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CLINICAL TRIAL

Prognostic impact of skeletal muscle volume derived from cross-sectional computed tomography images in breast cancer

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Abstract

Purpose This study aimed to determine whether the prognosis of breast cancer is affected by muscle or fat volume as measured from computed tomography (CT) images.

Methods We identified 1460 patients with chest CT who were diagnosed as having breast cancer at the National Cancer Center, Korea, between January 2001 and December 2009. Using CT images of 10-mm slices, we measured the cross-sectional areas of skeletal muscle and adipose tissue at the 3rd lumbar vertebrae, and derived their volumes. The skeletal muscle volume, fat volume, and muscle-to-fat ratio were evaluated for association with overall survival (OS) and recurrence-free survival (RFS).

Results The median skeletal muscle and fat volumes among the patients were 93.3 cc (range 39.6–236.9) and 420.1 cc (range 19.5–1392.3), respectively. Patients with higher muscle volume had better prognosis than those with lower muscle volume [hazard ratio (HR) 0.56, 95% confidence interval (CI) 0.34–0.92, $P=0.022$ for OS; HR 0.72, 95% CI 0.52–0.99, $P=0.046$ for RFS]. However, body mass index (BMI) and fat volume were not associated with prognosis. In addition, muscle volume was a significant prognosticator for OS, regardless of BMI (HR 0.55, 95% CI 0.32–0.93, $P=0.034$ in BMI <25.0; HR 0.44, 95% CI 0.21–0.91, $P=0.026$ in BMI ≥ 25.0). Among older patients (≥ 50), those with higher muscle volume showed better OS and RFS (HR 0.44, 95% CI 0.23–0.85, $P=0.015$; HR 0.55, 95% CI 0.34–0.90, $P=0.017$, respectively).

Conclusion This study demonstrated that breast cancer patients with higher skeletal muscle volume showed more favorable prognosis.

Keywords Skeletal muscle volume · Obesity · Breast cancer · Prognosis

Background

Obesity is a well-known causative and prognostic factor of breast cancer [1, 2]. Body mass index (BMI), which incorporates height and weight, is the representative index of obesity, and only falls short as a well-rounded index because it fails to represent body composition. The clinical importance of BMI has been studied and proven for diseases other than

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breast cancer, such as diabetes mellitus, chronic metabolic disease, and others. However, in the case of chronic metabolic diseases, it has been shown that low muscle volume is adversely prognostic of the disease, rather than obesity (specifically, high BMI), suggesting a prognostic value for not only fat but also muscle. Accordingly, many studies have investigated the potential mechanistic role of skeletal muscle in catabolism and in disease pathology [3, 4].

Skeletal muscle occupies a substantial volume of the body, and a loss in skeletal muscle leads to poorer outcome in many chronic diseases [5, 6]. Cachexia, for instance, in cancer patients is associated with morbidity and with mortality [7–9]. The importance of protein, the main constituent of muscle, has been emphasized for chronic diseases, such as cancer and chronic obstructive pulmonary disease [10–12]. Increasing the mass of skeletal muscle in obese patients through changes in lifestyle habits such as increased exercise is also associated with improved prognosis in chronic diseases.

With the development of imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI), we are now able to obtain a cross-sectional image of any body part and evaluate its composition. Thus, analysis of the patient's body composition is now becoming increasingly reliable and consistent. Reliability and consistency have been achieved through the identification of regions of the body where cross-sectional images can represent the entire organ or tissue, which can be used uniformly across examinations. Several studies have investigated the most representative region within the body for skeletal muscle volume, and have found that taking a cross-sectional CT image of the lumbar skeletal muscle, specifically at the 3rd vertebrae, provides this information [13–18].

Studies on the prognosis of breast cancer that are based on skeletal muscle volume are lacking [19]. Many studies have conclusively demonstrated the association between obesity and the incidence and prognosis of breast cancer; however, studies showing the association with quantitatively measured skeletal muscle are sparse, and only weakly demonstrate that relationship [1]. In this study, we investigated, using CT images of the chest to derive tissue volumes, whether the prognosis of breast cancer is affected by the patient's muscle or fat volume. We also investigated whether the prognosis of breast cancer differs according to skeletal muscle volume among patients with similar BMIs.

Methods

Study population

We analyzed the medical records of 3909 consecutive patients with a confirmed diagnosis of breast cancer between January 2001 and December 2009 at the National Cancer Center (NCC), Republic of Korea. The inclusion criteria consisted of having received a chest CT within 2 years of diagnosis, chest CT slices of 10 mm in thickness, and CT images that include the 3rd lumbar vertebrae. The patients without adequate CT image ($n=2414$), male breast cancer patients ($n=4$), patients with stage IV breast cancer ($n=15$), who has a final pathology of carcinoma *in situ*, breast sarcoma, or malignant phyllodes tumor ($n=6$), a previous history of breast cancer patients ($n=10$) were excluded.

Data were extracted from the electronic medical record system at NCC to identify the following patient information: age at the time of diagnosis, height, weight, BMI at the time of diagnosis, stage of breast cancer, pathological characteristics, date of last clinic visit, and death records. We generally used the pathological stage, but used the clinical stage for patients who underwent neoadjuvant chemotherapy. The number of patients who underwent neoadjuvant chemotherapy was 186 (12.4%). The information collected was retrospectively analyzed in this study. The study was reviewed and approved by the NCC's Institutional Review Board of Ethics (IRB), and the requirement of written informed consent was waived (IRB No.: NCC2015-0006).

