Early assessment of tumor response using ^{18}F-FDG PET/CT after one cycle of systemic therapy in patients with recurrent and metastatic breast cancer

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Abstract

Objective: This study was conducted to evaluate the usefulness of early assessment of tumor response using fluorine-18-fludeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) after one cycle of systemic therapy in patients with recurrent and metastatic breast cancer. **Subjects and Methods:** Thirty-three patients with recurrent or metastatic breast cancer underwent ^{18}F-FDG PET/CT before and after one cycle of systemic therapy. Based on the European Organization for Research and Treatment of Cancer (EORTC) criteria, the maximum standardized uptake value (SUVmax) of the same lesions (up to a total of five) noted in the baseline and follow-up scans were summed (maximum of two per organ) as target lesions, and therapeutic response was evaluated. Log-rank and Cox methods were employed to determine progression-free survival (PFS) and overall survival (OS). **Results:** Complete metabolic response (CMR), partial metabolic response (PMR), stable metabolic disease (SMD), and progressive metabolic disease (PMD) was seen in 2, 16, 11, and 4 patients, respectively. The mean reduction rates of SUVmax between 84 target lesions in 18 responders (CMR/PMR) and 75 target lesions in 15 non-responders (SMD/PMD) were -55.8% (range, -100% – -1.2%) and 0.47% (range, -48.7% – +209.4%), respectively, with a significant difference (P<0.0001). Every lesion site (local lesion, lymph node metastasis, bone metastasis, lung metastasis, and liver metastasis) showed a similar tendency. Thirty patients showed progression, and 17 died due to breast cancer after a median of 38.5 months. Responders showed significantly longer PFS than non-responders (P=0.0038). **Conclusions:** Fluorine-18-FDG PET/CT after one cycle of systemic therapy was able to reflect early metabolic changes regardless of the lesion site, and showed accuracy for early response evaluation and prediction of progression in patients with recurrent or metastatic breast cancer.

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Introduction

Adequate assessment of systemic treatment response is crucial for effective cancer treatment management, which includes effective means to monitor responsiveness of the tumor to systemic therapy, and extremely important for moderation of the high risk of mortality as well as toxic effects known to be associated with available systemic therapeutic regimens. Early identification of poor responders is important because they require aggressive treatment, and the use of ineffective, toxic systemic therapy agents should be avoided in these patients.

Approaches currently widely used for monitoring therapeutic responses are based on anatomical changes identified using computed tomography (CT). The criteria used to assess tumor burden, termed response evaluation criteria in solid tumors (RECIST), were updated by the World Health Organization in 2009 (version 1.1) [1]. However, anatomical imaging modalities, such as CT, may have limited capability to distinguish a viable residual tumor from reactive changes, such as edema and scar tissue as well as killed cells and tumor shrinkage, and evaluate the viability of bone metastasis. In contrast, fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) has been shown to be effective in evaluating metabolic activity [2, 3] and is considered useful for overcoming such limitations. Thus, it may be a more suitable assessment tool for therapeutic response evaluation. Moreover, as a change in tumor metabolism precedes tumor size [4], ^{18}F-FDG PET should allow visualization of the tumor response at an earlier stage than conventional imaging methods. The quantitative assessment of treatment response using ^{18}F-FDG PET is based on the differences in the standardized uptake value (SUV) between baseline and follow-up examinations. The European Organization for Research and Treatment of Cancer (EORTC), developed in 1999, recommends using SUV normalized to body surface area,

usually the maximum SUV (SUVmax), to reduce the influence of body weight on SUV [5].

Many groups have investigated the usefulness of ^{18}F-FDG PET/CT for the early prediction of neoadjuvant chemotherapy (NAC) in patients with breast cancer prior to surgical resection [6, 7]. In these studies, relative changes in SUVmax after the first or second cycle of NAC were strong predictors of pathological complete response. A recent meta-analysis [8] conducted on 15 studies, including 745 patients for the early prediction of primary tumor response to NAC, reported a pooled sensitivity of 80.5% and a specificity of 78.8% in identifying responders.

In contrast, several studies have demonstrated the usefulness of ^{18}F-FDG PET/CT performed at baseline and 2-3 months after the start of therapy for response to systemic therapy (endocrine therapy and chemotherapy) and predicting prognosis in patients with recurrent or metastatic breast cancer [9-13]. To the best of our knowledge, only one group has examined the performance of ^{18}F-FDG PET/CT (at baseline and 2 weeks after the start of therapy) for very early metabolic response as a predictor of treatment outcome [14]. The true usefulness of ^{18}F-FDG PET/CT in evaluating early treatment response in patients with recurrent or metastatic breast cancer has not been clarified. In the present study, we examined the usefulness of ^{18}F-FDG PET/CT for the evaluation of early treatment response in patients with recurrent or metastatic breast cancer who underwent ^{18}F-FDG PET/CT examinations before and after one cycle of systemic therapy, as well as prediction of prognosis using the EORTC method.

