Significance of Metabolic Tumor Volume at Baseline and Reduction of Mean Standardized Uptake Value in 18F-FDG-PET/CT Imaging for Predicting Pathological Complete Response in Breast Cancers Treated with Preoperative Chemotherapy

Tomoko Higuchi, MD 1, Yukie Fujimoto, MD 1, Hiromi Ozawa, MD 1, Ayako Bun, MD 1, Reiko Fukui, MD 1, Yoshimasa Miyagawa, MD, PhD 1, Michiko Imamura, MD, PhD 1, Kazuhiro Kitajima, MD, PhD 2, Koichiro Yamakado, MD, PhD 2, and Yasuo Miyoshi, MD, PhD 1

1Department of Surgery, Division of Breast and Endocrine Surgery, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan; 2Department of Nuclear Medicine and PET Center, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan

ABSTRACT

Background. The usefulness of 18F-fluorodeoxyglucose-positron emission tomography/computed tomography for evaluating the treatment efficacy of breast cancers is well-established; however, the predictive values of parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) remain unknown.

Methods. This study examined 199 breast cancers treated with primary systemic chemotherapy (PSC) followed by operation, and determined the values of maximum standardized uptake value (SUVmax), peak SUV (SUVpeak), mean SUV (SUVmean), MTV, and TLG at baseline. Among these cases, data on early changes in these metabolic parameters in 70 breast cancers were also assessed.

Results. A pathological complete response (pCR) was achieved in 64 breast cancers. Breast cancers with low MTV at baseline had a significantly higher pCR rate than breast cancers with high MTV (47.9% vs. 23.4%; p = 0.0005). High reduction rates (Δ) of SUVmax (ΔSUVmax; p = 0.0001), SUVpeak (ΔSUVpeak; p = 0.0001), and SUVmean (ΔSUVmean; p < 0.0001) resulted in an increased pCR compared with those for low Δ. The pCR rate was highest for the combination of low MTV and high ΔSUVmean (86.7%), and lowest for high MTV and low ΔSUVmean (15.4%); the remaining combinations were intermediate (58.6%; p < 0.0001). The combination of low MTV at baseline and high ΔSUVmean was a significant and independent predictor for pCR (odds ratio 28.63; 95% confidence interval 1.94–422.42; p = 0.0146) in multivariable analysis.

Conclusions. Low levels of MTV at baseline and a high reduction of SUVmean after PSC was significantly associated with pCR. These findings suggest the usefulness of these metabolic parameters for predicting the treatment efficacy of breast cancers.

Pathological complete response (pCR), defined as the lack of residual cancer after neoadjuvant chemotherapy (NAC), has been established as a surrogate marker for excellent prognosis of operable breast cancers. Small tumor size, higher tumor grade, and high proliferative activity are significant predictors for a high rate of pCR. However, the sensitivity and specificity of predicting pCR using these clinical factors are not high and the identification of more precise predictive factors is a critical issue.

In addition to the diagnostic ability of 18F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT), the usefulness of the maximum standardized uptake value (SUVmax) on FDG-PET for predicting the prognosis of operable breast cancers is well established. The value of SUVmax as a predictive tool for treatment efficacy was reported in metastatic and early breast cancers. In the NAC setting, a significant association between an increased SUVmax and a high rate of pCR has been reported. In addition to baseline values,
changes in these values after treatment are significantly associated with the response to chemotherapy. Since altered glucose metabolism occurs earlier than tumor shrinkage, it may be possible to evaluate the treatment efficacy as early as after one or two treatment cycles.

$SUV_{\text{max}}$ levels have been reported to be inaccurate compared with the actual uptake of FDG, due to the partial volume effect. Since volume-based parameters on FDG-PET, including metabolic tumor volume (MTV) and total lesion glycolysis (TLG), evaluate not only metabolic activity but also total tumor burden, recent studies have focused on these metabolic parameters rather than on $SUV_{\text{max}}$ for predicting the response to chemotherapy. Although early reductions of $SUV_{\text{max}}$ are reportedly associated with improved response to NAC, which metabolic parameter offers the most precise prediction remains unknown. In addition, the superiority of baseline or early response to treatment PET data is also undetermined.

The present study explored the predictive values of $SUV_{\text{max}}$, $SUV_{\text{peak}}$, $SUV_{\text{mean}}$, and volume-based parameters, including MTV and TLG, at baseline in breast cancers treated with primary systemic chemotherapy (PSC). Additionally, early changes in these parameters after treatment were also investigated in terms of their relationships with treatment efficacy.

PATIENTS AND METHODS

Patient Recruitment

This retrospective study constitutively recruited a total of 267 breast cancer patients who underwent surgery after preoperative chemotherapy between October 2008 and May 2018. Among these participants, 194 patients who underwent FDG-PET/CT before starting PSC were selected. Since five patients had bilateral breast cancers, we analyzed a total of 199 breast cancers in 194 patients. We evaluated response in the primary sites (breast), and nine patients with stage IV who had PSC followed by operation were also included. We also obtained FDG-PET/CT data after the start of PSC for 69 patients (70 breast cancers).

