# Volume-based Metabolic Tumor Response to Neoadjuvant Chemotherapy Is Associated with an Increased Risk of Recurrence in Breast Cancer[1]

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**Purpose:** To evaluate the prognostic value of a volume-based metabolic tumor response to neoadjuvant chemotherapy in patients with locally advanced breast cancer.

**Materials and Methods:** This study was approved by the institutional review board, with waivers of informed consent. One hundred sixty-seven patients (mean age, 44 years; range, 22–68 years) with clinical stage II or III breast cancer who underwent fluorine 18 fluorodeoxyglucose positron emission tomography/computed tomography scans at baseline and after completion of neoadjuvant chemotherapy between July 2006 and June 2013 were selected. The association between the metabolic response parameters and the disease-free survival was assessed by using a Cox proportional hazards regression model and time-dependent receiver operating characteristic curve analysis. Metabolic response parameters included the maximum standardized uptake value ($SUV_{max}$), the total metabolic tumor volume ($MTV_{total}$), and the relative decrease in $SUV_{max}$ and $MTV_{total}$.

**Results:** In the Cox model, posttreatment $SUV_{max}$ ($P = .029$) and $MTV_{total}$ ($P = .028$) and relative decreases in $SUV_{max}$ ($P = .032$) and $MTV_{total}$ ($P = .005$) after neoadjuvant chemotherapy were significantly associated with disease-free survival after adjusting for pretreatment clinical stage, yp stage, and tumor subtype. In the time-dependent receiver operating characteristic curve analysis, $MTV_{total}$ after neoadjuvant chemotherapy had the highest association with outcome compared with the other parameters ($P < .001$). $MTV_{total}$ of up to 0.2 $cm^3$ after neoadjuvant chemotherapy was significantly associated with a favorable outcome in patients who did not achieve pathologic complete response after neoadjuvant chemotherapy.

**Conclusion:** The volume-based metabolic tumor response to neoadjuvant chemotherapy is associated with an increased risk of recurrence, regardless of tumor subtype and pathologic tumor response.



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In patients with breast cancer, neoadjuvant chemotherapy (NAC) is a treatment option not only for unresectable locally advanced disease but also for large operable breast cancer, because it may reduce tumor size and allow for breast-conserving surgery (1). Although NAC itself did not improve survival compared with postoperative treatment, achievement of pathologic complete response in the primary tumor and regional lymph nodes after NAC is widely accepted as the most powerful surrogate marker for longer disease-free survival (DFS) and overall survival (1,2).

Noninvasive assessment of response to NAC may guide further treatment strategies. Identifying nonresponders earlier may allow patients to avoid further ineffective chemotherapy. Accurate evaluation of residual disease facilitates planning of the most optimal surgery. Furthermore, improved prognostication of partial responders may guide additional adjuvant treatment planning.

The most widely studied role of fluorine 18 ($^{18}$F) fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) in the response assessment of breast cancer during or after NAC was whether it could be used to predict pathologic response earlier (3). The investigators of a meta-analysis concluded that $^{18}$F-FDG PET or PET/CT imaging conducted after the first or second cycles of NAC has moderately high sensitivity, specificity, and positive predictive value in the early prediction of response (4,5). However, most of the PET studies in patients who have undergone NAC have common limitations of small patient numbers, variable cutoff value of percentage change in the standardized uptake value (SUV), and limited use of metabolic response parameters with only SUV. Recent studies showed that the relative decrease in volume-based PET parameters after two cycles of NAC could be used to predict pathologic complete response more accurately than SUV (6–8). Many investigators studied only the association between PET parameters and pathologic complete response and did not evaluate the relationship between PET parameters and prognosis in patients who failed to achieve pathologic complete response.

Our purpose was to evaluate the prognostic value of the volume-based metabolic tumor response to NAC in patients with locally advanced breast cancer.

## Advances in Knowledge

- In patients with locally advanced breast cancer who undergo neoadjuvant chemotherapy (NAC) followed by surgical resection, posttreatment maximum standardized uptake value ($SUV_{max}$, $P$ = .029) and total metabolic tumor volume ($MTV_{total}$, $P$ = .028) and relative decreases in $SUV_{max}$ ($P$ = .032) and $MTV_{total}$ ($P$ = .005) after completion of NAC were significantly associated with disease-free survival, independent of tumor subtype and yp stage.
- The volume-based metabolic tumor response ($MTV_{total}$ after NAC) had the highest association with treatment outcome compared with the other metabolic response parameters ($P < .001$); the metabolic tumor response ($MTV_{total}$ after NAC ≤ 0.2 cm$^3$) was significantly associated with a favorable outcome in patients who did not achieve pathologic complete response ($P < .001$).

## Materials and Methods

### Patients and Treatment

Our institutional review board approved this retrospective study, and informed consent was waived. We retrospectively reviewed data from all patients with histologically proven breast cancer (clinical stage II or III) who underwent NAC between July 2006 and June 2013. We identified 484 eligible patients from the tumor registry database. Among these patients, we excluded 14 patients who did not undergo at least three cycles of NAC before surgery. Patients were required to have undergone $^{18}$F-FDG PET/CT scans at baseline and after completion of NAC ($n$ = 201). Patients who did not undergo breast surgery after NAC ($n$ = 34) were excluded. The final study population consisted of 167 women (mean age, 44 years; range, 22–68 years) (Fig 1).

Clinical-pathologic characteristics and survival data were obtained from the patients' medical records. Post-therapy stage (yp stage) was obtained from surgical pathology reports. Subtype of breast cancer was determined by means of immunohistochemical testing for estrogen receptor (ER), progesterone receptor (PR), and human

## Implication for Patient Care

- The volume-based metabolic tumor response to NAC could be a new method for assessment of response to enable stratification of prognosis in patients with locally advanced breast cancer.