Subjects and Methods

Patients

The Ethics Committee of Hyogo College of Medicine approved the present prospective study (number 1641), and written informed consent was obtained from 33 patients (mean, 63.2 years; range, 41-84 years). Thirty-three patients (25 patients with recurrent breast cancer and 8 with pretreatment metastatic breast cancer) underwent ^{18}F-FDG PET/CT examinations before and after one cycle of systemic therapy (eribulin in 8 patients, palbociclib+fulvestrant in 4, trastuzumabemtansine in 4, carboplatin + gemcitabine in 3, everolimus+exemestane in 3, paclitaxel in 3, trastuzumab +pertuzumab+ capecitabine in 3, trastuzumab +pertuzumab+ docetaxel in 3, trastuzumab +pertuzumab+ eribulin in 3, and fulvestrant in 2) from November 2016 to July 2019. The patient and tumor characteristics are shown in Table 1. Baseline ^{18}F-FDG PET/CT scanning was performed at a median of 17 days (2-34 days) before systemic therapy initiation, while the second ^{18}F-FDG PET/CT scanning was performed at a median of 20 days (13-37 days) following the first systemic therapy administration.

^{18}F-FDG PET/CT

Four different PET/CT scanners installed at our institution (Gemini GXL16, Gemini TF64, Ingenuity TF: Philips Medical Systems, Eindhoven, The Netherlands; Discovery IQ: GE Healthcare, Waukesha, WI, USA) were used to perform the ^{18}F-FDG PET/CT examinations. Each patient was instructed to fast for five hours before the examination, and blood glucose was measured immediately prior to ^{18}F-FDG injection (4.0MBq/kg body weight for GXL16, 3.0MBq/kg for TF64, 3.7 MBq/kg body weight for Ingenuity TF and Discovery IQ), with all in the present cohort showing a level lower than 160 mg/dL. Static emission images were obtained approximately 60min after injection. For attenuation correction and anatomic localization, helical CT scan images from the top of the head to the mid-thigh were obtained using the following parameters: tube voltage, 120kV (all four scanners); effective tube current auto-mA up to 120mA (GXL16), 100mA (TF64), 155mA (Ingenuity TF), or 15-390mA (Smart mA: noise index 25) (Discovery IQ); gantry rotation speed,0.5s; detector configuration of 16mm×1.5mm (GXL16), 64mm× 0.625mm (TF64 and Ingenuity TF), or 16mm×1.25mm (Discovery IQ); slice thickness, 2mm; and transverse field of view of 600mm (GXL16, TF64, Ingenuity TF) or 700mm (Discovery IQ). Immediately after completion of the CT examination, PET imaging was performed from the head to the mid-thigh for 90s (GXL16, TF64, Ingenuity TF) or 180s (Discovery IQ) per bed position in the three-dimensional mode. The patient was allowed to breathe normally during the PET scanning. For GXL16, attenuation-corrected PET images were reconstructed with a line-of-response row-action maximum likelihood algorithm, while for TF64 and Ingenuity, an ordered-subset expectation maximization (OSEM) iterative reconstruction algorithm (33 subsets, three iterations) was used, and Q.Clear (block sequential regularized expectation maximization (BSREM)) (β=400) was utilized for Discovery IQ.

Image analysis

A board-certified nuclear medicine expert with 12 years of oncologic ^{18}F-FDG PET/CT experience and without any knowledge of the other imaging results, or clinical or histopathologic data for the present patients, retrospectively reviewed the ^{18}F-FDG PET/CT images. To assist the attending clinician with treatment response monitoring, the GI-PET software package (AZE Co., Ltd., Tokyo, Japan), which can harmonize SUV obtained with different PET/CT systems using phantom data [15], was employed. The SUVmax was defined as the maximum concentration of the target lesion (injected dose/body weight).

Criteria for treatment response

Treatment responses were classified as complete metabolic response (CMR), partial metabolic response (PMR), stable metabolic disease (SMD), or progressive metabolic disease (PMD).

