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Impact of different palliative systemic treatments on skeletal muscle mass in metastatic colorectal cancer patients

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Abstract

Background Observational studies suggest that loss of skeletal muscle mass (SMM) is associated with chemotherapy-related toxicity, poor quality of life, and poor survival in metastatic colorectal cancer (mCRC) patients. Little is known about the evolution of SMM during palliative systemic therapy. We investigated changes in SMM during various consecutive palliative systemic treatment regimens using repeated abdominal computed tomography scans of mCRC patients who participated in the randomized phase 3 CAIRO3 study.

Methods In the CAIRO3 study, mCRC patients with stable disease or better after 6 cycles of first-line treatment with capecitabine + oxaliplatin + bevacizumab (CAPOX-B) were randomized between maintenance treatment with capecitabine + bevacizumab (CAP-B) or observation. Upon first disease progression, in both groups, CAPOX-B or other treatment was reintroduced until the second disease progression, which was the primary study endpoint. We analysed 1355 computed tomography scans of 450 (81%) CAIRO3 patients (64 ± 9.0 years, CAP-B n = 223; observation n = 227) for SMM at four time points (i.e. prior to the start of pre-randomization initial treatment, at randomization, and at first and at second disease progression) using the Slice-o-matic software and single slice evaluation at the lumbar 3 level. By using accepted and widely used formulas, whole body SMM was calculated. A linear mixed effects model, adjusted for relevant confounders, was used to assess SMM changes for the total group and within and between study arms.

Results During 6 cycles of initial treatment with CAPOX-B prior to randomization, SMM decreased significantly in all patients [CAP-B arm: −0.53 kg (95% CI −1.12; −0.07) and observation arm: −0.85 kg (−1.45; −0.25)]. After randomization, SMM recovered during CAP-B treatment by 1.32 kg (0.73; 1.90) and observation by 1.20 kg (0.63; 1.78) (median time from randomization to first disease progression 8.6 and 4.1 months for CAP-B arm and observation arm, respectively). After first progression and during reintroduction treatment with CAPOX-B or other treatment, SMM again decreased significantly and comparable in both arms, CAP-B: −2.71 kg (−3.37; −2.03), and observation: −2.01 kg (−2.64; −1.41) (median time from first progression until second progression CAP-B arm: 4.7 months and observation arm: 6.6 months).

Conclusions This longitudinal study provides a unique insight in SMM changes in mCRC patients during palliative systemic treatment regimens, including observation. Our data show that muscle loss is reversible and may be influenced by the intensity of systemic regimens. Although studies have shown prognostic capacity for SMM, the effects of subsequent changes in SMM are unknown and may be clues for new future therapeutic interventions.

Keywords Metastatic colorectal cancer; Skeletal muscle; Sarcopenia; Body composition; Chemotherapy

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Introduction

Worldwide, colorectal cancer (CRC) is the third most common malignancy in men and second in women.[1] Over 50% of CRC patients will develop metastases during the course of the disease. For the majority of these patients, palliative systemic treatment is the standard of care, aiming to reduce tumour-related symptoms and prolongation of life.

Over the last two decades, the systemic therapeutic options for patients with metastatic colorectal cancer (mCRC) have increased. The presence of malnutrition and weight loss in mCRC patients (which are present in up to 60% of patients) have been identified as risk factors for adverse events during these treatments and may limit the outcome of these treatments.[2,3] The most devastating syndrome in patients with cancer-related malnutrition is cancer cachexia, which is defined as a progressive multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (SMM), with or without loss of fat, and which cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment.[4,5] Cancer cachexia results from reduced food intake caused by a range of symptoms like anorexia, gastro-intestinal symptoms, pain, and fatigue, occurring in combination with systemic inflammation and abnormal metabolism.[4] The most relevant phenotypic feature of cancer cachexia is low SMM (sarcopenia), as this relates to lower quality of life, increased dose limiting toxicities, and reduced overall survival.[4,6,7] The presence of sarcopenia and cachexia can be masked by excess body weight, leading to a diagnosis of cachexia at a late stage. When extensive weight loss has occurred, catabolism becomes refractory to treatment and eventually can lead to premature death.[5]

In recent years, the importance of early recognition and prevention of cancer cachexia by detecting underlying SMM loss has received more attention.[4] By the use of advanced imaging techniques for disease staging or response evaluation in standard oncology practice, such as computed tomography (CT) scanning or magnetic resonance imaging, reliable and precise quantification of SMM is possible, without any additional patient burden or costs.[8–10] However, to assess the role of SMM measurements as a valuable diagnostic and prognostic tool, knowledge on the specific behaviour of SMM during the course of disease is essential, and little is known on the evolution of SMM loss over time.[11] Furthermore, SMM loss in cancer patients has long been considered to be an irreversible process, but recent data indicate that muscle wasting in some patients is reversible.[11] Also, determinants that influence SMM loss and gain remain mostly unknown, and identification of these determinants might contribute to the implementation of interventions that aim for SMM to be maintained or increased. Based on the current knowledge of treatment-related side effects, it can be assumed that SMM is affected by both (systemic) cancer treatments and the disease itself, but studies that investigate SMM changes on more than two occasions during the course of the disease, thereby incorporating the effects of concomitant palliative systemic treatments, are lacking.

