Reproducibility of semi-quantitative parameters in FDG-PET using two different PET scanners: Influence of attenuation correction method and examination interval

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ABSTRACT

Purpose: To evaluate the reproducibility of semi-quantitative parameters obtained from two FDG-PET studies using two different PET scanners.   **Methods**: Forty-five patients underwent FDG-PET examination with two different PET scanners on separate days. Two PET images with different attenuation correction method were generated in each patient and three ROIs were placed on the lung tumor and normal organs (mediastinum and liver) in each image.   Mean and maximum SUVs, tumor-to-mediastinum and tumor-to-liver ratios (T/M and T/L) and the percentage difference in parameters between 2 PET images (% Diff.) were compared.   **Results:** All measured values except maximum SUV in the liver and tumor-related parameters (SUV in lung tumor, T/M, T/L) showed no significant difference between 2 PET images.   **Conclusion:** The mean measured values showed high reproducibility and demonstrate that follow-up study or measurement of tumor response to anticancer drugs can be undertaken by FDG-PET examination without specifying the particular type of PET scanner.

Key words: PET; PET/CT; reproducibility; standardized uptake value; lung tumor

Running title: Reproducibility of FDG-PET parameters

INTRODUCTION

Positron emission tomography (PET) using 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) is an established diagnostic tool for oncological imaging [1]. The role of PET imaging in clinical oncology and patient care has been expanding; however, PET has poor spatial resolution compared to other conventional morphologic modalities such as CT and MR, and the lack of anatomical landmarks can make the interpretation of PET images difficult. To overcome this problem, several approaches have been evaluated to fuse functional PET images with anatomical images [2], mainly for imaging of the brain and the head and neck [3-5]. The advent of scanners that combine PET and CT has enabled the acquisition of co-registered anatomical and functional images in a single scanning session; the PET/CT images are used both for diagnosing and staging disease and for evaluating the response to therapy [6,7].

Recently, it has become the norm for an institution to have multiple PET scanners; sometimes both PET and PET/CT are placed in the same institution. In evaluating lesions using PET, semi-quantitative parameters such as standardized uptake value (SUV) are commonly applied. In the assessment of therapies using quantitative parameters in PET, reproducibility of the parameters is critically important. SUV is defined as tissue concentration (MBq/mL) divided by activity injected per body weight

(MBq/kg); many authors have discussed multiple factors that affect SUV, such as weight, plasma glucose level, length of uptake period, partial-volume effects, and recovery coefficient [8-12].

Previous studies have expressed concern about the reproducibility of measured values using FDG-PET. Two factors affect the difference between two measured values: one arising from the type of attenuation correction method (CT vs. Germanium-68 or CT tube current) [13-15], and the other from the examination interval [16-19]. Previous reports have evaluated these two factors separately: there are no reports that account for them simultaneously.

In the future, different PET scanners will be used for follow-up studies and measurement of tumor response to treatment in the clinical situation. Before this occurs, it is important to determine whether it is appropriate to use different types of PET scanners interchangeably within the same institution.

In the evaluation of brain lesions, the lesion-to-normal ratio derived from FDG-PET image only was used as a semi-quantitative parameter [19] prior to the introduction of SUV. In the present study, we also sought to assess the reproducibility of this parameter by applying the mediastinum and liver as reference regions. The purpose of this study is to evaluate the reproducibility of semi-quantitative parameters

obtained from two FDG-PET studies using two different PET scanners, and to

determine the appropriate parameters for comparison between the two studies.

MATERIALS AND METHODS

Patients

This study included a total of 45 patients (32 male and 13 female; mean age, 69.5 ± 9.8 years; age range, 46–89 years) with tumors of the lung, with known or suspected malignant lung disease. All patients underwent FDG-PET examination with two different PET scanners in separate days; the examination interval ranged from 1 to 58 days (mean, 14.6 ±11.5 days). The tumor size ranged from 8 to 68 mm in diameter (mean, 30.2 ± 12.8 mm in diameter). The order of two scans with two scanners was randomized; 15 patients underwent PET/CT first and 30 underwent PET first. No treatment interventions were given to the patients between the two scans. Written informed consent was obtained from all patients participating in this study, which was approved by the institutional review board of the University of Fukui Hospital.

