ORIGINAL PAPER

Assessment of tumor response to neoadjuvant chemotherapy in patients with breast cancer using MRI and FDG-PET/CT-RECIST 1.1 vs. PERCIST 1.0

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ABSTRACT

Therapeutic response to neoadjuvant chemotherapy (NAC) for breast cancer based on Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) 1.0 with FDG-PET/CT measurements was evaluated, and the results compared to those obtained with currently widely used Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, based on MRI measurements. MRI and FDG-PET/CT examinations were performed in 32 breast cancer patients before and after the NAC prior to a surgical resection. Chemotherapeutic response of the primary tumor and relapse-free survival (RFS) were investigated using RECIST 1.1 and PERCIST 1.0. Pathological complete response (pCR) was seen in 14 (43.8%) patients, while complete response (CR) was noted in 5, partial response in 25, stable disease in 2, and progressive disease in 0 with RECIST 1.1, and in 28, 2, 1, and 1, respectively, with PERCIST 1.0. For pCR prediction, the sensitivity, specificity, and accuracy with RECIST 1.1 were 28.6% (4/14), 94.4% (17/18), and 65.6% (21/32), and those with PERCIST 1.0 were 100% (14/14), 22.2% (4/18), and 56.3% (18/32). Five patients (15.6%) had recurrent development after a median period of 24 months (range 7.8–66.8 months). Patients who achieved CR shown by RECIST 1.1 showed slightly longer RFS than those who did not (p=0.46), whereas those with complete metabolic response (CMR) based on PERCIST 1.0 showed a relatively longer RFS than non-CMR patients (p=0.087). For prediction of pathological response to NAC in breast cancer, RECIST 1.1 and PERCIST 1.0 have complementary functions, however, FDG-PET as a post-NAC treatment assessment modality remains to be confirmed.

Keywords: FDG-PET/CT, RECIST, PERCIST, treatment response, breast cancer

Abbreviations: NAC, neoadjuvant chemotherapy; PERCIST, Positron Emission Tomography Response Criteria in Solid Tumors; FDG, fluorodeoxyglucose; PET/CT, positron emission tomography/computed tomography; RECIST, Response Evaluation Criteria in Solid Tumors; MRI, magnetic resonance imaging; RFS, relapse-free survival; pCR, pathological complete response; CR, complete response; CMR, complete metabolic response; CT, computed tomography; SUVmax, maximum standardized uptake value; SULpeak, peak lean body mass standardized uptake value; TR, repetition time; TE, echo time; FOV, field of view; ROI, region of interest; PR, partial response; PD, progressive disease; SD, stable disease; PMR, partial metabolic response; PMD, progressive metabolic disease; SMD, stable metabolic disease; ER, estrogen receptor;

HER2, human epidermal growth factor receptor type 2

INTRODUCTION

Presently, the primary option for locally advanced breast cancer is neoadjuvant chemotherapy (NAC) and is increasingly used for early stage disease. Reasons for use of this therapy include an increase in use of breast-conserving surgical procedures, to eliminate micrometastatic disease, and for prediction of prognosis using response of the tumor as a parameter. Patients who gain pathological complete response (pCR) after NAC have a longer period without disease and better overall survival as compared to non-responders,[1-4] though a few cases of pCR develop recurrence.[5] As a result, accurate assessment of tumor response and residual cancer after undergoing NAC is considered crucial for reducing the number of local recurrence cases.

Effective methods for evaluation of therapeutic efficiency are crucial to successfully treat cancer. Present techniques for monitoring therapeutic response are typically based on anatomical changes seen with computed tomography (CT) imaging or other anatomical imaging methods, and the Response Evaluation Criteria in Solid Tumors (RECIST) was updated by the World Health Organization in 2009 (version 1.1).[6] However, anatomical imaging may be limited in regard to its applicability to distinguish viable residual tumors from reactive changes, such as those related to edema and scar tissue, or killed cells and shrunken tumors.

Functional evaluations of metabolic activity can be performed with ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET), and its use is considered helpful to overcome these limitations and believed to be more suitable for therapeutic response examinations. Quantitative FDG-PET treatment response assessment is based on alterations of maximum standardized uptake value (SUVmax) in comparisons between baseline and follow-up results, though that is affected by technical, physical, and biological factors.[7] To improve reproducibility for comparisons of results from separate trials, a widely accepted standardized protocol is needed. For this reason, Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) 1.0, which uses peak lean body mass SUV (SULpeak), was developed in 2009.[8]

Very few studies have compared PERCIST 1.0 with the current standard RECIST 1.1 in regard to response assessment in breast cancer patients[9,10] or those with other types of malignancy. Two studies are known to have evaluated intra-NAC response assessments,[9,10] however, none have directly compared breast cancer cases evaluated by both post-NAC PERCIST 1.0 and RECIST 1.1, thus the true usefulness of PERCIST 1.0 following NAC for assessment of breast cancer status has not been confirmed. In this study, we compared RECIST 1.1 with PERCIST 1.0 for evaluation of pathological therapeutic response to NAC, as well as correlation with prognosis in patients with locally advanced breast cancer who underwent both magnetic resonance imaging (MRI) and FDG-PET/CT examinations after undergoing NAC.

MATERIALS AND METHODS

Patients

This retrospective study was approved by our institutional review board, which waived the requirement for informed consent from the enrolled patients. We investigated the records of 32 patients (29–74 years old, mean ± standard deviation 52.4±12.4 years) with breast cancer who underwent MRI and FDG-PET/CT before and after NAC before undergoing a scheduled

surgical resection procedure between January 2012 and December 2016. The period between the initial MRI and FDG-PET/CT examinations was approximately 2 weeks (12.9±9.7 days), and that between the next MRI and FDG-PET/CT examinations was also approximately 2 weeks (13.3±13.2 days). The mean period between completion of NAC and second FDG-PET/ CT examination was 28.3 days (range 19–43 days), and that between the second FDG-PET/CT examination and surgery was 19.1 days (5–31 days).

