

Sarcopenia as a Determinant of Chemotherapy Toxicity and Time to Tumor Progression in Metastatic Breast Cancer Patients Receiving Capecitabine Treatment

Carla M.M. Prado,² Vickie E. Baracos,^{1,2} Linda J. McCargar,² Tony Reiman,¹ Marina Mourtzakis,¹ Katia Tonkin,¹ John R. Mackey,¹ Sheryl Koski,¹ Edith Pituskin,¹ and Michael B. Sawyer¹

Abstract Purpose: Body composition has emerged as an important prognostic factor in cancer patients. Severe depletion of skeletal muscle (sarcopenia) and, hence, of overall lean body mass may represent an occult condition in individuals with normal or even high body weight. Sarcopenia has been associated with poor performance status, 5-fluorouracil toxicity, and shortened survival in cancer patients. Here, we prospectively studied patients with metastatic breast cancer receiving capecitabine treatment in order to determine if sarcopenia was associated with a higher incidence of toxicity and a shorter time to tumor progression (TTP).

Experimental Design: Fifty-five women with metastatic breast cancer resistant to anthracycline and/or taxane treatment were included. Skeletal muscle cross-sectional area at the third lumbar vertebra was measured by computerized tomography, and sarcopenia was defined using a previously published cutoff point. Toxicity was assessed after cycle 1 of treatment, and TTP was determined prospectively.

Results: Approximately 25% of patients were classified as sarcopenic, and this feature was seen in normal weight, overweight, and obese individuals. Toxicity was present in 50% of sarcopenic patients, compared with only 20% of nonsarcopenic patients ($P = 0.03$), and TTP was shorter in sarcopenic patients (101.4 days; confidence interval, 59.8-142.9) versus nonsarcopenic patients (173.3 days; confidence interval, 126.1-220.5; $P = 0.05$).

Conclusion: Sarcopenia is a significant predictor of toxicity and TTP in metastatic breast cancer patients treated with capecitabine. Our results raise the potential use of body composition assessment to predict toxicity and individualize chemotherapy dosing.

There has been recent interest in exploring relationships between body composition, specifically proportions of lean and fat tissues, with cancer incidence and cancer outcomes. We have showed a wide degree of variability of muscularity and hence of lean body mass (LBM), in contemporary cancer patient populations (1, 2). Low relative muscularity or low overall LBM are apparently related to toxicity and survival (1, 2). Nevertheless, data are limited in scope in terms of the

drugs studied, the types of patients/tumor groups, and outcomes that have been evaluated.

Current evidence suggests that LBM may be a better measure for normalizing doses of drugs that are distributed in and metabolized in lean tissues, compared with body surface area (BSA) alone (1–8). The lean tissue compartment is composed of metabolic tissues such as the liver and kidney (3, 9), intracellular and extracellular water, and skeletal muscle (which contributes a high proportion of overall LBM).

The condition of low muscle mass is termed sarcopenia, and has been studied mainly in patients with nonmalignant diseases, or geriatric populations (9, 10). Sarcopenia was initially defined as a level of muscle mass 2 SD below sex-specific norms for young adults (11); however, we recently determined sex-specific cutoffs for cancer patients, based on mortality risks (2). Whether sarcopenia is a predictor of other clinical outcomes such as treatment response or tumor progression remains unknown.

Here, we extended our analysis (1) to capecitabine, a prodrug of 5-fluorouracil (5-FU) developed to improve tolerability and antitumor biological effect (12). Capecitabine is used as a single agent in metastatic breast cancer unresponsive to anthracyclines- and/or taxanes-based regimens (13). The standard Food and Drug Administration (FDA)-approved capecitabine dose (1,250 mg/m² twice daily) is associated with unacceptable toxicity in approximately one-third of breast cancer patients

Authors' Affiliations: ¹Departments of Oncology, Cross Cancer Institute, and ²Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, Alberta, Canada

Received 8/28/08; revised 12/8/08; accepted 1/15/09; published OnlineFirst 4/7/09.

Grant support: Canadian Breast Cancer Foundation, AB/NWT Chapter. M.B. Sawyer is a recipient of an American Society of Clinical Oncology Career Development Award; C.M.M. Prado was supported by Alberta Cancer Board Graduate Studentship from Alberta Cancer Foundation.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Michael B. Sawyer, Division of Medical Oncology, Department of Oncology, University of Alberta, Cross Cancer Institute, 11560 University Avenue, Edmonton, Alberta, Canada. T6G 1Z2. Phone: 780-432-8248; Fax: 780-432-8888; E-mail: michsawy@cancerboard.ab.ca.

