Dual time point $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography fusion imaging ($^{18}$F-FDG PET/CT) in primary breast cancer

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**Abstract**

**Background:** To evaluate the clinicopathological and prognostic significance of the percentage change between maximum standardized uptake value (SUV$_{max}$) at 60 min (SUV$_{max1}$) and SUV$_{max}$ at 120 min (SUV$_{max2}$) ($\Delta$SUV$_{max%}$) using dual time point $^{18}$F-fluorodeoxyglucose emission tomography/computed tomography ($^{18}$F-FDG PET/CT) in breast cancer.

**Methods:** Four hundred and sixty-four patients with primary breast cancer underwent $^{18}$F-FDG PET/CT for preoperative staging. $\Delta$SUV$_{max%}$ was defined as $(SUV_{max2} - SUV_{max1}) / SUV_{max1} \times 100$. We explored the optimal cutoff value of SUV$_{max}$ parameters (SUV$_{max1}$ and $\Delta$SUV$_{max%}$) referring to the event of relapse by using receiver operator characteristic curves. The clinicopathological and prognostic significances of the SUV$_{max1}$ and $\Delta$SUV$_{max%}$ were analyzed by Cox's univariate and multivariate analyses.

**Results:** The optimal cutoff values of SUV$_{max1}$ and $\Delta$SUV$_{max%}$ were 3.4 and 12.5, respectively. Relapse-free survival (RFS) curves were significantly different between high and low SUV$_{max1}$ groups ($P = 0.0003$) and also between high and low $\Delta$SUV$_{max%}$ groups ($P = 0.0151$). In Cox multivariate analysis for RFS, SUV$_{max1}$ was an independent prognostic factor ($P = 0.0267$) but $\Delta$SUV$_{max%}$ was not ($P = 0.152$). There was a weak correlation between SUV$_{max1}$ and $\Delta$SUV$_{max%}$ ($P < 0.0001$, $R^2 = 0.166$). On combining SUV$_{max1}$ and $\Delta$SUV$_{max%}$, the subgroups of high SUV$_{max1}$ and high $\Delta$SUV$_{max%}$ showed significantly worse prognosis than the other groups in terms of RFS ($P = 0.0002$).

**Conclusion:** Dual time point $^{18}$F-FDG PET/CT evaluation can be a useful method for predicting relapse in patients with breast cancer. The combination of SUV$_{max1}$ and $\Delta$SUV$_{max%}$ was able to identify subgroups with worse prognosis more accurately than SUV$_{max1}$ alone.

**Keywords:** Dual time point, $\Delta$SUV$_{max%}$, Primary breast cancer

**Background**

Breast cancer is the most frequent malignant disease and the fifth leading cause of cancer death in Japanese women. Most of these breast cancers are detected at relatively early stages, and the 5- and 10-year survival rates are reported to be > 90 and 80%, respectively [1]. However, even among stage I or node-negative cases, relapse or distant metastases can occur after initial therapies, and early detection of cases with high recurrence risk would be helpful in improving the overall prognosis of patients with breast cancer.

Conventional modalities for imaging diagnosis comprise mammography, ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and bone scintigraphy. It was reported that dynamic contrast enhanced MRI and diffusion weighted imaging were correlated with the status of hormone receptors and Ki-67 in primary breast cancer [2, 3]. In recent years, $^{18}$F-
fluorodeoxyglucose positron emission tomography/computed tomography (\(^{18}\)F-FDG PET/CT) has come to play an increasing role in the diagnosis of biological properties as well as staging, treatment monitoring of residual disease, and detection of disease recurrence in breast cancer patients [4, 5]. For that purpose, the maximum standardized uptake values (SUV\(_{\text{max}}\)) of \(^{18}\)F-FDG has been shown to be correlated with tumor size, nuclear grade (NG), and Ki-67 labeling index (LI) [6, 7]. Furthermore, several studies [8–11] have shown that the SUV\(_{\text{max}}\) of primary tumor, that reflects its metabolic activity, on \(^{18}\)F-FDG PET/CT can predict patients’ poor prognosis.

In malignant tumors, glucose metabolism is usually enhanced, and the uptake of \(^{18}\)F-FDG increases. Therefore, a higher level of \(^{18}\)F-FDG accumulation in PET/CT should reflect higher proliferative activity of the tumor cells. Recently, several studies and meta-analyses have been performed on the relationships between PET/CT and histopathological findings in the field of diagnostic oncology [6, 12–16]. Especially, the uptake of \(^{18}\)F-FDG was shown to be correlated with expressions of histopathological markers, e.g., Ki-67 LI, vascular endothelial growth factor, and hypoxia induced factor 1α, in head and neck cancer, lung cancer, and lymphoma [12–16].

Because the SUV\(_{\text{max}}\) is usually measured at a single time point, such as 1 h after \(^{18}\)F-FDG administration, the dynamic index of the tumor is not included in routine examination. Some articles reported the utility of measurement of \(^{18}\)F-FDG uptake levels at dual time points [17, 18]. The \(^{18}\)F-FDG uptake level at a later point has a tendency to increase in malignant lesions but to decrease in benign lesions, such as inflammatory reactions [19]. Therefore, the measurement of \(^{18}\)F-FDG uptake in dual time point \(^{18}\)F-FDG PET/CT may be able to estimate biological properties and predict patient prognosis more accurately.

The aim of this study was to investigate the clinicopathological significance of dual time point \(^{18}\)F-FDG PET/CT in patients with primary breast cancer. In addition, we assessed the prognostic significance of the measurement of dynamic \(^{18}\)F-FDG uptake levels.

Methods
This was a retrospective study in a single institute.

Ethics approval and consent to participate
This study was performed in accordance with the Declaration of Helsinki and was approved by the institutional review board of National Defense Medical College (registration number: 2695). All patients agreed to participate in this study, and written informed consent was obtained from all these patients.

