Harmonized pretreatment quantitative volume-based ^{18}F-FDG PET/CT parameters for stage IV breast cancer prognosis. Multicenter study in Japan

Kazuhiro Kitajima[1] MD,
Yasuo Miyoshi[2] MD,
Tetsuro Sekine[3] MD,
Hiroyuki Takei[4] MD,
Kimiteru Ito[5] MD,
Akihiko Suto[6] MD,
Hayato Kaida[7] MD,
Hiromitsu Daisaki[8] PhD,
Koichiro Yamakado[1] MD

1. Department of Radiology, Hyogo College of Medicine, Hyogo, Japan
2. Department of Breast and Endocrine Surgery, Hyogo College of Medicine, Hyogo, Japan
3. Department of Radiology, Nippon Medical School Hospital, Tokyo, Japan
4. Department of Breast Surgery and Oncology, Nippon Medical School Hospital, Tokyo, Japan
5. Department of Diagnostic Radiology, National Cancer Center Hospital, Tokyo Japan
6. Department of Breast surgery, National Cancer Center Hospital, Tokyo Japan
7. Department of Radiology, Kinki University Faculty of Medicine, Osaka, Japan
8. Department of Graduate School of Radiological Technology, Gunma Prefectural College of Health Sciences, Maebashi, Japan

Keywords: Metastatic breast cancer - Prognosis - ^{18}F-FDG -PET -Harmonization

Corresponding author:
Kazuhiro Kitajima MD,
Department of Radiology, Hyogo College of Medicine,
Nishinomiya, Hyogo, Japan
1-1 Mukogawa-cho, Nishinomiya,
Hyogo 663-8501 Japan
Phone:+81-798-45-6883,
Fax:+81-798-45-6262
kazu10041976@yahoo.co.jp

Received:
5 November 2020
Accepted revised:
14 December 2020

Abstract

Objective: The prognostic value of harmonized pretreatment volume-based quantitative fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) parameters in metastatic breast cancer patients was investigated. **Subjects and Methods:** Records of 65 stage IV breast cancer patients, including 29 estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative, 23 HER2-positive, and 13 triple-negative cases, from four different institutions were retrospectively reviewed. Harmonized standardized uptake value (SUVmax) of the primary tumor (pSUVmax), highest SUVmax of all malignant lesions (wSUVmax), whole-body metabolic tumor volume (WB MTV), and whole-body total lesion glycolysis (WB TLG) shown by pretreatment ^{18}F-FDG PET/CT imaging were calculated. Cox proportional hazards model and log-rank test results were used to evaluate relationships among clinicopathological factors, volume-based quantitative ^{18}F-FDG PET/CT parameters, progression-free survival, and overall survival (OS). **Results:** Disease progression occurred in 54 patients and 28 died during a median follow-up period of 52.5 months (range 2.6-133.6 months). Univariate analysis of all cases showed associations of negative ER and progesterone receptor (PR) status (P=0.0025), and high T/N stage (P=0.037/P=0.019), pSUVmax (P=0.049), WB MTV (P=0.021), and WB TLG (P=0.0010) with significantly shorter OS. Multivariate analysis confirmed negative ER and PR status (hazard ratio [HR]: 6.42, 95% confidence interval [CI]: 2.27-19.38; P=0.0054), high T stage (HR: 5.10, 95% CI:1.96-18.61, P=0.0064) and WB TLG (HR: 4.69, 95% CI:1.67-12.79, P=0.049) as independent negative OS predictors. In two groups of ER-positive/HER2-negative and triple-negative, WB TLG had a significant association with death (P= 0.021 and P=0.037, respectively) on univariate analysis. In a HER2-positive group, no independent negative OS predictors were observed. **Conclusion:** In metastatic breast cancer patients, harmonized pretreatment quantitative volume-based ^{18}F-FDG PET/CT parameters, especially whole-body TLG, are potential surrogate markers for prognosis.

Hell J Nucl Med 2020; 23(3): 272-289 *Published online: 28 December 2020*

Introduction

Despite improved techniques for breast cancer screening, approximately 6% of affected females have metastatic disease at diagnosis [1]. A variety of treatments are available for metastatic breast cancer, including chemotherapy, endocrine treatment, therapy with appropriate antibodies, and use of tyrosine kinase inhibitors, as well as supportive measures, with results from this wide range of therapeutic options contributing to remarkably improved prognosis in some patients. On other hand, despite impressive advances, survival of patients with metastasis shows great variance, with median survival duration ranging from less than 9 months to more than 3 years [2]. A heterogeneous group of diseases are categorized as breast cancer, with various histological differentiations as well as clinical courses and responses to treatment. When considering management options for affected patients, examinations of obtained specimens are typically performed to determine tumor-node-metastasis (TNM) stage, histologic tumor grade, and levels of hormone receptors and molecular markers [3]. As for immunohistochemical factors related to prognosis, hormone receptors, such as estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67, are generally considered, most of which can be fully evaluated following surgical resection. However, because metastatic breast cancer patients are not eligible for surgical resection as first-line treatment, they cannot be used as prognostic factors in those cases. On the other hand, noninvasive diagnostic tools for prediction of tumor behavior prediction in breast cancer patients are becoming popular [4, 5]. Those include quantitative parameters, such as standardized uptake value (SUV), meta-

bolic tumor volume (MTV), and tumor lesion glycolysis (TLG), which are determined using fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) findings, and known to reflect glucose metabolism related to increased glycolysis level in cancer cells. Additionally, those have also been shown to correlate with clinicopathological prognostic factors as well as have value for prognosis prediction.

Standardized uptake value varies widely based on biological and technical factors related to the PET scanner model used, and acquisition protocol and reconstruction algorithm employed, as well as other factors. Thus, a harmonization strategy for making semi-quantitative PET parameters comparable among different imaging systems is needed, and especially relevant for multicenter trials and centers that use multiple PET systems. The EANM/EARL program [6, 7] and Quantitative Imaging Biomarker Alliance (QIBA/UPICT) [8,9] are harmonization programs established to provide comparisons of SUV metrics among different systems, especially for use in multicenter studies, though they are also helpful for institutions with several different PET systems in place.

To the best of our knowledge, no prior study has performed evaluations related to harmonization of ^{18}F-FDG PET/CT quantitative parameters for use as potential surrogate markers in breast cancer. In the present study, we examined the utility of harmonized quantitative volume-based ^{18}F-FDG PET/CT parameters for prognosis prediction of patients with metastatic breast cancer according to three major molecular subtypes; ER-positive/HER2-negative, HER2-positive, and triple-negative.

