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The association between changes in muscle mass and quality of life in patients with metastatic colorectal cancer

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Abstract

Background Skeletal muscle mass (SMM) loss is common in metastatic colorectal cancer (mCRC) patients and associated with poor clinical outcomes, including increased treatment-related toxicities and reduced survival. Muscle loss may contribute to reduced health-related quality of life (HRQoL), including fatigue. Our aim was to study associations between changes in SMM and concomitant changes in patient-reported HRQoL.

Methods This was a secondary analysis of mCRC patients in the CAIRO3 randomized clinical trial who were—after initial treatment—randomized between maintenance treatment with capecitabine plus bevacizumab (CAP-B) and observation until first disease progression (PD1). Included patients had computed tomography images for SMM quantification, together with HRQoL assessments available at randomization and PD1. Changes in SMM (categorized as >2% loss, stable, and >2% gain) and HRQoL were computed between randomization and PD1. Changes in HRQoL score >10 points were considered clinically relevant. Associations between SMM and HRQoL changes were studied by multiple linear regression models. We also investigated whether associations differed by treatment arm for global health and the 13 other HRQoL subscales.

Results Of 221 patients included (mean age 63.5 ± 8.4 years), 24% lost, 27% remained stable, and 49% gained SMM. At randomization, mean global health status was 73.5 ± 15.9 in the CAP-B arm and 75.1 ± 17.5 in the observation arm (P = 0.48). A stable or gain in SMM was significantly associated with a clinically relevant improvement in global health status (9.9 and 14.7 points, respectively), compared with patients who lost SMM. From the subscales that did not show significant differences between the two treatment arms, we found significant and clinically relevant associations for stable or gain in SMM with improved role functioning (12.0 and 17.9, respectively) and with less fatigue (−10.0 and −15.0, respectively) and pain (−16.3 for SMM gain). From the subscales that did show significantly different associations with SMM between the two treatment arms, we only found significant results in the observation arm. Here, associations were found for stable or gain in SMM with clinically relevant improved physical (12.4 for SMM gain), cognitive (10.7 and 9.7, respectively), and social functioning (15.5 and 15.6, respectively) as well as reduced appetite loss (−28.5 and −30.7, respectively).

Conclusions In mCRC, SMM preservation during CAP-B and observation treatment is associated with significant and clinically relevant improvements in global health status and multiple functional and symptom scales. Studies are warranted to investigate whether interventions targeting SMM lead to improved HRQoL, fewer symptoms, and better functioning.

Keywords Skeletal muscle mass; Quality of life; Metastatic colorectal cancer; Supportive care

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Background

In approximately 20% of the patients with colorectal cancer, metastases are present at diagnosis, and another 20% of patients will eventually develop metachronous metastases.[1,2] For the treatment of unresectable metastatic colorectal cancer (mCRC), chemotherapy, radiation therapy, and biologically targeted therapies may be given alone or in combination to relieve symptoms and prolong survival. During these treatments, clinicians aim to minimize patients' side effects to maintain physical functioning and quality of life. In research, quality of life is often assessed and expressed as health-related quality of life (HRQoL), which focuses on the impact of (physical or mental) health on a person's ability to live a fulfilling life. Extensive knowledge on potentially modifiable factors related to HRQoL during palliative systemic therapy can contribute to the development of strategies that potentially have a positive influence on HRQoL. This is especially important given the slow but steady improvements in median survival of patients with mCRC.[2]

Advanced cancer is associated with metabolic reprogramming and reduced food intake, which are two main drivers of cancer-associated cachexia. This phenomenon is characterized by an ongoing loss of skeletal muscle mass (SMM), independent of fat mass, that cannot be reversed by conventional nutritional support and leads to functional impairment.[3–5] The presence of cancer-associated cachexia in conjunction with often low levels of physical activity can enhance the ongoing loss of muscle mass. In patients with mCRC, malnutrition and SMM loss are highly prevalent.[6,7] In the oncology setting, the analysis of routine computed tomography (CT) images is the preferred method to measure SMM and its changes over time.[8] Based on this approach, cross-sectional studies indicate that low SMM (sarcopenia) at start of treatment is associated with poor outcomes of systemic treatment in various cancers, including mCRC.[6,9,10] Furthermore, SMM loss is associated with poor outcomes including reduced overall survival, increased treatment-related toxicities, and progressive functional impairment.[4,11–14] This is in line with our previous findings from the same population used for the current analysis, because we observed that during capecitabine plus bevacizumab (CAP-B) treatment and observation, mCRC patients had the ability to gain muscle mass.[15] We also found that muscle loss occurring during CAP-B treatment and observation was associated with reduced survival[16] and with increased treatment-related toxicities.[17] Additionally, loss of SMM may influence muscle function, possibly leads to loss of strength and increased disability, and thus potentially affect HRQoL.