Eligible patients
Between September 2008 and December 2017, \(^{18}\)F-FDG PET/CT was performed for 820 consecutive preoperative patients with primary breast carcinoma. Of these, 356 patients were excluded from the study because of (1) history of malignant diseases other than breast cancer within 5 years, (2) preoperative medication therapy, (3) diabetes mellitus, (4) previous treatment of ipsilateral or contralateral breast cancer, (5) presence of distant metastases, (6) acquisition of only single time point data of \(^{18}\)F-FDG PET/CT, and/or (7) difficulty in measuring SUV\(_{\text{max}}\) due to low \(^{18}\)F-FDG accumulation. Finally, 464 female patients were eligible.

In all cases, diagnosis of breast cancer was made based on cytopathological and/or histopathological examination before surgery. \(^{18}\)F-FDG PET/CT was performed before surgery, and the interval between the PET/CT examination and surgery was 42 days on an average, ranging from 7 to 71 days. Postoperative surveillance for 5 years was performed through examination every 3 months and mammography every year. After 5 years, patients underwent mammography every year and were followed up to 10 years after surgery. If relapse was suspected in these tests, it was confirmed using CT or PET/CT.

Quantification of \(^{18}\)F-FDG uptake in primary breast cancer
All 464 patients underwent \(^{18}\)F-FDG PET/CT at the Tokorozawa PET Diagnostic Imaging Clinic (Tokorozawa, Japan). Patients fasted for at least 4 h before the examination. One hour after intravenous administration of 3.7 MBq/kg \(^{18}\)F-FDG, the first scanning was performed. The first examination involved whole-body imaging from the head to thigh, and the second scanning involved the chest only, within 50–60 min of the first examination. After image reconstruction, the region of interest (ROI) was placed in primary breast cancer. The SUV is defined as decay-corrected tissue activity divided by the injected dose per patient body and is calculated using the formula,

\[
\text{SUV} = \frac{\text{activity in ROI (MBq/ml)/injected dose (MBq/kg body weight)}.}
\]

The SUV\(_{\text{max}}\)\(_1\), and SUV\(_{\text{max}}\)\(_2\) were obtained at dual time points, and the ΔSUV\(_{\text{max}}\)% was calculated using the formula,

\[
\Delta\text{SUV}_{\text{max}}\% = \left(\frac{\text{SUV}_{\text{max}}\_2 - \text{SUV}_{\text{max}}\_1}{\text{SUV}_{\text{max}}\_1}\right) \times 100,
\]

where the SUV\(_{\text{max}}\)\(_1\) and SUV\(_{\text{max}}\)\(_2\) were the SUV\(_{\text{max}}\) at the initial phase (60 min) and SUV\(_{\text{max}}\) at delayed phase (120 min), respectively.
**Histological study**

Two observers (H.T., Y.Y.) performed pathological diagnosis. NG was defined according to the General Rules for Clinical and Pathological Recording of Breast Cancer, 17th edition [20]. NG was determined by the sum of the nuclear atypia score and the mitosis count score. Estrogen receptor (ER) and progesterone receptor (PgR) expression was assessed by immunohistochemistry and defined as positive if ≥1% of carcinoma cells were immunoreactive [21]. Human epidermal growth factor receptor 2 (HER2) positivity was determined according to the American Society of Clinical Oncology/College of American Pathologists guideline 2013 [22]. According to the recommendation of the Breast Cancer Working Group, Ki-67 LI was defined as high if 14% or higher of constituent carcinoma cells were immunoreactive [23, 24]. Pathological stage was determined by the clinical and pathological recording of breast cancer, 8th edition, by Union for International Cancer Control (UICC).

**Evaluation of 18F-FDG PET/CT results as prognostic factor**

Receiver operating characteristic (ROC) curves were drawn to determine the optimal cutoff values of SUV<sub>max1</sub> and ΔSUV<sub>max%</sub>. Furthermore, the Youden index (sensitivity – (1 – specificity)) of each cutoff value was calculated, and the highest value was taken as the optimal cutoff point.

**Statistical analysis according to clinicopathological factors and prognosis**

The correlations between SUV<sub>max</sub> parameters (SUV<sub>max1</sub>, SUV<sub>max2</sub>, and ΔSUV<sub>max%</sub>) and clinicopathological factors were evaluated using the non-parametric Wilcoxon and the Kruskal–Wallis tests. All statistical analyses were two-sided, with significance defined as P value < 0.05. The Kaplan-Meier curves for relapse-free survival (RFS) and overall survival (OS) were drawn, and their differences were tested by the log-rank test. A Cox proportional hazards model was used for univariate and multivariate analyses for RFS. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the accuracies of SUV<sub>max1</sub>, ΔSUV<sub>max%</sub>, and their combination for RFS were calculated. Statistical analyses were performed using JMP® 13 (SAS Institute Inc., Cary, NC, USA).

**Results**

**Patient characteristics**

Data obtained from the 464 patients on age, tumor invasion size, histological type, NG, lymphatic invasion, hormonal receptor status, HER2 status, Ki-67 LI, pathological stage, SUV<sub>max1</sub> and SUV<sub>max2</sub>, ΔSUV<sub>max%</sub>, RFS, and OS are summarized in Table 1. Mean SUV<sub>max1</sub>, mean SUV<sub>max2</sub>, and mean ΔSUV<sub>max%</sub> were 4.6 (± 3.5 standard deviation [SD]), 5.6 (± 4.9 SD), and 15.6% (± 20.2 SD), respectively. SUV<sub>max1</sub> and SUV<sub>max2</sub> did not show normal distribution whereas ΔSUV<sub>max%</sub> showed normal distribution (Additional file 1 Figure S1). Five and 10-year RFS rates were 92.0 and 84.9%, respectively. Five and 10-year overall survival rates were 97.3 and 88.5%, respectively (median follow up 4.9 years).