Subjects and Methods

Patients

This retrospective multicenter study of ^{18}F-FDG PET/CT findings was conducted by Hyogo College of Medicine Hospital, Kindai University Hospital, Nippon Medical School Hospital, and National Cancer Center Hospital in Japan. The review board at each institution gave approval for the study protocol and waived patient-informed consent requirements. The records of 71 females with newly diagnosed stage IV invasive breast cancer who underwent pretreatment whole-body ^{18}F-FDG PET/CT examinations between January 2010 and December 2016 were examined. Excluded were those with bilateral breast cancer (n=2) or no immunohistochemical data available (n=4), thus the records of 65 (mean age 59.9 years) were finally investigated. Tumor subtype in the enrolled cases was ER-positive/HER2-negative in 29, HER2-positive in 23, and triple-negative in 13. Magnetic resonance imaging (MRI) and ultrasound results, as well as clinical examination findings were used to determine T status. The pathological assessment of aspiration cytology was used to diagnose the axillary node status, whereas ^{18}F-FDG PET/CT result was used for determination of internal mammary, infraclavicular, and supraclavicular node status.

All patients were given systemic chemotherapy, hormone therapy, or novel target agent administration as first-line treatment. Eighteen of the 65 enrolled underwent palliative surgery as second-line treatment, when indicated. Mammography, breast ultrasound, CT, whole-body bone scintigraphy, and ^{18}F-FDG PET/CT results were used for determination of disease progression and metastasis during follow-up examinations.

^{18}F-FDG PET/CT

The whole-body PET/CT scanners employed for the present cases included Gemini GXL (Philips Medical Systems, Eindhoven, The Netherlands), Gemini TF (Philips Medical Systems, Eindhoven, The Netherlands), Biograph Duo (Siemens Healthcare, Erlangen, Germany), and Discovery 600 (GE Healthcare, WI, USA) systems, and the clinical parameters of these devices are shown in Table 1. Patients fasted for 5 hours prior to the examination and blood glucose was measured immediately prior to injection of ^{18}F-FDG at approximately 3.0-4.0MBq/kg of body weight. No blood glucose level greater than 160mg/dL was noted in any of the patients. Approximately 60 minutes after injection, static emission images were obtained. The patient was allowed to breathe normally during PET scanning. For reconstruction of attenuation-corrected PET images, a line-of-response row-action maximum likelihood algorithm (LOR-RAMLA), 3D-ordered-subset expectation maximization iterative reconstruction algorithm (3D-OSEM), or full-list mode time of flight (TOF) 3D-OSEM was used.

All ^{18}F-FDG PET/CT images were reviewed retrospectively by the same experienced reader, who had 12 years of experience with oncologic ^{18}F-FDG PET/CT imaging and no knowledge of other imaging results, or clinical or histopathologic findings, other than a breast cancer diagnosis. RAVAT (Nihon Medi-Physics Co. Ltd., Tokyo, Japan), a commercially available software package able to harmonize SUVs obtained with different PET/CT systems in a range recommended by the Japanese Society of Nuclear Medicine (JSNM) using phantom data, was employed [10]. Maximum standardized uptake value was defined as maximum SUV within the target volume and determined using the following formula: concentration of radioactivity in volume of interest (VOI) (Mbq/ mL)×total body weight (kg)/injected radioactivity (g/MBq). As for SUVmean, that was calculated based on the summed SUV in each voxel in the target volume divided by the number of voxels within the target volume. Metabolic tumor volume (milliliters) was automatically measured inside the tumor VOI with the margin threshold set at 40% of SUVmax. Then TLG (grams) was calculated as SUVmean×MTV, taking into consideration both metabolic activity and tumor burden. We also used "pSUVmax", which was defined as the SUVmax of the primary tumor, and "wSUVmax", defined as the highest SUVmax value of all malignant lesions including the primary tumor as well as nodal or distant metastatic lesions. Also, "whole-body (WB) MTV" and "WB TLG" were calculated by summing the corresponding values for each lesion in the case being examined. Two representative cases are shown in Figures 1 and 2.

Maximum-intensity-projection ^{18}F-FDG PET imaging showed increased ^{18}F-FDG uptake in the left breast, ipsilateral axillary lymph nodes, and supraclavicular lymph nodes. Additionally, multiple ^{18}F-FDG uptake foci were noted in the

Table 1. *Clinical parameters of PET scanners.*

Scanner	Gemini GXL	Gemini TF1	Gemini TF2	Biograph Duo	Discovery 600
Vender	**Philips**	**Philips**	**Philips**	**SIEMENS**	**GE**
PET scanning					
^{18}F-FDG injection dose (MBq/kg)	4	3	4	3	4
Scan time (mm) for each bed	90	90	80	110	120
TOF	no	yes	yes	no	no
PET reconstruction					
Reconstruction	line-of-response row-action maximum likelihood algorithm (LOR-RAMLA)	3D-OSEM	Full-list mode TOF 3D-OSEM	3D-OSEM	3D-OSEM
Iterations	2	3	3	2	2
Subsets	n/a	33	33	8	16
Smoothing	n/a	n/a	n/a	Gaussian	Gaussian
FWHM of filter (mm)				5	5
Matrix	144×144	144×144	144×144	128×128	192×192
Pixel size (mm)	4×4×4	4×4×4	4×4×4	5.31×5.31×5	2.6×2.6×2.6
PSF	no	no	no	no	no

^{18}F-FDG: fluorine-18-fluorodeoxyglucose, TOF: time of flight, OSEM: ordered-subset expectation maximization, FWHM: full-width at half maximum, PSF: point spread function

spine (C7), sternum, and lumbar spine (L5), reflecting bone metastasis. The harmonized maximum standardized uptake value (SUVmax) for the primary tumor was 5.9, while the maximum SUVmax for all malignant lesions was 10.6, whole-body metabolic tumor volume (MTV) was 25.2cm^3, and whole-body total lesion glycolysis (TLG) was 80.7. Following treatment, the patient was alive at 55.6 months after the initial diagnosis without disease progression.

Maximum-intensity-projection ^{18}F-FDG PET imaging showed increased ^{18}F-FDG uptake in the left breast, ipsilateral axillary lymph nodes, internal mammary nodes, supraclavicular lymph nodes, and mediastinal lymph nodes. Additionally, multiple ^{18}F-FDG uptake foci were noted in the liver, bone, and lung. The harmonized SUVmax value for the primary tumor was 9.55, while the maximum SUVmax value for all malignant lesions was 9.67, whole-body MTV was 1187.1cm^3, and whole-body TLG was 4825.9. Although chemotherapy was administered, the patient developed brain metastasis 8.1 months after the initial diagnosis and died of disease progression at 10.7 months.

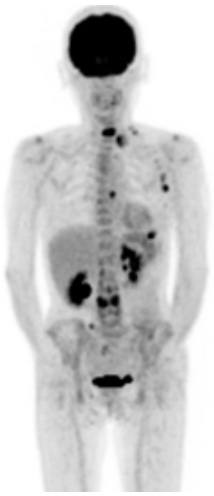

Figure 1. 69-year-old female with Luminal-HER2 (ER+/HER2+) invasive ductal carcinoma of the breast (T2N3cM1).

