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Body Composition as a Predictor of Toxicity in Patients Receiving Anthracycline and Taxane–Based Chemotherapy for Early-Stage Breast Cancer

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Abstract

Purpose: Poor body composition metrics (BCM) are associated with inferior cancer outcomes; however, in early breast cancer (EBC), there is a paucity of evidence regarding the impact of BCM on toxicities. This study investigates associations between BCM and treatment-related toxicity in patients with EBC receiving anthracyclines and taxane–based chemotherapy.

Experimental Design: Pretreatment computerized tomographic (CT) images were evaluated for skeletal muscle area (SMA), skeletal muscle density (SMD), and fat tissue at the third lumbar vertebrae. Skeletal muscle index (SMI = SMA/height^2) and skeletal muscle gauge (SMG = SMI × SMD) were also calculated. Relative risks (RR) are reported for associations between body composition measures and toxicity outcomes, after adjustment for age and body surface area (BSA).

Results: BCM were calculated for 151 patients with EBC (median age, 49 years; range, 23–75 years). Fifty patients (33%) developed grade 3/4 toxicity, which was significantly higher in those with low SMI (RR, 1.29; $P = 0.002$), low SMG (RR, 1.09; $P = 0.01$), and low lean body mass (RR, 1.48; $P = 0.002$). Receiver operating characteristic analysis showed the SMG measure to be the best predictor of grade 3/4 toxicity. Dividing SMG into tertiles showed toxicity rates of 46% and 22% for lowest versus highest tertile, respectively ($P = 0.005$). After adjusting for age and BSA, low SMG (<1,475 units) was significantly associated with hematologic (RR, 2.12; $P = 0.02$), gastrointestinal grade 3/4 toxicities (RR, 6.49; $P = 0.02$), and hospitalizations (RR, 1.91; $P = 0.05$).

Conclusions: Poor BCMs are significantly associated with increased treatment-related toxicities. Further studies are needed to investigate how these metrics can be used to more precisely dose chemotherapy to reduce treatment-related toxicity while maintaining efficacy. *Clin Cancer Res; 23(14); 3537–43. ©2017 AACR.*

Introduction

Breast cancer is the most common cancer diagnosis and the leading cause of cancer death among females worldwide (1). In the United States in 2016, there will be an estimated 246,660 new cases of breast cancer (2). The overall survival from breast cancer in the United States is 89.5% for all stages (3). The treatment of early-stage breast cancer (stage I–III) consists primarily of local therapy including surgery, with or without radiation, and systematic therapy such as endocrine, biologic treatment (i.e., trastuzumab), and/or chemotherapy. Chemotherapy is an essential component of treatment for early breast cancer (EBC), especially in hormone receptor (HR)-positive large/node-positive tumors, or HER2-positive and HR/HER2-negative tumors ("triple-negative"). Chemotherapy toxicity is a major issue. Among patients with EBC who undergo chemotherapy, up to 20% can experience non-hematologic and 39% experience hematologic toxicity (4). Of note, hospitalization due to toxicity is common with adjuvant chemotherapy and ranges from 6% to 24% in the adjuvant setting (5). Toxicity prediction in individual patients remains a major challenge in breast cancer care (6). However, with the established use of granulocyte colony-stimulating factor (G-CSF and related agents), the incidence of neutropenia has decreased substantially (7).

Sarcopenia (age-related muscle loss), myopenia (low muscle mass regardless of age; ref. 8), and other body composition measures have received increased attention as a focus of research in oncology using widely available computed tomographic (CT) imaging (9). Sarcopenia is a common finding in patients with cancer. In a recent meta-analysis, 19% to 74% of patients with solid tumors were found to be sarcopenic, and the presence of sarcopenia was correlated with poor overall survival (HR, 1.44; $P < 0.001$) in both metastatic and non-metastatic cohorts (9). However, in breast cancer, there is a paucity of data on the potential effect of sarcopenia and other body composition measures on treatment-related toxicities. Wong and colleagues examined the association between body composition and toxicity of anthracyclines and docetaxel used without growth factors in Asian patients with EBC ($n = 84$) and found that increased visceral fat significantly correlated with grade 4

