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Impact of Skeletal Muscle Loss and Visceral Obesity Measured Using Serial CT on the Prognosis of Operable Breast Cancers in Asian Patients

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Objective: This study aimed to investigate the impact of baseline values and temporal changes in body composition parameters, including skeletal muscle index (SMI) and visceral adipose tissue area (VAT), measured using serial computed tomography (CT) imaging on the prognosis of operable breast cancers in Asian patients.

Materials and Methods: This study retrospectively included 627 Asian female (mean age ± standard deviation [SD], 53.6 ± 8.3 years) who underwent surgery for stage I–III breast cancer between January 2011 and September 2012. Body composition parameters, including SMI and VAT, were semi-automatically calculated on baseline abdominal CT at the time of diagnosis and follow-up CT for post-treatment surveillance. Serial changes in SMI and VAT were calculated as the delta values. Multivariable Cox regression analysis was used to evaluate the association of baseline and delta SMI and VAT values with disease-free survival.

Results: Among 627 patients, 56 patients (9.2%) had breast cancer recurrence after a median of 40.5 months. The mean value ± SD of the baseline SMI and baseline VAT were 43.7 ± 5.8 cm^2/m^2 and 72.0 ± 46.0 cm^2, respectively. The mean value of the delta SMI was -0.9 cm^2/m^2 and the delta VAT was 0.5 cm^2. The baseline SMI and VAT were not significantly associated with disease-free survival (adjusted hazard ratio [HR], 0.983; 95% confidence interval [CI], 0.937–1.031; p = 0.475 and adjusted HR, 1.001; 95% CI, 0.995–1.006; p = 0.751, respectively). The delta SMI and VAT were also not significantly associated with disease-free survival (adjusted HR, 0.894; 95% CI, 0.766–1.043; p = 0.155 and adjusted HR, 1.001; 95% CI, 0.989–1.014; p = 0.848, respectively).

Conclusion: Our study revealed that baseline and early temporal changes in SMI and VAT were not independent prognostic factors regarding disease-free survival in Asian patients undergoing surgery for breast cancer.

Keywords: *Skeletal muscle index; Visceral adipose tissue area; Computed tomography; Disease-free survival; Recurrence; Breast cancer*

INTRODUCTION

Body composition parameters, including muscle mass and adipose tissue, have received attention in research on cancer prognosis. Sarcopenia is defined as an age-related progressive and generalized loss in skeletal muscle mass and muscle function, and is prevalent in patients with cancer and chronic morbidities [1,2]. Sarcopenia is associated

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with increased toxicity of chemotherapy, post-operative complications, and poorer overall survival of patients with cancer [3,4]. It is hypothesized that skeletal muscle is the predominant source of protein and acts as an energy storage compartment, which may be utilized in catabolic periods [5,6]. The impact of sarcopenia may be due to a combination of vulnerability to cancer and its treatment due to low physical reserves. One meta-analysis concluded that sarcopenia was a valuable prognostic factor for early breast cancer, and that patients with sarcopenia had more severe chemotherapy toxicity and shorter overall survival and time to tumor progression for metastatic breast cancers [7].

As other components of body composition, obesity and underweight status have been reported as risk factors for recurrence and death in patients with breast cancer. Body mass index (BMI) is the most commonly used parameter to indicate obesity. Female who were morbidly obese (BMI ≥ 40 kg/m^2) before the diagnosis of breast cancer were at the greatest risk of all-cause mortality and death due to breast cancer [8]. A meta-analysis of 43 studies demonstrated that obese female with breast cancer had worse survival than non-obese female [9]. Moreover, in a neoadjuvant chemotherapy setting, higher BMI was associated with a lower pathologic complete response rate to therapy or a shorter overall survival and disease-free survival (DFS) [10-12]. Increased BMI during neoadjuvant chemotherapy was inversely associated with both overall survival and DFS [12]. However, BMI may not correctly assess the impact of fat distribution because it scales weight to height without distinguishing between muscle and adipose tissue. Several quantitative imaging modalities, including computed tomography (CT), dual energy X-ray absorptiometry, magnetic resonance imaging, and bioelectrical impedance analysis, have been used to accurately measure body composition. Among them, CT is considered the gold standard imaging technique to quantify skeletal muscle and adipose tissue as it provides excellent precision in the measurement of tissue cross-sectional areas and has greater clinical accessibility [13]. The single-slice cross sectional area at the third lumbar (L3) vertebral level has been reported as the most representative region of the whole body muscle mass [14]. A recent review of 15 studies performed in more than 5000 female confirmed that sarcopenia assessed on CT, predominantly calculated at the L3 vertebral level, was an important prognostic risk factor of clinical outcomes in patients with breast cancer [15]. The adipose tissue area is generally measured at the L3 or L4 (umbilicus) vertebral level on CT [3,16-19].

Until now, most studies have concentrated on body composition status at the time of breast cancer diagnosis, and they have been conducted in western populations. To the best of our knowledge, information on the impact of early temporal changes in the composition of muscle and adipose tissue after cancer surgery measured using CT on recurrence is limited. Therefore, the purpose of our study was to investigate the impact of baseline and temporal changes in body composition parameters measured using serial CT imaging, including muscle and adipose tissue, on the prognosis of operable breast cancers in Asian patients.