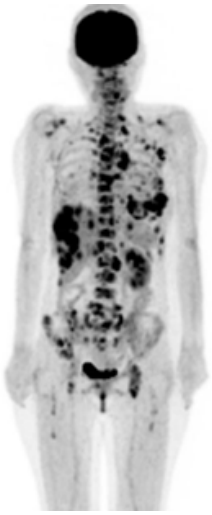

Figure 2. 42-year-old female Triple-negative type invasive ductal carcinoma of the breast (T4dN3cM1).

Histological analysis

Following immunohistochemical staining, expression levels of ER, PR, HER2, and Ki67 in tissue samples were examined after formalin fixation and paraffin embedding, with the quantitative expression levels of those proteins and antibodies determined. Furthermore, the percentage of nuclear staining for ER, PR, and Ki67 in cancer cells was also determined, with the cutoff value for ER and PR set at 1%, and that for Ki67 at 20%. Tumors were defined as HER2-positive when they had an immunohistochemical score of 3 or showed in situ hybridization-positive fluorescence with an immunohistochemical score of 2.

Statistical analysis

Continuous data are shown as median and range, while categorical data are presented as number and percentage. Welch's t test was used for comparisons of patients with or without disease progression or death, then to determine the optimal threshold, receiver operating characteristics (ROC) analysis was performed. In this long-term follow-up study, progression-free survival (PFS), defined as time elapsed from date of diagnosis to disease progression, and overall survival (OS), defined as time until death or date of last follow-up examination when neither progression nor death occurred during follow-up, were evaluated. The Kaplan-Meier method and log-rank test results were utilized to determine survival curves.

Cox proportional hazards logistic regression was used to evaluate the prognostic value of individual variables. To quantify the risk of disease progression and death from breast cancer age, ER status, PR status, HER2 status, Ki-67 index, palliative surgery, T and N classification, bone metastasis, visceral metastasis, pSUVmax, wSUVmax, WB MTV, and WB TLG were used as variables, and univariate Cox proportional hazards modeling was employed. Significant or borderline univariate variables ($P<0.1$) were then subjected to multivariate analysis, except when insufficient data was available for the parameter. Cox model results are expressed as hazard ratio with 95% confidence interval (CI). Statistical analysis was performed using the SAS software package, version 9.3 (SAS Institute Inc., Cary, NC, USA), with $P<0.05$ considered to indicate significance.

Results

Harmonization

Maximum standardized uptake value was within the JSNM reference range for the GXL and Biograph Duo (no filter needed for either system). The full-width at half maximum (FWHM) values for the additional gaussian filter resulting in an SUVmax value within the JSNM reference for the Discovery 600, Gemini TF1, and Gemini TF2 systems were 3.4, 5.9 and 5.8mm, respectively.

Patient characteristics

Patient and tumor characteristics are shown in Table 2. The mean age±standard deviation (SD) was 59.9±12.3 years (range 25-86 years). The tumors were classified histologically as invasive ductal carcinoma (n=60, 92.3%) or other specified types (n=5, 7.7%; two mucinous carcinomas, two invasive lobular carcinomas, one apocrine carcinoma). Positivity for ER, PR, and HER2 was observed in 46 (70.8%), 22 (33.9%), and 23 (35.4%) patients, respectively. Ki-67 values ≥20% were seen in 48 patients (73.8%). Patients classified as T1/T2/T3/T4 stage numbered 3/20/12/30, while those as N0/1/2/3 stage numbered 7/15/7/36.

The numbers of patients with distant metastasis shown by PET/CT imaging according to anatomic site were as follows; bone, 48 (73.8%); lymph node, 25 (38.5%); lung, 19 (29.2%); liver, 15 (23.1%); pleura, 4 (6.2%); muscle, 2 (3.1%) and skin, 2 (3.1%).

Table 2. *Patient and tumor characteristics.*

	Number	%
Number of patients	65	
Age (years, mean±SD)	59.9±12.3	
Histology		
IDC	60	92.3
Others (Myxoid/ILC/Apocrine)	2//2/1	3.1/3.1/1.5
Receptor positivity		
Estrogen receptor	46	70.8
Progesterone receptor	22	33.9
HER-2/neu	23	35.4
Ki-67 index status		
<20%	17	26.2
≧20%	48	73.8
Molecular phenotype		
Luminal A (ER+/HER2-, Ki67<20%)	13	20.0
Luminal B (ER+/HER2-, Ki67≥20%)	16	24.6
Luminal-HER2 (ER+/HER2+)	17	26.2
HER2 positive (nonluminal)	6	9.2
Triple-negative	13	20.0
Nuclear grade		
Grade1	23	35.4
Grade2	24	36.9
Grade3	18	27.7
T status		
T1	3	4.6
T2	20	30.8
T3	12	18.5
T4	30	46.2
N status		
N0	7	10.8
N1	15	23.1
N2	7	10.8
N3	36	55.4
Palliative surgery		
Yes	18	27.7
No	47	72.3

SD: standard deviation, IDC: invasive ductal cancer, ILC: invasive lobular cancer, ER: endocrine receptor, HER: human epidermal growth factor receptor

(continued)

Survival analysis

OS analysis

During a median follow-up period of 52.5 months (2.6-133.6 months), 28 (43.1%) of the 65 patients died. Those with death had a significantly higher pSUVmax than those without (10.2±5.5 vs. 6.6±3.0; P=0.0035). Receiver operating characteristic curve analysis and log-rank test results showed that patients with a high pSUVmax (≥7.8) had a significantly lower OS rate as compared to those with a low pSUVmax (<7.8; P=0.049) (Figure 3a). Also, patients with death had a higher wSUVmax than those without (11.9±5.4 vs. 9.5±5.1; P=0.071). The patients were divided into two groups based on ROC curve analysis and log-rank test results using wSUVmax (<8.9 vs. ≥8.9; P=0.15) (Figure 3b). Those who died had a significantly higher WB MTV as compared to those survived (258.9±328.9 vs. 115.7±143.3mL; P=0.0035). Additionally, ROC curve analysis and log-rank test results showed that patients with a high WB MTV (≥65.0mL) had a significantly lower OS rate than those with a low value (<65.0mL; P=0.021) (Figure 3c). Patients who died also had a significantly higher WB TLG value than those who survived (1713.9±2505.9 vs. 495.5±538.2g; P=0.017). Furthermore, ROC curve analysis and log-rank tests results showed that patients with a high WB TLG value (≥200.0g) had a significantly lower OS rate than those with a low value (<200.0 g; P=0.0010) (Figure 3d).

