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Computed Tomography-Based Body Composition Is Not Consistently Associated with Outcome in Older Patients with Colorectal Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Body composition • Computed tomography • Colorectal neoplasms • Aged • Surgery • Adjuvant chemotherapy

Abstract

Background. Current literature is inconsistent in the associations between computed tomography (CT)-based body composition measures and adverse outcomes in older patients with colorectal cancer (CRC). Moreover, the associations with consecutive treatment modalities have not been studied. This study compared the associations of CT-based body composition measures with surgery- and chemotherapy-related complications and survival in older patients with CRC.

Materials and Methods. A retrospective single-center cohort study was conducted in patients with CRC aged ≥65 years who underwent elective surgery between 2010 and 2014. Gender-specific standardized scores of preoperative CT-based skeletal muscle (SM), muscle density, intermuscular adipose tissue (IMAT), visceral adipose tissue (VAT), subcutaneous adipose tissue, IMAT percentage, SM/VAT, and body mass index (BMI) were tested for their associations with severe postoperative complications, prolonged length of stay (LOS), readmission, and dose-limiting toxicity using logistic regression and 1-year and long-term survival (range 3.7–6.6 years) using Cox regression. Bonferroni correction was applied to account for multiple testing.

Results. The study population consisted of 378 patients with CRC with a median age of 73.4 (interquartile range 69.5–78.4) years. Severe postoperative complications occurred in 13.0%, and 39.4% of patients died during follow-up. Dose-limiting toxicity occurred in 77.4% of patients receiving chemotherapy (n = 53). SM, muscle density, VAT, SM/VAT, and BMI were associated with surgery-related complications, and muscle density, IMAT, IMAT percentage, and SM/VAT were associated with long-term survival. After Bonferroni correction, no CT-based body composition measure was significantly associated with adverse outcomes. Higher BMI was associated with prolonged LOS.

Conclusion. The associations between CT-based body composition measures and adverse outcomes of consecutive treatment modalities in older patients with CRC were not consistent or statistically significant. ***The Oncologist*** 2019;25:1–10

Implications for Practice: Computed tomography (CT)-based body composition, including muscle mass, muscle density, and intermuscular, visceral, and subcutaneous adipose tissue, showed inconsistent and nonsignificant associations with surgery-related complications, dose-limiting toxicity, and overall survival in older adults with colorectal cancer. This study underscores the need to verify whether CT-based body composition measures are worth implementing in clinical practice.

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Introduction

Colorectal cancer (CRC) is a highly prevalent disease in older individuals, representing more than 10% of all new cancer cases worldwide [1]. The cornerstone of CRC treatment is surgical resection, potentially preceded by neoadjuvant (chemo) radiation in rectal cancer or followed by adjuvant chemotherapy in patients with high-risk stage II and stage III colon cancer [2]. Older patients with CRC are known to have a higher risk of adverse outcomes such as postoperative complications, prolonged length of stay (LOS), dose reductions and early discontinuation of chemotherapy, and higher overall and cancer-related mortality compared with younger patients [3–6].

Computed tomography (CT)-based body composition measures, and especially skeletal muscle mass (SM), muscle density, which is a measure of muscle quality determined by fat infiltration [7], and visceral adipose tissue (VAT), have been proposed as predictors of adverse outcomes in older patients with CRC [8–12]. However, although several studies have revealed an association between SM and severe or infectious postoperative complications [11, 13], a lack of association with severe postoperative complications was found in other studies [9, 10, 14]. Muscle density was found to be associated with long-term overall survival [15–17], in contrast to other studies [9–11]. For VAT, the association with prolonged LOS showed both positive and negative results [18]. Therefore, it remains to be proved if CT-based body composition measures show consistent and statistically significant associations with adverse outcomes in older patients with CRC to be clinically relevant. Moreover, the predictive value of CT-based body composition measures on consecutive treatment modalities including both surgery- and chemotherapy-related complications within the same cohort of (older/CRC) cancer patients has not been reported yet.

The aim of this study was to compare CT-based body composition measures regarding their predictive value of adverse outcomes in older patients with CRC, including surgery-related complications, dose-limiting chemotherapy toxicity, and overall survival.