Based on the EORTC criteria, the tumor response was also determined [5]. Complete metabolic responsewas defined as the complete resolution of ^{18}F-FDG uptake within the measurable target lesion, making it indistinguishable from the surrounding background with no new ^{18}F-FDG-avid lesions. The EORTC recommends defining regions of high ^{18}F-FDG uptake that represent a viable tumor by the use of pretreatment scan findings and utilization of the same region of in-

Table 1. *Patient and tumor characteristics.*

	Number	%
Number of patients	33	
Age (years, mean±SD)	63.2±9.7	
Histology		
ID (solid-tubular/ scirrhous/papillotubular)	32 (15/13/4)	97.0 (45.5/39.4/12.1)
Others (Apocrine)	1	3.0
Molecular phenotype		
Luminal A (ER+/HER2-, Ki67<20%)	6	18.2
Luminal B (ER+/HER2-, Ki67⩾20%)	6	18.2
Luminal-HER2 (ER+/HER2+)	10	30.3
HER2 positive (nonluminal)	3	9.1
Triple-negative	8	24.2
Systemic therapy regimen		
Eribulin	8	24.2
Palbociclib+fulvestrant	4	12.1
Trastuzumabemtansine	4	12.1
Everolimus+exemastane	3	9.1
Paclitaxel	3	9.1
Trastuzumab+Pertuzumab+Capecitabine	3	9.1
Trastuzumab+Pertuzumab+Docetaxel	3	9.1
Trastuzumab+Pertuzumab+Eribulin	3	9.1
Fulvestrant	2	6.1

SD: standard deviation, IDC: invasive ductal cancer

terest (ROI) volumes in subsequent scanning examinations positioned as close to the original tumor as possible, as well as determination of maximal tumor ROI count per pixel per second calibrated as MBq/L. The number of lesions to be measured is not recommended by the EORTC; thus, up to five with the highest level of ^{18}F-FDG uptake and up to two per organ, with the same lesions measured in subsequent follow-up scan imaging results, were the parameters used in the present study as well as in a previous study [14]. For patients with metabolically active lesions shown in the follow-up scanning, the SUVmax values of the same lesions (up to a total of five) noted in the baseline and follow-up scans were summed (maximum of two per organ). When the sum of the SUVmax values showed a decrease of ≥25%, the tumor response was classified as PMR. Progressive metabolic disease indicated a ≥25% increase in the sum of the SUVmax values or the detection of new ^{18}F-FDG-avid lesions characteristic of cancer. Stable metabolic diseasewas used to classify findings other than CMR, PMR, or PMD.

Statistical analysis

Data are presented as mean±SD. The difference between the pretreatment SUVmax and post treatment SUVmax was analyzed using a paired t-test. Progression-free survival (PFS) was defined based on the time elapsed from the start of chemotherapy to the date of disease progression revealed in radiological and/or clinical examination results, or death from any cause. Patients with no evidence of progressive disease were censored on the date of the last follow-up examination. Overall survival (OS) was defined as the start of chemotherapy until death from any cause. Patients alive at the final follow-up examination were censored with 'alive with disease' or 'no evidence of progression' used for the classification. Actuarial survival curves were generated using the Kaplan-Meier method, and a log-rank test was employed to examine differences between groups. The SAS software package, version 9.3 (SAS Institute Inc., Cary, NC, USA) was used for statistical analyses, with P values <0.05 considered to indicate statistical significance.

Results

In the 33 pretreatment ^{18}F-FDG PET/CT examinations, 106 ^{18}F-FDG-avid lesions were localized to the primary tumor (n=12), local recurrence (n=2), ipsilateral axillary lymph node (n=16), internal mammary node (n=4), supraclavicular node (n=9), contralateral axillary node (n=2), mediastinal/hilar node (n=16), abdominal node (n=3), bone (n=21), lung (n=9), liver (n=8), pleura (n=2), skin (n=1), and muscle (n=1).

SUVmax

The mean pretreatment and post treatment SUVmax for all 159 target lesions (12 primary tumors, 2 local recurrence, 26 ipsilateral axillary lymph nodes, 4 internal mammary nodes, 11 supraclavicular nodes, 4 contralateral axillary nodes, 25 mediastinal/hilar nodes, 5 abdominal nodes, 38 bony lesions, 14 lung metastasis, 12 liver metastases, 3 pleural metas-