The Ethics Committee of Hyogo College of Medicine approved the present study (numbers 1818 and 1708), and written informed consent was obtained from all 69 participants who underwent FDG-PET/CT after the start of PSC. In the remaining patients, only baseline FDG-PET/CT data from clinical practice were used and offered no risk to participants; thus, written informed consent was not required (number 1818).

Chemotherapy Regimen and Evaluation of Pathological Response

Preoperative chemotherapies involving anthracycline-containing, taxane-based, sequential use of anthracycline-containing and taxane, and unspecified regimens were administered in 6, 48, 137, and 3 patients, respectively. Concurrent use of trastuzumab with chemotherapy was administered to 64 patients. Pathological examinations of the whole area of pre-existing breast cancer lesions were performed, and pCR was defined as complete absence of invasive cancer cells in the breast.

$^{18}$F-Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography (FDG-PET/CT) Procedure

FDG-PET/CT was performed using a Gemini GXL16 or Gemini TF64 PET/CT scanner (Philips Medical Systems, Eindhoven, The Netherlands) following injection of 4.0 or 3.0 MBq/kg body weight FDG for the GXL16 and TF64, respectively. Scanning images were obtained approximately 60 min after injection, as described previously. The 194 patients underwent FDG-PET/CT examination before starting PSC, of whom 69 (70 breast cancers) underwent a repeat FDG-PET/CT examination after starting chemotherapy. We obtained FDG-PET/CT data after one cycle of PSC (2–3 weeks after the start of chemotherapy), except for one patient whose data were obtained after two cycles (electronic supplementary data).

Imaging Analyses

To quantify $^{18}$F-FDG uptake, the SUVs were measured. We set the volume of interest (VOI) as the area in which FDG accumulated in the breast, along the margin of tumor uptake. The SUV was calculated as the regional radioactivity concentration (Bq/mL)/[injected dose (Bq)/patient weight (g)] in the most intense area of $^{18}$F-FDG accumulation (a region of interest [ROI]). We selected the region containing the tumor in which the FDG in the breast was accumulated, as observed on the image, and set a target VOI manually in the breast cancer primary lesion with FDG accumulation. The maximum value of SUV in the VOI was defined as the $SUV_{\text{max}}$, and the volume of voxels of $\geq 40\%$ of the $SUV_{\text{max}}$ in the VOI was defined as the MTV.$^{21-23}$ The $SUV_{\text{peak}}$ was defined as the average activity concentration within a 1 cm$^3$ spherical VOI centered on the ‘hottest focus’ within the primary tumor. The average SUV value in the voxel that showed $\geq 40\%$ was defined as the $SUV_{\text{mean}}$ and TLG was defined as $\text{MTV} \times S UV_{\text{mean}}$. These parameters were all automatically calculated by the computer software package GI-PET.
Harmonization of data in different PET/CT systems was performed using phantom data. The percentage changes (Δ%) of PET data at baseline and after the start of PSC in each of the five parameters were calculated as follows: percentage change (Δ%) = (delayed parameter – baseline parameter)/baseline parameter × 100.

**Statistical Analysis**

The associations of clinicopathological characteristics between breast cancers that achieved pCR and those that did not were analyzed using the Fisher’s exact or Wilcoxon rank-sum tests. The relationships between pCR and levels of each metabolic parameter were calculated using Fisher’s exact tests, and logistic regression was used to obtain odds ratios (ORs) and 95% confidence intervals (CIs) by univariable and multivariable analyses of clinical factors or metabolic parameters and pCR. Statistical significance was set at p < 0.05. All statistical calculations were performed using JMP Pro 13 (SAS Institute Inc., Cary, NC, USA).

**RESULTS**

**Relationships Between Clinicopathological Factors and Pathological Response**

We defined pCR and non-pCR in 64 and 135 breast cancers, respectively. The pCR rates were significantly higher in those with small tumor size, higher nuclear grade, estrogen receptor (ER)-negative/human epidermal growth factor receptor 2 (HER2)-negative (triple-negative [TN]) and HER2-positive subtypes, high levels of Ki67, and an anthracycline and taxane regimen (electronic supplementary Table 1 and data). The SUVmax, SUVpeak, and SUVmean were significantly associated with nuclear grade and Ki67 expression levels. There were significant associations between tumor size and all parameters except SUVmax, and the subtypes were significantly associated with all parameters except TLG. Lymph node metastasis was significantly associated with MTV and TLG (electronic supplementary Table 2).