**Setting of optimal cutoff values for patient prognostication**

According to the Youden index, the optimal cutoff value of SUV<sub>max1</sub> was 3.4, and area under the curve (AUC) was 0.627 (95% confidence interval [CI] 0.536–0.719) (Fig. 1A). The patients were divided into the low SUV<sub>max1</sub> (< 3.4) (n = 223) and high SUV<sub>max1</sub> groups (≥ 3.4) (n = 241). The optimal cutoff value of ΔSUV<sub>max%</sub> was 12.5, and AUC was 0.594 (95% CI 0.505–0.683) (Fig. 1B). The patients were divided into the low ΔSUV<sub>max%</sub> (< 12.5) (n = 202) and high ΔSUV<sub>max%</sub> groups (≥ 12.5) (n = 262).

**Patient characteristics between high and low groups divided by SUV<sub>max1</sub> and ΔSUV<sub>max%</sub>**

The correlations between high and low SUV<sub>max1</sub> groups and clinicopathological parameters are presented in Table 2. Tumor size, pathological T factor, NG, lymphatic invasion, pathological N factor, pathological stage, and SUV parameters (SUV<sub>max1</sub>, SUV<sub>max2</sub>, ΔSUV<sub>max%</sub>) were significantly different between high and low SUV<sub>max1</sub> groups. High Ki-67 LI was more frequent in the high SUV<sub>max1</sub> group than in the low SUV<sub>max1</sub> group (P = 0.0001) whereas ER, PgR, HER2, and subtype were not correlated with SUV<sub>max1</sub>. The correlations between the high and low ΔSUV<sub>max%</sub> groups and clinicopathological parameters are presented in Table 3. The factors correlated with SUV<sub>max1</sub> were significantly different between the high and low ΔSUV<sub>max%</sub> groups. High Ki-67 LI was more frequent in the high ΔSUV<sub>max%</sub> group than in the low ΔSUV<sub>max%</sub> group (P = 0.0336) whereas ER, PgR and subtype were not correlated with ΔSUV<sub>max%</sub>. HER2 status was significantly different between high and low ΔSUV<sub>max%</sub> groups (P = 0.0304). Two patients with HER2-positive ductal carcinoma in situ (DCIS) were classified into the low ΔSUV<sub>max%</sub> group. Therefore, when these DCIS cases were excluded from the analysis, HER2 status showed no significant difference between these two groups.

**Correlation between SUV<sub>max1</sub> and ΔSUV<sub>max%</sub>**

There was a weak correlation between SUV<sub>max1</sub> and ΔSUV<sub>max%</sub> (R<sup>2</sup> = 0.166). In the high SUV<sub>max1</sub> group (≥ 3.4) (n = 241), 179 patients (68.3%) with high ΔSUV<sub>max%</sub> (≥ 12.5) were included. In contrast, in the
| Parameter                          | Number of cases | (%)         |
|-----------------------------------|-----------------|-------------|
| **Total**                         | 464             | (100.0)     |
| Age (year)                        | Mean ± SD (range) | 61.4 ± 12.6 | (28–91)   |
|                                   | < 45             | 113 (23.4)  |             |
|                                   | ≥ 45             | 351 (75.6)  |             |
| Tumor invasive size (mm)          | Mean ± SD (range) | 20.6 ± 17.6 | (0.0–150.0)|
|                                   | ≤ 20             | 297 (64.0)  |             |
|                                   | > 20             | 167 (36.0)  |             |
| Pathological T factor             | pTis             | 14 (3.0)    |             |
|                                   | pT1              | 283 (61.0)  |             |
|                                   | pT2              | 144 (31.0)  |             |
|                                   | pT3              | 23 (5.0)    |             |
| Histological type                 |                 |             |             |
|                                   | Ductal carcinoma in situ | 14 (3.0) |             |
|                                   | Invasive ductal carcinoma | 366 (78.9) |             |
|                                   | Special type     | 84 (18.1)   |             |
| Nuclear grade                     | 1                | 156 (33.6)  |             |
|                                   | 2                | 128 (27.6)  |             |
|                                   | 3                | 180 (38.8)  |             |
| Lymphatic invasion                | Negative         | 271 (58.4)  |             |
|                                   | Positive         | 193 (41.6)  |             |
| Pathological N factor             | pN0              | 334 (72.0)  |             |
|                                   | pN1              | 95 (20.5)   |             |
|                                   | pN2              | 26 (5.6)    |             |
|                                   | pN3              | 9 (1.9)     |             |
| Estrogen receptor                 | Negative         | 83 (17.9)   |             |
|                                   | Positive         | 381 (82.1)  |             |
| Progesterone receptor             | Negative         | 120 (25.9)  |             |
|                                   | Positive         | 344 (74.1)  |             |
| HER2                              | Negative         | 401 (86.4)  |             |
|                                   | Positive         | 50 (10.8)   |             |
|                                   | Not done         | 13 (2.8)    |             |
| Ki-67 labeling index (%)          | Mean ± SD (range) | 198 ± 16.6  | (0–90.0)   |
|                                   | < 14             | 192 (41.4)  |             |
|                                   | ≥ 14             | 239 (51.5)  |             |
|                                   | Not done         | 33 (7.1)    |             |
| Subtype                           | ER-positive/HER2-negative | 345 (74.3) |             |
|                                   | ER-positive/HER-positive | 26 (5.6)   |             |
|                                   | ER-negative/HER2-positive | 24 (5.2)   |             |
|                                   | ER-negative/HER2-negative | 56 (12.1)  |             |
|                                   | Not done         | 13 (2.8)    |             |
| Pathological stage                | 0                | 13 (2.8)    |             |
|                                   | I                | 236 (50.8)  |             |
|                                   | II               | 172 (37.1)  |             |
|                                   | III              | 43 (9.3)    |             |
| SUV<sub>max</sub>                 | Mean ± SD (range) | 4.6 ± 3.5  | (0.7–24.2) |
low SUV$_{\text{max}}^1$ group ($< 3.4$) ($n = 223$), 83 patients (31.7%) with high ΔSUV$_{\text{max}}^\%$ were included.