MATERIALS AND METHODS

Patient Selection

This retrospective study was approved by the Institutional Review Board (IRB No. 2020-04-177-001), and the requirement for written informed consent was waived. Patients were selected from the surgery database of a single institution based on the following criteria: 1) Asian female patients initially diagnosed with stage I–III primary breast cancer (American Joint Committee on Cancer [AJCC], version 7) between January 2011 and September 2012 without prior treatment before surgery, and 2) patients with abdominal CT scan performed for cancer staging within 1 month from the time of surgery, and follow-up abdominal CT scan performed for post-treatment surveillance at our hospital. To evaluate the impact of the early change on the prognosis, we included follow-up abdominal CT scans taken at least 6 months, but no more than 5 years, after surgery. The exclusion criteria were as follows: 1) patients with concurrent primary malignancy at other sites at the time of diagnosis (n = 10), and 2) patients with concordant diseases, which could affect muscle volume or metabolic rate (i.e., diabetes mellitus, chronic renal failure, liver cirrhosis) (n = 15). Finally, a total of 627 patients were included in this study. All patients received standard treatment (adjuvant chemotherapy, radiation therapy, endocrine therapy) after surgery according to National Comprehensive Cancer Network guidelines. In the case of human epidermal growth factor receptor 2 (HER2) positive cancers, an HER2-targeted agent was used according to the National insurance program. In the case of controversial patients, a multidisciplinary team approach was conducted to determine proper treatment. The follow-up period and

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time interval between CT scans were obtained.

Body Composition Assessment Based on CT

Baseline abdominal CT scans taken at the time of diagnosis and follow-up CT scans for post-treatment surveillance were collected. The transverse section of CT imaging at the endplate level of the L3 vertebra, which best showed both transverse processes, was selected for the assessment of body composition. Two radiologists used an in-house software to identify muscle and adipose tissue in CT images for body composition analysis based on Matlab version R2010a (MathWorks Inc.). This open-source software (BMI_CT) is available at the following URL (https://sourceforge.net/projects/muscle-fat-area-measurement/) [20]. The software comprises three image-processing steps. First, the background image was removed from the original CT image. Second, the boundary between the skeletal muscle and the inner organs was semi-automatically detected by manually marking the points and automatically making the boundary by connecting the points. The CT images were then segmented as inner or outer based on the boundary of the muscle. Pixels in the outer CT image were segmented into four clusters based on the Hounsfield unit (HU) of pixels, background, subcutaneous adipose tissue (SAT), muscle, and bone. HU thresholds of -29 to +150 were identified as muscle. Pixels in adipose tissue were identified using HU thresholds of -300 to -50 in the inner CT image. Finally, the cross-sectional skeletal muscle area (SMA) (cm^2), SAT area (cm^2), and visceral adipose tissue area (VAT) (cm^2) were obtained. The skeletal muscle index (SMI) was defined as the SMA divided by height in meters squared (m^2) [13]. The skeletal muscle radiodensity was defined as the average radiation attenuation of skeletal muscle in HU [19,21]. For follow-up abdominal CT, all the above parameters were assessed at the same L3 vertebral level as the initial scan. For consistency, the measurement of follow-up CT scan for each patient was performed by the same radiologist who measured the parameters of the initial abdominal CT scan (Fig. 1). Radiologists were blinded to the patient outcomes during the measurement of body composition parameters.

