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# Gain of visceral adipose tissue rather than low skeletal muscle mass is associated with overall survival in patients with colorectal liver metastases; results from the NewEPOC study

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ABSTRACT

*Introduction:* Sarcopenia and adiposity at diagnosis are important prognostic factors in cancer. Ongoing changes in body composition during chemotherapy treatment may have additional prognostic relevance. This study aimed to investigate the association between body composition changes during neoadjuvant treatment and survival in patients with colorectal liver metastases.

*Materials & methods:* In this subgroup analysis of the newEPOC RCT (NCT00482222), pre- and post-treatment CT-scans of patients undergoing neoadjuvant chemotherapy for colorectal liver metastases were studied. The total cross-sectional area of skeletal muscle tissue (SM), Visceral Adipose Tissue (VAT), Subcutaneous Adipose Tissue (SAT), Intra-Muscular Adipose Tissue (IMAT), and radiation attenuation for skeletal muscle (SM-RA) were determined.

*Results:* During neoadjuvant therapy, SM-index decreased from 50.6 ± 8.7 to 47.6 ± 8.6 $cm^2/m^2$, $p < 0.001$ for men and 40.5 ± 6.1 to 37.7 ± 5.9 $cm^2/m^2$, $p = 0.002$, for women. SM-RA decreased from 37.7 ± 7.8 to 36.0 ± 7.6 HU, $p < 0.001$ for men. VAT- and SAT-indices did not change significantly during treatment. Sarcopenia, SM-loss, SM-RA as baseline as well as change in SM-RA were not associated with overall survival, while intervention arm (HR1.96, 95 %CI1.21–3.19, $p = 0.009$), undergoing resection of the metastases (HR0.19, 95 %CI0.09–0.40, $p < 0.001$) and gaining >2 % VAT-index over 12 weeks (HR2.05, 95 %CI1.12–3.76, $p = 0.025$) were.

*Conclusions:* The body composition features SM and SM-RA decreased during chemotherapy, but were not associated with survival. On the contrary, although VAT did not significantly change, the gain of VAT was an independent prognostic factor for survival. These results should be validated in independent cohorts but may indicate that in this selected patient group, adipose tissue might be a more important prognostic factor than sarcopenia.

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## 1. Introduction

Colorectal cancer is the third most common type of cancer worldwide, and the second leading cause of cancer related death [1]. Approximately 30 % of colorectal cancer patients will have metastases at presentation or will develop metastases within 5 years from diagnosis. For up to 60 % of patients, metastases will occur in the liver [2–4]. The most effective treatment for colorectal liver metastases (CRLM) is surgical resection. However, recurrence of disease occurs in approximately 75 % of patients [5],. The addition of neo-adjuvant systemic chemotherapy confers a relapse-free survival benefit as it may treat micro metastases, and avoids surgery in patients with early systemic disease progression [6,7]. However, chemotherapy may cause significant side effects including reduced liver regeneration after surgery, that can reduce overall survival [8,9]. Improved patient selection is therefore important. As an example, the Fong score is used to predict prognosis after surgical resection of CRLM([10]). However, no such scoring system for systemic therapy exists, as little is known about factors associated with survival in patients treated with systemic chemotherapy.

Low skeletal muscle mass is associated with poorer tolerance to chemotherapy and increased overall and cancer specific mortality in a number of cancers, including colorectal cancer [11–13]. Skeletal muscle mass can be determined by measuring skeletal muscle area at the level of the third lumbar vertebra (L3) on computed tomography (CT) scans [14]. However, the association between survival and skeletal muscle mass in patients with CRLM is not consistent [15,16]. Furthermore, since several studies reported that loss of skeletal muscle mass rather than low skeletal muscle mass alone is predictive of outcome in CRLM patients [17,18], changes in skeletal muscle mass rather than a single measurement may contain more prognostic information. As there is evidence that patients lose considerable muscle mass during chemotherapeutic treatment [18,19], skeletal muscle mass loss could be an important prognostic factor in patients treated with neoadjuvant chemotherapy.

In addition to skeletal muscle areas, CT-scans contain information on other body compartments such as subcutaneous and visceral adipose tissue mass (SAT and VAT respectively), and triglyceride content, measured as radiation attenuation of skeletal muscle, visceral adipose and subcutaneous adipose tissue radiation attenuation (SM-RA, VAT-RA and SAT-RA respectively). For instance, myosteatosis (increased muscle fat content) has been associated with reduced overall survival in stage IV patients undergoing partial hepatectomy [17]. In contrast to skeletal muscle, the association between adipose tissue and survival in CRLM patients is less studied. Additionally, while a systematic review showed a reduced tumor response and reduced overall survival in patients with visceral adiposity undergoing chemotherapeutic treatment or resection [20], recent papers show the opposite [17,21]. Moreover, the presence and specifically evolution of fat distribution during chemotherapeutic treatment, and its impact on overall survival in patients undergoing systemic therapy has not yet been studied.

The aim of this study was therefore to assess the association between changes in body composition during neoadjuvant treatment and survival in CRLM patients [22], using data from a prospective, randomized controlled trial, with high-quality registration of complications, treatment adherence and survival. We hypothesized that body composition changes during treatment are better prognostic factors than a single body composition measurement at diagnosis.

## 2. Materials and methods

### 2.1. Study population

This study was a post-hoc analysis of a cohort of 272 patients who were originally included in the New EPOC study [23]. The New EPOC clinical trial was a multicenter, open-label, randomized, controlled, phase 3 trial that included adult patients with *KRAS* wild-type (codons 12, 13 and 61) resectable or suboptimally resectable colorectal liver metastases and a WHO performance status 0–2. Patients were randomly assigned to receive chemotherapy with or without cetuximab before and after liver resection. Specification of the treatment regimen that these patients received can be found in the original article [22]. The study was approved by the Southwest UK Research Ethics Committee (ISRCTN22944367). Written, informed consent was obtained from all patients before random assignment.

### 2.2. Data collection and outcome measures

Patient data were collected prospectively as part of the New EPOC clinical trial [23]. Baseline characteristics were available at trial entry including height, age, BMI, sex and WHO performance status and disease stage, and were used as covariates. Patients were considered obese if they had a BMI $\geq$30, overweight if they had a BMI $\geq$25 kg/m$^2$ and underweight at a BMI $<$18 kg/m$^2$.

CT-scans were performed as part of the original clinical trial to assess Response Evaluation Criteria in Solid Tumors (RECIST, version 1.018) before start of systemic treatment and every three months for two years. Patients were included in the analysis if a CT-scan undertaken within 12 weeks prior to start of chemotherapy could be obtained from the inclusion hospital, and if this baseline CT-scan met the quality requirements as defined below (section 2.3). If available, a post chemotherapy treatment CT-scan (preoperatively) was also analyzed to assess body composition changes during chemotherapy treatment. These scans were collected retrospectively for analysis of muscle and fat areas and triglyceride content. The primary covariates were (change in) body composition variables during neoadjuvant chemotherapy. For the original cohort, median follow-up was 20.7 months (95 % CI 17.9–25.6), and median progression-free survival was 14.1 months (95 % CI 11.8–15.9).

The primary outcome was overall survival (OS), and progression free survival (PFS) was a secondary outcome. Exploratory outcomes were associations between body composition changes, treatment response (response after the end of the preoperative treatment period assessed using RECIST version 1.018([24])), treatment complications (graded using the Common Terminology Criteria for Adverse Events version 3, CTCAE, before each cycle unless there was a presentation earlier), dose changes, cycle delays, relative dose intensity (RDI). The RDI per drug and RDI for combination therapy was calculated using equation (1) for individual cytotoxics and equation (2) for combination therapy. For combination therapy with 5-fluorouracil, the RDI of bolus and infusion were combined where the bolus was considered as 1/7th part and the infusion 6/7th part (equation (2.1)).

$$RDIdrug = \frac{DDI\left(\frac{mg}{m^2}/day\right)}{SDI} \times 100\% \tag{1}$$

$$where: DDI = delivered\,drug\,intensity = \frac{delivered\,total\,dose\left(\frac{mg}{m^2}\right)}{actual\,time\,to\,complete\,treatment\,(days)} \tag{1.1}$$

$$and: SDI = standard\,dose\,intensity = \frac{planned\,total\,dose\left(\frac{mg}{m^2}\right)}{planned\,time\,to\,complete\,treatment\,(days)} \tag{1.2}$$

Equation (1)**: Relative dose intensity calculations of individual drugs.** [1] Formula for the calculation of the relative drug intensity per individual drug in the regimen. (1.1) Formula for the calculation of delivered drug intensity. (1.2) Formula for the calculation of standard dose intensity. RDI, relative dose intensity; DDI, delivered dose intensity; SDI, standard dose intensity

$$so: RDI\ combination\ therapy = \frac{RDI\ drug\ 1 + RDI\ drug\ldots + RDI\ drug\ n}{n\ drugs} \tag{2}$$

$$n.b.: RDI\ 5FU\ based\ therapy = \frac{\frac{1}{7} RDI\ 5FU\ bolus + \frac{6}{7}\ RDI\ 5FU\ infusion + RDI\ drug\ldots + RDI\ drug\ n}{n\ drugs} \tag{2.1}$$

Equation (2)**: Relative dose intensity calculations of combination treatment.** [2] General formula for the calculation of relative drug intensity for combination treatment. (2.1) Formula for the calculation of relative drug intensity of combination therapy with 5-fluorouracil. RDI, relative dose intensity; DDI, delivered dose intensity; SDI, standard dose intensity.