©2009 American Association for Cancer Research.
doi:10.1158/1078-0432.CCR-08-2242

Translational Relevance

Our work bears upon a number of novel concepts and findings relevant to cancer therapy. Composition of a unit of body weight, specifically proportions of fat and lean tissues, has not been used to individualize chemotherapy. Here, we show that low muscle mass (sarcopenia) is a key predictor of chemotherapy toxicity and efficacy. Our results show a wide variation of body composition among patients with metastatic breast cancer and that sarcopenia accounts for an important degree of treatment toxicity, when chemotherapy is individualized by body surface area, a convention that does not take body composition into account. Moreover, time to tumor progression was shorter for sarcopenic patients. We adapted a gold standard approach for estimating body composition, using information that is almost ubiquitously available in the health records of cancer patients, raising the potential use of body composition assessment to predict toxicity and individualize chemotherapy dosing.

(13, 14). The study by Hennessy et al. (13) led to many breast cancer medical oncologists adopting a lower capecitabine dose of 1,000 mg/m² twice daily as opposed to the dose in the FDA-approved product monography. Therefore, as in with the majority of anticancer drugs, individualizing capecitabine dose by BSA does not reduce interpatient variability in toxicity (15). Capecitabine is a highly water soluble drug, and therefore, it is expected to distribute into and to be metabolized in the lean compartment (12).

Our purpose was to add to the base of evidence on sarcopenia and treatment toxicity and to further investigate clinical outcomes in patients with metastatic breast cancer, using time to tumor progression (TTP) as a study end point. This is the first study evaluating relationships between body composition on chemotherapy toxicity and TTP in patients with metastatic breast cancer. We hypothesized that an increased risk of toxicity, as well as a shorter TTP, would be observed in sarcopenic patients.

Materials and Methods

Patients and study design. The present study was conducted in the context of an investigation of capecitabine and thymidylate synthase gene polymorphisms, in which we prospectively evaluated toxicity and efficacy outcomes after capecitabine therapy for metastatic breast cancer. This study was carried out at the Cross Cancer Institute, from September 2002 to January 2005. The polymorphism data will be presented separately (16).

Eligible women had metastatic breast cancer, had failed anthracycline and/or taxane treatment, and were to receive capecitabine for the first time. Inclusion criteria included the following: an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, 2, or 3; creatinine of <1.5 times the upper limit of normal; an aspartate aminotransferase or alanine aminotransferase of ≤350 IU/L; bilirubin of ≤500 μmol/L; and adequate bone marrow reserve with a neutrophil count of ≥1.0 × 10⁹/L. Pretreatment albumin levels, estrogen receptor status, and human epidermal growth factor receptor status (HER-2) status were determined. Patients were excluded if they had hypersen-

sitivity to 5-FU, known dihydropyrimidine dehydrogenase deficiency, active uncontrolled bacterial or viral infections, or were pregnant or lactating. The study was approved by the Alberta Cancer Board Research Ethics Board and informed consent was obtained from all participants.

One hundred and twenty-seven women participated in the original study (16); and 66 had computerized tomography (CT) images that met criteria for analysis. Patients who did not have evaluable scans either had no scans on record ($n = 37$), or a scan >30 d from treatment initiation ($n = 4$), and were, therefore, not included in our analysis. Based on pharmacogenetic data from the original study, nine patients presented with four thymidylate synthase enhancers (TSER*3G/TSER*3G). This genotype confers a protective effect from capecitabine toxicity (17), and was not expected to have toxicity regardless of their body composition type (16). Therefore, these patients were excluded from the present analysis. In addition, two patients who were missing genotype data were also excluded. Therefore, 55 women with metastatic breast cancer were selected for the present study (Fig. 1A).

Treatment plan. The initial capecitabine dose was selected by the treating oncologist from 1 of 2 options: either the FDA-approved dosing of 1,250 mg/m² twice daily p.o. for 14 d every 3 wk, or 1,000 mg/m² twice daily on the same schedule. Because capecitabine is associated with significant toxicity, physicians were allowed to use their clinical

