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ORIGINAL ARTICLE

Association between partial-volume corrected SUV_{max} and Oncotype DX recurrence score in early-stage, ER-positive/HER2-negative invasive breast cancer

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Abstract

Purpose Oncotype DX, a 21-gene expression assay, provides a recurrence score (RS) which predicts prognosis and the benefit from adjuvant chemotherapy in patients with early-stage, estrogen receptor-positive (ER-positive), and human epidermal growth factor receptor 2-negative (HER2-negative) invasive breast cancer. However, Oncotype DX tests are expensive and not readily available in all institutions. The purpose of this study was to investigate whether metabolic parameters on ^{18}F-FDG PET/CT are associated with the Oncotype DX RS and whether ^{18}F-FDG PET/CT can be used to predict the Oncotype DX RS.

Methods The study group comprised 38 women with stage I/II, ER-positive/HER2-negative invasive breast cancer who underwent pretreatment ^{18}F-FDG PET/CT and Oncotype DX testing. On PET/CT, maximum (SUV_{max}) and average standardized uptake values, metabolic tumor volume, and total lesion glycolysis were measured. Partial volume-corrected SUV_{max} (PVC-SUV_{max}) determined using the recovery coefficient method was also evaluated. Oncotype DX RS (0 – 100) was categorized as low (<18), intermediate (18 – 30), or high (≥31). The associations between metabolic parameters and RS were analyzed. Multivariate logistic regression was used to identify significant independent predictors of low versus intermediate-to-high RS.

Results Of the 38 patients, 22 (58 %) had a low RS, 13 (34 %) had an intermediate RS, and 3 (8 %) had a high RS. In the analysis with 38 index tumors, PVC-SUV_{max} was higher in tumors in patients with intermediate-to-high RS than in those with low RS (5.68 vs. 4.06; $P = 0.067$, marginally significant). High PVC-SUV_{max} (≥4.96) was significantly associated with intermediate-to-high RS (odds ratio, OR, 10.556; $P = 0.004$) in univariate analysis. In multivariate analysis with

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clinicopathologic factors, PVC-SUV_{max} ≥4.96 (OR 8.459; $P = 0.013$) was a significant independent predictor of intermediate-to-high RS.
Conclusions High PVC-SUV_{max} on ^{18}F-FDG PET/CT was significantly associated with an intermediate-to-high Oncotype DX RS. PVC metabolic parameters on ^{18}F-FDG PET/CT can be used to predict the Oncotype DX RS in patients with early-stage, ER-positive/HER2-negative breast cancer.

Keywords Oncotype DX · Oncotype DX recurrence score · ^{18}F-FDG PET/CT · Breast cancer · Partial volume correction · Recovery coefficient

Introduction

Oncotype DX (Genomic Health, Redwood City, CA) is a multigene assay which provides prognostic information and predicts the benefit from adjuvant chemotherapy in patients with early-stage, estrogen receptor-positive (ER-positive), and human epidermal growth factor 2 receptor-negative (HER2-negative) invasive breast cancer [1–5]. This assay analyzes the expression of a 21-gene profile in formalin-fixed, paraffin-embedded tumor tissue by mRNA extraction and reverse-transcriptase polymerase chain reaction. A mathematical formula is used to derive a continuous score (recurrence score, RS) from the expression of 16 cancer-related genes relative to that of 5 reference genes. RS ranges from 0 to 100 and is proportional to the 10-year rate of distant recurrence in patients with ER-positive breast cancer treated with tamoxifen. RS is used to classify recurrence risk into three categories as follows: RS <18 (low risk), RS 18 – 30 (intermediate risk), RS ≥31 (high risk) [1].

In a prospective clinical validation trial, patients with a low RS showed minimal benefit from chemotherapy and low rates of recurrence at 5 years with endocrine therapy alone [2, 5]. Patients with a high RS showed a large benefit from chemotherapy and adjuvant chemotherapy is indicated in these patients. In patients with an intermediate RS, the benefit of adjuvant chemotherapy is uncertain and is being assessed in ongoing clinical validation trials. Oncotype DX is increasingly being used for individually tailored treatment of breast cancer and was incorporated in the National Comprehensive Cancer Network (NCCN) guidelines released in 2007 [6]. However, Oncotype DX tests are expensive and not readily available in all institutions.

^{18}F-FDG PET/CT is performed for preoperative staging work-up in patients with breast cancer [7]. ^{18}F-FDG PET/CT is useful not only for the detection of regional and distant metastasis, but also for the evaluation of primary tumors as it provides information on tumor glucose metabolism. In breast cancer, high maximum standardized uptake values (SUV_{max}) are known to correlate with poor prognostic factors such as high tumor grade, hormone receptor-negative or triple-negative cancers, high tumor proliferation index (Ki-67), and the presence of axillary lymph node metastasis [8–14]. In addition, SUV_{max} is an independent prognostic factor for recurrence-free survival particularly in hormone receptor-positive disease [15, 16]. A recent study has also shown that patients with ER-positive breast cancer have lower SUV_{max} and total lesion glycolysis (TLG), but metabolic tumor volume (MTV) does not depend on the histopathologic features of the tumor [17]. Recently, various partial volume correction methods have been suggested in view of the underestimation of SUVs in small tumors. Several studies using the simplest method, recovery coefficient (RC) correction, have validated the usefulness of partial volume correction in small lesions.