**Comparison of survival curves**
The RFS curves for the high and low SUV$_{\text{max}}^1$ groups were significantly different between these curves ($P = 0.0003$) (Fig. 2A). Although there was no significant difference in OS curves for the high and low SUV$_{\text{max}}^1$ groups, the high SUV$_{\text{max}}^1$ group tended to show worse prognosis ($P = 0.0553$) (data not shown). The RFS curves for the high and low ΔSUV$_{\text{max}}^\%$ groups were significantly different ($P = 0.0151$) (Fig. 2B). Although, there was no significant difference in OS curves between the high and low ΔSUV$_{\text{max}}^\%$ groups, the former groups tended to show worse prognosis ($P = 0.141$) (data not shown). Because the correlation of SUV$_{\text{max}}^2$ with RFS was weaker than that of SUV$_{\text{max}}^1$ ($P = 0.141$) (data not shown), we did not use SUV$_{\text{max}}^2$ for prognostic analysis (data not shown).

**Prognostication by the combination of SUV$_{\text{max}}^1$ and ΔSUV$_{\text{max}}^\%$**
The 464 patients were classified into three subgroups (group A, B, and C) by the combination of SUV$_{\text{max}}^1$ and ΔSUV$_{\text{max}}^\%$. Group A was SUV$_{\text{max}}^1 \geq 3.4$ and ΔSUV$_{\text{max}}^\% \geq 12.5$ ($n = 179$), group B was SUV$_{\text{max}}^1 \geq 3.4$ and ΔSUV$_{\text{max}}^\% < 12.5$ ($n = 62$), and group C was SUV$_{\text{max}}^1 < 3.4$ ($n = 223$). Although group C could also be subclassified into the high ΔSUV$_{\text{max}}^\%$ (n = 83) and low ΔSUV$_{\text{max}}^\%$ subgroups (n = 140), no significant difference in RFS was observed between these two subgroups ($P = 0.625$, data not shown).

There were significant differences in RFS curves between these three subgroups ($P = 0.0006$), and between groups A and C ($P = 0.0001$). On the other hand, there were no significant differences between groups A and B ($P = 0.285$), and between groups B and C ($P = 0.146$) (Fig. 3A). The 10-year RFS rates were 90.6% in group B and 89.0% in group C, whereas the rate was 78.8% in group A. Furthermore, RFS curves were significantly different between group A and group “B + C” ($P = 0.0002$) (Fig. 3B). By the combination of the ΔSUV$_{\text{max}}^\%$ and the SUV$_{\text{max}}^1$, it was possible to predict a group with the worse prognosis more sensitively than SUV$_{\text{max}}^1$ or ΔSUV$_{\text{max}}^\%$ alone.

In the subgroup analyses, there were significant differences in RFS between group A and group B/C in node-negative patients ($n = 334$) and in node-positive patients ($n = 130$) ($P = 0.0126$ and $P = 0.0455$, respectively). In the pTis/pT1 ($n = 297$) and pT2/pT3 groups ($n = 167$), there were no significant differences in RFS between group A and group B/C ($P = 0.120$ and $P = 0.131$, respectively). With regard to subtype, group A showed a significantly lower RFS than group B/C in the ER-positive/HER2-negative group ($P = 0.0008$, $n = 345$), but such a relationship was not found in the ER-positive/HER2-positive, ER-negative/HER2-positive, and ER-negative/HER2-negative patient groups ($P = 0.0614$, $P = 0.358$, $P = 0.823$, respectively).

**Univariate and multivariate analyses**
By Cox’s univariate analyses to estimate relapse risk, five clinicopathological parameters, invasive tumor size, lymph node metastasis, NG, lymphatic invasion, and Ki-67 LI, as well as SUV$_{\text{max}}^1$ and ΔSUV$_{\text{max}}^\%$ were statistically significant factors. The combined SUV$_{\text{max}}^1$ and ΔSUV$_{\text{max}}^\%$ was also a significant prognostic factor in RFS ($P = 0.0007$) (Table 4). Because SUV$_{\text{max}}^1$ and ΔSUV$_{\text{max}}^\%$ were correlated with together, we performed the Cox’s multivariate analyses including these five clinicopathological parameters with either SUV$_{\text{max}}^1$, ΔSUV$_{\text{max}}^\%$, or the combination of SUV$_{\text{max}}^1$ and ΔSUV$_{\text{max}}^\%$. In the multivariate analyses, SUV$_{\text{max}}^1$ or the combination of SUV$_{\text{max}}^1$ and ΔSUV$_{\text{max}}^\%$ was an independent prognostic factor ($P = 0.0267$ and $P = 0.0283$, respectively, Table 4). As the test to detect relapse, the combined measurement of SUV$_{\text{max}}^1$ and ΔSUV$_{\text{max}}^\%$ showed higher specificity, PPV, and accuracy than the measurement of SUV$_{\text{max}}^1$ or ΔSUV$_{\text{max}}^\%$ alone (Table 5).

**Discussion**
In malignant tumors, glucose metabolism is usually enhanced, and the extent of increase in glucose metabolism is often correlated with poor patient outcomes. SUV$_{\text{max}}$ and ΔSUV$_{\text{max}}$ can reflect glucose metabolism in tumors. In this study, SUV$_{\text{max}}$, or the combination of SUV$_{\text{max}}$ and ΔSUV$_{\text{max}}$, was a significant predictor of relapse-free survival. This result is consistent with previous studies in breast cancer and other malignancies, in which SUV$_{\text{max}}$, SUV$_{\text{max}}$ change, and other metabolic imaging criteria were associated with worse disease outcomes.