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Translational Relevance

Currently, chemotherapy dosing is commonly based on the body surface area (BSA) formula, which accounts for height and weight only but not for other potentially important body composition indices. This article presents the largest study to date assessing the impact of several body composition measures on chemotherapy toxicity in patients with early breast cancer receiving adjuvant chemotherapy. Our results show that skeletal muscle gauge (SMG), a new and innovative metric derived from the combination of muscle mass (quantity) and radiodensity (quality), is the best predictor of chemotherapy adverse outcomes including grade 3/4 chemotherapy toxicities, hospitalizations, and other adverse events. Receiver operating characteristic curves show that SMG is a better predictor of chemotherapy toxicity than either lean body mass or BSA. Our results suggest that body composition measurements obtained from routine computed tomographic (CT) images performed for staging might be used to individualize chemotherapy dosing and potentially improve its therapeutic index.

leukopenia ($P = 0.014$) and that low muscle volume trended ($n = 15$, $P = 0.051$) toward an association with grade 3/4 leukopenia and neutropenia (10). Skeletal muscle density (SMD) can also be obtained from routine CT imaging by indirectly measuring intramuscular lipid content. Low SMD as measured by mean Hounsfield units (HU), known as myosteatosis, indicates poor muscle "quality" and has been associated with impaired survival (11, 12). Sarcopenic obesity is another marker for worse outcomes in patients with cancer (12). While dosing is usually based on weight and height measures [body surface area (BSA)], there is evidence that pharmacokinetics and drug toxicities are more related to lean body mass (LBM), but to date, muscle measures have not been incorporated into routine chemotherapy dosing (13–16). As both muscle quantity [skeletal muscle index (SMI)] and quality (SMD) are significantly and independently associated with cancer outcomes, testing a mathematical combination of both has been proposed. Weinberg and colleagues were the first to generate the skeletal muscle gauge (SMG) by multiplying SMI times SMD as an alternative measure that showed higher correlation with aging than either SMD or SMI alone (17) and we have used this metric as part of our current analysis.

These findings raise the need and provide an opportunity to investigate the association between body composition measures, including the novel SMG in a large sample of patients with breast cancer focusing on adverse treatment-related toxicities. The aim of this study was to investigate whether body composition metrics in patients with EBC are independent predictors of: (i) chemotherapy toxicity, (ii) hospitalizations, and/or (iii) dose delays/reductions.

Materials and Methods

Participants

Eligible patients were treated at the North Carolina Cancer Hospital (NCCH) and identified through a review of patients in the North Carolina tumor registry in years 2008–2013. To be eligible for this study, patients needed to be females older than 21 years receiving neoadjuvant or adjuvant chemotherapy treatment for EBC (stage I–III) at NCCH. Only doxorubicin–cyclophosphamide (AC) taxane–based chemotherapy regimens for EBC were included as most of them had pretreatment staging CT scan. Patients also had to have a CT scan of the abdomen dating no more than 12 weeks prior to chemotherapy initiation. All data were extracted from electronic medical records at NCCH. The Institutional Review Board at the University of North Carolina (UNC) at Chapel Hill approved the study and there was no direct contact with patients.

Toxicity grading

Toxicity grades 3–5 according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE; Version 4.03; ref. 18) were extracted during and after the chemotherapy course through retrospective medical chart review. We examined hematologic toxicity (neutropenia, thrombocytopenia, anemia), febrile neutropenia, and common non-hematologic toxicities such as neurotoxicity and gastrointestinal (GI) toxicity (stomatitis, diarrhea, vomiting). Data on other toxicities—congestive heart failure (CHF), deep vein thrombosis (DVT), pulmonary emboli (PE), and leukemia—were also gathered from the medical record. Dose reductions (any dose reduction by the treating physician), treatment delays (any delay based on a toxicity event), and hospitalizations due to chemotherapy toxicity were also collected.

