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Muscle Loss Is Associated with Overall Survival in Patients with Metastatic Colorectal Cancer Independent of Tumor Mutational Status and Weight Loss

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Disclosures of potential conflicts of interest may be found at the end of this article.

Abstract

Background. Survival in patients with metastatic colorectal cancer (mCRC) has been associated with tumor mutational status, muscle loss, and weight loss. We sought to explore the combined effects of these variables on overall survival.

Materials and Methods. We performed an observational cohort study, prospectively enrolling patients receiving chemotherapy for mCRC. We retrospectively assessed changes in muscle (using computed tomography) and weight, each dichotomized as >5% or ≤5% loss, at 3, 6, and 12 months after diagnosis of mCRC. We used regression models to assess relationships between tumor mutational status, muscle loss, weight loss, and overall survival. Additionally, we evaluated associations between muscle loss, weight loss, and tumor mutational status.

Results. We included 226 patients (mean age 59 ± 13 years, 53% male). Tumor mutational status included 44% wild type, 42% *RAS-mutant,* and 14% *BRAF-mutant*. Patients with >5% muscle loss at 3 and 12 months experienced worse survival controlling for mutational status and weight (3 months hazard ratio, 2.66; *p* < .001; 12 months hazard ratio, 2.10; *p* = .031). We found an association of >5% muscle loss with *BRAF*-mutational status at 6 and 12 months. Weight loss was not associated with survival nor mutational status.

Conclusion. Increased muscle loss at 3 and 12 months may identify patients with mCRC at risk for decreased overall survival, independent of tumor mutational status. Specifically, >5% muscle loss identifies patients within each category of tumor mutational status with decreased overall survival in our sample. Our findings suggest that quantifying muscle loss on serial computed tomography scans may refine survival estimates in patients with mCRC. *The Oncologist* 2021;26:e963–e970

Implications for Practice: In this study of 226 patients with metastatic colorectal cancer, it was found that losing >5% skeletal muscle at 3 and 12 months after the diagnosis of metastatic disease was associated with worse overall survival, independent of tumor mutational status and weight loss. Interestingly, results did not show a significant association between weight loss and overall survival. These findings suggest that muscle quantification on serial computed tomography may refine survival estimates in patients with metastatic colorectal cancer beyond mutational status.

INTRODUCTION

Colorectal cancer is the third most common cancer worldwide, accounting for nearly one-tenth of all cancer-related deaths [1]. The prognosis for patients with metastatic colorectal cancer (mCRC) is approximately 2.5 to 3 years, with 5-year survival estimates up to 20% [2]. Notably, mutations in the *RAS*- and *BRAF*-oncogenes occur frequently in mCRC, and these oncogenes provide important predictive [3] and prognostic information [4]. *RAS* mutations can be found in 30%–40% of mCRC tumors, whereas *BRAF* mutations occur in 5%–10% of these tumors [5]. Prior work suggests that patients with *RAS*- or *BRAF*-mutant mCRC experience worse survival than patients with wild-type (WT) tumors [6]. Therefore, tumor mutational status informs the discussion of treatment options and anticipated outcomes for patients with mCRC [3, 5, 7].

Cancer cachexia is a multifactorial syndrome that has traditionally been defined using weight loss (e.g., >5% weight loss over 6 months) [8]. Although weight is routinely tracked as part of clinical care, basing the diagnosis and management of cachexia solely on weight loss is increasingly criticized by researchers and clinicians [8, 9]. Loss of skeletal muscle measured at the level of the third lumbar vertebral body (L3) on computed tomography (CT) is an objective parameter that can also inform anticipated outcomes in patients with mCRC, and may complement or even outperform weight loss [10–12]. For

example, data demonstrate that low skeletal muscle is associated with adverse postoperative outcomes, prolonged hospitalizations, treatment-related toxicity, and survival [9–16]. However, it is unclear whether skeletal muscle loss adds to risk stratification compared with tumor mutational status in patients with mCRC.

