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Volume-based metabolic parameter of breast cancer on preoperative ¹⁸F-FDG PET/CT could predict axillary lymph node metastasis

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Abstract

The purpose of our study was to evaluate the association between metabolic parameters on FDG PET/CT and axillary lymph node metastasis (ALNM) in patients with invasive breast cancer.

From January 2012 to December 2012, we analyzed 173 patients with invasive ductal carcinoma (IDC) who underwent both initial breast magnetic resonance imaging (MRI) and ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) examinations. All metabolic parameters were measured from the tumor volume segmented by a gradient-based method. Once the primary target lesion was segmented, maximum standardized uptake value (SUVmax), mean standardized uptake value (SUVmean), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were calculated automatically by the MIMvista software.

Mean age of 173 patients was 49 years. Of 173 patients, 45 (26%) showed ALNM. On univariate analysis, larger tumor size (>2.2 cm; $P = .002$), presence of lymphovascular invasion ($P < .001$), higher SUVmax (>2.82; $P = .038$), higher SUVmean (>1.2; $P = .027$), higher MTV (>2.38; $P < .001$), and higher TLG (>3.98; $P = .007$) were associated with a higher probability of ALNM. On multivariate analysis, presence of lymphovascular invasion (adjusted odds ratio [OR], 11.053; 95% CI, 4.403–27.751; $P < .001$) and higher MTV (>2.38) (adjusted OR, 2.696; 95% CI, 1.079–6.739; $P = .034$) maintained independent significance in predicting ALNM. In subgroup analysis of T2/T3 breast cancer, lymphovascular invasion (adjusted OR, 20.976; 95% CI, 5.431–81.010; $P < .001$) and higher MTV (>2.38) (adjusted OR, 4.906; 95% CI, 1.616–14.896; $P = .005$) were independent predictors of ALNM. However in T1 breast cancer, lymphovascular invasion (adjusted OR, 16.096; 95% CI, 2.517–102.939; $P = .003$) and larger SUV mean (>1.2) (adjusted OR, 13.275; 95% CI, 1.233–142.908; $P = .033$) were independent predictors while MTV was not.

MTV may be associated with ALNM in patients with invasive breast cancer, particularly T2 and T3 stages. In T1 breast cancer, SUVmean was associated with ALNM.

Abbreviations: ALNM = axillary lymph node metastasis, ER = estrogen receptor, FDG PET/CT = fluorodeoxyglucose positron emission tomography/computed tomography, HER2 = human epidermal growth factor receptor 2, IDC = invasive ductal carcinoma, MRI = magnetic resonance imaging, MTV = metabolic tumor volume, OR = odds ratio, PR = progesterone receptor, SUVmax = maximum standardized uptake value, SUVmean = mean standardized uptake value, TLG = total lesion glycolysis.

Keywords: axillary lymph node metastasis, breast cancer, ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography, metabolic tumor volume

1. Introduction

Axillary lymph node metastasis (ALNM) is one of the most significant prognostic factors in breast cancer patients, and axillary lymph node dissection (ALND) is a standard treatment for patients with ALNM.[1,2] Sentinel lymph node dissection (SLND) could accurately evaluate the status of ALN with decreased morbidity and has become the standard practice for nodal staging in patients with early-stage breast cancer. Preoperative prediction of ALNM is useful for surgeons to select patients with low risk of ALNM and avoid full ALND.

Primary tumor size, palpable mass, lymphovascular invasion, histologic grade, and Ki-67 index of >20% are known as clinical and pathologic predictors of ALNM.[3–7]

As an imaging biomarker, the breast tumor strain ratio on ultrasound elastography has been reported to be an independent predictor for ALNM in patients with invasive breast cancer.[8] The strain ratio was significantly higher in tumors with ALNM than in those without ALNM. The strain ratio was independent predictor for ALNM along with lymphovascular invasion and higher expression of Ki-67 (>14%) on multivariate analysis. Maximum standardized uptake value (SUVmax) of breast tumor on ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG PET/CT) has been associated with ALNM.[9] Higher tumor SUVmax (≥4.25) was independent predictor for ALNM along with large tumor size and lymphovascular invasion.

Volume-based parameters on ¹⁸F-FDG PET/CT such as metabolic tumor volume (MTV) or total lesion glycolysis

(TLG) represent total tumor burden as well as tumor metabolic activity. Therefore, many researchers have studied the value of volume-based PET parameter and it has been significantly associated with breast cancer subtype, tumor response after neoadjuvant chemotherapy (NAC) and prognosis.[10–21]

The purpose of our study was to evaluate the association between metabolic parameters on FDG PET/CT and ALNM in patients with invasive breast cancer.