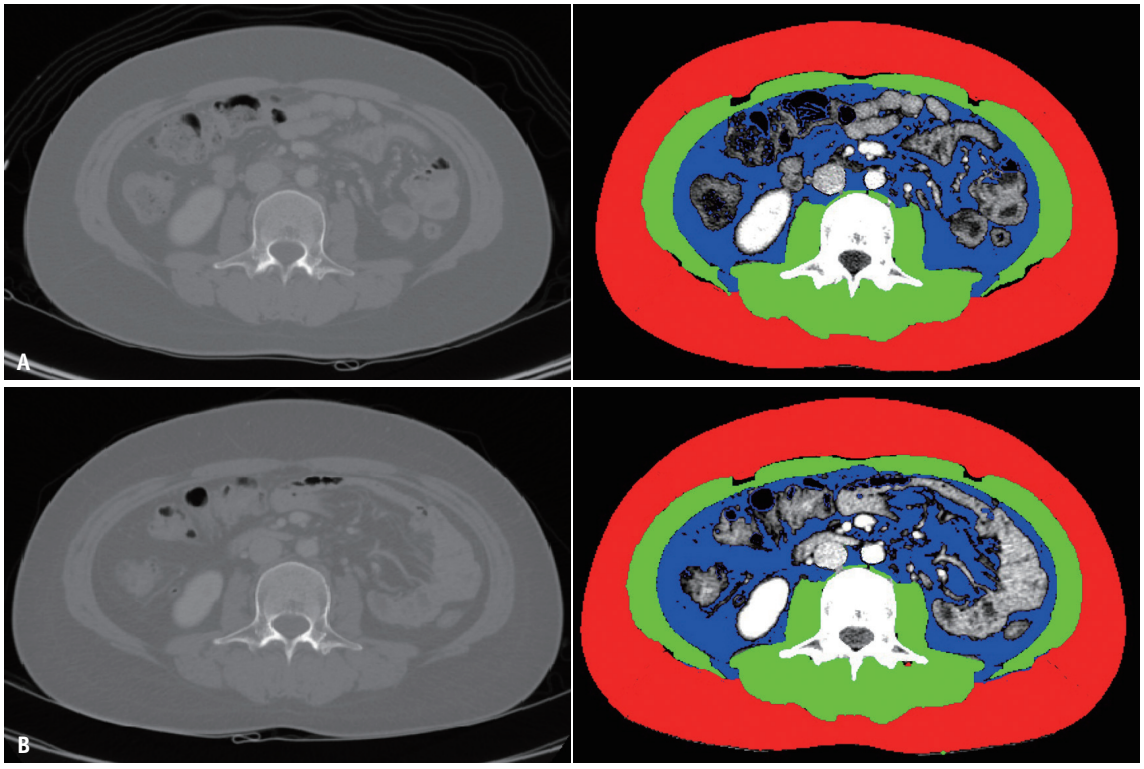

Fig. 1. Body composition measurements from baseline and follow-up abdominal CT images of a 31-year-old female with breast cancer using in-house software.
A. At the level endplate of the third lumbar vertebra, which best showed both transverse processes, the transverse section of the CT image is segmented into the SMA (green), VAT (blue), and SAT (red). The SMI and VAT measured at the baseline abdominal CT were 39.1 cm^2/m^2 and 78.3 cm^2, respectively. **B.** Follow-up CT assessed the SMA, VAT, and SAT at the same level as that of the baseline CT scan. At the follow-up abdominal CT (48 months after surgery), the SMI and VAT were 37.88 cm^2/m^2 and 82.12 cm^2, respectively. There was no recurrence until the last follow-up.
SAT = subcutaneous adipose tissue area, SMA = skeletal muscle area, SMI = skeletal muscle index, VAT = visceral adipose tissue area

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Data Collection and Analyses

Electronic medical records were reviewed to collect the clinical and pathological data, including patient age at the time of diagnosis, BMI, menopausal status, AJCC stage, T and N stages, histological type, histologic grade, lymphovascular invasion, extensive intraductal component, resection margin, estrogen receptor (ER), progesterone receptor (PR), HER2, Ki-67, and molecular subtype. Positivity of the ER and PR was defined with > 1% expression of staining nuclei at a magnification of x 10. Cancers with a 3+ score for the intensity of c-erbB-2 receptor staining or a 2+ score for the intensity with gene amplification were considered as HER2-positive [22]. The cutoff expression level of Ki-67 to distinguish between luminal A and B subtypes was established as 20% [23]. The four categories of tumor molecular subtypes were as follows: luminal A (ER+/ PR+, HER2-, low Ki-67), luminal B (ER+/ PR+, HER2-, high Ki-67 or ER+/ PR+, HER2+), HER2-enriched (ER-, PR-, HER2+), and triple-negative subtype (ER-, PR-, HER2-) [24]. In addition, variables regarding cancer treatment, including surgery type (total mastectomy or breast conserving surgery), adjuvant chemotherapy, radiation therapy, endocrine therapy, and targeted therapy, were recorded. Height and weight measured during a clinical visit close to the time of diagnosis were used to calculate the BMI. The BMI was calculated as weight in kg divided by height in m^2.

The end point of our study was DFS, which was defined as the time from the date of surgery to that of the first recurrence of the disease, the date of death from any cause, the date last known to have no evidence of disease, or the date of the most recent follow-up. Disease recurrence was defined as the outcome of breast cancer recurrence (local-regional or distant) or new primary contralateral breast cancer. Patients who did not have recurrence at the last follow-up or who were lost to follow-up were censored in the analysis. All-cause mortality was recorded. The last follow-up date was August 1, 2019.

Statistical Analyses

We conducted three types of analyses to evaluate the effect of SMI and VAT on DFS. First, univariable Cox proportional hazards analysis was performed to screen variables that might be associated with DFS for the overall study cohort, and the unadjusted hazard ratio (HR) with 95% confidence intervals (CIs) were calculated. Multivariable Cox regression model included variables with a p value < 0.05 on univariable analysis, and baseline SMI and VAT regardless of their p values on the univariable analysis [25]. Variance inflation factors were calculated to assess multicollinearity. Second, to reflect the time-varying effect of SMI and VAT on the DFS, univariable and multivariable time-varying Cox regression analyses were performed including all available measurement values. In the multivariable time-varying Cox regression analysis, adjustment for variables that were significant in the baseline univariable Cox regression analysis was performed. Lastly, univariable and multivariable Cox proportional hazards regression analyses including delta SMI and delta VAT were performed to evaluate the effect of the difference in SMI and VAT from baseline to the last follow up. The delta value was defined as the difference between the parameters measured at the last follow-up and the baseline CT. In cases of recurrence between follow-up CT scans, the delta value of the parameter was calculated as the difference between that measured at the follow-up CT, immediately before recurrence, and the baseline CT. Cases of recurrence detected before follow-up CT were excluded from this analysis. In the multivariable analysis including delta values, variables significant in the baseline univariable Cox regression analysis along with baseline SMI and VAT were adjusted. Patients were grouped according to whether the value was higher or lower than the median. Estimates of DFS were calculated using the Kaplan–Meier method. Subgroup analysis was performed based on clinicopathological factors to evaluate the association of SMI and VAT with DFS (Supplement). A two-tailed p value of < 0.05 was considered to indicate a significant difference. All statistical analyses were performed by dedicated statisticians using R Statistical Software (version 3.6.4; R Foundation for Statistical Computing) or SAS software (version 9.4, SAS Institute).