To our knowledge, there has been no study evaluating the association between various metabolic parameters on pretreatment ^{18}F-FDG PET/CT and Oncotype DX RS. Therefore, the purpose of this study was to investigate whether ^{18}F-FDG metabolic parameters with or without partial volume correction are associated with the Oncotype DX RS and whether ^{18}F-FDG PET/CT can be used to predict the Oncotype DX RS in patients with early-stage, ER-positive/HER2-negative invasive breast cancer.

Materials and methods

Subjects

A search of our database identified 143 consecutive women who were diagnosed with stage I/II, ER-positive/HER2-negative breast cancer and who had undergone Oncotype DX testing between August 2010 and February 2015. In 56 of these patients, ^{18}F-FDG PET/CT was performed for staging before definitive surgery, and none of these 56 patients showed distant metastases. One patient who had undergone surgical excision biopsy before the ^{18}F-FDG PET/CT examination was excluded. Additionally, 13 patients with multifocal/multicentric disease were excluded, because exact matching between pathologic reports for Oncotype DX RS and PET measurement was not possible due to the retrospective study design. Four patients with a tumor diameter less than 0.8 cm measured on the surgical specimen for application of partial volume correction were also excluded. Over-correction of the partial volume effect can affect PET parameter values in tumors with diameters less than 1.5 times the full-width at half-maximum (FWHM, 5 mm) [18]. Therefore, 38 patients with unilateral invasive breast cancer constituted the study population.

^{18}F-FDG PET/CT image acquisition

^{18}F-FDG PET/CT was performed a median of 22 days (range 2 – 41 days) prior to surgery. PET/CT images were acquired

using dedicated PET/CT scanners (Biograph True-Point, Biograph mCT 40, and Biograph mCT 64; Siemens, Erlangen, Germany). Time-of-flight and point-spread function were applied for scans on the Biograph mCT 40 and 64. After a 6-h fast and with blood sugar levels less than 210 mg/dL, the patients were injected with 5.18 MBq/kg of ^{18}F-FDG 1 h before the PET/CT scan. The ordered subsets expectation maximization algorithm with four iterations and eight subsets for the Biograph True-Point scanner and two iterations and 21 subsets for the Biograph mCT 40 and 64 scanners was used for image reconstruction. A 5.0-mm gaussian filter was used for image postprocessing.

^{18}F-FDG PET/CT image analysis

^{18}F-FDG PET/CT images were reviewed by two nuclear medicine physicians in consensus who were blinded to the histopathologic and Oncotype DX results using a software program (syngo.via; Siemens Medical Solution, Knoxville, TN). Clinical information on the tumor sites was provided at the time of review. The index tumor area was identified, and a spherical volume of interest (VOI) was manually placed to cover the entire tumor lesion on fusion ^{18}F-FDG PET/CT images. The tumors were then automatically segmented using an isocontour threshold method. The SUV threshold for tumor segmentation was defined as the mean SUV plus 1 standard deviation of the mediastinal blood pool activity (SUV_{MBP}, 1.78 ± 0.31) [19]. The total volume of the segmented VOI (MTV, centimeters cubed) and maximum SUV (SUV_{max}, grams per milliliter), and average SUV (SUV_{avg}, grams per milliliter) in the segmented VOI were measured. The product of MTV and SUV_{avg} yields the TLG (grams per milliliter·centimeters cubed) which is a measure of the total metabolic activity of the tumor.

Partial volume correction

RC profiles for each PET/CT scanner were experimentally determined from phantom studies using the IEC body phantom. Phantom images were obtained and reconstructed under the same conditions as used in the clinical studies. Activity concentrations for hot sphere and background were 1.12 and 0.14 μCi/mL, respectively (ratio 8:1). RC was calculated based on the maximum pixel value according to the following expression:

$$\text{RC for SUVmax} = \frac{\textit{measured hot region activity} - \textit{measured background activity}}{\textit{true hot region activity} - \textit{true background activity}}$$

Nonlinear regression fitting was applied for RC profile acquisition with the data from six hot spheres of 37, 28, 22, 17, 13, and 10 mm from the IEC body phantom (Fig. 1). Partial volume-corrected SUV_{max} (PVC-SUV_{max}) was calculated based on the tumor diameter in the surgical specimen according to the following expression:

$$\text{PVC-SUVmax} = \frac{\textit{Measured SUVmax} - \textit{background activity}}{\textit{RC for SUVmax}} + \text{background activity}$$

which was used in a previous study [20].

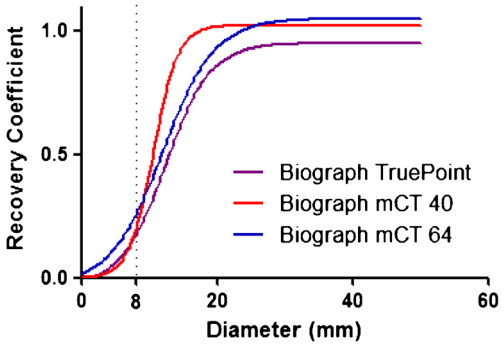

Fig. 1 Recovery coefficient (RC) profiles for the dedicated PET/CT scanners. To correct underestimation of activity in small lesions, RCs were measured using the IEC body phantom with six hot spheres (diameters 37, 28, 22, 17, 13, and 10 mm). Virtual input of RC 0 for diameter 0 mm and RC 1 for diameter 50 mm was hypothesized for RC profiles fitted by non-linear regression

Data collection

Clinical data collected included age at diagnosis, menopausal status, and presence or absence of a first-degree family history of breast cancer and palpable symptoms. Surgical data included the type of breast operation and axillary procedure. Pathologic data collected included histologic type of breast cancer, invasive tumor size, nuclear and histologic grade (*1* low, *2* intermediate, *3* high), carcinoma in situ components, lymphovascular invasion, and axillary lymph node metastasis. Tumor stage was classified according to the American Joint Committee on Cancer 7th edition [21]. Immunohistochemical (IHC) staining data for ER, PR, HER2, and Ki-67 were also collected. The study population included ER-positive patients (staining in ≥1 % of cells) and HER2-negative patients (defined as 0 or 1+ staining on IHC, or 2+ on IHC with nonamplification of the HER2 gene on fluorescence in situ hybridization). The percentages of cells stained for ER, PR and Ki-67 as well as the HER2 score (0, 1+, 2+) on IHC were recorded. The Oncotype DX RS (0–100) was recorded and categorized as low RS (<18), intermediate RS (18–30), or high RS (≥31).