We designed this retrospective study to assess whether skeletal muscle loss is associated with overall survival in patients with mCRC, independent of tumor mutational status and weight loss. Our a priori hypothesis was that in patients with mCRC, skeletal muscle loss negatively affects overall survival independent of tumor mutational status and weight loss.

MATERIALS AND METHODS

Study Design

We conducted a retrospective cohort study of patients who had voluntarily enrolled in a prospective biobanking
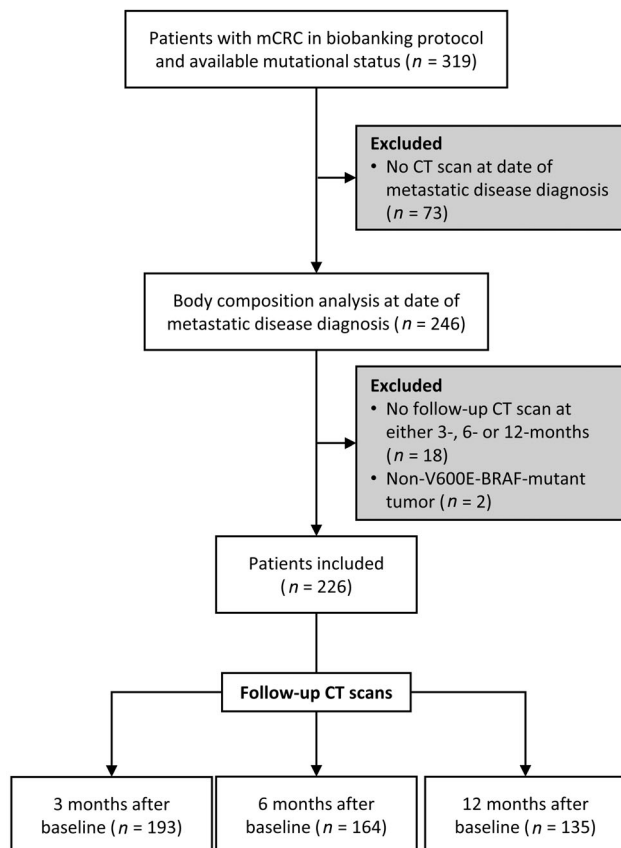

Figure 1. Consort diagram. Flow diagram specifying inclusion and exclusion criteria of patients and computed tomography (CT) scans. All time points ± 45 days.
Abbreviations: CT, computed tomography; mCRC, metastatic colorectal cancer.
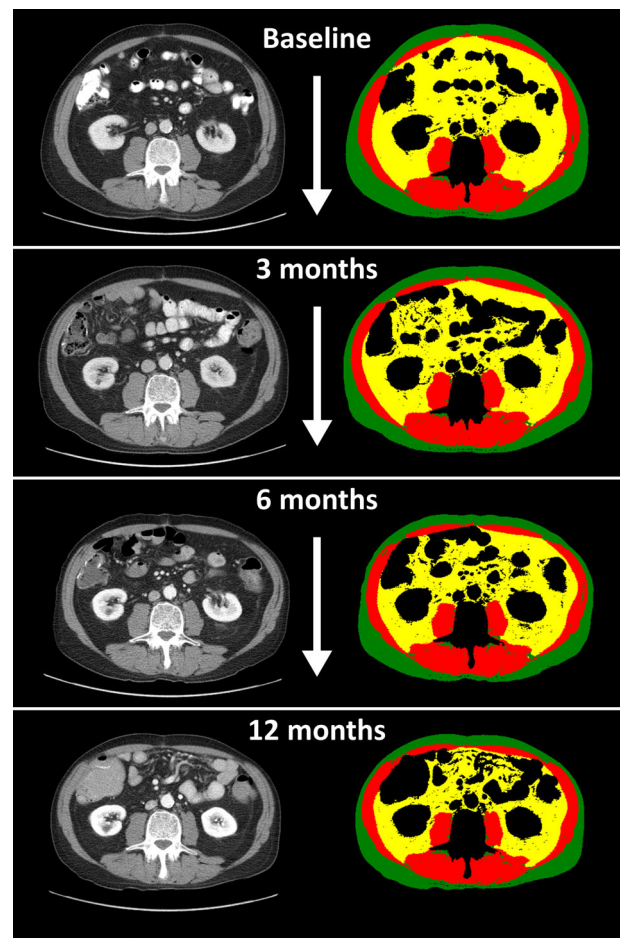

