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# CONSORT-Independent prognostic value of asphericity of pretherapeutic F-18 FDG uptake by primary tumors in patients with breast cancer

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**Abstract**

**Background:** The aim of this study was to evaluate the prognostic implication of asphericity (ASP); spatial irregularity; of pretherapeutic $^{18}$F 2-deoxy-2-fluoro-D-glucose ($^{18}$F FDG) tumor uptake in patients with invasive ductal carcinoma (IDC) of the breast.

**Methods:** One hundred thirty-one female IDC patients (mean age = 48.1 ± 10.4 years), with pathological tumor size greater than 2 cm were retrospectively evaluated using $^{18}$F FDG positron emission tomography/computed tomography (PET/CT). ASP of $^{18}$F FDG distribution was calculated on the basis of the deviation of the tumor shape from spherical symmetry. Progression-free survival (PFS) was predicted on the basis of the univariate and multivariate analyses of the measured clinicopathologic factors and metabolic PET parameters [maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG)].

**Results:** The PFS rate among the 131 patients was 90.1%. The mean follow-up time was 50 months for the entire study cohort and 26 months for the patients with recurrent disease. It is evident from the univariate analysis that N stage, hormonal receptor (Estrogen, ER/Progesterone, PR) status, MTV (≤4.2 mL), and ASP (≤15.1%) affected the PFS. Hazard ratios (HRs) estimated from the multivariate Cox regression analysis show that N stage (HR = 17.6), ASP (HR = 11.9), and hormonal receptor status (HR = 6.9) were independent prognostic factors in predicting PFS. In the subgroup of patients with lymph node metastasis, ASP (HR = 10.9) and hormonal receptor status (HR = 9.1) were independent prognostic factors for PFS.

**Conclusion:** ASP of $^{18}$F FDG uptake is an independent predictor of outcome in IDC patients, and can be used for prognostic stratification.

**Abbreviations:** $^{18}$F FDG = $^{18}$F 2-deoxy-2-fluoro-D-glucose, ASP = asphericity, CI = confidence interval, CT = computed tomography, ER = estrogen receptor, FISH = fluorescence in situ hybridization, HER2 = human epidermal growth factor receptor 2, HR = hazard ratio, IDC = invasive ductal breast cancer, IHC = immunohistochemical, LN = lymph node, MRI = magnetic resonance imaging, MTV = metabolic tumor volume, N- = negative-LN metastasis, PET = positron emission tomography, PET/CT = positron emission tomography/computed tomography, PFS = progression-free survival, positive-LN metastasis, N+, PR = progesterone receptor, ROC = receiver operating characteristic, STE = standard test equipment, SUVmax = maximum standardized uptake value, TLG = total lesion glycolysis, VOI = volumes of interest.

**Keywords:** $^{18}$F FDG-PET/CT, asphericity, breast cancer, Heterogeneity, invasive ductal carcinoma, prognosis

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*The study protocol had been approved by the Ethics Committee of the Kyungpook National University Hospital (KNUH 2015–05–013). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.*

*No informed consent was needed because of the retrospective design of our study.*

*The authors declare that they have no conflict of interest.*

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## 1. Introduction

In 2013, breast cancer was the cancer with the highest incidence for women in 161 countries and the most common cause for cancer-related deaths in women in 98 countries.[1] Although it is curable when detected early, about one-third of women with breast cancer eventually die of the disease. Breast cancer is a remarkably heterogeneous disease. Therefore, precise prediction of prognosis and selection of optimal treatment are important.[2] Tumor burden, represented by tumor size and the number of lymph nodes (LNs) involved, is the most important prognostic factor for breast cancer recurrence, as advanced-stage tumors are more likely to have distant metastases.[3–5]

$^{18}$F 2-deoxy-2-fluoro-D-glucose ($^{18}$F FDG) positron emission tomography (PET) is a useful tool in predicting tumor response or resistance to a specific treatment. $^{18}$F FDG-PET images reflect the in vivo tumor biology. In addition to the clinical and structural information, PET images provide information about the metabolic characteristics of the tumor.[6–8] The prognostic value of $^{18}$F FDG uptake by the primary tumor in patients with invasive ductal breast cancer (IDC) has been investigated in previous studies.[9–14] It is evident from these studies that there exists a relationship between the PET scan derived metabolic parameters, such as the maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV) and total lesion glycolysis (TLG) of primary tumors, and known prognostic parameters of breast cancer. These metabolic parameters can therefore serve as good surrogate markers for the prediction of disease progression in patients with IDC.[9–14]

There is increasing recognition that the heterogeneity of pretherapeutic $^{18}$F FDG uptake in the primary tumor can provide predictive information in several solid tumors. Therefore, quantifying the heterogeneity of $^{18}$F FDG uptake appears to be a promising factor in predicting therapeutic outcome, as it might reflect the biological variability causing this intratumoral heterogeneity.[15,16] Results from previous pretherapeutic $^{18}$F FDG-PET studies, characterizing heterogeneity of uptake in different carcinomas based on textural features in the images and predicting treatment outcome based on this heterogeneity, have been encouraging.[17–19]

The prognostic value of asphericity (ASP), a parameter quantifying the spatial irregularity of $^{18}$F-FDG uptake in tumors, in predicting tumor progression and treatment outcomes in patients with primary head and neck cancer[20,21] and nonsmall cell lung cancer[22] has been previously reported.