### 2.3. Computed tomography scan analysis

For each patient, a single CT image at the third lumbar level (L3) was obtained before and after neo-adjuvant chemotherapy treatment. Quality requirements of the CT-scans were as follows [1]: the timing between the baseline CT-scan and start of chemotherapy treatment could not be more than 12 weeks [2], the third lumbar level should be completely visible on the available CT scan [3], CT-scans had to be obtained in the portal-venous phase. Patients were excluded from the study if the baseline scan did not meet these requirements. Post-chemotherapy scans that did not meet the requirements were excluded from the analysis. The CT-scans were analyzed in anonymized format by two blinded independent researchers with a medical degree, trained in radiologic anatomy and body composition analysis. CT-scans of poor quality, missing parts of muscle tissue on the ventral, dorsal or both lateral sides, or with large radiation artefacts were excluded. The total cross-sectional area ($cm^2$) of skeletal muscle tissue (SM) (−29 to 150 HU), Visceral Adipose Tissue (VAT) (−150 to −50 HU) and Subcutaneous Adipose Tissue (SAT) (−190 to −30 HU) was determined using sliceOmatic 5.0 (Tomovision, Magog, Canada) software for windows®. In addition, the radiation attenuation for skeletal muscle (SM-RA) was assessed by calculating the average HU value of the total muscle area within the specified range of −29 to 150 HU.

The regions of interest for skeletal muscle consisted of internal and external obliques, transversus abdominus, rectus abdominus, psoas, quadratus lumborum and erector spinae muscles. For scans where muscle tissue was missing on one lateral side, the oblique and transverse abdominal muscles on this side were excluded from analysis, and total muscle tissue was calculated by multiplying the area of the other lateral muscle area by 2 and adding this to the area of the other muscles.

To evaluate inter-rater differences, thirty CT-scans were independently annotated by both researchers. Skeletal-muscle, VAT and SAT were significantly correlated with an intraclass correlation of >0.99 (see supplementary table S1). The total areas of skeletal muscle, VAT, and SAT were corrected for stature to calculate the L3-muscle index (SM-Index), L3-VAT-index (VAT-Index), and L3-SAT-index (SAT-Index) in $cm^2/m^2$ as an estimate of total body skeletal muscle, VAT, and SAT mass [14] (see equation (3)).

$$Body\ composition\ index = \frac{body\ composition\ area}{height^2} \tag{3}$$

Equation (3): Formula to calculate body composition indices and change.

As the present literature does not offer established thresholds for adipose tissue-index or radiation attenuation, and previously reported cut-off values for SM-Index and SM-RA were derived from a Canadian cohort and might not represent the current UK cohort [25,26], we divided the patients into high or low groups according to the sex-dependent median for all tissue-indices. Body composition differs between men and women. For instance, women have significantly lower skeletal muscle mass. Therefore, to be able to combine males and females in this cohort, we calculated sex-dependent z-scores. Z-scores indicate how many standard deviations a specific data point is from the mean of that dataset, and as such, each female and each male is compared to the mean of respectively the female or male patients. Cut-off values were set at z-score 0, which corresponds to the mean of the males or females in the cohort. We subsequently labeled patients with an SM-Index below the pre-chemotherapy median of their sex-group as having low muscle mass (i.e. baseline z-score <0). Z-scores were calculated using equation (4) (see equation (4)).

$$z = \frac{(X - \mu)}{\sigma} \tag{4}$$

Equation (4)**: Calculation for sex-dependent z-score for body composition.** z, z-score; X, body composition measurement (skeletal muscle-, visceral adipose tissue- or subcutaneous adipose tissue area ($cm^2/m^2$) or skeletal muscle radiation attenuation) of the patient; μ, average of the body composition measurement for males or females; σ, standard deviation of body composition measurement of all males or females.

For all L3-indices, the difference in percentage between the pre-chemotherapy and post-chemotherapy CT scan was calculated using the formula in equation (5).

$$\Delta Body\ composition = \left( \frac{CT_2 - CT_1}{CT_1} \times 100\% \right) \times (ndays)^{-1} \times 84\ days \tag{5}$$

Equation (5)**: Calculation for change in body composition measurements between the two subsequent scans** for all tissue indices (SM-index, VAT-index, SAT-index and SM-RA). $CT_1$ is the pre-chemotherapy scan and $CT_2$ is the post-chemotherapy CT scan resulting. $n_{days}$ is the number of days between the first and second scan. All values were normalized for the time between the two scans, and values were multiplied by the planned treatment duration of 84 days (12 weeks).

We used this formula to obtain all change measurements; SM-index change, SM-RA change, SAT-index change and VAT-index change. To account for measurement errors, a threshold of 2 % was adopted based on previously described accuracies for analysis of fat- and muscle tissue on CT-scans [14]. As a result, a negative Δbody composition signifies a loss in tissue area while a positive Δbody composition signifies a gain in tissue area, and a decrease in radiation attenuation signifies an increase in tissue fat content (increased myosteatosis) while an increase in radiation attenuation signifies a decrease in fat content.

### 2.4. Statistical analysis

Statistical analysis was performed using R version 4.1.3 for Windows [27]. Categorical variables were analyzed using Pearson's $\chi^2$ test or Fisher-Freeman-Halton exact test where applicable, and post-hoc tests were corrected for multiple comparisons using the Bonferroni method. Means were compared using *t*-test and medians using independent-samples median test. Repeated measurements were compared using paired samples *t*-test. For survival analysis, multiple imputation was performed to account for missing data using the mice package [28]. Predictor variables for the multiple imputation method were all variables entered into the multivariable cox regression model, as well as treatment regimen, tumor stage, KRAS status, WHO performance status and BMI. After 45 multiple imputations, Kaplan-Meier estimate and Cox regression analysis were used to assess factors associated with overall survival and progression-free survival. A multivariable model was constructed for all imputed dataset, and Backwards selection on the multivariable model was performed using the Akaike's Information Criterion (AIC). Variables selected in >50 % of the datasets were entered in the final model. The final model was established using pre-chemotherapy body composition measurements as continuous variables, after which the model was re-established using z-scores, and

change measurements as >2 % gain. These z-scores and change-groups were computed after imputation as explained above, in an "impute--then-transform" manner. Hazard ratio's and 95 % confidence intervals were calculated for the pooled results following Rubin's rules. Two-tailed *p*-values <0.05 were considered statistically significant.

## 3. Results

### 3.1. Patient cohort

The New EPOC study randomized 272 patients between February 26, 2007 and October 12, 2012, to receive treatment with chemotherapy alone, or chemotherapy with cetuximab. For 152 patients, the baseline CT-scan could be retrieved for analysis (see Fig. 1). The median interval between the baseline CT-scan and start of chemotherapy treatment was 3 weeks (IQR 4 weeks). From these 152 patients, for 123 patients a post-chemotherapy CT-scan could be used for the analysis of changes in body composition during chemotherapy treatment. Fig. 1 shows how many patients from either group were included in our study.

### 3.2. General, tumor, treatment and body composition characteristics of the whole cohort

The baseline characteristics of the 152 patients included in the study can be found in Table 1. For 18 patients, the subcutaneous adipose tissue (SAT) was not completely visualized on the pre-chemotherapy CT-scan. For 26 patients the SAT was not completely visualized on the post-chemotherapy CT scan. These patients were excluded from the analysis of SAT-index. For three patients, the abdominal muscles were not completely visualized on the pre-chemotherapy CT-scan, and for 12 on the post-chemotherapy CT scan. For these patients the skeletal muscle index was calculated as explained in section 2.3. In the pooled cohort, 70.4 % were male and the mean age was 65 years (IQR 10 years). The average BMI was 27.0 ± 4.4.Of the patients, 0.6 % were underweight (BMI <18 kg/m$^2$), 40.8 % were overweight (BMI between 25 and 30 kg/m$^2$) and 23.7 % were obese (BMI >30 kg/m$^2$). There were no significant differences in body composition at baseline between the two intervention groups of the original NewEPOC study (Supplementary Table S2).