**Determination of the Optimal Cut-Off Values for Pathological Complete Response (pCR) of Metabolic Parameters by PET/CT at Baseline and During Primary Systemic Chemotherapy**

Representative cases of PET imaging are shown in Fig. 1. The FDG uptake detected in the left breast at baseline was diminished after one cycle of chemotherapy (Fig. 1a, b) in patients who achieved pCR; however, the uptake of FDG at baseline in the right breast remained after one cycle of chemotherapy (Fig. 1c, d). The cut-off values of SUVmax, SUVpeak, SUVmean, MTV, and TLG at baseline for pCR were determined using receiver operating characteristic (ROC) curves calculated using the Youden index for the areas under the curve (AUC) (electronic supplementary Fig. 1). Similar methods were used to determine the cut-off values of the reduction rate in each metabolic parameter for pCR (electronic supplementary Fig. 2).

**Associations Between pCR After PSC and Each Metabolic Parameter**

Breast cancers with high baseline levels of SUVmax, SUVpeak, and SUVmean had a significantly higher rate of pCR than breast cancers with low levels. However, the frequency of pCR was significantly higher for low baseline levels of MTV and TLG (electronic supplementary Fig. 3). Of these baseline parameters, MTV was the most significant predictor for pCR (47.9% vs. 23.4%; p = 0.0005).

Similarly, breast cancers with high reduction rates had significantly higher frequencies of pCR for ΔSUVmax, ΔSUVpeak, ΔSUVmean, and ΔTLG, but not ΔMTV, in which the significance was marginal (electronic supplementary Fig. 4). The difference in pCR rates between the two groups was most significant for the ΔSUVmean (72.2% vs. 23.5%; p < 0.0001).

**Univariable and Multivariable Analyses of pCR, Including Metabolic Parameters at Baseline and During Treatment**

First, we analyzed data of all 199 breast cancers, including metabolic parameters at baseline. Tumor size, nuclear grade, Ki67 expression levels, subtypes, chemotherapy regimen, and all metabolic parameters at baseline, including SUVmax, SUVpeak, SUVmean, MTV, and TLG, were significantly associated with pCR in univariable analysis (Table 1). The multivariable analyses included these clinical factors with one of the metabolic parameters. As shown in Table 1, baseline MTV was significantly associated with pCR (OR 0.30, 95% CI 0.11–0.84; p = 0.0212).

Data of metabolic parameters during treatment in 70 breast cancers were further analyzed. All of ΔSUVmax, ΔSUVpeak, ΔSUVmean, and ΔTLG were significant predictive factors for pCR in the univariable analysis (Table 2). Since the association between pCR and ΔSUVmean was most significant, we performed multivariable analysis, including only ΔSUVmean as a metabolic parameter, and identified ΔSUVmean as a significant and
independent factor, as shown in Table 2 (OR 8.05, 95% CI 1.45–44.80; \(p = 0.0173\)).

**Predictive Ability of pCR for the Combination of Baseline Metabolic Tumor Volume (MTV) and ΔSUVmean Parameters**

Since both baseline MTV and ΔSUVmean were significantly associated with pCR, we further analyzed the combination of these parameters. The pCR rate was highest for low baseline MTV and high ΔSUVmean (86.7%), and lowest for high baseline MTV and low ΔSUVmean (15.4%) [Fig. 2a]. Since breast cancers with high baseline MTV and high ΔSUVmean, as well as those with low baseline MTV and low ΔSUVmean, showed intermediate pCR rates (61.9% and 50%, respectively), we further combined these two intermediate groups in Fig. 2b (pCR rate 58.6%). In multivariable analysis, the combination of baseline MTV and ΔSUVmean was a significant and independent predictor of pCR (OR 28.63, 95% CI 1.94–422.42; \(p = 0.0146\) for low baseline MTV and high ΔSUVmean) (Table 3).