MRI

All MRI breast examinations performed before and after NAC were done using a 3.0-Tesla MRI scanner (Magnetom Verio; Siemens Medical Solutions, Erlangen, Germany) equipped with a bilateral breast phased-array coil. Using a prone position, the following settings were employed: axial and sagittal, fat-suppressed, fast spin-echo T2-weighted imaging sequence (repetition time [TR]/echo time [TE], 5500/79 ms; slice thickness, 4 mm), axial spin-echo T1-weighted imaging sequence (TR/TE, 620/9.4 ms; slice thickness, 4 mm), and axial diffusion-weighted imaging sequence (b factors of 0 and 1000 s/mm^2; TR/TE, 6900/74 ms; slice thickness, 4 mm). A fat-suppressed T1-weighted fast low-angle-shot, three-dimensional, volume-interpolated breath-hold examination sequence [TR/TE, 3.7/1.4 ms; matrix, 384×384; field of view (FOV), 330×330 mm; slice thickness, 1 mm] was scanned before and then 1, 2, 3, and 5 minutes after gadolinium injection. Gadolinium contrast material (gadopentetate dimeglumine; Magnevist, Bayer Pharma) was given at a dose of 0.2 mL/kg using power injection at a speed of 2.0 mL/s and flushed with 20 mL of saline solution at the same rate. Standard subtraction images were obtained by subtracting pre-contrast images from the early peak post-contrast image, which were scanned 60 seconds after contrast injection, on a pixel-by-pixel basis.

All breast MR images were reviewed retrospectively by 2 experienced radiologists, each with at least 10 years of experience with breast MRI, and who had no knowledge of the other imaging results, or clinical and histopathologic data, other than the findings obtained before and after the NAC examinations for breast carcinoma, with decisions based on consensus. To determine lesion size, primary measurements of the long-axis of the tumor were made using the slice on which the lesion appeared largest among all contrast-enhanced imaging sequences. After NAC, if a primary tumor showed fragmentation into multiple smaller masses, the diameters of each fragment were added and we used the sum. The percentage long-diameter reduction rate of the primary lesion shown by MRI was calculated with the following equation: % reduction rate = ([pre-NAC value]–[post-NAC value])/(pre-NAC value)×100.

FDG-PET/CT

FDG-PET/CT examinations were performed using a Gemini GXL16 or Gemini TF64 PET/CT scanner (Philips Medical Systems, Eindhoven, The Netherlands) for the patients before and after undergoing NAC. Each fasted for 5 hours before the procedure, then blood glucose was measured just prior to injection of 4.0 MBq/kg body weight of FDG for the GXL16 or 3.0 MBq/kg for the TF64. No patient had a blood glucose level higher than 150 mg/dL. Static emission images were obtained approximately 60 minutes after injection. To obtain attenuation correction and anatomic localization, helical CT scans were taken from the top of the head to the bottom of the feet, with the following settings: tube voltage, 120 kV; effective tube current auto-mA up to 120 mA/second (GXL16) or 100 mA/second (TF64); gantry rotation speed, 0.5 seconds; detector configuration, 16×1.5 mm (GXL16) or 64×0.625 mm (TF64); slice thickness, 2 mm; and transverse FOV, 600 mm. Immediately following the CT examination, PET imaging of the region from the head to the mid-thigh was performed for 90 seconds for each bed position and from the mid-thigh to the toes for 30 seconds for each bed position in three-dimensional

mode. We reconstructed attenuation-corrected PET images using a line-of-response row-action maximum likelihood algorithm (LOR-RAMLA) (n/a subsets, 2 iterations) for the GXL16 or an ordered-subset expectation maximization iterative reconstruction algorithm (33 subsets, 3 iterations) for the TF64.

The FDG-PET/CT images were retrospectively reviewed by 2 experienced readers, 1 with 9 years of experience with oncologic FDG-PET/CT and the other with 4 years of that, who had no knowledge of other imaging results, or clinical and histopathologic data, other than those obtained before and after the NAC examinations for breast cancer, and their decisions were based on consensus. The commercially available GI-PET software package (AZE Co., Ltd., Tokyo, Japan), which can harmonize SUVs obtained with different PET/CT systems using phantom data, was used to assist the attending clinician for monitoring treatment response. SUVmax was defined as the maximum concentration in the primary tumor (injected dose/body weight). SUVpeak was calculated using a 1.2-cm diameter volume region of interest (ROI) placed on the hottest site of the tumor, then normalized to SULpeak (SUVpeak×[lean body mass]/[total body mass]). The percentage of SULpeak (% SULpeak) was calculated using the following equation: % SULpeak = (SULpeak [pre-NAC value]–SULpeak [post-NAC value])/SULpeak [pre-NAC value]×100.

RECIST 1.1

With RECIST 1.1[6] we utilized the following classifications for therapeutic response: complete response (CR), primary tumor disappearance; partial response (PR), 30% or greater decrease in longest diameter of primary tumor; progressive disease (PD), 20% or greater increase in longest diameter of primary tumor; stable disease (SD), tumors that did not show either sufficient shrink-age to be classified as PR or sufficient increase to be classified as PD.

PERCIST 1.0

To determine therapeutic response using PERCIST 1.0[8] we used these classifications: complete metabolic response (CMR), complete resolution of FDG uptake within the primary tumor that was lower than mean liver activity and indistinguishable from surrounding background; partial metabolic response (PMR), reduction of SULpeak by a minimum of 30% in target volume in the same lesion as the baseline measurement; progressive metabolic disease (PMD), 30% increase in SULpeak for FDG uptake; stable metabolic disease (SMD), disease that was not classified as CMR, PMR, or PMD. SUL values were calculated using a 1.2-cm diameter volume ROI placed on the primary tumor. We also determined whether the SULpeak value of the tumor was greater than 1.5 times or more that of the liver SUL (mean + 2 standard deviations) in a 3-cm diameter spherical ROI on the normal right lobe.

