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# Loss of Muscle Mass During Chemotherapy Is Predictive for Poor Survival of Patients With Metastatic Colorectal Cancer

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## ABSTRACT

### Purpose
Low muscle mass is present in approximately 40% of patients with metastatic colorectal cancer (mCRC) and may be associated with poor outcome. We studied change in skeletal muscle during palliative chemotherapy in patients with mCRC and its association with treatment modifications and overall survival.

### Patients and Methods
In 67 patients with mCRC (mean age ± standard deviation, 66.4 ± 10.6 years; 63% male), muscle area (square centimeters) was assessed using computed tomography scans of the third lumbar vertebra before and during palliative chemotherapy. Treatment modifications resulting from toxicity were evaluated, including delay, dose reduction, or termination of chemotherapy. Multiple regression analyses were performed for the association between change in muscle area and treatment modification and secondly overall survival.

### Results
Muscle area of patients with mCRC decreased significantly during 3 months of chemotherapy by 6.1% (95% CI, −8.4 to −3.8; $P < .001$). Change in muscle area was not associated with treatment modifications. However, patients with muscle loss during treatment of 9% or more (lowest tertile) had significantly lower survival rates than patients with muscle loss of less than 9% (at 6 months, 33% *v* 69% of patients alive; at 1 year, 17% *v* 49% of patients alive; log-rank $P = .001$). Muscle loss of 9% or more remained independently associated with survival when adjusted for sex, age, baseline lactate dehydrogenase concentration, comorbidity, mono-organ or multiorgan metastases, treatment line, and tumor progression at first evaluation by computed tomography scan (hazard ratio, 4.47; 95% CI, 2.21 to 9.05; $P < .001$).

### Conclusion
Muscle area decreased significantly during chemotherapy and was independently associated with survival in patients with mCRC. Further clinical evaluation is required to determine whether nutritional interventions and exercise training may preserve muscle area and thereby improve outcome.

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## INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in the world, with nearly 1.4 million new cases diagnosed in 2012.[1] Approximately one-fifth of patients are diagnosed with synchronic metastatic disease (mCRC), and almost 50% of patients will eventually develop metastatic disease after their primary diagnosis. A large number of patients with mCRC are overweight or obese, with prevalence ranging between 45% and 53%.[2-4] Low muscle mass is present in approximately 40% of patients, and not only in those who are underweight.[3] Low muscle mass in combination with a body mass index (BMI) greater than 30 kg/m$^2$ is referred to as sarcopenic obesity and was a prognostic indicator of worse overall survival in patients with pancreatic cancer[5] and patients with solid tumors of the respiratory or GI tract.[6]

Causes of low muscle mass may be found in a combination of reduced food intake, low physical activity, and abnormal metabolism.[7] Abnormal metabolism was found to be the most important contributor to low muscle mass in progressive end-stage disease[8-10] and is referred to as cachexia. Reversing muscle loss in patients with

cancer is difficult, because cachexia is caused by tumor activity and released cytokines. Nevertheless, during active anticancer treatment, there might be a window of opportunity for nutritional support and exercise programs.

Cross-sectional studies have shown that low muscle mass is associated with poor survival and increased treatment toxicity in patients with CRC undergoing treatment with chemotherapy.[2,3,11-13] However, longitudinal studies on change in muscle mass during chemotherapy for mCRC are lacking. The aim of this prospective study was to evaluate muscle mass change using single computed tomography (CT) images of the abdominal region (L3) in relation to chemotherapy toxicity and survival in patients with mCRC. Second, baseline muscle measurements in relation to clinical benefit and toxicity resulting from chemotherapy were evaluated.

## PATIENTS AND METHODS

Data were prospectively collected in a study on (pre)cachexia, in which nutritional and biochemical features from patients with advanced cancer were evaluated before start of chemotherapy at the Vrije Universiteit Medical Center (Amsterdam, the Netherlands). A first interim analysis of these data was published in 2014.[14] Patients were invited to enter the study before start of chemotherapy. Inclusion criteria were: adult patients with stage III to IV lung cancer, stage IV breast cancer, stage IV prostate cancer, or stage IV CRC for whom chemotherapy was planned. Exclusion criteria were: systemic treatment in the past month and clinically overt ascites or serious pitting edema.