Materials and Methods

Study Population

This is a retrospective single-center cohort study evaluating the PREdictive value of MUScle mass in CoLorectal cancer in Elderly (PREMUSCLE), in patients with primary CRC aged 65 years and older who underwent elective surgery between 2010 and 2014 at Medical Spectrum Twente, a large non-academic teaching hospital in The Netherlands. The study population of 472 older patients with CRC was selected from the Dutch ColoRectal Audit (DCRA), which contains prospectively collected information on patient and tumor characteristics, treatment, and outcomes of CRC surgery. Patients were excluded if (a) there were two or more primary tumors requiring surgery (n = 41); (b) pathology reports concluded the primary tumor was benign or noncolorectal (n = 12); (c) surgery was classified as acute, urgent, or elective after stent placement because of an increased risk of complications (n = 4); (d) data on body height and/or weight were missing (n = 4); (e) data on outcome measures were missing (n = 1); (f) there was no preoperative CT scan available on the level at the third lumbar vertebra (L3; n = 14); or (g) CT scan was not eligible for analysis because of quality issues such as artifacts or frame selection (n = 18). This led to the inclusion of 378 older patients with CRC, as is shown in Figure 1. Patient data were retrieved from the DCRA and hospital information system and included gender, age, body weight, height, preoperative number of comorbidities and medications (both retrieved by medical record review), Karnosfky Performance Scale score (range 0–100), tumor- and treatment-related characteristics, and predefined outcome measures. Survival data were extracted from the civil registry. The study has been approved by the Medical Ethics Committee of the Amsterdam University Medical Center, location VU Medical Center, with site-specific approval of Medical Spectrum Twente.

CT-Based Body Composition

Body composition was measured by analyzing single-slice abdominal CT scans at L3 that were obtained preoperatively for staging purposes. Single-slice CT scan analysis was performed because SM area and adipose tissue area at L3 are highly correlated with total body SM and total body adipose tissue volume [19, 20]. CT scans were analyzed using medical imaging software SliceOMatic version 5.0 (TomoVision, Montreal, QC, Canada), which identifies body tissues based on the Hounsfield Units (HU). CT scan analyses were performed by a trained and certified researcher (S.L.). Imaging quality was assessed on the identification of the following muscles: rectus abdominis, transversus abdominis, internal and external oblique, quadratus lumborum, erector spinae, and psoas. In case of unilateral quality issues in a symmetrical image, unilateral body composition area was determined and multiplied by two. CT scans in which total SM could not be determined were excluded. A second assessor was consulted in case of doubt (n = 15) about inclusion or multiplication of body composition area (W.L.). Tissues were identified by HU ranges: SM −29 to +150 HU; intermuscular adipose tissue (IMAT) and subcutaneous adipose tissue (SAT) −190 to −30 HU; VAT −150 to −50 HU [20, 21]. Total cross-sectional surface area in cm^2 of each tissue was computed by multiplying the pixel area with the amount of pixels. Skeletal muscle index (SMI) was calculated by dividing SM (cm^2) by height^2 (m^2). The percentage of IMAT was calculated as a measure of fattiness of the muscle by IMAT/(IMAT+SM)*100; the ratio between SM and VAT as a measure of sarcopenic obesity. Muscle density was determined by the mean HU of muscle tissue, lower HU is a sign of more fat infiltration within the muscle [7]. Median tube potential of CT scans was 120 kilovolts (range 100–135 kilovolts), and slice thickness was 3 millimeters (range 1–5 millimeters). All contrast-enhanced CT scans were used. The intra- and interobserver correlation coefficient for variability of body composition measures were calculated using a two-way mixed model with absolute agreement. Intraobserver correlation coefficient for variability was 0.991–1.000 based on a random selection of n = 10, and interindividual correlation coefficient for variability was 0.971–1.000 based on a random selection of n = 24 (A.V.).

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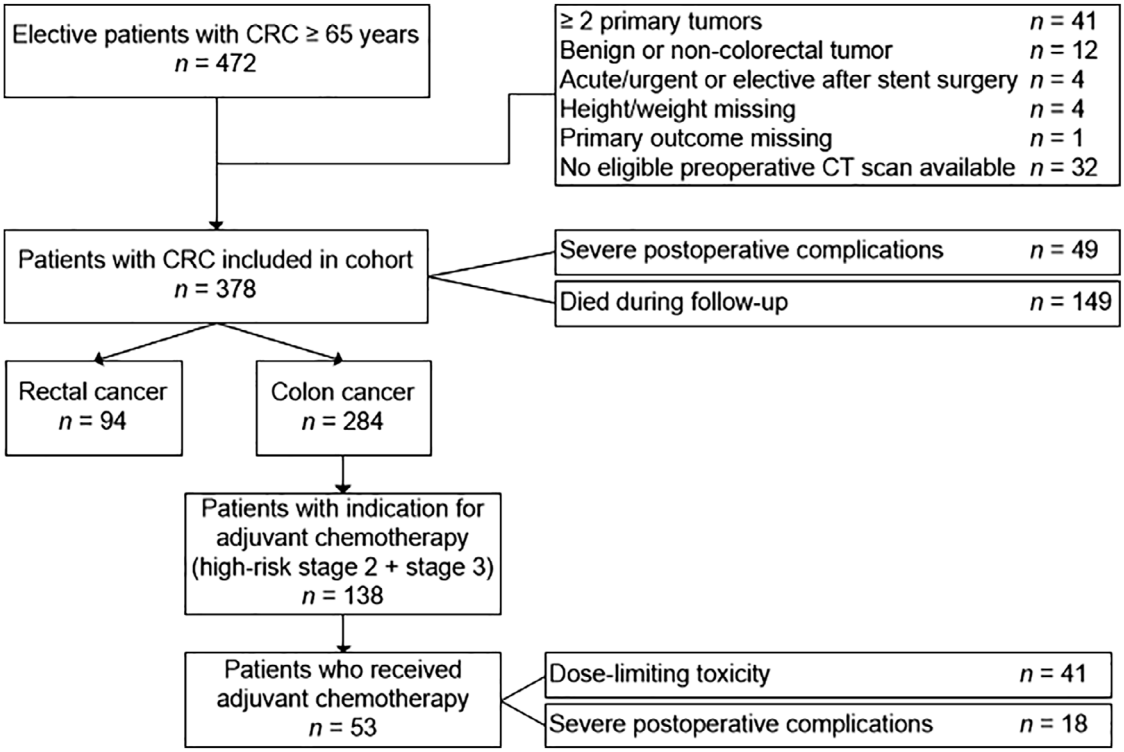

