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ORIGINAL ARTICLE

Usefulness of Combined Metabolic–Volumetric Indices of ^{18}F-FDG PET/CT for the Early Prediction of Neoadjuvant Chemotherapy Outcomes in Breast Cancer

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Abstract
Purpose The purpose of this study was to investigate the usefulness of metabolic-volumetric indices of ^{18}F-fluorodeoxy-D-glucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) for the evaluation of neoadjuvant chemotherapy outcomes in breast cancer.
Methods Twenty-four patients with locally advanced breast cancer were enrolled in the study. They underwent baseline ^{18}F-FDG PET/CT scan and received four or six cycles of neoadjuvant chemotherapy, interim ^{18}F-FDG PET/CT was done after second cycle of chemotherapy. Maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) of the primary lesions were calculated. Reduction rates of these parameters were obtained between baseline and interim ^{18}F-FDG PET/CT. Chemotherapy outcomes were assessed using tumor size reduction rate and histological grading system (Miller and Payne system). Reduction rates of SUVmax, MTV, and TLG correlated with chemotherapy outcomes.
Results MTV and TLG reduction rates showed significant correlation with tumor size reduction rate (R=0.68, P=0.0004; R=0.62, P=0.002, respectively). However, SUVmax reduction rate showed no significant correlation. MTV and TLG reduction rates were significantly higher in responders than nonresponders, as determined by Miller and Payne system (P<0.0007, P<0.002). However, SUVmax reduction rate showed no significant difference. On ROC analysis, the area under the MTV and TLG curves was 0.886, and that of SUVmax was 0.743. Sensitivity, specificity, positive predictive value, and negative predictive value to predict histopathologic response were the same for MTV and TLG, and the values were 100 %, 85.7 %, 83.3 %, and 100 %, respectively (at the reduction rate of 93.2 % for MTV, and 95.8 % for TLG).
Conclusion Changes of metabolic–volumetric indices successfully reflected the neoadjuvant chemotherapy outcomes. MTV and TLG could be robust indices in discriminating pathologic responder as SUVmax, after neoadjuvant chemotherapy.

Keywords Breast cancer · Neoadjuvant chemotherapy · Metabolic tumor volume · Total lesion glycolysis · ^{18}F-FDG PET/CT

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Introduction

Breast cancer is the most common malignancy among women, and locally advanced disease accounts for approximately 5–7 % at diagnosis in United States [1, 2]. Currently,

standard treatment for locally advanced breast cancer includes neoadjuvant chemotherapy, due to its several advantages. The main advantage of neoadjuvant chemotherapy is down-staging of the tumor load. As a result, inoperable advanced tumors may become operable, and patients with large operable tumors may be offered breast-conserving surgery. Another advantage of neoadjuvant chemotherapy is the possibility to monitor the response of the primary tumor to the chemotherapy agents that were used [3]. And early clinical response after two cycles of neoadjuvant chemotherapy was found to be a predictor of pathologic complete remission, and might be a predictor of long-term outcome [4]. Thus, early prediction of the response of neoadjuvant chemotherapy is invaluable, because early prediction could guarantee early guidance for proper treatment.

^{18}F-fluorodeoxy-D-glucose (^{18}F-FDG) positron emission tomography (PET) has been evaluated to be a useful tool for predicting the response after chemotherapy in various types of cancer, including breast cancer [5–7]. Especially in breast cancer, several studies showed possible roles of ^{18}F-FDG PET for early prediction of neoadjuvant chemotherapy response [8–11]. In these studies, relative changes in maximum standardized uptake value (SUVmax) after the first or second cycle of chemotherapy are a strong predictor of response. However, the diagnostic power was relatively low and optimal cutoff was highly heterogeneous, so that the role of early ^{18}F-FDG PET/computed tomography (CT) scan during neoadjuvant chemotherapy remains unclear in clinical practice.

We expected that volume–metabolism combinatorial indices, such as metabolic tumor volume (MTV) or total lesion glycolysis (TLG) of ^{18}F-FDG PET/CT, could be more reliable than SUVmax in predicting the chemotherapy response, because SUVmax represents only the most active tumor portions, and may not represent whole tumor status, especially after chemotherapy. MTV and TLG of ^{18}F-FDG PET/CT are suggested to be better indicators of whole tumor burden than SUVmax, and proved to be prognostic factors at diagnosis in a variety of malignancies. [12–17]. Moreover, these indices demonstrated the possibility of predicting chemotherapy effect in osteogenic sarcoma, not only at the end of the neoadjuvant chemotherapy [18, 19], but also after the second cycle [20].