Statistical analysis

The Oncotype DX RS categories were divided into low (<18) and intermediate-to-high (≥18) to determine the factors

associated with low RS or intermediate-to-high RS. Clinicopathologic factors were compared between the Oncotype DX RS categories using Fisher's exact test for categorical variables and the Mann-Whitney *U* test for continuous variables. Quantitative PET parameters were compared between the Oncotype DX RS categories using the Mann-Whitney *U* test. Receiver operating characteristic (ROC) curves for the PET parameters were analyzed to evaluate their overall performance for discriminating the Oncotype DX RS categories, and the optimal cut-off value for each parameter was identified. Univariate and multivariate logistic regression analyses were performed to determine independent predictors of the Oncotype DX RS categories.

Two-tailed *P* values of less than 0.05 were considered to indicate a statistically significant difference. Two-tailed *P* values in the range 0.05 – 0.10 were considered to indicate a marginally significant difference. All statistical analyses were performed using commercial software: SPSS v.18.0 (SPSS Inc., Chicago, IL) and MedCalc v14.8.1 (MedCalc Software bvba, Mariakerke, Belgium).

Results

RC profile from the phantom study

RC profiles for each PET/CT scanner are shown in Fig. 1. SUV_{max} was underestimated in small lesions. For lesions about 20 mm and larger in size, the RC profile curves were close to a plateau. RCs at 20 mm were 0.86 for the Biograph TruePoint, 1.0 for the Biograph mCT 40, and 0.94 for the Biograph mCT 64. The plateau was reached at a lesion size of 24 mm with RCs of 0.93 for the Biograph TruePoint, and 1.0 for both the Biograph mCT 40 and the Biograph mCT 64.

Clinicopathologic factors and the Oncotype DX RS

The median Oncotype DX RS in the 38 patients was 16 (range 6 – 35); 22 patients (58 %) had a low RS, 13 (34 %) had an intermediate RS, and only 3 (8 %) had a high RS. Table 1 presents the detailed clinical and pathologic information of the study population and differences in clinicopathologic factors between the groups with low and with intermediate-to-high Oncotype DX RS. The median age of the patients was 48 years (range 39 – 62 years). The major histologic tumor type was invasive ductal carcinoma (35 of 38 patients, 92 %). Two patients had invasive lobular carcinoma and one had mucinous carcinoma. No patient had nodal metastasis. The median invasive tumor size (longest diameter) was 16 mm (range 9 – 33 mm); 4 tumors were ≤10 mm, 13 tumors 10 – 15 mm, 10 tumors 15 – 20 mm, 10 tumors 20 – 30 mm, and 1 tumor >30 mm in size.

A low Oncotype DX RS was more frequent in patients with T1 tumors (18 of 27 patients, 67 %) than in those with T2 tumors (4 of 11 patients, 36 %; $P = 0.086$, marginally significant). All 38 patients were hormone receptor-positive (ER-positive/PR-positive in 33 and ER-positive/PR-negative in 5). Patients with an intermediate-to-high RS showed significantly lower ER expression levels than those with a low RS ($P = 0.035$), and a negative PR status was more frequent among patients with an intermediate-to-high RS than among those with a low RS ($P = 0.066$). In contrast, a HER2 IHC score of 2+ was significantly more frequent among patients with an intermediate-to-high RS than among those with a low RS ($P = 0.037$). High nuclear grades (grade 3) and high Ki-67 index (≥14 %) were more frequent among patients with an intermediate-to-high RS than among those with a low RS ($P = 0.090$ and 0.088, respectively, marginally significant). Other clinicopathologic factors including age, presence of a first-degree family history or palpable symptoms and histologic grade were not significantly associated with RS.

PET parameters and Oncotype DX RS

The quantitative PET parameters of the 38 index tumors were as follows: median MTV 1.44 (range 0 – 14.48), SUV_{max} 2.63 (1.00 – 12.16), SUV_{avg} 2.25 (0 – 4.80), TLG 2.58 (0 – 61.68), and PVC-SUV_{max} 4.50 (1.00 – 12.42). The quantitative PET parameters according to the pathologic tumor size are shown in Table 2. PVC-SUV_{max} was not different form SUV_{max} in large tumors (>20 mm; Figs. 2 and 3). PVC-SUV_{max} was higher than SUV_{max} in small tumors (≤20 mm) (Fig. 4).

