Body Composition, Relative Dose Intensity, and Adverse Events Among Patients with Colon Cancer

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Abstract

Background: Despite evidence that low muscle increases the risk of chemotoxicity, most chemotherapies are dosed on body surface area without considering body composition. Among 178 patients with colon cancer, we assessed muscle and adipose tissue with multiple techniques and examined their associations with relative dose intensity (RDI) and adverse events.

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Conflict of Interest:

Dr. Jeffrey A. Meyerhardt has served as an advisor/consultant to Merck Pharmaceutical and COTA Healthcare.

Methods: We estimated 1) cross-sectional skeletal muscle area (SMA) and total adipose tissue (TAT) area at L3 from computed tomography (CT); 2) appendicular lean mass (ALM) and total body fat (TBF) mass from dual-energy X-ray absorptiometry (DXA); and 3) total body skeletal muscle mass using D3-creatine (D3Cr) dilution. We standardized each measurement by its sex-specific standard deviation (SD). The primary outcome was reduced RDI (RDI <85%). The secondary outcome was the number of moderate and severe adverse events during each cycle of chemotherapy. We estimated the associations of muscle and adipose tissue measurements (per SD increase) with reduced RDI using logistic regression and adverse events using generalized estimating equations for repeated measures.

Results: Higher CT SMA and DXA ALM were significantly associated with lower risk of reduced RDI (odds ratios: 0.56 [0.38, 0.81] for CT SMA; 0.56 [0.37, 0.84] for DXA ALM). No measurements of muscle or adipose tissue were associated with adverse events.

Conclusions: More muscle was associated with improved chemotherapy completion among patients with colon cancer, whereas muscle and adipose tissue were not associated with adverse events.

Impact: Considering body composition may help personalize dosing for colon cancer chemotherapy by identifying patients at risk for poor chemotherapy outcomes.

INTRODUCTION

Adjuvant chemotherapy is the standard of care for patients with stage III colon cancer and recommended for patients with stage II colon cancer at high risk of recurrence (1,2). Several chemotherapeutic agents such as 5-fluorouracil, capecitabine, leucovorin, and oxaliplatin and their combinations are commonly used to treat colon cancer (1,2). For each patient, the doses of chemotherapeutic agents are calculated according to body surface area, which is derived from height and weight (3). However, this strategy does not consider muscle and adipose tissue, which can alter the pharmacokinetics of these agents, affect their volume of distribution and effectiveness, and increase the likelihood of adverse events (4,5). In light of this, the American Society for Clinical Oncology (ASCO) has recently updated the guideline on "*Appropriate Systemic Therapy Dosing for Obese Adult Patients With Cancer*" and called for additional research on the impact of sarcopenia and other measurements of body composition on optimal antineoplastic dosing (6).

Due to advances in imaging and biochemical technologies, there are multiple, validated techniques for assessing muscle and adipose tissue. Computed tomography (CT) imaging performed for colon cancer staging and surveillance is a reliable tool: cross-sectional skeletal muscle area (SMA) and total adipose tissue (TAT) area at the third lumbar vertebra (L3) correlate well with the whole-body volumes of muscle and adipose tissue on magnetic resonance imaging (MRI), respectively (7). Dual-Energy X-Ray Absorptiometry (DXA) is another accurate method to quantify lean body mass (LBM) and total body fat (TBF)

mass (8). Since DXA LBM includes muscle, organs, and other tissues, appendicular lean mass (ALM; a surrogate of limb muscles) is commonly used given its high correlation with the whole-body volume of muscle (9). In addition, there is a growing interest in applying the deuterated-creatine (D3-creatine) dilution method to cancer patients, which can provide an accurate estimate of total body skeletal muscle mass via measuring the whole-body creatine pool size (10). D3-creatine (D3Cr) muscle mass also strongly correlates with the whole-body volume of muscle, but the results from this technique have not been previously reported in any cancer population. Since these techniques reflect different constructs of muscle and adipose tissue, a study in colon cancer patients undertaking all three techniques can additionally inform the impact of different body composition measurements on chemotherapy outcomes.

Relative dose intensity (RDI), the ratio of the delivered dose intensity to planned dose intensity, is a summary measure that reflects dose delay, reduction, and discontinuation of chemotherapy treatment (11). RDI <85% is considered as a clinically significant deviation from standard chemotherapy (12), and the decrease of RDI was reported to be associated with early recurrence and mortality survival among patients with colorectal cancer (CRC) (13,14). An important reason for reduced RDI is the occurrence of adverse events during each cycle of chemotherapy, which is very common in chemotherapy treatment (15). As patients with higher RDI receive more chemotherapy dose, we hypothesize that patients with better chemotherapy completion may experience similar or even more adverse events (1,2). In sum, considering RDI and adverse events is important to inform the associations of body composition and chemotherapy effectiveness.