The purpose of this study is to predict pathologic outcome during neoadjuvant chemotherapy in breast cancer by ^{18}F-FDG PET/CT, and to compare the indices of SUVmax/MTV/TLG.

Materials and Methods

Patients

Twenty-four patients who were recommended to be treated with neoadjuvant chemotherapy for locally advanced breast cancer were retrospectively enrolled. The study was approved by the Institutional Review Board for review of medical records of the patients. Patients with breast cancer larger than 2 cm in diameter and/or lymph node metastasis are recommended to be treated with neoadjuvant chemotherapy in our institute. Among the 27 patients who underwent ^{18}F-FDG PET/CT before and during neoadjuvant chemotherapy in our institute between March 2009 and May 2010, three were excluded because the chemotherapy regimens were switched during neoadjuvant chemotherapy. All breast cancers were initially diagnosed by fine needle aspiration. Core needle biopsy was done to evaluate hormone receptors and human epidermal growth factor receptor 2 (HER2) status. We consider estrogen receptor and progesterone receptor positive when immunoreactive cell nuclei were more than 10 %. HER2 positivity was defined as 3+ by immunohistochemistry, and 1+, 2+ plus positive fluorescence in situ hybridization result. All patients underwent baseline magnetic resonance imaging (MRI) scan before neoadjuvant chemotherapy. Patients received four or six cycles of neoadjuvant chemotherapy before surgery, and interim ^{18}F-FDG PET/CT scan was done after the second cycle of chemotherapy. The age distribution of the patient group was 44±10 years old (range: 22–88). Most of them received anthracycline -based chemotherapy, and the most common type of chemo-regimen was four cycles of adriamycin with cyclophosphamide (AC) in 15 patients, while the second most common chemo-regimen was six cycles of docetaxel with adriamycin (DA) in six patients. The others received six cycles each of Paclitaxel/Avastin, Docetaxel/Herceptin, and Epirubicin/docetaxel. The mean duration of neoadjuvant chemotherapy was 89.6±49.8 days (Table 1), and mean duration between baseline and interim ^{18}F-FDG PET/CT scan was 53.6±25.1. After surgery, tumor specimens were examined to determine responders and nonresponders by the Miller and Payne system [21]. Patients who underwent breast-conserving surgery subsequently received local radiotherapy.

^{18}F-FDG PET/CT Protocol

^{18}F-FDG PET/CT was performed using a PET/CT scanner (Discovery VCT, GE Medical Systems, Milwaukee, WI) in 3D acquisition mode with a 128×128 matrix size. After fasting for at least 6 h, appropriate blood sugar level was checked (< 180 mg/dL). Amount of intravenous administration of ^{18}F-FDG was 5.18 MBq/Kg. CT acquisition were 120 kVp, 75 mm (6×0.625 mm) slice thickness. PET emission images were obtained 1 hour after injection of ^{18}F-FDG, 5–6 bed position (2.5 min/bed) covering from base of cerebellum to upper thigh, and attenuation correction was done by CT images. Images were reconstructed using an

Table 1 Patient characteristics

Characteristics	Value	%
Number of patients	24	
Age at diagnosis, years		
Median	44	
Range	22–88	
cT staging		
T1	1	4.2
T2	12	50
T3	9	37.5
T4	2	8.3
cN staging		
N1	17	70.8
N2	2	8.3
N3	5	20.8
Tumor histology		
Invasive ductal carcinoma	24	100
Hormone receptor status		
ER/PR positive	10	41.7
ER/PR negative	14	58.3
HER2 status		
Positive	11	45.8
Negative	13	54.2
Type of surgery		
Mastectomy	16	66.7
Breast conserving surgery	8	33.3
Chemotherapy regimen		
AC (adriamycin + cyclophosphamide)	15	62.5
DA (docetaxel with Adriamycin)	6	25
Others (Paclitaxel/Avastin, Docetaxel/Herceptin, Epirubicin/docetaxel)	3	12.5

iterative algorithm (ordered-subset expectation maximization, two iterations and eight subsets).