Table 3 shows the associations between PET parameters and Oncotype DX RS. Patients with an intermediate-to-high RS showed higher values of PVC-SUV_{max} (median 5.68, range 1.00 – 12.16) than those with a low RS (4.06, 2.00 – 12.42; $P = 0.067$, marginally significant). SUV_{max}, SUV_{avg}, MTV and TLG showed no differences between patients with an intermediate-to-high RS and those with a low RS (SUV_{max} $P = 0.151$, SUV_{avg} $P = 0.230$, MTV $P = 0.625$, and TLG $P = 0.477$). Changes in SUV_{max} after partial volume correction in individual tumors are shown in Fig. 5. After partial volume correction, SUV_{max} remained low in patients with a low RS, but tended to increase in patients with an intermediate-to-high RS. In the ROC curve analysis, PVC-SUV_{max} (continuous) had marginal significance for discriminating patients with a low RS from those with an intermediate-to-high RS; the area under the ROC curve (AUC) was 0.676 (95 % confidence interval, CI, 0.486 – 0.867) for PVC-SUV_{max} (continuous, $P = 0.067$). The optimal cut-off value was 4.96 for PVC-SUV_{max} with a sensitivity of 62.5 % (10/16) and a specificity 86.4 % (19/22).

Table 1 Associations between clinicopathologic factors and Oncotype DX RS

Variable	Total	Oncotype DX RS		
		Low (<18)	Intermediate-to-high (≥18)	*P*-value
No. of patients	38	22	16	
Age (years)	48 (39 – 62)	47 (38 – 59)	48 (31 – 62)	0.264
Menopausal status				
Premenopausal	31 (82)	18 (82)	13 (81)	0.964
Postmenopausal	7 (18)	4 (18)	3 (19)	
Family history of breast cancer				
Absent	35 (92)	20 (91)	15 (94)	0.748
Present	1 (8)	2 (9)	1 (6)	
Palpable symptoms				
Absent	18 (47)	12 (55)	6 (38)	0.299
Present[a]	20 (53)	10 (46)	10 (62)	
Surgery				
Breast-conserving surgery with sentinel lymph node biopsy	29 (76)	16 (73)	13 (81)	0.542
Mastectomy with sentinel lymph node biopsy	9 (24)	6 (27)	3 (19)	
Histologic tumor type				
Ductal	35 (92)	19 (86)	16 (100)	0.124
Lobular or other specific	3 (8)	3 (14)	0 (0)	
Invasive tumor size (mm)	16 (9 – 33)	15 (9 – 33)	20 (10 – 30)	0.264
pT stage				
1	27 (71)	18 (82)	9 (56)	0.086
2	11 (29)	4 (18)	7 (44)	
Nuclear grade				
1/2	18 (47)	13 (59)	5 (31)	0.090
3	20 (53)	9 (41)	11 (69)	
Histologic grade				
1/2	22 (58)	13 (59)	9 (56)	0.861
3	16 (42)	9 (41)	7 (44)	
Carcinoma in situ component				
Absent	10 (26)	6 (27)	4 (25)	0.875
Present	28 (74)	16 (73)	12 (75)	
Lymphovascular invasion				
Absent	30 (79)	17 (77)	13 (81)	0.767
Present	8 (21)	5 (23)	3 (19)	
Hormone receptor expression				
Estrogen receptor	90 (60 – 96)	90 (60 – 96)	85 (60 – 96)	0.035
Progesterone receptor				
Negative (<1 %)	5 (13)	1 (4)	4 (25)	0.066
Positive (≥1 %)	33 (87)	21 (96)	12 (75)	
HER2 expression on immunohistochemistry				
0 or 1+	28 (74)	19 (86)	9 (56)	0.037
2+[b]	10 (26)	3 (14)	7 (44)	
Ki-67				0.088
<14	36 (95)	22 (100)	14 (88)	
≥14	2 (5)	0	2 (12)	

Data are presented as number (%) of women or median (range) as appropriate

[a] Patients presented with a palpable lump in the breasts (palpable symptoms)

[b] HER2 gene amplification was not observed on fluorescence in situ hybridization in all patients with a HER2 immunohistochemical score of 2+

Table 2 Oncotype DX RS and metabolic parameters on ^{18}F-FDG PET/CT in relation to tumor size

Variable	Tumor size (mm)				
	≤10	10 – 15	15 – 20	20 – 30	>30
No. of patients	4	13	10	10	1
Oncotype DX RS	22 (6 – 27)	15 (6 – 34)	16 (6 – 24)	21 (9 – 35)	17
SUV_{max} (g/mL)	1.60 (1.50 – 2.16)	2.37 (1.60 – 5.50)	4.67 (2.00 – 9.69)	4.95 (1.00 – 12.16)	4.84
SUV_{avg} (g/mL)	0 (0 – 2.05)	2 (0 – 2.55)	2.51 (0 – 3.61)	3.16 (0 – 4.80)	3.34
MTV (cm^3)	0 (0 – 0.2)	0.50 (0 – 7.37)	2.44 (0 – 8.06)	4.01 (0 – 14.48)	6.86
TLG (g/mL·cm^3)	0 (0 – 0.41)	1.04 (0 – 16.73)	5.75 (0 – 22.49)	13.34 (0 – 61.68)	22.91
PVC-SUV_{max} (g/mL)	5.68 (3.57 – 5.71)	3.65 (2.22 – 7.64)	4.97 (2.00 – 12.42)	4.95 (1.00 – 12.16)	4.84

Data are presented as median (range)

Logistic regression analysis of predictors of Oncotype DX RS

To determine whether the PET parameters are independent predictors of Oncotype DX RS, univariate and multivariate logistic regression analyses were performed (Table 4). Multiple clinicopathologic parameters which tended to discriminate between patients with a low RS and an intermediate-to high RS were evaluated in the univariate and multivariate analyses. The optimal cut-off values for continuous variables including ER percentage and SUV_{max} were determined by ROC curve analysis. ER percentage was 90 % and was significantly discriminated patients with a low RS from those with an intermediate-to-high RS ($P = 0.040$, AUC 0.697, 95 % CI 0.523 – 0.872). High PVC-SUV_{max} (≥4.96), low ER (<90 %), and a high HER2 IHC score (2+) were significant predictors of an intermediate-to-high RS in the univariate analysis ($P = 0.004$, 0.019 and 0.046, respectively). Stage pT2, nuclear grade 3, and a negative PR status were marginally significant predictors of an intermediate-to-high RS ($P = 0.094$, 0.095, and 0.098, respectively).

