 years.

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References

1. Martin L, Birdsell L, Macdonald N et al (2013) Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol 31:1539–1547
2. Malietzis G, Currie AC, Athanasiou T et al (2016) Influence of body composition profile on outcomes following colorectal cancer surgery. Br J Surg 103:572–580
3. Prado CMM, Lieffers JR, McCargar LJ et al (2008) Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol 9:629–635
4. McSorley ST, Black DH, Horgan PG et al (2017) The relationship between tumour stage, systemic inflammation, body composition and survival in patients with colorectal cancer. Clin Nutr 37(4):1279–1285
5. Cespedes Feliciano EM, Kroenke CH, Meyerhardt JA et al (2017) Association of systemic inflammation and sarcopenia with survival in nonmetastatic colorectal cancer: results from the C SCANS study. JAMA Oncol 3:e172319
6. Cespedes Feliciano EM, Kroenke CH, Meyerhardt JA et al (2016) Metabolic dysfunction, obesity, and survival among patients with early-stage colorectal cancer. J Clin Oncol 34:3664–3671
7. Caan BJ, Meyerhardt JA, Kroenke CH et al (2017) Explaining the obesity paradox: the association between body composition and colorectal cancer survival (C-SCANS study). Cancer Epidemiol Biomarkers Prev 26:1008–1015
8. Malietzis G, Aziz O, Bagnall NM et al (2015) The role of body composition evaluation by computerized tomography in determining colorectal cancer treatment outcomes: a systematic review. Eur J Surg Oncol 41:186–196
9. Huang DD, Wang SL, Zhuang CL et al (2015) Sarcopenia, as defined by low muscle mass, strength and physical performance, predicts complications after surgery for colorectal cancer. Colorectal Dis 17:O256–264
10. Nakanishi R, Oki E, Sasaki S et al (2018) Sarcopenia is an independent predictor of complications after colorectal cancer surgery. Surg Today 48(2):151–157
11. Prado CM, Birdsell LA, Baracos VE (2009) The emerging role of computerized tomography in assessing cancer cachexia. Curr Opin Support Palliat Care 3:269–275
12. Margadant CC, Bruns ER, Sloothaak DA et al (2016) Lower muscle density is associated with major postoperative complications in older patients after surgery for colorectal cancer. Eur J Surg Oncol 42:1654–1659
13. Blauwhoff-Buskermolen S, Versteeg KS, de van der Schueren MA, et al (2016) Loss of muscle mass during chemotherapy is predictive for poor survival of patients with metastatic colorectal cancer. J Clin Oncol 34:1339–1344
14. Malietzis G, Currie AC, Johns N et al (2016) Skeletal muscle changes after elective colorectal cancer resection: a longitudinal study. Ann Surg Oncol 23:2539–2547
15. Rutten IJ, van Dijk DP, Kruitwagen RF et al (2016) Loss of skeletal muscle during neoadjuvant chemotherapy is related to decreased survival in ovarian cancer patients. J Cachexia Sarcopenia Muscle 7:458–466
16. Deng CY, Lin YC, Wu JS et al (2018) Progressive sarcopenia in patients with colorectal cancer predicts survival. AJR Am J Roentgenol 210:526–532
17. Reisinger KW, Bosmans JW, Uittenbogaart M et al (2015) Loss of skeletal muscle mass during neoadjuvant chemoradiotherapy predicts postoperative mortality in esophageal cancer surgery. Ann Surg Oncol 22:4445–4452
18. van der Werf A, Dekker IM, Meijerink MR et al (2018) Skeletal muscle analyses: agreement between non-contrast and contrast CT scan measurements of skeletal muscle area and mean muscle attenuation. Clin Physiol Funct Imaging 38(3):366–372
19. von Elm E, Altman D, Egger M et al (2007) The strengthening and reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 370:1453–1457
20. Shen W, Punyanitya M, Wang Z et al (1985) (2004) Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol 97:2333–2338
21. Popuri K, Cobzas D, Esfandiari N et al (2016) Body composition assessment in axial CT images using fem-based automatic segmentation of skeletal muscle. IEEE Trans Med Imaging 35:512–520
22. Harrell FE, Lee KL, Mark DB (1996) Multivariable prognostic models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 15:361–387
23. Williams BA, Mandrekar JN, Mandrekar SJ et al (2006) Finding optimal cutpoints for continuous covariates with binary and time-to-event outcomes: technical report. Division of Biostatistics, Mayo Clinic
24. Mourtzakis M, Prado CM, Lieffers JR et al (2008) A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab 33:997–1006
25. Eisenhauer EA, Therasse P, Bogaerts J et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228–247
26. Vickers A, Altman D (2001) Analysing controlled trials with baseline and follow up measurements. BMJ 323:1123–1124
27. Vickers A (2001) The use of percentage change from baseline as an outcome in a controlled trial is statistically inefficient: a simulation study. BMC Med Res Methodol 1:6
28. Meyerhardt JA, Kroenke CH, Prado CM et al (2017) Association of weight change after colorectal cancer diagnosis and outcomes in the Kaiser Permanente northern California population. Cancer Epidemiol Biomarkers Prev 26:30–37
29. Meyerhardt JA, Niedzwiecki D, Hollis D et al (2008) Impact of body mass index and weight change after treatment on cancer recurrence and survival in patients with stage III colon cancer: findings from Cancer and Leukemia Group B 89803. J Clin Oncol 26:4109–4115
30. Campbell PT, Newton CC, Dehal AN et al (2012) Impact of body mass index on survival after colorectal cancer diagnosis: the