**Published online before print**
10.1148/radiol.14141129 **Content codes:** BR NM

**Radiology 2015;** 275:235–244

**Abbreviations:**
AUC = area under the ROC curve
CI = confidence level
DFS = disease-free survival
ER = estrogen receptor
FDG = fluorodeoxyglucose
MTV = metabolic tumor volume
$MTV_{total}$ = total MTV
NAC = neoadjuvant chemotherapy
PR = progesterone receptor
ROC = receiver operating characteristic
SUV = standardized uptake value
$SUV_{max}$ = maximum SUV

**Author contributions:**
Guarantors of integrity of entire study, S.H.H., W.H.K., J.E.L., J.Y.C.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, S.H.H., H.K.A., W.H.K.; clinical studies, S.H.H., Y.H.P., Y.H.I., W.H.K., J.E.L., S.J.N., J.Y.C.; experimental studies, W.H.K., E.Y.C.; statistical analysis, S.H.H., W.H.K., J.Y.C.; and manuscript editing, S.H.H., H.K.A., W.H.K., J.E.L., J.Y.C.

Conflicts of interest are listed at the end of this article.

**Figure 1**

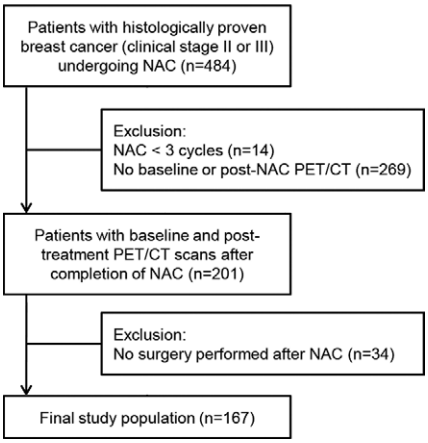


**Figure 1:** Flowchart shows study population selection, with exclusion criteria.

epidermal growth factor receptor 2 (HER2). HER2 status was considered positive when the immunohistochemical result was 3+. When the immunohistochemical result for HER2 was 2+, HER2 amplification was confirmed by means of silver in situ hybridization or fluorescence in situ hybridization analysis.

NAC included the following regimens: doxorubicin and cyclophosphamide, doxorubicin and cyclophosphamide followed by taxane, doxorubicin and docetaxel, or taxane with anti-HER2 agents. Pathologic complete response after NAC was defined as the absence of invasive carcinoma in the breast and the lymph nodes.

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

All patients fasted for at least 6 hours before the PET/CT study. Blood glucose levels were measured and were required to be less than 200 mg/dL (11.1 mmol/L). Whole-body PET and unenhanced CT images were acquired by using a PET/CT scanner (Discovery STE; GE Healthcare, Milwaukee, Wis). Whole-body CT was performed by using a 16-section helical CT scanner with 30–170 mAs adjusted to the patient's body weight at 140 kVp and 3.75-mm section width. After the CT scan, an emission scan was performed from the thigh to the head for 2.5 minutes per frame in three-dimensional mode, 60 minutes after the intravenous injection of $^{18}$F-FDG (5.5 MBq per kilogram of body weight). PET images were reconstructed by using CT for attenuation correction with the ordered subsets expectation maximization algorithm (20 subsets, two iterations) with a voxel size of $3.9 \times 3.9 \times 3.3$ mm. SUV was normalized to the patient's body weight.

### Assessment of Metabolic Tumor Response

Assessment of metabolic tumor response with the volume viewer software on a GE Advantage Workstation version 4.4 (GE Healthcare) was performed independently by two investigators (S.H.H., a nuclear medicine physician with 9 years of clinical experience in PET/CT imaging; and a nonauthor, a research technician with 3 years of experience in PET/CT image analysis), who were unaware of clinical information. One data set measured by S.H.H. was used for all subsequent analyses. The other data set measured by the nonauthor was used only for the assessment of interobserver variability. We placed a volume of interest over target lesions around the highest centers of metabolic activity in the primary tumor and all metastatic lymph nodes and then used software to measure the maximum SUV ($SUV_{max}$) and metabolic tumor volume (MTV). The baseline images were used to guide the volume of interest placements on the posttreatment images. MTV was defined as the tumor volume segmented with $^{18}$F-FDG uptake above a threshold SUV of 2.5. We measured the $SUV_{max}$ of the primary tumor and the total MTV ($MTV_{total}$) of the primary tumor and all metastatic lymph nodes on the baseline images (baseline $SUV_{max}$ and baseline $MTV_{total}$, respectively) and posttreatment images (posttreatment $SUV_{max}$ and posttreatment $MTV_{total}$, respectively). We also calculated the relative decreases in $SUV_{max}$ ($\Delta SUV_{max}$) and $MTV_{total}$ ($\Delta MTV_{total}$). Relative decrease parameters were calculated with the following equations: $\Delta SUV_{max}$ = (baseline $SUV_{max}$ − posttreatment $SUV_{max}$)/baseline $SUV_{max} \times 100\%$ and $\Delta MTV_{total}$ = (baseline $MTV_{total}$ − posttreatment $MTV_{total}$)/baseline $MTV_{total} \times 100\%$. If the target lesion was not visualized or could not be distinguished from the background after NAC, $SUV_{max}$ was measured with a 20-mm–diameter spherical volume of interest at the same position as the baseline target lesion. If the $SUV_{max}$ of the target lesion was less than 2.5, MTV was set as a single voxel with a volume of 0.05 $cm^3$.