Few studies have investigated the relation between SMM and HRQoL in cancer patients.[18–22] Three previous cross-sectional studies in patients with advanced cancer showed that higher levels of SMM at diagnosis or before start of palliative chemotherapy were associated with less cancer-related fatigue and better physical functioning, role functioning, and global quality of life.[18–20] In a small cross-sectional study with stage IV CRC patients, low SMM before start of chemotherapy was negatively associated with physical functioning, but not with other HRQoL outcomes.[21] Another recent study in stage I–III CRC survivors found no significant associations between SMM at diagnosis and long-term HRQoL outcomes.[22] Although disease progression and oncologic treatment likely impact both SMM change[14,15] and HRQoL,[23] none of the studies investigated longitudinal changes in muscle mass and the association with HRQoL changes during systemic treatment for mCRC. Therefore, our objective was to investigate whether changes in SMM are associated with concomitant changes in HRQoL in mCRC patients, and we hypothesized that maintenance or gain of SMM during either CAP-B and observation treatment is associated with an improvement in HRQoL.

Methods

The current analysis is a post hoc secondary analysis from the CAIRO3 study, a phase III randomized controlled trial of the Dutch Colorectal Cancer Group that investigated the effect of maintenance treatment with CAP-B versus observation in previously untreated mCRC patients who achieved stable disease or better (i.e. partial or complete response) after six cycles of initial treatment with capecitabine, oxaliplatin, and bevacizumab (CAPOX-B).[24] Main inclusion criteria were histological proof of colorectal cancer, unresectable metastatic disease, and World Health Organization performance status 0 or 1. On first progression of disease (defined as PD1), patients in both groups were to receive CAPOX-B reintroduction until second progression, which was the study's primary endpoint. The CAIRO3 study was approved by the Committee on Human-Related Research Arnhem-Nijmegen and by the local institutional review boards. CAIRO3 is registered with ClinicalTrials.gov number NCT00442637. Written informed consent was obtained from all participants, and research was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Patients

Of the total 558 randomized CAIRO3 patients, 221 patients were analysed, of whom both HRQoL and SMM data were available at randomization and PD1 (*Figure* 1).

Measurements

Data were prospectively collected from patients at each medical visit either as part of their routine medical care or for