CT-based body composition analysis

Abdominal CT images were acquired from the UNC Picture Archiving and Communication System (PACS) office. Measuring muscle metrics at L3 level is the most commonly used technique utilizing CT scans and validated as highly correlated to total body muscle mass ($r^2 = 0.86$; ref. 19). CT images were examined using AGFA-Impax (version 6) radiological software, and transverse sections at the L3 level were extracted for external analysis. L3 lumbar segments were processed using the "Automated Body Composition Analyzer using Computed tomography image Segmentation" (ABACS) software (20, 21). The software recognizes muscle tissue based on a density threshold between −29 and +150 HU while using *a priori* information about the L3 muscle shape to avoid mislabeling parts of the neighboring organs that have HU values in the (−29 to +150) range as muscle tissue. The program provides a highly accurate (22) and unbiased estimation of the cross-sectional lean tissue area and skeletal muscle area (SMA; Fig. 1). SMI was calculated using the following formula: (SMA, cm^2)/(patient height, m^2). Estimated LBM was calculated using the following formula: LBM (kg) = 0.30 × [skeletal muscle at L3 using CT (cm^2)] + 6.06 (14). Mean SMD was derived by averaging HU of skeletal muscle. To integrate both the SMI and the SMD, SMG was calculated by multiplying SMI and SMD. The actual units for SMG are (cm^2 tissue × average HU)/(m^2, height), and for simplicity, we present them as arbitrary units (AU). Subcutaneous adipose tissue (SAT) area was calculated from extramuscular tissue with density between −190 and −30 HU and visceral adipose tissue (VAT) from non-subcutaneous tissue with density between −150 and −50 HU. An investigator (M. Weinberg) was trained by a radiologist to obtain the images and a radiologist reviewed the images for quality assurance. The imaging results were masked from the investigator obtaining toxicity data.

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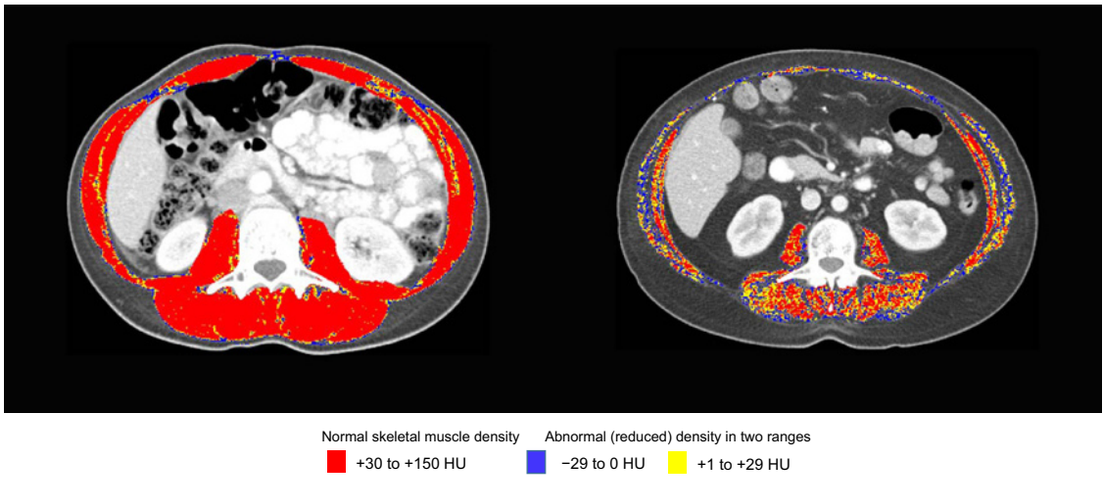

Figure 1.
SMG and toxicity—both females BSA 1.70. Left, normal SMG (2,535 AU), had no toxicity; right, low SMG (844 AU), had grade 3/4 toxicity.

Patient and clinical characteristics

In addition to toxicity data, we also collected age at diagnosis, HR and HER2 subtypes, stage at diagnosis, timing of chemotherapy (neoadjuvant/adjuvant), whether a biologic agent was used with chemotherapy, the type of taxane chemotherapy, height, and weight. BSA (m^2) was calculated as $\sqrt{\left[\frac{\text{height (cm)} \times \text{weight (kg)}}{3600}\right]}$. Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2). We defined sarcopenic obesity as a patient with a BMI $\geq$ 30.0 kg/m^2 and an SMI $\leq$ 41 cm^2/m^2 (12).

Statistical analysis

Relative risks (RR) and 95% confidence intervals (CI) are reported for associations between body composition measures and toxicity outcomes. Both unadjusted and adjusted RRs were calculated using Poisson regression models with robust variance (23). Receiver operating characteristic (ROC) curves were generated, as well as the area under the curve (AUC), to evaluate the predictive ability of each body composition measure. Using the Youden index, the point which maximizes both the sensitivity and specificity was determined to be the best cutoff point for SMG. All analyses were conducted using SAS v9.4 statistical software.