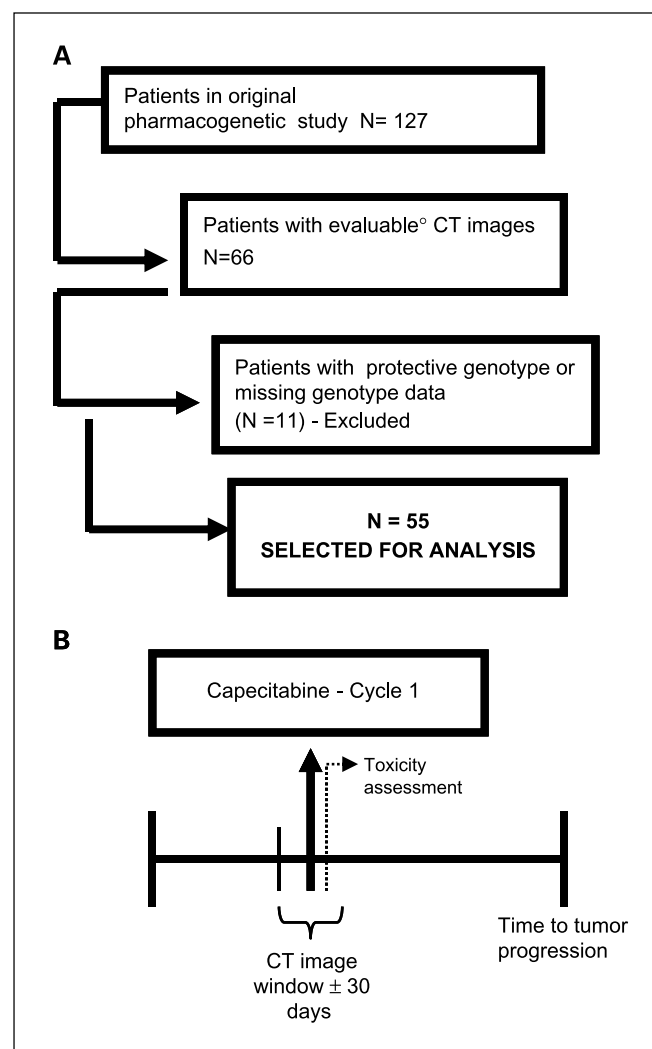


Fig. 1. A, selection of patients for the present study; 127 patients participated in the original study, and 66 had body composition data available. Eleven patients were excluded because of protective genotype data with 55 patients being included in the present analysis. B, study timelines.

judgment to start patients on 1,000 mg/m² if they considered that to be indicated. This was not due to prior toxicity but to a clinical assessment of each study participant. Only eight patients were treated at the FDA-approved dose. BSA was calculated using the Mosteller formula [BSA (m²) = ([height (cm) × weight (kg)]/3,600)^{1/2}].

Toxicity and efficacy assessment. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0. Patient toxicity assessments were obtained by a diary provided before each cycle of chemotherapy, and this was reviewed in person by a research nurse after each cycle. Toxicity profiles were obtained for all cycles, but only first-cycle toxicities were analyzed for this study because patients who had toxicity (defined as >grade 2) had dose reductions for subsequent cycles. Capecitabine treatment was interrupted (dose delays or reductions) if patients developed grade 2 or higher toxicity. Therefore, toxicity is hereby defined as incidence of any toxicity of ≥grade 2. Reported toxicities were palmar-plantar erythrodysesthesia or hand-foot syndrome, nausea, vomiting, stomatitis, or neutropenia.

Body composition measurements

Anthropometric measurements. Weight and height were recorded according to standard methods. Weight was measured with a medical balance beam scale and height was measured with a stadiometer. Body mass index (BMI) was calculated [weight (kg)/height (m²)].

Image analysis. CT has proven to be accurate for measuring human body composition (18, 19). Regional muscle tissue was measured by CT from electronically stored images, which had been done previously for diagnostic purposes. Images taken within ±30 d before or after initiation of cycle 1 were included (average ± SE = 17 ± 3.2 d; Fig. 1B). There were no interventions (such as surgery) between dates of the CT scan and the start of chemotherapy that would substantially alter body composition.

The third lumbar vertebrae (L3) was chosen as a standard landmark, and two consecutive images extending from L3 to the iliac crest were chosen to measure total muscle cross-sectional area. The L3 region contains *psaos*, paraspinal muscles (*erector spinae*, *quadratus lumborum*), and the abdominal wall muscles (*transversus abdominus*, external and internal obliques, *rectus abdominus*). These muscles were identified by a trained person, based on their anatomic features (the first image is chosen when both transverse processes are clearly visible, followed by one slice below), and the structure of those specific muscles were quantified based on preestablished thresholds of Hounsfield units (-29 to +150) of skeletal muscle tissue (18). Images were analyzed using SliceOmatic software V4.3 (Tomovision). Cross-sectional areas (cm²) of the sum of all of these muscles were computed for each image, and the average value for the two images was computed for each patient. The directly determined unit was area (cm²) of total L3 skeletal muscle. This value is linearly related to whole body muscle mass (20) and was thus normalized for stature (L3 skeletal muscle index, cm²/m²) as is conventional for BMI, and other body composition components (11).

Sarcopenia was defined using the cut off point for lumbar skeletal muscle index of <38.5 cm²/m² for women as described by Prado et al. (2). Total LBM was estimated from muscle cross-sectional areas as described in Mourtzakis et al. (21): LBM (kg) = 0.30 × [skeletal muscle at L3 using CT (cm²)] + 6.06 ($r = 0.94$; $P < 0.001$; Standard Error of Estimate, 0.72 kg). This is similar to the equation reported by Shen et al. (20) for healthy adults, except that the regression equation used in the present study was derived from assessing body composition of cancer patients.