Measurements of nutritional and biochemical features were performed at one time point: before start of chemotherapy treatment. For the current subgroup analyses, all consecutive patients with mCRC, recruited between October 2011 and January 2014, were selected. CT scans made for diagnostic purposes, at baseline, and during treatment with chemotherapy (according to standard evaluation schemes) were used to evaluate change in muscle mass during treatment.

The research protocol was approved by the Medical Ethics Committee of the Vrije Universiteit Medical Center Amsterdam, and the study was performed in accordance with the ethical standards described in the 1964 Declaration of Helsinki. Written informed consent was obtained from all participants.

### Measurements

*Skeletal muscle measurement.* Skeletal muscle area (square centimeters) was measured with SliceOmatic software (version 5.0; Tomovision, Magog, Quebec, Canada) using routine CT scans conducted for diagnostic purposes. We used two CT scans: one at baseline (before start of chemotherapy) and one during treatment, according to standard evaluation schemes. Median time between the two scans was 78 days (interquartile range, 67 to 92 days). The third lumbar vertebra (L3) was used as a standard landmark, because this correlates best with whole-body muscle mass[15,16]; the first image extending from L3 to the iliac crest was chosen to measure total muscle cross-sectional area. The L3 region contains psoas, paraspinal muscles, and the abdominal wall muscles. These muscles were identified on the basis of their anatomic features by two trained researchers (S.B.-B. and N.R.d.B.). The structures of those specific muscles were quantified on the basis of pre-established thresholds of Hounsfield units (−29 to 150) of skeletal muscle tissue.[17] Cross-sectional areas (square centimeters) of the sum of all these muscles were computed by adding tissue pixels and multiplying by the pixel surface area for each patient at each time point. We found a mean coefficient of variation between observers of 0.6% for skeletal muscle area in a random sample of 20 patients, which is regarded to be low.[18] To estimate total-body skeletal muscle mass, the regression equation of Shen et al[15] was used. Changes between the first and second scans were calculated as a rate of change per 3 months, meaning change per first evaluation, to compare with available literature.[19,20] Relative muscle change per 3 months was categorized into tertiles of muscle change: tertile one, highest muscle loss up to 9%; tertile two, muscle loss of 9% to 1.5%; and tertile three, muscle loss of 1.5% until highest gain in muscle.

Muscle density (MD) was measured using the muscle radiation attenuation rate (in Hounsfield units) because of its prognostic value in patients with cancer.[21,22] Skeletal muscle index (SMI) was calculated as the ratio of skeletal muscle area (square centimeters) divided by height (meters).[2] Body height was measured using a stadiometer; the patient stood barefoot, and height was determined to the nearest centimeter. Sex- and BMI-specific cutoff values of low SMI and low MD according to Martin et al[23] were used to define patients with normal and low values.

*Body weight.* Baseline body weight was measured within 0.2 kg on a calibrated scale (Seca type 888), and self-reported weight loss in the past 6 months was noted. Body weight during chemotherapy was obtained from medical records within 2 weeks of the date of the second CT scan. A correction factor for clothes or clothes and shoes was made by deducting weight by 1.6 and 2.0 kg for men and 1.0 and 1.3 kg for women, respectively.[24] To compare with change in muscle mass, we calculated the rate of change (percent) standardized to 3 months. BMI was calculated as the ratio of body weight (kilograms) divided by height (meters).[2]

### Treatment Modifications

Treatment modifications that were taken into account consisted of delay, dose reduction, or discontinuation of chemotherapy because of reported toxicity in the period between the two CT scans. Other modifications, such as delay because of patient preference or vacation, were not taken into consideration. Also, the number of treatment modifications was not taken into account, because treatment modifications were measured on a dichotomous scale (present or absent). Information on treatment modifications was obtained from medical records.

### Survival

Total follow-up time was 3.5 years. Survival time was defined as time from inclusion in the study until death or last consultation in the hospital.

### Covariates

The following variables were obtained from medical records and used in statistical analyses as covariates, because they carry prognostic value: sex, age, treatment line (≥ second *v* first, counted as consecutive chemotherapy line on the basis of the fact that a new type of chemotherapy was introduced), start dose of chemotherapy (normal or decreased), WHO performance status (≥ 2 *v* 0 or 1), Charlson comorbidity index[25] (≥ 1 *v* 0), serum lactate dehydrogenase (LDH; measured within 4 weeks before start of chemotherapy), severity of disease (multiorgan *v* monoorgan metastases), and outcome of first evaluation CT scan (progression *v* stable disease or regression of the tumor).