Assessment of Histopathologic Tumor Response

Surgical specimens were cut into 5-mm slices and fixed in 10% neutral-buffered formalin, then processed for histology, with each paraffin block sliced and stained with hematoxylin and eosin. In residual invasive cancer cases, the longest dimension was used for pathological size.

To assess therapeutic response in the present breast cancer patients, histological criteria were taken from the General Rules for Clinical and Pathological Recording of Breast Cancer 2007.[11] Evaluations of pathological response were only based on histological changes in the invasive area, while ductal components and/or lymph node metastasis were not evaluated. The definition of pCR (grade 3) was complete disappearance of breast cancer invasive components in the pathologic specimen, while substantially effective (grade 2) was defined as disappearance or marked degeneration of two-thirds or more of the tumor cells, moderately effective (grade 1b) was defined as disappearance or marked degeneration of one-third to less than two-thirds of the

tumor cells, and mildly effective (grade 1a) was defined as disappearance or marked degeneration of less than one-third of the tumor cells or mild tumor cell degeneration, regardless of percentage. Nearly no change in the cancer cells after treatment was defined as not effective (grade 0).

Statistical Analysis

For the parameters examined before and after NAC, differences were assessed using paired *t* tests. Assessment of concordance between RECIST 1.1 and PERCIST 1.0 was done using Cohen's *k* coefficient,[12)] with agreement noted as slight at *k* <0.21, fair at *k* from 0.21–0.40, moderate at *k* from 0.41–0.60, substantial at *k* from 0.61–0.80, and nearly perfect at *k* >0.80. We used McNemar's test to determine the significance of differences of the diagnostic parameters, i.e., sensitivity, specificity, and accuracy, for predicting pCR between RECIST 1.1 and PERCIST 1.0. Relapse-free survival (RFS) was calculated with Kaplan–Meier's test and statistically evaluated using a log-rank test. Statistical analysis was done using SAS, version 9.3 (SAS Institute Inc., Cary, NC, USA), with p<0.05 considered to be significant.

RESULTS

Clinicopathologic Characteristics

The clinicopathologic characteristics of all patients are presented in Table 1. Histological classification findings revealed invasive ductal carcinoma in 29 (90.6%), invasive lobular carcinoma in 1 (3.1%), and other specified cancers (mucinous carcinomas) in 2 (6.3%) of these cases. Immunohistochemical analysis showed positive for estrogen receptor (ER), progesterone receptor, and human epidermal growth factor receptor type 2 (HER2) in 17 (53.1%), 11 (34.4%), and 12 (37.5%) patients, respectively, while Ki-67 ≥20% was noted in 27 (84.4%). As for tumor subtype, 5 (15.6%) were luminal A (ER+/HER2-, Ki67 <20%), 7 (21.9%) were luminal B (ER+/HER2-, Ki67 ≥20%), 7 (21.9%) were luminal-HER2 (ER+/HER2+), 4 (12.5%) were HER2-positive (non-luminal), and 9 (28.1%) were triple-negative. We divided patients by T and N stages and found that 7 (21.9%) were T1, 15 (46.9%) were T2, 4 (12.5%) were T3, 6 (18.8%) were T4, 7 (21.9%) were N0, 21 (65.6%) were N1, 0 (0%) were N2, and 4 (12.5%) were N3. Regarding TNM stage, 3 (9.4%), 15 (46.9%), and 14 (43.8%) patients were classified as stage I, II, and III, respectively.

Table 1 Patient and tumor characteristics

Characteristics	Number	%
Total patients	32	
Age (years)		
Mean (Range)	52.4 (29–74)	
Histology		
IDC (scirrhous/solidtubular/papillary tubular)	29 (16/12/1)	90.6% (50.0%/37.5%/3.1%)
ILC	1	3.1%
Others (myxoid)	2	6.3%
Receptor positivity		
Estrogen receptor	17	53.1%
Progesteron receptor	11	34.4%
HER-2/neu	12	37.5%

Ki-67 index status		
<20% / ≧20%	5//27	15.6%/84.4%
Nuclear grade of IDC		
Grade 1/2/3	8//4/17	25.0%/12.5%/53.1%
Molecular phenotype		
Luminal A (ER+/HER2-, Ki67<20%)	5	15.6%
Luminal B (ER+/HER2-, Ki67≥20%)	7	21.9%
Luminal-HER2 (ER+/HER2+)	7	21.9%
HER2 positive (nonluminal)	4	12.5%
Triple-negative	9	28.1%
cT before NAC		
T1/T2/T3/T4	7/15/4/6	21.9%/46.9%/12.5%/18.8%
cN before NAC		
N0/N1/N2/N3	7/21/0/4	21.9%/65.6%/0%/12.5%
Initial clinical stage		
I/II/III	3/15/14	9.4%/46.9%/43.8%
Chemotherapy regimen		
TC	3	9.4%
FEC and docetaxel	7	21.9%
FEC and paclitaxel	1	3.1%
FEC, docetaxel, and Herceptin	6	18.8%
FEC, paclitaxel, and Herceptin	3	9.4%
EC and docetaxel	3	9.4%
EC, docetaxel, and capecitabine	4	12.5%
EC, paclitaxel, and Herceptin	1	3.1%
docetaxel and letrozole	2	6.3%
Herceptin and docetaxel	1	3.1%
Herceptin and capecitabine	1	3.1%
Type of Surgery		
Breast-conserving surgery	8	25.0%
Modified radical mastectomy	24	75.0%
Axillary operation		
SLNB	8	25.0%
ALND	12	37.5%
SLNB+ALND	12	37.5%
Pathological response		
1a/1b/2a/2b/3	5/5/5/3/14	15.6%/15.6%/15.6%/9.4%/43.8%

Abbreviations: IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor; HER2, human epidermal growth factor receptor-2; TC, docetaxel and cyclophosphamide; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; EC, 5-fluorouracil, epirubicin, and cyclophosphamide; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection

Table 2 Parameters before and after neoadjuvant therapy

Parameter	Before NAC	After NAC
Height (cm)		
Mean±SD	158.2±5.6	158.4±6.5
Range	144.7–168.7	145.8–169.5
Weight (kg)		
Mean±SD	54.8±9.4	55.0±9.2
Range	39.9–86.0	40.7–85.4
Blood glucose level (mg/dL)		
Mean±SD	92.7±12.1	95.8±12.3
Range	72–117	82–125
Dose of FDG (MBq)		
Mean±SD	202.2±45.7	215.6±38.9
Range	134–348	140–326
Uptake time (min)		
Mean±SD	62.7±2.7	62.3±2.6
Range	57–66	59–66

Abbreviations: NAC, neoadjuvant chemotherapy; SD, standard deviation; FDG, fluorodeoxyglucose

After undergoing NAC, definitive findings were obtained during surgery and those revealed pCR in 14 (43.8%) of the 32 patients, with breast cancer classified as grade 3 (pCR) in 14, grade 2b in 3, grade 2a in 5, grade 1b in 5, and grade 1a in 5. No significant differences were observed regarding patient height, weight, blood glucose level, injected dose of FDG, and uptake times between the 2 scan examinations performed before and after NAC (p>0.05) (Table 2).

RECIST 1.1 vs. PERCIST 1.0

Using MRI, the baseline and post-NAC long diameters of the primary tumor were 42.1±30.2 and 13.2±19.1 mm, respectively (p<0.0001). The rate of tumor diameter reduction was 69.9±31.6%. Treatment efficacy in the patients based on RECIST 1.1 using MRI measurements was CR in 5 (15.6%), PR in 25 (78.1%), SD in 2 (6.3%), and PD in 0. On the other hand, baseline and post-NAC SULpeak values for the primary tumor determined using FDG-PET/CT findings were 3.9±2.3 and 1.3±1.4, respectively (p<0.0001). The rate of reduction in SULpeak of the tumor was 62.8±34.6%. Treatment efficacy in these cases based on PERCIST 1.0 with FDG-PET/CT findings was CMR in 28 (87.5%), PMR in 2 (6.3%), SMD in 1 (3.1%), and PMD in 1 (3.1%).

Concordance between the RECIST 1.1 and PERCIST 1.0 response classifications was seen in 7 (21.9%) cases (Table 3), while discordance was seen in 25 (78.1%). A significant difference was observed between RECIST 1.1 and PERCIST 1.0 (k=0.103, p<0.0001) for response classification. Tumor response was upgraded in 23 and downgraded in 2 patients using PERCIST 1.0 as compared to RECIST 1.1. Of 28 patients classified as CMR based on PERCIST 1.0, 5

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Table 3   Comparison of treatment response assessments in RECIST 1.1 and PERCIST 1.0

	PERCIST 1.0				
	PMD	SMD	PMR	CMR	Total
RECIST 1.1					
PD	0	0	0	0	0
SD	1	0	0	1	2
PR	0	1	2	22	25
CR	0	0	0	5	5
Total	1	1	2	28	32

Abbreviation: RECIST, Response Evaluation Criteria in Solid Tumors; PD, progressive disease; SD, stable disease; PR, parital response; CR, complete response; PERCIST, Positron Emission Tomography Response Criteria in Solid Tumors; PMD, progressive metabolic disease; SMD, stable metabolic disease; PMR, partial metabolic response; CMR, complete metabolic response

Table 4   Comparison of treatment response assessments between pathologic response and either RECIST 1.1 or PERCIST 1.0

Criteria	PERCIST 1.0					
	Grade 1a	Grade 1b	Grade 2a	Grade 2b	Grade 3	Total
RECIST 1.1						
PD	0	0	0	0	0	0
SD	2	0	0	0	0	2
PR	3	5	4	3	10	25
CR	0	0	1	0	4	5
Total	5	5	5	3	14	32
PERCIST 1.0						
PMD	1	0	0	0	0	1
SMD	0	1	0	0	0	1
PMR	1	1	0	0	0	2
CMR	3	3	5	3	14	28
Total	5	5	5	3	14	32

Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors; PD, progressive disease; SD, stable disease; PR partial response; CR, complete response; PERCIST, Positron Emission Tomography Response Criteria in Solid Tumors; PMD, progressive metabolic disease; SMD, stable metabolic disease; PMR, partial metabolic response; CMR, complete metabolic response

were classified as CR, 22 as PR, and 1 as SD according to RECIST 1.1. Furthermore, of 25 patients classified as PR based on RECIST 1.1, PERCIST 1.0 classified 22 as CMR, 2 as PMR, and 1 as SMD.