Among patients with nonmetastatic colon cancer enrolled in a resistance training trial, we assessed their muscle (CT SMA, DXA ALM, and D3Cr muscle mass) and adipose tissue (CT TAT and DXA TBF) at enrollment (prior to or shortly after chemotherapy initiation). We examined the associations of body composition measurements with reduced RDI and the number of moderate and severe adverse events. To our knowledge, this is the first study to use multiple techniques (particularly D3-creatine for total body skeletal muscle mass) to assess body composition in relation to RDI and adverse events among a cancer population.

MATERIALS AND METHODS

Data Source and Study Population

FOcus on Reducing dose-limiting toxicities in Colon cancer with resistance Exercise (FORCE) was an NCI-sponsored multicenter clinical trial conducted in 181 patients with stage II or III colon cancer after curative resection (ClinicalTrials.gov Identifier: NCT03291951) (16). Patients were randomized to the intervention group (resistance training) or the control group (usual care) to examine the differences between RDI and number of moderate and severe adverse events during chemotherapy. As previously described (16), the intervention consisted of home-based prescribed resistance exercise under the supervision of nationally certified exercise professionals. Patients were eligible to enroll before the initiation of their third chemotherapy cycle. For this study, we combined all patients together as one cohort and adjusted for randomization arm in the analysis. Institutional review board approval was obtained from all participating institutions (Kaiser

Permanente Northern California, Dana-Farber Cancer Institute, and Penn State Cancer Institute), and all participants provided written, informed consent.

Computed tomography (CT) scans performed for colon cancer diagnosis were extracted from clinical imaging archives. Dual-energy X-ray absorptiometry (DXA) was conducted at the enrollment visit for body composition assessment. D3-creatine dilution was assessed as part of an ancillary study requiring additional consent, and an oral dose of D3-creatine was provided at the enrollment visit for patients who agreed to participate. Patients with at least one available body composition technique were combined as the final population (N = 178; Figure 1). Although not every patient undertook all three techniques, patients in each CT (N = 170), DXA (N = 162), and D3Cr (N=118) group were comparable to the final population (N = 178; Supplementary Table 1).

Muscle

To assess CT SMA at L3, a single research assistant segmented muscle from other tissues using anatomic knowledge and the muscle-specific Hounsfield unit range (−29 HU, 150 HU) on SliceOmatic Software (TomoVision Inc., Magog, Canada) (17). Our prior studies suggested high reliability for CT SMA assessment (coefficient of variation [CV]: 1.2%) (17). CT scans were performed at a median of 8.9 (interquartile: [6.4, 11.4]) weeks before study enrollment.

To assess DXA ALM, certified operators performed the scans using well-calibrated DXA machines in the total body scanning mode. We derived DXA ALM by subtracting adipose tissue mass and bone mass from the total mass of arms and legs. DXA assessment was performed at a median of 1 (interquartile: [0, 7]) day after study enrollment.

To assess D3Cr muscle mass, we provided each patient with a single, oral dose of 60mg D3-creatine at the FORCE enrollment visit. Between 3 and 6 days following the oral dose, patients collected their second voids of morning urine after an overnight fast and kept samples frozen until overnight shipment to a central laboratory facility (storage temperature: −20 °C). Samples were then delivered to University of California, Berkeley (Berkeley, CA) to analyze D3-creatinine enrichment. D3Cr muscle mass was calculated using the algorithm of D3Cr spillage correction as previously described (10,18). Prior studies suggest high reliability (CV: <10%) and robustness of D3Cr assessment to the variation of renal function and hydration status (10,18). D3-creatine assessment was performed at a median of 4 (interquartile: [0, 4]) days after study enrollment.

Adipose Tissue

From the CT scans, the same research staff member also segmented TAT (a sum of visceral, subcutaneous, and intermuscular adipose tissue at L3) using anatomic knowledge and adipose-tissue-specific Hounsfield unit ranges (17). From the DXA scans, certified operators also recorded DXA TBF from DXA machines (16). Prior studies suggested high reliability for CT and DXA in adipose tissue assessment (17,19).

Outcomes

The primary outcome was reduced RDI (RDI <85%) of the regimen, which was defined as the average RDI of chemotherapeutic agents (5-fluorouracil, capecitabine, and oxaliplatin). The RDI of each agent was calculated using the Weycker method (11):

$$\text{RDI} = \frac{\text{delivered dose intensity}}{\text{planned dose intensity}}$$

$$= \frac{(\text{delivered total dose in mg/m}^2)/(\text{actual time to complete chemotherapy})}{(\text{planned total dose in mg/m}^2)/(\text{planned time to complete chemotherapy})}$$

Given that DXA and D3-creatine dilution were assessed at enrollment, which was shortly before randomization (resistance training vs. usual care) but could occur after chemotherapy initiation (16), the starting time point of RDI calculation was selected from the first chemotherapy cycle after the intervention randomization.