Figure 2. Change in body composition over time is hard to detect with the naked eye. Serial body composition analysis of a 61-year-old male patient with metastatic colon cancer. **Left column:** Serial axial computed tomography images at the level of the third lumbar vertebral body obtained at the time of metastatic disease diagnosis (baseline), and 3-, 6-, and 12-month follow-up. **Right column:** Corresponding segmentation of skeletal muscle (red), subcutaneous adipose tissue (green), and visceral adipose tissue (yellow). Twelve months following the diagnosis of metastatic disease, skeletal muscle had decreased by 20% and adipose tissue had reduced by 44% compared with baseline.

Table 1. Patient characteristics at time of metastatic diagnosis and outcomes (n = 226)

Characteristic	n = 226
Age, yr	
Mean ± SD	59 ± 13
Median (25th, 75th percentile)	59 (50, 68)
Minimum–maximum	26–92
Sex, n (%)	
Male	119 (53)
Race and ethnicity, n (%)	
White	204 (90)
Asian	10 (4)
Black	2 (1)
Hispanic or Latino	1 (1)
Other	3 (1)
Unavailable	6 (3)
Weight at metastatic diagnosis, kg	
Mean ± SD	80 ± 21
Median (25th, 75th percentile)	77 (66, 91)
Minimum–maximum	43–153
Height, cm	
Mean ± SD	170 ± 11
Median (25th, 75th percentile)	168 (163, 178)
Minimum–maximum	145–196
Body mass index, kg/m^2	
Mean ± SD	27.5 ± 5.6
Median (25th, 75th percentile)	26.5 (23.7, 30.5)
Minimum–maximum	17.1–43.8
Organ of cancer origin, n (%)	
Colon	170 (75)
Rectum	56 (25)
Location of tumor, n (%)	
Left	149 (66)
Right	64 (28)
Transverse	13 (6)
Tumor mutation, n (%)	
Wild type	99 (44)
KRAS	86 (38)
NRAS	9 (4)
BRAF (V600 mutations only)	32 (14)
Therapy type of first treatment, n (%)	
Standard chemotherapy	205 (91)
Targeted + standard chemotherapy	21 (9)
No. of lines of systemic therapy after metastatic diagnosis	
Mean ± SD	2.4 ± 1.5
Median (25th, 75th percentile)	2 (1, 3)
Minimum–maximum	0–9

(continued)

Table 1. (continued)

Characteristic	n = 226
First-line metastatic chemotherapy regimens n (%)	
5FU/capecitabine	3 (1)
+ bevacizumab	2 (1)
FOLFOX	70 (31)
+ bevacizumab	61 (27)
+ EGFRi	1 (0.4)
FOLFIRI	13 (6)
+ bevacizumab	32 (14)
+ EGFRi	14 (6)
FOLFOXIRI	16 (7)
+ bevacizumab	5 (2)
Irinotecan + bevacizumab	1 (0.4)
None	8 (4)
>5% loss at 3 mo, n (%)	
Weight	43 (22)
Skeletal muscle	57 (30)

Abbreviations: EGFRi, epidermal growth factor inhibitor; 5FU, 5-fluorouracil; IQR, interquartile range.

protocol at the Massachusetts General Hospital Cancer Center between January 2014 and August 2018. All patients provided informed consent for participating in the biobanking protocol. We obtained approval from the Dana-Farber/Harvard Cancer Center Institutional Review Board for this study (protocol number: 14–046). The study was conducted according to the code of ethics of the world medical association (declaration of Helsinki).