The aim of this study was to evaluate the independent prognostic value of ASP, calculated from pretherapeutic $^{18}$F-FDG uptake in tumors, in predicting progression-free survival (PFS) in patients with IDC and to compare it with the PFS estimated from conventional quantitative PET parameters, such as SUVmax, MTV, and TLG as well as relevant clinicopathologic factors.

## 2. Materials and methods

### 2.1. Patients

From a pool of 661 patients, who underwent $^{18}$F FDG PET/computed tomography (PET/CT) scanning between January 2008 and December 2010 to determine the clinical stage of primary IDC before initial treatment, 131 women (mean age, $48.1 \pm 10.4$ years; range, 39–79 years) were included in this study. The inclusion criteria were as follows: primary tumor size $\geq 2$ cm[23,24]; available medical information and pathologic reports; no excisional biopsy before the PET/CT scanning; and no distant metastasis at the time of initial diagnosis.

Depending on the tumor size, location, multicentricity, and patient preference, all patients were surgically treated with either breast conserving surgery or modified radical mastectomy with sentinel LN biopsy or axillary LN dissection, following the pretherapeutic PET/CT scanning. Patients received a preoperative or postoperative taxane-based systemic chemotherapy regimen, comprising doxorubicin (Adriamycin; Pharmacia) and cyclophosphamide followed by docetaxel. Radiotherapy was given after surgery, and hormonal therapy was given to patients with hormonal receptor positive breast cancer. Patients with human epidermal growth factor receptor 2 (HER2) positive breast cancers were postoperatively treated with trastuzumab (Herceptin; Genentech) for 1 year. The need for adjuvant target therapy was determined by hormone receptor status and menopausal status. Patients were monitored every 3 months for the first 2 years and every 6 months thereafter for 5 years. During this follow-up period, breast sonography, magnetic resonance imaging (MRI), CT, bone scintigraphy, and $^{18}$F FDG-PET/CT were used for diagnosing disease recurrence, metastasis, and cancer progression. All suggestive lesions were confirmed histologically or the patients underwent a follow-up within 6 months.

Tumors were classified and staged according to the World Health Organization classification and the TNM staging system. In patients receiving neo-adjuvant chemotherapy, pathologic T and N staging may be influenced by systemic therapy before surgical procedures; thus, for these patients, we used the pretreatment clinical staging system. The study protocol had been approved by the Ethics Committee of the Kyungpook National University Hospital (KNUH 2015–05–013). No informed consent was needed because of the retrospective design of the study.

### 2.2. $^{18}$F FDG-PET/CT imaging

After fasting for at least 6 hours, patient blood glucose levels were checked before the administration of $^{18}$F FDG. Patients with elevated blood glucose levels had their examinations rescheduled. None of the patients had blood glucose levels exceeding 150 mg/dL at the time of the scan. $^{18}$F FDG was injected intravenously (4.8 MBq/kg of body weight) and the scans were performed 1 hour after the injection. $^{18}$F FDG-PET/CT scans were performed using a Reveal RT-HiREZ 6-slice CT apparatus (Reveal RT-HiREZ; CTI Molecular Imaging, Knoxville, TN) and a 16-slice CT Discovery standard test equipment (STE) apparatus (Discovery STE; GE Healthcare, Milwaukee, WI). For attenuation correction, a low-dose CT scan without contrast enhancement with the patient supine and breathing quietly, from the base of skull to the upper thigh was obtained before the PET scan. PET scans with a maximum spatial resolution of 6.5 mm (Reveal PET/CT) and 5.5 mm (Discovery PET/CT) were also obtained from the base of skull to the upper thigh for a period of 3 minutes per bed position. PET images obtained using the Reveal PET/CT and Discovery PET/CT scanners were reconstructed using an ordered subsets expectation maximization algorithm (4 iterations, 8 subsets). Image reconstruction was carried out using a $128 \times 128$ matrix, a Gaussian filter of 5.0 mm, and a slice thickness of either 3.0 mm (Reveal PET/CT) or 3.27 mm (Discovery PET/CT).

### 2.3. Image analysis

SUVmax based on body weight and MTV were determined by the attenuation-corrected PET data using the PMOD 3.5 software

(PMOD Technologies Ltd, Zurich, Switzerland). Several segmentation methods have been proposed for the analysis of PET images in breast cancer patients, but no widely accepted guidelines exist. Of the various methods described for determining metabolic volumes, a fixed threshold of SUV 2.5, as previously reported, was used.[12] An experienced nuclear medicine physician and a resident of nuclear medicine (blinded to the clinical data but not to tumor location) analyzed all PET/CT images retrospectively. The borders of volumes of interest (VOI) were adjusted manually to exclude adjacent physiological FDG-avid structures on PET/CT images. The VOIs were verified and validated by an independent senior nuclear medicine physician. The tumor boundaries were then automatically contoured based on the fixed threshold of SUV2.5.

The ASP of VOI was computed together with SUVmax, SUVmean, MTV, and TLG.