The secondary outcome was the number of moderate and severe adverse events that patients reported during each cycle of chemotherapy. To collect the information of adverse events, we would email or mail a questionnaire for every time when a chemotherapy appointment was scheduled. The questionnaire was modified based on Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) (15) and included nine common adverse events induced by colon cancer chemotherapy: nausea, vomiting, diarrhea, shortness of breath, hand-foot syndrome, numbness or tingling of hands or feet, pain, muscle aches, and fatigue (16). The collection of patient-reported toxicities (PRO-CTCAE), rather than physician-reported toxicities (CTCAE), was due to the primary goal of FORCE: this trial was focused on reducing patient-reported symptomatic toxicities through resistance training. Moderate and severe adverse events were defined as PRO-CTCAE grade 2 and summed at each cycle of chemotherapy. The median number of self-reported questionnaires that patients completed over the course of the study was 7 (range: 1–14).

Patient Characteristics

We collected patient characteristics through electronic medical records and physical exams at the FORCE enrollment visit: age (years), sex (men, women), race and ethnicity (Asian, Black, Hispanic, non-Hispanic White, and Others), stage (II, III), body mass index (BMI; derived from weight/height^2]), BSA (m^2), 5-fluorouracil per BSA (mg/m^2), capecitabine per BSA (mg/m^2), and oxaliplatin per BSA (mg/m^2).

Statistical Analysis

We compared patients' characteristics by RDI status using the t-test for continuous variables and the χ^2 test for categorical variables. We standardized each measurement of body composition by its sex-specific standard deviation (SD) (Supplementary Table 2). We estimated the associations of each body composition measurement (per SD increase) with reduced RDI using logistic regression, and the relative changes (%) in the number

of moderate and severe adverse events using negative binomial generalized estimating equations (GEE) for repeated measures at each cycle of chemotherapy. The outcome of clinically reduced RDI was dichotomized as <85% (outcome event = 1) vs. 85% (outcome event = 0). The relative change (%) was defined as the absolute difference of the number of adverse events divided by the previous number of adverse events, when the body composition measurement increased by 1 SD (20). Both models were adjusted for age, sex, height, regimen, and randomization arm; and GEE models were additionally adjusted for treatment duration (weeks).

For sensitivity analysis, first, we examined if the findings remained similar after applying common methods of scaling body composition measurements to body size (21,22). Rather than using absolute quantity, we scaled these body composition measurements: CT SMA, DXA ALM, CT TAT, and DXA TBF were divided by height squared (m^2) (21), whereas D3Cr muscle mass was divided body weight (kg) (22). Second, beyond the regimen, we estimated the associations of body composition with reduced RDI separately for each agent (e.g., 5-fluorouracil vs. capecitabine vs. oxaliplatin). Third, rather than counting from the first cycle after randomization, we calculated an alternative RDI by counting from the first cycle when patients started chemotherapy (rather than from randomization as in our main analyses) and estimated its associations with body composition accordingly.

A priori we examined the associations of each body composition measurement with RDI and adverse events separately by sex, given that men and women differ in quantity and distribution of muscle mass and adipose tissue. For stratification analysis, we included the interaction term between sex and each body composition measurement into its corresponding fully adjusted model.

We conducted analyses using SAS statistical software, version 9.4 (SAS Institute, Inc) and R, version 4.2.0 (R Foundation for Statistical Computing). Statistical significance was defined as $P<0.05$ or 95% confidence interval (CI) excluding 1.0 (for odds ratios [OR]) or 0 (for relative changes [%]).

Data Availability Statement

Data described in the manuscript, code book, and analytic code will be made available upon reasonable request.

RESULTS

Of 178 patients, the mean (standard deviation [SD]) age was 55.2 (12.8) years, 94 (52.8%) were men, 116 (65.2%) were non-Hispanic White, and 155 (87.1%) were stage III (Table 1). Eighty-seven (48.9%) experienced reduced RDI (RDI <85%). Of 165 patients self-reporting nine adverse events, 148 (89.7%) reported at least one moderate and severe adverse events during chemotherapy. The mean (SD) number of adverse events were 1.1 (1.5) for the first cycle and 2.1 (2.3) for the last cycle. Compared to patients with RDI 85%, patients with reduced RDI were more likely to be women and had lower BMI, BSA, oxaliplatin per BSA, CT SMA, and DXA ALM (Table 1).

RDI and Adverse Events

One SD increase in CT SMA and DXA ALM were significantly associated with lower risk of reduced RDI (OR: 0.56 [0.38, 0.81] for CT SMA and 0.56 [0.37, 0.84] for DXA ALM). An inverse (non-significant) association was also observed per SD increase in D3Cr muscle mass (OR: 0.80 [0.49, 1.30]), CT TAT (OR: 0.87 [0.63, 1.22]), and DXA TBF (OR: 0.75 [0.52, 1.07]), but confidence intervals were wide (Table 2 and Figure 2).

