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 (≥1.12; P = .027), higher MTV (≥2.83; P < .001), and higher TLG (>3.96; 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.1-21 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.18 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.9-14 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 18F-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 breast 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. 18F-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 AutoA 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 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...
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.

| 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 ± 2.6 | 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) | .113 |
| Pathologic T stage | | | | .389 |
| T1/T2/T3 | 68/95/10 | 56/65/7 | 12/30/3 | |
| Histologic finding | | | | .658 |
| 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 | | | | .477 |
| 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 | | | | .658 |
| 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 3) | 70 | 54 (43.3) | 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, DC = invasive ductal carcinoma, MTV = metabolic tumor volume, PR = progesterone receptor, SUVmax = maximum standardized uptake value, SUVmean = mean standardized uptake value, TLG = total lesion glycolysis.

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),
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 SUV mean. 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, 11.053; 95% CI, 4.403–27.751; P < .001) and higher TLG (>3.98) (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, 16.275; 95% CI, 1.233–142.908; P = .033) and triple negative subtype (TN vs non-TN) (adjusted OR, 2.096; 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.13–17 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

| Variable | Univariate analysis |
|----------|---------------------|
| 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 vs ≤1) | 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) | 0.736 | 0.359, 1.485 | .385 |
| ER (present vs absent) | 1.389 | 0.605, 3.189 | .438 |
| PR (present vs absent) | 1.012 | 0.402, 2.079 | .975 |
| HER2 positivity (positive vs negative) | 1.653 | 0.825, 4.163 | .135 |
| Triple negative subtype (TN vs non-TN) | 0.402 | 0.132, 1.227 | .109 |

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.
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 ductal carcinoma (adjusted OR: 2.696, 95% CI: 1.079, 60739, \(P = 0.034\)). However, in the subgroup analysis, MTV correlated well with ALNM for breast cancers with T2 and T3 stage (**\(P = 0.005\)), but not for T1 stage (**\(P = 0.741\)). We supposed that in case of small breast cancer <2cm, 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 18F-FDG PET/CT or breast tumor strain ratio on ultrasound elastography as imaging biomarker for ALNM.\(^\text{[10]}\) Higher SUVmax (\(\geq 4.25\)) was independent predictor for ALNM especially in ER-positive/HER2-negative and HER2-positive subtypes but not in triple negative subtype.\(^\text{[11]}\) 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 (**\(P = 0.038\) vs **\(P = 0.027\) 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.\(^\text{[24]}\) 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 (\(\geq 5.36\)).

Because MTV represents the total tumor burden not merely the metabolic activity, MTV has been suggested as a prognostic factor in breast cancer.\(^\text{[10,21]}\) Ulaner et al.\(^\text{[21]}\) examined 253

### Table 4

| Variable                        | T1 stage Adjusted OR (95% CI) | \(P\) | T2 and T3 stage Adjusted OR (95% CI) | \(P\) |
|---------------------------------|-------------------------------|-------|-------------------------------------|-------|
| Lymphovascular invasion         | 16.096 (2.517–102.939)        | .003* | 20.976 (5.431–81.910)               | <.001*|
| SUVmean (\(>1.2\) vs \(<1.2\)) | 13.275 (1.233–142.908)        | .033* | 4.438 (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.

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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. reported that in patients with metastatic triple negative breast cancer, patients with MTV < 5.15 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. 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. 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.

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 whereas others have found a lower prevalence or no significant association. 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. Our result also revealed that triple negative subtype was not associated with ALNM on univariate analysis (P = 0.109).

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 18F-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.

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 apply our results for axillary management in breast cancer patients.

References

[1] Arriagada R, Le MG, Dunant A, et al. Twenty-five years of follow-up in patients with operable breast carcinoma: correlation between clinical-pathologic factors and the risk of death in each 5-year period. Cancer 2006;106:743–50.

[2] Soerjomataram I, Louwman MW, Rivot JG, et al. An overview of prognostic factors for long-term survivors of breast cancer. Breast Cancer Res Treat 2008;107:309–30.

[3] Chung MJ, Lee JH, Kim SH, et al. Simple prediction model of axillary lymph node positivity after analyzing molecular and clinical factors in early breast cancer. Medicine (Baltimore) 2014;93:e3689.

[4] Lee JH, Kim SH, Suh YJ, et al. Predictors of axillary lymph node metastases (ALNM) in a Korean population with T1-2 breast carcinoma: triple negative breast cancer has a high incidence of ALNM irrespective of the tumor size. Cancer Res Treat 2010;42:30–6.

[5] Viale G, Zurrada S, Masorano E, et al. Predicting the status of axillary sentinel lymph nodes in 4351 patients with invasive breast carcinoma treated in a single institution. Cancer 2003;103:492–500.

[6] Colleoni M, Rotmensz N, Maisonneuve P, et al. Prognostic role of the extent of peritumoral vascular invasion in operable breast cancer. Ann Oncol 2007;18:163–420.

[7] Yoshisaka E, Smeets A, Laenen A, et al. Predictors of axillary lymph node metastases in early breast cancer and their applicability in clinical practice. Breast 2013;22:577–81.