Table 4 shows treatment response based on pathologic response shown by RECIST 1.1 and PERCIST 1.0. Of the 14 cases defined as pCR (grade 3), RECIST 1.1 classified 4 with CR and 10 with PR. However, all 14 were correctly classified CMR by PERCIST 1.0. Regarding the 18 cases defined as non-pCR (grades 1a, 1b, 2a, 2b), RECIST 1.1 classified 2 with SD, 15
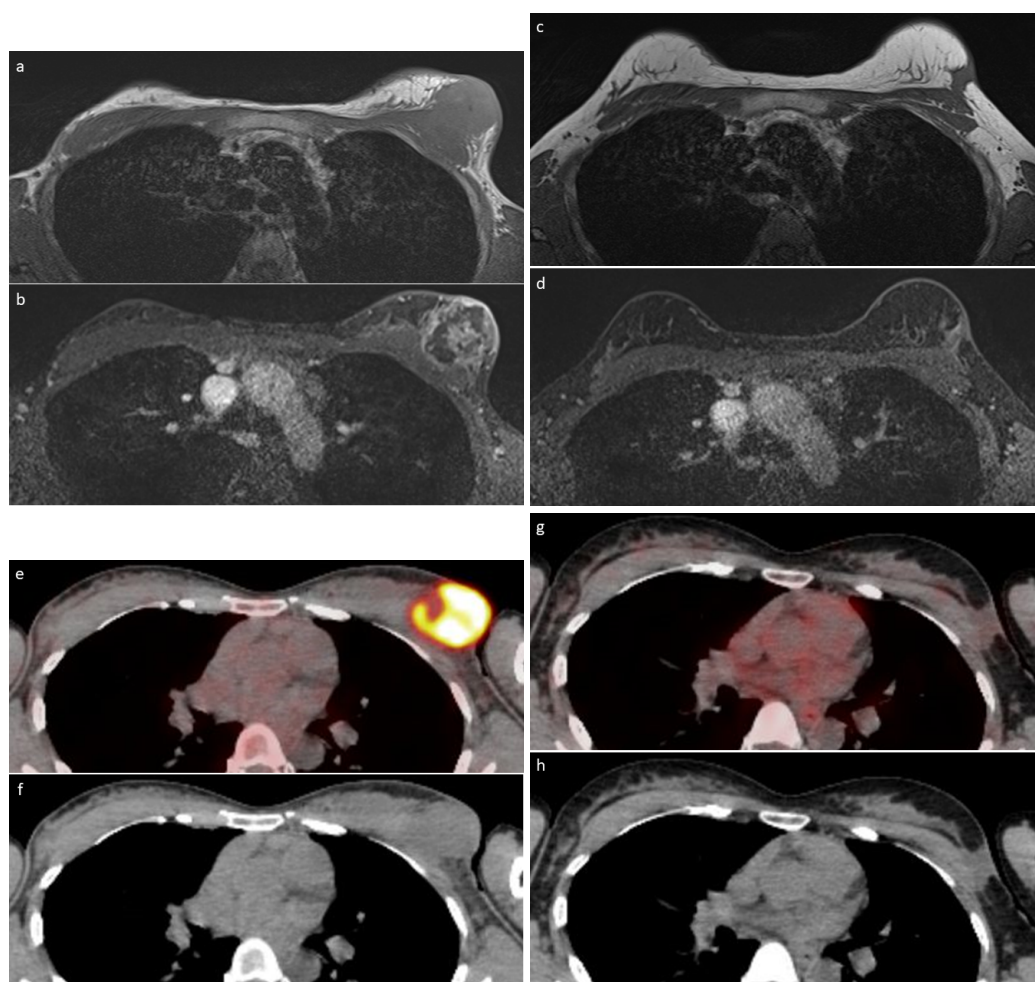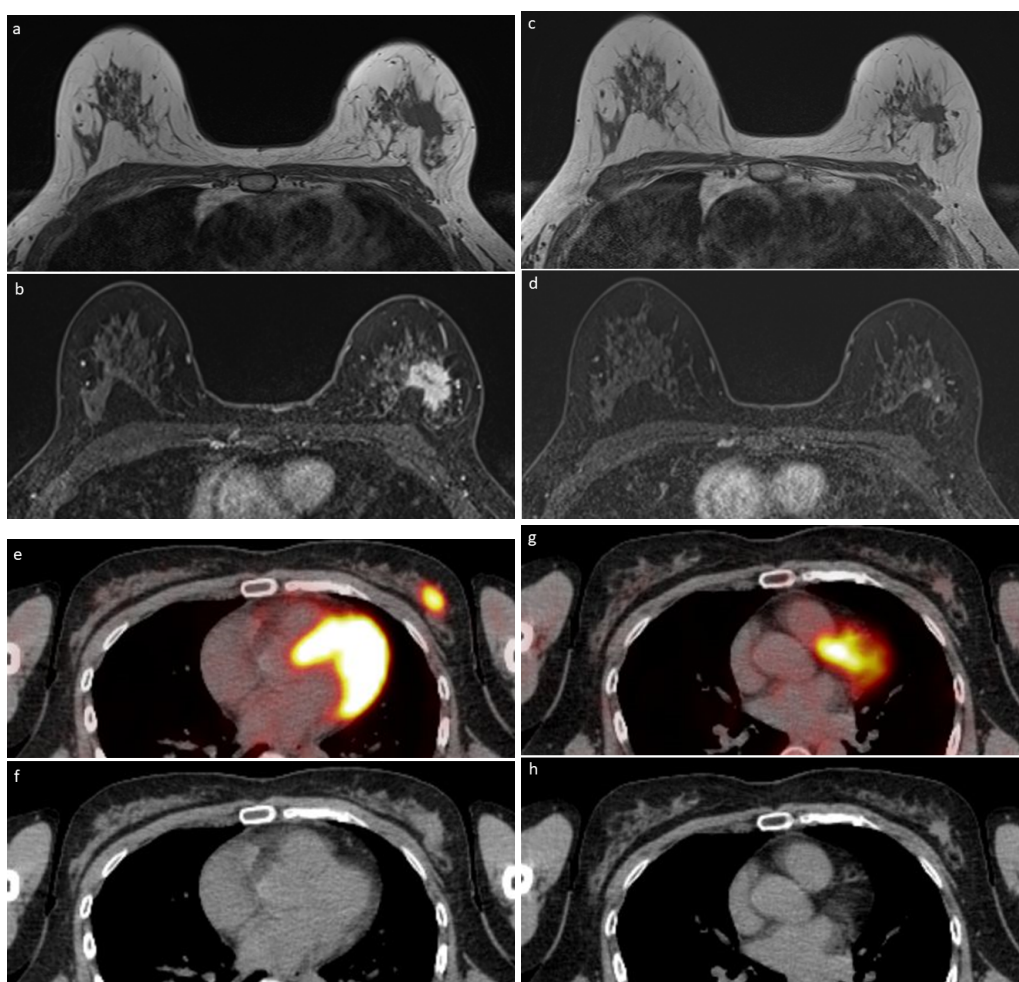
Fig. 1 The patient was a 36-year-old female with left invasive ductal cancer classified as pathological grade 3 (complete response). Shown are MRI and PET/CT scan images obtained following neoadjuvant chemotherapy. Baseline MRI: (a) pre-contrast T1-weighted and (b) dynamic contrast-enhanced images. Post-neoadjuvant chemotherapy MRI: (c) pre-contrast T1-weighted and (d) dynamic contrast-enhanced images with 75% long-diameter reduction from 48 to 12 mm. Baseline FDG-PET/CT: (e) fused PET and CT, and (f) CT alone images. Post-neoadjuvant chemotherapy FDG-PET/CT: (g) fused PET and CT, and (h) CT alone images with 84% SULpeak reduction from 5.7 to 0.7 (less than mean liver activity, indistinguishable from surrounding background). Response status based on RECIST 1.1 was PR and CMR based on PERCIST 1.0. No recurrence was seen at 27.3 months after the initial chemotherapy session.

with PR, and 1 with CR. However, PERCIST 1.0 classified 1 with PMD, 1 with SMD, 3 with PMR, and 14 with CMR. Two of these representative cases are presented as figures (Figs. 1, 2).