Figure 1. Flowchart of selection of patients.
Abbreviations: CRC, colorectal cancer; CT, computed tomography.

Adjuvant Chemotherapy

Based on the Tumor, Node, Metastasis classification, all patients were postoperatively classified into a cancer stage according to the American Joint Committee on Cancer guidelines [22]. Patients with high-risk stage II and stage III colon cancer were considered for adjuvant chemotherapy treatment [2], which consisted of folinic acid, fluorouracil and oxaliplatin, capecitabine and oxaliplatin, capecitabine monotherapy, or folinic acid and fluorouracil according to national guidelines. Equivalent variables were used to identify patients with high-risk stage II colon cancer in that era: (a) T4 tumor; (b) less than 10 lymph nodes found; (c) venous vascular or lymph invasion of the tumor; (d) poorly differentiated tumor; and (e) preoperative obstruction or perforation of the colon or rectum. Dihydropyrimidine dehydrogenase deficiency was not taken into consideration because this was not routinely tested in The Netherlands at the time of the study. A multidisciplinary team including a gastroenterologist, gastrointestinal surgeon, radiologist, radiotherapist, and medical oncologist decided whether a patient would be referred to the medical oncology department to discuss adjuvant chemotherapy treatment. If so, patients were directed to the medical oncologist, who decided together with the patient on the initiation of adjuvant chemotherapy treatment.

Outcome Measures

Surgery-related complications included severe postoperative complications, prolonged LOS, and readmission. Severe postoperative complications were defined as any grade 3 (requiring reintervention), grade 4 (requiring intensive care unit admittance), or grade 5 (death) surgical or medical complication according to the Clavien-Dindo Classification of Surgical Complications, during admission or within 30 days after surgery [23]. Surgical complications included anastomotic leakage, intra-abdominal abscess, wound or fascial dehiscence, stoma-related complications, blood loss >500 milliliters or postoperative hemorrhage, incisional hernia, bowel injury, or injury to another organ. Medical complications included respiratory, cardiac, thromboembolic, infectious, neurological, and other complications. LOS was calculated as the number of days between the day of surgery until the day of discharge after surgery and dichotomized into LOS ≤14 days and prolonged LOS of >14 days because prolonged LOS is associated with postoperative complications [24]. Readmissions included readmission to the hospital for any reason within 30 days after discharge.

Chemotherapy-related outcome for the subgroup receiving adjuvant chemotherapy was defined as dose-limiting toxicity, which was chemotherapy toxicity that led to a dose reduction or early discontinuation.

Survival was defined as 1-year and long-term overall survival, with a median follow-up of 5.3 (interquartile range [IQR] 3.7–6.6) years. Survival time was calculated from the day of surgery until the day of death of any cause (died) or the April 23, 2019 (censored).

Statistical Analyses

Variables are described by number (percentage), mean ± SD, or median (IQR). To avoid dichotomization of the determinants by using cutoff points, CT-based body composition measures (SM, SMI, muscle density, IMAT, VAT, SAT, IMAT percentage, and SM/VAT) and body mass index (BMI) were analyzed continuously, using gender-specific standardized *Z* scores to enable comparison of the body composition measures. Variables that were not normally distributed

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Table 1. Patient characteristics for all patients and stratified by adjuvant chemotherapy treatment