Table 1: Patient characteristics (Continued)

| Parameter | Number of cases (%) |
|-----------|---------------------|
| SUV$_{\text{max}}^2$ Mean ± SD (range) | 5.6 ± 4.9 (0.9–36.4) |
| ΔSUV$_{\text{max}}^\%$ Mean ± SD (range) | 15.6 ± 20.2 (−36.7–84.2) |

HER2, human epidermal growth factor receptor 2
SD, standard deviation
SUV, standardized uptake value

(Continued)
consumption was shown to be correlated with higher proliferation rates of cancer cells. Therefore, a higher level of accumulation of $^{18}$F-FDG in PET/CT is a sign of the primary breast cancer with high proliferative activities \cite{8–10,25}, and $^{18}$F-FDG PET/CT has been used not only for cancer diagnosis but also for functional assessments of breast cancer, i.e., clinical aggressiveness and higher sensitivity to neoadjuvant therapies \cite{26,27}. In fact, Deng et al. and Surov et al. summarized that the uptake of $^{18}$F-FDG was associated with Ki-67 LI in their meta-analyses \cite{6,7}. We were able to confirm their results in this study.

For the evaluation of PET/CT images, the most commonly used parameter is the SUV$_{\text{max}}$, which is usually measured 60 min after the injection of $^{18}$F-FDG. It has also been believed that the addition of information of the later phase can be used to determine the biological properties of the examined cancers in more detail. Some reported that $^{18}$F-FDG uptake in malignancy continued to increase until approximately 4–5 h after injection, but the uptake decreased in the benign lesion 30 min after the injection \cite{18,28}. Furthermore, the ΔSUV$_{\text{max}}$% was correlated with the grade of malignancy in lung cancer and lymphoma \cite{29,30}. Although the usefulness of ΔSUV$_{\text{max}}$% was generally considered acceptable, few reports have been published on its relationship with the prognosis of breast cancer.

In this report, we confirmed that SUV$_{\text{max,1}}$ was an independent prognostic factor for RFS. Furthermore, we showed that ΔSUV$_{\text{max,1}}$% was a significant prognostic indicator of RFS and that the combination of SUV$_{\text{max,1}}$ and ΔSUV$_{\text{max,1}}$% was possible to predict a group with poorer prognosis more sensitively than SUV$_{\text{max,1}}$ alone. With the optimal cutoff value (12.5 of ΔSUV$_{\text{max,1}}$%), the subgroup with better prognosis can be detected among the high SUV$_{\text{max,1}}$ (≥ 3.4) group. In contrast, the effectiveness of SUV$_{\text{max,1}}$ and ΔSUV$_{\text{max,1}}$% for OS could not be demonstrated. In the present patient cohort, follow up period is still short, and the number of events appears too small to analyze the effectiveness of ΔSUV$_{\text{max,1}}$% for OS prediction.

The RFS rate of patients with breast cancers of the ER-positive/HER2-negative subtype was significantly lower in the high-SUV$_{\text{max}}$/high-ΔSUV$_{\text{max,1}}$% group than in the other groups (P = 0.0008). SUV$_{\text{max}}$ was shown to be correlated with 21-gene recurrence score in ER-positive/HER2-negative breast cancer \cite{31}. Therefore, SUV-related parameters might be clinically useful, in addition to the 21-gene recurrence score, for the selection of high-risk node-negative luminal breast cancers, although a larger-scale study is necessary. Furthermore, the combination of SUV$_{\text{max,1}}$ and ΔSUV$_{\text{max,1}}$% would be able to increase the accuracy of preoperative diagnoses of lymph node metastasis and therapeutic response to neoadjuvant therapies.

In this study, patients with previous treatment were excluded. In these patient groups, 24 ER-negative/HER2-positive patients and 54 ER-negative/HER2-negative patients were included. Therefore, only 10.8% (50/464) were HER2-positive type and 11.6% (56/464) were ER-negative/HER2-negative type. These types of breast cancers were reported to have a higher SUV value than ER-positive types and to have worse prognosis than the ER-positive types \cite{32–34}. Furthermore, we excluded the
Table 2 Patient characteristics between high and low SUV$_{\text{max}1}$ groups