More muscle or adipose tissue was not significantly associated with the number of moderate and severe adverse events (Table 3 and Figure 3): relative changes in the number of adverse events were 9.7% (−8.2%, 31.1%) for CT SMA, 9.0% (−7.0%, 27.8%) for DXA ALM, −1.5% (−18.5%, 19.1%) for D3Cr muscle mass, 16.0% (−0.4%, 35.0%) for CT TAT, and 15.1% (−1.4%, 34.3%) for DXA TBF.

Unadjusted associations for RDI and adverse events were also included in the Tables 2 and 3 and generally aligned with the adjusted findings (Figures 2 and 3).

Sensitivity Analysis

Overall, the associations of body composition with RDI and adverse events remained similar (Supplementary Tables 3-5). For chemotherapy agents (Supplementary Table 4), associations were similar in magnitude and direction but may differ in statistical significance for capecitabine vs. 5-fluorouracil and oxaliplatin. For example, the associations of CT SMA with reduced RDI were not significant for capecitabine (OR: 0.64 [0.36, 1.12]), but significant for 5-fluorouracil (OR: 0.46 [0.27, 0.78]) and oxaliplatin (OR: 0.62 [0.43, 0.89]). This was very likely due to the differences of sample size for capecitabine (N = 74) vs. 5-fluorouracil (N = 96) and oxaliplatin (N = 155).

Stratification Analysis

Overall, the associations of body composition with RDI and adverse events did not differ by sex (Supplementary Table 6). For adverse events, we observed 1) only one significant interaction with sex ($P_{Interaction}$ = 0.03 for DXA ALM), which could be a chance finding; and 2) the directions of associations of muscle measurements were generally positive for men vs. negative for women. While the results of this secondary outcome and stratified analysis should be interpreted cautiously, this difference may be due to the larger body surface area and absolute and proportional quantities of muscle in men vs. women. This could have led to greater total chemotherapy dose in men and therefore a positive association with the number of adverse events.

DISCUSSION

To our knowledge, this is the first study to use multiple techniques to assess body composition in relation to RDI and adverse events in a cancer population. We found that higher CT SMA and DXA ALM were significantly associated with lower risk of reduced RDI (RDI <85%). However, no measurements of muscle or adipose tissue were significantly associated with the number of moderate and severe adverse events. Overall, these associations did not differ by sex.

Reduced RDI is a summary measure of dose delay, reduction, and discontinuation to signal the chemotherapy completion (11). Prior studies in CRC have investigated the associations of body composition with dose delay, reduction, and discontinuation (23–30), but few studies reported the associations of body composition with RDI among patients with colorectal or other gastrointestinal cancers. If reported, CT scans were most frequently used since they were available opportunistically as part of clinical care. Using 533 patients with colon cancer at stage II/III undertaking FOLFOX (a combination of leucovorin, 5-fluorouracil, and oxaliplatin), we previously reported that higher CT SMA was associated, but not significantly, with lower risk of reduced RDI (OR: 0.46 [0.21, 1.02]) (23). The findings remained similar for stratified chemotherapy agents: the ORs were 0.45 (0.20, 1.01) for 5-fluorouracil and 0.82 (0.40, 1.69) for oxaliplatin (23). Another study included 188 patients with gastric cancer at stage II/III undertaking fluoropyrimidine-based chemotherapy and found that patients with higher psoas muscle index ($3.2 \text{ cm}^2/\text{m}^2$) had higher RDI than those with lower psoas muscle index (<$3.2 \text{ cm}^2/\text{m}^2$): 72.0% vs. 51.6% ($P = 0.02$). However, this analysis was unadjusted for potential confounders such as age (31). No studies reported the association of adipose tissue with RDI among patients with CRC. One study investigated BMI, a surrogate of total body adiposity and found that average RDI of FOLFOX did not differ by BMI groups (32). Overall, our findings were consistent with the small number of previous studies addressing this topic: more muscle is associated with improved chemotherapy completion. The insignificant association between D3Cr muscle mass and reduced RDI (OR: 0.80 [0.49, 1.30]) was likely due to the smaller sample size of the D3Cr group (N = 119) compared to the groups of CT (n = 170) and DXA (N = 162). Such findings also aligned with our observation that women were more likely to have reduced RDI (Table 1), since women typically have less muscle than men (33). Thus, in this analysis, we considered sex differences in body composition and standardized body composition measurements by their sex-specific standard deviations. In addition to muscle assessment, our study is the first to directly assess adipose tissue and report that higher CT TAT and DXA TBF were not associated with reduced RDI: these findings added to the previous literature using BMI only.