Characteristics	All patients (*n* = 378)	Received chemotherapy (*n* = 53)
Demographics		
Gender, male	228 (60.3)	30 (56.6)
Age, median (IQR), years	73.4 (69.5–78.4)	70.9 (67.5–73.5)
Comorbidity, median (IQR), *n*	2.0 (1.0–3.0)	1.0 (1.0–2.5)
Medication, median (IQR), *n*	4.0 (2.0–6.5)[a]	2.0 (1.0–4.0)
Karnofsky score, ≥90	173 (51.2)[b]	39 (75.0)[c]
Tumor characteristics		
Primary tumor, colon	284 (75.1)	53 (100.0)
Tumor stage, colon cancer	284	53
Stage I	56 (19.7)	—
Stage II, low-risk	54 (19.0)	—
Stage II, high-risk	42 (14.8)	1 (1.9)
Stage III	96 (33.8)	52 (98.1)
Stage IV	26 (9.2)	—
Stage T0/unknown	10 (3.6)	—
Tumor stage, rectum cancer	94	
Stage I	34 (36.2)	—
Stage II	22 (23.4)	—
Stage III	20 (21.3)	—
Stage IV	4 (4.3)	—
Stage T0/unknown	14 (14.9)	—
Body composition		
Body weight, mean ± SD, kg	79.2 ± 14.4	82.7 ± 13.7
Height, mean ± SD, cm	170.7 ± 9.0	172.5 ± 7.8
BMI, mean ± SD, kg/m^2	27.1 ± 4.1	27.7 ± 3.7
SM, mean ± SD, cm^2	129.1 ± 29.7	138.7 ± 33.1
SMI, mean ± SD, cm^2/m^2	44.0 ± 8.1	46.3 ± 8.9
Muscle density, mean ± SD, HU	31.2 ± 8.0	32.4 ± 7.5
IMAT, median (IQR), cm^2	13.2 (9.1–19.7)	14.4 (10.0–18.2)
VAT, mean ± SD, cm^2	193.9 ± 107.3[d]	204.0 ± 117.0
SAT, median (IQR), cm^2	172.6 (126.9–220.5)[e]	180.6 (133.2–217.0)[f]
IMAT, median (IQR), %	9.3 (6.7–14.4)	9.1 (6.4–12.3)
SM/VAT, median (IQR), cm^2	0.7 (0.5–1.1)[d]	0.7 (0.5–1.2)
Surgery		
Surgical approach, laparoscopic	217 (57.4)	39 (73.6)
Postoperative complication <30 days	180 (47.6)	21 (39.6)
Severe postoperative complication	49 (13.0)	5 (9.4)
LOS, median (IQR), days	6.5 (5.0–11.0)	5.0 (4.0–7.5)
Prolonged LOS, ≥14 days	56 (14.8)	5 (9.4)
Readmission <30 days	46 (12.2)	4 (7.5)
Chemotherapy		
Chemotherapeutic agent		53
Capecitabine	—	26 (49.1)
CAPOX	—	23 (43.4)
FOLFOX	—	1 (1.9)
5FU/LV	—	3 (5.7)
Toxicity, all grade	—	46 (86.8)
Dose reduction	—	28 (52.8)

(continued)

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Table 1. (continued)

Characteristics	All patients (*n* = 378)	Received chemotherapy (*n* = 53)
Early discontinuation	—	26 (49.1)
Dose-limiting toxicity	—	41 (77.4)
Survival		
One-year overall survival, died	26 (6.9)	2 (3.8)
Long-term overall survival, died	149 (39.4)	18 (34.0)

All variables are presented in *n* (%) unless otherwise indicated. The subgroup of patients undergoing chemotherapy consisted of patients with high-risk stage II and stage III colon cancer.
Data available of [a]*n* = 373; [b]*n* = 338; [c]*n* = 52; [d]*n* = 376; [e]*n* = 310; and [f]*n* = 41.
Abbreviations: 5FU, fluorouracil; BMI, body mass index; CAPOX, capecitabine and oxaliplatin; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HU, Hounsfield units; IMAT, intermuscular adipose tissue; IQR, interquartile range; LOS, length of stay; LV, leucovorin (folinic acid); SAT, subcutaneous adipose tissue; SM, skeletal muscle; SMI, skeletal muscle index; VAT, visceral adipose tissue.