Here, we aimed to investigate SMM in a large cohort of mCRC patients on multiple occasions over time to further elucidate the evolution of SMM changes and to investigate whether SMM loss is a continuous process or whether losses are reversed. We used the data of patients from the randomized phase 3 CAIRO3 study[12] in which patients were evaluated by CT scans at regular time points during subsequent palliative systemic treatment regimens, including observation.

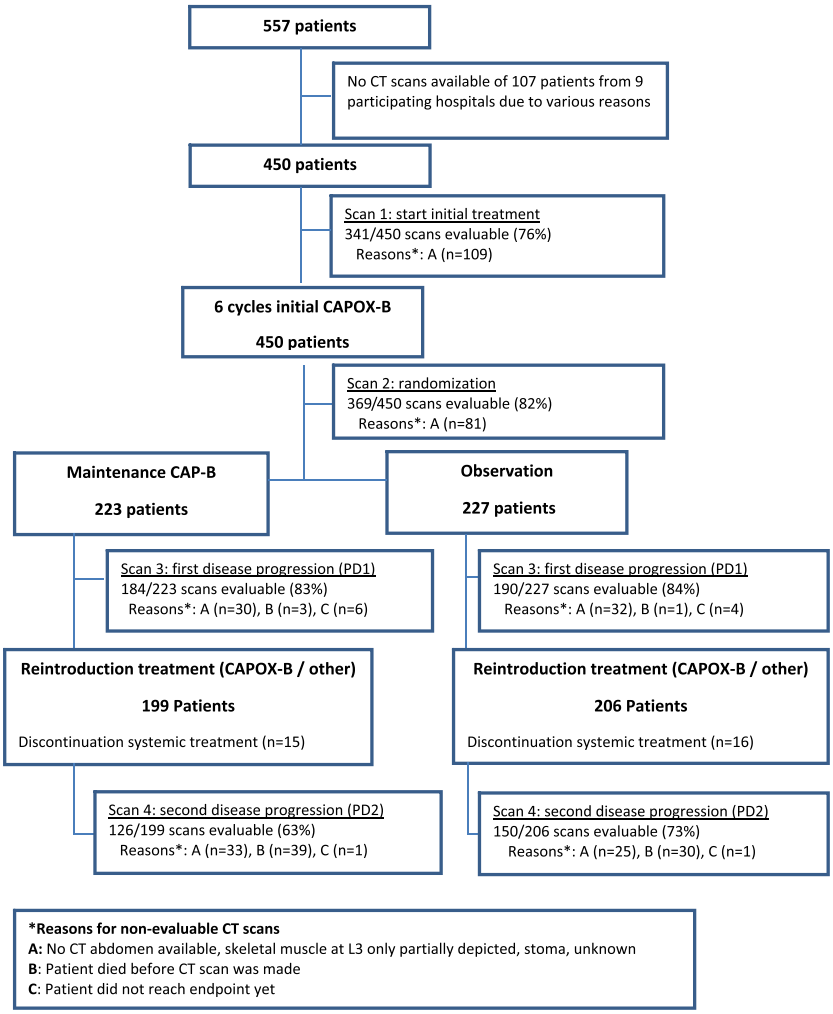
Patients and methods

The Dutch Colorectal Cancer Group CAIRO3 study[12] is a randomized phase 3 study that investigated the effect of maintenance treatment with low dose capecitabine + bevacizumab (CAP-B) vs. observation in previously untreated mCRC patients not progressing during first-line systemic treatment with 6 cycles of treatment with capecitabine + oxaliplatin + bevacizumab (CAPOX-B, further defined as initial treatment) (*Figure* 1). Main eligibility criteria for randomization were histological proof of CRC, unresectable metastatic disease, and World Health Organization performance status 0–1. During maintenance or observation treatment, patients were followed every 3 weeks by their physician and assessed for disease status every 9 weeks by CT scans according to response evaluation criteria in solid tumors criteria[13] or at any time when disease progression was suspected on the basis of clinical symptoms. Upon first disease progression (PD1), patients received reintroduction treatment with CAPOX-B or other treatment until the second disease progression (PD2), which was the primary endpoint of the original study. For this retrospective analysis, we collected digitally stored CT scans of participating patients. Approval for the research protocol was acquired by the Medical Ethics Committee of Nijmegen, The Netherlands. The trial protocol was registered at ClinicalTrials.gov, number NCT00442637.

Skeletal muscle measurements

Skeletal muscle area was analysed by the Slice-o-matic (version 5.0, TomoVision) software package using pre-specified thresholds for Hounsfield units (−29 to 150 Hounsfield units) to identify and demarcate the muscle compartments. We used single slice evaluation with the third lumbar level (L3) as a landmark, which has been proven to highly correlate with total body SMM (r^2 = 0.86).[8] Before selecting the L3 slice, per patient repeated CT scans were rotated and fused with a rigid fusion method and L3 as a boney landmark to

Figure 1 This flowchart displays the number of patients alive and the number of evaluable computed tomography (CT) scans per time point during the CAIRO3 study. CAP-B, capecitabine + bevacizumab; CAPOX-B, capecitabine + oxaliplatin + bevacizumab; L3, third lumbar level.



reduce measurement errors due to variation in the positioning of patients over time. After quantifying skeletal muscle area, we calculated the estimates for skeletal muscle index (SMI), skeletal muscle volume, and SMM using the previously published formulas.[8,14] Estimates were reported separately for men and women to address sex-specific muscle differences.