Inclusion/Exclusion Criteria and Scan Selection
To enroll in the prospective biobanking protocol, patients had to be at least 18 years and receive care at the Massachusetts General Hospital Cancer Center for gastrointestinal malignancy. Patients had to be enrolled in the biobanking protocol with a confirmed diagnosis of mCRC and known tumor mutational status to be eligible for the current study.

Patients were excluded if they (a) did not have a baseline abdominal CT scan at metastatic diagnosis ±45 days, (b) did not have a follow-up scan at 3, 6, or 12 months after the baseline CT scan ±45 days around each time point, or (c) had a BRAF-mutation other than BRAF^{V600} (Fig. 1). Patients were not required to have a CT scan at each follow-up time point. If patients had multiple CT scans around a given time point, we selected the scan obtained closest to the date of interest.

Body Composition Analysis
We submitted all included CT scans for processing with a previously described fully automated body composition analysis algorithm that can quantify the cross-sectional area of skeletal muscle, visceral adipose tissue, and subcutaneous adipose tissue on a single axial image at L3 in square centimeters [17]. Briefly, the algorithm consists of

convolutional neural networks that were developed using 595 manually segmented axial CT images at the L3 level. Attenuation thresholds used for both training and validation were −29 to +150 Hounsfield units for skeletal muscle and −190 to −30 Hounsfield units for adipose tissue. In the current study, a trained research assistant (T.D.B.) and a board-certified radiologist (F.J.F.) blinded to clinical outcomes reviewed the visual output of each segmentation performed by the algorithm. Figure 2 illustrates serial body composition analysis on abdominal CT scans.

Data Collection, Definitions, and Outcome

We obtained patients' demographics, date of mCRC diagnosis (confirmed by biopsy or imaging), mCRC mutational status, chemotherapy received, and body weight ±14 days around each CT scan from the electronic health record. We categorized mCRC tumor mutational status as WT, *RAS*-mutant (*KRAS* or *NRAS*), or *BRAF*-mutant. The tumor of one patient expressed a double mutation in *BRAF/NRAS* and was categorized as *NRAS*-mutant after expert review (R.B.C.).

We defined total adipose tissue as the sum of visceral adipose tissue and subcutaneous adipose tissue. We calculated the percentage change from baseline for skeletal muscle, total adipose tissue, and weight at 3, 6, and 12 months following the baseline scan. We selected time points based on common imaging intervals in clinical care. We chose to present percent change for skeletal muscle, total adipose tissue, and weight to facilitate clinical interpretation [10, 18]. We used linear interpolation to calculate percent change at 3, 6, and 12 months from the baseline scan date to account for the inclusion windows of CT scans and weight measurements (supplemental online Fig. 1; supplemental online Table 1).

We defined loss of skeletal muscle, total adipose tissue, and weight as a decrease of >5% because this represents a published cutoff value and a practical method for comparison [19–24]. Our outcome was overall survival, defined from the date of metastatic diagnosis to date of death, and we censored those patients still alive at the date of the last follow-up.

Statistical Analysis

We used descriptive statistics to estimate frequencies, means, SDs, medians, and interquartile ranges depending on data distribution. We used Cox proportional hazards models to assess whether the dichotomized change in skeletal muscle was associated with survival (independent of tumor mutational status and weight loss) while adjusting for a priori selected covariables age, sex, and total adipose tissue. We plotted Kaplan-Meier survival curves for skeletal muscle loss and tumor mutational status as well as skeletal muscle loss and weight loss. To account for the left-truncation in our survival analyses, patients were included in the risk set for an outcome event starting at the time of their follow-up scan and ending when they died or were censored. We used the Kaplan-Meier method to estimate median follow-up, with death as the censoring event. We also used logistic regression models to investigate associations between skeletal muscle loss, weight loss, and tumor mutational status, adjusting for a priori selected covariables age, sex, and baseline skeletal muscle or baseline weight values. We used a significance level of 0.05 for all analyses and did not adjust for multiple testing given this study's exploratory nature. We performed statistical analyses using SAS (version 9.3, SAS Institute Inc., Cary, NC) and R (version 3.5.3, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Inclusion and Descriptive Statistics