Data acquisition

FDG-PET was performed using both a commercial combined PET/CT scanner (Discovery LS, General Electric Medical Systems, Waukesha, WI) and a PET scanner (Advance, GE) in all patients. For both the PET/CT and PET scanners, 35 transaxial images were acquired simultaneously per field of view with an interslice spacing of

4.25 mm. The PET/CT scanner incorporates an integrated 4-slice multidetector CT scanner, which was used for attenuation correction. CT scanning parameters were as follows: Auto mA (upper limit, 40 mA; noise index, 20), 140 kV, 5-mm section thickness, 15-mm table feed, and pitch of 4. For attenuation correction of the PET scanner, the [68]Ge rod source was used.

The same acquisition protocol for the emission scan was used in PET/CT and PET scanner. After at least 4 hours fasting, patients received an intravenous injection of 185 MBq of FDG; image acquisition began 50 min after injection. A whole-body emission scan was performed from the head to the inguinal region with 2 min per bed position (7–8 bed positions). A transmission scan with CT was performed prior to the emission scan with PET/CT scanner. A post-injection transmission scan with [68]Ge rod source following the emission scan was performed for 1 min per bed position in the same area as the emission scan with PET scanner.

Image reconstruction

For PET/CT, the CT images were created with a matrix size of 512 x 512 before being converted to 128 x 128 matrices to correspond to the PET emission images. For PET, segmented attenuation correction (SAC) was used for conventional [68]Ge

correction. The reconstructed ^{68}Ge transmission map was automatically segmented into classes of differing average attenuation and the average attenuation coefficient within each class was substituted for the raw pixel-by-pixel values. These attenuation correction factors were then applied to the emission data, and the attenuation-corrected emission images were reconstructed with ordered-subset expectation maximization (OSEM) iterative reconstruction algorithm (2 iterations, 14 subsets). Reconstructed images were converted to SUV images with the patient's body weight and injected dose of FDG.

In following the above procedure, two different PET images were produced: one representing attenuation correction based on transmission data from the CT (PET/CT image), and the other based on transmission data from the ^{68}Ge (PET/Ge image).

Data analysis

In this study, image co-registration between PET/CT and PET/Ge image was not performed. The closest slice of each image was selected visually and identical regions of interests (ROIs) were placed over the same locations. ROIs were placed on both normal organs and lung tumor; for the normal organs, SUVs were measured in the mediastinum and liver. The shape of ROIs was all circular and their diameters were as

follows: 8 mm for lung tumor, 20 mm for mediastinum, and 60 mm for liver. Both

mean (average of all pixels within the ROI) and maximum (hottest single pixel within

the ROI) SUVs were compared between the two images for each patient. Mean and

maximum tumor-to-mediastinum and tumor-to-liver ratios (T/M and T/L, respectively)

were calculated as image-derived semi-quantitative parameters using the following

equations:

Mean T/M (T/L) = mean SUV in lung tumor / mean SUV in mediastinum (liver)

Maximum T/M (T/L) =

maximum SUV in lung tumor / mean SUV in mediastinum (liver).

Statistical analysis

Results are expressed as mean ± SD. The differences in individual SUVs

between the two images were compared using the paired t-test. $p < 0.05$ was

considered significant. To assess the intrasubject variability of all values including the

systematic difference between the two scanners and the scan order, the percentage of

absolute and signed difference (% Diff._abs, sig) of SUVs, T/M, and T/L were

calculated using the following formula:

% Diff._abs = $|X_1 - X_2|/X_m \times 100$

% Diff._sig = $(X_1 - X_2)/X_m \times 100$

where X_1 is SUV, T/M, and T/L in the PET/Ge or second scan image, X_2 is SUV, T/M, and T/L in the PET/CT or first scan image, and X_m is the mean value of X_1 and X_2. In addition, to estimate the degree of agreement between two different measured values the intraclass correlation coefficient (ICC) was calculated using the following formula: [20]