$$\text{Skeletal muscle volume (L)} = 0.166\ \text{L/cm}^2 \times \text{skeletal muscle area in cm}^2 + 2.142\ \text{L}.$$

$$\text{SMM (kg)} = \text{skeletal muscle volume in L} \times 1.06\ \text{g/cm}^3.$$

$$\text{SMI} = \text{skeletal muscle area in cm}^2/\text{squared height in m}^2.$$

To evaluate the evolution of SMM, we used CT scan data of four time points: (i) before the start of initial treatment with 6 cycles CAPOX-B, (ii) at time of randomization between CAP-B and observation, (iii) at PD1 before the start of reintroduction treatment with CAPOX-B or other treatment, and (iv) at PD2 (i.e. TT2PD endpoint in the CAIRO3 study) after patients showed progression on any systemic reintroduction treatment (*Figure* 1). These time points were chosen as they represent the start and the end of specific treatment periods, giving the opportunity to compare SMM changes during various treatment regimens, including observation.

Absolute and percentage of SMM changes were calculated for any two available consecutive CT scans. A measurement error of 2% was adopted based on previously reported accuracy of CT for skeletal muscle analysis.[9] SMM changes between −2% and +2% were considered SMM stable. Finally, SMM changes were categorized into SMM loss (SMM decrease $<-2\%$), SMM stable (SMM change between −2% and +2%), or SMM gain ($>2\%$ SMM increase).

Computed tomography scans were analysed by a trained Slice-o-matic analyst, who was blinded for the time of

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acquisition of the CT scans. A random sample of 140 slices was analysed twice by the same analyst and another time by a second trained analyst, during which both analysts were blinded for patient ID and the outcome of the first analysis. Mean coefficients of 1.7% and 1.2% were found for interobserver and intraobserver variation, respectively, which are consistent with other reports in literature.[5,15]

Differences in rate of skeletal muscle mass changes during maintenance and observation treatment

Additionally, to gain insight whether the rate of SMM changes differed shortly after randomization to maintenance or observation, we performed in-depth analysis in a subgroup of patients from seven hospitals that included the highest numbers of patients into the CAIRO3 study. CT scans acquired at 9 and 18 weeks after randomization were collected, and SMM was determined.

Other anthropometric measures

Additional information on height and body weight was retrieved from medical records. These measurements were used to calculate body mass index (BMI) [by weight (kg)/height $(m)^2$] and categorize patients in the World Health Organization-defined categories[16] [less than 18.5 (underweight), 18.5–24.9 (normal weight), 25.0–29.9 (overweight), and 30.0 or more (obesity)]. Sarcopenia in oncology usually refers to a situation in which muscle mass decreases to below a certain cut-off point that is associated with decreased survival. Presence of sarcopenia was determined by applying published sex-specific cut-off points for SMI and BMI of Martin *et al*. (*Table* 2).[6] Sarcopenic obesity, in which obesity and sarcopenia occur simultaneously, representing a patient group with poor prognosis because it combines the health risks of obesity and muscle loss,[7] was defined by being sarcopenic and BMI $\geq$ 30.

Data analysis

Patient, treatment, and outcome data were reported for the total group and per treatment arm to explore SMM changes for both treatment strategies. Baseline measures for the total group and by CAIRO3 treatment groups were described using descriptive statistics. Normally distributed continuous variables were shown as means ± standard deviation, or, if not normally distributed, as medians with first and third quartiles (Q1–Q3). Categorical variables were described in percentages.

To estimate mean changes in SMM and mean changes in body weight, a linear mixed effect model framework was used. We included the baseline value of the outcome in the outcome vector including the CAIRO3 treatment arm, time, and CAIRO3 treatment arm by time as fixed factors. We considered time as a within-subject factor via a random statement. This approach does not require that all subjects are measured at the same time point, and time can be defined as continuous variable. Adding time as a random factor, however, did not improve model fit as indicated by the Akaike information criterion, and time was therefore modelled as a fixed factor. As potential confounders, we investigated age, sex, lactate dehydrogenase levels at randomization, best response to initial treatment, whether the primary tumour was resected, and the number of metastatic sites involved and included these characteristics in the model when statistically significant. To assess whether SMM changes over time were different between CAIRO3 treatment arms, we checked the significance of the two-way interaction including treatment arm and time. In addition, we investigated whether results differed for the subgroup of sarcopenic patients compared with patients with normal SMM (determined at the start of initial treatment with 6 cycles CAPOX-B), and we used separate models for sarcopenic and non-sarcopenic patients. Furthermore, we assessed differences in the rate of SMM changes at 9 and 18 weeks after randomization between patients in the maintenance and observation arm. In this model, we included the subgroup of patients with the additional SMM measurements available at these time points and modelled SMM changes from randomization until 9 and 18 weeks thereafter. Finally, to get insight in the correlation between changes in SMM and changes in body weight, Pearson's correlation coefficient was used separately for men and women as differences between sexes were previously described.[15] All *P*-values were two-sided, and the level of significance was considered at $P < 0.05$. For all statistical analyses, we used SPSS version 21.

Results

Study population

Routine CT scans were available for 450 (81%) of the total of 557 CAIRO3 patients. A total of 1355 CT scans were evaluable for SMM measurements on any of the four chosen time points. These patients were recruited in 55 different hospitals in the Netherlands. Reasons for missing CT scans or non-evaluable scans are displayed in *Figure* 1.