Results

Study population

Patient characteristics are summarized in Supplementary Table S1 (selection process is shown in Supplementary Fig. S1). A total of 151 patients were identified who received adjuvant or neoadjuvant AC taxane chemotherapy (dosing and scheduling in Supplementary Table S2) were treated at NCCH. Mean age was 49 years (range, 23–75 years) and 74% were white. The mean time from CT scan to chemotherapy initiation was 23 days (SD, 19). All patients with HER2-positive tumors received concomitant anti-HER2 treatment during chemotherapy. No patients had grade 5 toxicity recorded (death).

Body composition as a predictor of any grade 3/4 toxicity

Fifty patients (33%) developed grade 3/4 toxicity during chemotherapy treatment, and these toxicities were associated with poorer body composition. The relationship of toxicity and body composition by tertile is presented in Fig. 2. Unadjusted RRs for each body composition measure are shown in Table 1. For every 5-kg decrease in LBM, the risk of any toxicity increased by 36% [RR = 1.36 (1.12–1.66), P = 0.002]. For every 5-unit decrease in SMI, the risk of any toxicity increased by 27% [RR = 1.27 (1.09–1.49), P = 0.002]. For every 100-AU decrease in SMG, the risk of any toxicity increased by 8% [RR = 1.08 (1.02–1.15), P = 0.006]. While not statistically significant, the risk of any toxicity also increased for every 5-unit decrease in SMD [RR = 1.11 (0.98–1.25), P = 0.08]. BMI, BSA, SAT/VAT area, and SAT/VAT density were not associated with any grade 3/4 toxicity. Significant associations observed in the unadjusted analysis remained statistically significant after adjustment for age and BSA (Table 2). Similarly, after adjusting for race and the use of G-CSF, SMG associations with toxicity risk remained significant.

In Supplementary Fig. S2, ROC curves along with AUC statistics are shown for each measure based on the outcome of "any toxicity." BMI and BSA show poor discrimination (AUC $\sim$ 0.5), whereas other measures demonstrate better discrimination, with SMG being the best (AUC = 0.65). Using the Youden index, we identified an SMG cutoff point of 1475. Figure 3 illustrates the proportion of patients above and below this cutoff point for different toxicities and demonstrates that patients with an SMG below the cutoff point had more hematologic and GI grade 3/4 toxicities as well as hospitalizations. Patients with low SMG (<1,475 AU) were about twice as likely to experience any toxicity compared with patients with high SMG [$\geq$1,475 AU; RR = 2.15 (1.36–3.40), P = 0.001]. Although there were only 5 patients with sarcopenic obesity in our sample (of them, 4 received G-CSF), all grade 3/4 hematologic toxicities [RR = 3.02 (1.38–6.63), P = 0.006], dose reductions or delays [RR = 2.65 (1.61–4.39), P < 0.001], and neutropenia [RR = 3.5 (1.57–7.8), P = 0.002] were significantly more likely to occur in these patients.

We additionally performed a sensitivity analysis of patients that received paclitaxel only (n = 142) and found that after generating SMG cutoff point based on this population, SMG remained a significant predictor of grade 3/4 toxicity (RR =

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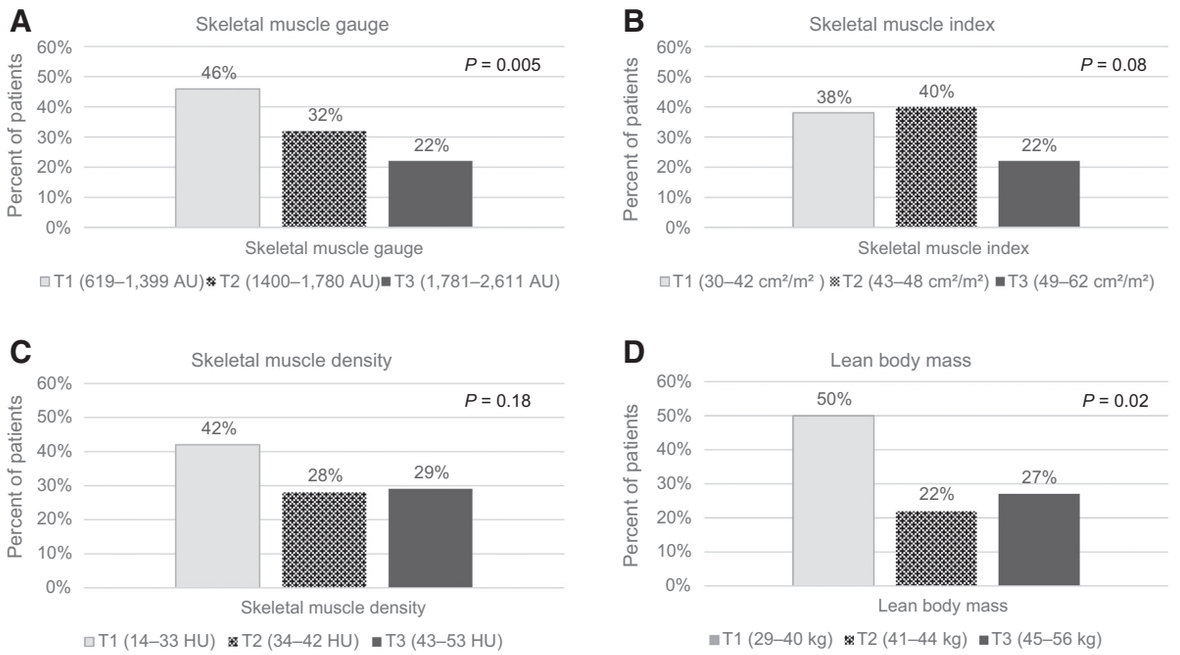