Evaluation of muscle volume and fat volume on CT

The total cross-sectional area of skeletal muscle on total 10-mm-thick CT slices taken at the 3rd lumbar vertebrae (Fig. 1) was measured by a radiology specialist (Lee) [12, 14, 15]. We derived the skeletal muscle volume encompassing the area of the CT slice just below the intervertebral disc between L2 and L3. Using the same CT image, we measured fat volume in the same manner. Visceral adipose tissue and subcutaneous adipose tissue were not distinguished when measuring fat volume. Images were analyzed using the Infinitt healthcare Xelis 3D program (Infinitt, Seoul, South Korea, version BN 10). We measured the cross-sectional areas by Hounsfield unit (HU), with skeletal muscle from + 100 to -30 and adipose tissue from − 250 to − 50.

Statistical analyses

The primary end-points of our study were overall survival (OS) and recurrence-free survival (RFS). In addition, we evaluated locoregional recurrence-free survival (LRFS) as a second end-point. RFS was defined as the time in years between the diagnosis date and distant metastasis or locoregional recurrence; LRFS was defined as the time in years between the diagnosis date and recurrence of ipsilateral breast, axilla, and chest wall. We defined muscle volume, fat volume, and muscle-to-fat ratio as dichotomous variables using the median as the cut point, because no benchmark values for these variables currently exist in Korean women.

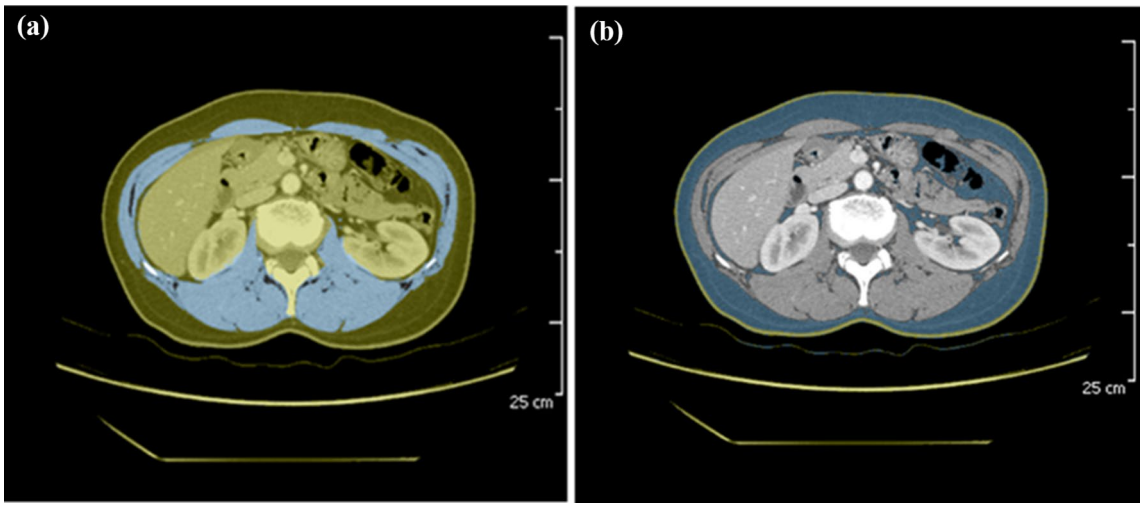

Fig. 1 Images of cross-sectional area of skeletal muscle **a** with the Hounsfield unit (HU) from + 100 to − 30, and of adipose tissue **b** from − 250 to − 50, using the Infinitt Healthcare Xelis 3D program (Infinitt, Seoul, South Korea, version BN 10). Blue colored area is the area of interest

Thus, the variables were grouped according whether the value was higher or lower than the median. Differences in baseline characteristics stratified according to muscle volume groups, fat volume groups, and muscle-to-fat ratio groups were examined through the Chi-square and the Wilcoxon rank-sum tests as appropriate. Estimates of survival times were calculated using the Kaplan–Meier method. The log-rank test and the univariate Cox regression model were used to evaluate whether each factor was prognostic for survival. Factors selected through univariate regression were included in the multivariable Cox regression model using a backward stepwise process. Muscle volume, fat volume, and muscle-to-fat ratio were then added to the optimal model after adjusting for all other factors, to evaluate whether each factor was prognostic for our three end-points. Statistical significance was defined as $P < 0.05$ and the confidence interval (CI) was set at 95%. We performed all statistical analyses with STATA v.13 (StataCorp LP, Texas).

Results

Patient characteristics

We analyzed a total of 1460 patients who were eligible, according to our inclusion and exclusion criteria, from the 3909 consecutive patients whose medical data we assessed. The median age of the patients was 46.0 years (range 25–77 years). The proportions of different stages of invasive breast cancer were as follows: stage I, 38.2%; stage II, 46.5%; and stage III, 15.3% (Table 1). We found that 70.3% and 65.3% of patients were positive for the estrogen receptor (ER) and progesterone receptor (PR), and that 14.8% were positive for human epidermal growth factor receptor-2 (HER-2).