Of 319 eligible patients, 246 had a baseline CT scan and 228 also had a CT scan at one or more of three possible follow-up time points. Two patients with *BRAF*^D594G-mutations were excluded, resulting in 226 included patients (Fig. 1). In our sample, 193 patients had a scan at 3 months, 164 had a scan at 6 months, and 135 had a scan at 12 months after baseline (Fig. 1). Table 1 describes the characteristics of study participants at the time of metastatic diagnosis (baseline). Supplemental online Table 2 shows the baseline characteristics grouped by available scans at each

Table 2. Multivariable Cox proportional hazard models showing associations between loss of skeletal muscle, weight and total adipose tissue at 3, 6, and 12 months following metastatic diagnosis with overall survival

Characteristic	3 mo Hazard Ratio (95% CI)	3 mo p value	6 mo Hazard ratio (95% CI)	6 mo p value	12 mo Hazard ratio (95% CI)	12 mo p value
Skeletal muscle loss: >5% vs. ≤5%	**2.667 (1.593–4.466)**	**.0002**	1.707 (0.939–3.103)	.0797	**2.103 (1.068–4.139)**	**.0314**
Weight loss: >5% vs. ≤5%	0.851 (0.435–1.666)	.6380	1.835 (0.839–4.015)	.1287	2.096 (0.838–5.244)	.1136
Mutation		.0004		.0002		
BRAF vs. WT	**3.918 (1.837–8.355)**		**4.013 (1.914–8.415)**		**4.834 (2.030–11.515)**	**.0004**
RAS vs. WT	1.489 (0.857–2.587)	.1580	1.618 (0.893–2.932)	.1123	1.467 (0.7435–2.894)	.2692
TAT loss: >5% vs. ≤5%	1.517 (0.836–2.753)	.1705	0.660 (0.326–1.334)	.2471	0.735 (0.297–1.818)	.5051
Age: ≥70 yr vs. <70 yr	1.156 (0.650–2.056)	.6208	1.325 (0.746–2.354)	.3374	**2.436 (1.230–4.825)**	**.0106**
Sex: Female vs. male	1.007 (0.607–1.673)	.9770	1.198 (0.679–2.112)	.5335	0.785 (0.409–1.508)	.4680

For each follow-up time point, a single model was fit using the CT scans performed at the given time point.
Abbreviations: CI, confidence interval; CT, computed tomography; TAT, total adipose tissue; WT, wild type.

follow-up time point. Patients had a mean ± SD age of 59 ± 13 years and a mean body mass index of 28 ± 6 kg/m^2. Most patients were male (52%) and White (90%) and had left-sided (66%) colon cancer primaries. Mutational status categories included WT (44%), *RAS* (42%), and *BRAF*^{V600E} (14%). Most patients (91%) received standard chemotherapy with a mean of 2 ± 1.5 lines of chemotherapy following their diagnosis of mCRC. At 3 months, we observed a >5% loss of weight in 22% (43/194) of patients whereas 30% (57/194) of patients had lost >5% of skeletal muscle compared with baseline.

Skeletal Muscle Loss and Overall Survival

The entire cohort's median overall survival was 40 months (95% confidence interval [CI], 32–48 months). The median follow-up time was 57 months (95% CI, 47–68 months). Patients with a *BRAF*-mutant tumor had the shortest median overall survival (OS) with 19 months (95% CI, 11–28 months), compared with 34 months (95% CI, 26–51 months) for patients with *KRAS*-mutant tumors and 50 months (95% CI, 35–62 months) for patients with WT tumors. In patients who had lost >5% skeletal muscle after 3 months, median OS was 27 months (95% CI, 16–42 months), compared with 44 months (95% CI, 32–51 months) for patients who had <5% skeletal muscle. Additional survival estimates, including the 5-year-survival rate are presented in supplemental Table 3.