Statistical analysis

Descriptive values are expressed as mean ± SD. All P values are two sided, and levels of significance are P values of ≤0.05. A comparison between patients with and without toxicity was conducted. Differences between two groups were assessed using Fisher's exact test and Person's χ^2 test, as appropriate. Performance status scores (ECOG) 0 to 1 were combined to reflect minimal performance impairment, and scores 2 to 3 were combined to reflect substantial performance impairment (22).

Table 1. Patient characteristics ($N = 55$)

Variables	Mean ± SD (range)
Age (y)	54.8 ± 10.4 (37-80)
BMI (kg/m ²)	27.0 ± 5.5 (18.2-46.1)
BSA (m ²)	1.8 ± 0.2 (1.4-2.3)
Muscle cross-sectional area (cm ²)	114.2 ± 19.5 (67.5-165.7)
Lumbar skeletal muscle index (cm ² /m ²)	44.2 ± 7.1 (26.4-59.4)
Estimated LBM (kg)*	40.3 ± 5.8 (26.3-55.8)

*Calculated from regression equation: whole lean body mass (kg) = 0.30 × [skeletal muscle at L3 using CT (cm²)] + 6.06;]¹⁷.

Site of metastasis was divided into four major groups: respiratory tract, liver, bone, and other metastasis (stomach, ovary, brain, and mediastinum). Sites of tumor progression represent prognostic indicators for this disease. Toxicity was modeled as a function of sarcopenia, age, performance status, and albumin levels as prognostic factors using logistic regression. TTP is defined as the number of days of tumor remission after cycle 1 and was analyzed by univariate and multivariate analysis, including major established predictors of outcome of advanced cancer reported in the literature: site of tumor recurrence/progression, albumin levels, estrogen receptor status, HER-2 status, age, and performance status. Methods of Kaplan-Meier were used to determine effects of each variable on TTP. Log-rank tests were used to compare curves of each variable. Variables known to influence TTP were entered into a multivariate Cox proportional hazards model, with 95% confidence intervals (CI) for estimated relative risk calculated. Statistical analysis was completed using SPSS (SPSS for Windows, version 16.0; SPSS).

Results

Patient characteristics and incidence of toxicity. Patient characteristics are described in Table 1. Patients presented with a wide range of BMI, LBM, and skeletal muscle index. Estimated LBM and BSA were only weakly related in this patient population (Fig. 2A). As a consequence, the administered dose of capecitabine was highly variable when expressed per kg of LBM, ranging over twice (67.4-137 mg/kg LBM).

A comparison between sarcopenic and nonsarcopenic patients is shown in Table 2. Among 55 patients, 14 (25.5%) had sarcopenia. Patients with sarcopenia received a higher amount of capecitabine dose per unit of LBM and also presented with a higher prevalence of toxicity [(50% or 7 of 14); compared with nonsarcopenic patients (20% or 8 of 41); $P = 0.03$; Table 2; Fig. 2B]. Significant differences in ECOG status, age, weight, height, BMI, BSA, estrogen receptor, and HER-2 status were not observed between sarcopenic and nonsarcopenic patients.

Prevalence of sarcopenia was not different between patients receiving the FDA dose compared with the alternate dose. Two (14%) sarcopenic patients received the FDA dose and 12 (86%) received the alternate dose whereas in the nonsarcopenic group, 6 (15%) patients received the FDA dose and 35 (85%) received the alternate one ($P = 1.000$; Fisher's exact test).

Common toxicities observed included hand-foot syndrome, diarrhea, stomatitis, nausea, and vomit. Only one patient presented with febrile neutropenia. Diarrhea and stomatitis were more commonly observed among sarcopenic patients ($P = 0.01$ and 0.008, respectively; Table 2).

Sarcopenia as a predictor of toxicity and TTP. Prevalence of toxicity was significantly higher in sarcopenic compared with

nonsarcopenic patients. Variables known to relate to chemotherapy toxicity (age, BSA, performance status, and albumin levels) were further modeled using logistic regression. Sarcopenia was the only significant predictor of toxicity (hazard ratio, 4.1; $P = 0.04$) even after controlling for performance status, albumin, and age. Sarcopenia and BSA were not modeled together because these variables are correlated. Correlations between albumin and skeletal muscle index were also weak.

After ~630 days after cycle 1, all patients had documented tumor progression. Median TTP was shorter for sarcopenic patients (62 days CI, 47.3-76.7) compared with those nonsarcopenic (105 days CI, 52.3-157.7; $P = 0.05$ log-rank test; Fig. 3). TTP was not influenced by age, BSA, performance status, site of metastasis, and HER-2 receptor status. Factors influencing TTP were subsequently modeled for 52 patients (3 missing values) using a multivariate Cox proportional hazards model (Table 3). Sarcopenia emerged as a significant predictor of shorter TTP (hazard ratio, 2.6; $P = 0.01$), independent of albumin, site of metastasis, and estrogen receptor status.