### Statistics

Statistical analyses were performed using SPSS software for Windows (version 20.0; SPSS, Chicago, IL). Descriptive statistics (count [percent], mean ± standard deviation, or median and interquartile range, as appropriate) were used to describe the study sample.

Paired-sample *t* tests were conducted to assess changes in skeletal muscle area, MD, and body weight. Spearman's correlation coefficient was used to assess correlation between body weight change and muscle area change.

Logistic regression analyses were used to test associations between treatment modification and muscle measurement (baseline SMI, low *v* normal [reference]; baseline MD, low *v* normal [reference]; and change in muscle area per percent). In multiple regression analyses, adjustments were made for age, sex, comorbidity score, start dose, treatment line, and WHO performance status.

Kaplan-Meier curves for overall survival were constructed separately for patients in the first, second, and third tertiles of relative muscle change. Differences between the curves were evaluated by log-rank tests. Six-month and 1-year survival proportions were also calculated. Cox proportional hazards analyses were performed to test associations between overall survival and muscle measurements (baseline SMI, low *v* normal [reference]; baseline MD, low *v* normal [reference]; and change in muscle area per percent). In multiple regression analyses, adjustments were made for age, sex, baseline serum LDH level, comorbidity score, severity of disease, and treatment line. For analyses including change in muscle mass during chemotherapy, an extra adjustment was performed for tumor progression at first evaluation by CT scan (progression *v* response or stable disease [reference]) as a potential confounder for rate of muscle loss and survival. Furthermore, overall survival times were calculated with the second CT scan as the starting point for these analyses. $P \leq .05$ was considered significant for all analyses.

## RESULTS

Sixty-seven patients with mCRC and evaluable CT scans at baseline were included. For longitudinal analyses, four patients were excluded because they had died (n = 2) or because they had no CT scans for other reasons (n = 2) at the time of evaluation.

### Baseline Patient and Treatment Characteristics

The mean age of patients (± standard deviation) was 66.4 ± 10.6 years, and 63% of patients were male. Eighty-two percent of patients had multiorgan metastases, and 78% received first-line chemotherapy. Patients received standard systemic treatment for CRC; the majority (n = 44; 66%) received a combination of capecitabine plus oxaliplatin with or without bevacizumab (CAPOX B or CAPOX, respectively; Table 1).

**Table 1.** Baseline Patient Characteristics (N = 67)

| Characteristic | No. (%) |
|---|---|
| Age, years | |
| Mean | 66.4 |
| SD | 10.6 |
| Sex | |
| Male | 42 (63) |
| Female | 25 (37) |
| Metastases | |
| Liver only | 12 (18) |
| Multiorgan | 55 (82) |
| Treatment line | |
| First | 52 (78) |
| ≥ Second | 15 (23) |
| Starting dose of chemotherapy | |
| Full | 52 (78) |
| Reduced | 15 (22) |
| Chemotherapy type | |
| CAPOX (± bevacizumab) | 44 (66) |
| FU plus oxaliplatin (± bevacizumab) | 5 (7) |
| Capecitabine plus irinotecan | 2 (3) |
| Capecitabine plus bevacizumab | 1 (1) |
| Capecitabine monotherapy | 5 (7) |
| Irinotecan monotherapy | 10 (15) |
| WHO performance status | |
| 0 | 27 (40) |
| 1 | 35 (52) |
| ≥ 2 | 5 (8) |
| Charlson comorbidity index | |
| 0 | 45 (67) |
| 1-2 | 19 (28) |
| ≥ 3 | 3 (5) |

Abbreviations: CAPOX, capecitabine plus oxaliplatin; FU, fluorouracil; SD, standard deviation.

**Table 2.** Nutritional Status at Baseline (N = 67)

| Variable | No. (%) |
|---|---|
| Weight change in 6 months before baseline | |
| Gain > 5% | 6 (9) |
| Stable | 39 (58) |
| Loss 5% to 10% | 15 (22) |
| Loss > 10% | 7 (10) |
| BMI, kg/m$^2$ | |
| < 20 | 4 (6) |
| 20-24.9 | 21 (31) |
| 25-29.9 | 37 (55) |
| > 30 | 5 (8) |
| SMI < reference value* | 38 (57) |
| MD < reference value* | 43 (64) |
| Sarcopenic obesity† | 1 (2) |

Abbreviations: BMI, body mass index; MD, muscle density; SMI, skeletal muscle index.
*Sex- and BMI-specific cutoff values according to Martin et al.[23]
†BMI ≥ 30 kg/m$^2$ and low SMI according to Martin et al.[23]

Critical weight loss of greater than 5% in 6 months before start of chemotherapy was prevalent in 33% of patients. At baseline, more than half of the patients were overweight (55%) or obese (8%), and 57% had low SMI. Sarcopenic obesity was present in one patient (Table 2).