Univariate analysis results indicated that negative ER and PR status (P=0.0025), high T stage (P=0.037), high N stage (P=0.019), high pSUVmax (P=0.049), high WB MTV (P=0.021), and high WB TLG (P=0.0010) each had a significant association with death from cancer, whereas age (P=0.89), HER2-positive status (P=0.14), high Ki-67 expression (P=0.062), palliative surgery procedure (P=0.11), presence of bone metastasis (P=0.96), presence of visceral metastasis (P=0.059), and high wSUVmax (P=0.15) did not have such an association (Table 3). Findings of multivariate analysis then confirmed negative ER and PR status (hazard ratio [HR]: 6.42, 95% CI: 2.27-19.38; P=0.0054), high T stage (HR: 5.10, 95% CI: 1.96-18.61, P=0.0064), and high WB TLG (HR: 4.69, 95% CI: 1.67-12.79, P=0.049) as independent negative predictors (Table 3).

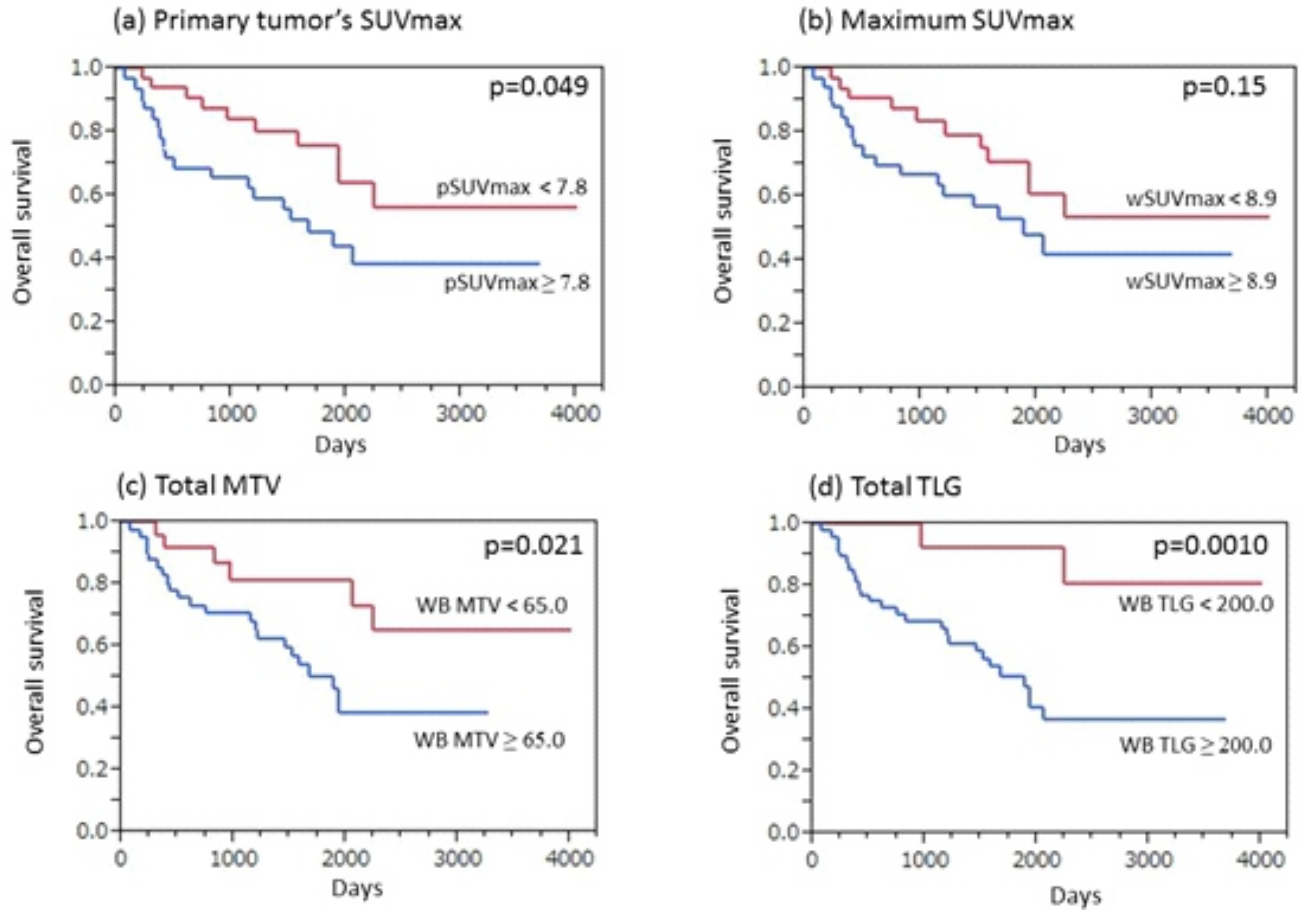

Figure 3. Overall survival (OS) of patients with metastatic breast cancer (n=65) (Kaplan-Meier survival analysis). a) Patients with a high standardized uptake value (pSUVmax) (≥7.8) for the primary tumor had a significantly lower OS rate as compared to those with a lower value (<7.8) (P=0.049). b) Patients with a high SUVmax value (wSUVmax) (≥8.9) for the entire malignant lesion had a significantly lower OS rate as compared to those with a lower value (<8.9) (P=0.15). c) Patients with a high total MTV value (≥65.0mL) had a significantly lower OS rate as compared to those with a lower value (<65.0mL) (P=0.021). d) Patients with a high total TLG value (≥200.0g) had a significantly lower OS rate as compared to those with a lower value (<200.0g) (P=0.0010).

Table 3. *Univariate and multivariate analysis of progression free survival (PFS) and overall survival (OS) in all 65 patients.*

		Progression free survival				Overall survival			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variable	**N**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**
Age (ys)		0.90				0.89			
≤ 50	14		1.00				1.00		
> 50	51		0.66 (0.35-1.19)				0.54 (0.21-1.22)		
ER or PR expressed		0.0068		0.0020		0.0025		0.0054	
Yes	46		1.00		1.00		1.00		1.00
No	19		2.95 (1.62-5.20)		3.02 (1.52-6.94)		3.32 (1.55-17.01)		6.42 (2.27-19.38)
HER2 overexpressed		0.59				0.14			
No	42		1.00				1.00		
Yes	23		0.85 (0.47-1.50)				0.94 (0.54-2.13)		
Ki-67 expression level		0.018		0.49		0.062		0.86	
<20%	17		1.00		1.00		1.00		1.00
≧20%	48		2.09 (1.13-4.16)		1.29 (0.63-2.74)		2.01 (0.96-4.15)		0.79 (0.29-2.18)

(continued)