Regarding body composition and adverse events in CRC, there were seven studies looking into CT SMA (26,27,29,30,34–36) and one study looking into CT TAT (30). To our knowledge, no prior study reported the associations of DXA ALM, D3Cr muscle mass, or DXA TBF with adverse events. Instead of using the number of moderate and severe events, prior studies focused on the occurrence of any severe event (grade 3) or any dose-limiting toxicity (a result of adverse events leading to dose delay, reduction, and discontinuation). Higher CT SMA was inconsistently associated with the occurrence of severe adverse events or dose limiting toxicities (26,27,29,30,34–36), and some studies with small sample size reported ORs with wide confidence intervals such as 12.99 (1.25, 134.80) and 13.55 (1.08, 169.31) (34,35). The only study examining CT TAT reported no association with dose limiting toxicities (30). In line with previous studies, we found that muscle and adipose tissue were not significantly associated with self-reported moderate or severe adverse events. Adding rigor to our approach, we repeatedly measured adverse events, assessed muscle and adipose tissue with multiple techniques, and adjusted for potential confounders in statistical analyses.

Since most chemotherapeutic agents have narrow therapeutic windows (37), it is important to individualize chemotherapy dosing. Most chemotherapy is dosed on BSA, given the belief that patients have different volumes of distribution and metabolizing capacities if they differ in body size (4). However, it is well-known that body composition often differs between patients with the same BSA (38), and body compartments including muscle and adipose tissue may have different impact on pharmacokinetics. For example, skeletal muscle accounts for 40% of body mass and is 75% water (39), which makes it the largest body compartment for the distribution of hydrophilic chemotherapy agents and many drugs to treat colon cancer (such as 5-fluorouracil) are hydrophilic (40). In this study, we found that more muscle was significantly associated with lower risk of reduced RDI, particularly for 5-fluorouracil (OR: 0.46 [0.27, 0.78] for CT SMA and 0.47 [0.26, 0.84] for DXA ALM) (41). Since patients with more muscle may have improved chemotherapy completion, one may hypothesize that patients with more muscle should have lower numbers of moderate and severe advents. However, adverse events are very common in the chemotherapy treatment and increase with duration of chemotherapy (42). In this study, we found that 89.7% of patients reported at least one adverse event during chemotherapy (similar to ~90% reported by prior studies (43,44)) and patients with more muscle safely endured more chemotherapy doses without more adverse events. For example, more muscle may attenuate chemotherapy-induced inflammatory responses that can contribute to neuropathy and other adverse events (45), whereas low muscle is an important indicator for frailty and accelerated biological age that have been frequently linked to increased risk of chemotherapy intolerance and adverse events (46,47). Increasing evidence suggests incorporating biomarkers of frailty and biological age may help personalize cancer treatment and supportive care (48,49), which further supports the importance of examining the role of muscle in chemotherapy dosing, completion, and adverse events.

As for adipose tissue, it was previously commonplace for oncologists to cap the chemotherapy dose for obese patients with high BSA (e.g., >2 m^2) (50). However, the latest ASCO guideline suggested full dosing, given that obese patients tolerate chemotherapy as well as nonobese patients (6). In line with this latest suggestion, our findings suggested that increased adiposity (CT TAT and DXA TBF) was not associated with unfavorable chemotherapy outcomes. One possible explanation is that most chemotherapeutic agents are partly distributed through adipose tissue unless they have weak lipophilicity (51). For example, while 5-fluorouracil and oxaliplatin are often considered as hydrophilic, they also have moderate lipophilicity, especially for lipophilic derivatives of 5-fluorouracil and oxaliplatin (52,53); and capecitabine is generally considered as a lipophilic chemotherapeutic agent (51). Thus, chemotherapy dosing should consider both adipose tissue and pharmacokinetics of specific drugs.

Clinical Impact

Our findings have the potential to inform clinical practice. Using multiple imaging and biochemical techniques, we assessed muscle and adipose tissue among patients with colon cancer and investigated their associations with chemotherapy completion and adverse events. We found that more muscle was associated with improved chemotherapy completion, whereas neither muscle nor adipose tissue was associated with adverse events. While most

chemotherapies are dosed on body surface area without considering body composition, these findings suggest that patients with increasing pre-chemotherapy muscle (as measured by 1 SD increase of CT SMA or DXA ALM) may tolerate treatment better and therefore are less likely to experience reduced RDI (RDI <85%). Future studies should investigate clinical thresholds of muscle, below which can identify patients at higher risk of reduced RDI (RDI <85%).

Strengths and Limitations

This study has several strengths including multiple techniques to assess muscle and adipose tissue and a variety of robust statistical and sensitivity analyses. However, several limitations should be noted. First, the sample size is relatively small, and a larger study is needed to generate more precise estimates of the impact of body composition on colon cancer chemotherapy outcomes. Second, this study focused on body composition at study enrollment: longitudinal studies with repeated body composition assessments are needed to confirm these findings. Third, each assessment may be subject to measurement error, which can weaken the associations. For example, multiple types of clinical CT and research DXA scanners were used across sites, which may lead to minor differences in the quantification of muscle and adiposity. Fourth, we assessed body composition using a single manually segmented CT slice, rather than over a larger field of view or at multiple anatomic landmarks. However, single-slice abdominal measurements of muscle and adipose tissue are considered a reference method for body composition, and they correlate well with the whole-body volumes from MRI (7). Fifth, we did not have information regarding adverse events for chemotherapy cycles prior to study enrollment. Sixth, our study population was derived from an intervention trial, which may be younger and have better physical function than the general colon cancer population.