### 3.3. Body composition changes during chemotherapy

During neoadjuvant therapy, the SM-index decreased significantly for both men and women, from 50.6 ± 9.2 cm$^2$/m$^2$ to 47.6 ± 8.6 cm$^2$/m$^2$, $p < 0.001$ and 39.6 ± 5.6 cm$^2$/m$^2$ to 37.7 ± 5.9 cm$^2$/m$^2$, $p = 0.002$, respectively (Fig. 2a and Table 2). This corresponded to a decrease in SM-Index of −4.4 ± 7.4 % and −3.9 ± 7.15 % per 12 weeks, respectively. The SM-RA decreased significantly for men with 4.8 % (±9.4 %, $p < 0.001$), but not-significantly for women (−2.5 % ± 8.7 %, $p = 0.062$) (Fig. 2b and Table 2). The VAT- and SAT-indices did not change significantly during preoperative chemotherapy treatment (Table 2 and Supplementary Figure S1).

Z-scores were used to divide patients into low- and high-body composition groups for each body composition measurement and evaluated proportions before and after treatment. None of the proportions of patients per body composition group were significantly different before or after chemotherapy treatment. Seventy-nine patients had low muscle mass at baseline. Seventeen patients lost muscle mass during chemotherapy treatment and where subsequently designated as having low muscle mass. Five patients gained muscle mass and developed high muscle mass. For VAT, 56 patients were designated as having high VAT at baseline (VAT area higher than the median of their sex-group). Seven patients gained VAT during chemotherapy treatment and were classified as high-VAT post-chemotherapy, while 3 patients lost VAT. Seventy-three patients had high SAT at baseline. Seven patients gained SAT to be classified as high SAT post-chemotherapy while 7 other patients lost SAT and were classified as low SAT. Sixty-five patients were classified as

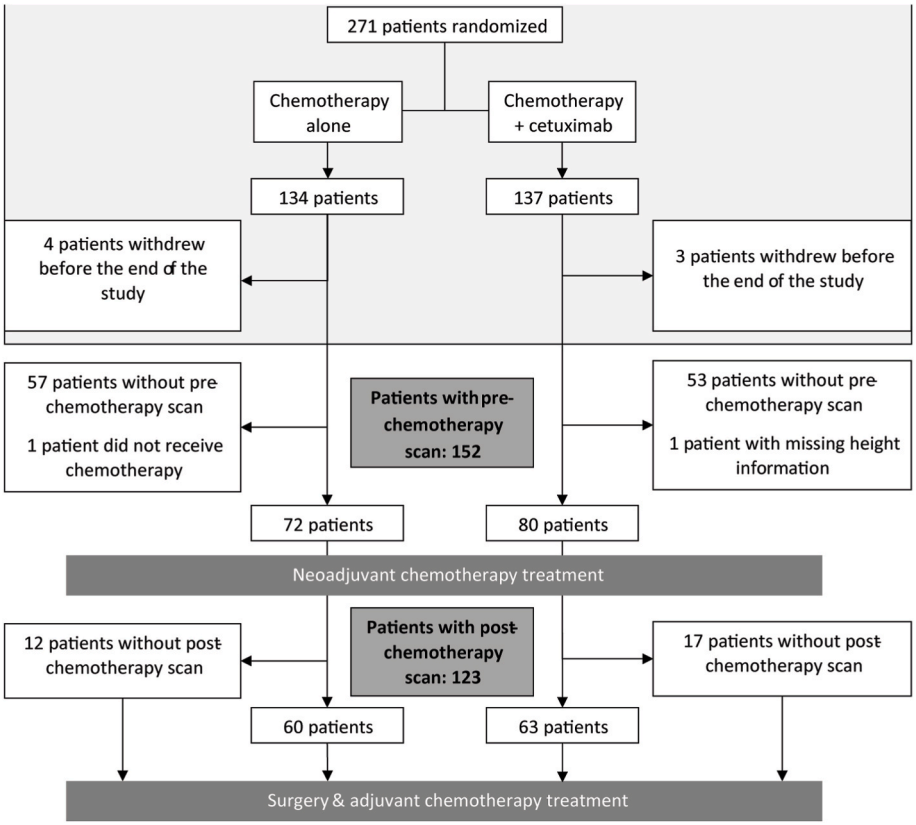


**Fig. 1.** Flow chart of the inclusion process.

**Table 1**
Baseline characteristics of the study population.

| | | Study population (n = 152) |
|---|---|---|
| *Baseline characteristics* | | |
| Sex, N (%) | Male | 107 (70.4 %) |
| | Female | 45 (29.6 %) |
| Median age, years (IQR) | | 65.0 (10) |
| Height (cm) ± SD | Male | 174.9 ± 0.7 |
| | Female | 159.9 ± 1.3 |
| Weight (kg) ± SD | Male | 82.9 ± 1.4 |
| | Female | 68.4 ± 2.1 |
| BSA ($m^2$) ± SD | Male | 1.97 ± 0.02 |
| | Female | 1.70 ± 0.03 |
| BMI ($kg/m^2$) ± SD | | 27.0 (±4.4) |
| Primary cancer site, N (%) | Right colon | 25 (16.4 %) |
| | Transverse colon | 5 (3.3 %) |
| | Descending colon | 35 (23.0 %) |
| | Sigmoid and rectosigmoid | 42 (27.6 %) |
| | Rectum | 43 (28.3 %) |
| Cancer stage, N (%) | T1 or T2 | 23 (15.1 %) |
| | T3 or T4 | 123 (80.9 %) |
| WHO performance status[a] N (%) | Grade 0 | 112 (73.7 %) |
| | Grade 1 | 39 (25.7 %) |
| | Grade 2 | 1 (0.7 %) |
| Treatment arm, N (%) | CTx | 72 (47.4 %) |
| | CTx + cetuximab | 80 (52.6 %) |
| Chemotherapy regimen, N (%) | Ox-5FU | 106 (69.7 %) |
| | Iri-5FU | 15 (9.9 %) |
| | CAPOX | 27 (17.8 %) |
| | CAPOX and Ox- 5FU | 2 (1.3 %) |
| | Iri-5FU and Ox-5FU | 2 (1.3 %) |
| Surgery performed, N (%) | | 138 (90.8 %) |
| Platelet count, ±SD | | 272.7 ± 81.0 |
| Billirubin, ±SD | | 9.6 ± 5.1 |
| Alkaline Phosphatase, ±SD | | 90.3 ± 36.0 |
| Amino transferases (ALAT or ASAT), ±SD | | 24.8 ± 13.0 |

[a] WHO performance status: 0 = "Able to carry out normal activity without restriction", 1 = "Restricted in physical strenuous activity but ambulatory and able to carry out light work", 2 = "Ambulatory and capable of self-care but unable to carry out any work; up and about more than 50 % of waking hours". CTx = chemotherapy. All statistics reported as mean ± SD, frequency (%), or median (IQR).

low SM-RA and 14 patients developed low SM-RA during chemotherapy treatment. For VAT-RA, 84 patients were classified as having low VAT-RA and 10 patients developed low VAT-RA during chemotherapy treatment. For SAT-RA 85 patients were classified as low SAT-RA and 17 patients developed low SAT-RA.

### 3.4. Correlation analysis of body composition

Correlation analysis was performed to investigate the relationships between changes of the different body composition compartments (Fig. 2c). Age was negatively correlated with change in VAT-index, SAT-index, but not with SM-index change. BMI at baseline was negatively correlated with both SM-index change and VAT-Index change. Change in SM-index was positively correlated with VAT-index change, SAT-index change, and SM-RA index change (Fig. 2c). Changes in adipose tissue were all positively correlated between themselves. Furthermore, SM-RA was negatively correlated with VAT-index, but not with SAT-index.