were log-transformed before standardization (IMAT, SAT, IMAT percentage, and SM/VAT). The associations between gender-specific standardized body composition measures and treatment-related adverse outcomes were analyzed using bivariate logistic regression for severe postoperative complications, prolonged LOS, readmission, and dose-limiting toxicity and Cox proportional hazards model for 1-year and long-term overall survival. For survival analyses, survival time in months was used. All analyses were performed using a crude model and an adjusted model for age, stage of disease, and number of medications (model 1) to adjust for possible confounders. Stage of disease was considered because of its association with cachexia [25] and cancer-related outcomes. Number of medications was considered as a reflection of overall health and severity of the number of comorbidities that could influence both body composition and the risk of adverse outcomes [26]. The associations between SM and SMI and adverse outcomes were additionally adjusted for BMI ≥30 kg/m^2 (model 2), to eliminate the potential influence of sarcopenic obesity. The cutoff BMI ≥30 kg/m^2 was chosen because it was identified as an independent predictor of complicated postoperative course in patients with CRC in The Netherlands [27]. Owing to the number of determinant variables (9) and outcome measures (6) that were tested, a Bonferroni correction for 54 tests was applied to avoid type 1 errors. Therefore, *p* values of <.001 were considered statistically significant. Sensitivity analyses were performed on the possible impact of (a) the time interval between CT scan and surgery, by excluding CT scans made more than 8 weeks before surgery (analyses with *n* = 304); (b) estimations based on unilaterally determined body composition area, by excluding CT scans in which surface area was multiplied (*n* = 352); and (c) stratification of colon cancer (*n* = 284) and rectum cancer (*n* = 94). Post hoc analyses were performed to clarify associations, by stratifying for Karnofsky Performance Scale score based on the median of the study population, ≤80 (*n* = 165) and ≥ 90 (*n* = 173). Statistical analyses were performed using IBM SPSS Statistics version 25 (IBM SPSS Statistics, Feltham, U.K.).

Results

Patient Characteristics

The study population of 378 older patients with CRC consisted of 284 with colon cancer (75.1%) and 94 with rectal cancer (24.9%). The median age of the total cohort was 73.4 (IQR 69.5–78.4) years, and 228 patients were male (60.3%). In total, 13.0% of all patients experienced a severe postoperative complication, prolonged LOS occurred in 14.8%, and 12.2% of patients were readmitted to the hospital within 30 days after discharge. After 1-year and more than 5-years of follow-up, 6.9% and 39.4%, respectively, of patients had died. The subgroup of patients who had an indication for adjuvant chemotherapy consisted of 138 patients with high-risk stage II or stage III colon cancer (36.5%). In 53 of these patients, of whom 1 had high-risk stage II colon cancer, adjuvant chemotherapy was initiated (38.4%). Reasons for not initiating adjuvant chemotherapy were decision by the medical oncologist or multidisciplinary team, patients' preference, or both. Of 53 patients with colon cancer, 41 (77.4%) treated with adjuvant chemotherapy experienced dose-limiting toxicity. Patient characteristics of the total cohort and the subgroup of patients who received adjuvant chemotherapy are shown in Table 1.

Surgery-Related Complications and Dose-Limiting Toxicity

Table 2 shows the associations between gender-specific standardized body composition measures and severe postoperative complications, prolonged LOS, readmission, and dose-limiting toxicity. Higher SM and SMI were associated with a higher risk of readmission, and higher SM was associated with prolonged LOS in the adjusted models. Lower muscle density was associated with severe postoperative complications in the adjusted model. Higher VAT was associated with a higher risk of severe postoperative complications, prolonged LOS, and readmission. Higher SM/VAT was associated with a lower risk of prolonged LOS and readmission. Higher BMI was associated with a higher risk of severe postoperative complications and prolonged LOS. BMI showed the strongest association of all body composition measures with severe postoperative complications and prolonged LOS. VAT was most strongly associated with the risk of readmission. After applying Bonferroni correction, BMI remained statistically significant in its association with prolonged LOS in the crude model. None of the body composition measures showed a significant association with dose-limiting toxicity in crude or adjusted analyses.

One-Year and Long-Term Overall Survival

None of the body composition measures were associated with 1-year overall survival. For long-term overall survival, muscle density was associated with a lower mortality risk whereas IMAT and IMAT percentage were associated with a higher mortality

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Table 2. Associations between computed tomography-based body composition and surgery-related complications and dose-limiting toxicity