Measurement of SUVmax, MTV and TLG

To quantify ^{18}F-FDG uptakes, standardized uptake values (SUV) were calculated as follows: SUV = (decay− corrected activity[kBq]per mL of tissue volume)/(injected ^{18}F − FDG activity[kBq]per lean body mass[g]).. SUVmax is value of highest SUV in the given volume of interest (VOI). VOI was drawn over the breast cancer lesion that showed increased ^{18}F-FDG uptake on corresponding soft tissue lesion in combined CT. Using PET VCAR application (Advanced workstation 4.4, GE Medical Systems, Milwaukee, WI), we drew a cuboid VOI covering a breast cancer lesion and then VOI was automatically drawn along the margin of the tumor uptake according to the specific SUV threshold. MTV refers to the volume of tumor that has SUV over a certain threshold SUV; in this study, we used 2.0 as threshold SUV [22] (Fig. 1). MTV and TLG were automatically calculated by PET VCAR application (Advanced workstation 4.4, GE Medical Systems, Milwaukee, WI). SUVmax, MTV, and TLG were calculated in baseline and interim PET/CT, and then reduction rates (RR) of these indices were calculated as follows.

$$\text{RR of SUV max} = [(\text{SUV max 1} - \text{SUV max 2})/\text{SUV max 1}] \times 100(\%)$$
$$\text{RR of MTV} = [(\text{MTV1} - \text{MTV2})/\text{MTV1}] \times 100(\%)$$
$$\text{RR of TLG} = [(\text{MTV1} \times \text{SUVmean1} - \text{MTV2} \times \text{SUVmean2})/\text{MTV1} \times \text{SUVmean1}] \times 100(\%)$$
$$(1, \text{value of baseline}^{18}\text{F}-\text{FDG PET/CT; } 2, \text{value of interim}^{18}\text{F}-\text{FDG PET/CT})$$

** If a lesion is indistinguishable with surrounding tissue on interim PET/CT, RR is considered as 100 %.

MRI

The MRI was performed as previously reported [23], with a 1.5 Tesla machine (GE Medical Systems, Milwaukee, WI) using a dedicated breast coil (GE Medical Systems, Milwaukee, WI). The following is the brief imaging protocol; fat-suppressed T2-weighted fast spin-echo sagittal images were obtained after an axial localizer image. Dynamic contrast-enhanced examinations include one pre-contrast and five post-contrast (76 s, 165 s, 345 s, 434 s, and 583 s after contrast injection). Gadobenate dimeglumine (0.1 mmol/kg Multihance; Bracco Imaging, Milan, Italy) was automatically injected through an indwelling IV catheter. Two dimensional diameters of the tumors were measured in post-contrast images by two experienced radiologists.

Determination of Chemotherapy Response

Response of neoadjuvant chemotherapy was evaluated with two different ways measuring reduction rate of tumor size and cellularity. Surgery was performed 30.5 ±2.6 days after completion of last cycle of chemotherapy. First, tumor size reduction rate was calculated. Baseline tumor size was estimated as the geometric mean of the largest two diameters (D1, D2) of the tumor in baseline MR images, and the tumor size after neoadjuvant chemotherapy was estimated as the geometric mean of the largest two diameters (d1, d2) of the viable tumor portion in surgical specimen after neoadjuvant chemotherapy [24]. The largest two diameters were obtained from pathologic reports.

Tumor size reduction rate

$$= [(\sqrt{\text{D1D2}} - \sqrt{\text{d1d2}})/(\sqrt{\text{D1D2}})] \times 100(\%)$$