### 3.5. Changes in adipose tissue rather than skeletal muscle are associated with survival

Median OS was 61 months (95 %CI 48.9–73.1). Using Kaplan-Meier analysis, no association was seen for low SM or myosteatosis (low SM-RA) at baseline on OS or PFS (see supplementary Figure S2). Instead, patients who gained >2 % VAT-Index had significantly shorter OS ($p = 0.004$) (Fig. 3a) and PFS ($p = 0.001$) (Supplementary Figure S3a). Since we observed an association between gain of visceral adipose tissue and reduced survival using Kaplan-Meier analysis, we next investigated the effect of all body composition measurements on overall and progression-free survival as continuous variables using cox-regression analysis (see Table 3). We performed imputation of missing data to reduce selection bias because for 29 (19 %) patients the scan after chemotherapeutic treatment was not obtained.

After imputation of missing data, in univariable cox regression analysis, intervention arm ($p = 0.021$), undergoing resection of the metastases ($p < 0.001$), SAT-RA ($p = 0.017$) and VAT-Index change over 12 weeks ($p = 0.021$) were significantly associated with overall survival (see Table 3). For PFS, intervention arm ($p = 0.0189$), undergoing resection of the metastases ($p < 0.001$), CEA >30 ($p = 0.043$), SAT-RA ($p = 0.0236$), VAT-Index change over 12 weeks ($p = 0.013$) and SAT-RA change over 12 weeks ($p = 0.035$) were significant predictors (see Supplementary Table S3). A multivariable model was established by entering all body composition variables as groups. Via backwards selection using Akaike's Information Criterion (AIC) the final model was established in each imputed dataset. Variables that were selected in >50 % of the imputations were entered in the pooled model. In the pooled model, variables that were independently associated with OS were intervention arm (HR 1.961, 95 %CI 1.205–3.192, $p = 0.009$), undergoing resection of the metastases (HR 0.189, 95 %CI 0.089–0.401, $p < 0.001$) and gaining >2 % VAT-index over 12 weeks (HR 2.05, 95 %CI 1.119–3.760, $p = 0.025$) (Table 3). In the pooled model, variables that were independently associated with PFS were; intervention arm (1.883, 95 %CI 1.162–3.052, $p = 0.012$), undergoing resection of the metastases (HR 0.187, 95 %CI 0.088–0.394, $p < 0.001$) and gaining >2 % VAT-index over 12 weeks (HR 1.932, 95 %CI 1.050–3.554, $p = 0.040$) (Supplementary Table S3). Results for univariable and multivariable regression without imputation of missing data can be found in Supplementary Table S4 and S5.

### 3.6. Baseline characteristics of patients who gained visceral adipose tissue

The baseline characteristics of the VAT-gain and VAT-stable or loss groups can be found in Table 4. Median age was lower in patients gaining >2 % VAT-index per 12 weeks (63.5 versus 67 years, $p = 0.023$), and female patients that gained VAT during treatment were taller (163.11 ± 7.95 cm versus 157.50 ± 7.60, $p = 0.033$). Tumor and treatment related characteristics did not differ significantly between patients who gained VAT and those who did not. Focusing on the body composition characteristics at baseline, male patients gaining VAT had lower VAT-index at baseline (47.7 ± 31.7 $cm^2/m^2$ versus 66.6 ± 31.2 $cm^2/m^2$, $p = 0.007$), less myosteatosis (40.5 HU versus 34.4 ± 7.4 HU, $p < 0.001$) and adipodensity of subcutaneous fat (−93.2 ± 9.1 HU versus −97.6 ± 7.63 HU, $p = 0.017$). For female patients, none of the body composition characteristics were significantly different between the groups.

### 3.7. Changes in other body composition compartments in patients who gained visceral adipose tissue

When looking at the changes in body composition variables during chemotherapy treatment between patients who gained VAT and patients who lost VAT, we observed that male patients who gained VAT lost less skeletal muscle (−2.1 ± 7.1 % versus −6.8 ± 6.9 %, $p = 0.003$) and gained more subcutaneous adipose tissue (15.2 ± 27.6 % versus −5.5 ± 13.4 %, $p < 0.001$). Moreover, male patients who gained VAT showed a larger decrease in radiation attenuation of skeletal muscle (−7.2 ± 9.9 % versus −1.9 ± 8.0 %, $p = 0.015$), VAT (−2.1 ± 5.4 % versus 1.6 ± 4.1 %, $p = 0.001$) and SAT (−3.6 ± 7.1 % versus 1.0 ± 5.3 %, $p = 0.001$) which may indicate an increase in triglyceride content in all three compartments. Female patients who gained VAT during chemotherapy gained more subcutaneous adipose tissue (15.9 ± 35.5 % versus −7.8 ±

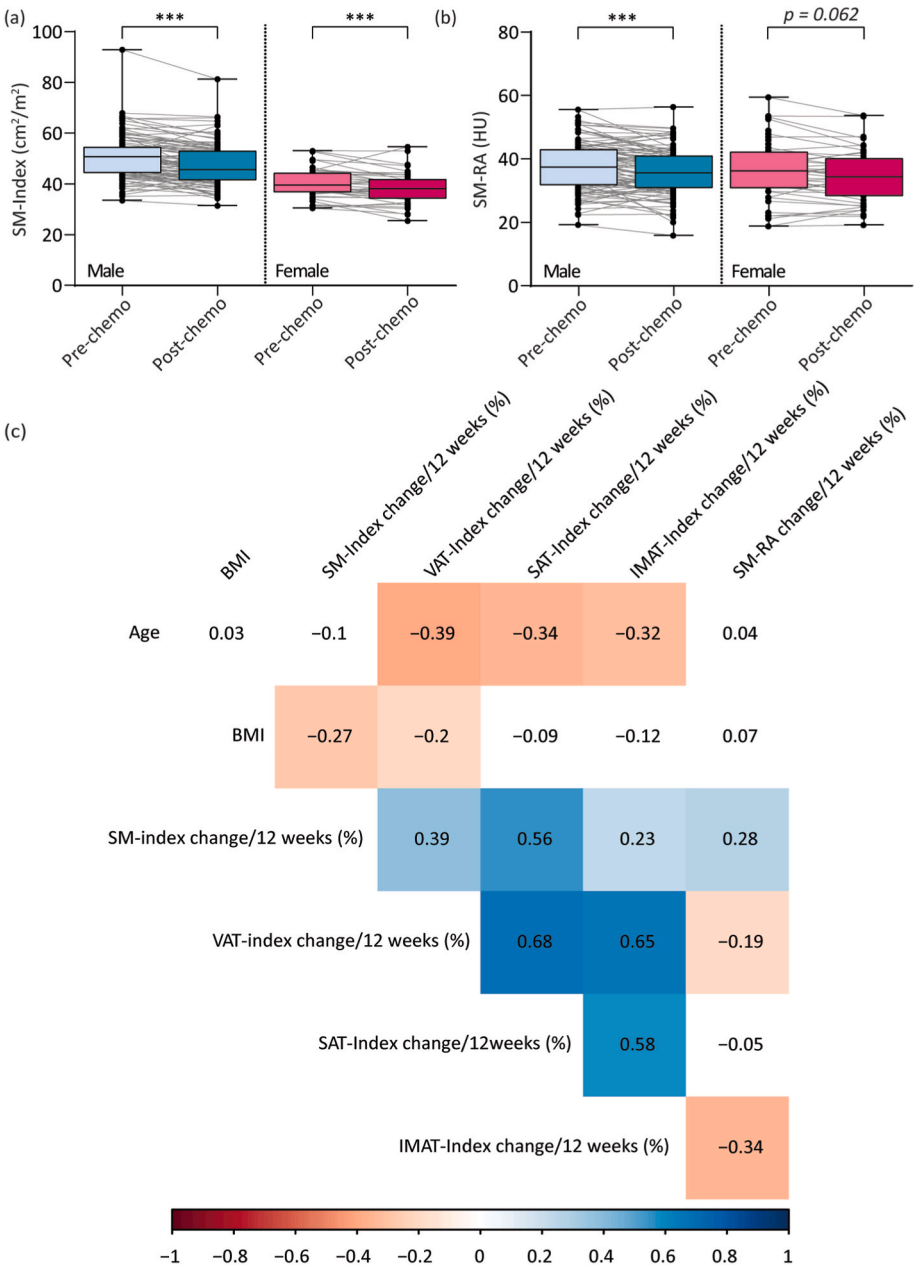


**Fig. 2. Analysis of changes in body composition during preoperative chemotherapy treatment** (a) Skeletal muscle index ($cm^2/m^2$) before and after preoperative chemotherapy treatment for male and female patients (b) radiation attenuation (HU) of skeletal muscle before and after preoperative chemotherapy treatment for male and female patients. ****$p < 0.0001$ (c) correlations between changes in body composition measurements. Pearson's correlation coefficients are represented in color according to the heat map legend (bottom). White squares indicate non-significant correlations ($p > 0.05$). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

25.2 %, $p = 0.045$), but not skeletal muscle (−3.5 ± 6.0 % versus −4.3 ± 8.2 %, $p = 0.716$), nor did they show an increase in triglyceride content in skeletal muscle (SM-RA, −4.0 ± 7.1 % versus −0.6 ± 10.4 %, $p = 0.294$). They did show an increase in triglyceride content in VAT (−2.2 ± 3.0 % versus 1.7 ± 2.8 %, $p < 0.001$) and SAT (−3.7 ± 8.2 % versus 2.0 ± 5.2 %, $p = 0.015$).