***2.3.1. Asphericity.*** The ASP of the primary tumor was defined as

$$ASP(\%) = 100*(\sqrt[3]{H}-1) \text{ with } H = \frac{1s^3}{36\pi V^2}$$

where S and V are the surface and volume of the MTV, respectively.

The rationale for this definition is described in detail in previous reports.[20–22] ASP is independent of the lesion size. It is zero for spherical lesions and is non-zero for all other lesion types. An ASP value of 0.5 or 50%, for example, means that the surface of the lesion is 50% larger than the surface of a sphere with the same volume. Thus, ASP is a quantitative measure of irregularity in shape indicating metabolic heterogeneity in the tumor caused by various biologic factors such as low metabolism in the necrotic regions of the tumor or metabolically active invasive regions in the tumor. Two representative orthogonal slices are shown in Fig. 1.

### 2.4. Pathologic examination

Immunohistochemical (IHC) staining was performed on formalin-fixed, paraffin-embedded tissue slices excised from representative breast tumors. Estrogen receptor (ER), progesterone receptor (PR), and HER2 expression was assessed by IHC analysis using commercial monoclonal antibodies for ER (1:200 dilution; Neomarker), PR (1:4500 dilution; Neomarker), and HER2 (1:300 dilution; DakoCytomation); the iView DAB detection kit (Ventana Medical Systems) was used for detection. Samples were scored positive for hormone receptors when the expression was ≥10%. The HER2 expression results by IHC analysis were scored as negative, 1+, 2+, or 3+ following the manufacturer's recommendations. Tissue samples with an HER2 IHC staining score of more than 2 were also tested by *HER2* gene amplification using the fluorescence in situ hybridization (FISH) method. Tissue samples with an IHC staining score of 3+ were defined as HER2 positive, or a score of 2+ in the case of FISH-based IHC staging. The results were recorded following the guidelines of the American Society of Clinical Oncology and the College of American Pathologists.[25]

### 2.5. Statistical analysis

Survival time was derived from the date of $^{18}$F FDG-PET/CT scan to the date of recurrence or last follow-up. The parameters were evaluated in relation to PFS using receiver operating characteristic (ROC) curve analysis. The optimal cut-off values were used to define the 2 groups. Cox regression analysis with forward selection was used to develop the univariate and multivariate models analyzing the relation between the independent variables and PFS. Independent variables analyzed included age, tumor size, LN status, neoadjuvant chemotherapy, histological grade, ER and PRs, HER2 status, SUVmax, MTV, TLG, and ASP. PFS curve was generated using Kaplan–Meier methods and survival difference between groups was assessed by the log-rank test. For specifically evaluating the prognostic value of ASP, we analyzed PFS in subgroups comprising patients with LN metastasis. Medcalc version 15.4 (Medcalc Software, Ostend, Belgium) was used for all analyses. All *P* values were 2-sided and values of $<.05$ were considered statistically significant.

## 3. Results

### 3.1. Patients' characteristics

The characteristics of the study participants are listed in Table 1. Among the 131 patients, 12 (9.2%) received neoadjuvant chemotherapy before surgical treatment, 112 (85.5%) received adjuvant chemotherapy, and 56 (42.7%) received radiation

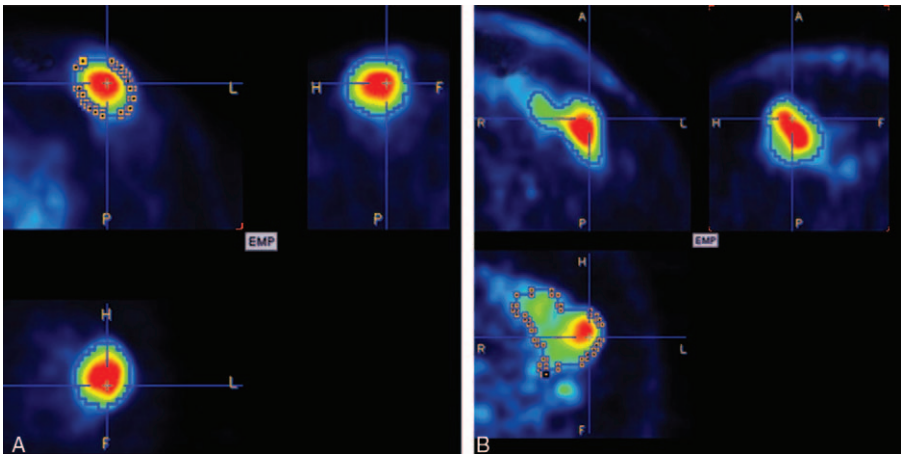


**Figure 1.** Representative orthogonal slices. The difference of the metabolic tumor volume (MTV) between A (10.9 mL) and B (20.1 mL) is twice. Whereas B (71%) has almost 9-fold asphericity (ASP) values compared with A (8%). The tumor delineation is marked with a blue line.