Table 1 shows the baseline characteristics for the total group and per CAIRO3 treatment arm, which were well balanced between groups and comparable with the baseline characteristics of the original CAIRO3 trial. The mean age of patients at randomization was 63 ± 9 years in the maintenance arm and 64 ± 9 years in the observation arm. In both arms, 63% of patients were male. At the start of initial treatment, 57% of the patients in the maintenance arm were overweight or obese and 53% in the observation arm. In total, 2%

Table 1 Baseline patient demographics and characteristics

	Maintenance arm (n = 223)	Observation arm (n = 227)	Total group (n = 450)
Age, mean in years (±SD)	63 (±9)	64 (±9)	64 (±9)
≤70	171 (77%)	161 (71%)	332 (74%)
>70	52 (23%)	66 (29%)	118 (26%)
Sex			
Women	82 (37%)	83 (37%)	165 (37%)
Men	141 (63%)	144 (63%)	285 (63%)
Primary site			
Colon only	109 (49%)	117 (52%)	226 (50%)
Rectum only	69 (31%)	62 (27%)	131 (29%)
Rectosigmoid	45 (20%)	48 (21%)	93 (21%)
Resection primary tumour			
Yes	131 (59%)	139 (61%)	270 (60%)
No	92 (41%)	88 (39%)	180 (40%)
WHO performance status			
0	139 (62%)	142 (63%)	281 (62%)
1	84 (38%)	85 (37%)	169 (38%)
Number of metastatic sites			
1	102 (47%)	94 (44%)	196 (45%)
>1	113 (53%)	122 (57%)	235 (55%)
Unknown	8	11	19
Lactate dehydrogenase (IU/L)[a]			
Elevated	125 (56%)	127 (56%)	252 (56%)
Normal	98 (44%)	100 (44%)	198 (44%)
BMI			
Underweight (<18.5)	5 (2%)	5 (2%)	10 (2%)
Normal (18.5–25)	86 (41%)	99 (45%)	185 (43%)
Overweight (25–30)	79 (38%)	87 (40%)	166 (39%)
Obese (30+)	40 (19%)	28 (13%)	68 (16%)
Unknown	13	8	21
Sarcopenia[a]			
Yes	89 (53%)	82 (50%)	171 (51%)
No	80 (47%)	82 (50%)	162 (49%)
Unknown	54	63	117
Sarcopenic obesity[b]			
Yes	9 (6%)	5 (3%)	14 (6%)
No	154 (94%)	155 (97%)	309 (94%)
Unknown	58	67	127
Best response to initial treatment			
Complete or partial response	150 (67%)	148 (65%)	298 (66%)
Stable disease	73 (33%)	79 (35%)	152 (34%)
Reintroduction treatment			
CAPOX-B	117 (48%)	137 (60%)	254 (56%)
Other	106 (53%)	90 (40%)	196 (44%)

BMI, body mass index; CAPOX-B, capecitabine + oxaliplatin + bevacizumab; SD, standard deviation; WHO, World Health Organization.
[a]Sarcopenia for males was defined as skeletal muscle index of <43 cm^2/m^2 if BMI <25 kg/m^2 or <53 cm^2/m^2 for males if BMI ≥25 kg/m^2, and sarcopenia for females was skeletal muscle index <41 cm^2/m^2 for any BMI.[6]
[b]Sarcopenic obesity was defined as being sarcopenic and BMI >30 kg/m^2.

of the patients were underweight. Sarcopenia was present in 51% of patients and observed across all BMI strata at the start of initial treatment (data not shown). Sarcopenic obesity was observed in 6% of the total population and 21% of the obese patients (14 patients out of a total of 68 obese patients). Mean BMI of sarcopenic patients was 25.3 kg/m^2 in the observation arm and 24.9 kg/m^2 in the maintenance arm.

For the in-depth analysis on differences in the rate of SMM change during maintenance and observation, 104 patients were included, with a total of 156 CT scans analysed at 9 and 18 weeks after randomization. Baseline characteristics for this subgroup of patients were on average comparable with the baseline characteristics of the total group (*Table* SS1).

Skeletal muscle mass and body weight during palliative systemic treatment

Table 2 displays detailed information on the available absolute skeletal muscle and body weight measures on the four evaluated time points during CAIRO3. As expected, SMA, SMM, and SMI and body weight on all time points were on average higher in males compared with females. Overall, mean SMM decreased during the CAIRO3 follow-up period, but for most patients, we observed that SMM losses were alternated by periods of SMM stability, reversal, and/or gain. Muscle loss was more frequently observed during time periods of more intensive treatment (i.e. during initial or reintroduction treatment with CAPOX-B or other treatment),