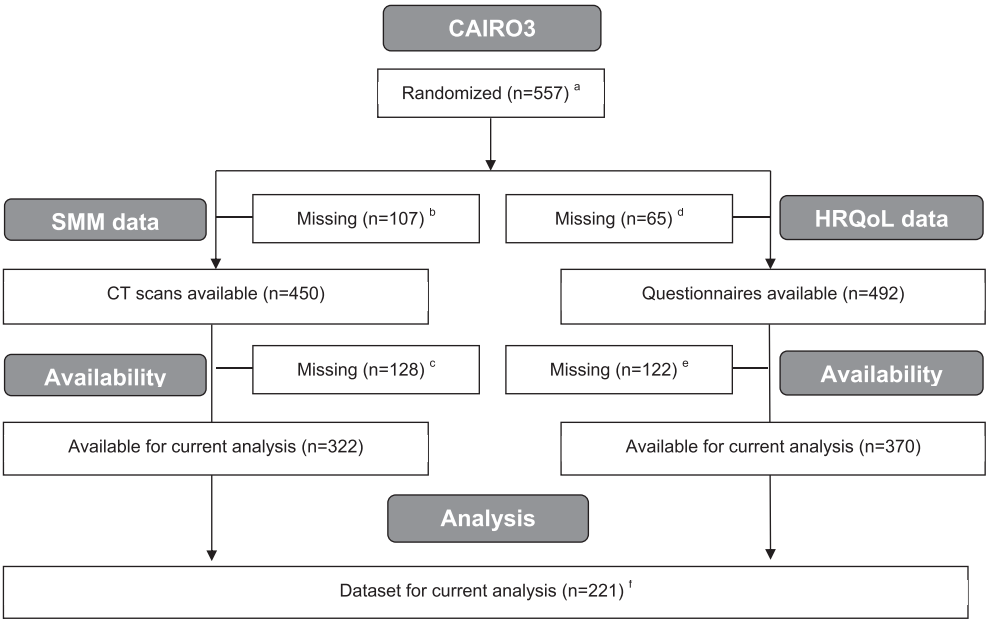

Figure 1 Flow diagram of the selection of individuals for the current analyses. [a]One participating patient revoked informed consent. [b]No CT scans available from nine participating hospitals, due to logistic reasons. [c]No CT scan at randomization and/or PD1 {reasons: non-evaluable, i.e. incomplete depiction of skeletal muscle at L3, stoma through muscle layer at L3, scan of insufficient quality [*n* = 114 (89%)] or patient did not reach PD1 yet [*n* = 10 (8%)] or patient deceased before CT was made [*n* = 4 (3%)]}. [d]Reason: questionnaires not sufficiently completed. [e]Reasons for no data at PD1: no more questionnaires returned after baseline, patient did not reach PD1 yet, or unknown. [f]The final dataset is based on combined SMM and HRQoL data (*n* = 322 and *n* = 370, respectively) and contains data from 221 patients, as the available SMM and HRQoL data do not necessarily include the same patients. CT, computed tomography; HRQoL, health-related quality of life; L3, third lumbar vertebra; PD1, first progression of disease; SMM, skeletal muscle mass.

study purposes. Data managers of The Netherlands Comprehensive Cancer Organisation (IKNL) extracted the data from medical records and also performed data monitoring.

Health-related quality of life

In CAIRO3, HRQoL was measured using the validated European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30, version 3.0)[25,26] to assess differences over time, between, and within study groups. This questionnaire is used to evaluate patients' global health, daily functioning, and complaints of common symptoms. A detailed description of HRQoL scales from the EORTC QLQ-C30 can be found in Supporting Information, *Table S3*. Patients were asked to complete the questionnaire at randomization, and every 9 weeks post-randomization until PD1. For this analysis, we used 14 HRQoL scores from the EORTC QLQ-C30, including global health status (score composed of two items, both with a 7-point ordinal scale ranging from 'very poor' to 'excellent'). Five functional scales (physical, role, emotional, cognitive, and social functioning: five, two, four, two, and two items, respectively), three multi-item symptom scales (fatigue, nausea and vomiting, and pain: three, two, and two items, respectively), and five single-item symptom scales (dyspnoea, insomnia, appetite loss, constipation, and diarrhoea) all use a 4-point ordinal scale ranging from 'not at all' to 'very much'. Raw scores for multi-item scales were calculated by taking the average of the contributing items. Linear transformation was used to standardize the raw scores to scores ranging from 0 to 100, where a higher score represents a higher ('better') level of functioning or a higher ('worse') level of symptoms.[27] Changes of 10 points or more are considered to be clinically relevant[28] and as such, perceptible to patients.

Skeletal muscle

Computed tomography scans were routinely made every 9 weeks (every three cycles) or at any time when disease progression was suspected based on clinical symptoms until the end of the study to evaluate disease progression according to RECIST criteria.[29] Using CT images acquired during routine care is a precise approach to quantify specific tissues and to predict whole body composition.[30] For the current analysis, we used CT scans at the time of CAIRO3 randomization and at the time of PD1 to quantify the change in muscle mass from start to end of maintenance and observation treatment. A single slice was selected to measure the skeletal muscle area (SMA; in cm^2) by using the third lumbar vertebra (L3) as a landmark, because of its high correlation with whole body muscle mass.[30,31] SMA at L3 consists of the entire cross-sectional area of skeletal muscle (i.e. musculus rectus abdominis, transversus, obliquus internus, obliquus externus, psoas major en minor, erector spinae, and quadratus

lumborum) and was measured by a trained and blinded researcher (S.A.K.) using Slice-O-Matic software (version 5.0; Tomovision, Magog, Quebec, Canada). The second scan of each patient was aligned to the first scan using a rigid fusion method to reduce measurement error due to variation in positioning of patients during the consecutive CT scans, as described in detail elsewhere.[15] For tissue demarcation, predetermined thresholds of Hounsfield unit ranging from −29 to +150 HU for muscle tissue were applied.[32,33] A random sample of 140 slices was analysed twice by the same researcher and another time by a second trained researcher (J.W.G.D.), during which both analysts were blinded for patient study ID and the outcome of the first measurement. Mean coefficients of variation were 1.7% and 1.2% for inter-observer and intra-observer variation, respectively, which are consistent with published data.[34] To estimate total body SMM, generally accepted regression equations were used[31]:

$$\text{Skeletal Muscle Volume (L)} = 0.166\ \text{L/cm}^2 \times \text{Skeletal Muscle Area in cm}^2 + 2.142\ \text{L},$$

$$\text{Skeletal Muscle Mass (kg)} = \text{Skeletal Muscle Volume in L} \times 1.06\ \text{g/cm}^3.$$

Percentages of SMM change between randomization and PD1 were calculated. A measurement error of 2% was adopted based on previously reported accuracy of CT for SMM analysis.[30] Therefore, changes in SMM were categorized into SMM loss (>2% loss), SMM stable (≤2% loss–≤2% gain), or SMM gain (>2% gain).