In our multivariable analysis, shorter overall survival was associated with >5% skeletal muscle loss at 3 months (hazard ratio [HR], 2.67; 95% CI, 1.59–4.47; *p* = .0002) and *BRAF*-mutational status (HR, 3.92; 95% CI, 1.84–8.36; *p* = .0004; Table 2). Figure 3 illustrates survival for patients with >5% skeletal muscle loss at 3-months compared with patients with ≤5% skeletal muscle at 3 months grouped according to weight loss (Fig. 3A) and tumor mutational status (Fig. 3B). We did not find an association between overall survival and loss of weight, loss of adipose tissue, or sex across all time points.

At 6 months, only *BRAF*-mutational status (HR, 4.01; 95% CI, 1.91–8.42; *p* = .0002) was associated with overall survival. Skeletal muscle loss >5% was not significantly associated with overall survival at this time point (HR 1.71; 95% CI, 0.94–3.10, *p* = .0797; Table 2). At 12 months, worse survival was significantly associated with >5% skeletal muscle loss (HR, 2.10; 95% CI, 1.07–4.14; *p* = .0314), *BRAF*-mutational status (HR, 4.83; 95% CI, 2.03–11.52; *p* = .0004), and age ≥ 70 years (HR, 2.44; 95% CI, 1.23–4.83; *p* = .0106; Table 2).

Associations of Tumor Mutational Status with Skeletal Muscle Loss and Weight Loss

We found a significant relationship between *BRAF*-mutational status and increased odds of >5% skeletal muscle loss at 6 months (OR, 3.37; 95% CI:,1.27–8.90; *p* = .0144) and at 12 months (OR, 5.53; 95% CI, 1.60–19.09; *p* = .0068; Table 3, supplemental online Table 4). We did not find an association between >5% weight loss and tumor mutational status across all time points. However, female sex was consistently associated with >5% weight loss (supplemental online Table 4). Additionally, we found a significant relationship between baseline weight and > 5%
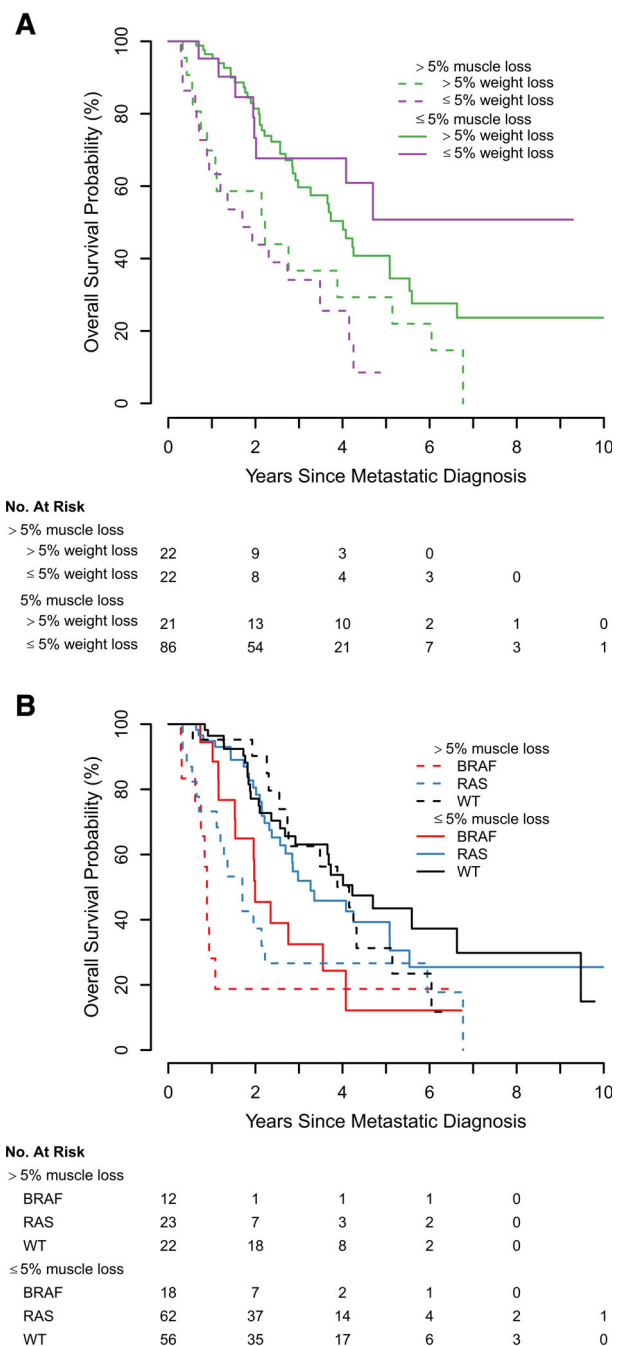
No. At Risk					
> 5% muscle loss					
> 5% weight loss	22	9	3	0	
≤ 5% weight loss	22	8	4	3	0
5% muscle loss					
> 5% weight loss	21	13	10	2	1	0
≤ 5% weight loss	86	54	21	7	3	1