### 3.8. Treatment response in patients who gained visceral adipose tissue

Dissimilarities in the treatment that the patients received might explain the survival differences between the two VAT-Index change groups. Moreover, body composition changes might affect treatment tolerance as well as eligibility for surgery. Therefore, we investigated differences in treatment administered to the two VAT-change groups. Significantly fewer patients who gained >2 % VAT-index during treatment experienced cycle delays (29 patients or 46.8 % versus 41 patients or 67.2 %, $p = 0.022$). There were no significant differences in relative dose intensity of pre- or postoperative treatment, and no significant differences in response to pre-operative chemotherapy (see Table 5). Additionally, there was no difference in the number of patients who underwent surgery after neo-adjuvant treatment between the two groups ($p = 0.748$).

### 3.9. Surgical complications, 30-day mortality and serious adverse events

As previous research has shown an association between body composition and surgical complications [29], we investigated whether the occurrence of post-operative complications was higher for patients

**Table 2**
Body composition characteristics before and after chemotherapy treatment.

| Measure | Before chemotherapy (n = 152) | After chemotherapy (n = 123) | Change after 12 weeks, % (n = 123) | |
|---|---|---|---|---|
| **Male (n = 85)** | **Mean ± SD** | **Mean ± SD** | **Mean % change ±SD** | ***p* value** |
| SM-index ($cm^2/m^2$) | 50.6 ± 8.7 | 47.6 ± 8.6 | −4.4 ± 7.4 | *<0.001*** |
| VAT-index ($cm^2/m^2$) | 55.7 ± 32.4 | 58.6 ± 31.9 | 10.0 ± 28.8 | *0.126* |
| SAT-index ($cm^2/m^2$)§ | 51.6 ± 25.8 | 52.4 ± 26.2 | 5.3 ± 24.2 | *0.378* |
| SM-RA (HU) | 37.7 ± 7.8 | 36.0 ± 7.6 | −4.8 ± 9.4 | *<0.001*** |
| VAT-RA (HU) | −90.3 ± 8.1 | −90.0 ± 7.6 | 0.4 ± 5.2 | *0.581* |
| SAT-RA (HU) | −94.9 ± 9.5 | −96.2 ± 9.2 | −1.5 ± 6.9 | *0.149* |
| **Female (n = 38)** | **Mean ± SD** | **Mean ± SD** | **Mean % change ±SD** | ***p* value** |
| SM-index ($cm^2/m^2$) | 40.5 ± 6.1 | 37.7 ± 5.9 | −3.9 ± 7.15 | *0.002*** |
| VAT-index ($cm^2/m^2$) | 34.9 ± 24.1 | 35.3 ± 23.0 | 11.8 ± 34.0 | *0.198* |
| SAT-index ($cm^2/m^2$)§ | 77.6 ± 41.3 | 74.5 ± 37.5 | 5.2 ± 33.1 | *0.670* |
| SM-RA (HU) | 36.3 ± 9.5 | 34.5 ± 8.3 | −2.5 ± 8.7 | *0.062* |
| VAT-RA (HU) | −88.5 ± 8.5 | −88.7 ± 8.6 | 0.2 ± 3.5 | *0.893* |
| SAT-RA (HU) | −98.4 ± 10.4 | −98.4 ± 10.6 | −1.1 ± 7.8 | *0.981* |
| **Combined (n = 123)** | **N (%)** | **N (%)** | **Patients changing body composition group, N (%)[b]** | ***p* value** |
| Low SM[a] | 79 (52 %) | 80 (65.0 %) | 17 (30.9 %) | *0.097* |
| High VAT[a] | 56 (41.8 %) | 51 (33.6 %) | 7 (10.5 %) | *0.385* |
| High SAT[a§] | 73 (48.0 %) | 63 (41.4 %) | 7 (11.9 %) | *0.442* |
| Low SM-RA[a] | 65 (45.1 %) | 77 (50.7 %) | 14 (24.1 %) | *0.507* |
| Low VAT-RA[a] | 84 (55.6 %) | 83 (55.0 %) | 10 (17.5 %) | *0.938* |
| Low SAT-RA[a] | 85 (56.3 %) | 89 (58.9 %) | 17 (31.5 %) | *0.729* |

[a] Low SM, high VAT, high SAT, low SM-RA, low VAT-RA and low SAT-RA defined z-score <0. §n = 134 for pre-chemo body composition variables or 102 for post-chemo body composition variables (18 and 21 missing resp. due to poor CT-scan quality).
[b] Percentage of patient changing groups after chemotherapy treatment, i.e. going from high SM group to low SM group. **$p < 0.01$, ***$p < 0.001$.

gaining >2 % VAT-index during treatment. Although there was no difference in the incidence of AEs or SAEs between patients gaining and losing VAT-index (see Table 6), patients gaining >2 % VAT-index experienced significantly fewer AE's per cycle (4.00 ± 2.38 versus 5.24 ± 2.94, $p = 0.011$) and SAE's per cycle (0.21 ± 0.29 versus 0.47 ± 0.98, $p = 0.049$) during the pre-operative treatment period. Because chemotherapy toxicity may be influenced by many factors, we performed multivariable logistic regression. Upon multivariable analysis, only RDI (HR 0.943, 95 %CI 0.912–0.976, $p < 0.001$) and number of chemotherapy cycles completed (HR 0.631, 95 %CI 0.479–0.832, $p = 0.001$) were associated with a reduced risk of SAEs (see Supplementary Table S6). Surgical complications were present in 34 patients. The incidence of postoperative complications was not different between patient gaining >2 % VAT-index and patients who did not gain VAT-index.

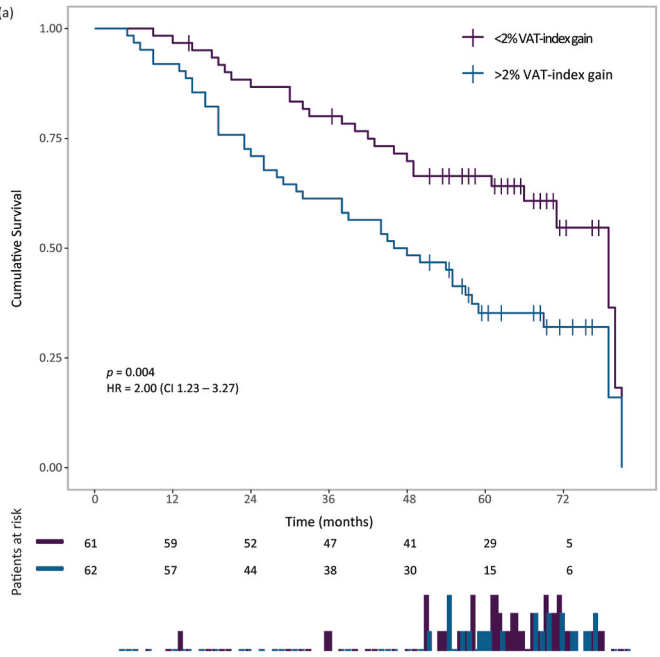


**Fig. 3. Effect of change in visceral adipose tissue on overall survival.** (a) Kaplan-Meier curve of overall survival for patients with >2 % VAT-index gain versus <2 % VAT-index gain. VAT-index: visceral adipose tissue index, CEA: carcinoembryonic antigen.

## 4. Discussion

This study identified gain of visceral adipose tissue during chemotherapy treatment as an independent prognostic factor for overall and progression free survival in patients with CRLM undergoing neoadjuvant chemotherapy before resection of liver metastases. The association between VAT-gain and decreased survival presented here has never been reported before. Research has historically focused on baseline skeletal muscle parameters while adipose tissue and adipose tissue changes have not frequently been reported on. One paper by van Dijk and colleagues (2019) has shown a survival benefit for CRLM patients undergoing resection with high VAT mass when using single CT-scan analysis [21]. And, contrary to our results, one paper by Choe and colleagues reported that VAT-gain after surgery was associated with increased survival specifically in a group of colorectal cancer patients treated with adjuvant chemotherapy [30].