| Table 2 Patient characteristics between high and low SUV$_{\text{max}1}$ groups |
|---------------------------------------------------------------|
| **Number of cases (%)** | **Total** | **High SUV$_{\text{max}1}$ group** | **Low SUV$_{\text{max}1}$ group** | **P-value** |
| Age (year) | | | | |
| Mean ± SD (range) | 62.2 ± 13.4 | (29 - 87) | 60.5 ± 11.7 | (33 - 91) | 0.0808 |
| < 45 | 113 | 61 | (54.0) | 52 | (48.7) | 0.617 |
| ≥ 45 | 351 | 180 | (51.3) | 171 | (46.0) | |
| Tumor invasive size (mm) | | | | |
| Mean ± SD (range) | 25.7 ± 21.9 | (0.0 - 150.0) | 15.0 ± 10.5 | (0.0 - 83.0) | < 0.0001 |
| pT | | | | |
| 0 | 14 | 6 | (42.9) | 8 | (57.1) | < 0.0001 |
| 1 | 283 | 113 | (39.9) | 170 | (60.1) | |
| 2 | 144 | 103 | (71.5) | 41 | (28.5) | |
| 3 | 23 | 19 | (82.6) | 4 | (17.4) | |
| Histological type | | | | |
| Ductal carcinoma in situ | 14 | 7 | (50.0) | 7 | (50.0) | 0.910 |
| Invasive ductal carcinoma | 366 | 192 | (52.5) | 174 | (47.5) | |
| Special type | 84 | 42 | (50.0) | 42 | (50.0) | |
| Nuclear grade | | | | |
| 1, 2 | 284 | 119 | (41.9) | 165 | (58.1) | < 0.0001 |
| 3 | 180 | 122 | (67.8) | 58 | (32.2) | |
| Lymphatic invasion | | | | |
| Negative | 271 | 122 | (45.0) | 149 | (55.0) | 0.0004 |
| Positive | 193 | 119 | (61.7) | 74 | (38.3) | |
| pN | | | | |
| 0 | 201 | 156 | (77.6) | 45 | (22.4) | 0.0003 |
| 1, 2, 3 | 263 | 85 | (32.3) | 178 | (67.7) | |
| Estrogen receptor | | | | |
| Negative | 83 | 49 | (59.0) | 34 | (41.0) | 0.133 |
| Positive | 381 | 192 | (50.4) | 189 | (49.6) | |
| Progesterone receptor | | | | |
| Negative | 120 | 68 | (56.7) | 52 | (43.3) | 0.228 |
| Positive | 364 | 173 | (50.3) | 171 | (49.7) | |
| HER2 | | | | |
| Negative | 401 | 207 | (51.6) | 194 | (48.4) | 0.959 |
| Positive | 59 | 26 | (52.0) | 24 | (48.0) | |
| Not done | 13 | 8 | (61.5) | 5 | (38.5) | |
| Ki-67 labelling index (%) | | | | |
| Mean ± SD (range) | 24.2 ± 18.8 | (0.0 - 90.0) | 16.0 ± 12.9 | (0.4 - 62.8) | < 0.0001 |
| < 14 | 192 | 79 | (41.1) | 113 | (58.9) | < 0.0001 |
| ≥ 14 | 239 | 154 | (64.4) | 85 | (35.6) | |
| Not done | 33 | 8 | (24.2) | 25 | (75.8) | |
| Subtype | | | | |
| ER-positive/HER2-negative | 345 | 173 | (50.1) | 172 | (49.9) | 0.523 |
| ER-positive/HER2-positive | 26 | 13 | (50.0) | 13 | (50.0) | |
| ER-negative/HER2-positive | 24 | 13 | (54.2) | 11 | (45.8) | |
| ER-negative/HER2-negative | 56 | 34 | (60.7) | 22 | (39.3) | |
| Not done | 13 | 8 | (61.5) | 5 | (38.5) | |
| Pathological stage | | | | |
| 0 | 13 | 5 | (38.5) | 8 | (61.5) | < 0.0001 |
| 1 | 236 | 90 | (38.1) | 146 | (61.9) | |
| II | 172 | 110 | (64.0) | 62 | (36.0) | |
| III | 43 | 36 | (83.7) | 7 | (16.3) | |
| SUV$_{\text{max}1}$ | | | | |
| Mean ± SD (range) | 6.9 ± 3.6 | (3.4 - 24.2) | 2.1 ± 0.7 | (0.7 - 3.4) | < 0.0001 |
| SUV$_{\text{max}2}$ | | | | |
| Mean ± SD (range) | 8.7 ± 5.1 | (3.0 - 36.4) | 2.3 ± 0.9 | (0.6 - 5.1) | < 0.0001 |
| ASUV$_{\text{max}1}$ | | | | |
| Mean ± SD (range) | 23.5 ± 16.9 | (16.1 - 84.2) | 7.2 ± 20.2 | (36.7 - 72.6) | < 0.0001 |

HER2, human epidermal growth factor receptor 2
SD, standard deviation
SUV, standardized uptake value
Table 3 Patient characteristics between high and low \(\Delta \text{SUV}_{\text{max}}\%\) groups