tases, 3 pleural metastases, 2 skin lesions, and 1 muscular lesion) in all 33 patients were 6.54±3.02 (range, 2.24-15.39) and 4.57±3.07 (0-12.62), respectively, with a significant reduction (P<0.0001). The mean rate of change was -28.9% (-100% – +209.4%). The mean pretreatment and post treatment SUVmax for 84 target lesions (8 primary tumors, 2 local recurrence, 15 ipsilateral axillary lymph nodes, 2 internal mammary nodes, 5 supraclavicular nodes, 4 contralateral axillary nodes, 12 mediastinal/hilar nodes, 2 abdominal nodes, 21 bony lesions, 7 lung metastasis, 4 liver metastases, 1 pleural metastases, and 1 muscular lesion) in 18 responders (CMR/PMR) were 6.88±3.11 (2.25-15.39) and 3.13±2.78 (0-11.74), respectively, with a significant difference (P<0.0001) (Figure1a). The mean reduction rate was -55.8% (range, -100% – -1.2%). The mean pretreatment and post treatment SUVmax for 75 target lesions (4 primary tumors, 9 ipsilateral axillary lymph nodes, 3 internal mammary nodes, 7 supraclavicular nodes, 1 contralateral axillary nodes, 11 mediastinal/hilar nodes, 4 abdominal nodes, 18 bony lesions, 7 lung metastasis, 7 liver metastases, 2 pleural metastases, and 2 skin lesions) in 15 non-responders (SMD/PMD) were 6.18±2.89 (range, 2.24-12.94) and 6.08±2.73 (1.46-12.62), respectively, with no significant difference (P=0.16) (Figure 1b). The mean rate of change was 0.47% (-48.7% - 209.4%).

The mean rate of change of SUVmax of primary tumors and local recurrence between responders and non-responders were -47.5% (range, -100% – -15.6%) and 3.2% (-33.9% - 48.9%), respectively, with a significant difference (P< 0.00001) (Table 2). The mean rate of change of SUVmax of lymph nodes (ipsilateral axillary lymph nodes, internal mammary nodes, supraclavicular nodes, contralateral axillary nodes, mediastinal/hilar nodes, and abdominal nodes) between responders and non-responders were -62.2% (-100% – -2.2%) and -0.8% (-48.7%–209.4%), respectively, with a significant difference (P<0.0001). The mean rate of change of SUVmax of bone metastasis between responders and non-responders were -42.2% (-100%–-1.2%) and 2.1% (-33.1%–79.4%), respectively, with a significant difference (P< 0.0001). The mean rate of change rate of SUVmax of lung vs. liver metastases between responders and non-responders were -58.0% (-100% – -32.4%) and 7.9% (-49.3%–76.3%), respectively, with a significant difference (P<0.0001).

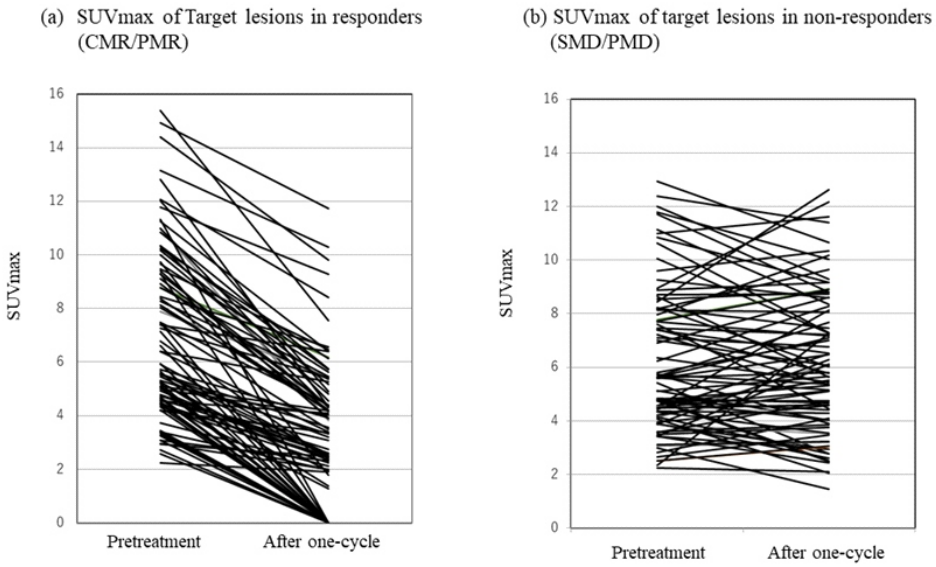

Figure 1. a. Graph shows the mean pretreatment and post treatment SUVmax for 84 target lesions in 18 responders (CMR/PMR) on EORTC, showing 6.88±3.11 (range, 2.25-15.39) and 3.13±2.78 (0-11.74), respectively, with a significant difference (P<0.0001).b. Graph shows the mean pretreatment and posttreatment SUVmax for 75 target lesions in 15 non-responders (SMD/PMD) on EORTC, showing 6.18±2.89 (range, 2.24-12.94) and 6.08±2.73 (1.46-12.62), respectively, with no significant difference (P=0.16).