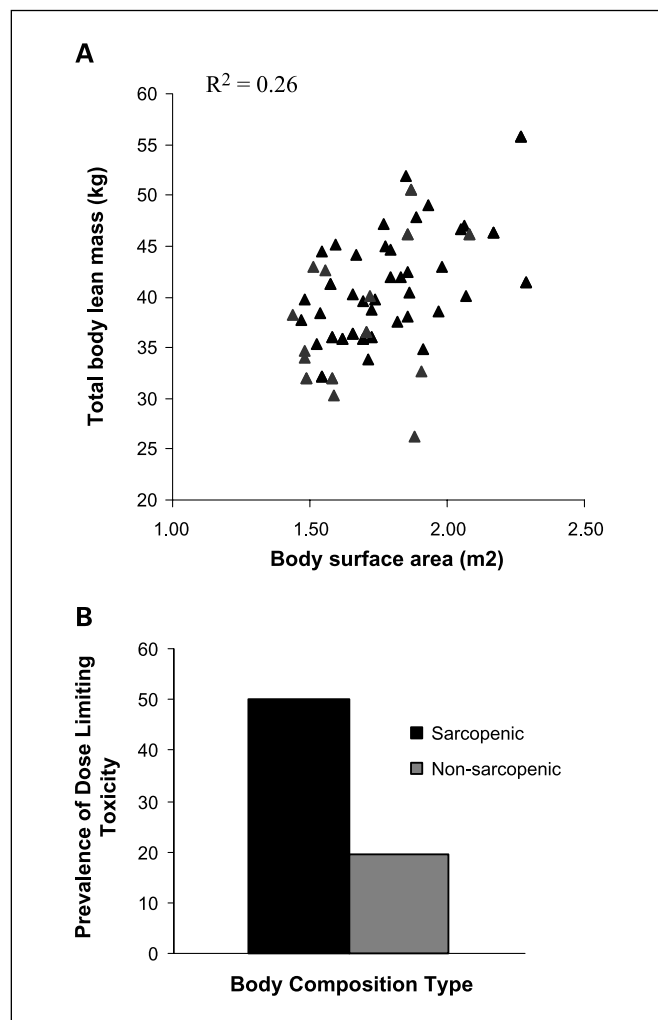


Fig. 2. A, relationship between total lean body mass and body surface area for metastatic breast cancer patients. B, prevalence of dose limiting toxicity between patients with metastatic breast cancer with (50%) and without (19.5%) sarcopenia ($n = 55$), $P = 0.039$, Fisher's exact test.

Discussion

Our study shows that sarcopenia is a significant predictor of toxicity and TTP in women with metastatic breast cancer receiving capecitabine treatment. Sarcopenic patients were three times more likely to present toxicity compared with nonsarcopenic patients, suggesting that variation in terms of toxicity is partially explained by this feature of body composition.

As shown by the wide range of muscularity in this population, body composition is extremely variable and was clearly related to the toxicities experienced by this cohort, whereas BSA, ECOG performance status, and serum albumin levels were not predictive of toxicity. Sarcopenia was not present exclusively in underweight patients; in fact, 98% of our cohort would not be considered underweight by commonly accepted criteria ($BMI \leq 18.5 \text{ kg/m}^2$). Therefore, sarcopenia is an occult condition that can be present in patients with any body weight and BMI. Moreover, depletion of lean tissue in sarcopenic patients was considerable. It is notable that the estimated LBM of sarcopenic patients studied here ($34 \pm 3.3 \text{ kg}$) is much lower than values reported for patients regarded as cachectic [i.e., 49.0 kg (23) and 43.4 kg (24)].

Our results are concordant with other studies. Aslani et al. (7) studied 31 patients treated with cyclophosphamide, methotrexate, and 5-FU using BSA-based dosing. They reported a 28-fold increase in the relative risk of grade 3 and 4 neutropenia (using multivariate analysis) if a patient's LBM was <89% of age and sex-adjusted norms. Although methods of body composition analysis (whole body nitrogen counting) differed in the study of Aslani et al. (7) from our study, both show that chemotherapy toxicity is strongly and inversely related to muscularity.

We hypothesize that the relationship between body composition and capecitabine toxicity is primarily due a pharmacokinetic effect. Capecitabine is a prodrug that is metabolized to 5-FU. Consistent with our findings, Gusella et al. (6) reported that fat-free mass (LBM plus bone tissue) and total body water were better predictors of 5-FU pharmacokinetics (clearance and volume of distribution) than BSA or total body weight.

We previously reported that patients with colorectal cancer may have low LBM relative to their BSA (1). A consequence of low LBM would be a low volume of distribution of cytotoxic chemotherapy drugs, and our earlier study suggested that higher doses of 5-FU/kg LBM were associated with a higher incidence of overall toxicity (1).