Variables that showed statistical significance in the univariate analysis were included in the multivariate analysis. Two different models were used with different P values (0.05 or 0.10) in the univariate analyses. In both multivariate analyses, only high PVC-SUV_{max} (≥4.96) was an independent predictor of an intermediate-to-high RS (model 1, odds ratio, OR, 8.459, $P = 0.013$, and 95 % CI 1.581 – 45.274; model 2, OR 9.893, $P = 0.026$, and 95 % CI 1.308 – 74.498). The AUCs were 0.817 for model 1 ($P = 0.001$, 95 % CI 0.671 – 0.962) and 0.875 for model 2 ($P < 0.001$, 95 % CI 0.760 – 0.990; Table 5, Fig. 6). Model 1 included binary parameters of PVC-SUV_{max} (≥4.96), ER (<90 %), and HER2 IHC score (2+), and model 2 included binary parameters of PVC-SUV_{max} (≥4.96), T stage (pT2), nuclear grade (3), ER (<90 %), PR (negative), and HER2 IHC score (2+). The difference in AUC between the two models was not statistically significant ($P = 0.251$). The AUCs, sensitivity, and specificity of the multivariate models, and the clinicopathologic parameters and PVC-SUV_{max} are shown in Table 5.

Discussion

In this study, metabolic parameters determined on pretreatment ^{18}F-FDG PET/CT and PVC-SUV_{max} were found to be associated with Oncotype DX RS. A higher maximum ^{18}F-FDG tumor uptake intensity (PVC-SUV_{max} ≥4.96) was a significant independent predictor of an intermediate-to-high RS. Conventional parameters, SUV_{max} and SUV_{avg} without partial

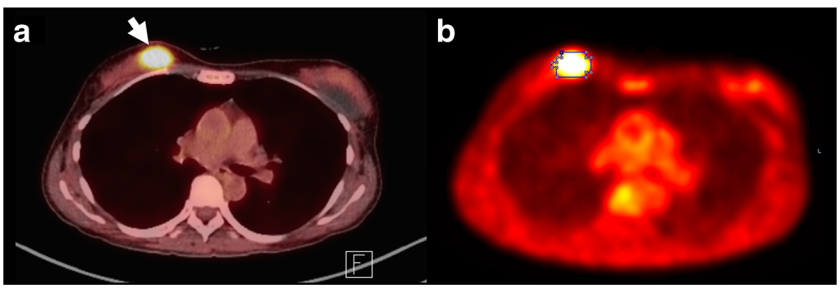

Fig. 2 ER-positive/HER2-negative invasive ductal carcinoma in a 45-year-old woman. The pathologic invasive tumor size was 3.0 cm without lymph node metastasis (pT2N0). The nuclear grade was 2, and the IHC expression profiles were ER 70 %, PR 96 %, HER2 score 2+, and Ki-67 4 %. **a** The preoperative ^{18}F-FDG PET/CT image shows high ^{18}F-FDG uptake in the upper inner quadrant of the right breast. On quantitative measurement, MTV of the primary tumor was 14.48 cm^3 with a high SUV_{max} (12.16). PVC-SUV_{max} was same as SUV_{max}, because the recovery coefficient (RC) was 1. TLG was 61.68 g/mL·cm^3. **b** The Oncotype DX RS was 22 (intermediate)

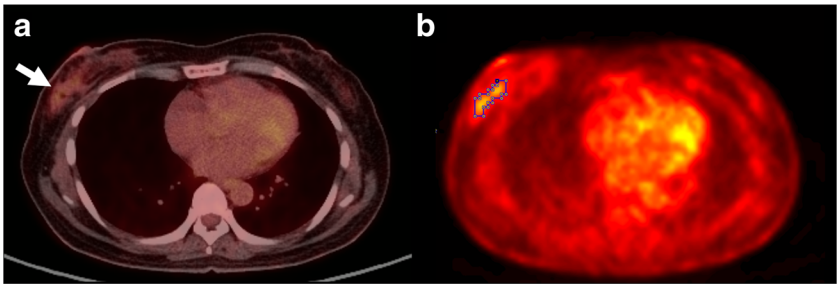

Fig. 3 ER-positive/HER2-negative invasive ductal carcinoma in a 42-year-old woman. The pathologic invasive tumor size was 3.5 cm without lymph node metastasis (pT2N0). The nuclear grade was 2, and the IHC expression profiles were ER 40 %, PR 50 %, HER2 score 0, and Ki-67 12 %. **a** The preoperative ^{18}F-FDG PET/CT image shows mild ^{18}F-FDG uptake in the outer portion of the right breast. On quantitative measurement, MTV of the primary tumor was 3.4 cm^3 with a low SUV_{max} (2.51). PVC-SUV_{max} was also 2.51. TLG was 6.46 g/mL·cm^3. **b** The Oncotype DX RS was 9 (low)