Cancer Prevention Study-II Nutrition Cohort. J Clin Oncol 30:42–52
31. Baade PD, Meng X, Youl PH et al (2011) The impact of body mass index and physical activity on mortality among patients with colorectal cancer in Queensland, Australia. Cancer Epidemiol Biomarkers Prev 20:1410–1420
32. Abellan van Kan G (2009) Epidemiology and consequences of sarcopenia. J Nutr Health Aging 13:708–712
33. Moon SW, Choi JS, Lee SH et al (2019) Thoracic skeletal muscle quantification: low muscle mass is related with worse prognosis in idiopathic pulmonary fibrosis patients. Respir Res 20:35
34. Moisey L, Mourtzakis M, Cotton B et al (2013) Skeletal muscle predicts ventilator-free days, ICU-free days, and mortality in elderly ICU patients. Respir Res 17(5):R206
35. Montano-Loza AJ, Meza-Junco J, Prado CM et al (2012) Muscle wasting is associated with mortality in patients with cirrhosis. Clin Gastroenterol Hepatol 10:166–173
36. Rier HN, Jager A, Sleijfer S et al (2018) Changes in body composition and muscle attenuation during taxane-based chemotherapy in patients with metastatic breast cancer. Breast Cancer Res Treat 168(1):95–105
37. Cooper AB, Slack R, Fogelman D et al (2015) Characterization of anthropometric changes that occur during neoadjuvant therapy for potentially resectable pancreatic cancer. Ann Surg Oncol 22:2416–2423
38. Daly LE, Ni Bhuachalla EB, Power DG et al (2018) Loss of skeletal muscle during systemic chemotherapy is prognostic of poor survival in patients with foregut cancer. J Cachexia Sarcopenia Muscle 9:315–325
39. Miyamoto Y, Baba Y, Sakamoto Y et al (2015) Negative impact of skeletal muscle loss after systemic chemotherapy in patients with unresectable colorectal cancer. PLoS One [Electronic Resource] 10:e0129742
40. Di Sebastiano KM, Yang L, Zbuk K et al (2013) Accelerated muscle and adipose tissue loss may predict survival in pancreatic cancer patients: the relationship with diabetes and anaemia. Br J Nutr 109:302–312
41. Dalal S, Hui D, Bidaut L et al (2012) Relationships among body mass index, longitudinal body composition alterations, and survival in patients with locally advanced pancreatic cancer receiving chemoradiation: a pilot study. J Pain Symptom Manag 44:181–191
42. Lieffers JR, Mourtzakis M, Hall KD et al (2009) 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 89:1173–1179