**DISCUSSION**

The results of the present study demonstrated that low levels of baseline MTV and early reduction of SUVmean after the start of treatment were significant and independent predictive factors for a higher rate of pCR in breast cancers treated with PSC. The combination of both parameters predicts pCR more precisely compared with that of baseline MTV or ΔSUVmean alone. The SUVmax was a significant predictor of pCR after NAC in 273 breast cancers (OR per one-unit increase 1.09, 95% CI 1.02–1.16; \(p = 0.008\)).24 However, consistent with our study, SUVmax, SUVpeak, and SUVmean at baseline were not associated with pathological response in previous studies.21,25–29 Contrary to SUVs, MTV is a volume-based metabolic parameter that represents both metabolic activity and total tumor burden in each tumor. However, Cho et al. reported no significant association between pCR and baseline TLG or MTV values.27 Although Cheng et al. reported no correlation between TLG and pCR,21 baseline MTV was marginally associated with pCR in the HER2-negative group (\(n = 30;\))
|                          | n   | Univariable [OR (95% CI)] | p value | Multivariable [OR (95% CI)] | p value |
|--------------------------|-----|---------------------------|---------|-----------------------------|---------|
| Menopausal status        |     |                           |         |                             |         |
| Premenopausal            | 80  | 1.00                      |         |                             |         |
| Postmenopausal           | 119 | 1.59 (0.85–2.96)          | 0.1447  |                             |         |
| T size (cm)              |     |                           |         |                             |         |
| ≤ 2.0                    | 43  | 1.00                      |         |                             |         |
| > 2                      | 156 | 0.40 (0.20–0.80)          | 0.0093  | 0.40 (0.13–1.20)            | 0.1024  |
| Lymph node metastasis    |     |                           |         |                             |         |
| Negative                 | 104 | 1.00                      |         |                             |         |
| Positive                 | 95  | 0.65 (0.36–1.20)          | 0.1677  |                             |         |
| Nuclear grade            |     |                           |         |                             |         |
| 1                        | 74  | 1.00                      |         |                             |         |
| 2 + 3                    | 115 | 5.76 (2.62–12.66)         | < 0.0001| 3.14 (1.09–9.04)            | 0.0342  |
| Ki67 expression levels\(^a\) |     |                           |         |                             |         |
| Low                      | 50  | 1.00                      |         |                             |         |
| High                     | 139 | 9.74 (2.89–32.89)         | 0.0002  | 20.58 (1.55–237.07)         | 0.0219  |
| Subtypes\(^b\)           |     |                           |         |                             |         |
| TN                       | 48  | 1.00                      |         |                             |         |
| Luminal A                | 31  | 0.04 (0.01–0.34)          | 0.0029  | 2.23 (0.08–65.78)           | 0.6418  |
| Luminal B                | 49  | 0.18 (0.06–0.50)          | 0.0010  | 0.20 (0.06–0.67)            | 0.0114  |
| Luminal-HER2             | 36  | 0.57 (0.23–1.41)          | 0.2198  | 1.18 (0.34–4.09)            | 0.7908  |
| HER2                     | 33  | 3.43 (1.32–8.91)          | 0.0114  | 5.45 (1.53–19.41)           | 0.0089  |
| Chemotherapy regimen     |     |                           |         |                             |         |
| Taxane                   | 48  | 1.00                      |         |                             |         |
| Anthracycline and taxane | 142 | 3.26 (1.42–7.47)          | 0.0053  | 2.83 (0.92–8.77)            | 0.0707  |
| SUV\(_{max}\)            |     |                           |         |                             |         |
| Low                      | 60  | 1.00                      |         |                             |         |
| High                     | 139 | 2.10 (1.04–4.24)          | 0.0396  | Not included                |         |
| SUV\(_{peak}\)\(^d\)    |     |                           |         |                             |         |
| Low                      | 62  | 1.00                      |         |                             |         |
| High                     | 137 | 2.24 (1.11–4.51)          | 0.0249  | Not included                |         |
| SUV\(_{mean}\)\(^e\)    |     |                           |         |                             |         |
| Low                      | 47  | 1.00                      |         |                             |         |
| High                     | 152 | 2.84 (1.24–6.52)          | 0.0135  | Not included                |         |
| MTV\(^f\)                |     |                           |         |                             |         |
| Low                      | 71  | 1.00                      |         |                             |         |
| High                     | 128 | 0.33 (0.18–0.62)          | 0.0005  | 0.30 (0.11–0.84)            | 0.0212  |
| TLG\(^g\)                |     |                           |         |                             |         |
| Low                      | 110 | 1.00                      |         |                             |         |
| High                     | 89  | 0.43 (0.23–0.81)          | 0.0092  | Not included                |         |

\(\text{OR}\) \text{ odds ratio}, \(\text{CI}\) \text{ confidence interval}, \(\text{TN}\) \text{ triple-negative}, \(\text{ER}\) \text{ estrogen-receptor}, \(\text{HER2}\) \text{ human epidermal growth factor receptor 2}, \(\text{SUV}\(_{max}\)\) \text{ maximum standardized uptake value}, \(\text{SUV}\(_{peak}\)\) \text{ peak standardized uptake value}, \(\text{SUV}\(_{mean}\)\) \text{ mean standardized uptake value}, \(\text{MTV}\) \text{ metabolic tumor volume}, \(\text{TLG}\) \text{ total lesion glycolysis}

\(^a\)Low < 20%, high ≥ 20%

\(^b\)TN, \text{ER-negative/HER2-negative}; Luminal A, \text{ER-positive/HER2-negative with Ki67 < 20%}; Luminal B, \text{ER-positive/HER2-negative with Ki67 ≥ 20%}; Luminal-HER2, \text{ER-positive/HER2-positive}; HER2, \text{ER-negative/HER2-positive}