Z-scores body composition measures	Surgery-related complications (n = 378)						Chemotherapy (n = 53)	
	Severe postoperative complications		LOS > 14 days		Readmission		Dose-limiting toxicity	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Z SM, cm^2								
Crude	1.255	0.936–1.681	1.253	0.949–1.654	1.445[a]	1.071–1.950	0.722	0.405–1.287
Model 1	1.309	0.942–1.819	1.452[a]	1.054–2.002	1.532[a]	1.097–2.140	0.676	0.360–1.270
Model 2	1.315	0.938–1.844	1.434[a]	1.033–1.991	1.603[a]	1.130–2.275	0.604	0.299–1.219
Z SMI, cm^2/m^2								
Crude	1.118	0.833–1.502	1.175	0.890–1.550	1.463[a]	1.089–1.965	0.634	0.350–1.146
Model 1	1.169	0.851–1.605	1.327	0.980–1.798	1.503[a]	1.096–2.062	0.603	0.320–1.139
Model 2	1.171	0.842–1.627	1.308	0.954–1.793	1.602[a]	1.145–2.242	0.518	0.249–1.076
Z Muscle density, HU								
Crude	0.740	0.546–1.002	0.759	0.570–1.011	0.850	0.624–1.157	0.669	0.337–1.331
Model 1	0.684[a]	0.486–0.962	0.773	0.561–1.066	0.884	0.633–1.235	0.564	0.259–1.229
Z IMAT, cm^2								
Crude	1.291	0.949–1.758	1.280	0.956–1.712	1.162	0.850–1.589	1.263	0.578–2.758
Model 1	1.366	0.980–1.902	1.297	0.947–1.777	1.130	0.817–1.563	1.340	0.586–3.065
Z VAT, cm^2								
Crude	1.341[a]	1.007–1.787	1.458[a]	1.111–1.914	1.551[a]	1.157–2.078	0.968	0.529–1.772
Model 1	1.355	0.996–1.845	1.465[a]	1.096–1.960	1.543[a]	1.137–2.093	1.005	0.539–1.872
Z SAT, cm^2								
Crude	0.996	0.711–1.394	1.283	0.914–1.802	1.195	0.839–1.703	1.532	0.597–3.929
Model 1	1.139	0.768–1.690	1.224	0.851–1.762	1.104	0.762–1.599	1.561	0.624–3.906
Z IMAT, %								
Crude	1.145	0.843–1.557	1.150	0.860–1.537	1.007	0.739–1.372	1.445	0.699–2.989
Model 1	1.203	0.861–1.680	1.121	0.816–1.539	0.977	0.705–1.355	1.572	0.722–3.425
Z SM/VAT, cm^2								
Crude	0.794	0.564–1.116	0.647[a]	0.454–0.922	0.605[a]	0.406–0.902	0.904	0.443–1.842
Model 1	0.716	0.480–1.069	0.650[a]	0.440–0.961	0.600[a]	0.390–0.923	0.831	0.388–1.777
Z BMI, kg/m^2								
Crude	1.343[a]	1.017–1.774	**1.541**	**1.182–2.010**	1.172	0.874–1.572	0.932	0.454–1.913
Model 1	1.357	0.998–1.845	1.571[a]	1.174–2.103	1.072	0.781–1.471	0.966	0.468–1.994

Body composition was analyzed with gender-specific standardized scores. Severe postoperative complications were defined as (0) no or grade 1–2 Clavien-Dindo complications; (1) grade 3–5 Clavien-Dindo complications (complications that led to reintervention, intensive care unit admittance, or death). Dose-limiting toxicity was defined as (0) no toxicity or no toxicity that led to dose reduction or early discontinuation of chemotherapy; (1) toxicity that led to dose reduction or early discontinuation of chemotherapy.

Model 1: adjusted for age, stage and number of medications. Dose-limiting toxicity was adjusted for age and number of medications. Model 2: + BMI ≥30 kg/m^2.

Bolded values ($p < .001$) are considered statistically significant after Bonferroni correction.

[a]$p < .05$.

Abbreviations: BMI, body mass index; CI, confidence interval; HU, Hounsfield units; IMAT, intermuscular adipose tissue; LOS, length of stay; OR, odds ratio; SM, skeletal muscle; SMI, skeletal muscle index; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

risk. The association was strongest for IMAT compared with other body composition measures. In the subgroup of patients who received adjuvant chemotherapy, SM/VAT was associated with a higher mortality risk during follow-up in the adjusted model. None of the survival analyses remained statistically significant after Bonferroni correction, as is shown in Table 3.

Sensitivity Analyses

The median number of days between CT scan and surgery was 36 days (range 8–209 days), with 80.4% of patients having a CT scan that was made a maximum of 8 weeks before surgery. Sensitivity analyses excluding CT scans that were made more than 8 weeks before surgery (supplemental online Table 1) and excluding scans in which body composition area was multiplied because of quality issues (supplemental online Table 2) showed results consistent with the total cohort. Stratification for colon and rectum cancer (supplemental online Tables 3, 4) showed similar results for both tumor types. Post hoc analyses stratified by Karnofsky Performance Scale score were performed to clarify the associations between higher SM and SMI

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Table 3. Associations between computed tomography-based body composition measures and overall survival