volume correction, and volumetric parameters of metabolism (MTV and TLG) were not significantly associated with RS. SUV_{max} is the most studied and widely used parameter for quantitating the metabolic activity of tumors. Ahn et al. found that recurrence-free survival in patients with hormone receptor-positive breast cancer was significantly different between those with SUV_{max} <4 and those with SUV_{max} ≥4 [15]. In a recent preliminary study, they also found that SUV_{max} 4 is a useful cut-off value for predicting Oncotype DX RS: patients with SUV_{max} <4 are likely to have a low-to-intermediate RS (≤24) [22]. In contrast to the results of the preliminary study, in this study SUV_{max} without partial volume correction was not significantly correlated with RS. The partial volume effect on tumor SUV should be considered when small tumors, including most early breast cancer for which Oncotype DX testing is indicated, are evaluated by PET/CT. This study indicates that the most appropriate PVC-SUV_{max} cut-off value is 4.96 with a sensitivity of 62.5 % and a specificity of 86.4 %. In addition, this study focused on the discrimination between patients with a low RS and those with an intermediate-to-high RS, which is clinically more important in decision making in relation to the use of adjuvant chemotherapy [5].

Three-dimensional image blurring from the partial volume effect occurs as a result of the limited spatial resolution of imaging systems including PET [23]. The activity in lesions spills out into relatively less active background causing qualitative and quantitative errors, especially for small lesions, leading to underestimation of quantitative measurements on PET images and overestimation of lesion size. Thus small tumors appear less aggressive than they should. The use of the RC for partial volume correction is the simplest and most feasible method among several types of partial volume correction methods. Considering the RC profiles obtained in the phantom study, the optimal lesion size cut-off value when utilizing partial volume correction is 24 mm. The cut-off value depends on the performance of each PET/CT scanner. In this study, PVC-SUV_{max} showed a clear difference between patients with a low RS and those with an intermediate-to-high RS.

Although SUV_{max} increased by more than 20 % after partial volume correction in 55 % of patients (12/22) with a low Oncotype DX RS, most patients (92 %, 11/12) had a PVC-SUV_{max} lower than 4.96. On the other hand, although PVC-SUV_{max} increased by more than 20 % in only 31 % of patients (5/16) with an intermediate-to-high RS, 75 % of patients (3/4) with increased PVC-SUV_{max} had a PVC-SUV_{max} greater than 4.96. One patient with a low RS of 13 exceptionally had a high PVC-SUV_{max} of 12.42. Despite the fact that a high PVC-SUV_{max} is a risk factor for an intermediate-to-high

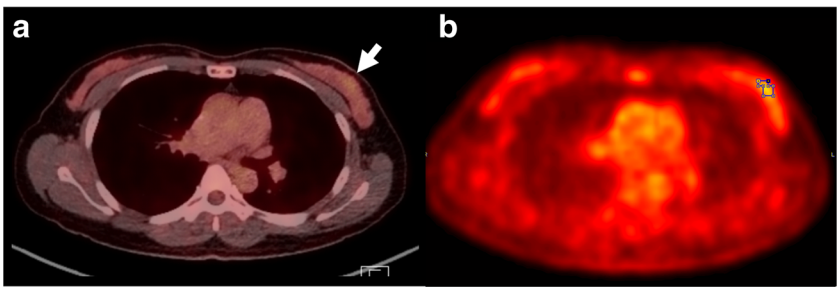

Fig. 4 ER-positive/HER2-negative invasive ductal carcinoma in a 43-year-old woman. The pathologic invasive tumor size was 1.2 cm without lymph node metastasis (pT1N0). The nuclear grade was 3, and the IHC expression profiles were ER 60 %, PR 5 %, HER2 score 1+, and Ki-67 10 %. **a** The preoperative ^{18}F-FDG PET/CT image shows low ^{18}F-FDG uptake in the upper outer quadrant of the left breast. On quantitative measurement, MTV of the primary tumor was 0.85 cm^3 with a low SUV_{max} (2.63), but relatively high PVC-SUV_{max} (4.78). TLG was 1.92 g/mL·cm^3. **b** The Oncotype DX RS was 34 (high)

Table 3 Associations between metabolic parameters determined on ^{18}F-FDG PET/CT and Oncotype DX RS

Variable (continuous)	All tumors	Oncotype DX RS		
		Low (<18)	Intermediate-to-high (≥18)	*P* value
SUV_{max} (g/mL)	2.63 (1.00 – 12.16)	2.55 (1.50 – 9.69)	4.05 (1.00 – 12.16)	0.151
SUV_{avg} (g/mL)	2.25 (0 – 4.80)	2.17 (0 – 3.34)	2.32 (0 – 4.80)	0.230
MTV (cm^3)	1.44 (0 – 14.48)	1.64 (0 – 8.06)	1.44 (0 – 14.48)	0.625
TLG (g/mL·cm^3)	2.58 (0 – 61.68)	2.74 (0 – 22.91)	2.58 (0 – 61.68)	0.477
PVC-SUV_{max} (g/mL)	4.50 (1.00 – 12.42)	4.06 (2.00 – 12.42)	5.68 (1.00 – 12.16)	0.067

Data are presented as median (range)

RS, in this patient other predictive factors (ER and HER2 IHC score) were favorable for a low RS (ER 90 % and HER2 IHC score 1+). The findings in this patient suggest that a multifactorial approach is needed for recurrence risk estimation.