Figure 2.
Risk of toxicity based on tertiles of body composition measures. *, *P* values from unadjusted Jonckheere–Terpstra tests.

2.48) as well as grade 3/4 hematologic toxicities (RR = 2.26), GI toxicities (RR = 12.17), and hospitalizations (RR = 2.10). hematologic toxicities in the low SMG group remained statistically significant.

Body composition as a predictor of grade 3/4 hematologic toxicity

Hematologic toxicities were reported in 35 patients (23%), including neutropenia, thrombocytopenia, and anemia (see Supplementary Table S1). Low SMG was significantly associated with a higher risk of hematologic toxicity—twice as high among the patients with SMG < 1,475 as compared with the patients with SMG ≥ 1,475 [RR = 2.00 (1.08–3.72), P = 0.03]. After adjusting for age and BSA, the high risk for

Body composition as a predictor of grade 3/4 GI toxicity and neuropathy

Seven patients (5%) had grade 3/4 GI toxicity and 11 (7%) had grade 3/4 neuropathy (see Tables 1 and 2). In unadjusted analyses, SMG was the only body composition measure significantly associated with GI toxicity. For every 100-unit decrease in SMG, the risk of GI toxicity increased by 28% [RR = 1.28 (1.08–1.51), P = 0.004]. However, after adjustment for age and BSA, lower LBM, SMI, SMD, and SMG were significantly associated with an

Table 1. Unadjusted RRs (95% CIs) of toxicity for body composition measures

	Any grade 3/4 toxicity (N = 50)	Grade 3/4 hematologic toxicity (N = 35)	Grade 3/4 GI toxicity (N = 7)	Grade 3/4 neuropathy (N = 11)	Hospitalization (N = 30)	Dose delay/reduction (N = 48)
Sarcopenic and obese[a]	1.86 (0.88–3.96)	3.02 (1.38–6.63)[b]	—	2.92 (0.46–18.61)	—	2.65 (1.61–4.39)[b]
BMI (1 kg/m^2 decrease)	1.00 (0.97–1.04)	1.00 (0.96–1.04)	1.00 (0.88–1.13)	0.94 (0.89–1.00)	0.98 (0.93–1.02)	1.00 (0.96–1.04)
BSA (1 m^2 decrease)	1.21 (0.41–3.55)	1.50 (0.35–6.45)	1.68 (0.02–161.2)	0.21 (0.02–2.29)	1.24 (0.29–5.33)	1.33 (0.43–4.16)
LBM (5 kg decrease)	1.36 (1.12–1.66)[b]	1.25 (0.95–1.65)	2.03 (0.90–4.59)	1.25 (0.78–2.00)	1.09 (0.81–1.48)	1.14 (0.92–1.43)
SMI (5 cm^2/m^2 decrease)	1.27 (1.09–1.49)[b]	1.13 (0.92–1.40)	1.69 (0.97–2.94)	1.12 (0.75–1.67)	1.29 (0.68–2.45)	1.05 (0.87–1.26)
SMD (5 HU decrease)	1.11 (0.98–1.25)	1.03 (0.87–1.21)	1.36 (0.91–2.03)	1.29 (0.96–1.75)	1.19 (1.00–1.43)[c]	1.08 (0.95–1.23)
SMG (100 AU decrease)	1.08 (1.02–1.15)[b]	1.03 (0.95–1.11)	1.28 (1.08–1.51)[b]	1.15 (1.00–1.31)[c]	1.07 (0.98–1.16)	1.04 (0.99–1.10)
SMG (<1,475 AU vs. ≥1,475)	2.15 (1.36–3.40)[b]	2.00 (1.08–3.72)[c]	3.90 (0.78–19.44)	2.73 (0.84–8.92)	1.82 (0.96–3.43)	1.56 (0.98–2.47)
VAT area (1 unit decrease)	1.00 (1.00–1.00)	1.00 (1.00–1.01)	1.00 (0.99–1.01)	1.00 (0.99–1.00)	1.00 (0.99–1.00)	1.00 (1.00–1.00)
VAT density (1 unit decrease)	1.00 (0.97–1.03)	0.99 (0.95–1.02)	0.99 (0.92–1.06)	1.04 (0.93–1.16)	1.01 (0.97–1.05)	0.99 (0.97–1.02)
SAT area (1 unit decrease)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (0.99–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
SAT density (1 unit decrease)	1.01 (0.97–1.05)	1.01 (0.96–1.06)	0.98 (0.89–1.08)	1.02 (0.92–1.13)	1.01 (0.96–1.06)	0.98 (0.95–1.02)