Table 2. *The mean change (range) of SUVmax of each lesion site.*

	Primary tumors and local recurrence	Lymph node metastasis	Bone metastasis	Lung and liver metastases
Responders (CMR+PMR)	-47.5% (-100% ~ -15.6%)	-62.2% (-100% ~ -2.2%)	-42.2% (-100% ~ -1.2%)	-58.0% (-100% ~ -32.4%)
Non-responders (SMD+PMD)	3.2% (-33.9% ~ 48.9%)	-0.8% (-48.7% ~ 209.4%)	2.1% (-33.1% ~ 79.4%)	7.9% (-49.3% ~ 76.3%)

CMR: complete metabolic response, PMR: partial metabolic response, SMD: stable metabolic disease, PMD: progressive metabolic disease

Treatment response assessment

The patient-based mean ΔSUVmax value for the target lesions based on the EORTC criteria was -27.1% (-100%–+69.8%).

The use of the EORTC criteria revealed CMR in two patients (6.1%), PMR in 16 (48.5%), SMD in 11 (33.3%), and PMD in 4 (12.1%) patients; although the appearance of new lesions (bone metastasis) was noted in one patient, the patient showed progression of other bone metastatic lesions as well as new bone metastatic lesions.

Data for two representative cases are presented in Figures 2 and 3.

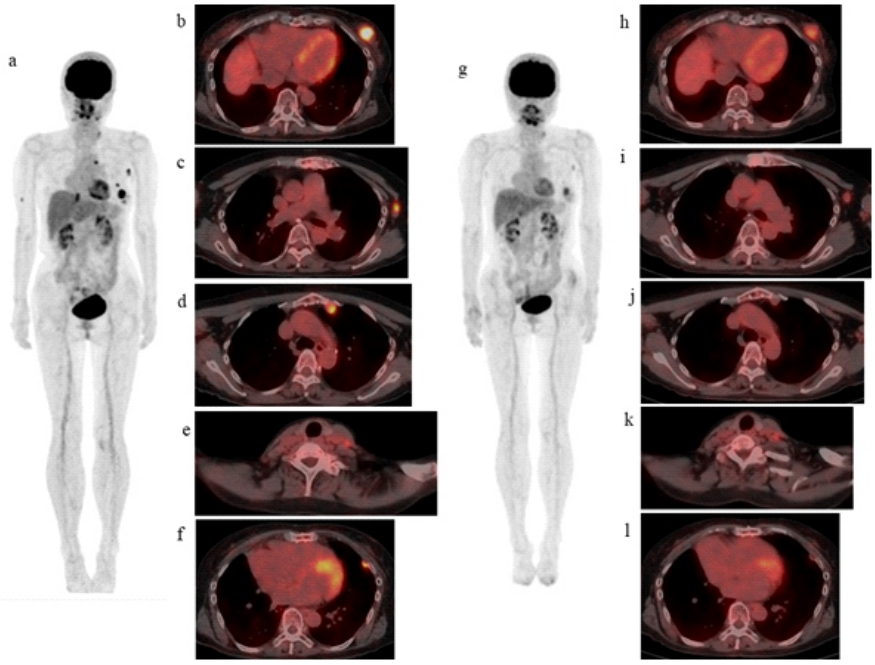

Figure 2. 2.A 59-year-old man with pretreatment breast cancer with ipsilateral axillary, internal mammary, supraclavicular node, and left pleural metastasis. Baseline ^{18}F-FDG PET/CT [(a) maximum intensity projection (MIP) and (b, c, d, e, f) fused transaxial images] showing abnormal ^{18}F-FDG uptake in the (b) primary tumor, (c) ipsilateral axillary node metastasis, (d) internal mammary node metastasis, (e) supraclavicular node metastases, and (f) pleural dissemination. Follow-up ^{18}F-FDG PET/CT after one course of fulvestrant therapy [(g) MIP and (h, i, j, k, l) fused transaxial images] shows decreased ^{18}F-FDG uptake in these lesions, with the almost disappeared uptake of internal mammary nide and pleural dissemination. Because the reduction in the sum of SUVmax was 68.8% (from 25.33 (7.41+5.24+5.26+2.93+4.49) to 7.9 (3.51+1.92+2.47)), the status was PMR according to the EORTC criteria. The patient was alive without progression 42.8 months after the initiation of chemotherapy.