Statistical methods

Descriptive statistics (mean with standard deviation, or median and interquartile range, as appropriate) were used to describe patient characteristics. Paired samples *t*-tests were used to study the HRQoL and SMM changes. To test whether demographic and clinical patient characteristics were different between CAIRO3 patients included in the present analyses vs. those who were not included, we used the independent samples *t*-test, χ^2 test, or Kruskal–Wallis test, as appropriate. After checking the model assumptions, multivariable linear regression analyses were used to assess the association between categorized change in SMM [loss (>2%), stable (≤2% loss–≤2% gain), and gain (>2%)] and concomitant change in HRQoL scales. Multivariable regression analyses were adjusted for the potential confounders' age (years), sex (male vs. female), treatment arm (observation vs. CAP-B), World Health Organization performance status (0 vs. 1), time from randomization to PD1 (days), abnormal

Table 1 Demographic and clinical patient characteristics

Characteristics	All analysed patients *n* (%)	>2% loss SMM *n* (%)	Stable (≤2% loss–≤2% gain) SMM *n* (%)	>2% gain SMM *n* (%)
Number of patients	221	53 (24)	60 (27)	108 (49)
Age (years)				
Mean	63.5	64.7	62.8	63.3
SD	8.4	6.6	9.2	8.8
Sex				
Male	142 (64)	36 (68)	36 (60)	70 (65)
Female	79 (36)	17 (32)	24 (40)	38 (35)
World Health Organization performance status				
0	132 (60)	33 (62)	38 (63)	61 (56)
1	89 (40)	20 (38)	22 (37)	47 (44)
Treatment arm				
Maintenance (CAP-B)	103 (47)	29 (55)	25 (42)	49 (45)
Observation	118 (53)	24 (45)	35 (58)	59 (55)
Time to PD1 (months)				
Maintenance				
Median	10.6	11.2	6.3	8.4
IQR	4.2–17.0	7.5–17.4	2.3–17.3	4.1–13.7
Observation				
Median	4.3	4.4	4.1	4.6
IQR	3.1–6.5	3.6–7.9	2.1–6.5	3.6–6.2
Prior adjuvant chemotherapy				
Yes	74 (33)	18 (34)	19 (32)	37 (34)
No	147 (67)	35 (66)	41 (68)	71 (66)
Response to induction treatment				
SD	73 (33)	19 (36)	15 (25)	39 (36)
PR/CR	148 (67)	34 (64)	45 (75)	69 (64)
Abnormal serum LDH				
Yes	117 (53)	29 (55)	29 (48)	59 (55)
No	104 (47)	24 (45)	31 (52)	49 (45)

CAP-B, capecitabine plus bevacizumab; CR, complete response; IQR, interquartile range; LDH, lactate dehydrogenase; PD1, first progression of disease; PR, partial response; SD, stable disease; SMM, skeletal muscle mass.

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serum lactate dehydrogenase level at randomization (LDH; no vs. yes), previous adjuvant chemotherapy (no vs. yes), best response to initial treatment with CAPOX-B (partial or complete response vs. stable disease), and hospital (number). From these models, we report the beta coefficients of the SMM change and corresponding 95% confidence intervals (CIs) for each HRQoL scale.

To investigate whether the association between SMM and HRQoL differed between treatment arms, we tested the interaction terms 'SMM change category multiplied by treatment arm' for global health status and all 13 other HRQoL subscales. We performed and present analyses stratified according to treatment arm when the interaction term was statistically significant. Akaike's Information Criteria (AIC)[35] with small sample adjustment (AICc)[36] was used to compare models in terms of their relative goodness of fit (using Occam's razor principle).[37] All *P*-values were two-sided, and interpretation of the 95% CI was used to determine statistical significance (significance level 0.05). Statistical analyses were performed using SPSS (version 24.0; SPSS, Chicago, IL).

Results

Patient characteristics

From the CAIRO3 study (n = 557), a subgroup of 221 patients were included in the current analysis. Patients in this analysis did not differ from patients that were not included (i.e. no CT scan or HRQoL data available), in terms of demographic and clinical patient characteristics ($P > 0.05$). The flow diagram in *Figure* 1 shows the number of participants reporting HRQoL at baseline and at PD1, as well as the availability of CT scans [reasons for no CT scan: non-evaluable (89%), patient did not reach PD1 yet (8%), and patient deceased before CT was made (3%)]. Demographic and clinical characteristics of the patients are summarized in *Table* 1. The mean age was 63.5 ± 8.4 years, 64% of the patients were men, and 47% received maintenance treatment (CAP-B). The median follow-up time (time from randomization to PD1) was 10.6 months (interquartile range: 4.2 to 17.0) in the maintenance group and 4.3 months (interquartile range: 3.1 to 6.5) in the observation group.