The median follow-up period was 8.07 years (range 0.63–13.32). During follow-up, 185 patients (12.7%) experienced disease recurrence, and 93 patients (6.4%) died. The 5 year OS rate was 96.5%, the 5 year RFS rate was 92.1%, and the 5 year LRFS rate was 98.6%.

The median level of total cholesterol was 184 mg/dL (range, 106–346 mg/dL), the median level of total protein was 7.3 g/dL (range, 3.8–9.1 g/dL), and the median level of albumin was 4.4 g/dL (range, 2.6–6.1 g/dL). Patients were co-morbid with the following proportions of co-morbidities relating to metabolic syndrome: 3.1% of patients had diabetes mellitus and 10.1% had hypertension.

The median volume of skeletal muscle was 93.3 cc (Supplement Fig. 1; range 39.6–236.9 cc) and the median volume of fat, analyzed from the same cross-sectional image as that used to analyze muscle volume, was 420.1 cc (range 19.5–1392.3 cc). The median muscle-to-fat ratio was 0.22 (range 0.08–3.18).

Differences of clinicopathologic characteristics and clinical outcomes by muscle volume, fat volume, and muscle-to-fat ratio

Table 1 shows the association of clinicopathologic factors with muscle volume and fat volume. Elderly patients (≥ 50) had higher fat volume ($P < 0.001$). Patients with higher BMI had higher muscle volume, fat volume, and muscle-to-fat ratio ($P < 0.001$). Patients with higher muscle volume had higher grade tumors ($P = 0.023$). Fat volume and muscle-to-fat volume were associated with advanced clinical stage ($P = 0.011$, $P = 0.003$) and large

Table 1 Clinicopathologic characteristics of the patients and association with muscle volume, fat volume, and muscle-to-fat ratio

Characteristics	Total		Muscle volume					Fat volume				
	N	%	≤Median		>Median		*P* value	≤Median		>Median		*P* value
Age												
<50	968	66.3	488	66.7%	480	65.9%	0.767	534	73.4%	434	59.3%	<0.001
≥50	492	33.7	244	33.3%	248	34.1%		194	26.6%	298	40.7%	
BMI by WHO												
<18.5	44	3.0	42	5.70%	2	0.3%	<0.001	44	6.00%	0	0.0%	<0.001
18.6–24.9	1022	70.0	580	0.792	442	60.7%		612	0.841	410	56.0%	
25–29.9	332	22.7	104	14.20%	228	31.3%		69	9.50%	263	35.9%	
≥30	62	4.2	6	0.80%	56	7.7%		3	0.40%	59	8.1%	
BMI												
<25.0	1066	73.0	622	85.0%	444	61.0%	<0.001	656	90.1%	410	56.0%	<0.001
≥25.0	394	27.0	110	15.0%	284	39.0%		72	9.9%	322	44.0%	
Stage												
I	558	38.2	289	39.5%	269	37.0%	0.454	306	42.0%	252	34.4%	0.011
II	678	46.5	328	44.8%	350	48.1%		315	43.3%	363	49.6%	
III	224	15.3	115	15.7%	109	15.0%		107	14.7%	117	16.0%	
T stage												
T1	905	62.0	452	61.7%	453	62.2%	0.851	470	64.6%	435	59.4%	0.043
T2–3	555	38.0	280	38.3%	275	37.8%		258	35.4%	297	40.6%	
N stage												
N0	860	58.9	419	57.2%	441	60.6%	0.195	434	59.6%	426	58.2%	0.582
N1–3	600	41.1	313	42.8%	287	39.4%		294	40.4%	306	41.8%	
Tumor grade												
1	112	7.7	71	9.7%	41	5.6%	0.023	67	9.2%	45	6.1%	0.128
2	677	46.4	341	46.6%	336	46.2%		325	44.6%	352	48.1%	
3	580	39.7	276	37.7%	304	41.8%		288	39.6%	292	39.9%	
Unknown	91	6.2	44	6.0%	47	6.5%		48	6.6%	43	5.9%	
ER												
Positive	1026	70.3	530	72.4%	496	68.1%	0.074	520	71.4%	506	69.1%	0.336
Negative	434	29.7	202	27.6%	232	31.9%		208	28.6%	226	30.9%	
PR												
Positive	953	65.3	470	64.2%	483	66.3%	0.405	461	63.3%	492	67.2%	0.170
Negative	506	34.7	262	35.8%	244	33.5%		267	36.7%	239	32.7%	
Unknown	1	0.1	0	0.0%	1	0.1%		0	0.0%	1	0.1%	
HER2												
Negative	1238	84.8	633	86.5%	605	83.1%	0.110	627	86.1%	611	83.5%	0.212
Positive	216	14.8	95	13.0%	121	16.6%		97	13.3%	119	16.3%	
Unknown	6	0.4	4	0.5%	2	0.3%		4	0.5%	2	0.3%	
Intrinsic subtype												
HR+ and HER2+	112	7.7	48	6.6%	64	8.8%	0.277	54	7.4%	58	7.9%	0.191
HR+ and HER2–	991	67.9	512	69.9%	479	65.8%		492	67.6%	499	68.2%	
HR– and HER2+	104	7.1	47	6.4%	57	7.8%		43	5.9%	61	8.3%	
HR– and HER2–	247	16.9	121	16.5%	126	17.3%		135	18.5%	112	15.3%	
Unknown	6	0.4	4	0.5%	2	0.3%		4	0.5%	2	0.3%	
Ki-67												
≤20	964	66.0	491	67.1%	473	65.0%	0.429	485	66.6%	479	65.4%	0.387
>20	370	25.3	175	23.9%	195	26.8%		175	24.0%	195	26.6%	
Unknown	126	8.6	66	9.0%	60	8.2%		68	9.3%	58	7.9%	
Operation												
MRM	287	19.7	172	23.5%	115	15.8%	<0.001	153	21.0%	134	18.3%	0.193
PM	1173	80.3	560	76.5%	613	84.2%		575	79.0%	598	81.7%	