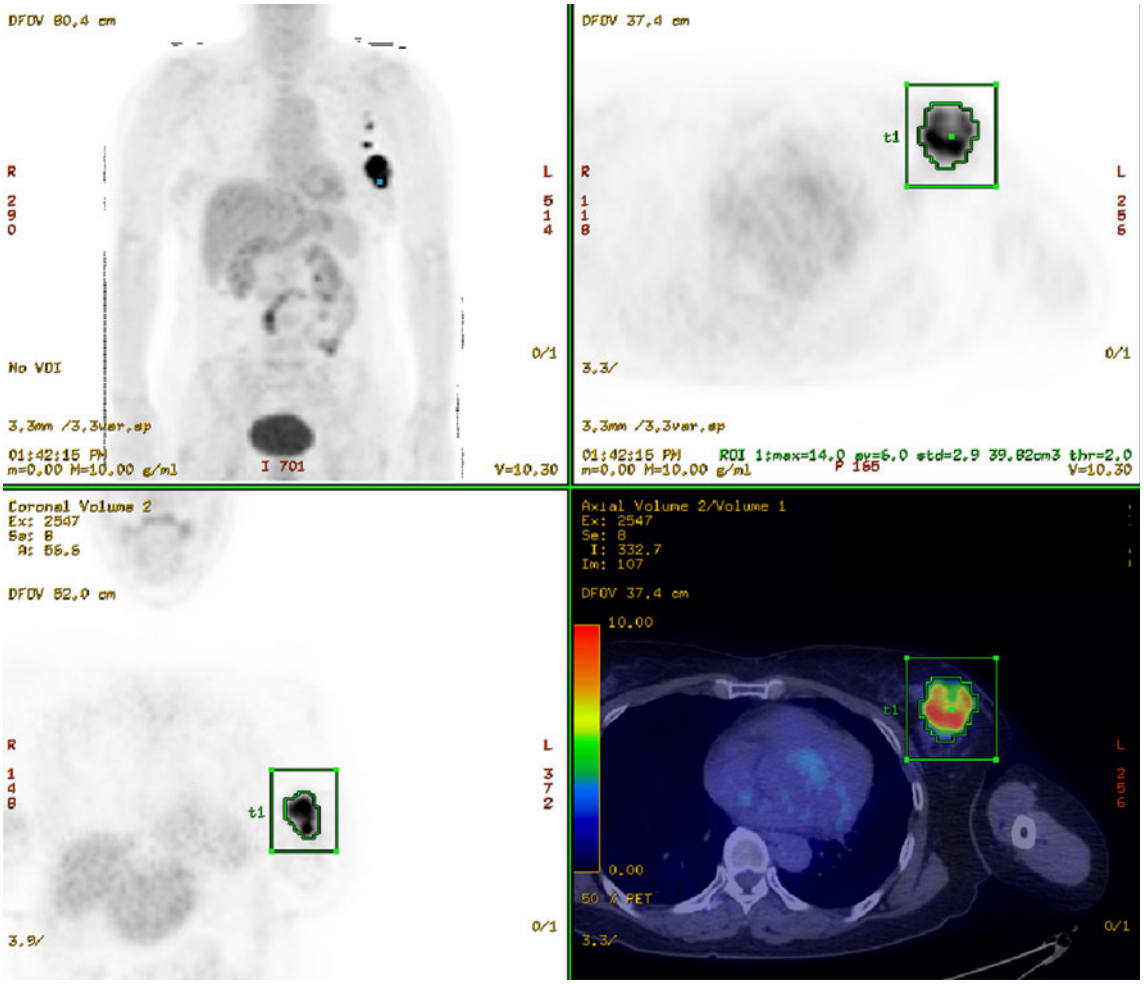

Fig. 1 Automatic calculation of MTV and TLG by PET VCAR application of Advanced workstation 4.4 (GE Medical Systems, Milwaukee, WI). Whole-body ^{18}F-FDG PET MIP image; the transaxial, coronal image, and the ^{18}F-FDG PET/CT fusion transaxial image of patient with left breast cancer and left axillary lymph node metastasis is shown. Inside the green cuboid VOI covering breast cancer lesion, another VOI is automatically delineated on FDG avid portion (SUV threshold>2.0). And MTV, TLG of the VOI are automatically calculated

√d1d2 Viable tumor dimension on specimen
√D1D2 Primary tumor dimension in baseline MR image

Next, tumor specimens were microscopically examined and poor responders and responders were classified by the Miller and Payne system. This grading system evaluates the degree of reduction in tumor cellularity, assessed by comparing the tumor cellularity observed in the residual breast tumor tissue at surgery with a pretreatment core biopsy. The tumors were graded on a scale from 1 to 5 as follows: tumor regression grade (TRG) 1, no response to treatment; TRG 2, < 30 % reduction in cellularity; TRG 3, from 30 % to 90 % reduction in cellularity; TRG 4, > 90 % and < 100 % reduction in cellularity; and TRG 5, a complete response with no residual tumor. Patients were grouped according to prognosis as established by the scale: responder (TGR 4, 5) and nonresponder (TGR 1–3) [21].

