The Relationship Between Body Composition and Response to Neoadjuvant Chemotherapy in Women with Operable Breast Cancer

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ABSTRACT

Introduction. Overweight women diagnosed with breast cancer have greater recurrence and mortality risks. Recent studies in advanced cancer showed that the combination of sarcopenia and an overweight or obese body mass index (BMI) is associated with poor clinical outcomes.

Objectives. To compare pathological complete response (pCR) cases with controls and evaluate associations among a pCR, survival outcome, and sarcopenia as well as the combination of both sarcopenia and a BMI ≥ 25 kg/m².

Methods. Sixty-seven breast cancer patients with a pCR to neoadjuvant chemotherapy (NC) were matched with controls who did not have a pCR to NC. Patients were matched by age, Black's nuclear grading system, clinical cancer stage, and estrogen receptor and progesterone re-

ceptor status. Body composition was analyzed using computed tomography images taken prior to NC.

Results. BMI was associated with pCR. Among normal weight patients, the pCR rate was higher in sarcopenic patients and the progression-free survival (PFS) interval was significantly longer than in overweight or obese BMI patients. The death hazard was 2% higher for each unit higher skeletal muscle index and 0.6% higher for each unit higher visceral adipose tissue.

Conclusions. Overweight patients treated with NC had a lower pCR rate and shorter PFS time. Among patients with a normal BMI, the pCR rate was better in sarcopenic patients. More research is required to evaluate the negative impact of sarcopenic obesity on prognosis and the contributors to better response rates in operable, normal weight breast cancer patients with sarcopenia. *The Oncologist* 2012;17:1240–1245

INTRODUCTION

Obesity is associated with several factors involved in carcinogenesis and cancer progression, including insulin resistance, lower adiponectin levels, and higher levels of leptin, plasminogen activator inhibitor-1, endogenous sex steroids, and chronic inflammation [1]. In addition to increasing the risk for incident breast cancer, obesity also adversely affects patients receiving definitive treatment. A comprehensive literature re-

view concluded that women with breast cancer who are overweight or gain weight after diagnosis are at greater risk for recurrence and death [2].

Although there are many population studies using well-defined criteria for obesity, there are few studies that evaluate body composition in patients with a high body mass index (BMI). Patients with the same BMI may have wide variations in their body composition of skeletal muscle and adipose tis-

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sue. Because of the obesity epidemic in the developed world, studies using BMI alone may be under-reporting patients with sarcopenia.

Sarcopenia can be defined as muscle mass greater than two standard deviations below that of healthy adults [3] and has been associated with both physical decline and mortality in noncancer [4] and cancer [5] patients. In patients with chemotherapy-resistant metastatic breast cancer being treated with capecitabine, sarcopenia predicted greater treatment toxicity and a shorter time to tumor progression [6]. In another small exploratory study of 24 stage II and stage III breast cancer patients receiving adjuvant 5-fluorouracil, epirubicin, and cyclophosphamide [7], patients with toxicity had a lower lean body mass than patients with no toxicity. The same group of investigators also reported that dose-limiting sorafenib toxicity was especially prevalent in sarcopenic male patients with a BMI $<25 \text{ kg/m}^2$ [8]. A potential consequence of a low lean body mass in relation to a person's height and weight could be a low volume of distribution of cytotoxic chemotherapy drugs in proportion to the body surface area (BSA), resulting in greater treatment toxicity.

Our study used the same data source of operable breast cancer patients as Litton et al. [9], comparing overweight and obese groups of operable breast cancer patients with those of normal weight. A higher BMI was associated with a lower pathologic complete response (pCR) rate to neoadjuvant chemotherapy (NC) and a shorter overall survival (OS) time. Obese patients had a significantly shorter survival time than did normal or underweight patients [9].

The objectives of this study were to compare pCR cases with matched controls and evaluate the associations between a pCR and sarcopenia as well as the combination of both sarcopenia and a BMI $\geq 25 \text{ kg/m}^2$. We also determined whether or not the OS, disease-specific survival, and progression-free survival (PFS) times from the start of NC were associated with sarcopenia or with the combination of sarcopenia and BMI.