In our cohort, we found that male patients who gained >2 % of VAT-index during treatment had significantly lower visceral adipose tissue at baseline and less myosteatosis. These measures indicate that adipose tissue stores are lower at baseline in the VAT-gain group, and this group may therefore consist of metabolically compromised patients that correspond to the "low-VAT" groups previously reported to have a survival deficit [31–33]. Additionally, we identified that patients who gained >2 % VAT during chemotherapy gained more subcutaneous fat, developed more myosteatosis and gained more triglyceride content of visceral and adipose tissue. One explanation may be that visceral adipose tissue is very metabolically active, more so than subcutaneous adipose tissue [34]. Visceral adiposity specifically is associated with metabolic syndrome, insulin resistance and increases in systemic inflammation and adipokine expression [35]. Those patients who are prone to gaining more visceral adipose tissue might be a subset of patients who are also more prone to developing these associated disorders. Additionally, it is thought that excess visceral adiposity contributes to lipid deposition in tissues that are not designed for fat storage, such as skeletal muscle. This process is called ectopic fat deposition [36], and in

**Table 3**
Univariable and multivariable Cox regression of overall survival with imputation for missing variables.

| | | Univariable | | Multivariable | | | |
|---|---|---|---|---|---|---|---|
| | | *p-value* | Exp(B) | Exp(B) | 95 % CI for Exp(B) | | *p* value |
| | | | | | Lower | Upper | |
| Intervention arm[a] | | *0.021** | 1.707 | 1.961 | 1.205 | 3.192 | *0.009*** |
| Chemotherapy regimen | OxMDG (n = 106) | | Ref | | | | |
| | IriMDG (n = 15) | *0.889* | 0.945 | | | | |
| | CAPOX (n = 27) | *0.319* | 1.317 | | | | |
| | CAPOX and OxMDG (n = 2) | *0.692* | 1.495 | | | | |
| | IriMDG and OxMDG (n = 2) | *0.149* | 2.865 | | | | |
| Resection of metastases | | *<0.001**** | 0.223 | 0.189 | 0.089 | 0.401 | *<0.001**** |
| Age of patient (years) | | *0.624* | 0.995 | 0.998 | 0.974 | 1.022 | *0.859* |
| Sex (female) | | *0.781* | 0.934 | 1.140 | 0.684 | 1.901 | *0.618* |
| Primary tumor stage T3 or T4 at diagnosis | | *0.358* | 1.369 | 1.440 | 0.670 | 3.095 | *0.354* |
| Lymph node stage N1 or N2 at diagnosis | | *0.136* | 1.451 | 1.523 | 0.887 | 2.616 | *0.132* |
| >4 liver metastases at diagnosis | | *0.333* | 1.308 | 1.146 | 0.634 | 2.070 | *0.654* |
| KRAS status (WT) | | *0.137* | 4.684 | | | | |
| Poor differentiation of primary tumor | | *0.803* | 1.089 | 1.350 | 0.683 | 2.671 | *0.391* |
| BMI (kg/m$^2$) | | *0.410* | 1.021 | | | | |
| Baseline BSA | | *0.463* | 1.439 | | | | |
| WHO performance status (≥1) | | *0.282* | 1.305 | | | | |
| CEA >30 ng/mL | | *0.075* | 1.532 | 1.503 | 0.908 | 2.486 | *0.118* |
| Pre-chemo SM-index (cm$^2$/m$^2$) | | *0.773* | 0.997 | | | | |
| Low SM-Index (Z-score <0) | | *0.705* | 0.919 | | | | |
| Pre-chemo VAT-index (cm$^2$/m$^2$) | | *0.768* | 1.001 | | | | |
| Low VAT-Index (Z-score <0) | | *0.388* | 0.823 | 0.692 | 0.431 | 1.110 | *0.132* |
| Pre-chemo SAT-index (cm$^2$/m$^2$) | | *0.848* | 1.000 | | | | |
| Low SAT-Index (Z-score <0) | | *0.989* | 0.997 | | | | |
| Pre-chemo SM-RA (HU) | | *0.765* | 1.003 | | | | |
| Low SM-RA (Z-score <0) | | *0.749* | 0.931 | | | | |
| Pre-chemo VAT-RA (HU) | | *0.240* | 1.016 | | | | |
| Low VAT-RA (Z-score <0) | | *0.634* | 1.113 | | | | |
| Pre-chemo SAT-RA (HU) | | *0.017** | 1.027 | | | | |
| Low SAT-RA (Z-score <0) | | *0.380* | 0.821 | | | | |
| SM-index change per 12 weeks (%) | | *0.278* | 1.017 | | | | |
| Patient loses >2 % SM-Index per 12 weeks | | *0.495* | 1.191 | | | | |
| VAT-index change per 12 weeks (%) | | *0.022** | 1.008 | | | | |
| Patient gains >2 % VAT-Index per 12 weeks | | *0.019** | 1.835 | 2.051 | 1.119 | 3.760 | *0.025** |
| SAT-index change per 12 weeks (%) | | *0.592* | 1.003 | | | | |
| Patient gains >2 % SAT-Index per 12 weeks | | *0.415* | 1.237 | | | | |
| SM-RA change per 12 weeks (%) | | *0.784* | 1.004 | | | | |
| SM-RA decreases >2 % per 12 weeks | | *0.988* | 0.996 | | | | |
| VAT-RA change per 12 weeks (%) | | *0.652* | 0.988 | | | | |
| VAT-RA decreases >2 % per 12 weeks | | *0.233* | 1.375 | | | | |
| SAT-RA change per 12 weeks (%) | | *0.053* | 0.964 | | | | |
| SAT-RA decreases >2 % per 12 weeks | | *0.174* | 1.436 | | | | |

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
[a] Arm A = OxMdG/IrMdG chemotherapy, Arm B = OxMdG/IrMdG chemotherapy + cetuximab.

muscles this is also called myosteatosis. However, further research is needed to investigate which metabolic processes are responsible for the continued gain of adipose tissue and myosteatosis that these patients experience.

Additionally, we identified sex specific body composition differences associated with VAT-gain during treatment. While male patients who gained VAT had significantly less VAT at baseline, this was not the case for females in our cohort. This may be due to the smaller sample size for female patients (n = 45), or because the visceral adipose compartment in females is thought to be less important in metabolic health. For females the visceral adipose compartment is significantly less large compared to males, while the subcutaneous compartment is larger for females. Additionally, studies have shown that when total fat mass increased in males, this was associated with a significantly greater increase in visceral adipose tissue in men, and not in women [37]. Moreover, we did not find a significant decrease in skeletal muscle mass or triglyceride content for females who gained VAT. Again, this might be due to the smaller sample size. However, because VAT is thought to be more metabolically active than SAT(36), this might indicate that factors associated with VAT gain are simultaneously responsible for muscle loss.

Future research should therefore focus on investigating these metabolic differences between the fat compartments, and how they influence prognosis. Importantly, visceral adiposity has been linked to pathologic metabolic conditions such as insulin resistance, impaired glucose and lipid metabolism and cardiovascular disease [38]. Glucose levels could be measured to identify insulin resistance, and lipid metabolism could be analyzed by measuring cholesterol and lipoprotein levels. Furthermore, inflammatory markers such as TNF-α, interleukin 6 and adiponectin could be measured as these factors are associated with excess VAT [36]. Since CT-scans are routinely obtained, and, due to the development of artificial intelligence, body composition analysis has become virtually effortless [39] it can easily be implemented in clinical practice. Alongside other measures of metabolic health such as lipid profile, inflammatory markers and insulin resistance, a personal profile of patients undergoing treatment could identify patients with a higher risk of mortality and show possible avenues to improve metabolic health. Measurement of visceral adipose tissue could aid in patient selection, which is essential to reduce unnecessary complications of treatment and improve the allocation of funds in medical treatment. Furthermore, if future research can elucidate the factors that are responsible for visceral fat gain in cancer patients, these factors may be investigated for their potential to be targeted to improve overall metabolic health, and hopefully thereby increase survival.