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy to predict pCR with RECIST 1.1 were 28.6% (4/14), 94.4% (17/18), 80% (4/5), 63.0% (17/27), and 65.6% (21/32), respectively, and those with PERCIST 1.0 were 100% (14/14), 22.2% (4/18), 50% (14/28), 100% (4/4), and 56.3% (18/32), respectively (Table 5). Sensitivity and specificity were significantly different between the RECIST 1.1 and PERCIST 1.0 response

Fig. 2 The patient was a 51-year-old female with left invasive ductal cancer classified as pathological grade 1b (non-complete response). Shown are MRI and PET/CT scan images obtained following neoadjuvant chemotherapy. Baseline MRI: (a) pre-contrast T1-weighted and (b) dynamic contrast-enhanced images. Post-neoadjuvant chemotherapy MRI: (c) pre-contrast T1-weighted and (d) dynamic contrast-enhanced images with 63% long-diameter reduction from 27 to 10 mm. Baseline FDG-PET/CT: (e) fused PET and CT, and (f) CT alone images. Post-neoadjuvant chemotherapy FDG-PET/CT: (g) fused PET and CT, and (h) CT alone images with 63% SULpeak reduction from 2.7 to 1.0 (less than mean liver activity, indistinguishable from surrounding background). Response status based on RECIST 1.1 was PR and CMR based on PERCIST 1.0. No recurrence was seen at 19.5 months after the initial chemotherapy session.

classification methods (p=0.00044 and p=0.00087). Diagnostic performance divided according to the 5 tumor phenotypes [luminal A, luminal B, luminal-HER2, HER2 positive (non-luminal), triple-negative] is also presented in Table 5. Those results showed pCR in 1 (20%) of 5 luminal A cases, 0 (0%) of 7 luminal B cases, 4 (57.1%) of 7 luminal-HER2 cases, 1 (20.0%) of 5 HER2 positive (non-luminal) cases, and 8 (88.9%) of 9 triple-negative cases. The accuracy of RECIST 1.1 for predicting pCR for each tumor type was 60%, 100%, 57.1%, 75%, and 44.4%, respectively, and that of PERCIST 1.0 was 20%, 28.6%, 57.1%, 75%, and 88.9%, respectively.

Table 5 Comparison of predicting pathological complete response in RECIST 1.1 and PERCIST 1.0

	Sensitivity (%) [95%CI]	Specificity (%) [95%CI]	PPV (%) [95%CI]	NPV (%) [95%CI]	Accuracy (%) [95%CI]
All patients (n=32)					
RECIST 1.1	28.6 (4/14)	94.4 (17/18)	80.0 (4/5)	63.0 (17/27)	65.6 (21/32)
	[4.9–52.2]	[83.9–100]	[44.9–100]	[44.7–81.2]	[49.2–82.1]
PERCIST 1.0	100 (14/14)	22.2 (4/18)	50.0 (14/28)	100 (4/4)	56.3 (18/32)
	[100]	[3.0–41.4]	[31.5–68.5]	[100]	[39.1–73.4]
p-value	0.00044	0.00087			0.25
Luminal A (n=5)					
RECIST 1.1	0 (0/1)	75 (3/4)	0 (0/1)	75.0 (3/4)	60.0 (3/5)
	[0]	[32.6–100]	[0]	[2.6–100]	[7.1–100]
PERCIST 1.0	100 (1/1)	0 (0/4)	20.0 (1/5)	n.a.	20.0 (1/5)
	[100]	[0]	[0–55.1]		[0–55.1]
p-value	1	0.25			0.48
Luminal B (n=7)					
RECIST 1.1	n.a.	100 (7/7)	n.a.	100 (7/7)	100 (7/7)
		[83.9–100]		[100]	[100]
PERCIST 1.0	n.a.	28.6 (2/7)	0 (0/5)	100 (2/2)	28.6 (2/7)
		[0–62.0]	[0]	[100]	[0–62.0]
p-value		0.074			0.074
Luminal-HER2 (n=7)					
RECIST 1.1	25.0 (1/4)	100 (3/3)	100 (1/1)	50.0 (3/6)	57.1 (4/7)
	[0–67.4]	[100]	[100]	[10.0–90.0]	[20.5–93.8]
PERCIST 1.0	100 (4/4)	0 (0/3)	57.1 (4/7)	n.a.	57.1 (4/7)
	[100]	[0]	[20.5–93.8]		[20.5–93.8]
p-value	0.25	0.25			1
HER2 positive (n=4)					
RECIST 1.1	0 (0/1)	100 (3/3)	n.a.	75.0 (3/4)	75.0 (3/4)
	[0]	[100]		[32.6–100]	[32.6–100]
PERCIST 1.0	100 (1/1)	66.7 (2/3)	50.0 (1/2)	100 (2/2)	75.0 (3/4)
	[100]	[13.3–100]	[0–100]	[100]	[32.6–100]
p-value	1	1			1
Triple-negative (n=9)					
RECIST 1.1	37.5 (3/8)	100 (1/1)	100 (3/3)	16.7 (1/6)	44.4 (4/9)
	[4.0–71.0]	[100]	[100]	[0–46.5]	[12.0–76.9]
PERCIST 1.0	100 (8/8)	0 (0/1)	88.9 (8/9)	n.a.	88.9 (8/9)
	[100]	[0]	[68.3–100]		[68.3–100]
p-value	0.074	1			0.13

Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors; PERCIST, Positron Emission Tomography Response Criteria in Solid Tumors; PPV, positive predictive value; NPV, negative predictive value; CI, confident interval; n.a., not applicable; HER2, human epidermal growth factor receptor-2

Recurrence was detected in 5 patients (15.6%) after a median period of 24 months (7.8–66.8 months). Those with CMR shown by PERCIST 1.0 had relatively longer RFS than non-CMR patients (PMR, SMD, PMD), though the difference was not significant (p=0.087) (Fig 3a). According to RECIST 1.1, CR patients showed slightly longer RFS as compared to those classified as non-CR (PR, SD, PD) (p=0.46) (Fig 3b). Of these 5 patients who showed recurrence, 3 were determined to be CMR by PERCIST 1.0 and 1 was as CR by RECIST 1.1.
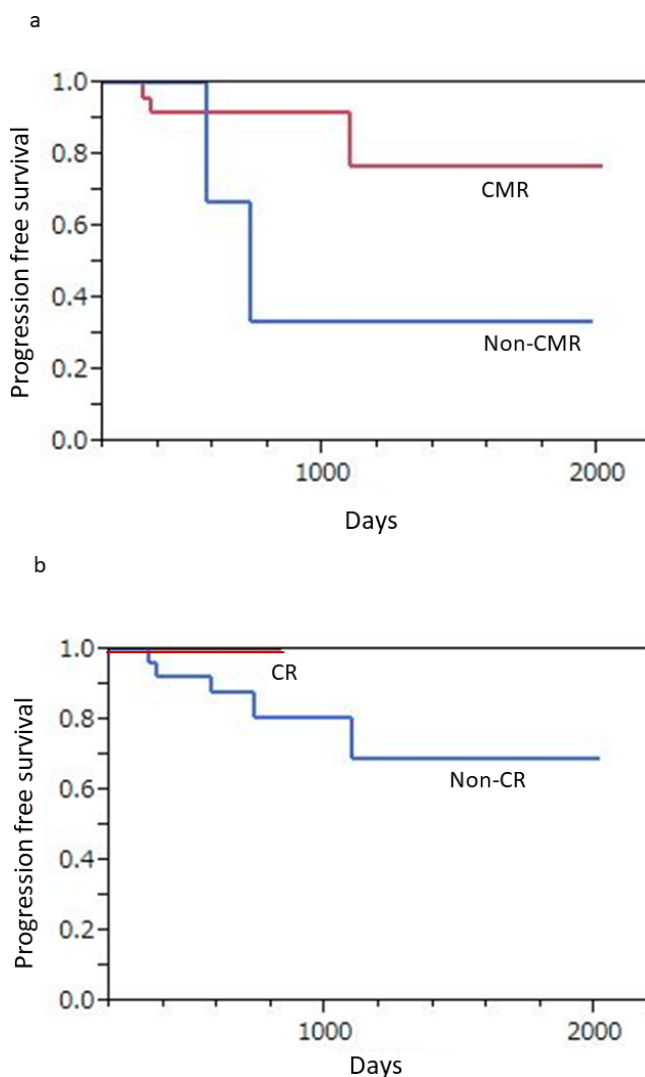
Fig. 3 Kaplan–Meier curves of progression-free survival (PFS) for PERCIST 1.0 and RECIST 1.1.
(a) PERCIST 1.0. Patients who achieved CMR had a relatively longer RFS as compared to those who did not (PMR, SMD, PMD), though the difference was not significant (p=0.087).
(b) RECIST 1.1. Patients who achieved CR had a slightly longer RFS as compared to those who did not (PR, SD, PD) (p=0.46).

DISCUSSION

This is the first known comparison of the response classifications RECIST 1.1 and PERCIST 1.0 used to determine pathological response to NAC. In addition, we also examined prediction of recurrence of breast cancer based on pre- and post-NAC MRI and FDG-PET/CT results. Our study revealed three major findings. First, considerable disagreement was noted between the classification systems for tumor response assessment, as tumor response rate was significantly upgraded by PERCIST 1.0 when compared to RECIST 1.1. Second, pathological assessment results for predicting pCR showed that PERCIST 1.0 had a tendency to overestimate, while RECIST 1.1 had a tendency to underestimate. Furthermore, PERCIST 1.0 showed higher levels of sensitivity and NPV, but lower levels of specificity, PPV, and accuracy when compared to RECIST 1.1. Also, the accuracy to predict pCR was higher for the triple-negative phenotype with PERCIST 1.0 as compared to RECIST 1.1, while that of PERCIST 1.0 was lower for luminal A and B. Third, neither classification system had a 100% correlation with the prognoses of our patients.

Two other known studies compared assessments of intra-NAC response by PERCIST 1.0 and RECIST 1.1 in breast cancer cases.[9,10)] In the one of those, both FDG-PET/CT and dynamic contrast-enhanced MRI scans performed at baseline and during treatment (after 2 cycles of NAC) in 142 breast cancer patients were examined, and it was found for predicting pCR, RECIST 1.1 had a sensitivity of 45.5%, specificity of 85.5%, and accuracy of 82.4%, while those for values for PERCIST 1.0 were 70.4%, 95.7%, and 90.8%, respectively.[9)] In the other study, Riedl *et al.*[10)] compared baseline FDG-PET/CT and contrast-enhanced CT scan results , as well as from those performed after first- or second-line systemic chemotherapy in 65 metastatic breast cancer patients. The found concordance between the response classifications in 31 (48%) cases, and also concluded that PERCIST 1.0 was superior for predicting progression-free and disease-specific survival. Others have also investigated FDG-PET/CT for useful assessment of early treatment response (intra-NAC assessment)[13)] and there is a report that FDG-PET/CT was better than MRI for early evaluation of pathologic response.[14)] A meta-analysis study of post-NAC cases indicated that FDG-PET/CT is not as effective as MRI to predict pathological response.[14)] That report also noted high pooled sensitivity [80% (95% confidence interval: CI 65–90%)] and low pooled specificity [57% (95% CI 40–71%)] for FDG-PET, and low pooled sensitivity [63% (95% CI 51–74%)] and high pooled specificity [88% (95% CI 71–96%)] for MRI in those cases. Regarding the diagnostic performance of these 2 modalities, NAC assessment imaging time is important and thought to have a major influence.