RESULTS

Patient Outcomes

The baseline characteristics of the 627 patients are summarized in Table 1. The mean age of the patients was 53.6 ± 8.3 years (range, 31–80 years). The proportions of patients with different stages of invasive breast cancer were as follows: stage I, 48.3% (303/627); stage II, 40.5% (254/627); and stage III, 11.2% (70/627). The histological types of invasive breast cancer were as follows: invasive carcinoma of no special type (NST) (n = 560, 89.3%), invasive lobular carcinoma (n = 30, 4.8%), mucinous carcinoma (n = 19, 3.0%), papillary carcinoma (n = 4, 0.6%),

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Table 1. Baseline Characteristics of the 627 Study Patients

Characteristics	Results
Age, years	
< 45	583 (93.0)
≥ 45	44 (7.0)
BMI	23.7 ± 3.1
Menstrual status	
Postmenopausal	372 (59.3)
Premenopausal	255 (40.7)
AJCC stage	
I	303 (48.3)
II	254 (40.5)
III	70 (11.2)
T stage	
1	405 (64.6)
2 and 3	222 (35.4)
N stage	
0	400 (63.8)
1	163 (26.0)
2 and 3	64 (10.2)
Histologic type	
Invasive carcinoma of no special type	560 (89.3)
Invasive lobular carcinoma	30 (4.8)
Others*	37 (5.9)
Histologic grade	
1	212 (33.8)
2	263 (42.0)
3	152 (24.2)
Lymphovascular invasion	
No	477 (76.1)
Yes	150 (23.9)
Extensive intraductal component	
Yes	193 (30.8)
No	434 (69.2)
Resection margin	
Positive	21 (3.4)
Negative	493 (78.6)
Less than 1 mm	113 (18.0)
ER	
Positive	470 (75.0)
Negative	157 (25.0)
PR	
Positive	429 (68.4)
Negative	198 (31.6)
HER2	
Negative	493 (78.6)
Positive	134 (21.4)
Ki-67, %	
< 20	283 (45.1)
≥ 20	344 (54.9)
Molecular subtype	
Luminal A	262 (41.7)
Luminal B	215 (34.3)
HER2-enriched	75 (12.0)
Triple negative	75 (12.0)
Surgery type	
Breast conserving surgery	456 (72.7)
Total mastectomy	171 (27.3)
Chemotherapy	
Yes	381 (60.8)
No	246 (39.2)
Radiation therapy	
Yes	495 (78.9)
No	132 (21.1)
Endocrine therapy	
Yes	475 (75.8)
No	152 (24.2)
SMA, cm^2	106.7 ± 13.6
SMI, cm^2/m^2	43.7 ± 5.8
SAT, cm^2	142.1 ± 50.2
VAT, cm^2	72.0 ± 46.0
Skeletal muscle radiodensity, HU	42.8 ± 9.2
SMI (delta) (n = 612)†	-0.9 ± 2.1
VAT (delta) (n = 612)†	0.5 ± 24.4

Data are number of patients with percentage in parentheses or mean ± standard deviation. *Mucinous carcinoma (n = 19, 3.0%), papillary carcinoma (n = 4, 0.6%), metaplastic carcinoma (n = 3, 0.5%), tubular carcinoma (n = 3, 0.5%), invasive apocrine carcinoma (n = 3, 0.5%), and others (n = 5, 0.8%), †Analysis of delta SMI and VAT excluded recurrence cases detected before follow-up CT. AJCC = American Joint Committee on Cancer, BMI = body mass index, ER = estrogen receptor, HER2 = human epidermal growth factor 2, HU = Hounsfield unit, PR = progesterone receptor, SAT = subcutaneous adipose tissue area, SMA = skeletal muscle area, SMI = skeletal muscle index, VAT = visceral adipose tissue area

metaplastic carcinoma (n = 3, 0.5%), tubular carcinoma (n = 3, 0.5%), invasive apocrine carcinoma (n = 3, 0.5%), and others (n = 5, 0.8%). All patients with a HER2-positive tumor > 1 cm underwent targeted therapy (trastuzumab) according to the national insurance guideline. Among 134 patients with HER2-positive cancers, 114 patients (85.1%) received targeted therapy.

The median follow-up period was 83 months (interquartile range [IQR], 75–90 months). A total of 56 patients (9.2%) had recurrence, including 26 cases of locoregional recurrence, 27 cases of distant metastasis, and three cases of contralateral recurrence after a median of 40.5 months (IQR, 18.3–59.8 months). In total, 24 deaths (3.8%,

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Table 2. Univariable and Multivariable Cox Regression Analyses of Baseline SMI and VAT to Evaluate Their Association with Disease-Free Survival