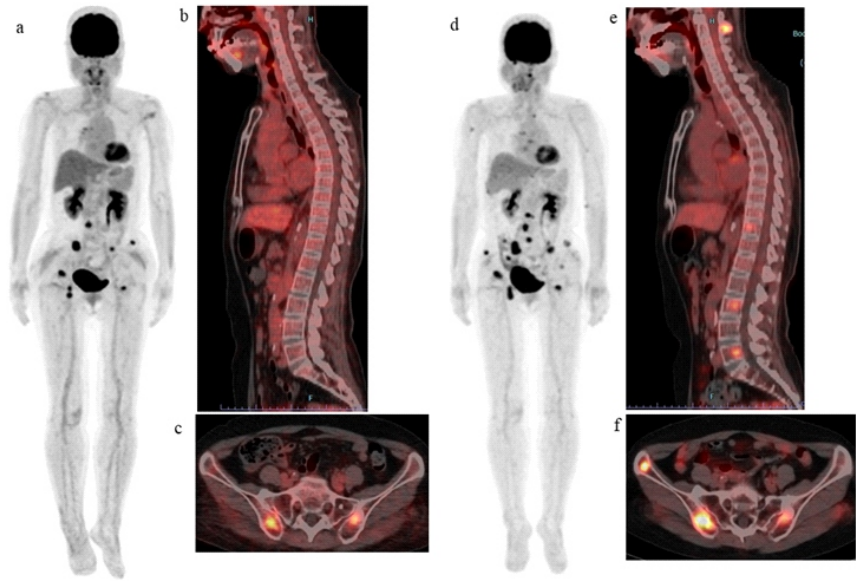

Figure 3. A 58-year-old woman with post-operative and chemotherapeutic recurrence breast cancer with multiple bone metastases. Baseline ^{18}F-FDG PET/CT [(a) MIP and (b, c) fused transaxial images] showing abnormal ^{18}F-FDG uptake in the spine, pelvis, and right rib. Follow-up ^{18}F-FDG PET/CT after one cycle of eribulin therapy [(d) MIP and (e, f) fused transaxial images] showsa slight ^{18}F-FDG uptake increase of known bone metastases with new appearance of bone metastases in the ilium and spine (C2, Th11, L3, L5). On pretreatment ^{18}F-FDG PET/CT, the SUVmax of two bone lesions with high uptake were 7.47 and 5.64. The status was PMD according to the EORTC criteria because of new lesions.The patient exhibited progressive disease at 29.1 months and died at 40.4 months after the initiation of chemotherapy.

Prognosis prediction

Progressive disease after a median period of 11.1 months (range, 0.93-55.1 months) was noted in 30 (90.9%) of the 33 cases. Responders (CMR/PMR) showed significantly longer PFS than non-responders (SMD/PMD) (P=0.0038) (Figure 4a).

Of the 33 patients, 17 (51.5%) died of breast cancer after a median 38.5 months (range, 10.2-61.8 months). Responders (CMR/PMR) showed longer OS than non-responders (SMD/PMD); however, the difference was not significant (P=0.085) (Figure 4b).

Discussion

To our knowledge, this is the first study to investigate the predictive value of very early metabolic response in breast cancer metastatic disease after the induction of several kinds of systemic therapy. We clarified that ^{18}F-FDG PET/CT after one cycle of systemic therapy could reflect early metabolic changes regardless of the lesion site, and showed accuracy for early response evaluation and prediction of progression in patients with recurrent or metastatic breast cancer. Fluorine-18-FDG PET/CT is a useful and minimally invasive tool that can be used to make decisions on personal treatment to enhance benefits while reducing collateral effects.

Several studies have demonstrated the usefulness of ^{18}F-FDG PET/CT at baseline and 2-3 months after the start of therapy for response to systemic therapy (endocrine therapy and chemotherapy) and predicting prognosis in patients with recurrent or metastatic breast cancer [9-13]. Mortazavi-Jehanno et al.(2012) [9] assessed the metabolic response to endocrine therapy according to the EORTC criteria in 22 metastatic breast cancer cases and showed that 1) CMR/PMR/SMD/PMD was seen in 0/11/5/6 patients and 2) PMR/SMD showed significantly longer PFS than PMD (P< 0.0001), whereas no difference in OS was observed among the three groups (P=0.34), similar to our study. Riedl et al. (2017) [10] compared ^{18}F-FDG PET/CT and contrast-enhanced CT for monitoring systemic therapy response in 65 patients with stage IV breast cancer and showed that 1) CR/PR/SD/PD with ^{18}F-FDG PET/CT and contrast-enhanced CT was observed in 22/18/8/17 and 3/19/28/15 patients, respectively, and 2) one-year PFS for responders vs. non-responders by EORTC was 63% vs. 0%, compared to 59% vs. 27% by RECIST1.1. They clarified the superiority of ^{18}F-FDG PET/CT for response assessment because 1) contrast-enhanced CT tended to report SD, while ^{18}F-FDG PET/CT reported CMR more often, and 2) EORTC (responders vs. non-responders) showed better correlation with PFS than RECIST1.1. One study evaluated the early metabolic response by ^{18}F-FDG PET/CT scans performed at baseline and 14 days after the start of everolimus+exemestane and demonstrated that patients with an 11% decrease in peak lean body mass SUV (SULpeak) high had a median PFS of 411 days and 90 days, respectively (P=0.0013), and had more frequently PMD within 3 months,11% and 70%, respectively [14].