Table 1 (continued)

Characteristics	Total		Muscle volume					Fat volume				
	N	%	≤Median		>Median		*P* value	≤Median		>Median		*P* value
Chemotherapy												
Not done	165	11.3	87	11.9%	78	10.7%	0.125	86	11.8%	79	10.8%	0.541
Done	1195	81.8	586	80.1%	609	83.7%		588	80.8%	607	82.9%	
Unknown	100	6.8	59	8.1%	41	5.6%		54	7.4%	46	6.3%	
Radiotherapy												
Not done	175	12.0	97	13.3%	78	10.7%	0.008	82	11.3%	93	12.7%	0.045
Done	1166	79.9	562	76.8%	604	83.0%		574	78.8%	592	80.9%	
Unknown	119	8.2	73	10.0%	46	6.3%		72	9.9%	47	6.4%	
Anti-hormonal therapy												
Not done	321	22.0	147	20.1%	174	23.9%	0.002	161	22.1%	160	21.9%	0.114
Done	1044	71.5	522	71.3%	522	71.7%		510	70.1%	534	73.0%	
Unknown	95	6.5	63	8.6%	32	4.4%		57	7.8%	38	5.2%	
Muscle volume (mL)												
≤Median	732	50.1						496	68.1%	236	32.2%	<0.001
>Median	728	49.9						232	31.9%	496	67.8%	
Fat volume (mL)												
≤Median	728	49.9	496	67.8%	232	31.9%	<0.001					
>Median	732	50.1	236	32.2%	496	68.1%						
Muscle/fat ratio												
≤Median	731	50.1	366	50.0%	365	50.1%	0.958	131	18.0%	600	82.0%	<0.001
>Median	729	49.9	366	50.0%	363	49.9%		597	82.0%	132	18.0%	

Characteristics	Total		Muscle/fat ratio				
	N	%	≤Median		>Median		*P* value
Age							
<50	968	66.3	426	58.3%	542	74.3%	<0.001
≥50	492	33.7	305	41.7%	187	25.7%	
BMI by WHO							
<18.5	44	3.0	3	0.40%	41	5.6%	<0.001
18.6–24.9	1022	70.0	419	0.575	603	82.5%	
25–29.9	332	22.7	250	34.30%	82	11.2%	
≥30	62	4.2	57	7.80%	5	0.7%	
BMI							
<25.0	1066	73.0	424	58.0%	642	88.1%	<0.001
≥25.0	394	27.0	307	42.0%	87	11.9%	
Stage							
I	558	38.2	252	34.5%	306	42.0%	0.003
II	678	46.5	349	47.7%	329	45.1%	
III	224	15.3	130	17.8%	94	12.9%	
T stage							
T1	905	62.0	423	57.9%	482	66.1%	0.001
T2–3	555	38.0	308	42.1%	247	33.9%	
N stage							
N0	860	58.9	418	57.2%	442	60.6%	0.180
N1–3	600	41.1	313	42.8%	287	39.4%	
Tumor grade							
1	112	7.7	49	6.7%	63	8.6%	0.416
2	677	46.4	349	47.7%	328	45.0%	
3	580	39.7	285	39.0%	295	40.5%	

Table 1 (continued)

Characteristics	Total		Muscle/fat ratio				
	N	%	≤Median		>Median		*P* value
Unknown	91	6.2	48	6.6%	43	5.9%	
ER							
Positive	1026	70.3	519	71.0%	507	69.5%	0.544
Negative	434	29.7	212	29.0%	222	30.5%	
PR							
Positive	953	65.3	493	67.4%	460	63.1%	0.125
Negative	506	34.7	237	32.4%	269	36.9%	
Unknown	1	0.1	1	0.1%	0	0.0%	
HER2							
Negative	1238	84.8	619	84.7%	619	84.9%	0.691
Positive	216	14.8	110	15.0%	106	14.5%	
Unknown	6	0.4	2	0.3%	4	0.5%	
Intrinsic subtype							
HR+ and HER2+	112	7.7	54	7.4%	58	8.0%	0.107
HR+ and HER2–	991	67.9	513	70.2%	478	65.6%	
HR– and HER2+	104	7.1	56	7.7%	48	6.6%	
HR– and HER2–	247	16.9	106	14.5%	141	19.3%	
Unknown	6	0.4	2	0.3%	4	0.5%	
Ki-67							
≤20	964	66.0	493	67.4%	471	64.6%	0.114
>20	370	25.3	186	25.4%	184	25.2%	
Unknown	126	8.6	52	7.1%	74	10.2%	
Operation							
MRM	287	19.7	159	21.8%	128	17.6%	0.044
PM	1173	80.3	572	78.2%	601	82.4%	
Chemotherapy							
Not done	165	11.3	71	9.7%	94	12.9%	0.145
Done	1195	81.8	607	83.0%	588	80.7%	
Unknown	100	6.8	53	7.3%	47	6.4%	
Radiotherapy							
Not done	175	12.0	100	13.7%	75	10.3%	0.095
Done	1166	79.9	577	78.9%	589	80.8%	
Unknown	119	8.2	54	7.4%	65	8.9%	
Anti-hormonal therapy							
Not done	321	22.0	149	20.4%	172	23.6%	0.208
Done	1044	71.5	538	73.6%	506	69.4%	
Unknown	95	6.5	44	6.0%	51	7.0%	
Muscle volume (mL)							
≤Median	732	50.1	366	50.1%	366	50.2%	.958
>Median	728	49.9	365	49.9%	363	49.8%	
Fat volume (mL)							
≤Median	728	49.9	131	17.9%	597	81.9%	<0.001–
>Median	732	50.1	600	82.1%	132	18.1%	
Muscle/fat ratio							
≤Median	731	50.1					
>Median	729	49.9					