Z-scores body composition measures	One-year survival		Long-term survival			
	All patients (*n* = 378)		All patients (*n* = 378)		Received chemotherapy (*n* = 53)	
	HR	95% CI	HR	95% CI	HR	95% CI
Z SM, cm^2						
Crude	0.753	0.498–1.138	0.976	0.834–1.142	0.861	0.561–1.320
Model 1	0.820	0.518–1.298	1.069	0.897–1.273	0.882	0.563–1.381
Model 2	0.832	0.523–1.325	1.125	0.936–1.351	0.900	0.566–1.430
Z SMI, cm^2/m^2						
Crude	0.706	0.463–1.076	0.953	0.812–1.119	0.861	0.557–1.332
Model 1	0.780	0.494–1.232	0.998	0.840–1.187	0.879	0.560–1.379
Model 2	0.793	0.498–1.263	1.054	0.879–1.264	0.898	0.561–1.436
Z Muscle density, HU						
Crude	0.687	0.470–1.006	0.814[a]	0.694–0.955	0.948	0.559–1.607
Model 1	0.786	0.511–1.209	0.918	0.771–1.093	0.957	0.544–1.686
Z IMAT, cm^2						
Crude	1.239	0.838–1.833	1.225[a]	1.039–1.444	1.161	0.622–2.165
Model 1	1.074	0.702–1.643	1.087	0.915–1.293	1.177	0.626–2.210
Z VAT, cm^2						
Crude	1.060	0.724–1.552	0.998	0.849–1.173	0.618	0.363–1.052
Model 1	0.984	0.639–1.515	0.941	0.792–1.118	0.593	0.338–1.042
Z SAT, cm^2						
Crude	0.997	0.657–1.514	0.934	0.785–1.111	0.789	0.368–1.694
Model 1	0.902	0.561–1.450	0.902	0.742–1.098	0.764	0.378–1.546
Z IMAT, %						
Crude	1.317	0.881–1.969	1.205[a]	1.021–1.423	1.210	0.690–2.124
Model 1	1.111	0.719–1.715	1.049	0.879–1.252	1.198	0.679–2.112
Z SM/VAT, cm^2						
Crude	0.864	0.564–1.324	0.995	0.844–1.174	1.588	0.951–2.651
Model 1	1.025	0.647–1.622	1.131	0.951–1.345	1.778[a]	1.002–3.156
Z BMI, kg/m^2						
Crude	0.951	0.638–1.417	0.988	0.835–1.169	0.834	0.470–1.481
Model 1	0.836	0.529–1.320	0.899	0.744–1.087	0.840	0.470–1.501

Body composition was analyzed with gender-specific standardized scores. The hazard ratio for death is given; survival time was calculated in months. Model 1: adjusted for age, stage, and number of medications. Associations with subgroup that received chemotherapy was adjusted for age and number of medications. Model 2: + BMI ≥30 kg/m^2.

[a]$p < .05$.

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; HU, Hounsfield units; IMAT, intermuscular adipose tissue; SAT, subcutaneous adipose tissue; SM, skeletal muscle; SMI, skeletal muscle index; VAT, visceral adipose tissue.

and higher risk of prolonged LOS and readmission (supplemental online Table 5). The associations between SM and SMI and higher risk of readmission were only present in the group with a Karnofsky Performance Scale score of ≥90.

Discussion

In a population of older patients with CRC, preoperative CT-based body composition measures were not consistently or statistically significantly associated with surgery-related complications, dose-limiting toxicity, and overall survival. SM, muscle density, VAT, SM/VAT, and BMI showed associations with surgery-related complications. Muscle density, IMAT, and IMAT percentage showed associations with long-term overall survival in the total cohort and SM/VAT in the subgroup of patients receiving adjuvant chemotherapy. However, associations of CT-based body composition measures were no longer statistically significant after Bonferroni correction for multiple testing was applied. The only statistically significant association was the association of higher BMI with prolonged LOS. The results of this study underscore the need for a meta-analysis to elucidate the value of CT-based body composition measures to predict adverse outcomes in patients with CRC.

The current body of evidence shows inconsistent associations between body composition measures and adverse outcomes in patients with CRC. Low SM has been shown to be associated with severe postoperative complications [11], LOS [13], dose-limiting toxicity [28–31], and long-term survival [10, 14–17, 32–34]. However, other studies did not show associations between low SM and overall [9–11, 14, 35–37]

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or severe postoperative complications [9, 10, 14], readmission [13], and long-term survival [9, 11]. These varying results may have been caused by the use of different cutoff points, limiting comparison of studies. Another explanation for the inconsistency in the literature could be the inclusion of all age groups, as only one study specifically included older patients and found a significant association between low muscle mass and overall survival in patients with rectal cancer receiving chemoradiation [34]. The association between CT-based body composition measures and adverse outcomes is expected to differ between younger and older populations as body composition measures are negatively affected by age [38] but still show inconsistency when only studies with a mean/median age of 65 years and older are considered. In this study, statistically significant associations between higher SM and higher risk of surgery-related complications were found before Bonferroni correction was applied. This was contrary to what was expected. Post hoc analyses revealed that these associations were mainly applicable in patients with a high Karnofsky Performance Scale score. This could indicate that patients with higher SM were treated more aggressively, leading to a higher risk of surgery-related complications. Another possibility is that these patients lost muscle mass prior to the preoperative CT scan, leading to higher risk of complications; however, this could not be proved owing to the design of this study. Potential influences of confounding factors, type of treatment and type of complications, or edema leading to an overestimation of muscle mass have been evaluated but could not further explain the unexpected association between higher SM and higher risk of surgery-related complications. On the contrary, higher SM/VAT was associated with lower risk of surgery-related complications before Bonferroni correction, which might imply that different body composition measures are needed to predict adverse outcomes than absolute muscle mass. After accounting for multiple testing, neither SM nor SM/VAT were significantly associated with surgery-related complications, dose-limiting toxicity, or overall survival.