Table 2 SMM and body weight measures per time point and per treatment arm

Maintenance arm	Scan 1 baseline (start of 6 cycles CAPOX-B)	Scan 2 randomization (start of maintenance treatment)	Scan 3 PD1 (start of reintroduction treatment)	Scan 4 PD2 (end of reintroduction treatment)
Available body weight measure (n =)	210	222	113	107
Body weight (mean in kg ± SD)				
Men	84.5 ± 15	84.9 ± 15	82.3 ± 12	84.4 ± 12
Women	71.1 ± 16	70.5 ± 16	73.4 ± 14	71.1 ± 16
BMI (mean ± SD kg/m^2)[a]	26.3 ± 4.8	26.3 ± 4.7	26.8 ± 4.1	26.1 ± 3.8
Available CT scans for muscle analysis[a, b] (n =)				
Men	110 (63%)	116 (63%)	118 (64%)	76 (63%)
Women	64 (37%)	67 (37%)	66 (36%)	45 (37%)
SMA (mean in cm^2 ± SD)[a]				
Men	157.3 ± 28.5	155.8 ± 27.0	162.3 ± 27.7	152.6 ± 26.8
Women	113.8 ± 19.2	112.8 ± 17.0	117.1 ± 19.5	110.5 ± 17.5
SMM (mean in kg ± SD)[a]				
Men	29.9 ± 7.3	29.7 ± 7.0	30.8 ± 7.1	27.5 ± 7.0
Women	22.3 ± 5.6	22.1 ± 5.3	21.6 ± 5.7	20.6 ± 5.3
SMI (mean in cm^2/m^2 ± SD)[a]				
Men	49.4 ± 8.6	48.9 ± 7.8	50.9 ± 8.0	47.4 ± 7.6
Women	41.0 ± 5.8	41.0 ± 5.9	42.7 ± 6.6	40.6 ± 5.8
Sarcopenia[a, b, c]				
Yes	89 (53%)	99 (54%)	58 (39%)	57 (55%)
No	80 (47%)	81 (37%)	92 (61%)	46 (45%)
Changes SMM in patients with available CT scans on two consecutive time points[a, b]		Change scan 1–2	Change scan 2–3	Change scan 3–4
Muscle loss (<−2%)	NA	69 (45%)	45 (28%)	80 (73%)
Muscle stable (−2% to 2%)	NA	35 (23%)	34 (21%)	20 (18%)
Muscle gain (>2%)	NA	48 (32%)	80 (50%)	9 (8%)

Observation arm	Scan 1 baseline (start of 6 cycles CAPOX-B)	Scan 2 randomization (start of observation)	Scan 3 PD1 (start of reintroduction treatment)	Scan 4 PD2 (end of reintroduction treatment)
Available body weight measure (n =)	219	220	177	166
Body weight (mean in kg ± SD)				
Men	82.6 ± 12	83.2 ± 12	85.0 ± 12	82.7 ± 10
Women	68.7 ± 12	67.4 ± 13	70.4 ± 12	70.0 ± 13
BMI (mean in kg/m^2 ± SD)[a]	25.8 ± 3.7	25.7 ± 3.7	26.5 ± 3.9	25.9 ± 3.4
Available CT scans for muscle analysis[a, b] (n =)				
Men	106 (63%)	118 (63%)	122 (64%)	103 (69%)
Women	61 (37%)	68 (37%)	68 (36%)	47 (31%)
SMA (mean in cm^2 ± SD)[a]				
Men	155.9 ± 22.9	155.9 ± 22.1	160.7 ± 22.3	150.3 ± 24.8
Women	111.4 ± 17.8	109.8 ± 15.7	109.7 ± 16.1	106.0 ± 13.4
SMM (mean in kg ± SD)[a]				
Men	29.7 ± 6.3	29.7 ± 6.2	30.5 ± 6.6	28.7 ± 4.7
Women	21.9 ± 5.4	21.6 ± 5.0	21.6 ± 5.1	20.9 ± 2.7
SMI (mean ± SD in cm^2/m^2)[a]				
Men	49.0 ± 7.1	49.2 ± 7.1	50.8 ± 7.3	48.0 ± 8.3
Women	40.8 ± 7.5	40.2 ± 5.8	40.3 ± 5.9	38.9 ± 4.4
Sarcopenia[b, c]				
Yes	82 (50%)	104 (56%)	85 (48%)	86 (61%)
No	82 (50%)	81 (44%)	92 (52%)	54 (59%)
Changes SMM in patients with available CT scans on two consecutive time points[a, b]	NA	Change scan 1–2	Change scan 2–3	Change scan 3–4
Muscle loss (<−2%)	NA	64 (43%)	32 (20%)	79 (58%)
Muscle stable (−2% to 2%)	NA	35 (24%)	43 (27%)	38 (28%)
Muscle gain (>2%)		49 (33%)	87 (54%)	20 (15%)

BMI, body mass index; CAPOX-B, capecitabine + oxaliplatin + bevacizumab; CT, computed tomography; NA, not applicable; PD1, first disease progression; PD2, second disease progression; SD, standard deviation; SMA, skeletal muscle area; SMI, skeletal muscle index; SMM, skeletal muscle mass.

[a]Due to missing values, patients that were included at one time point may be different from patients included on other time points.

[b]Column percentages did not include missing values.

[c]In patients with available measure on both BMI and SMI, sarcopenia for males was defined as SMI of <43 cm^2/m^2 if BMI <25 kg/m^2 or <53 cm^2/m^2 for males if BMI ≥25 kg/m^2, and sarcopenia for females was SMI <41 cm^2/m^2 for any BMI.