In particular, ^{18}F-FDG PET/CT is a useful tool for evaluating the treatment response to bone metastasis. Up to 70% of patients with metastatic breast cancer experience bone involvement during the disease period [17]. Bone lesions are hardly detected and monitored by CT because active malignant lesions in the bones are difficult to distinguish from osteosclerotic recovering lesions [18]. This poses a challenge when assessing whether bone metastases are progressing, stable, or responding to treatment [19]. In contrast, ^{18}F-FDG avidity reflects tumor viability and can differentiate between tumor progression and bone healing [20]. Additionally, ^{18}F-FDG PET/CT is more sensitive than CT in the detection of osseous metastases [21]. Therefore, disease progression is detected earlier with ^{18}F-FDG PET/CT than with CT. In addition, one group investigated the impact of better assessment of osseous disease on the prediction of patient outcome [22]. To overcome the low sensitivity of CT for osse-

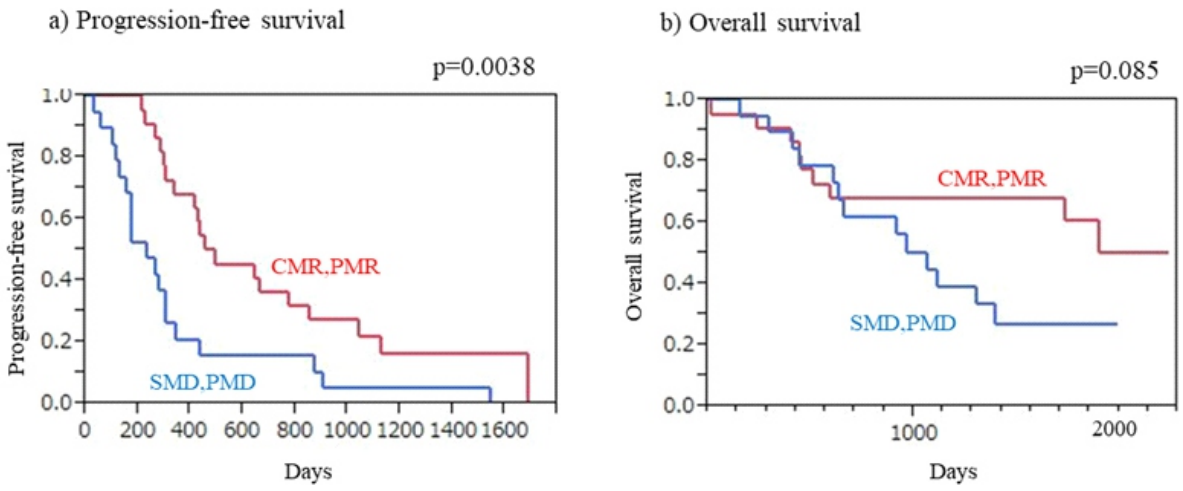

Figure 4. Progression-free survival (PFS) and overall survival (OS) of patients with breast cancer treated by systemic therapy.a) Responders (CMR/PMR) show significantly longer PFS than non-responders (SMD/PMD) (P=0.0038).b) Responders (CMR/PMR) show longer OS than non-responders (SMD/PMD), however the difference did not reach the significant level (P=0.085).

ous metastases, bone scintigraphy is sometimes combined with CT for the response evaluation of bone metastasis due to breast cancer. However, the osteoblastic reaction of the healing bone is known to initially increase radiotracer uptake on bone scans, which leads to false-positive findings, and there is no established quantitative analysis of bone scans. This renders bone scans less valuable than ^{18}F-FDG PET/CT for the assessment of tumor response [23]. Hence, ^{18}F-FDG PET/CT can accurately evaluate both the response and progression of bone metastasis, and is a better and simpler modality than CT combined with bone scintigraphy.