|                        | Total | Number of cases (%) | Number of cases (%) | \(P\)-value |
|------------------------|-------|---------------------|---------------------|-------------|
| Age (year)             |       |                     |                     |             |
| Mean ± SD (range)      | 62.1 ± 13.0 | (29 - 87) | 60.5 ± 12.1 | (33 - 91) | 0.116 |
| < 45                   | 113   | (54.0)              | 52                  | (46.0)      | 0.540 |
| ≥ 45                   | 351   | (57.3)              | 150                 | (42.7)      |       |
| Tumor invasive size (mm)|       |                     |                     |             |
| Mean ± SD (range)      | 23.9 ± 19.7 | (0.0 - 150.0) | 16.3 ± 13.4 | (0.0 - 125.0) | <0.0001 |
| pT                     |       |                     |                     |             |
| 0                      | 14    | (50.0)              | 7                   | (50.0)      | <0.0001 |
| 1                      | 283   | (48.1)              | 147                 | (51.9)      |       |
| 2                      | 144   | (70.8)              | 42                  | (29.2)      |       |
| 3                      | 23    | (73.9)              | 6                   | (26.1)      |       |
| Histological type      |       |                     |                     |             |
| Ductal carcinoma in situ | 14   | (50.0)              | 7                   | (50.0)      | 0.242 |
| Invasive ductal carcinoma | 366  | (58.5)              | 152                 | (41.5)      |       |
| Special type           | 84    | (48.8)              | 43                  | (51.2)      |       |
| Nuclear grade          |       |                     |                     |             |
| 1, 2                   | 284   | (51.4)              | 138                 | (46.6)      | 0.0058 |
| 3                      | 180   | (64.4)              | 64                  | (35.6)      |       |
| Lymphatic invasion     |       |                     |                     |             |
| Negative               | 271   | (49.8)              | 136                 | (50.2)      | 0.0006 |
| Positive               | 193   | (65.8)              | 66                  | (34.2)      |       |
| pN                     |       |                     |                     |             |
| 0                      | 334   | (54.2)              | 153                 | (45.8)      | 0.113 |
| 1, 2, 3                | 130   | (62.3)              | 49                  | (37.7)      |       |
| Estrogen receptor      |       |                     |                     |             |
| Negative               | 83    | (60.2)              | 33                  | (39.8)      | 0.444 |
| Positive               | 381   | (55.6)              | 169                 | (44.4)      |       |
| Progesterone receptor  |       |                     |                     |             |
| Negative               | 120   | (60.0)              | 48                  | (40.0)      | 0.364 |
| Positive               | 344   | (55.2)              | 154                 | (44.8)      |       |
| HER2                   |       |                     |                     |             |
| Negative               | 401   | (58.1)              | 168                 | (41.9)      | 0.0304 |
| Positive               | 50    | (42.0)              | 29                  | (58.0)      |       |
| Ki-67 labeling index (%) |     |                     |                     |             |
| Mean ± SD (range)      | 22.5 ± 18.5 | (0.0 - 90.0) | 17.6 ± 13.8 | (0.0 - 73.5) | 0.0144 |
| < 14                   | 192   | (52.6)              | 91                  | (47.4)      | 0.0336 |
| ≥ 14                   | 239   | (62.8)              | 89                  | (37.2)      |       |
| Not done               | 33    | (33.3)              | 22                  | (66.7)      |       |
| Subtype                |       |                     |                     |             |
| ER-positive/HER2-negative | 345  | (57.1)              | 148                 | (42.9)      | 0.0752 |
| ER-positive/HER2-positive | 26   | (34.6)              | 17                  | (65.4)      |       |
| ER-negative/HER2-positive | 24   | (50.0)              | 12                  | (50.0)      |       |
| ER-negative/HER2-negative | 56   | (64.3)              | 20                  | (35.7)      |       |
| Not done               | 13    | (61.5)              | 5                   | (38.5)      |       |
| Pathological stage     |       |                     |                     |             |
| 0                      | 13    | (46.2)              | 7                   | (53.8)      | <0.0001 |
| I                      | 236   | (47.9)              | 123                 | (52.1)      |       |
| II                     | 172   | (63.4)              | 63                  | (36.6)      |       |
| III                    | 43    | (79.1)              | 9                   | (20.9)      |       |
| SUV_{max}1             |       |                     |                     |             |
| Mean ± SD (range)      | 5.8 ± 4.0 | (0.9 - 24.2) | 3.1 ± 2.1 | (0.7 - 18.7) | <0.0001 |
| SUV_{max}2             |       |                     |                     |             |
| Mean ± SD (range)      | 7.6 ± 5.5 | (1.0 - 36.4) | 3.1 ± 2.2 | (0.6 - 18.1) | <0.0001 |
| ΔSUV_{max}3%           |       |                     |                     |             |
| Mean ± SD (range)      | 29.9 ± 13.0 | (12.5 - 84.2) | 2.9 ± 10.7 | (36.7 - 12.1) | <0.0001 |

HER2, human epidermal growth factor receptor 2
SD, standard deviation
SUV, standardized uptake value
Fig. 2 Relapse-free survival (RFS) curves for (a) patient groups with high and low SUV<sub>max1</sub> values and (b) for patient groups with high and low ΔSUV<sub>max</sub>%.

(a) RFS curves were significantly different between two patient groups ($P = 0.0003$).

(b) RFS curves were significantly different between two patient groups ($P = 0.0151$).

Fig. 3 (a) RFS curves for the patients of subgroups a, b and c classified by the combination of SUV<sub>max1</sub> and ΔSUV<sub>max</sub>%. RFS curves were significantly different among these three groups ($P = 0.0006$).

(b) RFS curves for the patients of subgroup A and subgroup “B + C”. RFS curves were significantly different between these two groups ($P = 0.0002$). Ten-year RFS rates were 78.8% in group A and 89.0% in group “B + C”.
Table 4: The univariate and multivariate analyses for relapse

| Parameter (Favorable vs. Unfavorable) | Univariate | Multivariate |
|--------------------------------------|------------|--------------|
|                                      | Hazard ratio (95% CI) | Hazard ratio (95% CI) |
|                                      | P-value | Hazard ratio (95% CI) | P-value |
| Pathological T factor                | 4.9 (2.48–10.3) | 2.35 (1.12–5.24) |
| (pT2, pT3 vs. pTis, pT1)             | < 0.0001 | 0.0229 (1.18–5.62) |
| Nuclear grade                        | 4.79 (2.34–10.7) | 2.46 (1.08–6.10) |
| (3 vs. 1, 2)                         | < 0.0001 | 0.0303 (1.23–6.97) |
| Lymphovascular invasion              | 7.32 (3.28–19.5) | 4.83 (1.87–14.6) |
| (Positive vs. Negative)              | < 0.0001 | 0.0007 (1.70–13.0) |
| Estrogen receptor                    | 1.46 (0.65–2.97) | 1.62 (0.72–4.04) |
| (Negative vs. Positive)              | 0.339     | 0.247 (0.83–4.50) |
| Progesterone receptor                | 1.34 (0.65–2.63) | 1.52 (0.82–4.07) |
| (Negative vs. Positive)              | 0.404     | 0.261 (0.73–3.35) |
| HER2                                 | 1.08 (0.32–2.73) | 1.52 (0.73–3.35) |
| (Positive vs. Negative)              | 0.879     | 0.268 (0.72–3.30) |
| Ki-67 labeling index                 | 3.38 (1.58–8.06) | 1.62 (0.72–4.04) |
| (≥ 140 vs. < 140)                    | 0.0012    | 0.247 (0.83–4.50) |
| Pathological N factor                | 4.47 (2.32–8.92) | 1.52 (0.73–3.32) |
| (pN1, pN2, pN3 vs. pN0)              | < 0.0001 | 0.261 (0.73–3.32) |
| SUVmax1                              | 3.61 (1.77–8.13) | 2.54 (1.10–6.46) |
| (≥ 3.4 vs. < 3.4)                    | 0.0003    | 0.0267 (1.74–15.2) |
| ΔSUVmax%                             | 2.46 (1.20–5.53) | 1.74 (0.82–4.07) |
| (≥ 12.5 vs. < 12.5)                  | 0.0122    | 0.152 (1.20–5.53) |
| SUVmax1/ΔSUVmax%                     | 3.24 (1.62–6.72) | 2.33 (1.09–5.31) |
| (Group A vs. Group B/C)              | 0.0007    | (Group A vs. Group B/C) |