BMI body mass index, *ER* estrogen receptor, *HER2* human epidermal growth factor 2, *HR* hormone receptor, *MRM* modified radical mastectomy, *N stage* nodal stage, *PM* partial mastectomy, *PR* progesterone receptor, *T stage* tumor stage

tumor ($P = 0.043$, $P = 0.001$). However, hormone receptor status was not statistically correlated with muscle volume and fat volume. Muscle volume showed a positive correlation with fat volume ($P < 0.001$), but not with muscle-to-fat ratio ($P = 0.958$).

When the median was used as the cut point, patients with higher muscle volume than the median volume showed significantly more favorable outcomes than those with lower muscle volume (5 year OS rate, 98.0% vs. 94.9%, $P = 0.008$ and 5 year RFS rate 94.6% vs. 89.6%, $P = 0.031$, Fig. 2). However, muscle volume had no impact on LRFS (99.0% vs. 98.3%, $P = 0.899$). In addition, fat volume did not affect clinical outcomes (5-year OS rate, 96.8% vs. 96.1%, $P = 0.629$, 5-year RFS rate 92.1% vs. 92.1%, $P = 0.463$, and 5-year LRFS 98.3% vs. 99.0%, $P = 0.290$).

Univariate and multivariable analysis for rates of OS and RFS

In the univariate analysis, we found that the following factors were statistically significant for OS: patient's age at diagnosis, stage including T stage and N stage, tumor grade, ER, PR, Ki-67, type of operation, anti-hormone therapy, and muscle volume (Table 2). After adjusting for these factors in the multivariate model, we found that muscle volume remained a significant, strong prognostic variable for survival (HR 0.56, 95% CI 0.34–0.92, $P = 0.022$).

Statistically significant prognostic factors for RFS were stage, PR, type of operation, radiotherapy, anti-hormone therapy, and muscle volume. In multivariate analysis, muscle volume was an independent factor significantly associated with recurrence (HR 0.72, 95% CI 0.52–0.99, $P = 0.046$).