Variable	Univariable Analysis				Multivariable Analysis (SMI)				Multivariable Analysis (VAT)			
	HR	95% CI		*P*	Adjusted HR	95% CI		*P*	Adjusted HR	95% CI		*P*
SMI	0.983	0.938	1.029	0.461	0.983	0.937	1.031	0.475				
VAT	1.003	0.998	1.009	0.226					1.001	0.995	1.006	0.751
Age, years												
< 45	Ref											
≥ 45	0.979	0.354	2.708	0.967								
BMI	1.003	0.921	1.091	0.949								
Menstrual status												
Postmenopausal	Ref											
Premenopausal	0.668	0.381	1.171	0.159								
T stage												
1	Ref				Ref				Ref			
2 and 3	2.283	1.347	3.868	0.002	1.461	0.817	2.611	0.201	1.432	0.800	2.563	0.227
N stage				< 0.001				0.132				
0	Ref				Ref				Ref			0.124
1	1.406	0.745	2.655	0.293	0.824	0.402	1.688	0.597	0.802	0.393	1.638	0.544
2 and 3	3.843	2.034	7.263	< 0.001	1.744	0.793	3.835	0.167	1.724	0.786	3.780	0.174
Histologic grade				< 0.001				0.171				0.180
1	Ref				Ref				Ref			
2	4.330	1.667	11.247	0.003	2.682	0.959	7.503	0.060	2.631	0.942	7.348	0.065
3	6.987	2.666	18.313	< 0.001	2.526	0.786	8.125	0.120	2.603	0.814	8.319	0.107
Lymphovascular invasion												
No	Ref				Ref				Ref			
Yes	3.395	2.010	5.735	< 0.001	2.713	1.452	5.068	0.002	2.739	1.471	5.101	0.001
Extensive intraductal component												
Yes	Ref											
No	0.968	0.548	1.712	0.912								
Resection margin				0.089								
Positive	Ref											
Negative	0.364	0.130	1.021	0.055								
Close (less than 1 mm)	0.562	0.183	1.725	0.314								
ER												
Positive	Ref				Ref				Ref			
Negative	2.629	1.551	4.457	< 0.001	0.921	0.368	2.307	0.861	0.932	0.373	2.330	0.880
PR												
Positive	Ref				Ref				Ref			
Negative	2.943	1.735	4.991	< 0.001	2.594	1.089	6.183	0.031	2.579	1.076	6.181	0.034
HER2												
Negative	Ref											
Positive	1.095	0.589	2.036	0.775								

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Table 2. Univariable and Multivariable Cox Regression Analyses of Baseline SMI and VAT to Evaluate Their Association with Disease-Free Survival (Continued)

Variable	Univariable Analysis			Multivariable Analysis (SMI)			Multivariable Analysis (VAT)		
	HR	95% CI	*P*	Adjusted HR	95% CI	*P*	Adjusted HR	95% CI	*P*
Ki-67, %									
< 20	Ref			Ref			Ref		
≥ 20	3.436	1.777	6.644	< 0.001	1.605	0.745	3.458	0.227	1.543	0.718	3.317	0.266
Surgery type												
Breast conserving surgery	Ref											
Total mastectomy	1.517	0.878	2.622	0.135								
Chemotherapy												
Yes	Ref			Ref					Ref			
No	0.383	0.198	0.740	0.004	1.229	0.553	2.729	0.613	1.222	0.550	2.716	0.623
Radiation therapy												
Yes	Ref											
No	1.423	0.788	2.572	0.242								
Endocrine therapy												
Yes	Ref											
No	2.521	1.484	4.283	0.001								

Adjuvant endocrine therapy was excluded due to mutlicollinearity at multivariable analysis. BMI = body mass index, CI = confidence interval, ER = estrogen receptor, HER2 = human epidermal growth factor 2, HR = hazard ratio, PR = progesterone receptor, Ref = reference, SMI = skeletal muscle index, VAT = visceral adipose tissue area

24/627) were recorded until the last follow-up.

Quantitative Measurements

Abdominal CT scans were performed an average of 2.4 times per patient. The mean interval between the CT scans was 20.7 ± 11.6 months, and the mean interval between the baseline and last follow-up CT scan was 29.1 ± 12.2 months (range, 6–59 months).

The mean values of BMI, SMA, SMI, VAT, SAT, and skeletal muscle radiodensity at the time of diagnosis are summarized in Table 1. The mean SMI was 43.7 ± 5.8 cm^2/m^2 and the mean VAT was 72.0 ± 46.0 cm^2. The SMI decreased (mean 0.9 cm^2/m^2) and the VAT increased (mean 0.5 cm^2) during post-treatment surveillance.

Relationship between Body Composition and Survival Outcomes

The results of univariable Cox regression analysis showed that higher T stage ($p = 0.002$), higher N stage ($p < 0.001$), higher histologic grade ($p < 0.001$), presence of lymphovascular invasion ($p < 0.001$), ER negativity ($p < 0.001$), PR negativity ($p < 0.001$), high Ki-67 ($p < 0.001$), adjuvant chemotherapy ($p = 0.004$), and cases without adjuvant endocrine therapy ($p = 0.001$) were significantly associated with worse DFS (Table 2). After adjusting for these factors in the multivariable model, lymphovascular invasion (adjusted HR, 2.713 and 2.739; 95% CI, 1.452–5.068 and 1.471–5.101, $p = 0.002$ and 0.001, respectively) and PR negativity (adjusted HR, 2.594 and 2.579; 95% CI, 1.089–6.183 and 1.076–6.181, $p = 0.031$ and 0.034, respectively) were significant risk factors for worse DFS. Baseline SMI and VAT were not significantly associated with DFS (adjusted HR, 0.983; 95% CI, 0.937–1.031; $p = 0.475$ and adjusted HR, 1.001; 95% CI, 0.995–1.006; $p = 0.751$, respectively).