For the present analysis, we further conjectured that a previously used sex-specific cutpoint to define sarcopenia is also predictive of toxicity. Moreover, patients with sarcopenia presented with higher doses of capecitabine/kg LBM. For a person with sarcopenia, a lower volume of distribution of a drug would result in higher concentrations in a shorter period of time; therefore, this person would be less physiologically able to clear the drug from the systemic circulation.

Explanations for the observation that sarcopenia is associated with TTP are unclear. In this study, we showed that the presence of sarcopenia was associated with a significantly shorter TTP (hazard ratio, 2.6; CI 1.2-5.6). TTP is an important clinical end point, as it indicates when a patient requires treatment changes, and correlates with overall survival in women

Table 2. Comparisons between patients with and without sarcopenia

	Sarcopenic (n = 14; 25.5%)	Nonsarcopenic (n = 41; 74.5%)	P
Toxicity			
Present	7 (50.0%)	8 (20%)	0.03
Absent	7 (50.0%)	33 (80%)	
ECOG performance status*			
No performance impairment (scores 0-1)	9 (64%)	25 (65%)	1.00
Performance impairment (scores 2-3)	5 (36%)	14 (35%)	
Estrogen receptor status			
Positive	8 (57%)	31 (76%)	0.31
Negative	6 (43%)	10 (24%)	
HER-2 status			
Positive	3 (21%)	15 (37%)	0.35
Negative	11 (79%)	26 (63%)	
Characteristics mean (SD)			
Age	56.6 (11.4)	54.1 (10.1)	0.43
Weight (kg)	65.6 (11.4)	71.4 (16.7)	0.23
Height (m)	1.6 (0.1)	1.6 (0.1)	0.11
BMI (kg/m ²)	24.6 (4.0)	27.8 (5.7)	0.06
BSA (m ²)	1.7 (0.2)	1.8 (0.2)	0.42
Albumin †	39.8 (4.9)	39.1 (4.5)	0.60
Lumbar skeletal muscle index (cm ² /m ²)	35.0 (3.3)	47.4 (5.0)	<0.0001
Whole body lean mass (kg)	34.0 (3.3)	42.5 (5.0)	<0.0001
Mg capecitabine/kg LBM	104.2 (16.1)	86.9 (13.7)	<0.0001
Toxicity prevalence ‡			
Hand-foot syndrome	3 (21%)	4 (8%)	0.35
Diarrhea	4 (29%)	1 (2.4)	0.01
Stomatitis	5 (36%)	2 (4.9%)	0.008
Nausea	3 (21%)	3 (7%)	0.17
Vomit	1 (7%)	1 (2.4)	0.45
Neutropenia	1 (7.1%)	0	0.25

*ECOG performance status score missing for one patient (n = 54).

†Albumin status missing for 2 patients (n = 53).

‡Grade 2 or higher toxicity (associated with dose delays or reductions).

receiving chemotherapy for metastatic breast cancer (25). Sarcopenia has been associated with unfavorable clinical outcomes such as increased length of hospital stay, increased incidence of infections for hospitalized patients, and mortality,

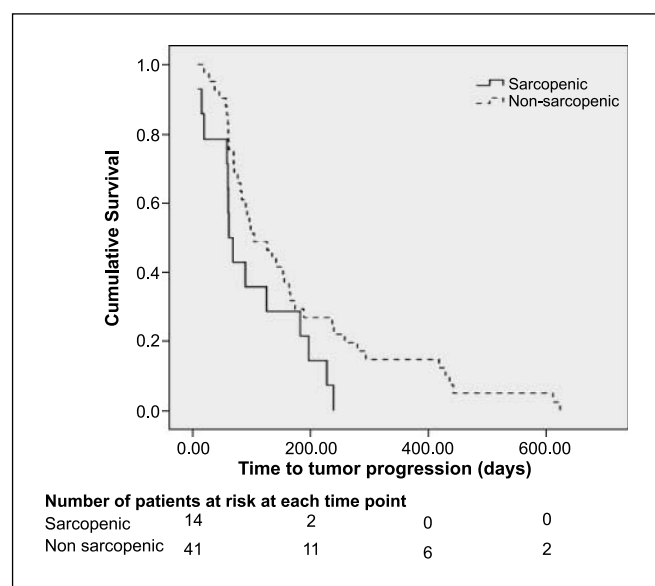


Fig. 3. Comparison of time to tumor progression between sarcopenic and non-sarcopenic patients (P = 0.05).

among others (26–28). Whether muscle catabolism directly promotes tumor progression (29), or whether the impaired immunologic responses that accompany sarcopenia (30) contribute to shortened TTP, remains speculative. Kadar et al. (31) reported a positive and significant association between the amount of muscle mass and recurrence-free survival in patients with lung cancer receiving radiation therapy. The authors used *in vivo* neutron activation analysis to measure body protein content, an indirect measure of muscle mass in the body. According to the authors, changes in body protein content preceded changes in body weight and albumin levels. We speculate that a very aggressive or advanced underlying disease is associated with low muscle mass, which in turn is a prognostic factor for the disease, as well as a predictor of toxicity.