Our initial hypothesis was that breast cancer patients with a pCR have a lower BMI and greater lean body mass than patients without a pCR and that sarcopenia and a high BMI are associated with worse OS and PFS outcomes.

METHODS

The Breast Cancer Management System database of MD Anderson Cancer Center (MDACC) was used to identify women with nonmetastatic, primary, invasive ductal or lobular noninflammatory breast cancer treated with NC prior to being eligible for surgical treatment at MDACC from December 2000 through December 2004. The database contains detailed information on patient demographics (race, age), clinical characteristics (height and weight at the start of NC, chemotherapy and endocrine treatment, surgery type, and assessment of pathologic response in the breast and axilla), and tumor characteristics at diagnosis (clinical stage, estrogen receptor [ER] and progesterone receptor [PR] status, histologic grade, and human epidermal growth factor receptor [HER]-2/*neu* status) and has been described previously [10]. Annual follow-up letters are sent to each patient registered at MDACC who is known to be

alive in order to determine the patient's current clinical status. The MDACC Tumor Registry cross references the Social Security Death Index and the Texas Bureau of Vital Statistics for the status of patients who do not respond to the follow-up letters.

From this database, we obtained a study sample of 67 breast cancer patients who had a pCR to NC. These patients were matched with controls who did not have a pCR to NC. Controls were matched on age category (<50 versus ≥ 50 years), Black's nuclear grading system grade (1 versus 2 or 3), clinical cancer stage (1 or 2 versus 3), and ER and PR status (both negative versus at least one positive). At the time of the analysis, five of the controls were found to be metastatic at presentation and were removed from the analysis, leaving 67 patients with a pCR to NC and 62 patients who did not have a pCR.

All patients included in the study had nonmetastatic breast cancer treated with NC and computed tomography (CT) scans prior to chemotherapy with axial slices over the third lumbar vertebra (L3). Primary invasive ductal or lobular noninflammatory breast cancer was diagnosed using core needle biopsy, and tissue was evaluated using pathology before the initiation of NC. The pCR group was defined as having no residual invasive carcinoma in either the breast or the axillary lymph nodes. Patients with residual ductal carcinoma in situ were included in the pCR group [11]. Patients who had partial or definitive surgery before receiving NC, were pregnant, refused surgery after NC, or had a pathological response assessment >1 year after NC were excluded.

Measurements

Weight was assessed using BMI, calculated as weight (in kg) divided by height (in m^2), and patients were categorized as obese (BMI $\geq 30 \text{ kg/m}^2$), overweight ($25 \text{ kg/m}^2 \leq \text{BMI} < 30 \text{ kg/m}^2$), and normal or underweight (BMI $< 25 \text{ kg/m}^2$), as described by the National Institutes of Health and National Heart, Lung, and Blood Institute [12].

Sarcopenia was assessed using muscle mass as estimated by analysis of available CT images taken prior to NC. Depending on the thickness of the individual CT slices, up to three consecutive transverse images centered on L3 were assessed. Scans were read using Tomovision software (Montreal, Canada) by two of the authors (H.P. and K.P.), who were blinded to the identity and clinical outcomes of the patients. The muscles in the L3 region include the psoas, erector spinae, quadratus lumborum, transversus abdominus, external and internal obliques, and rectus abdominus. Hounsfield unit (HU) thresholds were used for initial identification of likely adipose tissues: -190 to $[\text{minus}]30$ HU for s.c. and i.m. adipose tissue [13] and -150 to -50 HU for visceral adipose tissue. Cutoffs for sarcopenia were based on a CT-based sarcopenic obesity study of cancer patients by Prado et al. [14] (i.e., L3 skeletal muscle index $\leq 38.5 \text{ cm}^2/\text{m}^2$ for women and $\leq 52.4 \text{ cm}^2/\text{m}^2$ for men).