ICC = (MSBS – MSWS) / {MSBS + $(k$-1)MSWS}

where MSBS and MSWS are the mean sum of squares between and within subjects, respectively. The equation for calculating MSBS and MSWS is $k\sigma_b^2+\sigma_w^2$ and σ_w^2. σ_b^2 and σ_w^2 is the variance between and within subjects and k is the number of within-subject measurements, being 2 in the present study. The ICC is a coefficient of reliability and generalizability that is calculated using variance estimates obtained via an analysis of variance; it is considered to be an average correlation across testers. ICC ranges between 0.00 and 1.00; values closer to 1.00 represent stronger reliability. A lower 95% ICC confidence boundary was also calculated to test the statistical significance of the observed ICC. The equation for calculating lower 95% ICC confidence boundary is $(F_L – 1) / (F_L + 1)$ [21]. F_L is obtained from the following equation with F-test:

F_L = $F_0/F_{1-\alpha/2}$[(n-1), n(k-1)].

F_0 is MSBS/MSWS, and α, n, k is 0.05, 45, 2 in this study.

RESULTS

T/M and T/L values and SUVs are summarized in Table 1 (mean measured values) and Table 2 (maximum measured values), along with p-values.   Except for maximum SUV in the liver and tumor-related parameters (SUV in lung tumor, T/M, T/L), no significant difference was observed between the two images.

A summary of % Diff. and ICC is provided in Table 3 (for mean measured values) and Table 4 (for maximum measured values), along with the 95% confidence interval (95% CI).   All mean measured values demonstrated smaller % Diff._abs and better ICC compared with maximum measured values.   In mean measured values, mean % Diff_sig was less than 5 % although larger % diff_sig between the two scanners were observed in SUVmax, T/M(L)max.

The ICC was significantly positive for all types of measured values, which means that ICC was higher than the lower 95% ICC confidence boundary.

For the evaluation of tumor-related parameters, all patients were divided into two groups according to the examination interval and the ICCs of each group were compared.   One group underwent the two PET examinations with an interval of more than 15 days, while the interval was less than 15 days in the other group.   There was good agreement between the groups, as shown in Table 5; the results were significantly

positive.

DISCUSSION

In the present study, measured semi-quantitative values obtained by different attenuation correction methods and on different days showed significant reliability, although significant difference was observed for some parameters. PET enables direct quantification of lesion radioactivity levels as an alternative to measuring tumor size. SUV, a semi-quantitative parameter commonly used in PET imaging, is also referred to as the dose uptake ratio (DUR), i.e., radioactivity concentration adjusted by body weight and injected dose, and its characteristics, significance, and limitations have been described in several reports [8,22]. Other reports concern the reproducibility of the value measured with FDG-PET. Two factors affect the difference between the two measured values: one arises from differences in the method of attenuation correction, the other from the examination interval. In reports regarding differences between the two different attenuation correction methods [13-15], the differences in the measured values between CT-corrected images and [68]Ge-corrected images were 2.3 % (SUVmean) and 2.1% (SUVmax) in non-osseous lesions[13], and 3.0 ± 8.3 % at 20 MBq/cc of tissue activity in tumorous lesions [14]. Souvatzoglou et al. [15] reported that max and mean SUVs measured with PET and PET/CT showed no significant difference. Studies concerned with differences in examination intervals report high

reproducibility of the measured values; that is, within 1 week to 10 days of the examination interval the approximate average percentage difference for cancerous lesions was 10% [16-18]. The SUVs measured in normal liver and mediastinum in cancer-free patients were stable over time [19]; the % differences of SUVmean and SUVmax between the two studies were also approximately 10%. In these reports, the % difference was calculated as either absolute [13,17,18] or signed difference [16]. As we calculated both absolute and signed difference, we compared our results and there reports.