Time-varying Cox regression analysis revealed that SMI and VAT were not significantly associated with DFS (adjusted HR, 0.983; 95% CI, 0.936–1.032; $p = 0.484$ and adjusted HR, 1.001; 95% CI, 0.995–1.006; $p = 0.752$, respectively). Among clinicopathologic characteristics, only lymphovascular invasion (adjusted HR, 2.713 and 2.739; 95% CI, 1.477–4.983 and 1.500–5.000, $p = 0.001$, respectively) was significantly associated with DFS (Table 3). The delta SMI and delta VAT were not significantly related to DFS (adjusted HR, 0.894; 95% CI, 0.766–1.043; $p = 0.155$ and adjusted HR, 1.001; 95% CI, 0.989–1.014; $p = 0.848$, respectively) (Table 4). The Kaplan–Meier curves of DFS

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Table 3. Univariable and Multivariable Time-Varying Cox Regression Analyses of Baseline SMI and VAT to Evaluate Their Association with Disease-Free Survival

Univariable Analysis								
Variable	HR	95% CI		*P*	HR	95% CI		*P*
SMI	0.983	0.938	1.029	0.461				
VAT					1.003	0.998	1.009	0.226
Multivariable Analysis								
Variable	Adjusted HR	95% CI		*P*	Adjusted HR	95% CI		*P*
SMI	0.983	0.936	1.032	0.484	Not included			
VAT	Not included				1.001	0.995	1.006	0.752
T stage								
1	Ref				Ref			
2 and 3	1.461	0.806	2.647	0.212	1.432	0.785	2.611	0.242
N stage				0.132				
0	Ref				Ref			
1	0.824	0.419	1.620	0.575	0.802	0.409	1.573	0.521
2 and 3	1.744	0.797	3.816	0.164	1.724	0.796	3.734	0.167
Histologic grade								
1	Ref				Ref			
2	2.682	0.969	7.422	0.058	2.631	0.939	7.368	0.066
3	2.526	0.764	8.351	0.129	2.603	0.798	8.486	0.113
Lymphovascular invasion								
No	Ref				Ref			
Yes	2.713	1.477	4.983	0.001	2.739	1.500	5.000	0.001
ER								
Positive	Ref				Ref			
Negative	0.921	0.350	2.422	0.868	0.932	0.357	2.432	0.886
PR								
Positive	Ref				Ref			
Negative	2.594	1.002	6.714	0.049	2.579	0.992	6.703	0.052
Ki-67, %								
< 20	Ref				Ref			
≥ 20	1.605	0.699	3.685	0.264	1.543	0.681	3.496	0.298
Chemotherapy								
Yes	Ref				Ref			
No	1.229	0.559	2.699	0.608	1.222	0.551	2.709	0.622

Variables including lymphovascular invasion, histologic grade, T stage, N stage, ER, PR, Ki-67 and chemotherapy were adjusted. CI = confidence interval, ER = estrogen receptor, HR = hazard ratio, PR = progesterone receptor, Ref = reference, SMI = skeletal muscle index, VAT = visceral adipose tissue area

according to SMI, VAT, and their delta values are shown in Figure 2. The results of subgroup analysis are provided in the Supplement.

DISCUSSION

Numerous studies on body composition and outcomes of breast cancer have been published to date. Although some studies have evaluated the association between changes in body composition and outcomes of breast cancer [12,26-28], they commonly investigated BMI, changes in weight, or focused on changes in body composition related to neoadjuvant or palliative chemotherapy. Instead, we attempted to quantitatively analyze the association between both baseline and temporal changes in body composition measured by serial CT scans and clinical outcomes in patients with breast cancer.

In the current study, baseline SMI and VAT at the time of diagnosis were not predictive of worse DFS in the whole study population. In addition, early temporal changes in

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Table 4. Univariable and Multivariable Cox Regression Analyses of Delta SMI and VAT Values to Evaluate Their Association with Disease-Free Survival

Univariable Analysis								
Variable	HR	95% CI		*P*	HR	95% CI		*P*
SMI (delta)	0.906	0.779	1.054	0.200				
SMI	0.966	0.913	1.023	0.236				
VAT (delta)					1.001	0.989	1.013	0.881
VAT					1.002	0.996	1.008	0.538
Multivariable Analysis								
Variable	Adjusted HR	95% CI		*P*	Adjusted HR	95% CI		*P*
SMI (delta)	0.894	0.766	1.043	0.155	Not included			
SMI	0.964	0.910	1.021	0.207	Not included			
VAT (delta)	Not included				1.001	0.989	1.014	0.848
VAT	Not included				0.999	0.993	1.006	0.797
T stage								
1	Ref				Ref			
2 and 3	1.941	0.989	3.808	0.054	1.910	0.965	3.783	0.063
N stage				0.866				0.906
0	Ref				Ref			
1	0.820	0.376	1.788	0.618	0.845	0.391	1.822	0.667
2 and 3	0.809	0.295	2.215	0.680	0.859	0.314	2.351	0.768
Histologic grade								
1	Ref			0.595	Ref			0.601
2	1.712	0.585	5.005	0.326	1.729	0.592	5.049	0.317
3	1.465	0.429	5.003	0.543	1.570	0.462	5.333	0.470
Lymphovascular invasion								
No	Ref				Ref			
Yes	3.216	1.594	6.489	0.001	3.257	1.618	6.559	0.001
ER								
Positive	Ref				Ref			
Negative	0.828	0.299	2.295	0.717	0.794	0.287	2.194	0.656
PR								
Positive	Ref				Ref			
Negative	3.156	1.173	8.495	0.023	3.055	1.129	8.268	0.028
Ki-67, %								
< 20	Ref				Ref			
≥ 20	2.225	0.882	5.614	0.090	2.116	0.836	5.357	0.114
Chemotherapy								
Yes	Ref				Ref			
No	1.159	0.446	3.014	0.762	1.109	0.432	2.847	0.830