Table 3 Modelled SMM and body weight changes during systemic treatment

	Observation arm	CAP-B arm	Total group
Changes scan 1–2 (6 cycles CAPOX-B)			
SMM, mean in kg (95% CI)[a]	−0.85 kg (−1.45; −0.25)	−0.53 kg (−1.12; −0.07)	−0.69 kg (−1.11; −0.26)
Body weight, mean in kg (95% CI)[b]	−0.15 kg (−0.85; 0.55)	+0.06 kg (−0.65; 0.77)	−0.05 kg (−0.54; 0.45)
Median time scan 1–2 (Q1–Q3)	4.3 months (4.1–4.5)	4.3 months (4.0–4.5)	4.3 months (4.0–4.5)
Changes scan 2–3 (CAP-B vs. observation)			
SMM, mean in kg (95% CI)[a]	1.20 kg (0.63; 1.78)	1.32 kg (0.73; 1.90)	1.26 kg (0.84; 1.66)
Body weight, mean in kg (95% CI)[b]	2.09 kg (1.33; 2.85)	1.97 kg (1.05; 2.87)	2.08 kg (1.50; 2.67)
Median time scan 2–3 (Q1–Q3)	4.1 months (2.1–6.2)	8.6 months (4.0–17.0)	5.3 months (2.5–10.7)
Changes scan 3–4 (reintroduction with CAPOX-B or other systemic treatment)			
SMM, mean in kg (95% CI)[a]	−2.01 kg (−2.64; −1.41)	−2.71 kg (−3.37; −2.03)	−2.34 kg (−2.78; −1.88)
Body weight, mean in kg (95% CI)[b]	−1.24 kg (−2.03; −0.45)	−1.72 kg (−2.70; −0.73)	−1.43 kg (−2.04; −0.81)
Median time scan 3–4 (Q1–Q3)	6.6 months (3.9–9.9)	4.7 months (2.4–7.6)	5.6 months (2.8–9.0)
Changes scan 1–4 (start of initial treatment to end of reintroduction treatment)			
SMM, mean in kg (95% CI)[a]	−1.67 kg (−2.31; −1.03)	−1.92 kg (−2.61; −1.24)	−1.79 kg (−2.26; −1.32)
Body weight, mean in kg (95% CI)[b]	0.85 kg (0.07; 1.62)	0.23 kg (−0.7; 1.17)	0.61 kg (0.01; 1.21)
Median time scan 1–4 (Q1–Q3)	15.5 months (11.3–20.4)	18.3 months (12.7–28.4)	16.8 months (12.0–23.4)

CAP-B, capecitabine + bevacizumab; CAPOX-B, capecitabine + oxaliplatin + bevacizumab; SMM, skeletal muscle mass.
[a]As determined for outcome variable SMM using mixed model analysis with CAIRO3 treatment arm, age, sex, and resection primary tumour as fixed effects.
[b]As determined for outcome variable body weight by mixed model analysis with CAIRO3 treatment arm, age, sex, and resection primary tumour as fixed effects.

and SMM stability or gain was mostly observed during periods of less intensive treatment (i.e. during maintenance treatment with CAP-B or observation). In contrast to SMM, mean body weight and BMI at the start of initial treatment were comparable with the mean body weight and BMI at the end of reintroduction treatment, but again, fluctuations in changes throughout the follow-up period were observed. Furthermore, during all time periods, i.e. from the start of initial treatment to PD2, patients were on average overweight (BMI >26 kg/m^2), also in the subgroup of sarcopenic patients (BMI ≥ 25 kg/m^2).

Modelled skeletal muscle mass changes during palliative systemic treatment

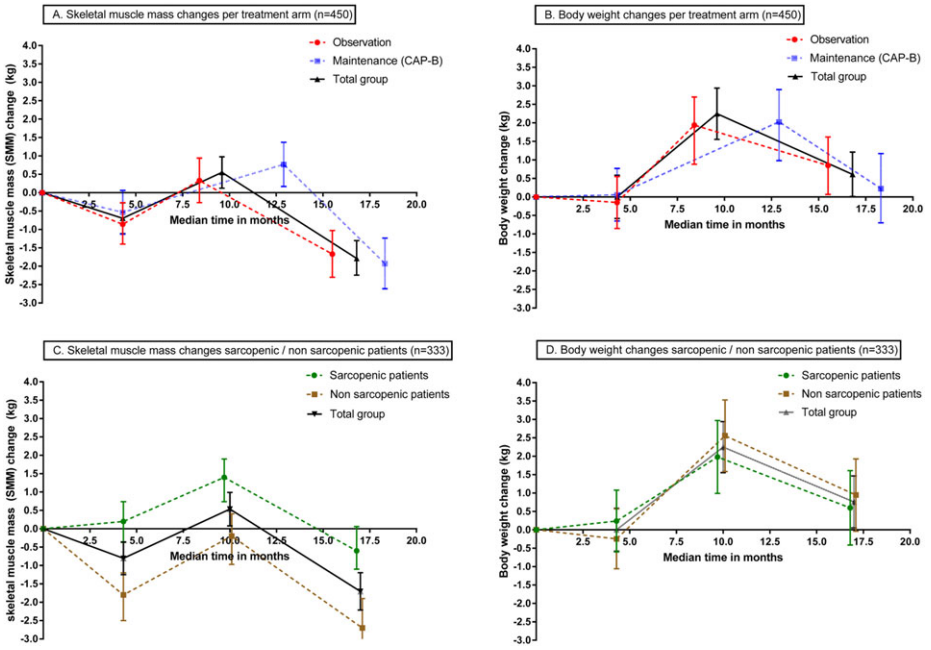
To estimate the mean SMM changes over time, we used the repeated data on SMM and modelled the changes during palliative systemic treatment (*Table* 3 and *Figure* 2). Mean SMM changes per CAIRO3 treatment arm were not significantly different between treatment arms ($p_{interaction}$ CAIRO3 treatment arm by time = 0.78). For the total group during initial treatment with 6 cycles CAPOX-B, SMM on average decreased [−0.69 kg (95% CI −1.11; −0.26)], and the median time of initial treatment was 4.3 months (Q1–Q3 4.0–4.5). During subsequent less intensive maintenance or no treatment, SMM on average recovered [+1.26 kg (95% CI 0.84; 1.66)], and the median time from randomization to PD1 was 5.3 months (Q1–Q3 2.5–10.7). After PD1 and during reintroduction treatment, SMM again decreased [−2.34 kg (95% CI −2.78; −1.88)], and the median time of PD1 to PD2 was 5.6 months (Q1–Q3 2.8–9.0). The mean SMM change between the start of initial treatment and the end of reintroduction treatment was −1.79 kg (95% CI −2.26; −1.32).