In this study, we were unable to confirm the previously published

**Table 4**
Baseline characteristics of patients divided by >2 % VAT-index gain.

| | | <2 % VAT-index gain[a] (n = 62) | >2 % VAT-index gain[a] (n = 61) | *p*-value |
|---|---|---|---|---|
| *Baseline characteristics* | | | | |
| Sex, N (%) | Male | 41 (67.2 %) | 44 (71.0 %) | *0.038* |
| | Female | 20 (32.8 %) | 18 (29.0 %) | |
| Median age, years (IQR) | | 67.0 (13.5) | 63.5 (13.25) | *0.023** |
| Height (cm) ± SD | Male | 173.3 ± 6.4 | 175.95 ± 6.58 | *0.068* |
| | Female | 157.5 ± 7.6 | 163.11 ± 7.95 | *0.033** |
| Weight (kg) ± SD | Male | 82.3 ± 12.7 | 84.11 ± 16.18 | *0.568* |
| | Female | 68.1 ± 16.0 | 67.40 ± 10.83 | *0.875* |
| BSA ($m^2$) ± SD | Male | 1.96 ± 0.15 | 2.00 ± 0.20 | *0.331* |
| | Female | 1.67 ± 0.20 | 1.71 ± 0.16 | *0.515* |
| BMI ($kg/m^2$) ± SD | Male | 27.4 ± 4.0 | 27.1 ± 4.6 | |
| | Female | 27.3 ± 5.2 | 25.3 ± 3.5 | |
| Primary cancer site, N (%) | Right colon | 10 (16.4 %) | 9 (14.5) | *0.527* |
| | Transverse colon | 0 (0.0 %) | 3 (4.8 %) | |
| | Descending colon | 14 (23.0 %) | 15 (24.2 %) | |
| | Sigmoid and rectosigmoid | 16 (26.3 %) | 19 (30.7 %) | |
| | Rectum | 21 (34.4 %) | 16 (25.8 %) | |
| Cancer stage, N (%) | T1 or T2 | 11 (18.3 %) | 11 (19.3 %) | *0.894* |
| | T3 or T4 | 49 (81.7 %) | 46 (80.7 %) | |
| Lymph node stage | N0 | 23 (39.0 %) | 17 (29.8 %) | *0.300* |
| | N1 or N2 | 36 (61.0 %) | 40 (70.2 %) | |
| Number of liver metastases | 1–3 | 54 (88.5 %) | 47 (75.8 %) | *0.066* |
| | >4 | 7 (11.5 %) | 15 (24.2 %) | |
| Poor differentiation of primary tumor biopsy | | 6 (10.9 %) | 7 (12.1 %) | *0.847* |
| KRAS status | Mutant | 1 (1.6 %) | 2 (3.2 %) | *0.568* |
| | Wildtype | 60 (98.4 %) | 60 (96.8 %) | |
| WHO performance status[b], N (%) | Grade 0 | 42 (68.9 %) | 47 (75.8 %) | *0.362* |
| | Grade 1 | 19 (31.1 %) | 14 (22.6 %) | |
| | Grade 2 | 0 (0.0 %) | 1 (1.6 %) | |
| Treatment arm, N (%) | CTx | 29 (47.5 %) | 31 (50.0 %) | *0.785* |
| | CTx + cetuximab | 32 (52.5 %) | 31 (50.0 %) | |
| Chemotherapy regimen, N (%) | Ox-5FU | 43 (70.5 %) | 46 (74.2 %) | *0.690* |
| | Iri-5FU | 4 (6.6 %) | 5 (8.1 %) | |
| | CAPOX | 12 (19.7 %) | 11 (17.7 %) | |
| | CAPOX and Ox- 5FU | 1 (1.6 %) | 0 (0.0 %) | |
| | Iri-5FU and Ox-5FU | 1 (1.6 %) | 0 (0.0 %) | |
| Platelet count, ±SD | | 277.8 ± 80.6 | 272.1 ± 85.0 | *0.705* |
| Bilirubin, ±SD | | 9.7 ± 5.6 | 8.8 ± 4.7 | *0.375* |
| Alkaline Phosphatase, ±SD | | 92.5 ± 44.3 | 89.6 ± 31.0 | *0.668* |
| Amino transferases (ALAT or ASAT), ±SD | | 25.8 ± 11.4 | 22.2 ± 11.6 | *0.085* |
| *Body composition characteristics at baseline* | | | | |
| SM-Index ($cm^2/m^2$), ±SD | Male | 49.5 ± 10.5 | 51.6 ± 7.9 | *0.313* |
| | Female | 40.3 ± 6.7 | 38.8 ± 4.0 | *0.421* |
| VAT-Index ($cm^2/m^2$) ± SD | Male | 66.6 ± 31.2 | 47.7 ± 31.7 | *0.007*** |
| | Female | 36.9 ± 27.0 | 30.5 ± 20.5 | *0.418* |
| SAT-Index ($cm^2/m^2$), ±SD | Male | 53.8 ± 20.9 | 49.9 ± 30.2 | *0.521* |
| | Female | 77.3 ± 42.6 | 70.6 ± 36.2 | *0.633* |
| SM-RA (mean HU), ±SD | Male | 34.4 ± 7.4 | 40.5 ± 7.1 | *<0.001**** |
| | Female | 33.2 ± 10.0 | 38.5 ± 5.4 | *0.087* |
| VAT-RA (mean HU), ±SD | Male | −92.0 ± 6.2 | −88.8 ± 8.6 | *0.055* |
| | Female | −87.2 ± 8.9 | −88.9 ± 7.9 | *0.546* |
| SAT-RA (mean HU), ±SD | Male | −97.6 ± 7.6 | −93.2 ± 9.1 | *0.017** |
| | Female | −96.3 ± 11.0 | −98.71 ± 10.0 | *0.486* |
| *Body composition change from baseline (% per 12 weeks)* | | | | |
| SM-Index (%), ±SD | Male | −6.8 ± 6.9 | −2.1 ± 7.1 | *0.003*** |
| | Female | −4.3 ± 8.2 | −3.5 ± 6.0 | *0.716* |
| VAT-Index (%), ±SD | Male | −8.6 ± 9.6 | 27.3 ± 30.0 | *<0.001**** |
| | Female | −9.1 ± 8.7 | 35.0 ± 36.7 | *<0.001**** |
| SAT-Index (%), ±SD | Male | −5.5 ± 13.4 | 15.2 ± 27.6 | *<0.001**** |
| | Female | −7.8 ± 25.2 | 15.9 ± 35.5 | *0.045** |
| SM-RA (%), ±SD | Male | −1.9 ± 8.0 | −7.2 ± 9.9 | *0.015** |
| | Female | −0.6 ± 10.4 | −4.0 ± 7.1 | *0.294* |
| VAT-RA (%), ±SD | Male | 1.6 ± 4.1 | −2.1 ± 5.4 | *0.001*** |
| | Female | 1.7 ± 2.8 | −2.2 ± 3.0 | *<0.001**** |
| SAT-RA (%), ±SD | Male | 1.0 ± 5.3 | −3.6 ± 7.1 | *0.001*** |
| | Female | 2.0 ± 5.2 | −3.7 ± 8.2 | *0.015** |

All statistics reported as mean ± SD, frequency (%), or median (IQR). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
[a] Groups divided by >2 % gain in VAT-Index over 12 weeks.
[b] WHO performance status: 0 = "Able to carry out normal activity without restriction", 1 = "Restricted in physical strenuous activity but ambulatory and able to carry out light work", 2 = "Ambulatory and capable of self-care but unable to carry out any work; up and about more than 50 % of waking hours". CTx = chemotherapy.

findings that low skeletal muscle mass and loss of skeletal muscle mass during neoadjuvant chemotherapy treatment were associated with a significant decrease in OS([11,17,40–42]). Although both skeletal muscle mass and muscle radiation attenuation decreased significantly during chemotherapy treatment in this prospective cohort, we did not observe an effect of low skeletal muscle mass or continued skeletal muscle loss on OS or PFS. This may be caused by multiple reasons. First of all, we defined low skeletal muscle mass by dividing the group at the median. Other studies have used cut-off points previously defined in a large Canadian cohort of gastrointestinal patients by Prado and colleagues [26]. In comparison to this Canadian cohort, the cohort presented here consists of a homogeneous group of CRLM patients from the UK. We believe that, although the study by Martin and colleagues was performed in a large cohort, the inclusion of multiple tumor entities, and the different patient population precludes the use of these cut-off points in our cohort. Moreover, in univariable regression, no association was found between skeletal muscle mass and OS or PFS as continuous variables. Additionally, the influence of low skeletal muscle mass and skeletal muscle loss may not be as important in this selected cohort.