### Statistical Analysis

Univariable and multivariable analyses conducted by using a Cox proportional hazards regression model were performed for assessment of the relationship between the metabolic response parameters and DFS. Continuous PET parameters were examined for normality and skewness. A $\log_2$ transformation was applied to the skewed variables, $SUV_{max}$ and MTV. Metabolic response parameters were analyzed in each separate model ($SUV_{max}$, $\Delta SUV_{max}$, $MTV_{total}$, and $\Delta MTV_{total}$ models) because there was multicollinearity between MTV and $SUV_{max}$. The overall discriminatory capacity of the Cox model was assessed by using the Harrell concordance index (*C* index), which was validated by bootstrapping with 1000 replications (9).

DFS was defined as the time from the date of surgery to the date of local-regional or distant recurrence, death from breast cancer, or the last follow-up date. Survival curves were estimated by using the Kaplan-Meier method and compared by using the log-rank test. We applied maximally selected rank statistics to identify an optimal cutoff of the metabolic response parameter (10). To assess and compare the predictive performance of the metabolic response parameters, we used the time-dependent receiver operating characteristic (ROC) curve for censored survival data and the area under the ROC curve (AUC) as criteria (11). We derived the integrated AUC as a measure of overall prediction from the results of the time-dependent ROC curves.

The "maxstat" package for maximally selected rank statistics, the "survcomp" package for time-dependent ROC curve, and the "rms" package for boot-strapped internal validation in the R open source statistical software (R Foundation, Vienna, Austria; *http://*

*www.R-project.org*) were used. Interobserver variability for the measurement was assessed by using the concordance correlation coefficient in MedCalc version 13.1 (MedCalc Software, Mariakerke, Belgium) (12). Differences of metabolic response parameters between the two independent groups were determined by using a Mann-Whitney *U* test. All tests were two sided, all confidence intervals (CIs) were reported at the 95% level, and *P* values less than .05 were considered to indicate a statistically significant difference. To account for multiple testing, we used Bonferroni correction, and *P* values less than .0125 (.05/4 = .0125) were considered to indicate a significant difference.

## Results

### Patient Characteristics

Patient characteristics are summarized in Table 1. All patients had clinical stage II or III disease at baseline and underwent NAC with a median of eight cycles of regimens that contained anthracycline or taxane. There was no primary tumor that showed an $SUV_{max}$ less than 2.5 at staging (range, 2.5–30.4). The mean interval between the baseline and post-NAC scans was 5 months, with a range of 2–7 months. A post-NAC scan was performed a mean of 19 days after the completion of NAC, with a range of 1–49 days. After the completion of NAC, 103 patients (61.7%) underwent breast-conserving surgery, and the other 64 patients (38.3%) underwent modified radical mastectomy or total mastectomy a mean of 10 days after the post-NAC scan, with a range of 1–29 days.

Additional adjuvant chemotherapy was performed in 89 patients, including 31 of 43 patients who had received only anthracycline as NAC and were then treated with additional taxane as adjuvant treatment. Among 45 patients with HER2-positive breast cancer, 16 patients received anti-HER2 treatment preoperatively, and 34 patients were additionally administered HER2-targeted chemotherapy postoperatively. Adjuvant radiation therapy was performed in 161 patients (96.4%), and adjuvant endocrine therapy was administered for all hormone receptor–positive disease.

There was excellent agreement between the two observers for measurement of baseline $SUV_{max}$ (concordance correlation coefficient = 0.999; 95% CI: 0.998, 0.999), posttreatment $SUV_{max}$ (concordance correlation coefficient = 1.000; 95% CI: 0.999, 1.000), baseline $MTV_{total}$ (concordance correlation coefficient = 0.982; 95% CI: 0.977, 0.985), and posttreatment $MTV_{total}$ (concordance correlation coefficient = 0.996; 95% CI: 0.993, 0.998).

### Prognostic Factors for DFS

The median follow-up duration was 19 months, with a range of 3–85 months. At the time of analysis, 33 patients (19.8%) had local-regional or distant recurrence, and no patients had died. In the univariable analyses, clinical stage at diagnosis, yp stage after neoadjuvant treatment, breast cancer subtype, posttreatment $SUV_{max}$, $\Delta SUV_{max}$, baseline $MTV_{total}$, posttreatment $MTV_{total}$, and $\Delta MTV_{total}$ were significant prognostic factors for DFS (Table 2). In the multivariable analyses, posttreatment $SUV_{max}$ (hazard ratio = 1.51 for a doubling of posttreatment $SUV_{max}$, $P$ = .029), $\Delta SUV_{max}$ (hazard ratio = 0.98, $P$ = .032), posttreatment $MTV_{total}$ (hazard ratio = 1.14 for a doubling of posttreatment $MTV_{total}$, $P$ = .028), and $\Delta MTV_{total}$ (hazard ratio = 0.99, $P$ = .005) were significantly associated with DFS after adjusting for clinical stage, yp stage, and tumor subtype. Baseline $MTV_{total}$ was not a significant prognostic factor. However, if the multiple testing had been taken into account, $\Delta MTV_{total}$ would have remained significant after adjustment for a family-wise error rate via Bonferroni correction (Table 3). The Cox model with posttreatment $MTV_{total}$ ($C$ index, 0.790; bootstrap corrected, 0.765) had a higher discriminative ability than the $\Delta MTV_{total}$ model ($C$ index, 0.768; bootstrap corrected, 0.750).