Figure 2C displays separate models for the subgroup of sarcopenic vs. non-sarcopenic patients, which showed comparable patterns of loss and gain in both groups, except during initial treatment in which sarcopenic patients did not show a significant change in SMM [+0.20 kg (95% CI −0.37; 0.74)], compared with non-sarcopenic patients who lost SMM [−1.8 kg (95% CI −2.50; −1.20)].

Modelled body weight changes during palliative systemic treatment

Table 3 and *Figure* 2B show body weight changes in the total group of patients and per CAIRO3 treatment arm. Again, changes were not significantly different between CAIRO3 treatment arms ($p_{interaction}$ CAIRO3 treatment arm by time = 0.20). Mean body weight did not change during initial treatment −0.05 kg (95% CI −0.54; 0.45). Weight gain was observed during maintenance treatment or observation [+2.08 kg (95% CI 1.50–2.67)], and weight loss was observed after reaching PD1 during reintroduction treatment [−1.43 kg (95% CI −2.04; −0.81)]. Comparable with SMM, body weight fluctuated during the different treatment phases; however, throughout the CAIRO3 follow-up period, body weight increased on average with 0.61 kg (95% CI 0.01; 1.21), in contrast to the mean decrease in SMM of −1.79 kg (95% CI −2.26; −1.32) that was observed from the start of initial treatment to PD2. *Figure* 2D displays body weight changes in the subgroup of sarcopenic and non-sarcopenic patients, which showed comparable patterns of body weight changes over time in both groups.

Figure 2 Modelled skeletal muscle mass (SMM) and body weight changes during CAIRO3. *Figure* 2A and 2B display the modelled mean SMM changes and mean body weight changes over time per treatment arm and for the total group. *Figure* 2C and 2D display the modelled mean SMM and body weight changes for a subgroup of patients that were sarcopenic and non-sarcopenic, determined at the start of initial treatment with 6 cycles capecitabine + oxaliplatin + bevacizumab. CAP-B, capecitabine + bevacizumab.



Differences in rate of skeletal muscle mass gain during maintenance and observation treatment

For the subgroup of 104 patients with extra SMM measures at 9 and 18 weeks after randomization, the change in SMM over time did not significantly differ between patients randomized to maintenance CAP-B or observation ($p_{interaction}$ treatment arm * time = 0.84). For both arms, we observed a steep increase in SMM gain during the first 9 weeks after randomization [SMM maintenance +1.09 kg (95% CI 0.71; 1.46) and observation +0.97 kg (95% CI 0.57; 1.38)]. Consecutively, between 9 and 18 weeks after randomization, SMM gain stabilized [maintenance +0.06 kg (95% CI −0.32; 0.43) and observation +0.01 kg (95% CI −0.43; 0.40)].

Correlation skeletal muscle mass change and body weight change

Correlations were calculated for the group of patients with available measurements on both SMM change and body weight change at the start and the end of any of the investigated time periods. We found a significant correlation between SMM change and body weight change during the first 6 cycles of initial CAPOX-B treatment (Pearson Men 0.51, $P < 0.01$ and Women 0.25, $P = 0.01$) and during maintenance and observation treatment (Pearson Men 0.25, $P = 0.002$ and Women 0.43, $P = 0.002$). Between PD1 and PD2, during reintroduction treatment with CAPOX-B or other treatment, a significant correlation was observed only for females (Pearson Men −0.07, $P = 0.46$ and Women 0.28, $P = 0.02$).

Discussion

This large longitudinal study provides a unique insight in the SMM changes of mCRC patients during various palliative systemic treatment regimens, including observation. We found that SMM loss during initial treatment with 6 cycles CAPOX-B was reversible during subsequent less intensive maintenance treatment with CAP-B or during observation. After reintroduction of more intensive treatment (CAPOX-B or other systemic treatment), SMM again decreased. Hence, rather than a continuous process, SMM loss in the palliative setting appears to be reversible and to be influenced by the intensity of systemic treatment. In addition, we found that the changes in SMM are not reflected by the observed changes in body weight. This is in agreement with previous studies that state that body weight and BMI are not appropriate tools to understand the effect of systemic treatment on body composition.[4,6]