No. At Risk					
> 5% muscle loss					
BRAF	12	1	1	1	0
RAS	23	7	3	2	0
WT	22	18	8	2	0
≤ 5% muscle loss					
BRAF	18	7	2	1	0
RAS	62	37	14	4	2	1
WT	56	35	17	6	3	0

Figure 3. Kaplan-Meier plots for overall survival. **(A)** Kaplan-Meier plots depicting the relationship of the combination of dichotomized skeletal muscle loss with weight loss at 3 months. **(B)** Relationship of the combination of dichotomized skeletal muscle loss at 3 months with tumor mutational status. Both skeletal muscle and weight loss were dichotomized by >5% versus ≤5%). Abbreviation: WT, wild type.

weight loss at 3 and 6 months (OR, 1.03; 95% CI, 1.01–1.05; *p* = .0159) but not at 12 months (supplemental online Table 4).

DISCUSSION

In this study of patients with mCRC, we provide evidence that skeletal muscle loss may identify patients at risk for

Table 3. Multivariable model demonstrating the relationship of tumor mutation status with >5% loss of skeletal muscle and >5% loss of weight

Time point, mutation	>5% weight loss		>5% skeletal muscle loss	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
3 mo				
WT	Ref		Ref	
BRAF	1.543 (0.521 − 4.568)	.4332	1.786 (0.727 − 4.387)	.2057
RAS	0.840 (0.366 − 1.926)	.6801	0.972 (0.483 − 1.975)	.9355
6 mo				
WT	Ref		Ref	
BRAF	2.379 (0.778 − 7.274)	.1284	**3.372 (1.273 − 8.933)**	**.0144**
RAS	1.188 (0.493 − 2.862)	.7016	1.144 (0.538 − 2.435)	.7261
12 mo				
WT	Ref		Ref	
BRAF	4.426 (0.982 − 19.957)	.0529	**5.533 (1.604 − 19.091)**	**.0068**
RAS	2.217 (0.717 − 6.853)	.1666	1.577 (0.667 − 3.727)	.2991

Body composition change was evaluated on computed tomography scans obtained 3, 6, and 12 months following the date of metastatic diagnosis. Estimates are adjusted for potential confounders, including age, sex, and baseline skeletal muscle or baseline weight. For the values of all covariables see supplemental online Table 4.

Abbreviations: CI, confidence interval; OR, odds ratio; Ref, reference; WT, wild type.

decreased survival as early as 3 months following the diagnosis of metastatic disease, independent of tumor mutational status and weight. Additionally, we found associations between skeletal muscle loss and *BRAF*-mutational status. Notably, our finding that weight loss was not associated with survival nor tumor mutational status supports the concept that weight loss alone cannot reliably predict outcomes in patients with mCRC.