In conclusion, more muscle was associated with improved chemotherapy completion among patients with nonmetastatic colon cancer. No measurements of muscle or adipose tissue were significantly associated with percent changes in the number of self-reported moderate and severe adverse events over time following enrollment into the FORCE study. Considering body composition in colon cancer treatment may help personalize chemotherapy dosing and identify patients at high risk of reduced dose intensity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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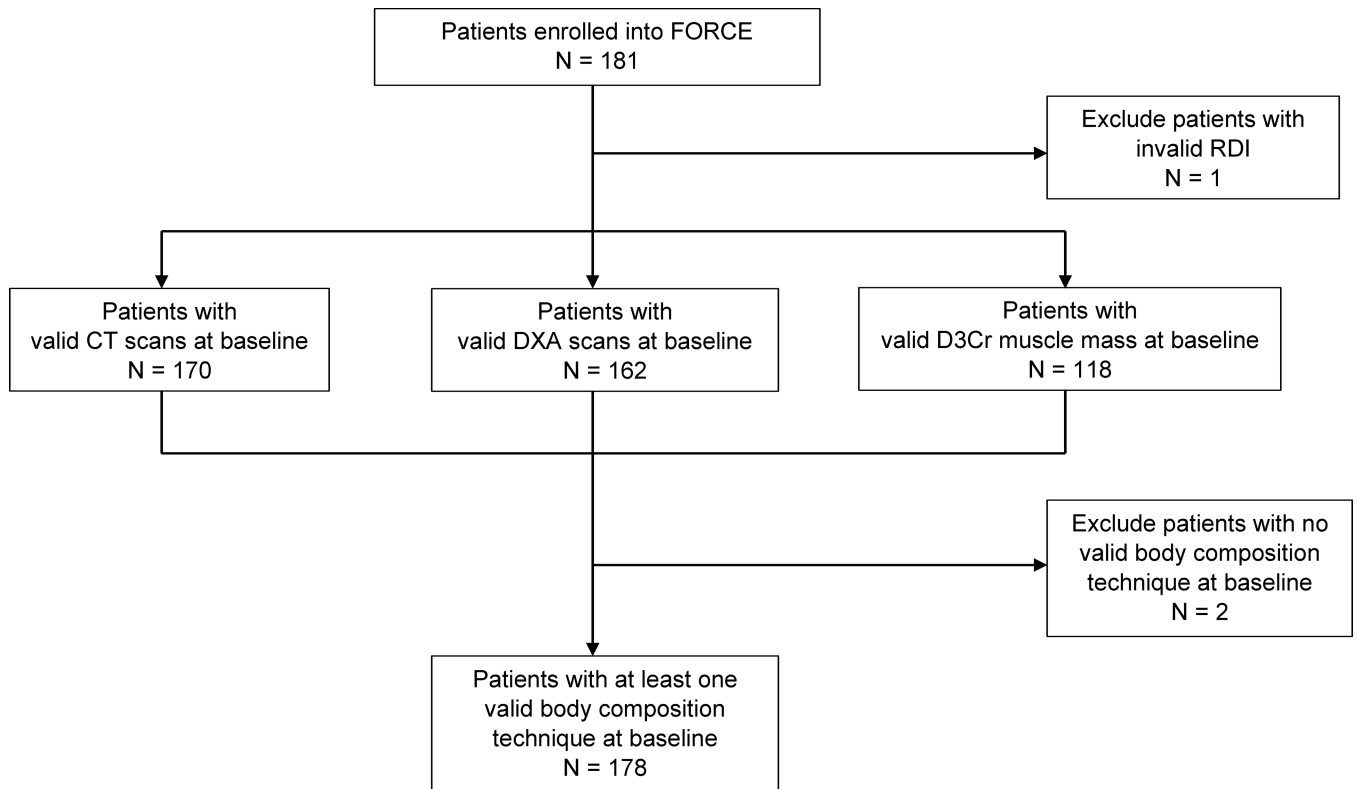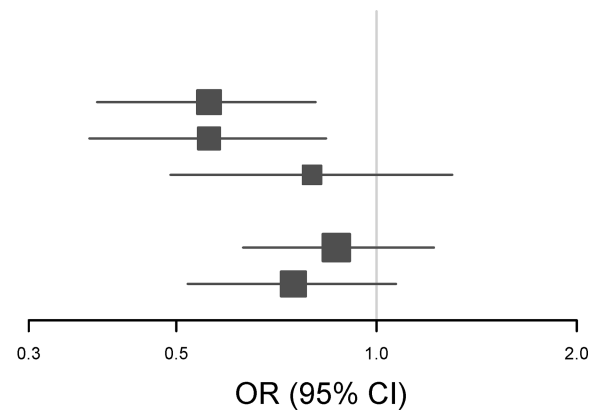
Figure 1.