Statistical Analysis

All of the statistical analyses were performed using MedCalc for Windows, version 9.4.2.0 (MedCalc Software 10.1, Belgium). Correlation analysis was done between estimated tumor sizes by MR and MTV of ^{18}F-FDG PET/CT, and between tumor size reduction rate and reduction rate of the ^{18}F-FDG PET indices. T-tests were done between reduction rates of the parameters of responders and nonresponders classified by Miller and Payne system. Receiver operating characteristic (ROC) curve analysis was used to compare diagnostic power of the indices and find optimal cutoff. McNemar's chi square test was done to compare sensitivity and specificity of each index.

Results

Patients and Histopathologic Response

All 24 breast cancers were histologically confirmed as invasive ductal carcinoma. Half of the patients had cT2 and except for one patient, the others had higher T stage. All patients had lymph node metastasis and the majority of them were cN1 (70.8 %). After neoadjuvant chemotherapy, all patients underwent definitive operation; the majority of them (66.7 %) had mastectomy and the others had breast-conserving surgery. By histopathology examination, ten of the 24 classified as responder, and 14 as nonresponder by the Miller and Payne system. Estrogen and progesterone receptor was positive in ten cases, and HER2 was positive in 11 (Table 1).

Correlation Between Tumor Size Reduction Rate and Reduction Rate of Interim ^{18}F-FDG PET Indices

All ^{18}F-FDG PET/CT indices reduced significantly after the second cycle of chemotherapy ($P<0.05$). Tumor size, which is estimated by MRI (before neoadjuvant chemotherapy) and pathologic specimen (after neoadjuvant chemotherapy), also significantly reduced after neoadjuvant chemotherapy ($P<0.05$). SUVmax at baseline was 7.9±6.9 (mean ± SD) and 2.5±1.7 at interim ^{18}F-FDG PET/CT. MTV at baseline was 14.8±13.6 mL and 1.6±2.4 mL at interim ^{18}F-FDG PET/CT. TLG at baseline and at interim ^{18}F-FDG PET/CT was 74.8±95.8 g and 4.6±6.6 g respectively. Tumor size estimated by pretreatment MRI was 4.6±2.6 cm^2 and size of viable tumor portion after chemotherapy on surgical specimen was 1.8±1.9 cm^2.

MTV and TLG reduction rates showed significant correlation with tumor size reduction rate ($r=0.68$, $P=0.0004$; $r=0.62$, $P=0.002$, respectively). However, there was no significant correlation between tumor size reduction rate and reduction rate of SUVmax ($r=0.38$, $P=0.07$) (Fig. 2).

Reduction Rate of Interim ^{18}F-FDG PET/CT Indices According to Histopathologic Tumor Response

Reduction rates of interim ^{18}F-FDG PET/CT indices of responders (TRG 4,5) and nonresponders (TRG 1–3) were compared. Reduction rate of MTV and TLG were significantly higher in responders than in nonresponders ($P=0.0007$, $P=0.002$). SUVmax reduction rate showed a trend toward difference; however, it did not reach statistical significance ($P=0.08$) (Table 2, Fig. 3).

Determination of the Optimal Cutoff Value of the Reduction Rate of Interim ^{18}F-FDG PET/CT Indices to Predict Tumor Response

Receiver operating characteristic (ROC) curve analysis was done to determine the optimal cutoff value of the reduction rate of interim ^{18}F-FDG PET/CT indices to predict tumor response. ROC curves of reduction rate of MTV and TLG to predict histopathologic response (Miller and Payne system) were equally drawn with an area under curve of 0.886 (95%CI 0.690 to 0.977, $P=0.0001$). AUC by reduction rate of SUVmax was 0.743 (95 % CI, 0.525–0.897, $P=0.02$) (Fig. 4). With the cutoff value to differentiate responder from nonresponder at the reduction rate of MTV 93.2 %, and TLG 95.8 %, sensitivity, specificity, positive predictive value, and negative predictive value were 100 %, 85.7 %, 83.3 %, and 100 % respectively (same values between MTV and TLG). By the reduction rate of SUVmax, at the cutoff value of 63.6 %, sensitivity, and negative predictive value were lower than those of MTV and TLG, and specificity and positive predictive value were comparable with those of MTV and TLG (Table 3). However, differences of sensitivity and specificity between indices were not statistically significant (P = n.s.).