Collectively, our findings suggest that skeletal muscle derived from serial CT scans is an imaging biomarker with the potential to refine survival estimates for patients with mCRC beyond tumor mutational status and weight. Within each mutational status category (WT, *RAS*, *BRAF*), skeletal muscle loss identified patients who experience worse overall survival than patients with the same tumor mutational status and ≤5% skeletal muscle loss (Fig. 3B). Interestingly, in our sample, a new prognostic pattern of poor overall survival emerges, as demonstrated by patients with >5% skeletal muscle loss and *RAS*-mutation experiencing similar overall survival compared with patients with *BRAF*-mutant tumors. In contrast, we observed that patients with *BRAF*-mutant mCRC experience significantly more skeletal muscle loss compared with patients with WT tumors, supporting previously published data describing more aggressive biology of *BRAF*-mutant mCRC. Although we found a significant association between >5% skeletal muscle loss and overall survival at 3 and 12 months, the absence of statistical significance at 6 months merits additional investigation. We believe this is due to a lack of power in the 6-months subgroup as the overall direction of effect and magnitude of effect size is similar to that of the 12-months subgroup.

Our finding that weight loss was not associated with overall survival or tumor mutational status is of particular clinical interest. First, this further supports a more focused definition of cancer cachexia based on skeletal muscle loss rather than a reliance on weight loss alone [8, 9]. By focusing only on weight loss rather than loss of skeletal muscle, oncologists may limit recognition of cachexia to its later stages [9]. This is particularly true when third-spacing of fluid (e.g., ascites, lower extremity edema) leads to stable or increased weight, thereby obscuring skeletal muscle loss [21, 25]. For example, 30% of patients in our study lost >5% skeletal muscle within 3 months following the diagnosis of mCRC, whereas only 22% of patients lost >5% weight in the same period. Second, skeletal muscle loss represents a viable target for prehabilitation and interventions such as exercise, nutrition, and drug therapy [20, 26]. By showing that patients with *BRAF*-mutant mCRC are particularly vulnerable to skeletal muscle loss, we define an enriched cohort of patients likely to benefit from prospective studies examining causality between muscle loss and overall survival.

This study relies on an innovative method to obtain body composition data for translational research. We demonstrate that machine learning enables a fully automated workflow to analyze body composition on serial CT scans obtained as part of routine cancer care [17, 27–30]. Without segmentation tools, change in skeletal muscle and adipose tissue is difficult to appreciate as illustrated in Figure 2. For example, this patient lost 20% of his skeletal muscle and 44% of his total adipose tissue between baseline and 12-month follow-up. However, manual segmentation of skeletal muscle and adipose tissue is time-consuming and requires trained experts, which were not necessary in this study [31, 32]. Therefore, we believe that machine learning-based body composition analysis will increasingly make body composition data available across clinical care settings [17, 27, 33, 34].

Limitations

We note several limitations of this study, including its retrospective, single-center design in a population with limited sociodemographic diversity. These factors limit the generalizability to more diverse populations. Furthermore, we note

that our findings are explorative due to the small sample size in the strata of tumor mutational status. In this sample, we did not observe associations between overall survival and changes in adipose tissue, possibly due to sample size, and should be further explored in larger cohorts. We also lack information about metabolism, diet, and exercise measures, which may impact skeletal muscle, weight, and survival [35–38]. Additionally, we lack data on other important clinical outcomes, such as chemotherapy treatment intensity, toxicities, and patient-reported outcomes.

Conclusion

In this study, we found that early skeletal muscle loss may identify patients with mCRC at risk for decreased overall survival, independent of mutational status and weight loss. We also discovered a new survival pattern within each tumor mutational category with >5% skeletal muscle loss demarcating high-risk subgroups. As expected, patients with *BRAF*-mutant tumors experience greater skeletal muscle loss and worse survival than those with WT or *RAS*-mutant tumors. Weight loss was not significantly associated with survival, further underscoring that weight loss alone provides incomplete prognostic information. Additionally, the use of automated body composition analysis demonstrated in this study represents a viable mechanism to integrate longitudinal body composition data more readily into routine cancer care. Ultimately, our findings offer novel information highlighting the importance of serial muscle assessment as a reliable, practical method that may further refine survival estimates in patients with mCRC.

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