Time-dependent ROC curve analysis showed the AUC at a given follow-up time from the date of surgery (Fig 2). Integrated AUC as a measure of overall prediction was the best with posttreatment

**Table 1**

**Clinical Characteristics of Patients with Breast Cancer**

| Characteristic | No. of Patients ($n$ = 167) |
|---|---|
| Median age (y)* | 44 (22–68) |
| Histologic finding | |
| Invasive ductal carcinoma | 158 (94.6) |
| Invasive lobular carcinoma | 4 (2.4) |
| Other | 5 (3.0) |
| Clinical T stage before NAC | |
| T1/T2/T3/T4 | 6/76/71/14 |
| Clinical N stage before NAC | |
| N0/N1/N2/N3 | 20/63/38/46 |
| ypT stage after NAC | |
| T0/Tis/T1/T2/T3/T4 | 19/17/56/38/33/4 |
| ypN stage after NAC | |
| N0/N1/N2/N3 | 66/50/28/23 |
| Clinical stage before NAC | |
| Stage II | 53 (31.7) |
| Stage III | 114 (68.3) |
| yp stage after NAC | |
| Stage 0 | 29 (17.4) |
| Stage I | 25 (15.0) |
| Stage II | 53 (31.7) |
| Stage III | 60 (35.9) |
| Tumor subtype | |
| ER and PR positive, HER2 negative | 67 (40.1) |
| ER and PR positive, HER2 positive | 18 (10.8) |
| ER and PR negative, HER2 positive | 27 (16.2) |
| ER and PR negative, HER2 negative | 55 (32.9) |
| Type of surgery | |
| Breast-conserving surgery | 103 (61.7) |
| Mastectomy | 64 (38.3) |
| NAC regimens | |
| Anthracycline and taxane based | 107 (64.1) |
| Anthracycline based | 43 (25.7) |
| Taxane based | 17 (10.2) |
| Anti-HER2 treatment in 45 patients with HER2-positive status | |
| Neoadjuvant and adjuvant | 16 (35.6) |

*Table 1 (continues)*

**Table 1 (continued)**

**Clinical Characteristics of Patients with Breast Cancer**

| Characteristic | No. of Patients ($n$ = 167) |
|---|---|
| Adjuvant only | 18 (40.0) |
| None | 11 (24.4) |

Note.—Data are numbers of patients, with percentages in parentheses, unless specified otherwise.

* The age range appears in parentheses.

**Table 2**

**Univariable Cox Regression Analysis for DFS**

| Variable | Hazard Ratio | 95% CI | *P* Value |
|---|---|---|---|
| Age (1-year increase) | 0.982 | 0.942, 1.024 | .400 |
| Clinical stage group before NAC | | | |
| Stage III vs II | 2.482 | 1.024, 6.018 | .044 |
| yp stage group after NAC | | | |
| Stage 0 or I | 1.000 | … | .001 |
| Stage II | 2.860 | 0.737, 11.092 | .129 |
| Stage III | 7.916 | 2.375, 26.383 | .001 |
| Tumor subtype | | | |
| ER and PR positive, HER2 negative | 1.000 | … | .026 |
| ER and PR positive or negative, HER2 positive | 0.814 | 0.301, 2.204 | .686 |
| ER and PR negative, HER2 negative | 2.367 | 1.097, 5.111 | .028 |
| Baseline $SUV_{max}$* | 0.965 | 0.627, 1.485 | .872 |
| Posttreatment $SUV_{max}$* | 1.863 | 1.381, 2.514 | <.001 |
| Baseline $MTV_{total}$* | 1.223 | 1.012, 1.477 | .037 |
| Posttreatment $MTV_{total}$* | 1.262 | 1.151, 1.383 | <.001 |
| $\Delta SUV_{max}$ (%) | 0.977 | 0.968, 0.986 | <.001 |
| $\Delta MTV_{total}$ (%) | 0.993 | 0.989, 0.996 | <.001 |

* Continuous variables in $\log_2$ scale.

**Table 3**

**Multivariable Cox Regression Models for DFS**

| Model and Variable | Hazard Ratio | 95% CI | *P* Value |
|---|---|---|---|
| $MTV_{total}$ model | | | |
| Baseline $MTV_{total}$* | 1.002 | 0.815, 1.231 | .984 |
| Posttreatment $MTV_{total}$* | 1.135 | 1.014, 1.270 | .028 |
| $SUV_{max}$ model | | | |
| Baseline $SUV_{max}$* | 0.722 | 0.419, 1.243 | .242 |
| Posttreatment $SUV_{max}$* | 1.511 | 1.043, 2.188 | .029 |
| $\Delta MTV_{total}$ (%) | 0.995 | 0.992, 0.998 | .005 |
| $\Delta SUV_{max}$ (%) | 0.989 | 0.978, 0.999 | .032 |

Note.—These models were adjusted for pretreatment clinical stage, yp stage, and tumor subtype.

* Continuous variables in $\log_2$ scale.

$MTV_{total}$ of 0.740, followed by $\Delta MTV_{total}$ of 0.713, $\Delta SUV_{max}$ of 0.702, posttreatment $SUV_{max}$ of 0.645, baseline $MTV_{total}$ of 0.611, and baseline $SUV_{max}$ of 0.484. Postneoadjuvant PET parameters (posttreatment $SUV_{max}$ and posttreatment $MTV_{total}$) demonstrated better predictive performance than pretreatment PET parameters (baseline $SUV_{max}$ and baseline $MTV_{total}$). Relative decrease parameters ($\Delta SUV_{max}$ and $\Delta MTV_{total}$) showed good predictive performance. Posttreatment $MTV_{total}$ was a significantly better metabolic response parameter than the other PET parameters ($P < .001$).