In a recent study, partial volume correction based on RC was found to be a useful method for standardizing SUVs from different PET machines [24]. In our study, SUVs of the tumors were measured using three different scanners. Because the performance of these scanners was different, the measured SUVs were also slightly different from one another, especially in small lesions, as shown on the RC profiles from the phantom study. Correcting the measured SUV_{max} to give PVC-SUV_{max}, an estimate of actual SUV_{max}, had the additional effect of harmonizing SUV_{max} among the different scanners. However, this approach is not suitable for tumors with diameter less than 1.5 times the FWHM because of overcorrection of activity. Thus we restricted the inclusion of tumors to those with a diameter of more than 0.8 cm. RC is also limited by the assumption that the lesion is located in a background with no radioactivity. Breast parenchyma usually shows mild physiologic activity. These considerations might have affected the accuracy of PVC-SUV_{max} and undermined the statistical power of the analysis of the association between

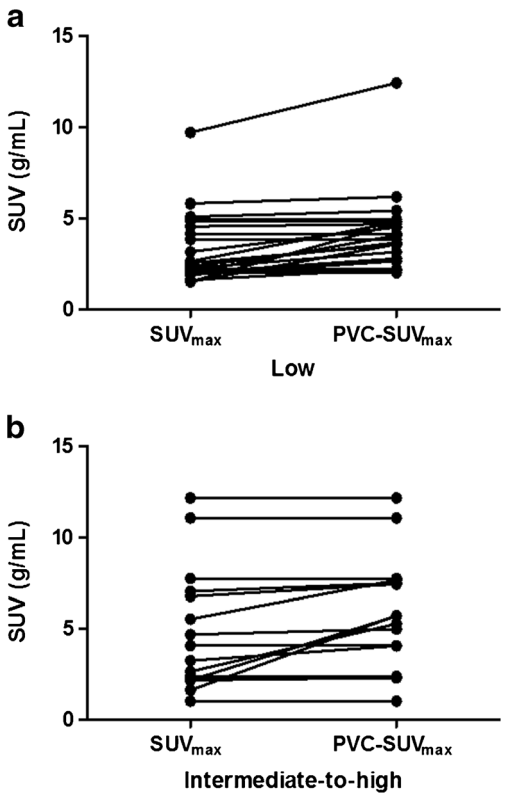

Fig. 5 Changes in SUV_{max} after partial volume correction in individual tumors. SUV_{max} of tumors with a low Oncotype DX RS remained low levels (**a**). On the other hand, SUV_{max} of tumors with an intermediate-to-high Oncotype DX RS tended to increase (**b**)

Table 4 Univariate and multivariate logistic regression of variables for discriminating patients with a low Oncotype DX RS from those with an intermediate-to-high RS

Variable (binary)	Odds ratio	95 % CI	*P* value
Univariate analysis			
PVC-SUV_{max} (≥4.96 g/mL)	10.556	2.167 – 51.420	0.004
pT stage (pT2)	3.500	0.808 – 15.163	0.094
Nuclear grade (3)	3.178	0.819 – 12.337	0.095
ER (ER <90 %)	5.786	1.336 – 25.065	0.019
PR (PR-negative)	7.000	0.700 – 70.045	0.098
HER2 IHC score (2+)	4.926	1.027 – 23.627	0.046
Ki-67 (≥14 %)	–	–	0.999
Multivariate analysis			
Model 1			
PVC-SUV_{max} (≥4.96 g/mL)	8.459	1.581 – 45.274	0.013
ER (ER <90 %)	2.903	0.472 – 17.837	0.250
HER2 IHC score (2+)	2.698	0.386 – 18.834	0.317
Model 2			
PVC-SUV_{max} (≥4.96 g/mL)	9.893	1.308 – 74.498	0.026
pT stage (pT2)	2.654	0.240 – 29.354	0.426
Nuclear grade (3)	6.313	0.821 – 48.546	0.077
ER (ER <90 %)	4.529	0.484 – 42.377	0.185
PR (PR-negative)	4.437	0.133 – 147.568	0.405
HER2 IHC score (2+)	1.583	0.147 – 17.019	0.705

Table 5 Receiver operating characteristic curve analysis of variables for discriminating patients with a low Oncotype DX RS from those with an intermediate-to-high RS

Variable	AUC	95 % CI	*P* value	Sensitivity (%)	Specificity (%)
Multivariate model 1 (continuous)	0.817	0.658 – 0.923	<0.001	81.3	72.7
Multivariate model 2 (continuous)	0.875	0.727 – 0.960	<0.001	68.8	95.5
PVC-SUV_{max} (≥4.96 g/mL)[a,b]	0.744	0.577 – 0.872	0.001	62.5	86.4
pT stage (pT2)[b]	0.628	0.456 – 0.779	0.095	43.8	81.8
Nuclear grade (Gr 3)[b]	0.639	0.468 – 0.788	0.083	68.8	59.1
ER (ER < 90 %)[a,b]	0.690	0.520 – 0.830	0.013	56.3	81.8
PR (PR-negative) [b]	0.602	0.431 – 0.757	0.090	25.0	95.5
HER2 IHC status (2+)[a,b]	0.651	0.479 – 0.798	0.042	43.8	86.4

[a] In multivariate model 1

[b] In multivariate model 2

PVC-SUV_{max} and Oncotype DX RS, and thus we also excluded patients with multifocal/multicentric breast cancer.

Among the clinicopathologic factors analyzed in this study, only nuclear grade was a marginally significant independent predictor of Oncotype DX RS in the univariate and multivariate analyses. Higher pT stage (pT2), low ER (<90 %), negative PR and HER2 IHC score 2+ were more frequent in patients with an intermediate-to-high RS than in those with a low RS in the univariate analysis of 38 index tumors (all $P < 0.10$). Our results are consistent with those of previous studies showing that Oncotype DX RS is significantly correlated with nuclear grade, mitotic count, and IHC scores for ER, PR, and HER2 [25, 26]. They also showed that the RS estimated from pathology-generated equations such as the Magee equation and the IHC4 score can provide similar prognostic information to that provided by the Oncotype DX RS.