Other studies have examined the efficacy of post-NAC MRI for predicting pCR and shown that it is dependent on the phenotype of breast cancer. MRI following NAC was found useful for predicting pCR in HER2 positive (non-luminal) and triple-negative cases, and also those with hormone receptor-negative tumors.[15)] In our series, we found a similar tendency with post-NAC FDG-PET (PERCIST 1.0), though further investigations with more patients are needed.

Our study has some limitations. It was performed at a single center with a small sample size, thus limiting generalization of the findings and possibly introducing statistical errors. Also, we did not assess overall survival because there were few deaths among the present patients (n=3). Additional, overall survival analysis with a larger patient population as well as longer follow-up periods is important. Furthermore, only primary breast lesions were analyzed to assess tumor response. Even though all levels of regional tumor extent can be monitored by PET/CET findings, including axillary and supraclavicular lymph nodes, the FOV of MRI is limited to the breast and occasionally lower axillary fossa, thus we only breast findings were analyzed in the present study. PERCIST 1.0 recommends using the hottest single lesion as the target, multiple lesions (no more than 2 per organ, up to 5 of the hottest lesions) should be measured as a secondary

analysis.[8] Previous response evaluations performed in patients with both multiple lesions and a single lesion were found to be quite similar in patients with breast[16] and lung[17] cancer

Based on our results, for examinations of breast cancer patients we consider that RECIST 1.1, with a high level of specificity and NPV, and PERCIST 1.0, which showed a high level of sensitivity and PPV, are complementary for predicting pathological response to NAC. On the other hand, FDG-PET for assessing the results of post-NAC treatment remains to be clarified in regard to usefulness and additional studies with more patients are needed.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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REFERENCES

1) Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, *et al.* Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol*, 1998; 16: 2672–2685.

2) Fisher ER, Wang J, Bryant J, Fisher B, Mamounas E, Wolmark N. Pathobiology of preoperative chemotherapy: findings from the National Surgical Adjuvant Breast and Bowel (NSABP) Protocol B-18. *Cancer*, 2002; 95: 681–695.

3) Chia S, Swain SM, Byrd DR, Mankoff DA. Locallyadvanced and inflammatory breast cancer. *J Clin Oncol*, 2008; 26: 786–790.

4) Rastogi P, Anderson SJ, Bear HD, Geyer CE, Kahlenberg MS, Robidoux A, *et al.* Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. *J Clin Oncol*, 2008; 26: 778–785.

5) Gonzalez-Angulo AM, McGuire SE, Buchholz TA, Tucker SL, Kuerer HM, Rouzier R, *et al.* Factors predictive of distant metastases in patients with breast cancer who have a pathologic complete response after neoadjuvant chemotherapy. *J Clin Oncol*, 2005; 23: 7098–7104.

6) Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*, 2009; 45: 228–247.

7) Boellaard R. Standards for PET image acquisition and quantitative data analysis. *J Nucl Med*, 2009; 50 Suppl 1: 11S–20S.

8) Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. *J Nucl Med*, 2009; 50(Suppl 1): 122S–150S.

9) Tateishi U, Miyake M, Nagaoka T, Terauchi T, Kubota K, Kinoshita T, *et al.* Neoadjuvant chemotherapy in breast cancer: prediction of pathologic response with PET/CT and dynamic contrast-enhanced MR imaging--prospective assessment. *Radiology*, 2012; 263: 53–63.

10) Riedl CC, Pinker K, Ulaner GA, Ong LT, Baltzer P, Jochelson MS, *et al.* Comparison of FDG-PET/CT and contrast-enhanced CT for monitoring therapy response in patients with metastatic breast cancer. *Eur J Nucl Med Mol Imaging*, 2017; 44: 1428–1437.

11) Kurosumi M, Akashi-Tanaka S, Akiyama F, Komoike Y, Mukai H, Nakamura S, *et al.* Histopathological criteria for assessment of therapeutic response in breast cancer (2007 version). *Breast Cancer*, 2008; 15: 5–7.

12) Kundel HL, Polansky M. Measurement of observer agreement. *Radiology*, 2003; 228: 303–308.

13) Kitajima K, Miyoshi Y. Present and future role of FDG-PET/CT imaging in the management of breast cancer. **Jpn J Radiol**, 2016; 34: 167–180.

14) Sheikhbahaei S, Trahan TJ, Xiao J, Taghipour M, Mena E, Connolly RM, *et al.* FDG-PET/CT and MRI for evaluation of pathologic response to neoadjuvant chemotherapy in patients with breast cancer: A meta-

Analysis of diagnostic accuracy studies. *Oncologist*, 2016; 21: 931–939.

15) Hayashi Y, Takei H, Nozu S, Tochigi Y, Ichikawa A, Kobayashi N, *et al.* Analysis of complete response by MRI following neoadjuvant chemotherapy predicts pathological tumor responses differently for molecular subtypes of breast cancer. *Oncol Lett*, 2013; 5: 83–89.

16) Pinker K, Riedl CC, Ong L, Jochelson M, Ulaner GA, McArthur H, *et al.* The impact that number of analyzed metastatic breast cancer lesions has on response assessment by ^{18}F-FDG PET/CT using PERCIST. *J Nucl Med*, 2016; 57: 1102–1104.

17) Shang J, Ling X, Zhang L, Tang Y, Xiao Z, Cheng Y, *et al.* Comparison of RECIST, EORTC criteria and PERCIST for evaluation of early response to chemotherapy in patients with non-small-cell lung cancer. *Eur J Nucl Med Mol Imaging*, 2016; 43: 1945–1953.