2. Materials and methods

2.1. Patients

This retrospective study has been approved by our institutional review board. Neither patient approval nor informed consent was required for the review of medical records or images.

From January 2012 to December 2012, consecutive 379 patients were newly diagnosed as breast cancer and underwent breast MRI in our hospital. Of 379 patients, we excluded 75 patients who received neoadjuvant chemotherapy, 11 patients who were diagnosed as pure ductal carcinoma in situ, 5 patients who did not have visible enhancing lesion on MRI and 115 patients who did not undergo initial ^{18}F-FDG PET/CT examination. Finally, we included 173 patients with invasive ductal carcinoma (IDC) who underwent both initial breast MRI and FDG PET/CT examinations.

2.2. MRI examination

Breast MRI was performed with a 1.5-T system (Signa HDxt, GE Healthcare, Milwaukee, WI) with a dedicated 8-channel breast coil. Patients underwent imaging in the prone position with the breasts immobilized. Contrast material was injected (0.1 mmol/kg gadopentetate dimeglumine [Magnevist]; Bayer Schering Pharma, Berlin, Germany) and followed by a 20-mL saline flush at a rate of 2 mL/s. The imaging protocol of a 1.5-T scanner consisted of fat-suppressed axial fast spin-echo T2-weighted images (repetition time/time to echo, 4000/74; slice thickness, 3 mm) and 3-dimensional, T1-weighted, fast spoiled gradient-echo sequence with bilateral axial images (6.5/2.5; flip angle, 0 degrees; image matrix, 320 × 160; field of view, 200 × 200 mm; section thickness, 1.5 mm; and section gap, 0 mm).

2.3. ^{18}F-FDG PET/CT examination

After fasting for at least 6 hours, patients were administered 5 MBq/kg of FDG intravenously. The blood glucose level at the time of injection of FDG was <150 mg/dL in all patients. Patients were instructed to rest comfortably for 60 minutes and to urinate before scanning. Whole-body PET/CT images were obtained with a Discovery ST scanner (GE Healthcare, Milwaukee, WI). Seven or 8 frames (3 min/frame) of emission PET data were acquired in 3-dimensional (3D) mode after a non-contrast CT scan from the base of the skull to the upper thigh (120 kV, 30–100 mA in the AutomA mode; section width = 3.75 mm). Emission PET images were reconstructed using an iterative method (ordered-subsets expectation maximization with 2 iterations and 20 subsets, field of view = 600 mm, slice thickness = 3.27 mm) and attenuation corrected with non-contrast CT.

2.4. Image analysis

A specialist in nuclear medicine with 11 years of PET experience reviewed the FDG PET/CT images on a MIMvista workstation (ver. 6.5; MIM Software Inc, Cleveland, OH). All metabolic parameters were measured from the tumor volume segmented by a gradient-based method, as previously described.[22,23] A gradient segmentation method is available in the MIMvista software with an operator-defined starting point near the center of the breast tumor lesion. Once the primary target lesion was segmented, SUVmax, mean standardized uptake value (SUVmean), MTV, and TLG were calculated automatically by the MIMvista software (Fig. 1). TLG was calculated by multiplying the SUVmean by the MTV. All SUVs were estimated based on injected dose and body weight.

All MR images were reviewed by a radiologist with 9 years of experience in interpreting breast imaging data. The lesion size was measured as the longest diameter of the lesion on the MIP image using a picture archiving and communication system workstation with electronic calipers. For multiple lesions, the longest diameter of each lesion was recorded separately and the sum of the lesions was calculated.