Our results provide relevant information for patients with mCRC and cancer (treatment) related SMM loss. Previously, several studies found a strong link between sarcopenia, SMM loss, and poor outcome, whereas others did not.[11,15,17–22] Possible explanations are the heterogeneity in time points during the course of the disease that previous studies used when determining SMM and/or the heterogeneity of treatment regimens. Furthermore, most studies quantified SMM at one time point (usually pre-treatment), and some investigated muscle changes between two time points during the course of the disease. This is the first study to investigate SMM changes on multiple time points during consecutive concomitant systemic treatment regimens. An important finding is that mCRC patients, including sarcopenic patients, have the capability to gain SMM while receiving systemic treatment. Multiple possible factors could have influenced this observed SMM gain. SMM loss during initial treatment could be an effect of the administration of oxaliplatin and its side effects, which include reduced nutritional intake and reduced physical activity. These side effects are less likely to occur during less intensive maintenance treatment or observation.[23] Furthermore, there is evidence from pre-clinical and murine studies that oxaliplatin may promote skeletal muscle damage, for example, by targeting mitochondria.[24,25] Unfortunately, no data on lifestyle factors are available from the CAIRO3 study. An interesting next step will be to investigate whether interventions, such as nutritional and exercise interventions, which have the potential to counteract the SMM loss during intensive treatment and support potential gain during less intensive treatment, also result in improved outcome of treatment. A gain in SMM has recently be shown in nutritional intervention studies in which protein and/or omega 3 fatty acids enriched high energy were added to the diet of non-small cell lung carcinoma patients,[26–28] and in an exercise intervention study performed during chemotherapy for breast cancer, a significant increase of muscle strength was observed in the intervention group.[29] Especially, a multimodal approach in which nutrition and exercise are combined might provide a promising future strategy to prevent SMM loss and subsequent reduced treatment outcomes.[30]

We found no statistical significant differences in SMM changes between patients in the maintenance and the observation arm, neither for the SMM change during different treatments in the total group of patients nor for the rate of SMM changes during the first 9 and 18 weeks of maintenance and observation treatment in a subgroup of 104 patients. This implies that the numerical extra SMM gain in patients on maintenance treatment as compared with observation is most likely caused by the longer time to progression in the maintenance arm. This observation strengthens our hypothesis that oxaliplatin may potentially drive muscle loss and sarcopenia.

In advanced cancer patients, muscle wasting may develop through different stages of anabolic resistance, and refractory catabolism is most likely to occur during end-stage progressive disease.[5,10] The presence of sarcopenia therefore might reflect a status in which patients are less likely to gain SMM. Interestingly, sarcopenic and non-sarcopenic patients showed comparable overall patterns of muscle change over time (gain and loss). Another important finding was that throughout the follow-up period of CAIRO3, we observed a small or no correlation between body weight changes and SMM changes. Even more, from initial treatment until PD2, patients on average gained body weight, whereas SMM decreased. Furthermore, patients were on average overweight (BMI $\geq$26 kg/m^2), also in the subgroup of sarcopenic patients. This indicates once more that a stable body weight is not very informative on SMM loss and might potentially wrongly reassure clinicians. CT scan images allow an early identification of SMM wasting, which facilitates the use of experimental therapeutic interventions that aim to maintain or improve SMM.

The strength of this study is that we analysed SMM in a large and homogeneous population of mCRC patients using CT scan data of multiple time points from a prospective randomized phase 3 trial. This provided high-quality data for the comparison of SMM changes during different treatment regimens, including observation.

We are aware of several limitations of this study. Firstly, this concerns the amount of missing data. In our analysis, we used a mixed model analysis, which reliably accounts for missing data when missing is unrelated to the outcome. Patients in whom a CT scan was not available due to death or discontinuation of systemic treatment at PD1 and PD2 could not be incorporated in this analysis. This may have caused a selection bias. Secondly, CAIRO3 excluded patients who demonstrated disease progression or unacceptable toxicity during the initial treatment; therefore, a poor prognostic group of patients was not included in this study. Thirdly, we used a two-dimensional method to quantify SMM changes over time, which may have resulted in measurement errors as a result of variance in the positioning of patients during the different consecutive CT scans. We used a software tool (MeVis Medical Solutions AG, Fraunhofer MEVIS, Bremen, Germany) to rotate and fuse the CT scans of individual patients to reduce these measurement errors. A three-dimensional method using multiple slices or whole abdomen or whole body CT scans to quantify SMM would further improve accuracy, but this is a time-consuming method, and fully automated software for SMM analysis on more than one slice is not available. The lack of a fully automated three-dimensional analysis was also the reason why we did not incorporate fat measurements in our study. During our analyses, we observed that single slice repeated fat measurements were highly influenced by the positioning of the organs (e.g. bowel extension) and measurement of

changes in fat tissue deemed as not reliable. Lastly, no consensus for sarcopenia cut-off points exist, which complicates cross-study comparisons. Commonly used definitions for sarcopenia in literature are those published by Martin *et al*.[6] and Prado *et al*.[7] They defined sarcopenia based on cut-off points for SMI that were associated with reduced survival times in normal and overweight North American advanced cancer populations. Previously, it has been questioned whether these cut-off points are generalizable to other ethnicities.[31–33] In addition, average Western Europeans are taller and less overweight compared with North Americans, and low SMM in Western European patient cohorts was not always associated with treatment-related toxicities and reduced overall survival times.[15] Recently, new sarcopenia definitions in stages I–III of CRC patients have been proposed,[34] but further large-scale studies are warranted to reach consensus on definitions of sarcopenia in European populations of mCRC patients.

In conclusion, this longitudinal study provides insight in SMM changes during different palliative systemic treatment regimens in mCRC patients. Our data show that muscle loss is reversible and may be influenced by the intensity of treatment. Although studies have shown prognostic capacity for SMM, the effect of subsequent changes in SMM on treatment outcome is unknown and may be clues for new future interventions, including nutritional and/or exercise interventions.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 baseline characteristics of the subgroup of 104 patients with skeletal muscle mass assessment at 9 and 18 weeks.

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