Palliative surgery		0.17			0.11			
Yes	18		1.00			1.00		
No	47		1.08 (0.66-1.95)			0.97 (0.57-2.15)		
T classification		0.69			0.037		0.0064	
T1, T2	23		1.00			1.00		1.00
T3, T4	42		0.82 (0.45-1.42)			2.45 (1.05-6.65)		5.10 (1.96-18.61)
N classification		0.036		0.54	0.019		0.21	
N0, N1	22		1.00	1.00		1.00		1.00
N2, N3	43		1.94 (1.04-4.12)	1.24 (0.63-2.59)		2.87 (1.18-8.60)		1.85 (0.72-5.69)
Bone metastasis		0.047		0.0051	0.96			
No	17		1.00	1.00		1.00		
Yes	48		1.84 (1.01-3.73)	2.67 (1.32-5.92)		0.49 (0.18-1.15)		
Visceral metastasis		0.47			0.059		0.93	
No	36		1.00			1.00		1.00
Yes	29		0.89 (0.49-1.57)			2.04 (0.99-4.43)		0.72 (0.24-2.03)

(continued)

pSUVmax		0.89			0.049		0.64	
< 7.8	33		1.00			1.00		1.00
≧7.8	32		0.69 (0.38-1.27)			2.13 (1.00-4.81)		0.91 (0.28-2.56)
wSUVmax		0.86			0.15			
< 8.9	32		1.00			1.00		
≧8.9	33		0.71 (0.39-1.33)			0.93 (0.53-2.01)		
WB MTV (mL)		0.077		0.87		0.021		0.59
< 65.0	24		1.00		1.00		1.00	
≧65.0	41		1.66 (0.95-3.04)		0.88 (0.30-1.91)		2.78 (1.15-7.31)	0.96 (0.36-2.62)
WB TLG (g)		0.057		0.83		0.0010		0.049
< 200.0	17		1.00		1.00		1.00	
≧200.0	48		1.82 (0.98-3.67)		0.92 (0.31-1.99)		6.51 (1.93-40.58)	4.69 (1.67-12.79)

HR: hazard ratio, CI: confidence interval, ER: estrogen receptor, PR: progesterone receptor, HER: human epidermal growth factor receptor, pSUVmax: standardized uptake value of primary tumor, wSUVmax: highest SUVmax of whole malignant lesions, WB MTV: whole-body metabolic tumor volume, WB TLG: whole-body total lesion glycolysis

PFS analysis

During a median follow-up of 22.4 months (0.8-133.6 months), 54 (83.1%) of the present patients had disease progression. Those with disease progression had a higher pSUVmax than those without (8.4±4.8 vs. 6.9±3.3; P=0.22). Using ROC curve analysis and log-rank test results, the patients were divided into two groups according to pSUVmax (<7.8 vs. ≥7.8; P=0.89) (Figure 4a). Those with disease progression had a similar wSUVmax as compared to those without (10.2±4.5 vs. 11.9±8.6; P=0.52). When the patients were divided into groups based on ROC curve analysis and log-rank test results using wSUVmax (<8.9 vs. ≥8.9; P=0.86) (Figure 4b), those with disease progression had a significantly higher WB MTV as compared to those without disease progression (199.5± 267.8 vs. 69.2±56.3mL; P=0.0019). Additionally, ROC curve analysis and log-rank test results showed that patients with a high WB MTV (≥65.0mL) had a lower PFS rate than those with a low value (<65.0mL; P=0.077) (Figure 4c). Patients with disease progression also had a significantly higher WB TLG value than those without (1144.4±1926.5 vs. 402.9± 436.9g; P=0.014). Furthermore, ROC curve analysis and log-rank test results showed that patients with a high WB TLG value (≥200.0g) had a lower PFS rate than those with a low value (<200.0g; P=0.057) (Figure 4d).

Univariate analysis results showed that negative ER and PR status (P=0.0068), high Ki-67 expression (P=0.018), high N stage (P=0.036), and presence of bone metastasis (P=0.047) each had a significant association with disease progression, whereas age (P=0.90), HER2-positive status (P=0.59), palliative surgery (P=0.17), high T stage (P=0.69), presence of visceral metastasis (P=0.47), high pSUVmax (P=0.89), high wSUVmax (P=0.86), high WB MTV (P=0.077), and high WB TLG (P=0.057) were not significantly associated with disease progression (Table 3). Also, multivariate analysis results indicated that negative ER and PR status (HR: 3.02, 95% CI: 1.52-6.94; P=0.0020), as well as presence of bone metastasis (HR: 2.67, 95% CI: 1.32-5.92, P=0.0051) were independent factors for progression (Table 3).

ER-positive/HER2-negative type (n=29)

OS analysis

During a median follow-up of 59.9 months (13.8-133.6 months), nine (31.0%) of the 29 ER-positive/HER2-negative type breast cancer patients died. Univariate analysis showed a significant association of high N stage (P=0.022), high WB MTV (P=0.019), and high WB TLG (P=0.021) with death from cancer, whereas there was no such association with age (P=0.13), high Ki-67 expression (P=0.12), palliative surgery procedure (P=0.74), high T stage (P=0.10), presence of bone metastasis (P=0.48), presence of visceral metastasis (P=0.79), high pSUVmax (P=0.11), or high wSUVmax (P=0.38) (Table 4). In multivariate analysis results, no independent predictors of OS were identified (Table 4).