Discussion

^{18}F-FDG PET/CT has been used in predicting early response of chemotherapy in various types of malignancy.

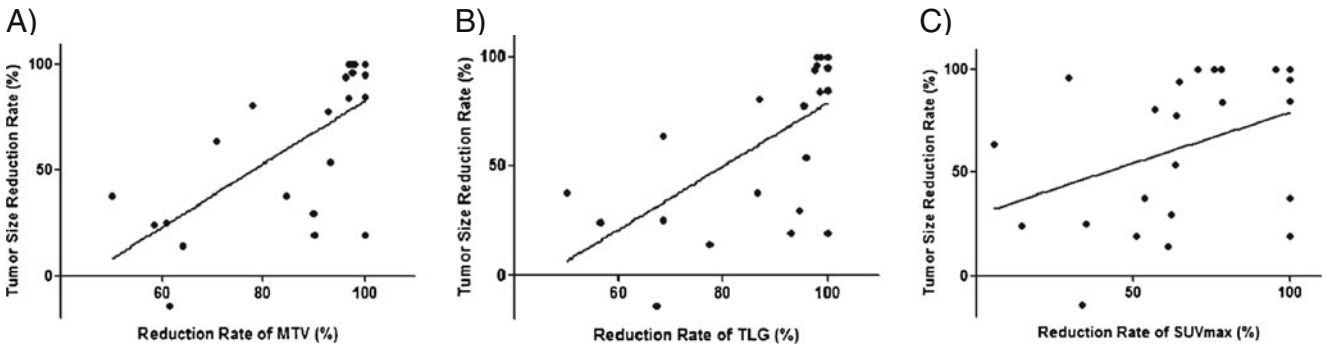

Fig. 2 Scatter-gram and linear regression line between tumor size reduction rate and reduction rate (RR) of ^{18}F-FDG PET/CT indices; Significant correlation was found in MTV (**a**, $r=0.68$, $P=0.0004$) and TLG (**b**, $r=0.62$, $P=0.002$), but not in SUVmax (**c**, $r=0.38$, $P=0.07$)

Table 2 Reduction rate of ^{18}F-FDG PET indices in responders and nonresponders

Indices	Reduction rate %			*P* value
	Total (*N*=24)	Responders (*n*=10)	Nonresponders (*n*=14)	
SUVmax	55.1±23.9	72.8±23.2	53.6±25.7	0.08
MTV	86.6±15.9	98.3±1.4	78.1±16.3	0.0007
TLG	88.8±15.0	98.9±0.9	81.5±16.1	0.002

^{18} F-FDG PET ^{18} F- fluorodeoxy-D-glucose positron emission tomography; SUVmax Maximum standardized uptake value; MTV metabolic tumor volume; TLG total lesion glycolysis

Particularly, change in ^{18}F-FDG PET after one or two cycles of chemotherapy reflects the response to chemotherapy, and is related to prognosis [4, 25]. The present study was conducted to show usefulness of MTV and TLG over SUVmax in predicting tumor response, and the present study showed that firstly, MTV and TLG correlated more precisely with tumor size reduction rate than SUVmax. This result is probably due to the help of volumetric information of MTV and TLG. MTV and tumor size estimated by MRI at baseline showed moderate correlation (r=0.62, P=0.002). Secondly, MTV and TLG showed better ability to predict responder, as classified by the Miller and Payne system, than SUVmax. The Miller and Payne system reflects the decrease in viable cancer cellularity, not tumor size. In previous studies, ^{18}F-FDG PET has been shown to discriminate responders according to the Miller and Payne system with SUVmax, which reflects metabolic status of viable cancer [11–14]. Similarly, in the present study, SUVmax decreased more in responders (72.8±23.2 %) than in nonresponders (53.6±25.7 %) the second cycle of chemotherapy. Also, the level of decrement in responders and nonresponder is similar to previous studies [4, 8]. However, the difference was not statistically significant, probably due to the small number of patients in the present study. On the other hand, MTV and TLG discriminate responders from nonresponder with statistical significance, despite the small number of patients (P=0.0007, 0.002). SUVmax represent only one spot that has the highest SUV; however, pathologic examination may not be done at the point that showed highest SUV, but is done at several points of the tumor bed to assess whole tumor status. Thus, we could assume that metabolic status of whole tumor can be more correctly reflected by MTV and TLG than SUVmax. For example, SUVmax of one patient modestly decreased after neoadjuvant chemotherapy (from 3.4 to 2.4, reduction rate=29.4 %), but that patient was found to be a responder in histopathologic examination. On the contrary, change of MTV (from 4 to 0.1, reduction rate=97.5 %) and TLG (from 9.2 to 0.2, reduction rate=97.9 %) of the patient correctly predicted the tumor response. This result is in accordance with the ressult of a previous study done in an osteosarcoma cohort [20].