### Prognostic Stratification according to Posttreatment $MTV_{total}$

The optimal cutoff value of posttreatment $MTV_{total}$ that allowed risk stratification was 0.2 $cm^3$ on the basis of the result of this study by using maximally selected rank statistics. Patients were classified as metabolic responders (posttreatment $MTV_{total} \leq 0.2$ $cm^3$) or metabolic nonresponders (posttreatment $MTV_{total} > 0.2$ $cm^3$) (Fig 3). $SUV_{max}$ and $MTV_{total}$ before and after NAC were significantly higher in metabolic nonresponders than in metabolic responders. $\Delta SUV_{max}$ and $\Delta MTV_{total}$ showed a significant difference between metabolic responders and metabolic nonresponders (Table 4).

Pathologic complete response was achieved in 29 patients (17.4%). None of these patients had local-regional or distant failure during the follow-up period. In the subgroup of patients ($n$ = 138) who did not achieve pathologic complete response, posttreatment $MTV_{total}$ of up to 0.2 $cm^3$ was significantly associated with a favorable outcome ($P < .001$). DFS was significantly longer in metabolic responders in each stratum of tumor subtype (Fig 4) and yp stage (Fig 5), except for the subgroup with the ER- and PR-negative, HER2-negative subtype and those with yp stage I. A subgroup analysis with a more homogeneous population was performed on patients ($n$ = 78) without pathologic complete response after the same NAC (with eight cycles of anthracycline and cyclophosphamide, followed by taxane). The multivariable analysis showed that the metabolic nonresponse after NAC was significantly associated with worse DFS after adjusting for clinical stage, yp stage, and tumor subtype (Table 5).

## Discussion

In this study, the volume-based metabolic tumor response was a significant prognostic factor for DFS, independent

**Figure 2**

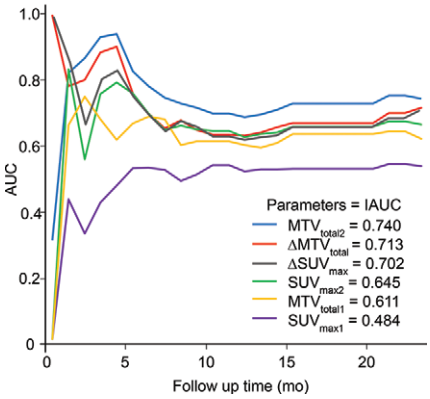


**Figure 2:** Graph shows time-dependent ROC curve analysis for prediction of DFS. *IAUC* = integrated AUC, $MTV_{total1}$ = baseline $MTV_{total}$, $MTV_{total2}$ = posttreatment $MTV_{total}$, $SUV_{max1}$ = baseline $SUV_{max}$, $SUV_{max2}$ = posttreatment $SUV_{max}$.

**Figure 3**

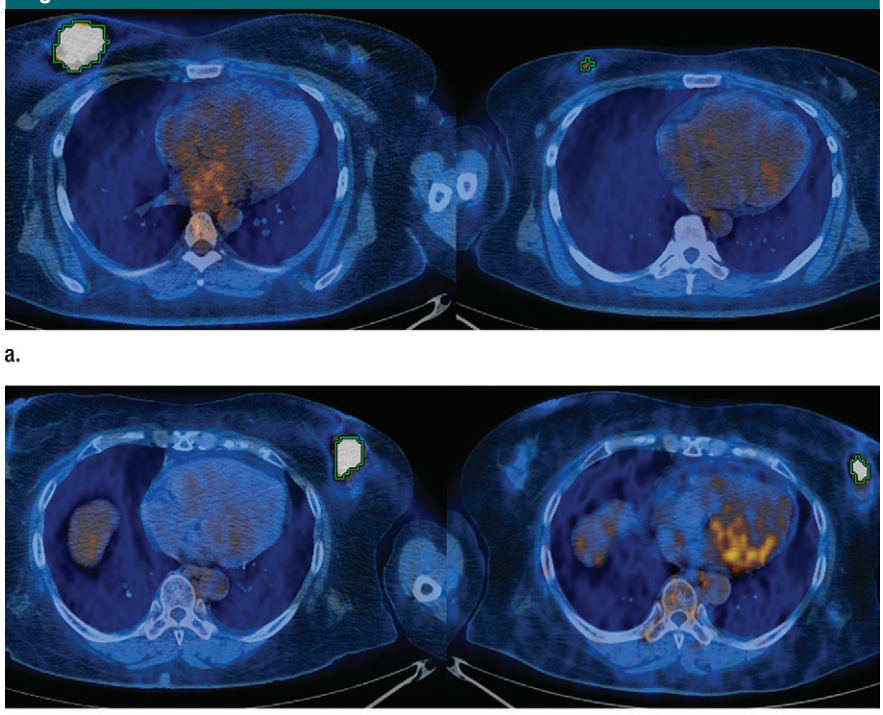


**Figure 3:** Baseline (left) and post-NAC (right) $^{18}$F-FDG PET/CT images in **(a)** a 36-year-old woman with ER- and PR-positive, HER2-negative breast cancer and **(b)** a 57-year-old woman with ER- and PR-negative, HER2-negative breast cancer. These two patients with ypT1N0 breast cancer underwent NAC with eight cycles of anthracycline and cyclophosphamide, followed by taxane and breast-conserving surgery. Axial fused PET/CT images show **(a)** a metabolic responder (baseline $SUV_{max}$ = 23.4, posttreatment $SUV_{max}$ = 3.2, $\Delta SUV_{max}$ = 86.3%, baseline $MTV_{total}$ = 59.9 $cm^3$, posttreatment $MTV_{total}$ = 0.15 $cm^3$, $\Delta MTV_{total}$ = 99.7%) and **(b)** a metabolic nonresponder (baseline $SUV_{max}$ = 15.7, posttreatment $SUV_{max}$ = 19, $\Delta SUV_{max}$ = −21%, baseline $MTV_{total}$ = 12.5 $cm^3$, posttreatment $MTV_{total}$ = 9.2 $cm^3$, $\Delta MTV_{total}$ = 26.4%).

of tumor subtype and yp stage in patients with locally advanced breast cancer. $MTV_{total}$ of up to 0.2 $cm^3$ after NAC was significantly associated with a favorable outcome in patients who did not achieve pathologic complete response. $MTV_{total}$ after NAC was used to predict disease outcome more accurately than were $SUV_{max}$ parameters.