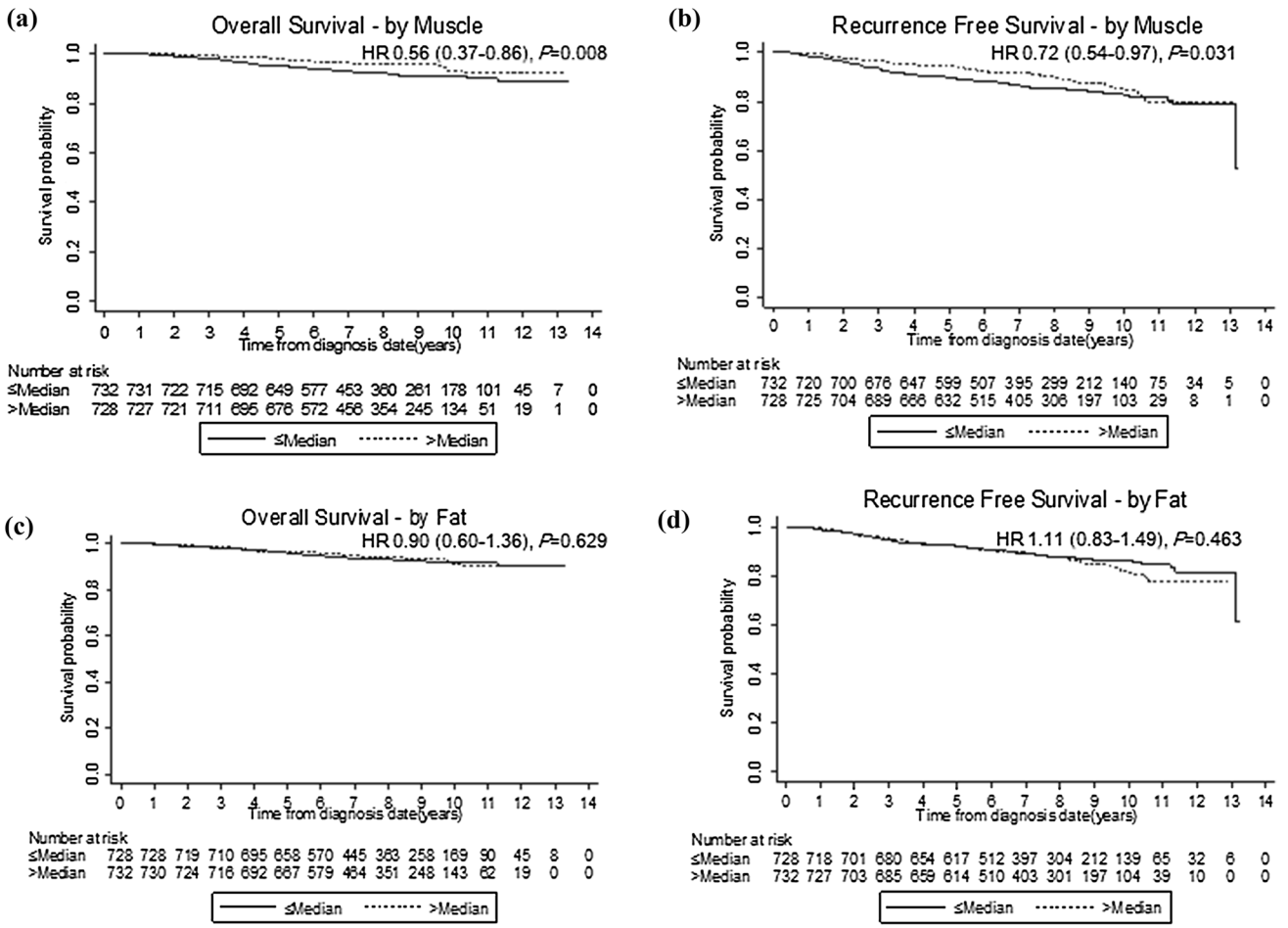

Fig. 2 Overall survival curves and recurrence-free survival curves of breast cancer patients by muscle volume (**a, b**) and fat volume (**c, d**)

Table 2 Univariate and multivariate analyses on overall survival and on recurrence-free survival

Characteristics	Overall survival					
	Univariate analysis			Multivariable analysis		
	HR	*P* value	95% CI	HR	*P* value	95% CI
Age						
< 50	1.00			1.00		
≥ 50	1.65	0.016	1.10–2.48	1.36	0.207	0.84–2.21
BMI						
< 25.0	1.00			1.00		
≥ 25.0	1.19	0.432	0.77–1.85	1.26	0.389	0.74–2.15
(Continuous)	1.02	0.609	0.96–1.08			
Stage						
I	1.00			1.00		
II	2.55	0.005	1.33–4.89	2.22	0.038	1.05–4.72
III	9.17	< 0.001	4.84–17.40	6.76	< 0.001	3.19–14.30
Grade						
1, 2	1.00			1.00		
3	2.67	< 0.001	1.72–4.16	2.61	< 0.001	1.53–4.48
ER						
Positive	1.00			1.00		
Negative	1.90	0.002	1.26–2.86	0.64	0.369	0.24–1.71
PR						
Positive	1.00			1.00		
Negative	3.04	< 0.001	2.00–4.62	1.74	0.110	0.88–3.42
HER2						
Positive	1.00					
Negative	1.30	0.332	0.77–2.20			
Intrinsic subtype, No. (%)						
HR+ and HER2−	1.00					
HR+ and HER2+	1.30	0.514	0.59–2.88			
HR− and HER2+	2.41	< 0.001	1.50–3.86			
HR− and HER2−	2.75	0.316	0.38–19.99			
Ki-67, No. (%)						
≤ 20	1.00			1.00		
> 20	1.56	0.045	1.01–2.40	0.99	0.957	0.57–1.69
Operation						
MRM	1.00			1.00		
PM	0.35	< 0.001	0.23–0.53	0.57	0.022	0.35–0.92
Chemotherapy						
Not done	1.00					
Done	1.94	0.118	0.85–4.43			
Radiotherapy						
Not done	1.00					
Done	0.60	0.052	0.35–1.00			
Anti-hormonal therapy						
Not done	1.00			1.00		
Done	0.38	< 0.001	0.24–0.58	0.59	0.300	0.22–1.60
Muscle volume (mL)						
≤ Median	1.00			1.00		
> Median	0.56	0.008	0.37–0.86	0.56	0.022	0.34–0.92
(continuous)	0.98	0.005	0.97–0.99			

Table 2 (continued)