\(^c\)Low < 3.664, high ≥ 3.664

\(^d\)Low < 3.279, high ≥ 3.279

\(^e\)Low < 1.782, high ≥ 1.782

\(^f\)Low < 4.416, high ≥ 4.416

\(^g\)Low < 20.138, high ≥ 20.138
| Menopausal status            | $n$ | Univariable [OR (95% CI)] | $p$ value | Multivariable [OR (95% CI)] | $p$ value |
|-----------------------------|-----|--------------------------|-----------|-----------------------------|-----------|
| Premenopausal               | 31  | 1.00                     |           |                             |           |
| Postmenopausal              | 39  | 1.28 (0.50–3.29)         | 0.6110    |                             |           |
| T size (cm)                 |     |                          |           |                             |           |
| $\leq 2.0$                  | 14  | 1.00                     |           | 1.00                        |           |
| $> 2$                       | 56  | 0.11 (0.02–0.53)         | 0.0060    | 0.07 (0.004–1.03)           | 0.0522    |
| Lymph node metastasis      |     |                          |           |                             |           |
| Negative                    | 29  | 1.00                     |           |                             |           |
| Positive                    | 41  | 0.64 (0.24–1.66)         | 0.3538    |                             |           |
| Nuclear grade               |     |                          |           |                             |           |
| 1                           | 16  | 1.00                     |           | 1.00                        |           |
| 2 + 3                       | 50  | 11.42 (2.33–55.88)       | 0.0026    | 14.89 (1.07–207.75)         | 0.0446    |
| Ki67 expression levels      |     |                          |           |                             |           |
| Low                         | 9   | 1.00                     |           |                             |           |
| High                        | 58  | 8.57 (1.01–72.98)        | 0.0493    | Not calculated              |           |
| Subtypes                    |     |                          |           |                             |           |
| TN                          | 19  | 1.00                     |           | 1.00                        |           |
| Luminal A                   | 7   | Not calculated           |           | Not calculated              |           |
| Luminal B                   | 18  | 0.09 (0.02–0.45)         | 0.0030    | 0.11 (0.01–0.84)            | 0.0335    |
| Luminal-HER2                | 11  | 0.55 (0.12–2.56)         | 0.4944    | 0.34 (0.04–3.01)            | 0.3352    |
| HER2                        | 14  | 1.69 (0.34–8.40)         | 0.5197    | 0.71 (0.07–6.79)            | 0.7692    |
| Chemotherapy regimen        |     |                          |           |                             |           |
| Taxane                      | 6   | 1.00                     |           |                             |           |
| Anthracycline and taxane    | 63  | 5.50 (0.61–49.80)        | 0.1294    |                             |           |
| $\Delta$SUV$_{\text{max}}$ |     |                          |           |                             |           |
| Low                         | 33  | 1.00                     |           |                             |           |
| High                        | 37  | 7.39 (2.55–21.39)        | 0.0002    | Not included                |           |
| $\Delta$SUV$_{\text{peak}}$|     |                          |           |                             |           |
| Low                         | 33  | 1.00                     |           |                             |           |
| High                        | 37  | 7.39 (2.55–21.39)        | 0.0002    | Not included                |           |
| $\Delta$SUV$_{\text{mean}}$|     |                          |           |                             |           |
| Low                         | 34  | 1.00                     |           |                             |           |
| High                        | 36  | 8.45 (2.88–24.81)        | 0.0001    | 8.05 (1.45–44.80)           | 0.0173    |
| $\Delta$MTV$^f$            |     |                          |           |                             |           |
| Low                         | 26  | 1.00                     |           |                             |           |
| High                        | 44  | 2.49 (0.91–6.79)         | 0.0756    | Not included                |           |
| $\Delta$TLG$^g$            |     |                          |           |                             |           |
| Low                         | 32  | 1.00                     |           |                             |           |
| High                        | 38  | 6.50 (2.27–18.62)        | 0.0005    | Not included                |           |

OR odds ratio, CI confidence interval, TN triple-negative, ER estrogen receptor, HER2 human epidermal growth factor receptor 2, SUV$_{\text{max}}$ maximum standardized uptake value, SUV$_{\text{peak}}$ peak standardized uptake value, SUV$_{\text{mean}}$ mean standardized uptake value, MTV metabolic tumor volume, TLG total lesion glycolysis, $\Delta$ reduction rate

$^a$Low $\leq 20\%$, high $\geq 20\%$

$^b$TN, ER-negative/HER2-negative; Luminal A, ER-positive/HER2-negative with Ki67 $< 20\%$; Luminal B, ER-positive/HER2-negative with Ki67 $\geq 20\%$; Luminal-HER2, ER-positive/HER2-positive; HER2, ER-negative/HER2-positive