Abbreviations: BMI, body mass index; BSA, body surface area; CI, confidence interval; GI, gastrointestinal; LBM, lean body mass; RR, relative risk; SAT, subcutaneous adipose tissue; SMD, skeletal muscle density; SMG, skeletal muscle gauge; SMI, skeletal muscle index; VAT, visceral adipose tissue.
[a]n = 5.
[b]P < 0.01.
[c]P < 0.05.

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Table 2. Adjusted RRs (95% CIs) of toxicity for body composition measures

Parameter	Any grade 3/4 toxicity	Grade 3/4 hematologic toxicity	Grade 3/4 GI toxicity	Grade 3/4 neuropathy	Hospitalization	Dose delay/reduction
LBM (5 kg decrease)	1.48 (1.15–1.89)[a]	1.27 (0.88–1.84)	2.87 (1.60–5.15)[b]	1.52 (0.92–2.51)	1.07 (0.74–1.55)	1.14 (0.86–1.53)
SMI (5 cm^2/m^2 decrease)	1.29 (1.10–1.53)[a]	1.11 (0.86–1.43)	1.83 (1.20–2.80)[a]	1.20 (0.78–1.83)	0.91 (0.71–1.16)	1.02 (0.83–1.26)
SMD (5 HU decrease)	1.13 (0.97–1.32)	1.03 (0.83–1.27)	1.75 (1.30–2.36)[b]	1.09 (0.67–1.75)	1.34 (1.07–1.68)[c]	1.14 (0.97–1.33)
SMG (100 AU decrease)	1.09 (1.02–1.16)[c]	1.02 (0.94–1.11)	1.41 (1.19–1.67)[b]	1.08 (0.90–1.28)	1.08 (0.98–1.20)	1.05 (0.99–1.12)
SMG (<1,475 AU vs. ≥1,475)	2.18 (1.34–3.54)[a]	2.12 (1.11–4.04)[c]	6.49 (1.42–29.63)[c]	1.63 (0.43–6.27)	1.91 (1.00–3.66)[c]	1.63 (0.98–2.73)

NOTE: Adjusted for age and BSA at diagnosis.

Abbreviations: BSA, body surface area; CI, confidence interval; LBM, lean body mass; RR, relative risk; SMD, skeletal muscle density; SMG, skeletal muscle gauge; SMI, skeletal muscle index.

[a]$P < 0.01$.

[b]$P < 0.001$.

[c]$P < 0.05$.

increased risk for GI toxicity. In unadjusted analyses, SMG was the only body composition measure significantly associated with grade 3/4 neuropathy. For every 100-unit decrease in SMG, the risk of neuropathy increased by 15% [RR = 1.15 (1.00–1.31), $P = 0.04$]. However after adjusting for age and BSA, the association between SMG and neuropathy was no longer statistically significant.