Descriptive statistics on skeletal muscle mass and health-related quality of life

In the total group, 24% of patients lost, 27% remained stable, and 49% gained SMM (*Table* 1). On average, patients in the maintenance and observation arm gained 0.4 kg (95% CI: 0.0 to 0.8 kg) and 0.5 kg (95% CI: 0.3 to 0.8 kg) SMM, respectively. Mean global health status at randomization was 73.5 ± 15.9 for patients in the maintenance arm and 75.1 ± 17.5 for patients in the observation arm (P = 0.48). Other mean HRQoL scores at randomization were also comparable between both arms (Supporting Information, *Table S1*), except for patients in the maintenance arm who reported slightly higher levels of appetite loss at randomization as compared with patients in the observation arm (17.2 ± 25.5 and 10.6 ± 20.4, respectively). We did not observe relevant differences in changes of HRQoL scores from randomization to PD1 between treatment arms (Supporting Information, *Table S1*).

Associations between change in skeletal muscle mass and change in health-related quality of life (Figures 2 and 3)

In terms of the subscale reflecting the patients' overall quality of life, a stable SMM was associated with an increase in global health of 9.9 points (95% CI: 2.4 to 17.5), compared with SMM loss. An increase in SMM was associated with a 14.7 point (95% CI: 8.0 to 21.4) increase in global health, compared with SMM loss. Both were statistically significant and clinically relevant. These associations did not differ between treatment arms. Interestingly, change in SMM was the only significant factor related to changes in overall quality of life (see Supporting Information, *Table S2* for the full model).

For 9 of the 13 remaining subscales, we also observed no significant differences between the two treatment arms. Of these subscales, role and emotional functioning, fatigue, nausea and vomiting, pain, and diarrhoea showed improvements when SMM remained stable or increased. Specifically, role functioning [12.0 points (95% CI: 2.2 to 21.7) for stable and 17.9 points (95% CI: 9.4 to 26.5) for gain in SMM], fatigue [−10.0 points (95% CI: −17.4 to −2.5) for stable and −15.0 points (95% CI: −21.6 to −8.5) for gain in SMM], and pain [−16.3 points (95% CI: −24.6 to −8.1) for gain in SMM] were observed to be statistically significant and clinically relevant.

For four subscales (physical, cognitive, and social function and appetite loss), we found significantly different associations between the two treatment arms ($P_{\text{interactions}} < 0.05$). In the observation arm, statistically significant and clinically relevant associations were found for improved physical functioning [12.4 points (95% CI: 3.8 to 20.9) for gain in SMM], cognitive functioning [10.7 points (95% CI: 3.2 to 18.2) for stable and 9.7 points (95% CI: 2.8 to 16.6) for gain in SMM], and social functioning [15.5 points (95% CI: 5.8 to 25.2) for stable and 15.6 points (95% CI: 6.7 to 24.5) for gain in SMM] and reduced appetite loss [−28.5 points (95% CI: −42.5 to −14.5) for stable and −30.7 points (95% CI: −43.6 to −17.9) for gain in SMM]. The association between stable SMM and improved physical functioning showed a trend towards significance [9.2 points (95% CI: −0.1 to 18.6)]. In patients receiving maintenance therapy, no statistically significant relations were observed.