Since pathologic complete response is the most powerful prognostic marker for longer survival after NAC, most studies on the use of imaging modalities after NAC have focused on predicting pathologic complete response accurately before surgery. MR imaging was reported to have high accuracy for prediction of pathologic complete response (13) and is currently the standard imaging modality recommended by the National Comprehensive Cancer Network for response evaluation in patients with breast cancer who are undergoing NAC (14). SUV at PET after completion of NAC is associated with pathologic complete response; however, this PET parameter demonstrated inferior accuracy in the prediction of pathologic complete response compared with MR imaging (15,16), which suggests that improvements in PET/CT analysis will be important to better demonstrate the benefit of $^{18}$F-FDG PET/CT in clinical practice.

**Table 4**

**Comparisons of Metabolic Response Parameters between Metabolic Responders and Metabolic Nonresponders**

| Parameter | Responders ($n$ = 113) | Nonresponders ($n$ = 54) | $P$ Value |
|---|---|---|---|
| Baseline $SUV_{max}$ | 8.5 (6.0–11.7) | 11.1 (8.8–16.0) | <.001 |
| Posttreatment $SUV_{max}$ | 1.6 (1.3–2.0) | 5.2 (3.5–10.9) | <.001 |
| Baseline $MTV_{total}$ | 19.7 (8.5–41.7) | 26.3 (12.7–48.7) | .028 |
| Posttreatment $MTV_{total}$ | 0.05 (0.05–0.05) | 2.1 (0.7–11.8) | <.001 |
| $\Delta SUV_{max}$ (%) | 80.0 (69.9–87.3) | 51.9 (12.5–68.5) | <.001 |
| $\Delta MTV_{total}$ (%) | 99.7 (99.2–99.9) | 89.8 (69.1–97.4) | <.001 |

Note.—Data are median values, with interquartile ranges in parentheses.

In most of the previous $^{18}$F-FDG PET/CT studies regarding the early prediction of tumor response, the PET/CT scan was performed only after several cycles of NAC, not after completion of all planned cycles. A meta-analysis showed that the pooled sensitivity and specificity of SUV in the prediction of tumor response was 80.5% (95% CI: 75.9%, 84.5%) and