$^c$Low $< 56.3$, high $\geq 56.3$

$^d$Low $< 55.1$, high $\geq 55.1$

$^e$Low $< 55.8$, high $\geq 55.8$

$^f$Low $< 22.2$, high $\geq 22.2$

$^g$Low $< 65.0$, high $\geq 65.0$
The reason for this discrepancy may be the smaller number of participants ($n=26$ and $n=30$) compared with our study ($n=199$). Although SUV$_{\text{max}}$ levels at baseline and after one cycle were not correlated with pCR in 50 TN breast cancers, higher ΔSUV$_{\text{max}}$ values were significantly associated with increased pCR in multivariable analysis (OR 7.1; $p=0.014$).$^{30}$ Similarly, early changes in SUV$_{\text{max}}$ corrected for lean body mass (SUL$_{\text{max}}$) values between those achieving pCR and those not achieving pCR differed significantly in 59 HER2-negative breast cancers (63.0% vs. 32.9%; $p=0.003$).$^{31}$ Further studies demonstrated that not at baseline, but rather ΔSUV$_{\text{max}}$ after the start of NAC, was significantly associated with pCR.$^{25,28,29,32,33}$ In addition, the mean percentage of ΔTLG$_{30\%}$ ($p=0.005$), but not ΔMTV$_{30\%}$ ($p=0.262$), was significantly greater in the pCR group$^{27}$; however, neither ΔTLG nor ΔMTV were significantly associated with pCR in the report by Cheng et al.$^{21}$ Despite the significant correlation between tumor size reduction rate and the reduction rates of MTV ($p=0.0004$) or TLG ($p=0.002$), but not SUV$_{\text{max}}$ ($p=0.07$),$^{34}$ the ΔMTV and ΔTLG might be less useful than ΔSUV$_{\text{max}}$ when considering their pCR predicting ability.

Groheux et al. reported the AUC of pCR prediction increased from 0.63 to 0.76 when combined ΔSUV$_{\text{max}}$ with genomic grade index (GGI; $p=0.016$) in TN breast cancer patients.$^{28}$ We identified the significance of the combination of baseline MTV and ΔSUV$_{\text{mean}}$ in terms of pCR prediction. Interestingly, MTV was significantly associated with tumor size, but not with grade. Conversely, SUV$_{\text{max}}$ was significantly associated with grade, but not with tumor size.$^{33}$ Thus, MTV and ΔSUV may be a useful combination for predicting pCR mediating through different mechanisms. Small metabolic tumor size evaluable by MTV and high reduction rate of metabolic activity evaluable by SUV$_{\text{mean}}$ may be linked to achieving a pCR. We obtained data regarding metabolic parameters after treatment in 22 breast cancers; all six breast cancers that retained FDG uptake had non-pCR. Even though FDG uptake diminished after treatment, 5 of 16 (31.3%) breast cancers were defined as non-pCR (electronic supplementary data). Thus, the data obtained after treatment may not improve the ability to predict pCR.

We set the optimal cut-off values of ΔSUV$_{\text{max}}$, ΔSUV$_{\text{peak}}$, and ΔSUV$_{\text{mean}}$ at 56.3%, 55.1%, and 55.8%, respectively, and the predictive values of these metabolic parameters were similar. Previous studies reported ΔSUV$_{\text{max}}$ cut-off values ranging from 50 to 82.2%.$^{35}$ In addition, we used the average SUV value in the voxel that showed ≥ 40% of SUV$_{\text{max}}$ as the SUV$_{\text{mean}}$, as used in previous studies.$^{21–23}$ In other studies, thresholds of VOI were set to values between 30 and 50%.$^{27}$ Although the best threshold was unknown, we obtained similar results when calculated with other cut-off values and the reproducibility of SUV$_{\text{mean}}$ measurement was confirmed by a coauthor (data not shown). Issues regarding which parameter of SUV is most useful, and the best optimal cut-off value or threshold, require confirmation in future studies. In addition, we concluded, based on 70 breast cancers, that the sample size was not enough. Further studies involving large numbers of participants are needed.

To our knowledge, this is the first study to demonstrate the
TABLE 3 Univariable and multivariable analyses of the clinicopathological characteristics and the combination of MTV at baseline with the reduction of SUVmean in 70 breast cancers

|                      | n  | Univariable analysis | p value | Multivariable analysisa | p value |
|----------------------|----|----------------------|---------|-------------------------|---------|
|                      |    | [OR (95% CI)]        |         | [OR (95% CI)]          |         |
| MTVb                 |    |                      |         |                        |         |
| Low                  | 47 | 1.00                 |         | 1.00                    |         |
| High                 | 23 | 0.20 (0.07–0.60)     | 0.0043  | 0.18 (0.03–1.19)        | 0.0749  |
| ΔSUVmean             |    |                      |         |                        |         |
| Low                  | 34 | 1.00                 |         |                        |         |
| High                 | 36 | 8.45 (2.88–24.81)    | 0.0001  | 8.05 (1.45–44.80)       | 0.0173  |
| MTV and ΔSUVmean     |    |                      |         |                        |         |
| High and low         | 26 | 1.00                 |         | 1.00                    |         |
| Both high, or both low |29| 7.79 (2.13–28.49)    | 0.0019  | 6.89 (1.10–43.24)       | 0.0394  |
| Low and high         | 15 | 35.75 (5.73–223.00)  | 0.0001  | 28.63 (1.94–422.42)     | 0.0146  |

MTV metabolic tumor volume, SUVmean mean standardized uptake value, OR odds ratio, CI confidence interval, pCR pathological complete response, Δ reduction rate

aAdjusted for tumor size, nuclear grade, and subtypes that were significantly associated with pCR by univariable analysis in Table 2

bLow < 4.416, high ≥ 4.416
cLow < −55.8, high ≥ −55.8

useful combination of metabolic parameters obtained by PET for pCR in breast cancers treated with preoperative chemotherapy.