### Changes in Muscle Mass and Body Weight

Skeletal muscle area decreased, in both men and women, by 6.1% (95% CI, −8.4 to −3.8; $P < .001$) in 3 months, corresponding to 1.7 kg in men and 1.1 kg in women. The proportion of patients with low SMI increased from 57% at baseline to 70% at the second CT scan (Table 3).

Body weight decreased significantly in women by 4.4% (95% CI, −8.5 to −0.4; $P = .031$), corresponding with −2.9 kg (n = 18), but not in men (change, −3.3%; 95% CI, −8.1 to 1.5; $P = .167$). Change in muscle area correlated significantly with change in body weight for men, but not for women (Spearman's rho for men, 0.34; $P = .050$; for women, 0.36; $P = .140$). MD decreased in men by 5.8% (95% CI, −11.5 to −0.03; $P = .049$) but remained stable in women (−0.3%; 95% CI, −11.7 to 11.1; $P = .957$; Table 3).

### Treatment Modifications

Treatment modifications resulting from toxicity occurred in 29 patients (43%), including delay of treatment in 13 patients (19%), dose reduction in 18 patients (27%), and discontinuation of treatment in six patients (9%). SMI and MD at baseline were not associated with treatment modifications (SMI: odds ratio [OR], 1.01; 95% CI, 0.35 to 2.91; $P = .99$; MD: OR, 1.43; 95% CI, 0.44 to 4.63; $P = .555$). In the more homogenous group of patients undergoing first-line treatment with CAPOX, no association was found either (n = 35; SMI: OR, 0.64; 95% CI, 0.07 to 5.71; $P = 0.692$; MD: OR, 1.21; 95% CI, 0.15 to 9.96; $P = .857$). A change in skeletal muscle area during treatment was not associated with treatment modifications in the total cohort (OR per 1% decrease,

**Table 3.** Muscle Area and Density During Chemotherapy (n = 63)

| Variable | First CT Scan | | Second CT Scan | | Change | | | Change Per 3 Months | | | Relative Change Per 3 Months (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | 95% CI | *P* | Mean | 95% CI | *P* | Mean | 95%CI | *P* |
| Muscle area, $cm^2$ | 138.6 | 32.1 | 131.9 | 31.7 | −6.6 | −8.9 to −4.3 | < .001 | −8.6 | −11.8 to −5.3 | < .001 | −6.1 | −8.4 to −3.8 | < .001 |
| Men | 156.8 | 24.4 | 149.2 | 25.3 | −7.6 | −11.0 to −4.3 | < .001 | −9.7 | −14.6 to −4.9 | < .001 | −6.2 | −9.3 to −3.1 | < .001 |
| Women | 108.9 | 17.5 | 103.9 | 17.9 | −5.0 | −8.0 to −1.9 | .003 | −6.6 | −10.5 to −2.7 | .002 | −6.0 | −9.5 to −2.5 | .002 |
| Muscle density, HU | 33.8 | 8.1 | 32.8 | 8.8 | −1.1 | −2.4 to 0.2 | .106 | −1.6 | −3.2 to 0.0 | .045 | −3.7 | −9.2 to 1.8 | .182 |
| Men | 35.2 | 7.5 | 33.6 | 9.0 | −1.6 | −3.2 to −0.1 | .037 | −2.0 | −3.9 to −0.2 | .031 | −5.8 | −11.5 to −0.03 | .049 |
| Women | 31.6 | 8.8 | 31.5 | 8.4 | −0.1 | −2.6 to 2.3 | .905 | −0.9* | −4.0 to 2.1 | .530 | −0.3 | −11.7 to 11.1 | .957 |

Abbreviations: CT, computed tomography; HU, Hounsfield unit; SD, standard deviation.
*Skewed data: median, −0.3; interquartile range, −3.8 to 4.1.

1.03; 95% CI, 0.95 to 1.12; $P = 0.441$) or a homogenous group of patients undergoing first-line treatment with CAPOX (n = 34; OR, 1.07; 95% CI, 0.95 to 1.22; $P = .274$).