**Table 1**

**Patient characteristics.**

| Characteristics | No. of patients (%) | Median (range) |
|---|---|---|
| Age | | 46 (29–79) |
| Follow-up period, mo | | |
| Disease-free | 118 (90.1) | 59 (4–60) |
| Recurrence | 13 (9.9) | 25 (1–58) |
| Neoadjuvant chemotherapy | 12 (9.2) | |
| Adjuvant chemotherapy | 112 (85.5) | |
| Radiation therapy | 56 (42.7) | |
| Histologic grade | | |
| I | 18 (13.7) | |
| II | 56 (42.7) | |
| III | 57 (43.5) | |
| PET parameters | | |
| SUVmax | | 6.8 (2.6–18.9) |
| MTV, mL | | 5.1 (0.1–63.4) |
| TLG | | 19.9 (0.1–382.5) |
| ASP (%) | | 17.6 (3.6–263.4) |

ASP = asphericity, MTV = metabolic tumor volume, PET = positron emission tomography, SUVmax = maximum standardized uptake value, TLG = total lesion glycolysis.

therapy. Sixty-four patients (48.9%) had negative-LN metastasis (N-) and 67 patients (51.1%) had positive-LN metastasis (N+). In N+ patients, N stage was categorized on the basis of the staging system of the American Joint Committee on cancer[26] and 39 patients (58.2%) were assigned to N stage 1, 21 (31.3%) to N stage 2, and 7 (10.4%) to N stage 3. There were 5 patients (3.8%) in stage I, 98 patients (74.8%) in stage II, and 28 (21.4%) with stage III IDC.

### 3.2. Patient outcome

Patients had a 5-year PFS rate of 90.1% (n = 118) with a mean follow-up time of 59 months. Recurrence or progression occurred in 13 patients after a mean time period of 25 months, as regional recurrence (n = 1), distant metastatic disease (n = 10), and a combination of both (n = 2). Five-year PFS rate in N+ patients was 82.1% (55 of 67) with a mean follow-up time of 48 months.

### 3.3. Relationship between ASP and clinicopathologic parameters

Table 2 summarizes ASP differences according to the clinicopathologic parameters. The mean ASP was 31.5% ± 37.5 (range, 3.6–263.4) and was significantly different among the N stage groups ($P = .029$). The mean ASP increases with an increase in the N stage. However, there was no significant difference in ASP according to T stage, ER, PR, and HER2 status.

### 3.4. PFS analysis

In all patients, univariate Cox regression analysis revealed the presence of metastatic LNs, hormonal receptor status, MTV (≤4.2 vs >4.2 mL), TLG (≤15.1 vs >15.1), and ASP (≤15.1% vs >15.1%) as significant predictors of decreased PFS, whereas age, T stage (T1 vs T2/3) as well as HER2 status showed no significant effect (Table 3). From the multivariate Cox regression analysis, it was seen that the presence of metastatic LNs [hazard ratio (HR) = 17.6; 95% confidence interval (95% CI) = 2.24–138.40; $P = .0067$], negative hormonal receptor (HR = 6.9; 95% CI = 2.18–21.82; $P = .0011$), and high ASP (HR = 11.9; 95% CI = 1.52–92.24; $P = .0188$) were significant predictors of PFS.

**Table 2**

**Comparisons of asphericity according to clinicopathologic parameters.**

| Characteristic | No. of patients (%) | ASP (%) (mean ± SD) | *P* |
|---|---|---|---|
| T stage* | | | .864 |
| T1 | 16 | 26.53 ± 29.84 | |
| T2 | 112 | 32.03 ± 38.80 | |
| T3 | 3 | 36.25 ± 18.75 | |
| T4 | 0 | — | |
| ER | | | .554 |
| Positive | 82 | 29.00 ± 27.25 | |
| Negative | 49 | 33.16 ± 42.79 | |
| PR | | | .668 |
| Positive | 70 | 30.04 ± 28.92 | |
| Negative | 61 | 32.98 ± 44.27 | |
| HER2 | | | .826 |
| Positive† | 36 | 31.06 ± 38.38 | |
| Negative | 95 | 32.72 ± 35.58 | |
| N stage* | | | **.029** |
| N0 | 64 | 25.79 ± 29.57 | |
| N1 | 39 | 31.68 ± 37.69 | |
| N2 | 21 | 35.39 ± 24.55 | |
| N3 | 7 | 72.88 ± 94.06 | |
| Stage* | | | .146 |
| I | 5 | 19.11 ± 9.71 | |
| II | 98 | 28.34 ± 33.31 | |
| III | 28 | 43.72 ± 49.17 | |

ASP = asphericity, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, PR = progesterone receptor.

* Staging system of American Joint Committee on Cancer (7th edition).

† Immunohistochemical 3+ or, in case of immunohistochemical 2+, positive on fluorescence in situ hybridization for *HER2* gene amplification.

The status of LN metastasis was the most significant predictor and the ASP was significantly different among the N stage groups. Subgroup analysis for PFS in patients with LN metastasis was performed. Among these 67 patients, 55 (82.1%) were disease-free and 12 (17.9%) had disease recurrence. Univariate analysis by Cox regression analysis revealed that hormonal receptor status, SUVmax, MTV, TLG, and ASP were significant predictors. Among these 5 variables, ASP (HR = 10.9; 95% CI = 1.39–86.41; $P = .0240$) and hormonal receptor status (HR = 9.1; 95% CI = 2.65–30.95; $P = .0005$) were found to be predictors of PFS by multivariate analysis (Table 4). Kaplan–Meier curves with respect to PFS for SUVmax, MTV, TLG, and ASP for all the patients and specifically for N+ patients are given in Figs. 2 and 3.