2.5. Histopathological evaluation

All patients underwent surgical resection for breast cancer with sentinel lymph node biopsy and/or axillary lymph node dissection. The routinely formalin-fixed, paraffin-embedded tissue blocks of tumors and axillary lymph nodes were sectioned to 4-mm thickness and stained with hematoxylin-eosin. The specimens of tumor and axillary lymph nodes were evaluated according to the following histopathological features: tumor size, histological type of carcinoma, perinodal extension of tumor in ALN, size of tumor
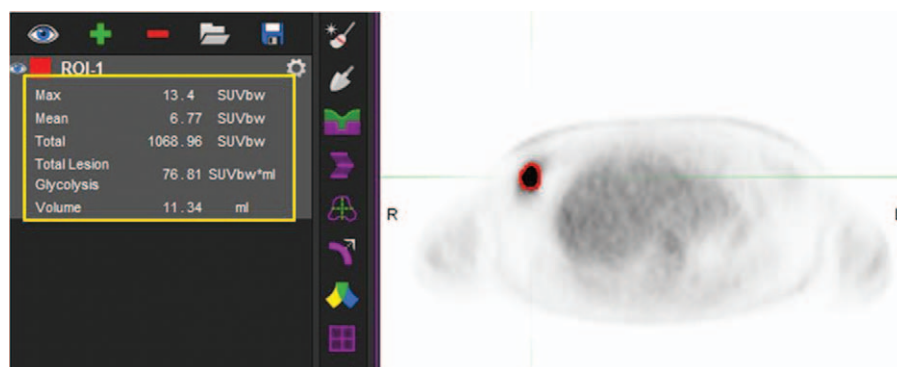
Figure 1. The representative image of measuring metabolic parameters using the MIMvista software. Auto-contouring of tumor volume on PET image was initiated by the operator by doing a left click near the center of the breast mass lesion on transaxial image, and dragged to a point near the edge of the object. Five additional edge points are automatically determined at equal angular increments from the operator defined edge point. The red contour of breast mass lesion was drawn by segmentation of PET tumor volume, then metabolic parameters including SUVmax, SUVmean, MTV, and TLG were automatically calculated (yellow box).

deposit in ALN, Black nuclear grade (nuclear grade 1, poorly differentiated; grade 2, moderately differentiated; and grade 3, well differentiated) and modified Bloom-Richardson histological grade (histological grade 1, well differentiated; grade 2, moderately differentiated; and grade 3, poorly differentiated). For dichotomous-dependent variables, nuclear grade was classified as high (grade 1) vs low (grades 2 and 3) and histological grade as low (grades 1 and 2) vs high (grade 3). We classified micrometastasis as positive LN. There was no case of isolated tumor cells in our study.

### 2.6. Statistical analysis

Clinicopathologic characteristics were compared between patients with and without ALNM using the independent sample t test for the continuous variables and chi-square test for the categorical variables. Receiver operating characteristic (ROC) curve was performed to determine the optimal cut-off values of SUVmax, SUVmean, MTV, and TLG. ROC curve analysis was also used to evaluate the performance of MTV for the prediction of ALNM.

Multivariate logistic regression analysis was performed to determine the independent variables associated with ALNM by including all of the significant factors ($P < .05$) from univariate analysis.

All analyses were performed using the SPSS 23.0 statistical software package (IBM, Armonk, NY) and MedCalc (MedCalc, Mariakerke, Belgium) software with a value of $P < .05$ considered to be significant.

3. Results

Mean age of 173 patients was 49 years. Of 173 patients, 45 (26%) showed ALNM by surgical histopathologic analysis.
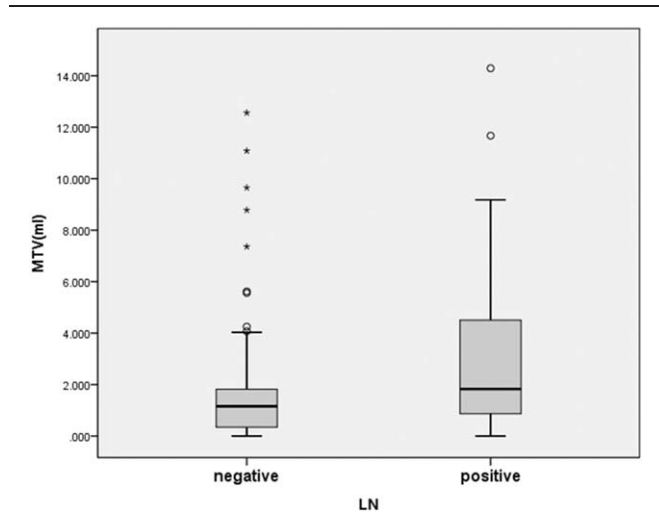
Figure 2. Boxplot graph shows statistically significant difference in metabolic tumor volume (MTV) of breast tumor between node-positive and node-negative groups.