Statistical Analysis

Study sample characteristics were described using frequencies, percentages, medians, and minimum and maximum values. Univariate and multivariate logistic regression models to

Table 1. Univariate logistic regression models to predict pCR to neoadjuvant chemotherapy

Variable	Value	Total	pCR, n (%)		OR	95% CI	p-value
			No	Yes			
Sarcopenic	Yes	18	5 (28)	13 (72)	2.74	0.92–8.22	.0711
	No	111	57 (51)	54 (49)	1.00	–	–
BMI, kg/m ²		129	62 (48)	67 (52)	0.99	0.95–1.04	.8282
BMI category	Obese (≥ 30)	51	21 (41)	30 (59)	1.03	0.44–2.25	.9789
	Overweight (25 to <30)	34	23 (68)	11 (32)	0.33	0.13–0.85	.0208
	Normal (<25)	44	18 (41)	26 (59)	1.00	–	–
Patient age at diagnosis, yrs		125	58 (46)	67 (54)	1.00	0.97–1.03	.9165
Patient race or ethnicity	African-American	17	7 (41)	10 (59)	1.63	0.56–4.72	.3702
	Asian or Pacific Islander	13	5 (38)	8 (62)	1.82	0.55–6.07	.3285
	Hispanic	22	9 (41)	13 (59)	1.65	0.63–4.30	.3098
	White	77	41 (53)	36 (47)	1.00	–	–
Clinical cancer stage	II	94	43 (46)	51 (54)	2.96	0.55–16.04	.2075
	III	28	14 (50)	14 (50)	2.50	0.41–15.10	.3186
	I	7	5 (71)	2 (29)	1.00	–	–
Clinical cancer stage	III	28	14 (50)	14 (50)	0.91	0.39–2.09	.8165
	I or II	101	48 (48)	53 (52)	1.00	–	–
ER status	Negative	96	41 (43)	55 (57)	2.35	1.04–5.31	.0405
	Positive	33	21 (64)	12 (36)	1.00	–	–
PR status	Positive	27	9 (33)	18 (67)	2.16	0.89–5.26	.0891
	Negative	102	53 (52)	49 (48)	1.00	–	–
Nuclear grade	III	114	54 (47)	60 (53)	1.48	0.48–4.54	.4918
	II	14	8 (57)	6 (43)	1.00	–	–
HER-2/neu status	Positive	44	17 (39)	27 (61)	1.67	0.79–3.53	.1796
	Negative	80	41 (51)	39 (49)	1.00	–	–

Abbreviations: BMI, body mass index; CI, confidence interval; ER, estrogen receptor; HER-2, human epidermal growth factor receptor 2; OR, odds ratio; pCR, pathological complete response; PR, progesterone receptor.

predict pCR were run to compute odds ratios (ORs) and corresponding 95% confidence intervals (CIs).

Cox proportional hazards regression methods were used to model OS and PFS outcomes as a function of sarcopenia, BMI, and other variables of interest. In addition, Kaplan–Meier's product limit methods were used, and equality across strata was evaluated using the log-rank test.

The OS time was calculated as the interval from the date of NC initiation to the date of death. Survival times for patients alive at the end of follow-up were censored at the date of last follow-up. The PFS interval was calculated from the date of NC initiation to the date of disease recurrence or metastasis, or, if no recurrence or metastasis was recorded, to the time of last follow-up. Survival times for patients who had not experienced progression were censored at the date of last follow-up.

No adjustments were made for multiple comparisons. All *p*-values were two tailed and considered significant if $<.05$. Analyses were conducted using SAS for Windows (release 9.2, SAS Institute, Cary, NC).

RESULTS

Eighteen (14%) of the 129 patients were sarcopenic based on the analysis of CT scans. BMI was categorized as normal for 44 (34%), overweight for 34 (26%), and obese for 51 (40%) patients. There were 10 patients with a BMI ≥ 40 kg/m². The two patients considered underweight (BMI = 17.1 kg/m² and 18 kg/m²) were grouped with normal BMI patients. Fourteen (78%) of the sarcopenic patients had a normal BMI, one (5%) was overweight, and three (17%) were obese. There was a significant association between being sarcopenic and BMI category, with a higher percentage of sarcopenic patients having a normal BMI ($p = .0002$).