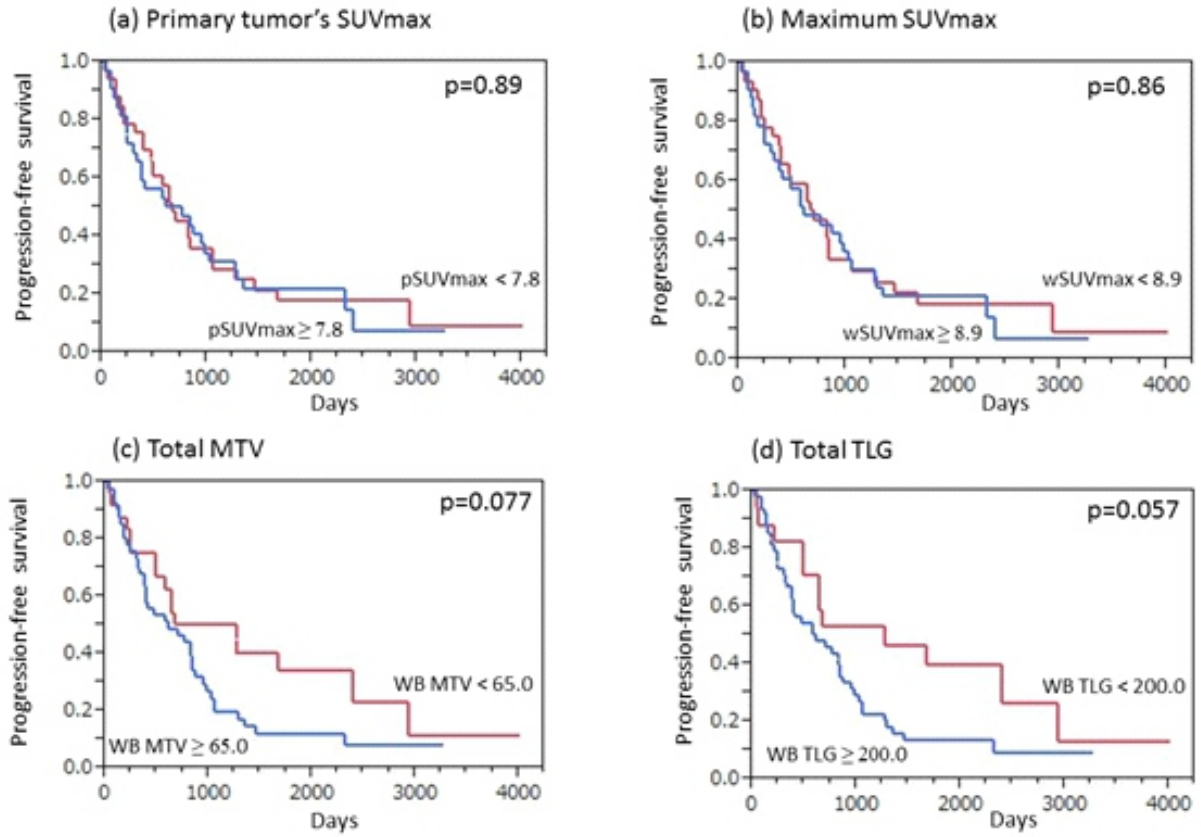

Figure 4. Progression-free survival (PFS) of patients with metastatic breast cancer (n=65) (Kaplan-Meier survival analysis). a) Patients with a high standardized uptake value (pSUVmax) (≥7.8) for the primary tumor had a significantly lower PFS rate as compared to those with a lower value (<7.8) (P=0.89). b) Patients with a high SUVmax value (wSUVmax) (≥8.9) for the entire malignant lesion had a significantly lower PFS rate as compared to those with a lower value (<8.9) (P=0.86). c) Patients with a high total MTV value (≥65.0mL) had a significantly lower PFS rate as compared to those with a lower value (<65.0mL) (P=0.077). d) Patients with a high total TLG value (≥200.0g) had a significantly lower PFS rate as compared to those with a lower value (<200.0g) (P=0.057).

Table 4. *Univariate and multivariate analysis of progression free survival (PFS) and overall survival (OS) in 29 patients with ER-positive/HER2-negative breast cancer.*

		Progression free survival				Overall survival			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variable	**N**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**
Age (ys)		0.39				0.13			
≤ 50	8		1.00				1.00		
> 50	21		1.52 (0.63-3.34)				1.21 (0.57-2.02)		
Ki-67 expression level		0.036		0.10		0.12			
<20%	12		1.00		1.00		1.00		
≧20%	17		3.62 (1.23-7.14)		0.96 (0.52-1.41)		1.27 (0.59-2.11)		
Palliative surgery		0.42				0.74			
Yes	9		1.00				1.00		
No	20		1.38 (0.61-2.95)				0.79 (0.46-1.39)		
T classification		0.34				0.10			
T1, T2	8		1.00				1.00		
T3, T4	21		1.56 (0.71-3.62)				1.32 (0.62-2.32)		
N classification		0.27				0.022		0.87	
N0, N1	15		1.00				1.00		1.00
N2, N3	14		1.63 (0.69-3.84)				7.35 (1.30-37.74)		1.13 (0.19-4.84)

(continued)

Bone metastasis		0.044		0.13		0.48		
No	5		1.00		1.00		1.00	
Yes	24		3.58 (1.17-6.69)		0.96 (0.52-1.41)		0.87 (0.51-1.57)	
Visceral metastasis		0.90				0.79		
No	20		1.00				1.00	
Yes	9		0.64 (0.27-1.19)				0.72 (0.41-1.36)	
pSUVmax		0.35				0.11		
< 7.8	16		1.00				1.00	
≧7.8	13		1.55 (0.66-3.59)				1.31 (0.61-2.29)	
wSUVmax		0.29				0.38		
< 8.9	15		1.00				1.00	
≧8.9	14		1.56 (0.61-3.63)				0.92 (0.53-1.63)	
WB MTV (mL)		0.11				0.019		0.64
< 65.0	11		1.00				1.00	1.00
≧65.0	18		2.03 (0.89-4.36)				7.55 (1.34-41.85)	1.23 (0.31-5.62)
WB TLG (g)		0.17				0.021		0.86
< 200.0	11		1.00				1.00	1.00
≧200.0	18		1.84 (0.87-4.23)				7.37 (1.31-38.81)	1.14 (0.20-4.96)

HR: hazard ratio, CI: confidence interval, ER: estrogen receptor, PR: progesterone receptor, HER: human epidermal growth factor receptor, SUVmax: maximum standardized uptake value, MTV: metabolic tumor volume, TLG: total lesion glycolysis

PFS analysis

During a median follow-up of 31.7 months (10.0-133.6 months), 24 (82.8%) of the ER-positive/HER2-negative type breast cancer patients showed disease progression. Univariate analysis showed that high Ki-67 expression (P=0.036) and presence of bone metastasis (P=0.044) each had a significant association with disease progression, whereas age (P=0.39), palliative surgery (P=0.42), high T stage (P=0.34), high N stage (P=0.27), presence of visceral metastasis (P=0.90), high pSUVmax (P=0.35), high wSUVmax (P=0.29), high WB MTV (P=0.11), and high WB TLG (P=0.17) did not have such an association (Table 4). In multivariate analysis results, no independent predictors of OS were identified (Table 4).

HER2-positive type (n=23)

OS analysis

During a median follow-up of 55.2 months (7.5-123.0 months), seven (30.4%) of the 23 HER2-positive type breast cancer patients died. Univariate analysis showed no significant factors associated with death, including age (P=0.75), negative ER and PR status (P=0.24), high Ki-67 expression (P=0.95), palliative surgery (P=0.084), high T stage (P=0.45), high N stage (P=0.082), presence of bone metastasis (P=0.52), presence of visceral metastasis (P=0.33), high pSUVmax (P=0.20), high wSUVmax (P=0.58), high WB MTV (P=0.70), and high WB TLG (P=0.12) (Table 5).

PFS analysis

During a median follow-up of 23.6 months (1.6-108.9 months), seventeen (73.9%) of the HER2-positive type breast cancer patients showed disease progression. Univariate analysis showed that presence of bone metastasis (P=0.034) and high pSUVmax (P=0.039) each had a significant association with disease progression, whereas age (P=0.42), negative ER and PR status (P=0.56), high Ki-67 expression (P=0.69), palliative surgery (P=0.77), high T stage (P=0.36), high N stage (P=0.26), presence of visceral metastasis (P=0.93), high wSUVmax (P=0.11), high WB MTV (P=0.27), and high WB TLG (P=0.28) did not (Table 5). In multivariate analysis, presence of bone metastasis (HR: 4.42, 95% CI: 1.23-18.19, P=0.019) and high pSUVmax (HR: 3.23, 95% CI: 1.17-10.38; P=0.023) were independent factors for progression (Table 5).