The Flow Diagram of Patients in FORCE for Analysis of Body Composition, Relative Dose Intensity, and Adverse Events

Abbreviations: CT, computed tomography; D3Cr, D3-creatine; DXA, Dual X-Ray Absorptiometry; FORCE, FOcus on Reducing Dose-Limiting Toxicities in Colon Cancer with Resistance Exercise; RDI, relative dose intensity.

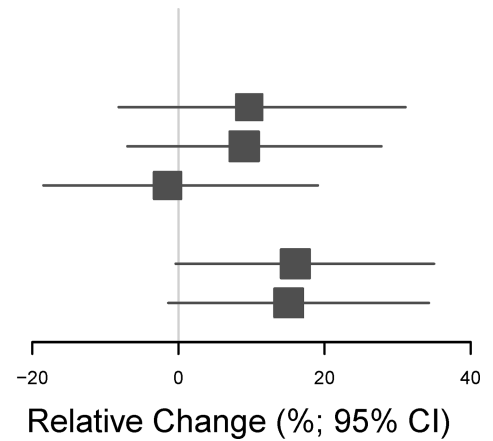| Body Composition Measurements	OR (95% CI)
Muscle	
CT SMA	0.56 (0.38, 0.81)
DXA ALM	0.56 (0.37, 0.84)
D3Cr Muscle Mass	0.80 (0.49, 1.30)
Adipose Tissue	
CT TAT	0.87 (0.63, 1.22)
DXA TBF	0.75 (0.52, 1.07)

OR (95% CI)

Figure 2.

The Adjusted[a] Associations of Body Composition Measurements (Per SD Increase) with Reduced RDI

Abbreviations: ALM, appendicular lean mass; CI, confidence interval; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; D3Cr, D3-creatine; RDI, relative dose intensity; OR, odds ratio; SD, standard deviation; SMA, skeletal muscle area; TAT, total adipose tissue; TBF, total body fat.

[a] Adjusted for age (years), sex (men, women), height (cm), regimen (FOLFOX/5FU-LV, CAPOX/CAPE), and randomization arm (resistance training, usual care).

Body Composition Measurements	Relative Change (%)
Muscle	
CT SMA	9.7 (−8.2, 31.1)
DXA ALM	9.0 (−7.0, 27.8)
D3Cr Muscle Mass	−1.5 (−18.5, 19.1)
Adipose Tissue	
CT TAT	16.0 (−0.4, 35.0)
DXA TBF	15.1 (−1.4, 34.3)

Relative Change (%; 95% CI)

Figure 3.

The Adjusted[a] Associations of Body Composition Measurements (Per SD Increase) with the Relative Changes (%) in the Number of Moderate and Severe Adverse Events

Abbreviations: ALM, appendicular lean mass; CI, confidence interval; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; D3Cr, D3-creatine; SD, standard deviation; SMA, skeletal muscle area; TAT, total adipose tissue; TBF, total body fat.

[a] Adjusted for age (years), sex (men, women), height (cm), regimen (FOLFOX/5FU-LV, CAPOX/CAPE), randomization arm (resistance training, usual care), and treatment duration (weeks).

Table 1.

Patient Characteristics Among 178 Patients with Nonmetastatic Colon Cancer by RDI Status (<85% vs. 85%)

Characteristics[a]	All (N = 178)	RDI <85% (N = 87)	RDI 85% (N = 91)	P-value[b]
Age (years)	55.2 (12.8)	55.6 (13.5)	54.8 (12.2)	0.66
Sex				0.02
Men	94 (52.8)	38 (43.7)	56 (61.5)	
Women	84 (47.2)	49 (56.3)	35 (38.5)	
Race				0.89
Asian	22 (12.4)	12 (13.8)	10 (11.0)	
Black	13 (7.3)	5 (5.7)	8 (8.8)	
Hispanic	18 (10.1)	8 (9.2)	10 (11.0)	
Non-Hispanic White	116 (65.2)	57 (65.5)	59 (64.8)	
Others[c]	9 (5.1)	8 (9.2)	4 (4.4)	
Stage				0.22
II	23 (12.9)	15 (16.1)	9 (9.89)	
III	155 (87.1)	78 (83.9)	77 (90.6)	
BMI (kg/m^2)	27.4 (5.6)	26.4 (5.6)	28.4 (5.4)	0.02
BMI Categories				0.04
Underweight (<18.5 kg/m^2)	1 (0.6)	1 (1.1)	0 (0)	
Normal (18.5– 24.9 kg/m^2)	68 (38.2)	41 (47.1)	27 (29.7)	
Overweight (25–29.9 kg/m^2)	55 (30.9)	24 (27.6)	31 (34.1)	
Obese (30 kg/m^2)	54 (30.3)	21 (24.1)	33 (36.3)	
BSA (m^2)	1.9 (0.3)	1.9 (0.2)	2.0 (0.3)	0.02
5-fluorouracil per BSA (mg/m^2)	2,732.4 (334.3)	2,706.8 (421.3)	2,769.9 (122.4)	0.34
Capecitabine per BSA (mg/m^2)	1,884.7 (238.4)	1,900.7 (244.1)	1,874.7 (236.7)	0.64
Oxaliplatin per BSA (mg/m^2)	101.1 (21.9)	97.2 (19.9)	104.6 (23.2)	0.03
CT SMA (cm^2)	144.3 (39.1)	132.3 (35.0)	154.8 (39.6)	<0.001
DXA ALM (kg)	20.9 (5.6)	19.5 (5.5)	22.1 (5.3)	0.002
D3Cr Muscle (kg)	26.7 (7.5)	25.5 (7.4)	27.8 (7.4)	0.10
CT TAT (cm^2)	364.7 (198.9)	343.9 (197.3)	382.8 (199.6)	0.21