pCR

In univariate modeling, the response to NC was not significantly associated with sarcopenic status ($p = .0711$), although there was a trend toward a higher rate of response among those who were sarcopenic (OR, 2.74; 95% CI, 0.92–8.22) (Table 1). Response was significantly associated with ER status and with BMI category. Patients with ER⁺ tumors had a 2.35-fold

Table 2. Multivariate logistic regression analysis to predict response to neoadjuvant chemotherapy ($n = 123$)

Variable	Value	OR	95% CI	<i>p</i> -value
Sarcopenia	Yes	4.097	0.995–16.871	.0508
	No	1.000		
BMI, kg/m ²		1.026	0.962–1.094	.4416
Age at diagnosis, yrs		0.988	0.949–1.029	.5670
Patient race or ethnicity	African-American	2.712	0.713–10.313	.1431
	Asian or Pacific Islander	1.998	0.523–7.636	.3114
	Hispanic	2.715	0.809–9.106	.1058
	White	1.000		
Clinical cancer stage	I	0.344	0.039–2.998	.3341
	II	1.249	0.421–3.706	.6887
	III	1.000		
ER status	Negative	6.987	1.836–26.588	.0044
	Positive	1.000		
PR status	Positive	6.412	1.638–25.098	.0076
	Negative	1.000		
Nuclear grade	II	1.668	0.397–7.011	.4852
	III	1.000		
HER-2/ <i>neu</i> status	Negative	0.577	0.238–1.400	.2242
	Positive	1.000		

Abbreviations: BMI, body mass index; CI, confidence interval; ER, estrogen receptor; HER-2, human epidermal growth factor receptor 2; OR, odds ratio; PR, progesterone receptor.

greater odds for a pCR to NC (OR, 2.35; 95% CI, 1.04–5.31; $p = .0405$). In addition, overweight patients had a significantly lower odds for a response than normal weight patients (OR, 0.33; 95% CI, 0.13–0.85; $p = .0208$); however, response did not differ between obese patients and patients with a normal BMI ($p = .9789$).

A multivariate model was fit to predict response using patient age, race, BMI, sarcopenic status, tumor stage, grade, and ER, PR, and HER-2/*neu* status as independent predictors (Table 2). ER status and PR status were both significant predictors of response ($p = .0044$ and $p = .0076$, respectively). In addition, sarcopenia was of borderline significance ($p = .0508$). There appeared to be a significant interaction between BMI and sarcopenia in predicting response to neoadjuvant therapy ($p = .0322$). In patients who were sarcopenic ($n = 18$), the odds for a response were ~28.5% lower for each unit higher BMI (OR, 0.72; 95% CI, 0.52–0.98; $p = .0386$). This association between BMI and response was not observed among the 111 nonsarcopenic patients ($p = .2994$).

Among normal weight patients (26 pCRs of 44 total), the odds for a response were higher among patients who were sarcopenic (OR, 6.86; 95% CI, 1.30–36.04; $p = .0230$). The association between sarcopenia and BMI was not significant among patients with an above normal BMI.

Survival

There were 21 deaths observed during follow-up and data were missing for two patients. The median follow-up duration from the start of NC for the 106 patients alive at the end of follow-up was

7.74 years (range, 0.17–10.38 years). Although sarcopenia and BMI were not significantly associated with the OS time, skeletal muscle index and visceral adipose tissue score were associated with the OS time. Every unit greater skeletal muscle index resulted in a 2% higher hazard for death (hazard ratio [HR], 1.02; 95% CI, 1.00–1.04; $p = .0309$), and every unit greater visceral adipose tissue score resulted in a 0.6% higher hazard for death (HR, 1.006; 95% CI, 1.001–1.012; $p = .0193$).

The PFS interval was significantly longer in the normal BMI group ($p = .0389$) than in those with a BMI above the normal range. The estimated 5-year PFS rate was 92% (CI, 78%–98%) among those with a normal BMI and 78% (CI, 66%–86%) among those with an above normal BMI.