CONCLUSIONS

The combination of baseline MTV and ΔSUVmean precisely predicted the pCR in breast cancers treated with chemotherapy. The predictive value of this combination was independent and strong compared with that of other clinical factors, including tumor size, tumor grade, Ki67 levels, and subtypes. Small metabolic tumor size evaluable by MTV, and a high metabolic activity reduction as determined by SUV mean, might be useful for predicting improved pCR in breast cancers treated with preoperative chemotherapy.

FUNDING This study was supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (No. 26461963).

DISCLOSURE Tomoko Higuchi, Yukie Fujimoto, Hiromi Ozawa, Ayako Bun, Reiko Fukui, Yoshimasa Miyagawa, Michiko Imamura, Kazuhiro Kitajima, Koichiro Yamakado, and Yasuo Miyoshi declare that they have no competing interests.

OPEN ACCESS This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

REFERENCES

1. Mazouni C, Kau SW, Frye D, et al. Inclusion of taxanes, particularly weekly paclitaxel, in preoperative chemotherapy improves pathologic complete response rate in estrogen receptor-positive breast cancers. Ann Oncol. 2007; 18:874–880.
2. Munkacsy G, Szasz MA, Menyhart O. Gene expression-based prognostic and predictive tools in breast cancer. Breast Cancer. 2015; 22:245–252.
3. Parker JS, Mullins M, Cheang MC, et al. Supervised risk predictor of breast cancer based on intrinsic subtypes. J Clin Oncol. 2009; 27:1160–1167.
4. Lin CY, Lin CL, Kao CH. Staging/restaging performance of F18-fluorodeoxyglucose positron emission tomography/magnetic resonance imaging in breast cancer: a review and meta-analysis. Eur J Radiol. 2018; 107:158–165.
5. Kadoya T, Aogi K, Kiyoto S, Masumoto N, Sugawara Y, Okada M. Role of maximum standardized uptake value in fluorodeoxyglucose positron emission tomography/computed tomography predicts malignancy grade and prognosis of operable breast cancer: a multi-institute study. Breast Cancer Res Treat. 2013; 141:269–275.
6. Ahn SG, Park JT, Lee HM, et al. Standardized uptake value of 18F-fluorodeoxyglucose positron emission tomography for prediction of tumor recurrence in breast cancer beyond tumor burden. Breast Cancer Res. 2014; 16:302.
7. 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 who are at a high risk of recurrence after mastectomy. Cancer Res Treat. 2016; 48:508–517.
8. Evangelista L, Cervino AR, Ghiotto C, et al. Could semiquantitative FDG analysis add information to the prognosis in patients with stage II/III breast cancer undergoing neoadjuvant treatment? Eur J Nucl Med Mol Imaging. 2015; 42:1648–1655.
9. Higuchi T, Nishimukai A, Ozawa H, et al. Prognostic significance of preoperative 18F-FDG PET/CT for breast cancer subtypes. *Breast* 2016; 30:5–12.
10. Goulon D, Necib H, Henaff B, Rousseau C, Carlier T, Kraebber-Bodere F. Quantitative evaluation of therapeutic response by FDG-PET-CT in metastatic breast cancer. *Front Med (Lausanne)*. 2016; 3:19.

11. Andrade WP, Lima EN, Osório CA, et al. Can FDG-PET/CT predict early response to neoadjuvant chemotherapy in breast cancer? *Eur J Surg Oncol*. 2013; 39:1358–1363.
12. Avril S, Muzic RF Jr, Plecha D, Traugher BJ, Vinayak S, Avril N. 18-F-FDG PET/CT for monitoring of treatment response in breast cancer. *J Nucl Med*. 2016; 57:343–359.
13. Groheux D, Mankoff D, Espie M, Hindle E. 18F-FDG PET/CT in the early prediction of pathological response in aggressive subtypes of breast cancer: review of the literature and recommendations for use in clinical trials. *Eur J Nucl Med Mol Imaging*. 2016; 43:983–993.

14. Akimoto E, Kadoya T, Kajitani K, et al. Role of 18F-PET/CT in predicting prognosis of patients with breast cancer after neoadjuvant chemotherapy. *Clin Breast Cancer*. 2018; 18:45–52.
15. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving considerations for PET response criteria in solid tumors. *J Nucl Med*. 2009; 50:122S–150S.
16. Soret M, Bacharach SL, Buvat I. Partial-volume effect in PET tumor imaging. *J Nucl Med*. 2007; 48:932–945.
17. Groheux D, Sanna A, Majdoub M, et al. Baseline tumor 18F-FDG uptake and modifications after 2 cycles of neoadjuvant chemotherapy are prognostic of outcome in ER+/HER2- breast cancer. *J Nucl Med*. 2015; 56:824–831.
18. Lee HW, Lee HM, Choi SE, et al. The prognostic impact of early change in 18F-FDG PET SUV after neoadjuvant chemotherapy in patients with locally advanced breast cancer. *J Nucl Med*. 2016; 57:1183–1188.