The results of the present study revealed larger percentage differences for measured values compared with the previous studies stated above. There were two factors in our study that might have caused differences in the measured values: (i) differences in the attenuation correction methods and examination intervals and the additive effect of the percentage difference; and (ii) variation in the study protocol, that is, difference in transmission scan duration. Previous studies reported transmission scan durations with [68]Ge rod source as 3 [13], 4–5 [17,18], and 15 min [16], which are longer than that in the present study. Visvikis et al [23] reported that a larger percentage difference in SUV results from a shorter transmission duration. This may have caused the larger percentage difference in the present study compared with those

of previous reports.

In the present study, significant difference in the measured value was observed for maximum SUV in the liver and tumor-related parameters. Nakamoto et al. [13] also reported significant difference in the measured value between CT- and ^{68}Ge-corrected images in some regions; this difference might arise from the different attenuation correction methods. For patients with lung tumors, significant difference was demonstrated only in the group with a longer examination interval (> 15 days; data not shown). This difference might be explained by the effect of tumor growth.

We also evaluated the reproducibility of the lesion/normal ratio (T/M and T/L) in the present study. This semi-quantitative parameter, which was used for the assessment of brain tumors [24] until the advent of SUV and is still in use, is regarded as a more reliable method than SUV [25]. In whole-body FDG-PET imaging, SUVs measured in normal liver and mediastinum are stable over time [19]; these areas are considered to be good reference regions. In our results, no significant difference was observed in mean T/M and T/L between the images of the two different studies, and the % Diff._abs and ICC values were comparable to that of SUVs in lung tumor. Therefore, it is thought that specifying semi-quantitative parameter will not be required. The difference in maximum T/M and T/L between the two images might reflect the

difference in maximum SUV for lung tumor, as stated above.

Compared with maximum measured value, the % Diff._abs and ICC for mean measured value showed a better trend because it was less affected by statistical noise.

In the assessment of the systematic difference with % signed difference between the two scanners and the scan order, less than 5 % of difference was observed in most parameters, except SUVmax_L and T/M(L)max. This means the systematic difference does not exist regarding with the scanner and scan order.

Regarding the clinical implications of this study, the European Organization for Research and Treatment of Cancer (EORTC) PET study group recommends that reproducibility data for tumor FDG measurement should be collected to assess precisely the level of change that can be measured for follow-up study, if the differences in tumor measurements performed on conventional PET scanners made with no intervening chemotherapy are in the order of 10–20% [11].   In this respect, we consider overall that the differences in SUVs measured in our report using two different devices on separate days are within the permissible range.   Both PET and PET/CT can be used in the clinical situation for follow-up study or measurement of tumor response to anticancer drugs, without specifying a particular type of PET scanner for following-up a certain patient.   Accounting for the % Diff., ICC, and the significance of the two

measured values between PET/Ge and PET/CT images, the present study demonstrates

the high reproducibility of the mean SUV, T/M, and T/L, although the size and shape of

the ROIs require further consideration.

In this study, two PET scanner from the same vendor was used. To extrapolate

our conclusion to other scanners from different vendors, further examination will be

required.

CONCLUSION

In the present study, we assessed the reproducibility of semi-quantitative measured values obtained in two different PET scanners. The mean measured value and lesion/normal ratio showed high reproducibility and demonstrate that follow-up study or measurement of tumor response to anticancer drugs can be undertaken by FDG-PET examination without specifying the type of PET scanner.

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TABLE 1

Mean measured values for PET/Ge and PET/CT

	PET/Ge	PET/CT	p
SUV_T	8.40 ± 4.30	8.22 ± 3.92	0.35
SUV_M	1.67 ± 0.26	1.73 ± 0.25	0.09
SUV_L	2.05 ± 0.30	2.06 ± 0.30	0.77
T/M	5.20 ± 2.89	5.03 ± 2.88	0.20
T/L	4.24 ± 2.33	4.12 ± 2.16	0.29

SUV_T (M, L): mean SUV in lung tumor (mediastinum, liver)

T/M (T/L): lung tumor/mediastinum (/liver) ratio

TABLE 2

Maximum measured values for PET/Ge and PET/CT

	PET/Ge	PET/CT	p
SUVmax_T	11.0 ± 5.03	10.2 ± 4.61	0.02*
SUVmax_M	2.15 ± 0.36	2.08 ± 0.28	0.11
SUVmax_L	2.89 ± 0.46	2.71 ± 0.38	0.004*
T/Mmax	6.43 ± 3.43	5.79 ± 3.37	0.004*
T/Lmax	5.23 ± 2.73	4.87 ± 2.74	0.02*