### *Survival*

Median overall survival was 17.5 months (95% CI, 13.3 to 21.7) for patients receiving first-line chemotherapy and 8.5 months (95% CI, 4.4 to 12.6) for patients receiving second-line chemotherapy or beyond. Survival curves were significantly different for the tertiles of muscle change (log-rank $P = .005$; Fig 1). In pairwise comparison, the survival curve of tertile one (≥ 9% muscle loss) was significantly different from the survival curve of tertile two (muscle loss of 1.5% to 9%; log-rank $P = .007$) and also from the survival curve of tertile three (muscle loss of 1.5% to highest gain in muscle; log-rank $P = .009$). However, the survival curve of tertile two was not significantly different from the survival curve of tertile three (log-rank $P = .961$); therefore tertiles two and three were pooled (cutoff, 9% muscle loss).

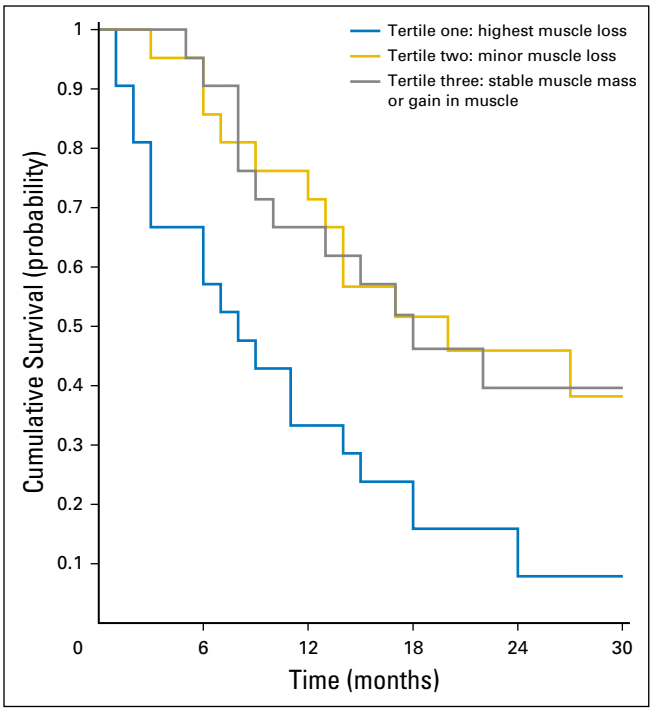


**Fig 1.** Kaplan-Meier curves for tertiles of muscle change.

Patients with muscle loss of 9% or more (tertile one) during chemotherapy had significantly lower overall survival rates than patients with muscle loss of less than 9% (tertiles two and three); at 6 months, 33% versus 69% of patients were alive, and at 1 year, 17% versus 49% of patients were alive (log- rank $P = .001$). Muscle loss of 9% or more remained independently associated with shorter survival when adjusted for sex, age, baseline LDH concentration, comorbidity, mono-organ or multiorgan metastases, treatment line, and tumor progression at first evaluation by CT scan (hazard ratio, 4.47; 95% CI, 2.21 to 9.05; $P < .01$). Low MD at baseline was associated with shorter survival after adjustment for covariates (hazard ratio, 2.38; 95% CI, 1.16 to 4.87; $P = .018$). Low SMI at baseline was not associated with survival (Table 4).

## DISCUSSION

This is the first study to our knowledge to present a change in muscle area during palliative chemotherapy for patients with mCRC. Patients with a decrease in muscle area during chemotherapy of 9% or more—the lowest tertile of patients—had significantly lower overall survival rates than patients with a decrease of less than 9%, independent of known prognostic covariates.

Previously, a rapid decrease in skeletal muscle mass was shown in patients with CRC in the last year of their life.[8,9] In our study, patients lost skeletal muscle during active anticancer treatment. The rate of muscle loss was comparable to that of patients with cholangiocarcinoma or esophageal cancer during treatment.[19,20] Compared with muscle loss that occurs in normal aging, patients with cancer experience a 24-fold more rapid loss of muscle mass: 6% muscle loss in 3 months (Table 2) versus 1% per year.[26] Overall consequences of muscle atrophy in humans have been found to be devastating: increased risk of falling,[27] diminished self-reliance,[28] decreased quality of life, increased risk of treatment-related complications, and shorter survival.[29]