19. The Japanese Breast Cancer Society. General rules for clinical and pathological recording of breast cancer, 18th ed. Tokyo: Kanehara Co., Ltd; 2018.
20. Kitajima K, Miyoshi Y, Yamano T, Odawara S, Higuchi T, Yamakado K. Prognostic value of FDG-PET and DWI in breast cancer. *Ann Nucl Med*. 2018; 32:44–53.

21. Cheng L, Zhang J, Wang Y, et al. Textural features of 18F-FDG PET after two cycles of neoadjuvant chemotherapy can predict pCR in patients with locally advanced breast cancer. *Ann Nucl Med*. 2017; 31:544–552.
22. Jena A, Tanega S, Singh A, et al. Association of pharmacokinetic and metabolic parameters derived using simultaneous PET/MRI: initial findings and impact on response evaluation in breast cancer. *Eur J Radiol*. 2017; 92:30–36.
23. Garcia-Vicente AM, Pérez-Beteta J, Pérez-García VM, Molina D, Jiménez-Londoño GA, et al. Metabolic tumor burden assessed by dual time point [18F]FDG PET/CT in locally advanced breast cancer: relation with tumor biology. *Mol Imaging Biol*. 2017; 19:636–644.
24. Jin S, Kim SB, Ahn JH, et al. 18 F-fluorodeoxyglucose uptake predicts pathological complete response after neoadjuvant chemotherapy for breast cancer: a retrospective cohort study. *J Surg Oncol*. 2013; 107:180–187.
25. Pakh K, Rhee S, Cho J, et al. The role of interim 18F-FDG PET/CT in predicting early response to neoadjuvant chemotherapy in breast cancer. *Anticancer Res*. 2014; 34:4447–4455.
26. Groheux D, Majdoub M, Sanna A, et al. Early metabolic response to neoadjuvant treatment: FDG PET/CT criteria according to breast cancer subtype. *Radiology*. 2015; 277:358–371.
27. Cho N, Im SA, Cheon GJ, et al. Integrated 18F-FDG PET/MRI in breast cancer: early prediction of response to neoadjuvant chemotherapy. *Eur J Nucl Med Mol Imaging*. 2018; 45:328–339.
28. Groheux D, Biard L, Lehmann-Che J, et al. Tumor metabolism assessed by FDG-PET/CT and tumor proliferation assessed by genomic grade index to predict response to neoadjuvant chemotherapy in triple negative breast cancer. *Eur J Nucl Med Mol Imaging*. 2018; 45:1279–1288.
29. de Cremoux P, Biard L, Poiriot B, et al. 18F-PET/CT and molecular markers to predict response to neoadjuvant chemotherapy and outcome in HER2-negative advanced luminal breast cancers patients. *Oncotarget*. 2018; 9:16343–16353.
30. Humbert O, Riedinger JM, Charon-Barra C, et al. Identification of biomarkers including 18F-FDG-PET/CT for early prediction of response to neoadjuvant chemotherapy in triple-negative breast cancer. *Clin Cancer Res*. 2015; 21:5460–5468.
31. Connolly RM, Leal JP, Goetz MP, et al. TBCRC 008: Early change in 18F-FDG uptake on PET predicts response to preoperative systemic therapy in human epidermal growth factor receptor 2–negative primary operable breast cancer. *J Nucl Med*. 2015; 56:31–37.
32. Kiyoto S, Sugawara Y, Hosokawa K, Nishimura R, Yamashita N, Ohsumi S, et al. Predictive ability of 18F-fluorodeoxyglucose positron emission tomography/computed tomography for pathological complete response and prognosis after neoadjuvant chemotherapy in triple-negative breast cancer patients. *Asia Ocean J Nucl Med Biol*. 2016; 4:3–11.
33. Lemairignier C, Martineau A, Teixeira L, Vercellino L, Espie M, Merlet P, et al. Correlation between tumour characteristics, SUV measurements, metabolic tumour volume, TLG and textural features assessed with 18F-FDG PET in a large cohort of oestrogen receptor-positive breast cancer patients. *Eur J Nucl Med Mol Imaging*. 2017; 44:1145–1154.
34. Im HJ, Kim YK, Kim YI, Lee JJ, Lee WW, Kim SE. Usefulness of combined metabolic-volumetric indices of (18)F-FDG PET/CT for the early prediction of neoadjuvant chemotherapy outcomes in breast cancer. *Nucl Med Mol Imaging* 2013; 47:36–43.
35. Li H, Yao L, Jin P, Hu L, Li X, Guo T, Yang K. MRI and PET/CT for evaluation of the pathological response to neoadjuvant chemotherapy in breast cancer: a systematic review and meta-analysis. *Breast*. 2018; 40:106–115.

**Publisher’s Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.