### 3.5. Discussion and conclusion

For patients with breast cancer, pathologic determination of tumor size, axillary LN involvement, hormonal receptor status, and HER2 status have been used as prognostic factors. Traditionally, it has long been recognized that breast cancer patients with histologically confirmed LN involvement have a significantly poorer prognosis than those without nodal metastases. This is because LN involvement is closely associated with the development of distant metastases.[3,4,14,27] Our results also show that the presence of metastatic LNs was an independent prognostic factor (HR = 17.61, $P = .0067$). However, an accurate LN status can be obtained only after surgery and cannot completely explain the extent of variability in the clinical course, as breast cancer is a remarkably heterogeneous disease.

**Table 3**

**Factors associated with progression-free survival.**

| Risk factor for recurrence | Total no. of patients | Patients with disease recurrence | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|---|
| | | | *P* | HR | 95% CI | *P* | HR | 95% CI |
| Age, y | | | | | | | | |
| <45 | 61 | 5 | — | 1.00 | | | | |
| ≥45 | 70 | 8 | .5300 | 1.43 | 0.47–4.35 | | | |
| T stage | | | | | | | | |
| T1 | 16 | 3 | — | 1.00 | | | | |
| T2, T3 | 115 | 10 | .1847 | 0.4172 | 0.12–1.51 | | | |
| Lymph node metastasis | | | | | | | | |
| N0 | 64 | 1 | — | 1.00 | | — | 1.00 | |
| N+ | 67 | 12 | **.0153** | 12.51 | 1.64–95.26 | **.0067** | 17.61 | 2.24–138.40 |
| ER/PR hormonal receptor | | | | | | | | |
| Positive | 87 | 5 | — | 1.00 | | — | 1.00 | |
| Negative | 44 | 8 | **.0224** | 3.6 | 1.18–10.95 | **.0011** | 6.90 | 2.18–21.82 |
| HER2 | | | | | | | | |
| Negative | 95 | 9 | — | 1.00 | | | | |
| Positive | 36 | 4 | .8009 | 1.16 | 0.36–3.76 | | | |
| SUVmax | | | | | | | | |
| ≤5.5 | 47 | 2 | — | 1.00 | | | | |
| >5.5 | 84 | 11 | .1065 | 3.46 | 0.77–15.50 | | | |
| MTV | | | | | | | | |
| ≤4.2 mL | 56 | 2 | — | 1.00 | | | | |
| >4.2 mL | 73 | 11 | **.0469** | 4.61 | 1.03–20.65 | | | |
| TLG | | | | | | | | |
| ≤15.1 | 55 | 2 | — | 1.00 | | | | |
| >15.1 | 76 | 11 | .0512 | 4.48 | 1.00–20.08 | | | |
| ASP | | | | | | | | |
| ≤15.1% | 60 | 1 | — | 1.00 | | — | 1.00 | |
| >15.1% | 71 | 12 | **.0220** | 10.85 | 1.42–82.63 | **.0188** | 11.85 | 1.52–92.24 |

ASP = asphericity, CI = confidence interval, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, HR = hazard ratio, MTV = metabolic tumor volume, PR = progesterone receptor, SUVmax = maximum standardized uptake value, TLG = total lesion glycolysis.

**Table 4**

**Factors associated with progression-free survival in patients with lymph node metastasis.**

| Risk factor for recurrence | Total no. of patients | Patients with disease recurrence | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|---|
| | | | *P* | HR | 95% CI | *P* | HR | 95% CI |
| Age, y | | | | | | | | |
| <45 | 28 | 5 | — | 1.00 | | | | |
| ≥45 | 39 | 7 | .9653 | 1.03 | 0.33–3.21 | | | |
| T stage | | | | | | | | |
| T1 | 11 | 3 | — | 1.00 | | | | |
| T2, T3 | 56 | 9 | .3702 | 0.55 | 0.15–2.02 | | | |
| ER/PR hormonal receptor | | | | | | | | |
| Positive | 48 | 4 | — | 1.00 | | — | 1.00 | |
| Negative | 19 | 8 | **.0021** | 6.63 | 2.00–21.97 | **.0005** | 9.06 | 2.65–30.95 |
| HER2 | | | | | | | | |
| Negative | 45 | 8 | — | 1.00 | | | | |
| Positive | 22 | 4 | .9025 | 1.08 | 0.33–3.57 | | | |
| SUVmax | | | | | | | | |
| ≤5.5 | 25 | 1 | — | 1.00 | | | | |
| >5.5 | 42 | 11 | .0494 | 7.80 | 1.02–59.87 | | | |
| MTV | | | | | | | | |
| ≤4.2 mL | 30 | 1 | — | 1.00 | | | | |
| >4.2 mL | 37 | 11 | **.0253** | 10.38 | 1.35–79.75 | | | |
| TLG | | | | | | | | |
| ≤15.1 | 29 | 1 | — | 1.00 | | | | |
| >15.1 | 38 | 11 | **.0293** | 9.77 | 1.27–75.17 | | | |
| ASP | | | | | | | | |
| ≤15.1% | 24 | 1 | — | 1.00 | | — | 1.00 | |
| >15.1% | 43 | 11 | **.0047** | 10.52 | 3.54–31.28 | **.0240** | 10.94 | 1.39–86.41 |

ASP = asphericity, CI = confidence interval, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, HR = hazard ratio, MTV = metabolic tumor volume, PR = progesterone receptor, SUVmax = maximum standardized uptake value, TLG = total lesion glycolysis.