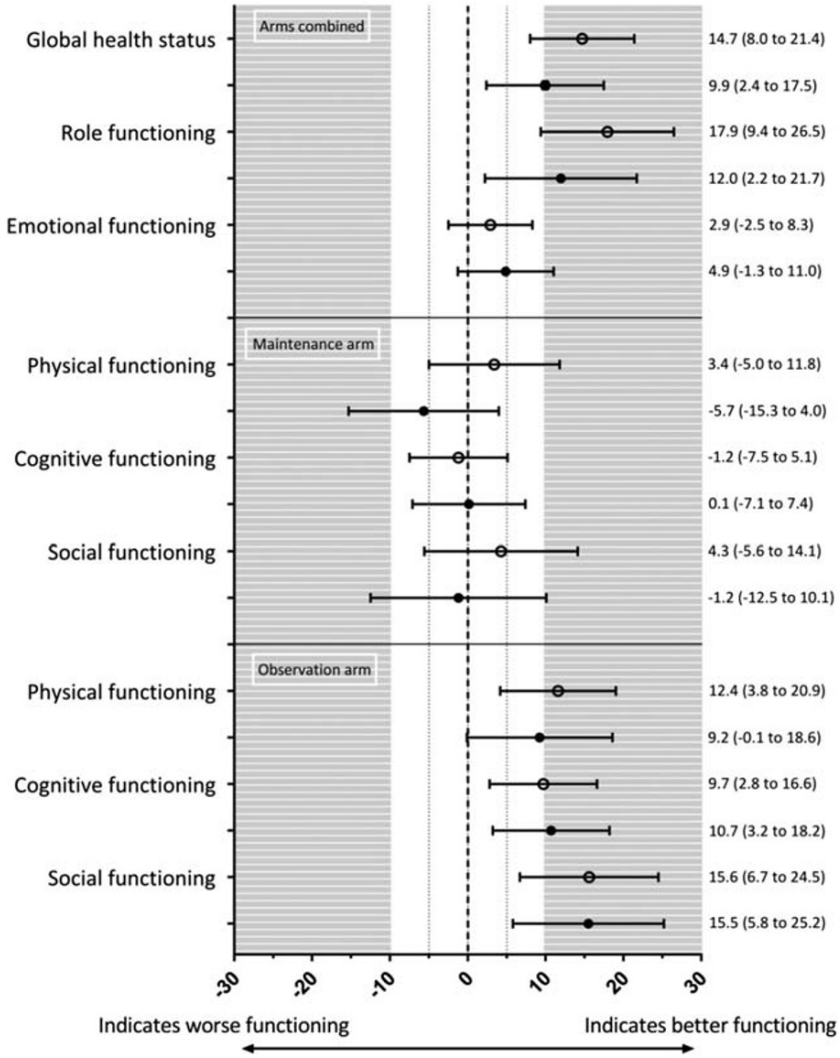

Figure 2 Associations between stable (solid circles) or gain in SMM (open circles) vs. loss of SMM (reference) and change in global health status and functional subscales of HRQoL, for both CAIRO3 arms combined or stratified by treatment arm in case of a significant interaction (n = 221). Results from a multivariable linear regression analysis, which highlight the change in HRQoL scores for patients with stable SMM and patients who gained SMM. Grey zones show the cut-off for clinically relevant (i.e. ≥10 points) changes. Models were adjusted for age, sex, treatment arm, World Health Organization performance status, time to PD1, LDH at randomization, previous adjuvant chemotherapy, response to induction treatment, and hospital. Treatment arm was taken out of the model when stratified on treatment arm. This stratification is based on the relative goodness of fit (AICc) of the model with vs. without the interaction terms. Change scores are shown as means with 95% confidence interval. Confidence intervals not including 0 ($P < .05$) are considered statistically significant. HRQoL, health-related quality of life; LDH, lactate dehydrogenase; PD1, first progression of disease; SMM, skeletal muscle mass.

Discussion

This is the first study that investigates the relationship between changes in SMM and associated changes in patient-reported HRQoL in patients with mCRC. We found that on average SMM increased in both the maintenance and observation arm. This increase may be influenced by the intensity of systemic regimens (i.e. after initial treatment patients switched to a lighter maintenance treatment without oxaliplatin or no treatment).[15] Regarding patients' overall health and quality of life, we found that preserving muscle mass (i.e. stable or gain of SMM), compared with muscle loss during treatment with CAP-B and during observation as well, was associated with a significant and clinically relevant improvement in global health status. In addition, independent of treatment arm, we observed stable or gain of SMM to be significantly associated with a clinically relevant improvement of role function and decrease of fatigue and pain. Significant and clinically relevant associations of stable or gain of SMM with improvements in physical, cognitive, and social function and decrease of appetite loss were only observed in the observation arm and not in the maintenance arm. This