After testing various thresholds, we used threshold SUV 2.0 for calculating MTV and TLG. Although previously, SUV 2.5 has been used most frequently as the threshold in head and neck cancer and esophageal cancer [12–14], SUV 2.5 neglects a considerable portion of tumor, especially after chemotherapy in breast cancer. Further, one previous report also showed that MTV with threshold SUV 2.0 was the most robust predictor of outcome in head and neck cancer among MTV with various thresholds of SUV 2.0 to~4.0 [22]. In addition, using lower threshold could be suggested in breast cancer for sensitive tumor detection, because there is almost no FDG avid area with more than SUV 2.0 in

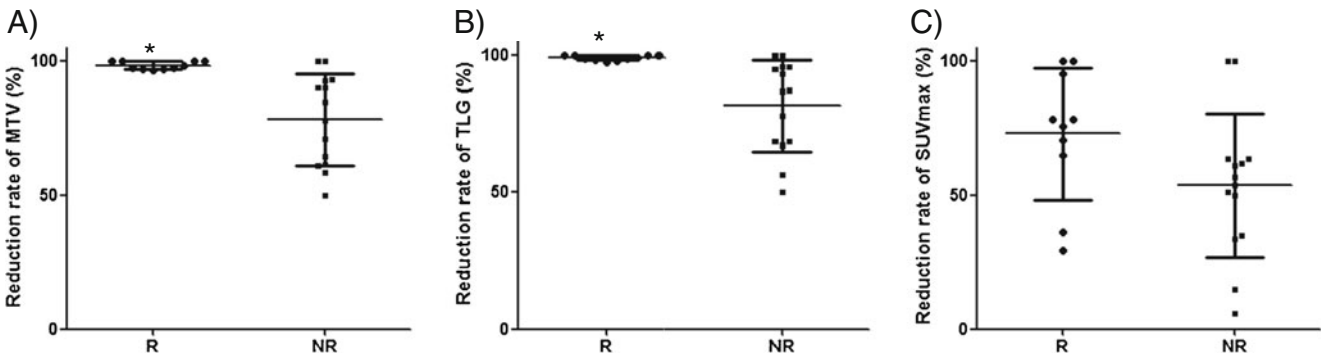

Fig. 3 Reduction rates of the indices (**a**, MTV; **b**, TLG; **c**, SUVmax) in responders and nonresponders classified by the Miller and Payne system. Reduction rate (RR) of MTV and TLG were significantly higher in responders than in nonresponders (P=0.0007, P=0.002) but SUVmax reduction rate was not (P=0.08); R = responders; NR = nonresponders; *=P<0.05