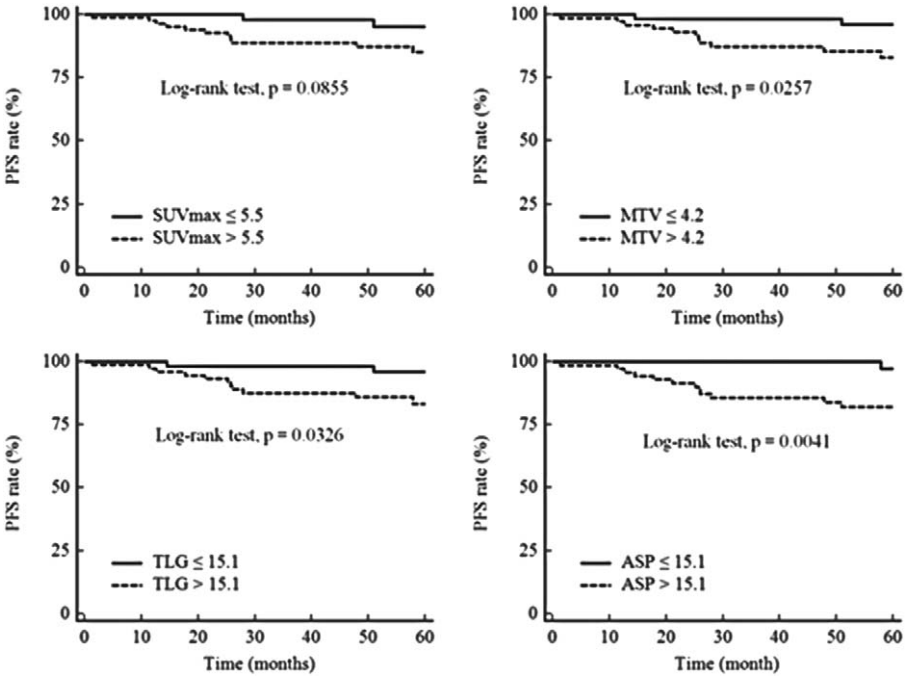


**Figure 2.** Kaplan–Meier curves with respect to progression-free survival for all patients. Kaplan–Meier curves for the quantitative PET parameters, maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), total lesion glycolysis (TLG), and asphericity (ASP) with respect to progression-free survival (PFS) for all patients (n = 131). Cut-off values and *P* values are shown on each panel.

Preoperative $^{18}$F FDG-PET/CT is a noninvasive diagnostic modality that can indicate the degree of glucose metabolism in tumors, which represents the aggressiveness of the malignant lesion.[7,28] There have been several reports suggesting that high SUV is associated with poor prognosis, whereas others did not find a similar prognostic power of SUVs in breast cancer patients.[10,11,14] Although several studies indicate that tumor burden, as measured by MTV and TLG, was significantly associated with poor prognosis, it remains controversial.[9,12,13] In the current study, none of these conventional metabolic PET

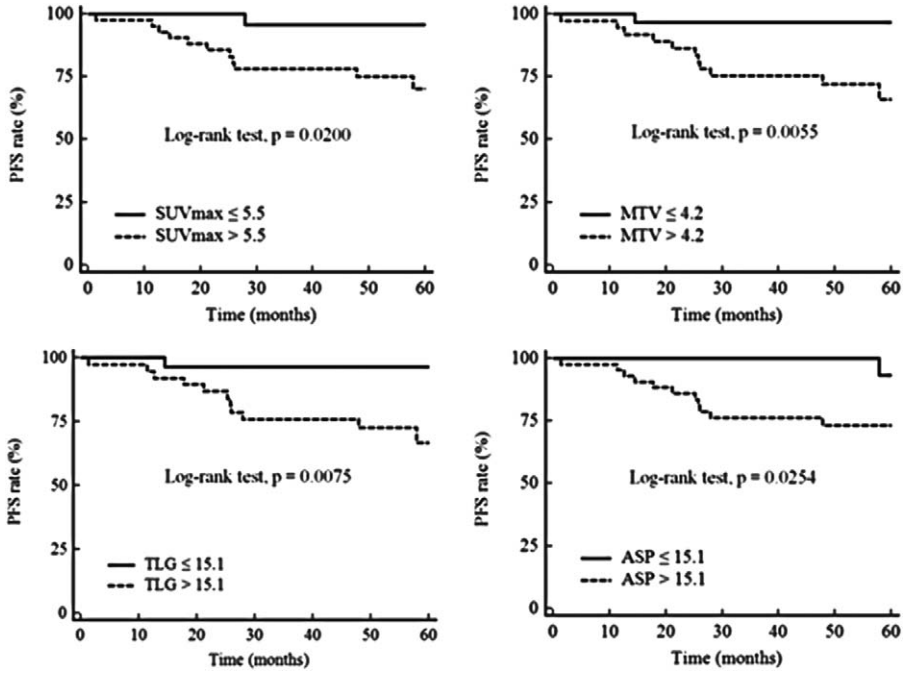


**Figure 3.** Kaplan–Meier curves with respect to progression-free survival for patients with lymph node metastasis. Kaplan–Meier curves for the quantitative PET parameters, maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), total lesion glycolysis (TLG), and asphericity (ASP) with respect to progression-free survival (PFS) for patients with lymph node metastasis (n = 67). Cut-off values and *P* values are shown on each panel.