Clinical characteristics of patients and axillary lymph node status are summarized in Table 1. Mean value of tumor size, MTV, and the presence of lymphovascular invasion were significantly different between node negative and node positive groups. The mean MTV of tumors with node positive status was 3.2 ± 3.4, which was significantly higher than that of node negative tumors (1.9 ± 2.9, $P = .025$) (Fig. 2).

On univariate analysis (Table 2), larger tumor size (>2.2 cm; $P = .002$), presence of lymphovascular invasion ($P < .001$), higher SUVmax (>2.82; $P = .038$), higher SUVmean (>1.2; $P = .027$),

Table 1

Clinical characteristics of patients and axillary lymph node status.

Characteristic	Total (n = 173)	Node negative (n = 128)	Node positive (n = 45)	P
Patient age, y, mean ± SD	49.2 ± 10.9	48.9 ± 11.1	50.1 ± 10.7	.52
Tumor size, cm, mean ± SD	2.5 ± 1.4	2.4 ± 1.3	2.9 ± 1.5	.037
SUVmax, mean ± SD	4.7 ± 4.3	4.6 ± 4.5	4.9 ± 3.3	.621
SUVmean, mean ± SD	3.0 ± 2.5	3.0 ± 2.7	3.0 ± 1.9	.972
MTV, mean ± SD	2.2 ± 3.1	1.9 ± 2.9	3.2 ± 3.4	.025
TLG, mean ± SD	7.8 ± 14.9	6.6 ± 14.7	11.2 ± 15.3	.082
Lymphovascular invasion				<.001
Negative	138 (79.8)	117 (91.4)	21 (46.7)	
Positive	35 (20.2)	11 (8.6)	24 (53.3)	
Pathologic T stage				.113
T1/T2/T3	68/95/10	56/65/7	12/30/3	
Histologic finding				.389
IDC	158 (90.3)	116 (90.6)	42 (93.3)	
Invasive lobular carcinoma	5 (2.9)	3 (2.3)	2 (4.4)	
Other	10 (5.7)	9 (7.0)	1 (2.2)	
Tumor subtype				.224
ER and PR positive, HER2 negative	111 (64.2)	82 (64.1)	29 (64.4)	
ER and PR positive, HER2 positive	20 (11.6)	13 (10.2)	7 (15.6)	
ER and PR negative, HER2 positive	13 (7.5)	8 (6.3)	5 (11.1)	
Triple negative	29 (16.8)	25 (19.5)	4 (8.9)	
Histologic grade				.858
Low (grade 1 and grade 2)	104	76 (61.3)	28 (63.6)	
High (grade 3)	64	48 (38.7)	16 (36.4)	
Nuclear grade				.477
Low (grade 2 and grade 3)	98	69 (56.1)	28 (63.6)	
High (grade 1)	70	54 (43.9)	16 (36.4)	

Note: Data are numbers of patients, with percentages in parentheses, unless specified otherwise.
ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, IDC = invasive ductal carcinoma, MTV = metabolic tumor volume, PR = progesterone receptor, SUVmax = maximum standardized uptake value, SUVmean = mean standardized uptake value, TLG = total lesion glycolysis.

Table 2

Univariate analysis for axillary lymph node metastasis.

Variable	Univariate analysis		
	OR	95% CI	P
Tumor size on MRI (>2.2 vs ≤2.2 cm)	3.021	1.489, 6.129	.002*
Lymphovascular invasion (present vs absent)	12.156	5.188, 28.483	<.001*
SUVmax (>2.82 vs ≤2.82)	2.146	1.045, 4.409	.038*
SUVmean (>1.2 vs ≤1.2)	3.474	1.155, 10.451	.027*
MTV (>2.38 vs ≤2.38)	4.32	1.999, 9.334	<.001*
TLG (>3.98 vs ≤3.98)	2.636	1.3, 5.343	.007*
Histologic grade (grade 3 vs grades 1 and 2)	0.905	0.444, 1.845	.783
Nuclear grade (grade 1 vs grade 2 and 3)	0.73	0.359, 1.485	.385
ER (present vs absent)	1.389	0.605, 3.189	.438
PR (present vs absent)	1.012	0.492, 2.079	.975
HER2 positivity (positive vs negative)	1.853	0.825, 4.163	.135
Triple negative subtype (TN vs non-TN)	0.402	0.132, 1.227	.109

ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, MTV = metabolic tumor volume, OR = odds ratio, PR = progesterone receptor, SUVmax = maximum standardized uptake value, SUVmean = mean standardized uptake value, TLG = total lesion glycolysis.
* Denotes statistically significant OR.