Triple-negative (n=13)

OS analysis

During a median follow-up of 11.9 months (2.6-96.7 months), twelve (92.3%) of the 13 patients with triple-negative type breast cancer died. Univariate analysis results indicated that high WB TLG (P=0.037) alone had a significant association with death from cancer, whereas, age (P=0.68), high Ki-67 expression (P=0.75), palliative surgery procedure (P=0.22), high T stage (P=0.91), high N stage (P=0.74), presence of bone metastasis (P=0.23), presence of visceral metastasis (P=0.29), high pSUVmax (P=0.12), high wSUVmax (P=0.19), and high WB MTV (P=0.17) did not (Table 6).

PFS analysis

During a median follow-up of 5.1 months (0.8-25.4 months), all 13 patients with triple-negative type breast cancer showed disease progression. Univariate analysis showed no significant factors associated with disease progression, including age (P=0.35), high Ki-67 expression (P=0.91), palliative surgery (P=0.22), high T stage (P=0.18), high N stage (P=0.24), presence of bone metastasis (P=0.11), presence of visceral metastasis (P=0.85), high pSUVmax (P=0.96), high wSUVmax (P=0.99), high WB MTV (P=0.98), and high WB TLG (P=0.80) (Table 6).

Discussion

To the best of our knowledge, this is the first report of use of harmonized pretreatment quantitative volume-based ^{18}F-FDG PET/CT parameters (SUVmax, MTV, TLG) for prediction of prognosis (PFS, OS) in patients with stage IV breast cancer. The present results are notable, as they revealed harmonized quantitative volume-based parameters, especially whole-lesion TLG, to be potential surrogate markers for prognosis in patients with breast cancer metastasis and can thus be used to provide important information for individualized care.

It is becoming more common for different types of PET/CT scanners to be established at the same institution, and methods for harmonization of PET quantitative values are needed for both clinical practice and multicenter trials. Several studies have investigated SUVmax harmonization for evaluation of chemotherapy treatment response in various types of patients, such as those affected by lung, cervical, or rectal cancer, as well as colorectal liver metastasis, malignant lymphoma, and malignant melanoma cases [11-13]. Those findings showed a greater association of harmonized metabolic PET response classification with final clinical response assessment, indicating a superior level of disease-free survival prediction as compared to a non-harmonized PET classification. Additionally, a recent study clarified that harmonized SUVmax is an independent prognostic factor related to PFS in patients with non-small-cell lung cancer [14].

The usefulness of harmonized pretreatment quantitative volume-based ^{18}F-FDG PET/CT parameters for predicting prognosis of stage IV breast cancer patients has been reported by several institutions [15-17]. Son et al. (2015) [15] examined 40 cases of metastatic breast cancer and found that T category, palliative surgery, presence of visceral metastasis, wSUVmax, WB MTV, and WB TLG were prognostic factors for OS in univariate analysis results, while multivariate analysis revealed only WB MTV as an independent predictor of OS (HR, 4.10; 95% CI, 1.17-14.31; P=0.028). In another study of 47 metastatic triple negative breast cancer patients, Marinelli et al. (2016) [16] showed that patients with WB MTV <51.5mL lived nearly three times longer (22 vs 7.1 months) as compared those with a higher WB MTV level (P<0.0001) and their multivariate analysis results confirmed WB MTV as

Table 5. *Univariate and multivariate analysis of progression free survival (PFS) and overall survival (OS) in 23 patients with HER2-positive breast cancer.*

		Progression free survival				Overall survival			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variable	**N**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**
Age (ys)		0.42				0.75			
⩽ 50	2		1.00				1.00		
> 50	21		1.66 (0.59-2.27)				1.11 (0.49-1.76)		
ER or PR expressed		0.56				0.24			
Yes	17		1.00				1.00		
No	6		1.41 (0.56-2.02)				2.71 (0.71-4.82)		
Ki-67 expression level		0.69				0.95			
<20%	3		1.00				1.00		
⩾20%	20		1.38 (0.55-1.88)				0.95 (0.46-1.47)		
Palliative surgery		0.77				0.084		0.094	
Yes	8		1.00				1.00		1.00
No	15		1.19 (0.51-1.75)				5.11 (0.79-17.51)		4.38 (0.69-47.8)
T classification		0.36				0.45			
T1, T2	13		1.00				1.00		
T3, T4	10		1.71 (0.62-2.46)				1.48 (0.63-2.57)		
N classification		0.26				0.082		0.091	
N0, N1	5		1.00				1.00		1.00
N2, N3	18		1.82 (0.66-2.61)				5.13 (0.82-17.94)		4.84 (0.79-53.2)

(continued)

Bone metastasis		0.034		0.019		0.52	
No	5		1.00		1.00		1.00
Yes	18		3.91 (1.09-14.81)		4.42 (1.23-18.19)		1.41 (0.59-2.22)
Visceral metastasis		0.93				0.33	
No	11		1.00				1.00
Yes	12		0.89 (0.47-1.59)				2.41 (0.67-4.02)
pSUVmax		0.039		0.023		0.20	
< 7.8	14		1.00		1.00		1.00
≧7.8	9		3.18 (1.05-9.28)		3.23 (1.17-10.38)		2.76 (0.72-4.87)
wSUVmax		0.11				0.58	
< 8.9	13		1.00				1.00
≧8.9	10		2.16 (0.70-3.68)				1.37 (0.57-1.96)
WB MTV (mL)		0.27				0.70	
< 65.0	9		1.00				1.00
≧65.0	14		1.81 (0.65-2.57)				1.21 (0.55-1.82)
WB TLG (g)		0.28				0.12	
< 200.0	5		1.00				1.00
≧200.0	18		1.79 (0.64-2.53)				2.91 (0.75-5.10)

HR: hazard ratio, CI: confidence interval, ER: estrogen receptor, PR: progesterone receptor, HER: human epidermal growth factor receptor, SUVmax: maximum standardized uptake value, MTV: metabolic tumor volume, TLG: total lesion glycolysis

Table 6. *Univariate and multivariate analysis of progression free survival (PFS) and overall survival (OS) in 13 patients with triple-negative breast cancer.*

		Progression free survival				Overall survival			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variable	**N**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**
Age (ys)		0.35				0.68			
≤ 50	4		1.00				1.00		
> 50	9		1.56 (0.69-2.27)				1.11 (0.54-1.92)		
Ki-67 expression level		0.91				0.75			
<20%	1		1.00				1.00		
≧20%	12		0.68 (0.43-1.34)				0.87 (0.52-1.72)		
Palliative surgery		0.22				0.22			
Yes	1		1.00				1.00		
No	12		1.88 (0.77-3.65)				2.13 (0.77-4.36)		
T classification		0.18				0.91			
T1, T2	2		1.00				1.00		
T3, T4	11		2.14 (0.88-4.57)				0.75 (0.48-1.53)		
N classification		0.24				0.74			
N0, N1	2		1.00				1.00		
N2, N3	11		1.82 (0.76-3.47)				4.38 (2.48-8.74)		