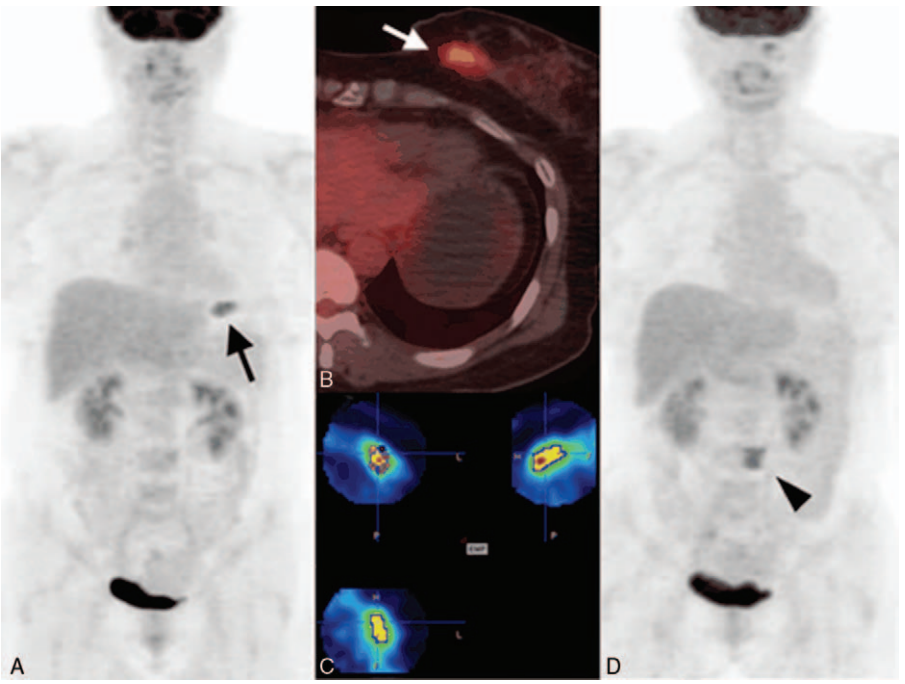


**Figure 4.** $^{18}$F FDG-PET/CT images of the patient had progression in N0 group. The patient was a 52-year-old woman with invasive ductal carcinoma in the left breast. Maximal intensity projection image of $^{18}$F FDG-PET/CT shows focal $^{18}$F FDG uptake (black arrow) in the inner portion of the left breast (A). Axial fusion image shows hypermetabolic lesion (white arrow) with maximum standardized uptake value (SUVmax) = 4.5, metabolic tumor volume (MTV) = 2.9 mL, and total lesion glycolysis (TLG) = 12.1 (B). PMOD image shows an ovoid mass with asphericity (ASP) = 34.9% (C). The patient underwent surgery and the tumor was classified as stage 2 (T2N0M0), ER/PR+, and HER2-. However, 51 months after the surgery, bone metastasis in lumbar spine (arrow head) was detected using a whole-body $^{18}$F FDG-PET/CT scan (D).

parameters, including SUVmax, MTV, and TLG, were independent prognostic factors for PFS, while the ASP was an independent, significant prognostic factor (HR = 11.85; $P = .0188$). The probability of 5-year PFS decreased from 98.3% in patients with low ASP ($\leq$15.1%) to 83.1% in the patients with high ASP (>15.1%). Furthermore, ASP was the most important prognostic factor for PFS in patients with LN metastasis (HR = 10.94; $P = .0240$). Although we cannot evaluate the prognostic power of ASP in patients without LN metastasis, because only 1 patient showed recurrence, this patient had a high ASP (Fig. 4.) The results from the current study demonstrate that the spatial heterogeneity of signal intensity in the PET images, resulting from heterogeneous $^{18}$F FDG uptake, is associated with tumor recurrence. Previous studies revealed that relevant improvement in prognosis can be achieved by the ASP, a novel parameter for quantitatively characterizing the spatial heterogeneity in $^{18}$F FDG uptake by the primary tumor.[20–22] Apostolova et al[20] reasoned that the observed ASP results from heterogeneous FDG uptake by the tumor, which in turn results from the prominent intratumoral spatial variation in cellularity, angiogenesis, extravascular and extracellular matrices, and necrosis in aggressive and heterogeneous tumors. ASP were correlated with Ki-67 index and EGFR expression and showed a tendency for a significant association with the extent of VEGF expression in lung cancer patients.[29] A high Ki-67 index has been reported to reflect the degree of proliferation of tumors and to predict a poor survival. Activation of EGFR inhibits tumor cell apoptosis and induces angiogenesis. And VEGF expression suggests that angiogenesis of tumors might contribute to increased shape irregularity.[29] It has been shown that high tumor heterogeneity with respect to various biological parameters is known to be associated with aggressive tumor behavior, response to therapy, and survival in a number of cancer types. $^{18}$F FDG-PET based measurement of heterogeneity has been found to be superior to SUVs for various indications.[10,15] In a recent study, Son et al[16] quantified intratumoral heterogeneity of FDG uptake by defining the heterogeneity factor as the slope of a straight line obtained from a linear regression of a plot of the MTV as a function of the threshold (% SUVmax) for delineation of the tumor. Low heterogeneity factor was associated with longer PFS in patients with breast cancer.