higher MTV (>2.38; $P < .001$), and higher TLG (>3.98; $P = .007$) were associated with a higher probability of ALNM. Histologic grade ($P = .783$), nuclear grade ($P = .385$), estrogen receptor (ER) ($P = .438$), progesterone receptor (PR) ($P = .975$), ErbB-2 ($P = .135$), and triple negative subtype ($P = .109$) showed no significant association with ALNM on univariate analysis. Those factors showing statistical significance ($P < .05$) on univariate analysis were used for the multivariate analysis. Of SUVmax and SUVmean, only SUV mean was included for multivariate analysis because there was multicollinearity between SUV max and SUVmean. Of MTV and TLG, we included only MTV for multivariate analysis for the aforementioned reason.

On multivariate analysis, presence of lymphovascular invasion (adjusted odds ratio [OR], 11.053; 95% CI, 4.403–27.751; $P < .001$) and higher MTV (>2.38) (adjusted OR, 2.696; 95% CI, 1.079–6.739; $P = .034$) maintained independent significance in predicting ALNM (Table 3). The area under the ROC curve (AUC) of MTV was 0.64 for the prediction of ALNM (Fig. 3).

Subgroup analysis was performed in T1 breast cancer and T2/T3 breast cancer (Table 4). Of 68 breast cancers with T1 stage, 12 (18%) had ALNM, and of 105 cancers with T2 or T3 stage, 33 (31%) had ALNM.

In T1 breast cancer, multivariate analysis showed that presence of lymphovascular invasion (adjusted OR, 16.096; 95% CI, 2.517–102.939; $P = .003$) and larger SUV mean (>1.2) (adjusted OR, 13.275; 95% CI, 1.233–142.908; $P = .033$) were independent predictors of ALNM while MTV was not ($P = .741$). In T2

and T3 breast cancers, lymphovascular invasion (adjusted OR, 20.976; 95% CI, 5.431–81.010; $P < .001$) and higher MTV (>2.38) (adjusted OR, 4.906; 95% CI, 1.616–14.896; $P = .005$) were independent predictors of ALNM (Table 4).

Representative cases are presented in Figures 4 and 5.

4. Discussion

We found that lymphovascular invasion and MTV were significant predictors of ALNM. Lymphovascular invasion has been reported as significant pathologic factor for ALNM in previous studies and we found the same result.[3–7] However, the presence of lymphovascular invasion could be assessed only after surgical excision and pathologic examination. Preoperative knowledge of axillary lymph node status could help surgeons

Table 3

Multivariate logistic regression analysis for axillary lymph node metastasis.

Variable	Multivariate analysis		
	Adjusted OR	95% CI	P
Tumor size on MRI >2.2 vs ≤2.2 cm)	2.093	0.861, 5.086	.103
Lymphovascular invasion (present vs absent)	11.053	4.403, 27.751	<.001*
SUVmean (>1.2 vs ≤1.2)	2.205	0.62, 7.843	.222
MTV (>2.38 vs ≤2.38)	2.696	1.079, 6.739	.034*

MTV = metabolic tumor volume, OR = odds ratio, SUVmean = mean standardized uptake value.
* Denotes statistically significant OR.
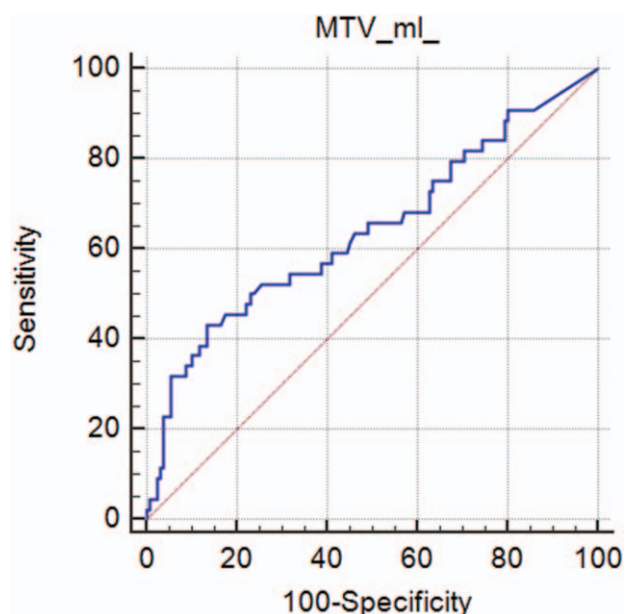
Figure 3. Receiver operating characteristic curve analysis of MTV for the prediction of ALNM (AUC = 0.64). ALNM = axillary lymph node metastasis.