Another unclear point is whether toxicity-related follow up changes in treatment schedule could have been responsible for shorter TTP. Although we can only speculate on this discussion, patients' intolerance to the drug may have contributed to a decrease in TTP as a reflection of a lower dose and therefore lower likelihood of response. Conversely, although these patients received a high dose in cycle 1, their response rate was still poor (shorter TTP). We believe that the presence of toxicity was a reflection that patients were overdosed based on their small LBM and that a decrease in the dose for sarcopenic patients would have translated into an adequate exposure of the biological dose with acceptable

Table 3. Hazard ratios for proportional hazards model evaluating effects of variables on TTP

Variables	Univariate analysis			Multivariate analysis*		
	Coefficient (SE)	Hazard ratio (CI 95%)	P	Coefficient (SE)	Hazard ratio (CI 95%)	P
Sarcopenia †	0.62 (0.3)	1.9 (1.0-3.5)	0.05	0.97 (0.4)	2.6 (1.2-5.6)	0.01
Respiratory tract metastasis ‡	-0.13 (0.3)	0.9 (0.5-1.4)	0.61	-0.20 (0.4)	0.8 (0.3-1.9)	0.57
Liver metastasis ‡	0.21 (0.2)	1.2 (0.8-1.9)	0.34	0.41 (0.4)	1.5 (0.7-3.2)	0.30
Other metastasis ‡	0.00 (0.3)	1.0 (0.6-1.7)	0.10	-0.29 (0.5)	0.8 (0.3-2.1)	0.58
Albumin	-0.06 (0.0)	0.9 (0.9-1.0)	0.03	-0.09 (0.03)	0.9 (0.9-1.0)	0.002
Estrogen receptor status§	0.66 (0.3)	1.9 (1.1-3.6)	0.03	0.75 (0.4)	2.1 (1.1-4.2)	0.03
HER-2 status	-0.08 (0.3)	0.9 (0.5-1.6)	0.92	0.58 (0.4)	1.8 (0.9-3.6)	0.11
Age	0.01 (0.0)	1.0 (1.0-1.0)	0.36			
ECOG performance status¶	0.15 (0.3)	1.2 (0.6-2.1)	0.62			
BSA	-0.94 (0.7)	0.4 (0.1-1.4)	0.15			

NOTE: A univariate and a multivariate Cox regression model were used. Age was not a significant prognostic factor.

**n* = 52 (3 missing values).

†Versus nonsarcopenic patients.

‡Versus bone metastasis.

§Versus estrogen receptor present.

||HER-2 status, versus HER-2 receptor not overexpressed.

¶ECOG, versus patients with ECOG performance status 2 to 3.

side effects. Future prospective studies can be used to test these hypotheses.

CT is increasingly used to evaluate human body composition (18, 32) and is routinely used to evaluate tumor response in cancer patients. Using CT image analysis and a previously validated cutpoint to identify sarcopenia (2) has provided data to suggest that differences in toxicities between patients are partially due to variation in muscularity. Determining an optimal cutpoint for toxicity prediction will require additional prospective studies with larger sample sizes.

Our results highlight the potential use of body composition assessment to improve toxicity risk and to individualize drug dosing in a population of patients with advanced cancer of the

breast. This concept warrants formal validation in studies evaluating drug dosing based on pretreatment body composition analysis.

Disclosure of Potential Conflicts of Interest

M.B. Sawyer, research support, advisory board, Roche. J.R. Mackey, advisory board, Roche. The other authors disclosed no potential conflicts of interest.

Acknowledgments

We thank Sunita Ghosh, PhD, for statistical advice, Linda Harris for assistance in literature searches, and Vishesh Kumar for assistance with image analysis.