Characteristics	Overall survival					
	Univariate analysis			Multivariable analysis		
	HR	*P* value	95% CI	HR	*P* value	95% CI
Fat volume (mL)						
≤Median	1.00					
>Median	0.90	0.629	0.60–1.36			
(Continuous)	1.00	0.41	0.99–1.01			
Muscle/fat ratio						
≤Median	1.00					
>Median	0.76	0.183	0.50–1.14			
(Continuous)	1.82	0.02	1.09–3.04			
Characteristics	Recurrence-free survival					
	Univariate analysis			Multivariable analysis		
	HR	*P* value	95% CI	HR	*P* value	95% CI
Age						
<50	1.00					
≥50	1.21	0.205	0.90–1.63			
BMI						
<25.0	1.00			1.00		
≥25.0	1.09	0.598	0.79–1.50	1.05	0.769	0.74–1.49
(Continuous)	1.03	0.215	0.98–1.07			
Stage						
I	1.00			1.00		
II	1.77	0.004	1.20–2.60	2.04	0.001	1.33–3.13
III	4.64	<0.001	3.11–6.93	4.68	<0.001	2.96–7.42
Grade						
1, 2	1.00					
3	1.28	0.107	0.95–1.73			
ER						
Positive	1.00					
Negative	1.12	0.482	0.82–1.53			
PR						
Positive	1.00			1.00		
Negative	1.81	<0.001	1.36–2.42	1.47	0.082	0.95–2.28
HER2						
Positive	1.00					
Negative	1.32	0.144	0.91–1.92			
Intrinsic subtype, No. (%)						
HR+ and HER2−	1.00					
HR+ and HER2+	1.09	0.766	0.62–1.89			
HR− and HER2+	1.71	0.027	1.06–2.76			
HR− and HER2−	1.25	0.248	0.85–1.84			
Ki-67, No. (%)						
≤20	1.00					
>20	1.18	0.307	0.86–1.64			
Operation						
MRM	1.00			1.00		
PM	0.50	<0.001	0.37–0.68	0.73	0.147	0.48–1.11
Chemotherapy						

Table 2 (continued)

Characteristics	Recurrence-free survival					
	Univariate analysis			Multivariable analysis		
	HR	*P* value	95% CI	HR	*P* value	95% CI
Not done	1.00					
Done	1.30	0.298	0.79–2.15			
Radiotherapy						
Not done	1.00			1.00		
Done	0.68	0.050	0.46–1.00	0.83	0.457	0.51–1.35
Anti-hormonal therapy						
Not done	1.00					
Done	0.60	0.002	0.43–0.83	0.90	0.648	0.57–1.42
Muscle volume (mL)						
≤ Median	1.00					
> Median	0.72	0.031	0.54–0.97	0.72	0.046	0.52–0.99
(continuous)	0.989	0.006	0.981–0.996			
Fat volume (mL)						
≤ Median	1.00					
> Median	1.11	0.463	0.83–1.49			
(Continuous)	1.00	0.23	0.999–1.001			
Muscle/fat ratio			–			
≤ Median	1.00					
> Median	0.62	0.001	0.46–0.83			
(Continuous)	1.00	0.995	0.60–1.68			

BMI body mass index, *CI* confidence interval, *ER* estrogen receptor, *HER2* human epidermal growth factor 2, *HR* hormone receptor, *HR* hazard ratio, *MRM* modified radical mastectomy, *N stage* nodal stage, *PM* partial mastectomy, *PR* progesterone receptor, *T stage* tumor stage

Subgroup analysis for clinical impact of muscle volume

Prognosis in breast cancer patients differs according to intrinsic subtypes and stage at diagnosis; we therefore analyzed the association with muscle volume in each subtype. In the triple-negative breast cancer group, those with higher muscle volume showed better OS and RFS (HR 0.33, 95% CI 0.14–0.77 for OS; HR 0.34, 95% CI 0.16–0.72 for RFS, Supplement Fig. 2a). However, there were no statistical differences in OS and RFS between those with higher muscle volume and lower muscle volume. In subgroup analysis for stage at diagnosis, those with higher muscle volume in stage III showed better OS and RFS (HR 0.49, 95% CI 0.26–0.93 for OS; HR 0.53, 95% CI 0.32–0.89, for RFS, Supplement Fig. 2b), but not in those with stage I or II.

In subgroup analyses with respect to different BMIs and ages, muscle volume was a significant prognosticator for OS in patients with normal BMI and those with higher BMI (HR 0.55, 95% CI 0.32–0.93, $P = 0.034$ in BMI < 25.0; HR 0.44, 95% CI 0.21–0.91, $P = 0.026$ in BMI ≥ 25.0, Table 3). In addition, older patients (≥ 50) with higher muscle volume showed better OS and RFS (HR 0.44, 95% CI 0.23–0.85, $P = 0.015$ for OS; HR 0.55, 95% CI 0.34–0.90, $P = 0.017$ for RFS). However, fat volume was not a prognostic factor, regardless of BMI and age.

Discussion

Obesity is a well-known causative and prognostic factor in breast cancer [1, 2]. Several studies have investigated the role of obesity and the associated microenvironment that promotes obesity in obese patients. With the development of imaging modalities such as CT and MRI, these techniques can now be used to differentiate body composition accurately, and to quantitatively assess the different tissue types within a specific area of interest. Such three-dimensional volumetric imaging techniques are gaining focus from a healthcare perspective, because information derived from such techniques can be utilized to make disease-specific evaluations and recommendations. For instance, a study on patients with sarcopenic obesity recruited from a single institution found that the prognosis in patients with less muscle mass, determined using CT and MRI, is poorer than those with more muscle mass. Consequently, a recommendation for sarcopenically obese patients based on this study

Table 3 Prognostic impact of muscle volume and fat volume according to BMI and age group