Table 4

Multivariate logistic regression analysis for axillary lymph node metastasis in patients with T1 and T2/T3 breast cancer.

Variable	T1 stage		T2 and T3 stage	
	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Lymphovascular invasion (present vs absent)	16.096 (2.517–102.939)	.003*	20.976 (5.431–81.010)	<.001*
SUVmean (>1.2 vs ≤1.2)	13.275 (1.233–142.908)	.033*	0.438 (0.094–2.054)	.295
MTV (>2.38 vs ≤2.38)	0.638 (0.045–9.110)	.741	4.906 (1.616–14.896)	.005*

MTV = metabolic tumor volume, OR = odds ratio, SUVmean = mean standardized uptake value.
* Denotes statistically significant OR.
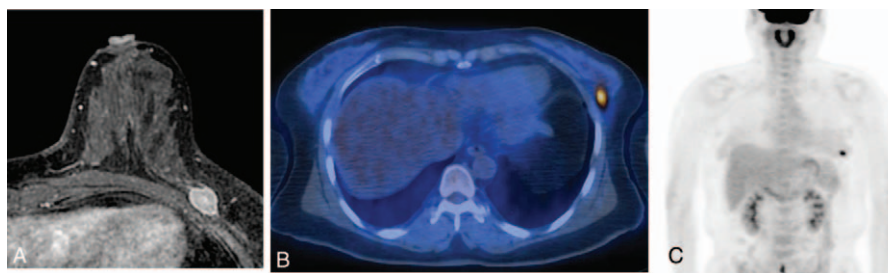
Figure 4. A 49-y-old female who has been diagnosed with breast cancer in her left breast. Contrast-enhanced axial MRI shows 1.7 cm enhancing mass in her left breast (A). ^{18}F-FDG PET/CT shows a hypermetabolic mass in left breast with relatively high SUVmean of 4.49 and low MTV of 0.836 (B, C). Surgical histopathology revealed IDC with T1 stage and negative lymphovascular invasion. ALNM was found in 1 out of 5 resected nodes. ALNM = axillary lymph node metastasis, IDC = invasive ductal carcinoma.

to select candidate for axillary dissection and could reduce unnecessary sentinel lymph node biopsy. We also found that MTV was significant biomarker in 173 patients with invasive ducal carcinoma (adjusted OR: 2.696, 95% CI: 1.079, 60739, P = .034). However, in the subgroup analysis, MTV correlated well with ALNM for breast cancers with T2 and T3 stage (P = .005), but not for T1 stage (P = .741). We supposed that in case of small breast cancer <2 cm, the tumor volume would be small in most cases regardless of the axillary lymph node status, and SUVmean would be mainly different between 2 groups with or without ALNM.

Several studies reported SUVmax on ^{18}F-FDG PET/CT or breast tumor strain ratio on ultrasound elastography as imaging biomarker for ALNM.[8,9] Higher SUVmax (≥4.25) was independent predictor for ALNM especially in ER-positive/HER2-negative and HER2-positive subtypes but not in triple

negative subtype.[9] In this study, we measured not only SUVmax but also SUVmean, MTV, and TLG. On univariate analysis, both SUVmax and SUVmean were associated with ALNM showing more statistical power in SUVmean (P = .038 vs P = .027 for SUVmax and SUVmean).

There are many studies reporting the clinical importance of PET parameters meaning the metabolic activity or total tumor burden. Recent study reported that SUVmax was useful for identifying patients who had high risk of recurrence after mastectomy in a subgroup of patients with T1-T2/N1 breast cancer.[24] In their study, SUVmax threshold of 5.36 showed best predictive performance and the prognosis was much worse when the lymph node showed more than high SUVmax (≥5.36).