Variables including lymphovascular invasion, histologic grade, T stage, N stage, ER, PR, Ki-67 and chemotherapy were adjusted. CI = confidence interval, ER = estrogen receptor, HR = hazard ratio, PR = progesterone receptor, Ref = reference, SMI = skeletal muscle index, VAT = visceral adipose tissue area

the body composition parameters were not significantly associated with recurrence in breast cancer patients. These results are not consistent with those of prior studies, but they are meaningful when considering meticulous statistical analyses. We assume that the difference in the study population has influenced our negative results. One large study of 3241 patients with non-metastatic breast cancer in the United States demonstrated that patients with sarcopenia assessed by CT exhibited higher overall mortality (HR, 1.41; 95% CI, 1.18–1.69) than those without sarcopenia [19]. Compared to this study, our study recruited patients with breast cancer in a single institution in Korea, who had a relatively low SMA (mean 106.7 cm^2 vs. 115.4 cm^2) and BMI (mean ± SD 23.7 ± 3.1 kg/m^2 vs.

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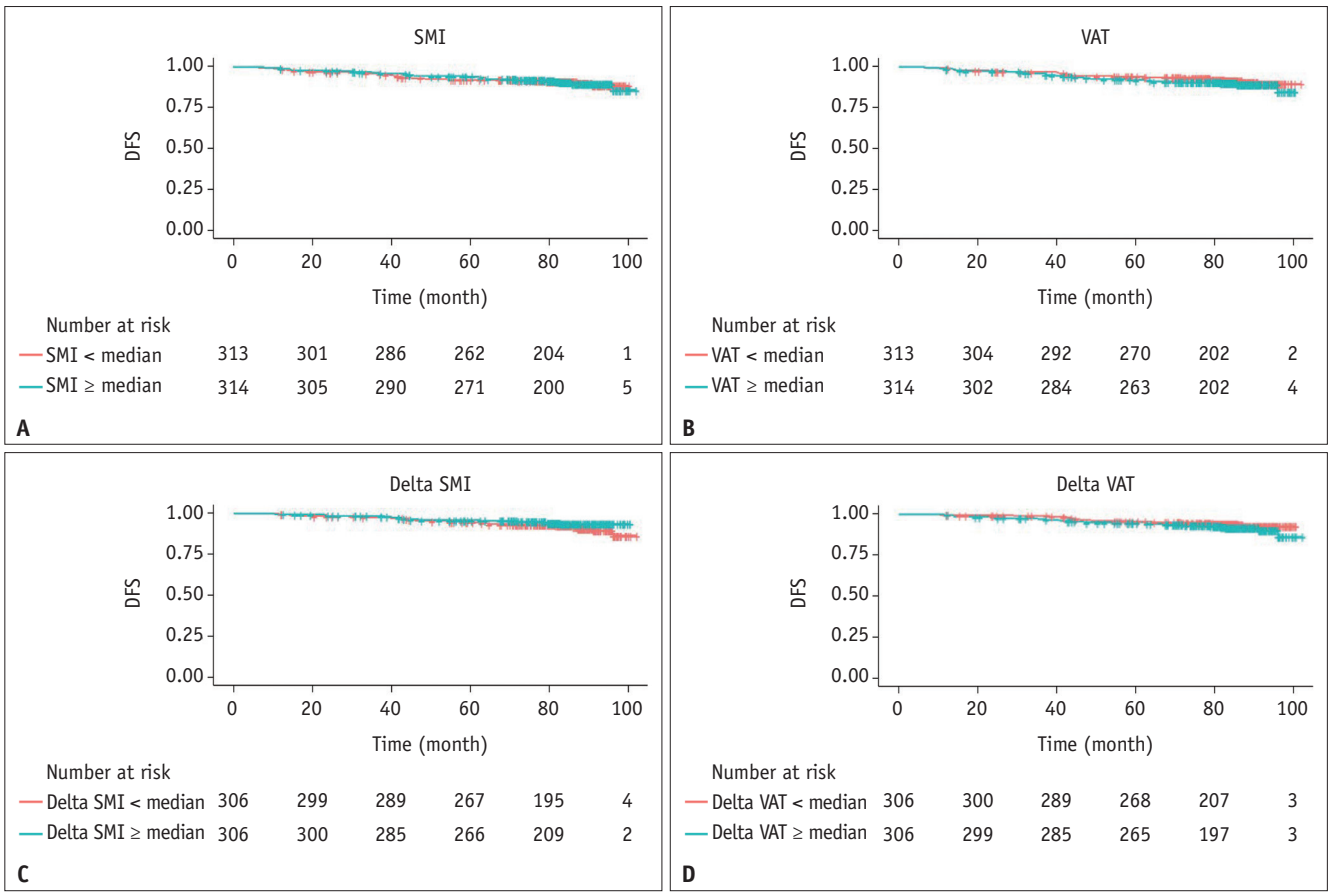