**Figure 4**

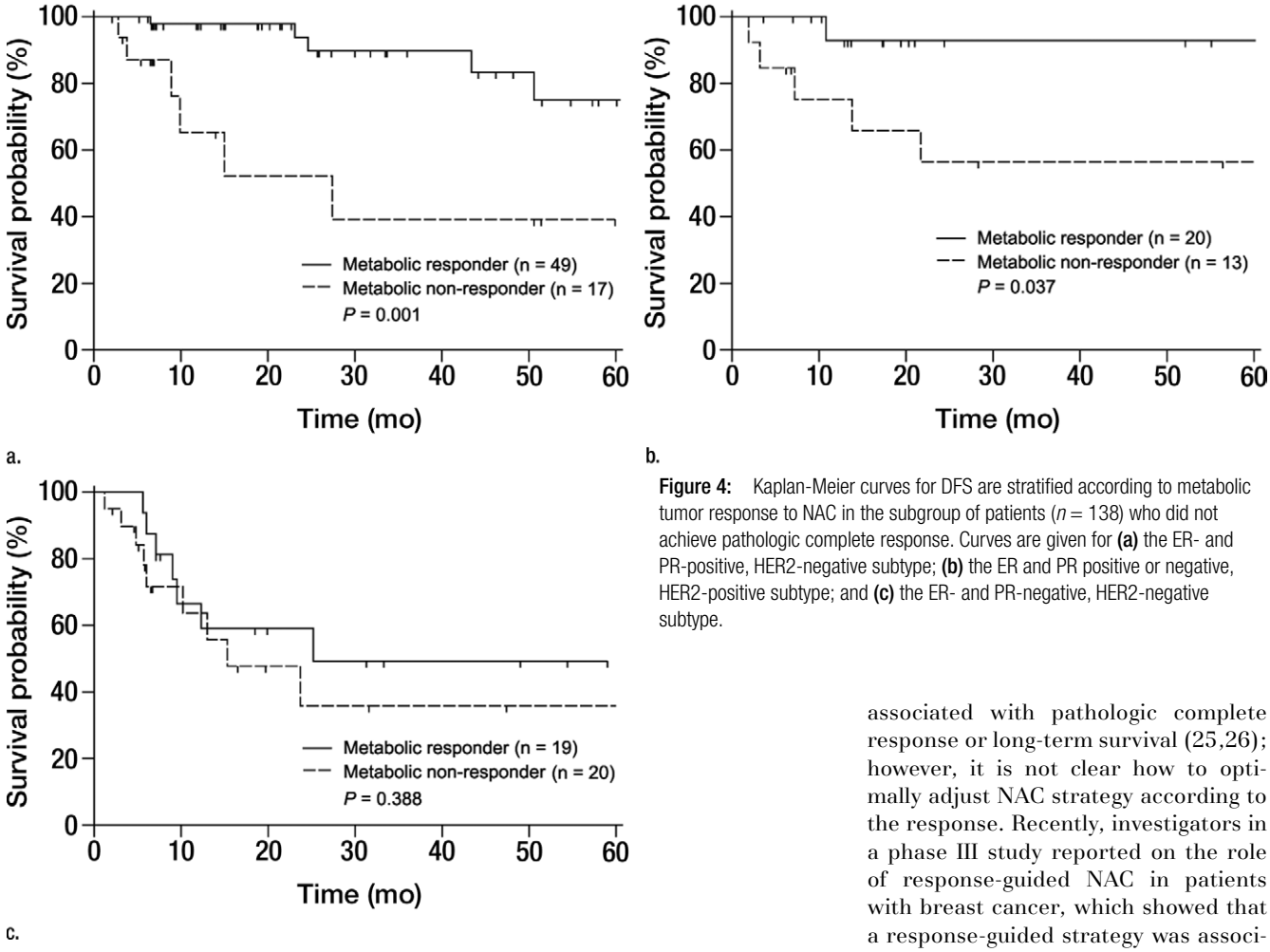


**Figure 4:** Kaplan-Meier curves for DFS are stratified according to metabolic tumor response to NAC in the subgroup of patients ($n$ = 138) who did not achieve pathologic complete response. Curves are given for **(a)** the ER- and PR-positive, HER2-negative subtype; **(b)** the ER and PR positive or negative, HER2-positive subtype; and **(c)** the ER- and PR-negative, HER2-negative subtype.

78.8% (95% CI: 74.1%, 83.0%), respectively (4); however, it is hard to standardize the optimal timing of PET/CT evaluation and the SUV threshold value of interval change between baseline and after NAC. The previously suggested optimal timing of $^{18}$F-FDG PET/CT evaluation varies from one to four cycles of NAC. Various SUV threshold values of interval change were also suggested. Another limitation of previous studies is that SUV was the only analyzed PET parameter. Although $SUV_{max}$ is a widely used index for $^{18}$F-FDG uptake of the tumor, it represents only the highest single-voxel value in the tumor and has limitations in the evaluation of heterogeneous tumor activity and the total tumor burden. $SUV_{max}$ is also highly sensitive to noise and is affected by many factors (17–20). Volume-based PET parameters such as MTV incorporate total tumor burden, as well as tumor metabolic activity. Many investigators have therefore studied the value of the volume-based PET parameters for treatment response assessment and prognosis prediction. In various tumor types, a volume-based PET parameter was significantly associated with prognosis, though all were retrospective studies, and the extent of the target lesion varied from primary tumor only to all malignant lesions, including regional or distant metastases (21–24).

In several studies, early clinical response after several cycles of NAC was associated with pathologic complete response or long-term survival (25,26); however, it is not clear how to optimally adjust NAC strategy according to the response. Recently, investigators in a phase III study reported on the role of response-guided NAC in patients with breast cancer, which showed that a response-guided strategy was associated with improved DFS, especially in patients with hormone receptor–positive status (27). The early response was assessed clinically by means of physical examination, ultrasonography, and mammography after two cycles of NAC.

Our data suggest that the post-treatment $^{18}$F-FDG PET/CT data provide additional prognostic information and allow stratification of the patients that would benefit from further treatment among the patients without pathologic complete response after NAC. Currently, there is no standard guideline for metabolic tumor response–guided NAC strategy in breast cancer. Although our study showed that metabolic tumor response provided independent prognostic information in