[8] Kim JY, Shin JK, Lee SH. The breast tumor strain ratio is a predictive parameter for axillary lymph node metastasis in patients with invasive breast cancer. AJR Am J Roentgenol 2015;205:W630–8.

[9] Kim JY, Lee SH, Kim S, et al. Tumor 18 F-FDG Uptake on preoperative PET/CT may predict axillary lymph node metastasis in ER-positive/HER2-negative and HER2-positive breast cancer subtypes. Eur Radiol 2015;25:1172–81.

[10] Marinelli B, Espinet-Col C, Ulaner GA, et al. Prognostic value of FDG PET/CT-based metabolic tumor volumes in metastatic triple negative breast cancer patients. Am J Nucl Med Mol Imaging 2016;6:120–7.

[11] Kajary K, Tokés T, Dank M, et al. Correlation of the value of 18F-FDG uptake, described by SUVmax, SUVavg, metabolic tumour volume and total lesion glycolysis, to clinicopathological prognostic factors and biological subtypes in breast cancer. Nucl Med Commun 2015;36:28–37.

[12] Champion L, Lerebours F, Alberini JL, et al. 18F-FDG PET/CT to predict response to neoadjuvant chemotherapy and prognosis in inflammatory breast cancer. J Nucl Med 2015;56:1315–21.

[13] Chen S, Ibrahim NK, Yan Y, et al. Risk stratification in patients with advanced-stage breast cancer by pretreatment [(18) F]FDG PET/CT. Cancer 2015;121:3965–74.

[14] Groheux D, Maitdoub M, Sanna A, et al. Early metabolic response to neoadjuvant treatment: FDG PET/CT Criteria according to breast cancer subtype. Radiology 2015;277:358–71.

[15] Hyun SH, Ahn HK, Park YH, et al. Volume-based metabolic tumor response to neoadjuvant chemotherapy is associated with an increased risk of recurrence in breast cancer. Radiology 2015;275:235–44.

[16] Kim J, Yoo SW, Kang SR, et al. Prognostic significance of metabolic tumor volume measured by [(18)F]FDG PET/CT in operable primary breast cancer. Nucl Med Mol Imaging 2012;46:278–85.

[17] Kim TH, Yoon JK, Kang DK, et al. Value of volume-based metabolic parameters for predicting survival in breast cancer patients treated with neoadjuvant chemotherapy. Medicine (Baltimore) 2016;95:e4605.

[18] Lee SM, Bae SK, Kim TH, et al. Value of 18F-FDG PET/CT for early prediction of pathologic response (by residual cancer burden criteria) of locally advanced breast cancer to neoadjuvant chemotherapy. Clin Nucl Med 2014;39:882–6.

[19] Son SH, Lee SW, Jeong SY, et al. Whole-body metabolic tumor volume, as determined by [(18)F]FDG PET/CT, as a prognostic factor of outcome for patients with breast cancer who have distant metastasis. AJR Am J Roentgenol 2015;205:878–85.

[20] Yue Y, Cui X, Bose S, et al. Stratifying triple-negative breast cancer prognosis using 18F-FDG-PET/CT imaging. Breast Cancer Res Treat 2015;153:607–16.

[21] Ulaner GA, Eaton A, Morris PG, et al. Prognostic value of quantitative fluorodeoxyglucose measurements in newly diagnosed metastatic breast cancer. Cancer Med 2013;2:725–33.

[22] Geets X, Lee JA, Bol A, et al. A gradient-based method for segmenting FDG-PET images: methodology and validation. Eur J Nucl Med Mol Imaging 2007;34:1427–38.

[23] Werner-Wasik M, Nelson AD, Choi W, et al. What is the best way to contour lung tumors on PET scans? Multiserver validation of a gradient-based method using a NSCLC digital PET phantom. Int J Radiat Oncol Biol Phys 2012;82:1164–71.

[24] Chang JS, Lee J, Kim HJ, et al. (18)F-FDG/PET may help to identify a subgroup of patients with T1-T2 breast cancer and 1-3 positive lymph nodes.
nodes who are at a high risk of recurrence after mastectomy. Cancer Res Treat 2016;48:508–17.

[25] Dent R, Trudeau M, Pritchard KI, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res 2007;13 (part 1):4429–34.

[26] Tischkowitz M, Brunet JS, Bégin LR, et al. Use of immunohistochemical markers can refine prognosis in triple negative breast cancer. BMC Cancer 2007;7:134.

[27] Rakha EA, El-Sayed ME, Green AR, et al. Prognostic markers in triple-negative breast cancer. Cancer 2007;109:25–32.

[28] Fulford LG, Reis-Filho JS, Ryder K, et al. Basal-like grade III invasive ductal carcinoma of the breast: patterns of metastasis and long-term survival. Breast Cancer Res 2007;9:R4.

[29] Tsuda H, Takarabe T, Hasegawa F, et al. Large, central acellular zones indicating myoepithelial tumor differentiation in high-grade invasive ductal carcinomas as markers of predisposition to lung and brain metastases. Am J Surg Pathol 2000;24:197–202.

[30] Rodríguez-Pinilla SM, Sarrió D, Honrado E, et al. Prognostic significance of basal-like phenotype and fascin expression in node-negative invasive breast carcinomas. Clin Cancer Res 2006;12:1533–9.