Characteristics	Overall survival									
	Muscle vol. (mL)	HR	*P* value	95% CI		Fat vol. (mL)	HR	*P* value	95% CI	
BMI										
< 25.0	(Continuous)	0.98	0.002	0.96	0.99	(Continuous)	1.00	0.187	1.00	1.00
	≤ Median	1.00				≤ Median	1.00			
	> Median	0.55	0.034	0.32	0.95	> Median	0.68	0.159	0.40	1.16
≥ 25.0	(Continuous)	0.99	0.253	0.97	1.01	(Continuous)	1.00	0.562	1.00	1.00
	≤ Median	1.00				≤ Median	1.00			
	> Median	0.44	0.026	0.21	0.91	> Median	1.53	0.427	0.53	4.41
Age										
< 50	(Continuous)	0.98	0.017	0.97	1.00	(Continuous)	1.00	0.304	1.00	1.00
	≤ Median	1.00				≤ Median	1.00			
	> Median	0.67	0.158	0.38	1.17	> Median	0.68	0.189	0.38	1.21
≥ 50	(Continuous)	0.99	0.130	0.97	1.00	(Continuous)	1.00	0.410	1.00	1.00
	≤ Median	1.00				≤ Median	1.00			
	> Median	0.44	0.015	0.23	0.85	> Median	1.05	0.871	0.56	1.96
Characteristics	Recurrence-free survival									
	Muscle vol. (mL)	HR	*P* value	95% CI		Fat vol. (mL)	HR	*P* value	95% CI	
BMI										
< 25.0	(Continuous)	0.98	0.001	0.97	0.99	(Continuous)	1.00	0.808	1.00	1.00
	≤ Median	1.00				≤ Median	1.00			
	> Median	0.71	0.067	0.50	1.02	> Median	0.99	0.956	0.69	1.41
≥ 25.0	(Continuous)	0.99	0.492	0.98	1.01	(Continuous)	1.00	0.095	1.00	1.00
	≤ Median	1.00				≤ Median	1.00			
	> Median	0.64	0.114	0.37	1.11	> Median	1.72	0.183	0.77	3.81
Age										
< 50	(Continuous)	0.99	0.027	0.98	1.00	(Continuous)	1.00	0.923	1.00	1.00
	≤ Median	1.00				≤ Median	1.00			
	> Median	0.85	0.372	0.59	1.22	> Median	0.92	0.665	0.64	1.33
≥ 50	(Continuous)	0.99	0.110	0.98	1.00	(Continuous)	1.00	0.079	1.00	1.00
	≤ Median	1.00				≤ Median	1.00			
	> Median	0.55	0.017	0.34	0.90	> Median	1.48	0.134	0.89	2.48

BMI body mass index, *CI* confidence interval, *HR* hazard ratio, *vol*. volume

is to implement changes in diet, lifestyle, or care that would promote build-up of muscle mass.

Here, we report the results of a retrospective study on a large cohort of breast cancer patients recruited from a single institution. We quantitatively measured skeletal muscle volume and fat volume based on patients' CT images, which were 1 cm in thickness and taken at the intervertebral disc between the 2nd and 3rd lumbar vertebra. Our optimized regression model showed that the amount of muscle was significantly correlated with OS, RFS, and LRFS, after adjusting for other significant factors. In particular, we found that having a high muscle-to-fat ratio was more prognostic for favorable survival than having a lower ratio. Using the multivariable Cox regression model, muscle volume and muscle-to-fat ratio was demonstrated to have a positive impact on prognosis, especially on RFS. But fat volume alone did not show a correlation with survival, even with relapse of the disease.

There are a number of limitations to this study. As our study was undertaken retrospectively, we found that two variables were inconsistent and uncontrolled among patients: the time between the date of diagnosis and the date of chest CT; and the diverse imaging protocol such as different slice thickness. A large number of patients had to be excluded because they did not fit the inclusion criteria for these variables. So, selection bias may have arisen during the process of patient recruitment. Second, we used CT image for evaluating muscle and fat volume instead of MRI imaging. Although CT has relatively short time for image acquisition, low cost compared with MRI, MRI has been widely used in

these days because it is more useful for physiologic imaging, diagnosis, and prediction of prognosis [20–23]. Third, important factors related to prognosis of the disease, such as the type of chemotherapy, radiation therapy, and antihormonal therapy, were not analyzed in this study. Lastly, the written records of the patients were made several years ago; therefore some data, such as immunohistochemistry staining, were unavailable. Despite the limitations, the study deserves merit for highlighting a strong, positive correlation between muscle volume and breast cancer prognosis in 1494 breast cancer patients recruited from a single institution. The results of this study are anticipated to provide evidence for the necessity of increasing muscle mass by adopting a healthier lifestyle for cancer patients to enhance prognosis. The limitations of the present study may be overcome by investigating the impact of muscle volume on survival not only in cancer patients, but also in patients with muscle wasting disease. Further, a parallel study investigating the effect of muscle volume on prognosis in patients treated with other anti-cancer treatments would improve the qualitative findings of this study.

Conclusion

This study showed that breast cancer patients with higher skeletal muscle volumes showed more favorable prognosis regardless of BMI. In addition, muscle volume affects clinical outcomes in older patients.

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Compliance with ethical standards

Conflict of interest Eun Jin Song has received research grant from the National Cancer Center. All authors except Eun Jin Song declare that they no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals. The study protocol was approved by the institutional review board of the National Cancer Center (IRB No.: NCC2015-0006).

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