Besides muscle mass, several CT-based adipose measures were considered, including muscle density, IMAT, and VAT. Based on the negative effects that low muscle density and high IMAT and VAT can impose on the body, associations with adverse outcomes were expected. The negative effect of VAT, in contrast to SAT, is caused by provoked insulin resistance and pro-inflammatory cytokines, which increases the risk of detrimental health outcomes [39, 40]. IMAT, on the other hand, which includes both inter- and intramuscular fat [41], results in a misbalance in pro- and anti-inflammatory cytokines, which can lead to a higher risk of adverse health outcomes independent of VAT [42]. IMAT, in its turn, highly correlates with muscle density, which is a measure of fat infiltration in skeletal muscle fibers [7]. Low muscle density has been associated with reduced muscle strength and physical performance, which are determinants of adverse outcomes in older patients [43, 44]. However, although muscle density, IMAT, and VAT appeared to be associated with adverse outcomes in this study, the associations were weak and no longer present after correction for multiple testing. This inconsistency is in line with available literature. Low muscle density has been associated with postoperative complications [9–11, 37] and long-term survival [15–17], although other studies have found no associations with overall [35] or severe postoperative complications [10] and long-term survival [9–11, 17]. The same counts for VAT or visceral obesity, which was found to be associated with postoperative complications [36, 45–48], LOS [36, 46, 48], readmission [49], and 2-year survival [50] in some studies. However, in other studies, associations with overall postoperative complications [35, 51], LOS [45, 47, 51, 52], readmission [36], dose-limiting toxicity [29], and long-term survival [16, 33, 51, 53] were not found. The use of cutoff points and inclusion of all age groups could have contributed to the inconsistency of these results. BMI was the only body composition measure that remained statistically significant after Bonferroni correction and was associated with prolonged LOS. This can be explained by the higher risk of surgical complications such as fascial dehiscence and surgical incisional site infections and thromboembolic complications in patients with higher BMI [27, 54]. These are complications that could have been classified as mild complications (grade 1 or 2) because they do not necessarily lead to reintervention but can still lead to longer LOS.

Apart from looking at CT-based body composition at one moment in time, changes in body composition over time might be important. A few studies have shown that body composition in patients with CRC is dynamic and loss of muscle and visceral fat tissue can lead to a higher risk of adverse outcomes [55–58]. Furthermore, muscle function might be more relevant than absolute mass, as has been shown in a recent study in older patients with advanced cancer in which higher muscle strength was associated with overall survival whereas SM and muscle density were not [59]. An earlier study showed that a combination of CT-based low SM, handgrip strength, and gait speed was predictive of postoperative complications in patients with CRC [60]. Possibly, CT-based body composition measures need to be combined with functional measures such as handgrip strength and physical performance to predict relevant patient outcomes. Moreover, other domains of the Comprehensive Geriatric Assessment such as nutritional status and cognition have prognostic value and could contribute to the prediction of adverse outcomes in older patients with CRC [61]. Future research needs to clarify the prognostic value of these measures in addition to CT-based body composition measures over time, to predict the risk of adverse outcomes in older patients with CRC. This is also important in the development of preoperative interventions, also known as prehabilitation, which can be effective in older patients with CRC [62, 63].

The strength of this study is the comparison of the associations of various standardized CT-based body composition measures on consecutive treatment modalities in older patients with CRC. By omitting cutoff points and using gender-specific standardized *Z* scores, body composition measures could be compared with one another. Limitations of this study are that it is a single-center cohort study and may not be representative for other populations. Moreover, because of the retrospective design, other prognostic measures such as nutrition and physical performance could not be taken into account. The subgroup of patients receiving adjuvant chemotherapy was small, resulting in limited power, and only included patients who were considered fit enough for chemotherapy treatment by the multidisciplinary team, and almost half of all patients

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received capecitabine monotherapy. Concerning the CT scans, the time period between preoperative CT scan and surgery and chemotherapy was not standardized, although sensitivity analyses showed similar results excluding CT scans with a longer time period before surgery. A small proportion of 5% of CT scans was not suitable for body composition measurement because of artifacts or frame selection.

Conclusion

In a cohort of older patients with CRC, associations between preoperative CT-based body composition measures and surgery-related complications, dose-limiting toxicity, and overall survival were not consistent or statistically significant. Associations between CT-based body composition measures and consecutive treatment modalities could not be confirmed. Future research should focus on the change in body composition over time combined with muscle strength, physical performance, and other geriatric domains to predict adverse outcomes in older patients with CRC.

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