In the current study, we used a fixed threshold of SUV 2.5 for delineation of the tumor. Several segmentation methods have been proposed for the analysis of PET images in breast cancer patients, including a minimum SUV threshold, a fixed percentage threshold of the local SUVmax, and adaptive threshold methods, but no widely accepted guidelines exist.[19,22] Not only MTV but also ASP may range widely even in the same tumor, according to the method used. The adaptive threshold method is more tedious and requires preliminary calibration of the machine. However, commercial tools with a threshold method allows for automated segmentation, limiting inter-observer variability and can enable more rapid and easier measurement of volumetric parameters. The fixed 40% or 50% of local maximum intensity were used as the threshold intensity values in previous studies.[10,16,30] Using the fixed percentage threshold, VOIs were usually contoured by internal portion of tumor diminishing protruding portions. Thus, these thresholds made ASP to be underestimated. For evaluating ASP, it is very important to contain the entire tumor, especially protruding portion. In addition, previous studies reported that ER-positive tumors are usually characterized by rather low SUVs compared with other breast cancer phenotypes.[9,31] Thus, using

fixed percentage threshold of the SUVmax may result in overestimation in ER-positive tumors or underestimation in ER-negative tumor. As a result, ASP using fixed percentage threshold did not significantly predict PFS. On the contrary, the minimum SUV 2.0 or 2.5 threshold were also used in many studies.[12,13,32] However, ASP using the fixed SUV 2.0 could not reflect the correct tumor volume. Because breast tissue might show moderate uptake of FDG, normal tissue was contained in VOI.[33] It leads to overestimated MTV and underestimated ASP. Whereas a fixed threshold of SUV 2.5 can contain all malignant lesions and reflect the tumor burden more accurately.[34,35] A fixed threshold of SUV 2.5 has been shown to be a reliable correlation in clinical studies.[12,13] However, as a consensus has yet to be reached, there needs to be further discussion of the most appropriate segmentation method for validation.

Previous studies indicate that HER2 overexpression is strongly associated with increased disease recurrence and a poor prognosis.[36] However, the results of our study did not show a significantly decreased PFS rate in patients who were HER2-positive. The lack of prognostic value for HER2 could be linked to trastuzumab treatment, which was postoperatively administered for 1 year to patients with HER2-positive breast cancer. In addition, the small number of enrolled patients and the relatively short-term follow-up periods can affect the prognostic value for HER2.

Our study has several limitations. First, it had a retrospective design, which may have predisposed to selection bias and the general applicability of our results may therefore be limited. To mitigate this problem, however, we used obviously defined inclusion and exclusion criteria and included all consecutive patients. The exclusion of patients with a primary tumor size less than 2 cm, to overcome the limited spatial resolution of PET, and the resulting inability to characterize tracer distribution for small lesions may limit the generalizability of our results and prevent the risk stratification from being applicable to patients with small primary tumors. We observed that T stage is not a statistically significant prognostic factor. This could be caused by this exclusion and then our sample size of patients with T1 stage does not provide sufficient statistical power to detect such an effect. We are also limited by the use of 2 different imaging systems for data acquisition. This might lead to additional variability in the SUV measures, which possibly resulted in the underestimation of their prognostic power. However, the impact of the 2 different systems on MTV and ASP is expected to be minimal, as the Gaussian filter of 5.0 mm made the spatial resolution be essentially the same for both. Nevertheless, the same cut-off value of ASP, when used at different institutions and for different imaging systems, worked significantly for risk stratification in previous studies.[21] Therefore, ASP appears to provide a significant independent value for the prediction of outcome in breast cancer and is most likely unaffected by this limitation. Finally, we could not perform survival analysis and determine prognostic significance after relapse because of the relatively short follow-up periods. Thus, further prospective multi-institutional studies are required for the acceptance of ASP as a decisive prognostic factor for disease recurrence in IDC patients. Nevertheless, this report is noteworthy because it is the first study to show the prognostic value of ASP of primary tumor in patients with IDC.

In conclusion, the present study shows that ASP calculated from $^{18}$F FDG-PET/CT images, acquired before initial treatment, could be an independent prognostic factor for disease recurrence in IDC patients. Therefore, ASP can be useful in the identifying patients with a high-risk for recurrence and in deciding whether IDC patients with a high ASP require either a more aggressive local or systemic therapy or a careful recurrence work up.

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