**Table 5**
Treatment information and treatment response.

| | | <2 % VAT gain[a] (n = 61) | >2 % VAT-index gain[a] (n = 62) | p-value |
|---|---|---|---|---|
| *Preoperative treatment period* | | | | |
| All CTx cycles completed[b], N (%) | | 50 (82.0 %) | 50 (80.6 %) | *0.851* |
| Number of CTx cycles completed, mean ± SD | | 5.30 ± 1.19 | 5.34 ± 1.09 | *0.832* |
| At least one cycle delay, N (%) | | 41 (67.2 %) | 29 (46.8 %) | *0.022** |
| At least one dose reduction, N (%) | | 32 (52.5 %) | 33 (53.2 %) | *0.932* |
| RDI of preoperative CTx | | 81.96 ± 12.00 | 82.91 ± 11.89 | *0.664* |
| *Treatment response* | | | | |
| Surgery performed, N (%) | | 57 (93.4 %) | 57 (91.9 %) | *0.748* |
| Response according to RECIST[a,b] | CR | 2 (3.3 %) | 3 (4.9 %) | *0.173* |
| | PR | 39 (63.9 %) | 41 (67.2 %) | |
| | SD | 17 (27.9 %) | 9 (14.8 %) | |
| | PD | 3 (4.9 %) | 8 (13.1 %) | |
| *Post-operative treatment period* | | | | |
| All CTx cycles completed[b], N (%) | | 34 (70.8 %) | 28 (63.6 %) | *0.509* |
| Number of CTx cycles completed, mean ± SD | | 3.75 ± 2.64 | 2.81 ± 2.91 | *0.061* |
| At least one cycle delay, N (%) | | 13 (26.5 %) | 6 (13.6 %) | *0.124* |
| At least one dose reduction, N (%) | | 28 (57.1 %) | 22 (50.0 %) | *0.490* |

CTx = chemotherapy treatment, RDI = Relative Dose Intensity.
[a] Groups divided by >2 % gain in VAT-Index over 12 weeks.[§] Response graded using RECIST criteria version 1.0 where CR = Complete Response. PR = Partial Response. SD = Stable Disease and PD = Progressive Disease.
[b] For one patient information on preoperative chemotherapy treatment and RECIST response was not available. This patient was excluded from the corresponding analyses. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Since only patients with ECOG stage 0–2 were eligible for inclusion, and there was only 1 patient with ECOG stage 2 in the current cohort, this may have resulted in a selection of patients with a favorable body composition, which may explain why we could not validate results published by others [11–13]. However, the mean SM-index of the cohort (50.6 ± 8.7 $cm^2/m^2$ for males and 40.5 ± 6.1 $cm^2/m^2$ for females) was not significantly higher than in other cohorts in the literature that did show an association between low skeletal muscle mass and survival [13, 26].

However, we are hesitant to draw conclusions from our results, as there are multiple limitations to our study, and we believe that these associations should be validated in other independent cohorts. First of all, there may have been selection bias, as not all CT-scans from all patients could be obtained. For 120 patients of the original cohort, we could not retrieve a pre-treatment scan that was within 12 weeks before the start of chemotherapy treatment. Furthermore, for 29 patients we could not retrieve the post-treatment scan, and we performed imputation of missing variables to compensate for this. This may have resulted in bias. While we have tried to address this by using imputation of missing data, the imputation model might fail to account for some important factors and relationships in the data that may explain our findings. Additionally, while data was collected in a prospective manner, in the context of a clinical trial, we cannot draw conclusions on the causality of our findings as this was an observational secondary analysis. Nevertheless, VAT-gain remained independently associated with survival even when performing imputation of missing data and when correcting for multiple known confounding factors such as age and sex. Finally, we could not find an explanation for the association between gain of visceral fat, as the only differences between the groups were a lower occurrence of adverse events in the preoperative setting, that was not translated to a difference in pre-operative RDI.

**Table 6**
Serious Adverse events during preoperative and postoperative chemotherapy treatment.

| | <2 % VAT gain[a] (n = 61) | >2 % VAT-index gain[a] (n = 62) | p value |
|---|---|---|---|
| *Preoperative treatment period* | | | |
| At least one AE, N (%) | 61 (100.0 %) | 61 (98.4 %) | *0.319* |
| At least one SAE, N (%) | 35 (57.4 %) | 33 (53.2 %) | *0.643* |
| Number of AE per cycle, mean ± SD | 5.24 ± 2.94 | 4.00 ± 2.38 | *0.011** |
| Number of SAE per cycle, mean ± SD | 0.47 ± 0.98 | 0.21 ± 0.29 | *0.049** |
| *Surgical complications (number of patients with)* | | | |
| Any surgical complication, N (%) | 17 (30.9 %) | 17 (29.3 %) | *0.853* |
| Postoperative bleeding, N (%) | 1 (1.8 %) | 5 (8.6 %) | *0.107* |
| Biliary fistula, N (%) | 4 (7.3 %) | 3 (5.2 %) | *0.643* |
| Cardio-pulmonary failure, N (%) | 2 (3.6 %) | 3 (5.2 %) | *0.691* |
| Hepatic failure, N (%) | 3 (5.5 %) | 2 (3.4 %) | *0.604* |
| Wound infection, N (%) | 5 (9.1 %) | 4 (6.9 %) | *0.667* |
| Intra abdominal infection, N (%) | 3 (5.5 %) | 1 (1.7 %) | *0.283* |
| Reoperation needed, N (%) | 1 (1.8 %) | 1 (1.7 %) | *0.970* |
| Other surgical complications, N (%) | 10 (18.2 %) | 10 (17.2 %) | *0.896* |
| *Postoperative treatment period* | | | |
| At least one AE, N (%) | 43 (100.0 %) | 31 (100.0 %) | *n.a.* |
| At least one SAE, N (%) | 20 (46.5 %) | 8 (25.8 %) | *0.070* |
| Number of AE per cycle, mean ± SD | 4.59 ± 2.74 | 4.11 ± 2.45 | *0.436* |
| Number of SAE per cycle, mean ± SD | 0.24 ± 0.51 | 0.09 ± 0.20 | *0.143* |

CTx = chemotherapy treatment, RDI = Relative Dose Intensity.
All statistics reported as mean ± SD, frequency (%), or median (IQR). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
[a] Groups divided by >2 % gain in VAT-Index over 12 weeks.[‡] For one patient information on preoperative chemotherapy treatment and RECIST response was not available. This patient was excluded from the corresponding analyses.

In conclusion, we identified gain of visceral adipose tissue as an independent prognostic factor for overall and progression free survival in patients with CRLM undergoing neo-adjuvant chemotherapy treatment before liver resection. We could not validate the impact of low skeletal muscle mass and loss of skeletal muscle mass during neoadjuvant treatment on survival in a prospective trial. The results are from the most homogeneous cohort described to date. Treatment outcomes, adverse events and complications were meticulously reported and well divided over the different treatment arms. Furthermore, CT-scan analysis was performed using established methods [14]. Based on this, and previous studies in the literature, we believe that analysis of body composition in CRLM patients treated with neoadjuvant chemotherapy is important.

## Informed consent statement

Informed consent was obtained from all subjects involved in the study.

## Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the South West Research Ethics Committee on 01-12-2006 and the protocol was submitted to ISRCTN registry (ISRCTN22944367) and Clinicaltrials.gov (NCT00482222).

## Author contributions

Conceptualization, S.W.M. Olde Damink and J.N. Primrose; Methodology, M.R. Aberle and M.A.P. Ligthart.; Validation, S.A. Pugh D.P.J. van Dijk and M.A. West; Formal Analysis, M.R. Aberle and M.A.P. Ligthart.; Investigation, M.R. Aberle and M.A.P. Ligthart.; Resources, S.W.M. Olde Damink, S.S. Rensen, and J.A. Bridgewater and J.N. Primrose; Data Curation, Z. Eminton, M.R. Aberle and M.A.P. Ligthart.; Writing – Original Draft Preparation, M.R. Aberle and M.A.P. Ligthart.; Writing – Review & Editing, M.A. West and S.W.M. Olde Damink, S.S. Rensen, and S.A. Pugh and J.A. Bridgewater and J.N. Primrose.; Visualization, M.R. Aberle and M.A.P. Ligthart.; Supervision, S.W.M. Olde Damink, S.S. Rensen, and J.A. Bridgewater and J.N. Primrose.; Project Administration, M.R. Aberle and M.A.P. Ligthart.; Funding Acquisition, S.W.M. Olde Damink, S.S. Rensen.

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## Conflicts of interest

SP: Honoraria – Merck, Takeda, Servier, Travel expenses – Takeda.

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## Appendix ASupplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2025.111179.

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