Characteristics[a]	All (N = 178)	RDI <85% (N = 87)	RDI 85% (N = 91)	P-value[b]
DXA TBF (kg)	27.2 (10.0)	26.2 (9.7)	28.1 (10.2)	0.23

Abbreviations: ALM, appendicular lean mass; BMI, body mass index; BSA, body surface area; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; D3Cr, D3-creatine; SMA, skeletal muscle area; TAT, total adipose tissue; TBF, total body fat.

[a] Continuous variables were presented as mean (standard deviation) and categorical variables as number (%). Percentages may not add up to 100% because of rounding.

[b] P-values were calculated using the t-test for continuous variables and the χ^2 test for categorical variables. If the assumption of the χ^2 test was violated, the Fisher exact test was used instead.

[c] Patients who did not self-identify as Asian, Black, Hispanic, or non-Hispanic White were classified as others for race.

Table 2.

The Adjusted and Unadjusted Associations of Body Composition Measurements (Per SD Increase) with the Odds Ratios for Reduced RDI (RDI <85%)

Body Composition Measurements	Sample Size	Events[a]	Reduced RDI	
			Unadjusted	Adjusted[b]
Muscle				
CT SMA	170	79	0.76 (0.57, 1.03)	0.56 (0.38, 0.81)
DXA ALM	162	76	0.66 (0.49, 0.89)	0.56 (0.37, 0.84)
D3Cr Muscle Mass	118	56	1.09 (0.80, 1.49)	0.80 (0.49, 1.30)
Adipose Tissue				
CT TAT	170	79	0.83 (0.61, 1.13)	0.87 (0.63, 1.22)
DXA TBF	162	76	0.75 (0.54, 1.03)	0.75 (0.52, 1.07)

Abbreviations: ALM, appendicular lean mass; CI, confidence interval; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; D3Cr, D3-creatine; RDI, relative dose intensity; SD, standard deviation; SMA, skeletal muscle area; TAT, total adipose tissue; TBF, total body fat.

[a]Events refer to the number of reduced RDI.

[b]Adjusted for age (years), sex (men, women), height (cm), regimen (FOLFOX/5FU-LV, CAPOX/CAPE), and randomization arm (resistance training, usual care).

Table 3.

The Adjusted and Unadjusted Associations of Body Composition Measurements (Per SD Increase) with the Relative Changes (%) in the Number of Moderate and Severe Adverse Events

Body Composition Measurements	Sample Size	Occurrence Number (%)	Event Number at First Cycle[a]	Event Number at Last Cycle[a]	Relative Changes(%)	
					Unadjusted	Adjusted[b]
Muscle						
CT SMA	157	140 (89.2%)	1.1 (1.5)	2.0 (2.4)	11.0 (−3.4, 27.6)	9.7 (−8.2, 31.1)
DXA ALM	156	139 (89.1%)	1.1 (1.5)	2.0 (2.4)	6.3 (−7.3, 22.0)	9.0 (−7.0, 27.8)
D3Cr Muscle Mass	113	97 (85.8%)	0.9 (1.5)	1.7 (2.0)	2.2 (−9.4, 15.3)	-1.5 (−18.5, 19.1)
Adipose Tissue						
CT TAT	157	140 (89.2%)	1.1 (1.5)	2.0 (2.4)	13.9 (−1.6, 31.8)	16.0 (−0.4, 35.0)
DXA TBF	156	139 (89.1%)	1.1 (1.5)	2.0 (2.4)	13.6 (−1.9, 31.6)	15.1 (−1.4, 34.3)

Abbreviations: ALM, appendicular lean mass; CI, confidence interval; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; D3Cr, D3-creatine; SD, standard deviation; SMA, skeletal muscle area; TAT, total adipose tissue; TBF, total body fat.

[a] Event number refers to the mean (SD) number of moderate and severe adverse events.

[b] Adjusted for age (years), sex (men, women), height (cm), regimen (FOLFOX/5FU-LV, CAPOX/CAPE), randomization arm (resistance training, usual care), and treatment duration (weeks).