CI, confidence interval
HER2, human epidermal growth factor receptor 2
SUV, standardized uptake value

Table 5: Accuracy of SUVmax1, ΔSUVmax%, and their combination for prediction of relapse

| Parameter | Number of case | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Accuracy (%) |
|-----------|---------------|----------------|----------------|---------|---------|--------------|
|           | Total | Relapse | No relapse |         |         |              |
| SUVmax1   | ≥ 3.4 | 241     | 28      | 213     | 75.7   | 50.1         | 11.6 | 96.0 | 52.2 |
|           | < 3.4 | 223     | 9       | 214     |         |              |
| ΔSUVmax%  | ≥ 12.5 | 262     | 28      | 234     | 75.7   | 45.2         | 10.7 | 95.5 | 47.6 |
|           | < 12.5 | 202     | 9       | 193     |         |              |
| Combination of SUVmax1 and ΔSUVmax% | SUVmax1 ≥ 3.4 and ΔSUVmax% ≥ 12.5 | 179     | 24      | 155     | 64.9   | 63.7         | 13.4 | 95.4 | 63.8 |
|           | Other | 285     | 13      | 272     |         |              |

NPV, negative predictive value
PPV, positive predictive value
SUV, standardized uptake value
109 patients whose 18F-FDG accumulation was not visible and SUV<sub>max</sub> was not measurable from the study. These cases appear to show very low SUV<sub>max</sub> values and accordingly, were also expected to have a good prognosis. For these reasons, it seemed that the true efficacy of ΔSUV<sub>max</sub>% and combined measurement of SUV<sub>max</sub>1 and ΔSUV<sub>max</sub>% as prognostic indicators might be higher than the present results.

The pN factor was a very strong prognostic factor in the univariate analysis but did not have an independent prognostic power in the multivariate analysis. In these analyses, pN was divided into pN0 and pN1–3. Because pN1 was shown to reveal relatively good prognosis and a majority of pN-positive patients showed pN1 in this study, the impact of node-positivity might have been diluted by the good-prognosis effect in pN1 cases. Lymphatic invasion and pT might also have been confounding factors along with pN.

The limitations of this study include its retrospective nature, single center data, and a relatively small number of events. A multicenter, prospective study is needed to highlight the effectiveness of ΔSUV<sub>max</sub>% in the prognostication of primary breast cancer.

Nonetheless, the strength of the present study involves the large number of images reviewed, the correlation between relevant clinicopathological and prognostic data, and exclusion of patients with diabetes. Furthermore, SUV<sub>max</sub> parameters were easy to compute and reproducible, and dual time point imaging could be performed in a relatively short time with minimal inconvenience to the patient and be readily performed at most centers.

Conclusions
In conclusion, dual time point 18F-FDG PET/CT can be a useful modality for prediction of relapse in patients with breast cancer. The combination of SUV<sub>max</sub>1 and ΔSUV<sub>max</sub>% was able to identify the patient groups with worse prognosis more accurately than SUV<sub>max</sub>1 alone.

Supplementary information
Supplementary information accompanies this paper at https://doi.org/10.1186/s12885-019-6315-8.

Additional file 1: Figure S1. Distribution of SUV<sub>max</sub>1, SUV<sub>max</sub>2, and ΔSUV<sub>max</sub>% in 464 breast cancer patients. (A) SUV<sub>max</sub>1; (B) SUV<sub>max</sub>2; (C) ΔSUV<sub>max</sub>%; (A) and (B) do not follow normal distribution (P < 0.0001, each), but (C) demonstrates normal distribution (P = 0.680) by Shapiro-Wilk test.

Abbreviations
18F-FDG PET/CT: 18F-fluorodeoxyglucose positron emission tomography/computed tomography; AUC: Area under the curve; CI: Confidence interval; CT: Computed tomography; DCIS: Ductal carcinoma in situ; ER: Estrogen receptor; HER2: Human epidermal growth factor receptor 2; Ki-67: LI: Ki-67 labeling index; MRI: Magnetic resonance imaging; NG: Nuclear grade; NPV: Negative predictive value; OS: Overall survival; PgR: Progesterone receptor; PPV: Positive predictive value; RFS: Relapse-free survival; ROC: Receiver operating characteristic; ROI: Region of interest; SD: Standard deviation; SUV: Standardized uptake value; SUV<sub>max</sub>: Maximum standardized uptake values; SUV<sub>max</sub>1: SUV<sub>max</sub> at 60 min; SUV<sub>max</sub>2: SUV<sub>max</sub> at 120 min; ΔSUV<sub>max</sub>%: (SUV<sub>max</sub>2 - SUV<sub>max</sub>1) / SUV<sub>max</sub>1 × 100; UICC: Union for International Cancer Control

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Authors’ contributions
YY, ToK, and HT performed the planning, acquisition of data, analysis of data, and writing of the manuscript. TY, TE, MF, and MH acquired clinical data, TaK acquired pathological data, and KH and JI conducted tumoral SUV data acquisition and data analysis. HU substantively revised the draft. All authors read and approved the final manuscript.

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Availability of data and materials
Datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The study was approved by the institutional review board of National Defense Medical College.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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