Stratified by sarcopenic status, the PFS interval difference did not achieve statistical significance between patients with a normal BMI and those with an above normal BMI among the 111 patients who were not sarcopenic. Among the 18 sarcopenic patients, the PFS estimates differed significantly by BMI group ($p = .0100$). Only two of the 18 progressed and both had an above normal BMI; however, the numbers were small, with 14 in the normal BMI group and 4 in the above normal BMI group.

DISCUSSION

The results are consistent with the previous study at our institution by Litton et al. [9] showing an association between an overweight BMI and a poor pathological response in breast cancer patients. As in other trials [14, 15], sarcopenic obesity

was found to be an adverse factor so that sarcopenic patients with an elevated BMI had a poorer prognosis than those with a normal BMI. However, unlike recent studies [8, 15], the majority of our patients with sarcopenia had a better prognosis. Patients with a normal BMI and sarcopenia had a better prognosis than those with a normal BMI and no sarcopenia. The superior pCR and PFS outcomes of sarcopenic patients and the longer OS time of those with a lower skeletal muscle index are unexpected, because studies in pancreatic [15], renal [8], and metastatic breast [6] cancer patients have shown shorter survival times and greater treatment toxicity associated with sarcopenia.

The reasons for the remarkable benefit associated with sarcopenia are unclear, but may be related to a relatively higher chemotherapy dose and the patients' ability to tolerate the accompanying toxicity. Our patients were relatively healthier than sarcopenic patients in previous reports, because they were evaluated using a CT scan early in their disease and treated with curative intent for operable breast cancer. In addition, lean body mass (LBM) has been shown to be superior to other measures of body size as a predictor of dosage for many drugs [16]. Total LBM also correlates with liver volume and liver blood flow [17], and there is a relationship between LBM and drug clearance for several pharmacological agents metabolized by the liver. The volume of distribution of relatively hydrophilic drugs correlates very well with LBM, so that LBM can accurately predict the loading dose required to attain a target peak plasma concentration. Consequently, although our sarcopenic patients may have received a relatively higher chemotherapy dose, resulting in a higher response rate, they were also better able to tolerate chemotherapy toxicity than patients with advanced cancer evaluated in other studies [6–8, 14, 15].

Factors other than a relatively higher chemotherapy dose may have contributed to the benefit experienced by sarcopenic patients. Patients with more advanced disease and with tumors other than breast cancer [18] are more likely to be sarcopenic as a result of the cachexia syndrome that is associated with disease progression and intolerance to chemotherapy. Our patients with early-stage breast cancer and sarcopenia were unlikely to have diminished muscle mass as a result of the cancer cachexia syndrome [19]. Finally, there may be a gender influence on cancer outcome and weight loss such that female patients are not as susceptible as males to cancer-related weight loss [20, 21] or its association with a poor survival outcome [22].

Sarcopenic patients who were overweight or obese had worse clinical outcomes than sarcopenic normal weight patients. Possible causes include the deleterious effects of excessive adipose tissue, including insulin resistance and chronic inflammation. Further research is justified because the assessment of body composition using CT imaging is a relatively inexpensive and accurate technique and can be incorporated into routine clinical assessments.

The analysis has limitations particularly because it is a retrospective cohort study. The chemotherapy dose was based on BSA but the database does not track the actual dose of chemotherapy given, only the agents used. Other limitations include the small number of patients found to be sarcopenic, so that in the sarcopenic subgroup analysis, although the difference in PFS outcome between normal BMI patients ($n = 14$) and patients with an above normal BMI ($n = 4$) was statistically significant, the numbers are very small and results should be interpreted with caution. In addition, among normal weight patients, although the odds for a response were higher among patients who were sarcopenic, the CIs were wide. Finally, four of the CT images were cropped and we were unable to accurately measure s.c. fat in all our patients, although this did not impact the analysis of skeletal muscle.

CONCLUSION

Overweight, operable breast cancer patients treated with NC had a lower pCR rate than those with a normal BMI. The PFS interval was significantly longer in sarcopenic patients with a normal BMI than in those with an overweight BMI. This is consistent with previous studies and supports the concept of overweight and obesity as being poor prognostic factors in patients with breast cancer. Unlike other studies, however, we found that, among patients with a normal BMI, the pCR rate was significantly higher in those who were sarcopenic, and a shorter OS time was associated with a higher skeletal muscle index and adipose tissue mass. More research is required to evaluate the negative impact of sarcopenic obesity on prognosis and the contributors to better response rates in operable, normal weight breast cancer patients with sarcopenia.