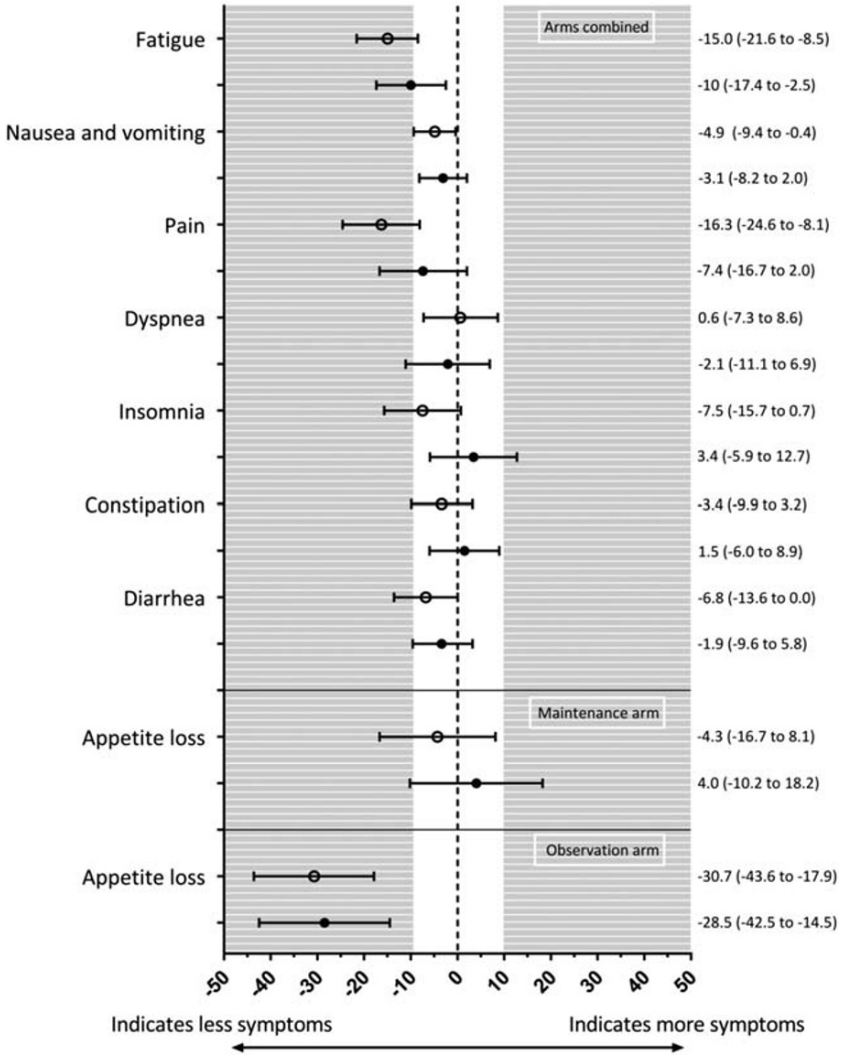

Figure 3 Associations between stable (solid circles) or gain in SMM (open circles) vs. loss of SMM (reference) and change in symptomatic aspects of HRQoL, for both CAIRO3 arms combined or stratified by treatment arm in case of a significant interaction (n = 221). Results from a multivariable linear regression analysis, which highlight the change in HRQoL scores for patients with stable SMM and patients who gained SMM. Grey zones show the cut-off for clinically relevant (i.e. ≥10 points) changes. Models were adjusted for age, sex, treatment arm, World Health Organization performance status, time to PD1, LDH at randomization, previous adjuvant chemotherapy, response to induction treatment, and hospital. Treatment arm was taken out of the model when stratified on treatment arm. This stratification is based on the relative goodness of fit (AICc) of the model with vs. without the interaction terms. Change scores are shown as means with 95% confidence interval. Confidence intervals not including 0 ($P < .05$) are considered statistically significant. HRQoL, health-related quality of life; LDH, lactate dehydrogenase; PD1, first progression of disease; SMM, skeletal muscle mass.

may indicate that these factors are strongly related to treatment with CAP-B.

For several HRQoL subscales, we observed significantly different associations with SMM changes. Frequent side effects of CAP-B include gastrointestinal toxicities such as abdominal pain, diarrhoea, and stomatitis, as well as anorexia (appetite loss), fatigue, hand–foot syndrome, and neuropathy,[38] which may have an impact on the relation between muscle mass and HRQoL. Indeed, for appetite loss, treatment arm was found to be an effect modifier. Patients in the observation arm with stable or gain in SMM reported a substantial reduction (approximately 30 points) in appetite loss compared with patients with SMM loss. In contrast, patients in the maintenance arm with stable or gain in SMM did not report a change in appetite loss in the period from randomization to PD1 compared with patient with SMM loss. Additionally, the relation between SMM change and several functional scales seems to be affected by concurrent treatment. Preservation of muscle mass was significantly associated with a clinically relevant improvement in physical, cognitive, and social functioning for patients in the observation arm but not for patients receiving maintenance therapy.