(continued)

Bone metastasis		0.11		0.23		
No	6		1.00		1.00	
Yes	7		2.27 (0.93-4.91)		2.11 (0.75-4.02)	
Visceral metastasis		0.85		0.29		
No	5		1.00		1.00	
Yes	8		0.71 (0.53-1.48)		1.91 (0.72-3.72)	
pSUVmax		0.96		0.12		
< 7.8	3		1.00		1.00	
≧7.8	10		0.66 (0.41-1.24)		3.02 (1.46-10.26)	
wSUVmax		0.99		0.18		
< 8.9	4		1.00		1.00	
≧8.9	9		0.62 (0.34-1.13)		2.38 (1.19-8.90)	
WB MTV (mL)		0.98		0.17		
< 65.0	4		1.00		1.00	
≧65.0	9		0.63 (0.35-1.18)		2.41 (1.11-9.02)	
WB TLG (g)		0.80		0.037	0.037	
< 200.0	2		1.00		1.00	1.00
≧200.0	11		0.72 (0.55-1.53)		6.07 (1.62-64.13)	6.07 (1.62-64.13)

HR: hazard ratio, CI: confidence interval, ER: estrogen receptor, PR: progesterone receptor, HER: human epidermal growth factor receptor, SUVmax: maximum standardized uptake value, MTV: metabolic tumor volume, TLG: total lesion glycolysis

an independent negative OS predictor. Ulaner et al. (2013) [17] calculated SUVmax, MTV, and TLG values in four target lesions (bone, lymph node, liver, lung) in 253 cases of metastatic breast cancer, and noted that SUVmax and TLG were both predictors of OS, and also speculated that TLG may be a more informative biomarker of OS than SUVmax for patients with lymph node and liver metastases.

The present study has some limitations, including its retrospective design and relatively low number of patients. Furthermore, tumor background ratios were not assessed, and the cohort was a heterogeneous population in terms of variable follow-up imaging (timing and modality) and administered treatment regimens. Since all patients at the participating institutions with possible metastatic breast cancer did not undergo ^{18}F-FDG PET/CT imaging, selection bias may have had an influence on the results. We understand that an ideal gold standard for analysis is histological confirmation of findings, though it would have been unethical to examine all lesions detected by ^{18}F-FDG PET/CT using invasive procedures.

In conclusion, harmonized quantitative volume-based values obtained with ^{18}F-FDG PET/CT, especially regarding whole-body TLG, are useful for providing prognostic information regarding death prediction for patients with metastatic invasive breast cancer cases. Such information is quite useful for providing individualized care.

Acknowledgement
This work was supported by JSPS KAKENHI grant numbers 19K08187.

The authors declare that they have no conflicts of interest.

Bibliography

1. Brewster AM, Hortobagyi GN, Broglio KR et al. Residual risk of breast cancer recurrence 5 years after adjuvant therapy. *J Natl Cancer Inst* 2008; 100: 1179-83.
2. Chang J, Clark GM, Allred DC et al. Survival of patients with metastatic breast carcinoma: importance of prognostic markers of the primary tumor. *Cancer* 2003; 97: 545-53.
3. Runowicz CD, Leach CR, Henry NL et al. American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. *CA Cancer J Clin* 2016; 66: 43-73.
4. Ravina M, Saboury B, Chauhan MS et al. Utility of ^{18}F-FDG PET/CT in pre-surgical risk stratification of patients with breast cancer. *Hell J Nucl Med* 2019; 22: 165-71.
5. Kitajima K, Yamano T, Miyoshi Y et al. Prognostic value of ^{18}F-FDG PET/CT prior to breast cancer treatment. Comparison with magnetic resonance spectroscopy and diffusion weighted imaging. *Hell J Nucl Med* 2019; 22: 25-35.
6. Aide N, Lasnon C, Veit-Haibach P et al. EANM/EARL harmonization strategies in PET quantification: from daily practice to multicentre oncological studies. *Eur J Nucl Med Mol Imaging* 2017; 44: 17-31.
7. Kaalep A, Sera T, OyenW et al. EANM/EARL FDG-PET/CT accreditation-summary results from the first 200 accredited imaging systems. *Eur J Nucl Med Mol Imaging* 2018; 45: 412-22.
8. Graham MM, Wahl RL, Hoffman JM et al. Summary of the UPICT protocol for ^{18}F-FDG PET/CT imaging in oncology clinical trials. *J Nucl Med* 2015; 56: 955-61.
9. Makris NE, Huisman MC, Kinahan PE et al. Evaluation of strategies towards harmonization of FDG PET/CT studies in multicentre trials: comparison of scanner validation phantoms and data analysis procedures. *Eur J Nucl Med Mol Imaging* 2013; 40: 1507-15.
10. Tsutsui Y, Daisaki H, Akamatsu G et al. Multicentre analysis of PET SUV using vendor-neutral software: the Japanese harmonization technology (J-Hart) study. *EJNMMI Res* 2018; 8: 83.
11. Lasnon C, Desmonts C, Quak E et al. Harmonizing SUVs in multicentre trials when using different generation PET systems: prospective validation in non-small cell lung cancer patients. *Eur J Nucl Med Mol Imaging* 2013; 40: 985-96.
12. Quak E, Le Roux PY, Lasnon C, et al. Does PET SUV harmonization affect PERCIST response classification? *J Nucl Med* 2016; 57: 1699-706.
13. Mattoli MV, Calcagni ML, Taralli S et al. How often do we fail to classify the treatment response with [18F]FDG PET/CT acquired on different scanners? Data from clinical oncological practice using an automatic tool for SUV harmonization. *Mol imaging Biol* 2019; 21: 1210-9.
14. Houdu B, Lasnon C, Licaj I et al. Why harmonization is needed when using FDG PET/CT as a prognosticator: demonstration with EARL-compliant SUV as an independent prognostic factor in lung cancer. *Eur J Nucl Med Mol Imaging* 2019; 46: 421-8.
15. Son SH, Lee SW, Jeong SY et al. Whole-body metabolic tumor volume, as determined by ^{18}F-FDG PET/CT, as a prognostic factor of outcome for patients with breast cancer who have distant metastasis. *AJR Am J Roentgenol* 2015; 205: 878-85.
16. Marinelli B, Espinet-Col C, Ulaner GA et al. Prognostic value of FDG PET/CT-based metabolic tumor volumes in metastatic triple negative breast cancer patients. *Am J Nucl Med Mol Imaging* 2016; 6: 120-7.
17. Ulaner GA, Eaton A, Morris PG et al. Prognostic value of quantitative fluorodeoxyglucose measurements in newly diagnosed metastatic breast cancer. *Cancer Med* 2013; 2: 725-33.