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REFERENCES

1. van Kruijsdijk RC, van der Wall E, Visseren FL. Obesity and cancer: The role of dysfunctional adipose tissue. *Cancer Epidemiol Biomarkers Prev* 2009;18:2569–2578.
2. Chlebowski RT, Aiello E, McTiernan A. Weight loss in breast cancer patient management. *J Clin Oncol* 2002;20:1128–1143.
3. Baumgartner RN, Koehler KM, Gallagher D et al. Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol* 1998;147:755–763.
4. Roubenoff R. Sarcopenia: Effects on body composition and function. *J Gerontol A Biol Sci Med Sci* 2003;58:1012–1017.
5. Parsons HA, Baracos VE, Dhillon N et al. Body composition, symptoms, and survival in advanced cancer patients referred to a phase I service. *PLoS One* 2012;7:e29330.

6. Prado CM, Baracos VE, McCargar LJ et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. *Clin Cancer Res* 2009;15:2920–2926.
7. Prado CM, Lima IS, Baracos VE et al. An exploratory study of body composition as a determinant of epirubicin pharmacokinetics and toxicity. *Cancer Chemother Pharmacol* 2011;67:93–101.
8. Antoun S, Baracos VE, Birdsell L et al. Low body mass index and sarcopenia associated with dose-limiting toxicity of sorafenib in patients with renal cell carcinoma. *Ann Oncol* 2010;21:1594–1598.
9. Litton JK, Gonzalez-Angulo AM, Warneke CL et al. Relationship between obesity and pathologic response to neoadjuvant chemotherapy among women with operable breast cancer. *J Clin Oncol* 2008;26:4072–4077.
10. Guarneri V, Broglio K, Kau SW et al. Prognostic value of pathologic complete response after primary chemotherapy in relation to hormone receptor status and other factors. *J Clin Oncol* 2006;24:1037–1044.
11. Hennessy BT, Hortobagyi GN, Rouzier R et al. Outcome after pathologic complete eradication of cytologically proven breast cancer axillary node metastases following primary chemotherapy. *J Clin Oncol* 2005;23:9304–9311.
12. National Institutes of Health/National Heart, Lung, and Blood Institute: Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. Available at http://www.nhlbi.nih.gov/guidelines/obesity/ob_gdlns.htm, accessed July 25, 2012.
13. Kvist H, Sjöström L, Tylén U. Adipose tissue volume determinations in women by computed tomography: Technical considerations. *Int J Obes* 1986;10:53–67.
14. 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;9:629–635.
15. Tan BH, Birdsell LA, Martin L et al. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. *Clin Cancer Res* 2009;15:6973–6979.
16. Morgan DJ, Bray KM. Lean body mass as a predictor of drug dosage. Implications for drug therapy. *Clin Pharmacokinet* 1994;26:292–307.
17. 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;90:124–127.
18. Dewys WD, Begg C, Lavin PT et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. *Am J Med* 1980;69:491–497.
19. Fearon K, Strasser F, Anker SD et al. Definition and classification of cancer cachexia: An international consensus. *Lancet Oncol* 2011;12:489–495.
20. Baracos VE, Reiman T, Mourtzakis M et al. Body composition in patients with non-small cell lung cancer: A contemporary view of cancer cachexia with the use of computed tomography image analysis. *Am J Clin Nutr* 2010;91:1133S–1137S.
21. Stephens NA, Gray C, Macdonald AJ et al. Sexual dimorphism modulates the impact of cancer cachexia on lower limb muscle mass and function. *Clin Nutr* 2012;31:499–505.
22. Palomares MR, Sayre JW, Shekar KC et al. Gender influence on weight-loss pattern and survival of non-small cell lung carcinoma patients. *Cancer* 1996;78:2119–2126.