In previous studies in patients with advanced cancer, higher amounts of muscle mass at diagnosis[18,19] or at start

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of chemotherapy[21] were found to be associated with better physical functioning. In our study, however, stable or gain in SMM was not associated with improved physical functioning in patients who received maintenance treatment. Interestingly, for the symptoms, fatigue and pain, which are frequent side effects of CAP-B treatment, we did not find a significant difference in the association of muscle mass changes and HRQoL scales between maintenance treatment and observation. This is of special interest, because both pain and fatigue are known to be independent predictors of survival in different cancer populations.[39]

Our study differs in design and outcome with a previously published study in 28 stage IV mCRC patients.[21] In that study, a single CT scan was used to assess the relation between muscle mass and HRQoL at start of chemotherapy, but HRQoL assessment was performed using the same EORTC quality of life questionnaire as in our study. After adjusting for gender, they reported an association between low muscle mass and lower physical functioning but not with other HRQoL subscales. In our study, using two repeated measures of SMM and HRQoL in a larger sample size, we provide information about how changes in SMM are related to patients' HRQoL. However, given the observational design, we can only report associations and cannot disentangle the direction of the relationships.

This analysis contributed to the identification of a potentially modifiable factor related to patients' HRQoL, which is valuable input to future intervention studies aiming to improve clinical outcomes. Studying the effects of interventions, for example, physical exercise programmes and/or nutritional support (e.g. high-energy/high-protein/omega-3 polyunsaturated fatty acids containing oral nutritional supplement) prior to or during first-line treatment, will provide insight into the potential causality of associations between body composition parameters and HRQoL. A recent systematic review concluded that specific nutritional interventions (high-energy enriched with high-protein, n-3 polyunsaturated fatty acid-enriched) had a beneficial effect on muscle mass support and improved several aspects of HRQoL in cancer patients during chemotherapy treatment.[40] In addition, several studies have already shown that individualized dietary counselling during treatment has beneficial effects on nutritional status and HRQoL in patients with head and neck squamous cell cancer,[41] as well as in patients with colorectal cancer.[42,43] In terms of physical exercise interventions investigating HRQoL in patients with CRC, currently only patients treated with curative intent have been studied.[44–48] Research has shown inconclusive but mostly beneficial effects of physical exercise during and after treatment such as improved functional capacity and HRQoL.[44,45,49] However, the current evidence remains sparse, which highlights the need for future research.

The main limitation of this analysis, which affects most HRQoL studies, is the concern that missing data may have potentially led to biased results.[50,51] Nevertheless, approximately 75% of CAIRO3 patients who completed the HRQoL questionnaire at randomization also completed the questionnaire at PD1. Moreover, baseline characteristic of patients included in the analysis were comparable to baseline characteristics of the total CAIRO3 population. To note, this analysis was performed in mCRC patients with a good response (stable disease or better) to an intensive first-line induction treatment with CAPOX-B. This selection might restrict the generalizability to other mCRC patients. However, performing an analysis in a select group of patients can also be seen as a strength as it minimizes extraneous effects and thus, the amount of (residual) confounding.

A strength of this study is that data originated from a Dutch nationwide, clinical RCT with a homogeneous patient population.[24] Regarding the assessment methods, using CT images is a well-acknowledged, accurate, and precise quantification method to measure body composition.[8,30] Using questionnaires for the assessment of HRQoL provides the opportunity to study outcomes directly reported by the patient without interpretation by a clinician or anyone else. Additionally, it should be emphasized that the results were not just based on HRQoL changes that were statistically significant but, more importantly, on changes that were clinically meaningful. HRQoL assessment was performed using validated and widely used EORTC questionnaires,[26] which is favourable when comparing results with other (future) studies.

To conclude, our data indicate that patients with a stable or gain in SMM reported to perceive significantly and clinically relevant improved global health status and multiple functional and symptomatic aspects of HRQoL. This suggests that interventions aiming for muscle mass preservation (e.g. exercise and nutritional interventions) during treatment may provide a window of opportunity to improve HRQoL. Further studies are warranted to confirm our findings and to investigate whether interventions targeting SMM in patients with mCRC lead to improved HRQoL, fewer symptoms, and better functioning.

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Conflict of interest

B.D. and M.J. work at Nutricia Research. All other authors declare that they have no conflict of interest.

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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. Skeletal muscle mass and health-related quality of life scores at randomization, and changes from randomization to PD1, per treatment arm (n = 221).Caption: [a] Changes in muscle mass from randomization to PD1 in a subgroup of patients from the CAIRO3 study. The changes therefore differ from previously published data [15].

Table S2. Full MLR model for the associations between stable or gain in SMM (vs. loss of SMM as reference) and change in global health status, for both CAIRO3 arms combined (n = 221).Caption: In bold: covariates that showed a statistically significant association with change in global health status.

Table S3. Description of HRQoL scales from the EORTC QLQ-C30, v.3.0.Caption: The EORTC QLQ-C30 questionnaire v.3.0 consists of 30 questions. Question 28 refers to the item 'financial difficulties' which is not included in the current analysis. In CAIRO3, the Dutch translated version was used. Original EORTC manuals and guidelines can be found at: https://qol.eortc.org/manuals.

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