Fig. 2. Kaplan–Meier curves for DFS.
A-D. Kaplan–Meier curves for DFS according to grouping by SMI **(A)** and VAT **(B)**, and their delta values **(C, D)** show no significant difference between the groups. DFS = disease-free survival, SMI = skeletal muscle index, VAT = visceral adipose tissue area

28.3 ± 6.3 kg/m^2) and had a more homogenous study population. In general, Asians tend to have lower muscle mass and lower BMI than people from Western countries, and the prevalence of sarcopenia in Asia is lower than that in Western countries, especially among older female [29-31]. In addition, the high proportion of stage I cancer (48.3%) in our study may explain the negative results. Compared to prior studies [7,15,19], we attempted to assess the exact impact of body composition parameters on patients with breast cancer by excluding those with comorbidities, which can influence muscle mass and the metabolic rate. Moreover, breast cancer itself has relatively favorable prognosis compared to other cancers, and usually does not affect oral intake until the advanced stages. Many socio-demographic characteristics that we could not control, such as lifestyle, physical activities, and economic status, may also affect skeletal muscle loss and visceral obesity. Further dedicated large-scale studies are needed to evaluate sarcopenia and the outcomes of breast cancer in Asian female.

Adipose tissue plays an important role in the development and progression of breast cancer [32,33]. Hormones, growth factors, and adipokines secreted by adipose tissue are linked to endocrine and paracrine dysregulation in obesity, and stimulate the growth and proliferation of breast tumor cells. Tumor-surrounding adipocytes exhibit phenotypic changes and contribute to tumor cell invasion and disease progression or metastasis [34]. Assessment of the adipose tissue area is an important issue in obesity research because the distribution of adipose tissue in the body is reported to be a better indicator of metabolic fitness compared to BMI [35]. Moreover, VAT, adipose tissue within the main cavities of the abdomen, is more metabolically active and susceptible to hormonal changes than SAT given its high lipolytic activity and release of large amounts of free fatty acids. VAT is linked to the development of breast cancer as a result of the increased bioavailability of estradiol within the larger fat stores [36]. Studies have reported that higher VAT increased the risk of breast cancer and was

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associated with poor treatment outcomes in patients with cancer [16-18]. Our study showed that VAT had no clinical significance in the total population, but showed significance in patients with HER2-positive cancers (Supplement). This finding was consistent with that of a previous study, which reported that obese patients with HER2-positive breast cancer had worse clinical outcomes owing to stimulation of tumor growth and even reduced trastuzumab sensitivity in response to adipocyte-secreted factors [37-40]. However, these results need further investigation because of the statistical limitation of subgroup analysis.

The present study has several limitations. First, this was a retrospective study performed in a single institution. Second, the size of the study population and the rate of recurrence (56 of 627; 8.9%) was relatively small, and the follow-up period was relatively short (median 83 months). Further larger-scale research with a longer follow-up period is needed to validate our results. Third, although we attempted to evaluate body composition in follow-up CT scans at the same level as the baseline scans, it was often impossible to obtain the exactly same slices in patients with relatively poor respiratory cooperation. Moreover, the varying interval between the first and the last follow up surveillance CTs (6–59 months) may have interfered with the ability to accurately analyze the effect of temporal changes in body composition parameters on DFS. Finally, we attempted to evaluate the relationship between body composition parameters and DFS in subgroups, and some subgroups showed significant results. However, further investigation is necessary as the results may be inaccurate owing to the small number of patients in subgroups and potential confounding variables.

In conclusion, body composition parameters measured at the time of diagnosis and early temporal changes in these parameters were not independent prognostic factors regarding DFS in Asian patients undergoing surgery for breast cancer.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2020.1475.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

Boo-Kyung Han who is on the editorial board of the *Korean Journal of Radiology* was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Author Contributions

Conceptualization: Eun Sook Ko, Woo Kyoung Jeong. Data curation: Mi-ri Kwon, Eun Sook Ko, Min Su Park. Formal analysis: Mi-ri Kwon, Eun Sook Ko, Min Su Park, Na Young Hwang. Investigation: Eun Sook Ko, Mi-ri Kwon. Methodology: Min Su Park, Na Young Hwang. Project administration: Eun Sook Ko. Resources: Jeong Eon Lee, Seok Won Kim, Jong Han Yu. Software: Jae-Hun Kim, Woo Kyoung Jeong. Supervision: Eun Sook Ko. Validation: Boo-Kyung Han, Eun Young Ko, Ji Soo Choi, Ko Woon Park. Visualization: Mi-ri Kwon, Eun Sook Ko. Writing—original draft: Mi-ri Kwon. Writing—review & editing: Eun Sook Ko, Jeong Eon Lee, Boo-Kyung Han, Eun Young Ko, Ji Soo Choi, Ko Woon Park.

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