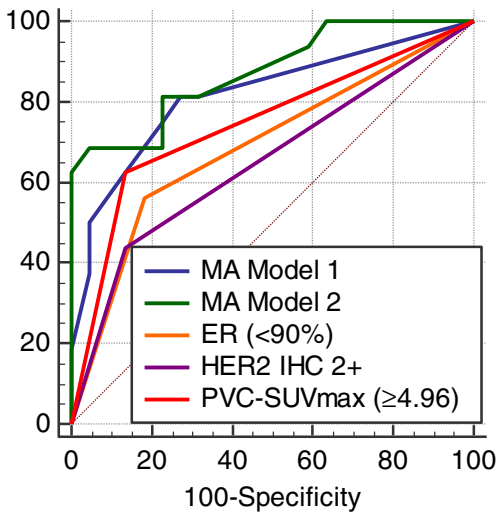

Fig. 6 Receiver operator characteristic (ROC) curves for the multivariate logistic models predicting an intermediate-to-high recurrence score. The ROC curves for ER (<90 %), HER2 IHC score (2+), and PVC-SUV_{max} (≥4.96) are also shown. The AUC is 0.817 for model 1 with PVC-SUV_{max} (≥4.96), ER (<90 %) and HER2 IHC score (2+) as predictors, and 0.875 for model 2 with PVC-SUV_{max} (≥4.96), pT stage (pT2), nuclear grade (3), ER (<90 %), PR (negative), and HER2 IHC score (2+) as predictors. The AUCs of the two multivariate models were not significantly different ($P = 0.251$). The AUCs of ER (<90 %), HER2 IHC (score 2+), and PVC-SUV_{max} (≥4.96) were 0.690, 0.651, and 0.744, respectively

In addition to the histopathologic variables, i.e., microscopic phenotype, studies using various imaging modalities of the correlation between macroscopic phenotype and genotype have recently been performed. Yepes et al. found that the morphologic features of breast cancers on mammography and ultrasonography can predict Oncotype DX RS [27]. Features of enhancement dynamics on magnetic resonance imaging have been found to be significantly correlated with the Oncotype DX RS [28]. Our study showed the association between ^{18}F-FDG metabolism and Oncotype DX RS. The additive value of PVC-SUV_{max} to the established clinicopathologic parameters including ER for recurrence risk estimation based on Oncotype DX RS was validated by the multivariate analysis, which showed the independence of PVC-SUV_{max} and enhanced predictive accuracy. Imaging plays a complementary role to genetic profiling tests although it cannot replace the latter completely. Oncotype DX RS is known to be affected by various factors such as admixture of noninvasive tumor tissue components, and variation in tissue handling and fixation [29]. Imaging features can be used for the validation of Oncotype DX results and further investigation may be recommended if the test results are significantly different from those expected based on imaging features.

In addition, ^{18}F-FDG PET/CT imaging can provide metabolic information for each tumor site in patients with multifocal/multicentric disease and can give information about the tumor site for which the Oncotype DX test is indicated. Multifocal/multicentric breast cancer has been recognized as having a more aggressive character and worse recurrence outcome than unifocal breast cancer [30]. A retrospective study including 22 patients with multiple breast tumors who underwent Oncotype DX testing, the genetic profiles in tumors in different breasts

appeared to show greater differences than tumors in the same breast [31]. The average difference in Oncotype DX RS between tumors in the same breast was 4.6 in contrast to 13.0 between tumors in different breasts. The change in Oncotype risk group was 22.2 % for tumors in the same breast and 50.0 % for tumors in different breasts. There has so far been no study focusing on the role of imaging in patients with multiple breast cancer for the assessment Oncotype DX RS. Unfortunately, 13 patients with multifocal/multicentric disease were excluded from our study, because due to the retrospective nature of the study, we were not able to determine which tumor was evaluated by the Oncotype DX test. Therefore, our results do no allow conclusions to drawn as to the value of PET/CT for recurrence risk evaluation in patients with multiple breast cancer. If validated by further studies, ^{18}F-FDG PET/CT might be used to select patients and lesions that are suitable for Oncotype DX testing even in patients with multifocal/multicentric breast cancer.

Our study had several limitations. The major limitation was that this was a retrospective study with a limited number of patients. Among the 143 patients who underwent Oncotype DX testing, only 38 (27 %) were included and only three had a high Oncotype DX RS. We excluded 13 patients with multifocal/multicentric breast cancer and FDG PET/CT scans, as discussed above. This enhanced the reliability of the results on the association between Oncotype DX RS and PVC-SUV_{max} in specific lesions, but led to a decrease in the sample size of the study. Therefore, considering the relatively small sample size, our results should be viewed with caution and further studies with larger populations are needed to validate our results. Second, the matching of the Oncotype DX RS results to the PET/CT results was difficult in patients with multifocal/multicentric breast cancer due to the retrospective nature of the study, as discussed above. Third, the association between the metabolic parameters and actual recurrence-free survival could not be evaluated due to the short duration of follow-up.

Conclusion

Higher PVC-SUV_{max} was significantly associated with an intermediate-to-high Oncotype DX RS regardless of histopathologic status. Therefore, ^{18}F-FDG PET/CT can be used to predict the Oncotype DX RS in patients with early-stage, ER-positive/HER2-negative breast cancer. Partial volume correction is needed for determining metabolic activity in small lesions to estimate Oncotype DX RS.

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Compliance with ethical standards

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Conflict of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent This retrospective study was approved by institutional review board. The requirement for written informed consent was waived due to the retrospective design.

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