*$p < 0.05$

SUVmax_T (M, L): maximum SUV in lung tumor (mediastinum, liver)

T/M (T/L)max: maximum T/M (T/L)

TABLE 3

% Diff. and ICC for mean measured values

	% Diff._abs	95% CI	ICC
SUV_T	12.0 ± 10.2	8.93 - 15.2	0.95
SUV_M	11.2 ± 9.91	7.91 - 13.9	0.52
SUV_L	8.85 ± 8.22	6.12 - 11.1	0.67
T/M	11.2 ± 9.91	7.91 - 13.9	0.95
T/L	14.3 ± 11.4	10.9 - 17.8	0.94

	% Diff_sig(scanner)	range	% Diff_sig(order)	range
SUV_T	2.47 ± 15.6	-32.9 - 36.2	3.10 ± 15.5	-32.9 - 36.2
SUV_M	-3.87 ± 14.5	-38.7 - 29.6	0.10 ± 15.0	-38.7 - 32.2
SUV_L	-0.53 ± 12.1	-19.5 - 33.3	0.94 ± 12.1	-19.5 - 33.3
T/M	3.87 ± 14.5	-29.6 - 38.7	-0.72 ± 15.0	-32.2 - 38.7
T/L	2.98 ± 18.1	-37.6 - 49.8	2.17 ± 18.2	-49.8 - 42.8

SUV_T (M, L): mean SUV in lung tumor (mediastinum, liver)

T/M (T/L): lung tumor/mediastinum (/liver) ratio

% Diff_abs: percentage of absolute difference

% Diff_sig (scanner): percentage of signed difference between the two scanners

% Diff_sig (order): percentage of signed difference between the scan order

TABLE 4

% Diff. and ICC for maximum measured values

	% Diff._abs	95% CI	ICC
SUVmax_T	16.1 ± 10.5	13.0 - 19.4	0.93
SUVmax_M	12.1 ± 9.60	8.86 - 14.2	0.47
SUVmax_L	13.0 ± 8.13	10.5 - 15.4	0.48
T/Mmax	19.1 ± 12.3	15.4 - 23.0	0.90
T/Lmax	17.1 ± 12.0	13.5 - 20.9	0.92

	% Diff_sig(scanner)	range	% Diff_sig(order)	range
SUVmax_T	0.90 ± 17.0	-21.5 - 49.3	4.82 ± 18.7	-25.0 - 49.3
SUVmax_M	3.26 ± 15.2	-32.7 - 39.6	4.59 ± 14.9	-32.7 - 39.6
SUVmax_L	6.37 ± 14.1	-26.9 - 36.4	2.97 ± 15.2	-24.2 - 36.4
T/Mmax	12.8 ± 18.9	-23.1 - 54.5	4.13 ± 22.6	-54.5 - 50.1
T/Lmax	9.51 ± 18.7	-30.9 - 60.6	3.92 ± 20.7	-60.6 - 37.9

SUVmax_T (M, L): maximum SUV in lung tumor (mediastinum, liver)

T/M (T/L)max: maximum T/M (T/L)

% Diff_abs: percentage of absolute difference

% Diff_sig (scanner): percentage of signed difference between the two scanners

% Diff_sig (order): percentage of signed difference between the scan order

TABLE 5

ICC for lung tumor accounting for tumor growth

	within 15 days	over 15 days
SUV_T	0.96	0.93
SUVmax_T	0.93	0.93
T/M	0.97	0.93
T/Mmax	0.88	0.80
T/L	0.94	0.92
T/Lmax	0.92	0.92

SUV_T: mean SUV for lung tumor

SUVmax_T: maximum SUV for lung tumor

T/M (T/L): lung tumor/mediastinum (/liver) ratio

T/M (T/L)max: maximum T/M (T/L)