Although previous studies have described an association between reduced muscle mass before treatment and treatment modifications,[2,11] we did not observe this association. A possible explanation for this may be found in the heterogeneity regarding treatment regimens and follow-up time; six different treatment regimens were recorded, and follow-up time depended on the timing of the second CT scan. Prado et al[11] and Barrett et al[2] looked at homogeneous groups of patients with mCRC receiving one type of chemotherapy and specific follow-up time (eg, number of

  

**Table 4.** Associations Between SMI, MD, and Muscle Change With Overall Survival

| Variable | Unadjusted | | Adjusted | |
|---|---|---|---|---|
| | HR (95% CI) | *P* | HR (95% CI) | *P* |
| Low SMI at baseline (N = 67) | 1.30 (0.72 to 2.35) | .390 | 1.65 (0.85 to 3.18)* | .138 |
| Low MD at baseline (N = 67) | 1.36 (0.74 to 2.50) | .321 | 2.38 (1.16 to 4.87)* | .018 |
| ≥ 9% muscle loss (n = 63) | 2.69 (1.45 to 5.01) | .002 | 4.47 (2.21 to 9.05)† | < .001 |

Abbreviations: HR, hazard ratio; MD, muscle density; SMI, skeletal muscle index.
*Adjusted for sex, age, lactate dehydrogenase concentration, comorbidity, metastases, and chemotherapy line.
†Adjusted for sex, age, lactate dehydrogenase concentration, comorbidity, metastases, chemotherapy line, and tumor progression at first evaluation by computed tomography scan.

cycles). Nevertheless, in post hoc analyses, no association between skeletal muscle and treatment toxicity in a homogeneous group of patients treated with CAPOX in first-line chemotherapy was found. We hypothesize that muscle mass may not be related to bone marrow toxicity, one of the most important types of toxicity resulting from this treatment regimen.[30] Furthermore, peripheral neuropathy is a type of toxicity that might be related to muscle loss but has been regarded as a more long-term type of toxicity and therefore may not yet be present in the first 3 months of treatment.

Although there was an association with low MD at baseline (in multiple regression analysis only), low SMI at baseline was not associated with survival in the evaluated group of patients with mCRC. This is in contrast with some[5,6,12,31,32] but not all previous findings. Stene et al[33] described comparable results in non–small-cell lung cancer, and Antoun et al[22] also reported comparable results in patients with melanoma. One possible explanation might be found in the phenomenon of sarcopenic obesity; patients with sarcopenic obesity had worse prognosis compared with patients without sarcopenic obesity in earlier studies.[5,6] Although the number of obese patients in our study was too small for subgroup analyses, we found that the prevalence of low muscle mass in obese patients in our study was comparable to the prevalence found in the study by Prado et al[6]: 20% (one of five) versus 15% (38 of 250), respectively. Muscle loss during chemotherapy was associated with worse overall survival, independent of important prognostic covariates. This is a new finding and raises the question whether interventions aimed at preservation of muscle mass during treatment are effective in improving outcome. One example of a promising intervention might be increasing physical activity during treatment, because this has been proven to improve muscle strength in cancer survivors[34] and in patients during chemotherapy.[35] Another promising intervention might be nutritional counseling, with consumption of high amounts of protein during the day[36] with high-enough thresholds per meal,[37] because this has also been proven to increase protein synthesis in healthy elderly populations. Potentially, the two interventions may be optimal when combined.[38] The use of ghrelin agonists for the treatment of cancer-associated anorexia could also be considered.[39] Furthermore, future studies should consider recruiting patients beyond those with severe weight loss or cachexia, because we have shown that muscle loss during treatment was a predictor of poor survival independent of the amount of muscle mass at baseline.

Alternatively, causes of muscle loss could be studied more in depth to find rational intervention possibilities. For example, the intervention strategy will be different when anorexia is the most important cause of muscle loss than when cachexia is the most important cause of muscle loss. To study this, a larger number of patients is required to also evaluate food intake and energy expenditure before and during chemotherapy.

In conclusion, significant muscle loss occurred in patients with mCRC during chemotherapy. Muscle loss of 9% or more during chemotherapy was independently associated with poorer survival. Future studies should investigate causes of muscle loss and whether interventions may attenuate or improve muscle mass during treatment and may lead to improvement in clinical outcomes such as survival.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

## AUTHOR CONTRIBUTIONS

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**Manuscript writing:** All authors
**Final approval of manuscript:** All authors

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Loss of Muscle Mass During Chemotherapy Is Predictive for Poor Survival of Patients With Metastatic Colorectal Cancer**

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