References

- Prado CM, Baracos VE, McCargar LJ, et al. Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. *Clin Cancer Res* 2007;13:3264-8.
- Prado CM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol* 2008;9:629-35.
- Morgan DJ, Bray KM. Lean body mass as a predictor of drug dosage. Implications for drug therapy. *Clin Pharmacokinet* 1994;26:292-307.
- Cosolo WC, Morgan DJ, Seeman E, Zimet AS, McKendrick JJ, Zalcberg JR. Lean body mass, body surface area and epirubicin kinetics. *Anticancer Drugs* 1994;5:293-7.
- Santini F, Pinchera A, Marsili A, et al. Lean body mass is a major determinant of levothyroxine dosage in the treatment of thyroid diseases. *J Clin Endocrinol Metab* 2005;90:124-7.
- Gusella M, Toso S, Ferrazzi E, Ferrari M, Padriani R. Relationships between body composition parameters and fluorouracil pharmacokinetics. *Br J Clin Pharmacol* 2002;54:131-9.
- Aslani A, Smith RC, Allen BJ, Pavliakis N, Levi JA. The predictive value of body protein for chemotherapy-induced toxicity. *Cancer* 2000;88:796-803.
- Gurney HP, Ackland S, GebSKI V, Farrell G. Factors affecting epirubicin pharmacokinetics and toxicity: evidence against using body-surface area for dose calculation. *J Clin Oncol* 1998;16:2299-304.
- Roubenoff R, Kehayias JJ. The meaning and measurement of lean body mass. *Nutr Rev* 1991;49:163-75.
- Rosenberg I. The epidemiologic and methodologic problems in determining nutritional status of older persons. (Summary comments). *Am J Clin Nutr* 1989;50:1231-33.
- Baumgartner RN, Koehler KM, Gallagher D, et al. Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol* 1998;147:755-63.
- Walko CM, Lindley C. Capecitabine: a review. *Clin Ther* 2005;27:23-44.
- Hennessy BT, Gauthier AM, Michaud LB, Hortobagyi G, Valero V. Lower dose capecitabine has a more favorable therapeutic index in metastatic breast cancer: retrospective analysis of patients treated at M. D. Anderson Cancer Center and a review of capecitabine toxicity in the literature. *Ann Oncol* 2005;16:1289-96.
- Oshaughnessy JA, Blum J, Moiseyenko V, et al. Randomized, open-label, phase II trial of oral capecitabine (Xeloda) vs. a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer. *Ann Oncol* 2001;12:1247-54.
- Sawyer M, Ratain MJ. Body surface area as a determinant of pharmacokinetics and drug dosing. *Invest New Drugs* 2001;19:171-7.
- Sawyer MB, Au HJ, Scarfe A, et al. A prospective pharmacogenetic study of capecitabine in metastatic breast cancer. In: *Proceedings of the American Association for Cancer Research*; 2004 April 16-20. Orlando, Florida; 2004.
- Marsh S, McKay JA, Cassidy J, McLeod HL. Polymorphism in the thymidylate synthase promoter enhancer region in colorectal cancer. *Int J Oncol* 2001;19:383-6.
- Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. *J Appl Physiol* 1998;85:115-22.
- Heymsfield SB, Wang Z, Baumgartner RN, Ross R. Human body composition: advances in models and methods. *Annu Rev Nutr* 1997;17:527-58.
- Shen W, Punyanitya M, Wang Z, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *J Appl Physiol* 2004;97:2333-8.
- Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab* 2008;33:997-1006.
- Dewys WD, Begg C, Lavin PT, et al. Eastern Cooperative Oncology Group. Prognostic effect of weight

- loss prior to chemotherapy in cancer patients. *Am J Med* 1980;69:491–7.
23. Fearon KC, Von Meyenfeldt MF, Moses AG, et al. Effect of a protein and energy dense N-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer cachexia: a randomised double blind trial. *Gut* 2003;52:1479–86.
24. Simons JP, Schols AM, Hoefnagels JM, Westertep KR, ten Velde GP, Wouters EF. Effects of medroxyprogesterone acetate on food intake, body composition, and resting energy expenditure in patients with advanced, nonhormone-sensitive cancer: a randomized, placebo-controlled trial. *Cancer* 1998;82:553–60.
25. Burzykowski T, Buyse M, Piccart-Gebhart MJ, et al. Evaluation of tumor response, disease control, progression-free survival, and time to progression as potential surrogate end points in metastatic breast cancer. *J Clin Oncol* 2008;26:1987–92.
26. Cosqueric G, Sebag A, Ducolombier C, Thomas C, Piette F, Weill-Engerer S. Sarcopenia is predictive of nosocomial infection in care of the elderly. *Br J Nutr* 2006;96:895–901.
27. Morley JE, Baumgartner RN, Roubenoff R, Mayer J, Nair KS. Sarcopenia. *J Lab Clin Med* 2001;137:231–43.
28. Pichard C, Kyle UG, Morabia A, Perrier A, Vermeulen B, Unger P. Nutritional assessment: lean body mass depletion at hospital admission is associated with an increased length of stay. *Am J Clin Nutr* 2004;79:613–8.
29. Tisdale MJ. Loss of skeletal muscle in cancer: biochemical mechanisms. *Front Biosci* 2001;6:D164–74.
30. Wolfe RR. The underappreciated role of muscle in health and disease. *Am J Clin Nutr* 2006;84:475–82.
31. Kadar L, Albertsson M, Areberg J, Landberg T, Mattsson S. The prognostic value of body protein in patients with lung cancer. *Ann N Y Acad Sci* 2000;904:584–91.
32. Pietrobelli A, Wang Z, Heymsfield SB. Techniques used in measuring human body composition. *Curr Opin Clin Nutr Metab Care* 1998;1:439–48.