Body composition as a predictor of hospitalizations

Thirty patients (20.7%) of 145 patients with full hospitalization records were hospitalized for treatment-related toxicity. For every 5-unit decrease in SMD, the risk of hospitalization increased by 19% [RR = 1.19 (1.00–1.43), $P = 0.05$]. After adjustment for age and BSA, SMD remained a significant predictor, and patients with SMG < 1,475 as compared with the patients with SMG ≥ 1,475 had twice the hospitalization risk [RR = 1.91 (1.00–3.66), $P = 0.05$]. All other body composition measures were unrelated to hospitalization in both unadjusted and adjusted models.

Discussion

This is the first study, to our knowledge, to evaluate the relationship of LBM, SMG, and other body composition measures with treatment toxicity in a large sample of patients with EBC receiving the commonly used chemotherapy regimens of an anthracycline and taxane. After adjusting for age and BSA, lower LBM was significantly associated with having any grade 3/4 toxicity as well as grade 3/4 GI toxicity. SMG, a novel integrated measure of body composition, was significantly associated with having any grade 3/4 toxicity as well as grade 3/4 GI toxicities, hematologic toxicities, and hospitalizations. As illustrated by the large number of body composition measures analyzed in this study, body composition is extremely variable. However, measures that include muscle metrics are clearly related to the toxicity, whereas adipose metrics (VAT and SAT) are not. In addition, the small number of patients with sarcopenic obesity had significantly more dose adjustments and hematologic toxicities compared with patients who were not both sarcopenic and obese. Of note, aging is associated with decreasing muscle mass and lower muscle density, and age-related changes are more correlated with SMG than either SMI or SMD alone (17).

Our findings are supported by other studies. Prado and colleagues in a small ($n = 24$) but novel study found that higher toxicity was associated with lower LBM in patients with EBC receiving epirubicin containing adjuvant therapy (56.2 vs. 41.6 kg, $P = 0.002$). In that study, LBM was also an independent and significant predictor of epirubicin pharmacokinetics (PK) and

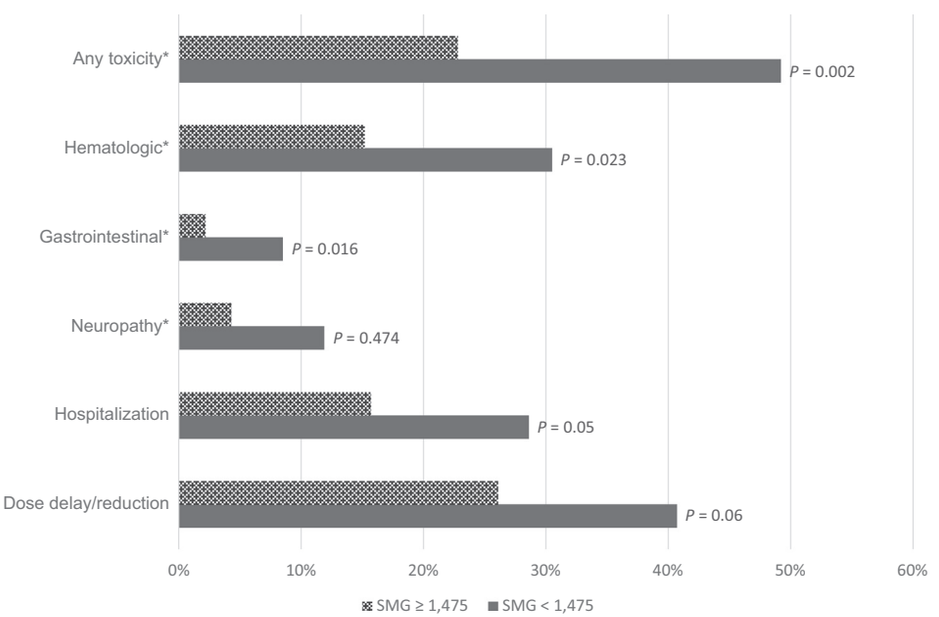

Figure 3.
Risk of toxicity based on SMG[a]. [a], *P* values from Poisson regression models adjusting for age at diagnosis and BSA. *, Grade 3/4 toxicity.

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toxicity (15). Tamandl and colleagues observed that low SMD was associated with poorer survival in patients with gastric cancer (HR, 1.91; 95 % CI, 1.12–3.28; $P = 0.019$; ref. 11). Others have also found an association of body composition with toxicity and survival in early cancer (13, 15, 24).