Fluorine-18-FDG PET/CT for evaluating treatment response has drawbacks in many criteria and the number of lesions measured. Because SUVmax is a simple, commonly used biomarker derived from ^{18}F-FDG PET/CT scans, EORTC using only ΔSUVmax is clinically available for the evaluation of patient response to treatments. Although the Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) 1.0, which mainly uses the change in SULpeak, was developed for the response to chemotherapy in 2009 [24], the calculation of SULpeak and total lesion glycolysis (TLG) is a complicated and time-consuming task in daily practice. Because several groups demonstrated no apparent difference between the changes in SULpeak and SUVmax and the EORTC and PERCIST criteria [10, 14, 25] in patients with metastatic breast cancer undergoing systemic therapy, in the present study, we chose to apply EORTC. Riedl et al. (2017) [10] clarified that the changes in SULpeak and SUVmax were highly correlated (r=0.998), and the response classification between EORTC and PERCIST was the same in all 65 patients with stage IV breast cancer undergoing systemic therapy. Goulon et al. (2016) [25] showed similar results, where PERCIST-derived response evaluation of patients with metastatic breast cancer showed no significant differences between the use of maximum, mean, or peak SUV normalized to total body mass (SUVmax, SUVmean, and SUVpeak). Willemsen et al. (2018) [14] demonstrated that EORTC showed a better correlation with PFS than PERCIST in patients with breast cancer treated with everolimus and exemestane. Many other criteria such as imPERCIST [26], PECRIT [27], PERCIMT [28], and iPERCIST [29] have been proposedas a PET/CT criteria in treatment response of immune checkpoint inhibitors.

The PERCIST guidelines propose that the number of lesions to be measured could range from the most ^{18}F-FDG-avid lesion (one lesion) to five lesions, as also used in RECIST1.1. The impact of analyzing one or up to five lesions was investigated by Pinker et al. (2016) [30], who assessed the response in 60 patients using the SULpeak of the most ^{18}F-FDG-avid lesion (PERCIST1) and by the change in the sum of SULpeak for five lesions (maximum two per organ) (PERCIST5). The two approaches yielded responses that were equally and significantly correlated with PFS and disease-specific survival. The EORTC also provides no information about the right number of lesions to measure, and it is likely that the highest SUVmax of the same lesion (one lesion) was recorded for two ^{18}F-FDG PET/CT studies. Although the one-lesion method is simple and easy, patients with recurrent and metastatic breast cancer have many lesions. We believe that the one-lesion method is insufficient to evaluate treatment response in this study. Following the method of a previous study [15,16, 30], we chose up to five lesions with the highest ^{18}F-FDG uptake and up to two lesions per organ, and measured the same lesions on the subsequent follow-up scan. Although many previous studies evaluating the treatment response to systemic therapy in patients with recurrent and metastatic breast cancer have adopted the one-lesion method [9-14], the five-lesion method used here is a strong point of our study.

In our study, it is not surprising that EORTC (responders vs. non-responders) significantly did not correlate with OS. Progression-free survival seems to be a better surrogate measure for treatment response in patients with recurrent or metastatic breast cancer than OS, mainly because PFS represents a period in which the patient benefits from current treatment, whereas OS is influenced by all subsequent treatment regimens, comorbidities, and other disease courses.

The literature search also yielded other interesting and promising methods for response evaluation. These studies suggest that ^{18}F-fluorotymidine PET [32], ^{18}F-fluoromisonidazole PET [33], human epidermal growth factor receptor-2 (HER-2)-imaging [34], and estrogen receptor-imaging [35] alone or combined with ^{18}F-FDG PET/CT might be useful for response evaluation in personalized treatment in the future. Hence, with a potential future shift of the treatment of metastatic breast cancer away from traditional chemotherapy and towards more personalized treatment types, PET/CT with the use of specific tracers may also contribute valuable knowledge on response prediction, such as for HER2-receptor targeting treatments [36]. This provides an exciting platform for further studies, but is beyond the scope of this study.

This study had some limitations, including its small sample size. In addition, histological verification of the ^{18}F-FDG PET/CT results was not performed. Furthermore, the enrolled subject population was heterogeneous and included patients undergoing various treatment procedures, which may have introduced complicated confounding factors in the analysis. A larger prospective study for arranging treatment methods is required to validate the present results.

In conclusion, in a small group of patients with metastatic breast cancer at either the initial diagnosis or relapse, ^{18}F-FDG PET/CT after one cycle of systemic therapy was able to reflect very early metabolic changes and showed accuracy for very early response evaluation of systemic therapy and prediction of progression. Fluorine-18-FDG-PET/CT is a useful and minimally invasive tool that can be used to make decisions on personal treatment to enhance benefits while reducing collateral effects. Nevertheless, future studies with larger sample sizes are needed to better determine the value of ^{18}F-FDG PET/CT.

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