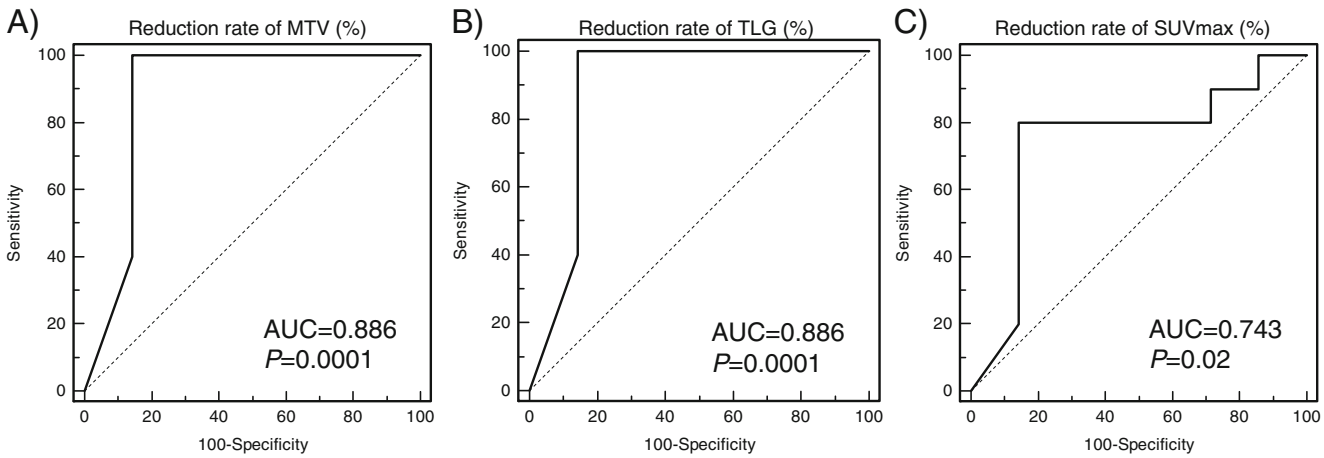

Fig. 4 ROC curve analysis of response prediction by reduction rate of ^{18}F-FDG PET/CT indices (**a**, reduction rate of MTV; **b**, reduction rate of TLG; **c**, reduction rate of SUVmax). AUCs of reduction rate of MTV, TLG, SUVmax were 0.886, 0.886 and 0.743

breast and chest wall under normal conditions [26]. Finally, MTV with a threshold of SUV 2.0 are well correlated with MRI-based tumor size in our study.

Response prediction capability of reduction rate of MTV and TLG were compared when different thresholds of SUV were used. MTV with lower SUV threshold (1.5 and 1.0) or another suggested method, fixed percentage of SUVmax (25 %. 50 %, 75 %), were tested, but showed major discordance in lesion delineation between ^{18}F-FDG PET image and combined CT/corresponding MRI. On comparison of MTV reduction rate with threshold SUV 2.5 and SUV 2.0, there were two more false positives and one more false negative case with SUV 2.5 threshold, which might be caused by underestimation of residual MTV or underestimation of primary tumor before chemotherapy. And on comparison of TLG reduction rate, there were four more false positives with threshold SUV 2.5 than with threshold SUV 2.0.

The present study has a few limitations. The first is the retrospective design with inhomogeneous chemo-regimen of the study. However, duration of chemotherapy and interval between baseline and interim ^{18}F-FDG PET/CT were relatively homogenous. Secondly, we could not demonstrate the statistical difference between diagnostic performances to differentiate responders between SUVmax, MTL and TLG. However, considering that SUVmax is the only used ^{18}F-FDG PET/CT parameter to assess response to chemotherapy in breast cancer despite of several limitations, showing non-inferiority of MTV and TLG in this study could be important information. Finally, the small number of patients is a limitation of the study. However, as far as we know, no study has been performed to assess the ability of MTV or TLG in predicting the chemotherapy response in breast cancer. Thus, the promising results of the present study could give rise to more studies with prospective design and large populations, to assess MTV and TLG as a predictor during neoadjuvant chemotherapy in breast cancer.

Conclusion

Changes of combined metabolic–volumetric indices, MTV and TLG, between baseline and interim ^{18}F-FDG PET/CT after the second cycle of neoadjuvant chemotherapy successfully predicted the pathologic outcomes of neoadjuvant chemotherapy in breast cancer. Larger case studies are needed to determine the most useful ^{18}F-FDG PET/CT index for evaluating neoadjuvant chemotherapy outcomes in breast cancer.

Table 3 Diagnostic accuracy of reduction rate of PET/CT indices

	Cutoff (%)	AUC	Sen (%)	Spe (%)	PPV (%)	NPV (%)	Accuracy (%)
RR of SUVmax	63.6	0.743	80	85.7	80	85.7	83.3
RR of MTV	93.2	0.886	100	85.7	83.3	100	91.7
RR of TLG	95.8	0.886	100	85.7	83.3	100	91.7

RR Reduction rate; *AUC* Area under Receiver Operative Characteristics Curve; *Sen* sensitivity; *Spe* specificity; *PPV* positive predictive value; *NPV* negative predictive value; SUVmax Maximum standardized uptake value; MTV metabolic tumor volume; TLG total lesion glycolysis

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Conflict of Interest The authors declare that they have no conflict of interest.

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