A unique aspect of our study is the use of a new metric—SMG—that takes into account both muscle quantity (SMI) and quality (SMD). Of all the metrics, SMG was the single most predictive of toxicity. On the basis of ROC analyses for any grade 3/4 toxicity, we determined the best cutoff point for SMG to be 1,475. Using this cutoff point, we found that low SMG was associated with grade 3/4 GI toxicity and grade 3/4 hematologic toxicity and hospitalizations after adjusting age and BSA (Fig. 3). Furthermore, after adjusting for G-CSF usage and race, this SMG cutoff point remained significant. This cutoff point might be helpful in identifying patients at high risk for toxicity and should be explored in future trials. Moreover, we have previously shown that low SMG in an older cancer population is correlated with lower physical function and increased frailty (22, 23), both of which are associated with poorer cancer outcomes and shortened survival (25).

Our study has some limitations. First, our cohort included only a small sample of older patients (>65 years; $n = 9$). Older patients comprise a large portion of the breast cancer population and age is associated with decreased muscle mass and muscle density. Second, many patients now receive non–anthracycline-containing chemotherapy and future work will be needed to explore the role of muscle metrics and body composition for these chemotherapy regimens. This may be challenging, as many patients treated with non-anthracycline regimens present with stage I or II breast cancer where baseline CT scans are not recommended (26). Third, performance status (PS) was recorded only for 78 patients in our sample, all of whom had excellent scores of 0 or 1 (ECOG) and comorbidities were not consistently reported in the medical chart. However, PS scores of 0 or 1 are typical of patients in clinical trials, as well as those who are treated with more toxic anthracycline and taxane–based chemotherapy regimens. Furthermore, the clinical decision to use chemotherapy was made by the physician with patient input, and we assumed that comorbidities were taken into account when recommending the treatment plan. Another potential limitation is the use of different taxane regimens, but a sensitivity analysis of the 142 patients who received paclitaxel only showed that SMG remained a significant predictor of grade 3/4 hematologic toxicities, GI toxicities, and hospitalizations. The final limitation is the use of retrospective data in assessing toxicity outcomes; for this reason, we chose to collect only grade 3/4 toxicities which are medically meaningful and usually documented in the patient chart (27).

Despite major limitations in its accuracy at predicting treatment efficacy and toxicity, BSA has traditionally been used in oncology to dose chemotherapy (28, 29). After controlling for BSA, we showed that LBM and SMG were still highly effective predictors of grade 3/4 toxicities. On the basis of ROC analyses, we found that LBM and SMG were the best predictors of severe chemotherapy toxicity (see Supplementary Fig. S2). BSA dosing based only on weight and height ignores whether the weight is related to increased adipose tissue or to LBM, which is problematic in light of the low correlation between LBM and BSA (30). In patients with increased adiposity and low LBM in our study, standard BSA-based dosing was associated with high toxicity rates (see Fig. 1 for an example). There is growing evidence to support our conclusion that LBM is better at predicting treatment toxicity than BSA for both anthracyclines and 5-fluorouracil (13, 15).

Our results add to the increasing body of research showing that chemotherapy toxicity is clearly associated with body composition. Moreover, we have defined the importance of body composition in predicting toxicity for patients with EBC, one of the most common cancers worldwide, and for chemotherapy regimens that are widely used. Our results demonstrate that the importance of LBM and body composition in patients with cancer highlights the need for specific interventions to improve unfavorable body composition and to potentially decrease treatment-related toxicity. Several treatments for sarcopenia of potential benefit include anamerolin (31), exercise (32, 33), and omega-3 fatty acid dietary supplementation (34). The generation of individualized body composition measures from readily available CT scans holds great promise in individualizing and improving chemotherapy outcomes and validation of these measures in prospective trials is urgently needed. Such trials should compare body composition measures with both toxicity and efficacy outcomes and should ideally include PK measures of the chemotherapeutic or biologic agents.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The funding sources had no involvement in study design, collection of data, data interpretation, or writing of this report.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.S. Shachar, H.B. Muss
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.S. Shachar, A.M. Deal, G.R. Williams, S.K. Choi, H.B. Muss
Writing, review, and/or revision of the manuscript: S.S. Shachar, A.M. Deal, G.R. Williams, K.A. Nyrop, K. Popuri, H.B. Muss
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