Because MTV represents the total tumor burden not merely the metabolic activity, MTV has been suggested as a prognostic factor in breast cancer.[10,21] Ulaner et al[21] examined 253
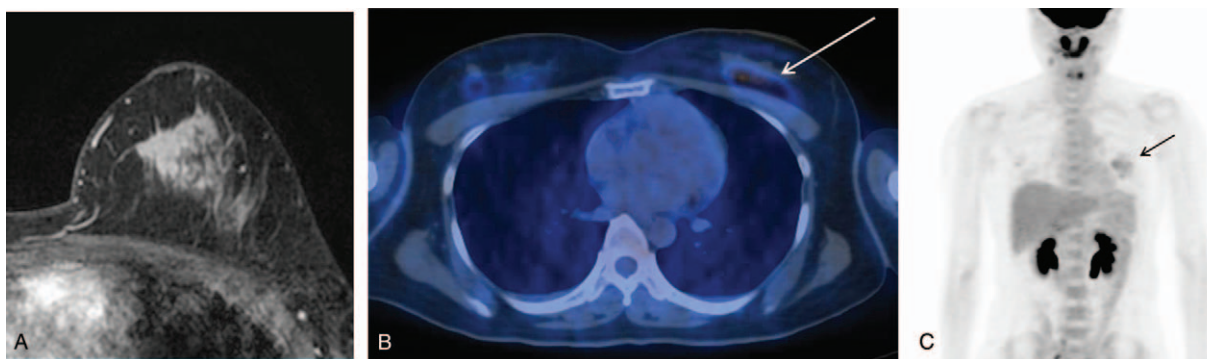
Figure 5. A 39-y-old female who has been diagnosed with breast cancer in her left breast. Contrast-enhanced axial MRI shows 3.8 cm enhancing mass in left breast (A). ^{18}F-FDG PET/CT shows a hypermetabolic mass in left breast with relatively high MTV of 7.09 and low SUVmean of 1.68 (arrows in B and C). Surgical histopathology revealed IDC with T2 stage and negative lymphovascular invasion. ALNM was found in 5 out of 15 resected nodes. ALNM = axillary lymph node metastasis, IDC = invasive ductal carcinoma.

patients with metastases in bone, LN, liver, or lung at the time of metastatic diagnosis. They measured metabolic parameters in target lesions of bone, LN, liver, and lung. Higher SUVmax tertile was correlated with worse survival in bone metastasis, higher MTV in LN and liver metastases, and higher TLG in bone, LN, and liver metastases. Marinelli et al[10] reported that in patients with metastatic triple negative breast cancer, patients with MTV <51.5 mL lived 3 times longer than those with a higher MTV. In multivariate Cox regression analysis, MTV was significantly correlated with survival. Our results revealed that MTV was significantly correlated with ALNM in multivariate analysis and it could be useful.

Metabolic parameters were also useful for the evaluation of response to NAC. After NAC treatment, posttreatment SUVmax and MTVtotal, and relative decrease in SUVmax and MTVtotal were significantly associated with disease-free survival.[15]

The important point of our study is that we used gradient-based method for the acquisition of volume-based metabolic parameters. The gradient-based method has been reported to be more accurate than conventional threshold methods showing excellent reproducibility for volume contouring in PET images.[23] In fixed-threshold method, volume-based PET parameters are acquired at SUV 2.5 or given percentage of the maximal activity (25–70%). In gradient-based method, the boundaries of tumor are associated with the gradient intensity crests which are achieved using the watershed transform.[22]

Previous studies reported conflicting results about the initial status of ALNM in triple negative breast cancers. Some studies reported a higher prevalence of lymph node metastasis in triple negative breast cancer[25] whereas others have found a lower prevalence[26] or no significant association.[27] The proposed mechanism is that the pattern of metastatic spread is different between triple negative and hormone receptor positive cancers and triple negative breast cancer favors hematogenous metastasis, resulting in more frequent metastatic deposit in lung and brain than in bone and axillary lymph node.[28–30] Our result also revealed that triple negative subtype was not associated with ALNM on univariate analysis ($P = .109$).

Our study has several limitations. First, the present study is retrospective with small number of patients and heterogeneous study population. The results of our study need to be validated in a larger cohort of patients who have more homogeneous characteristics. Second, we did not analyze the association of metabolic parameters and long-term clinical outcomes because the treatment modality was heterogeneous between patients and the follow-up duration was short. Further prospective study is needed to validate our results. Finally, we did not assess the reproducibility of metabolic parameter acquisition on ^{18}F-FDG PET/CT. However, we used gradient-based method for the acquisition of volume-based metabolic parameters and this has been reported as more accurate and reproducible method.[23]

In conclusion, MTV may be associated with ALNM in breast cancer patients, particularly T2 and T3 stages. In T1 breast cancer, SUVmean was associated with ALNM. Further study is needed to applicate our results for axillary management in breast cancer patients.

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