**Figure 5**

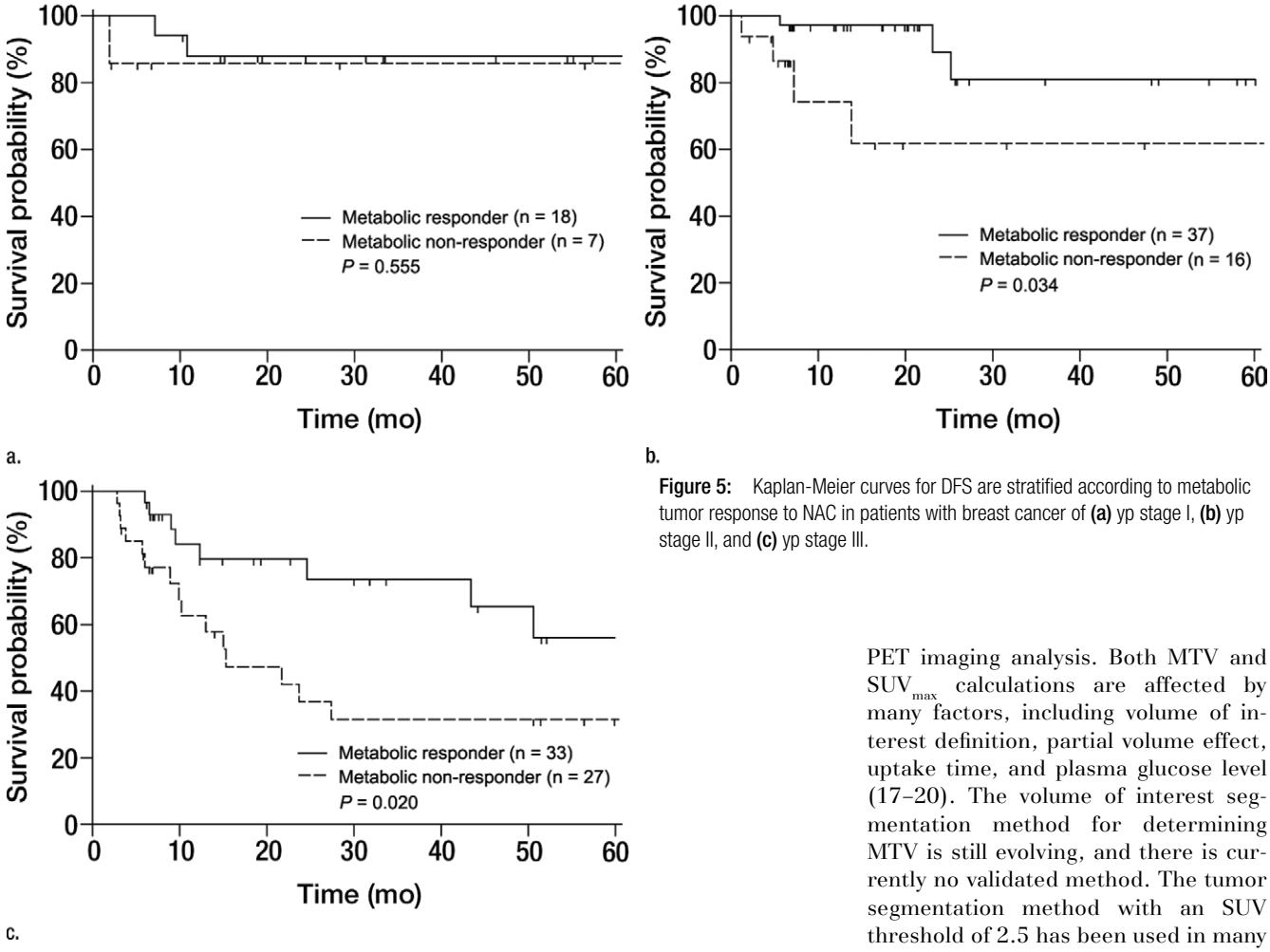


**Figure 5:** Kaplan-Meier curves for DFS are stratified according to metabolic tumor response to NAC in patients with breast cancer of **(a)** yp stage I, **(b)** yp stage II, and **(c)** yp stage III.

addition to yp stage, a metabolic tumor response–guided treatment strategy that optimizes additional adjuvant treatment is not yet an area of standard treatment. It is not yet known whether treatment decisions based on this information can improve patient outcomes. Therefore, further prospective clinical trials in patients with breast cancer who are undergoing NAC are warranted to assess the role of metabolic tumor response in therapeutic decision making.

There are several limitations to this study. First, the patients who did not respond to NAC enough to proceed to surgery or the patients who did not undergo both PET/CT scans before and after NAC were not included in this study cohort. During the earlier period of study, $^{18}$F-FDG PET/CT was not performed routinely for NAC setting in our institution. Second, our subject population was heterogeneous because of various numbers of cycles and regimens of NAC. Third, the relatively short follow-up duration of this study is not enough time to determine the long-term prognostic effect. Fourth, the choice of an optimal cutoff point for the risk stratification was based on the result of this study by using maximally selected rank statistics. This can lead to overestimation of the results. External validation is therefore required.

There are still several technical limitations in the method for quantitative PET imaging analysis. Both MTV and $SUV_{max}$ calculations are affected by many factors, including volume of interest definition, partial volume effect, uptake time, and plasma glucose level (17–20). The volume of interest segmentation method for determining MTV is still evolving, and there is currently no validated method. The tumor segmentation method with an SUV threshold of 2.5 has been used in many prior studies and is more straightforward than other methods, such as gradient-based or background threshold approaches. Although the partial volume effect is an important issue for the smaller lesions, we did not perform the partial volume effect correction because there was no widely accepted solution. We assumed that there was little effect of the plasma glucose level and uptake time on our results because we used a standard imaging protocol for this study.

In conclusion, in patients with breast cancer who are undergoing NAC followed by surgical resection, volume-based metabolic tumor response to NAC is associated with an increased risk of recurrence in locally advanced breast cancer, regardless of tumor subtype

**Table 5**

**Multivariable Cox Regression Analysis for DFS in the Subgroup of Patients (*n* = 78) Who Did Not Achieve Pathologic Complete Response after the Same Regimen of NAC (with eight cycles of anthracycline and cyclophosphamide followed by taxane)**

| Variable | Hazard Ratio | 95% CI | *P* Value |
|---|---|---|---|
| Clinical stage before NAC | | | |
| Stage III vs II | 1.222 | 0.194, 7.677 | .831 |
| yp stage group after NAC | | | |
| Stage I | 1.000 | … | .445 |
| Stage II | 0.619 | 0.113, 3.407 | .582 |
| Stage III | 1.895 | 0.360, 9.963 | .450 |
| Tumor subtype | | | |
| ER and PR positive, HER2 negative | 1.000 | … | .304 |
| ER and PR positive or negative, HER2 positive | 2.778 | 0.586, 13.169 | .198 |
| ER and PR negative, HER2 negative | 2.737 | 0.654, 11.456 | .168 |
| Metabolic nonresponse after NAC | 6.277 | 1.954, 20.166 | .002 |

and pathologic tumor response. The volume-based metabolic tumor response to NAC could be an aid in stratification of prognosis in patients with breast cancer who did not achieve pathologic complete response after NAC and may guide treatment planning for those who need further treatment. Further validation by using a prospective trial is warranted.

**Acknowledgments:** The authors thank Seung Ah Yang and Sang Il Byun in the Department of Nuclear Medicine, Samsung Medical Center, for assistance with data analysis.

**Disclosures of Conflicts of Interest: S.H.H.** disclosed no relevant relationships. **H.K.A.** disclosed no relevant relationships. **Y.H.P.** disclosed no relevant relationships. **Y.H.I.** disclosed no relevant relationships. **W.H.K.** disclosed no relevant relationships. **J.E.L.** disclosed no relevant relationships. **S.J.N.** disclosed no relevant relationships. **E.Y.C.** disclosed no relevant relationships. **J.Y.C.** disclosed no relevant relationships.

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