Article Type: Research Article

Internal radiation dose estimation using multiple D-shuttle dosimeters for positron emission tomography (PET): a validation study using NEMA body phantom

By line: Radiation dose estimation in PET study

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Abstract

Purpose: Internal radiation dosimetry plays an important role in ensuring the safe use of positron emission tomography (PET) technology and is a legal requirement in most countries. We propose a new technique to estimate the internal radiation dose in PET studies by means of multiple D-shuttle dosimeters attached on the body surface of the patient.

Methods: Radioactivity in a source organ was estimated iteratively using measurements from multiple D-shuttle dosimeters with a maximum-likelihood expectation-maximization (MLEM) algorithm with dose response from a source to a D-shuttle dosimeter computed by Monte Carlo simulation. To validate our technique, we performed a phantom study using a National Electrical Manufacturers Association (NEMA) body phantom. The fillable compartments (torso cavity and six spheres) of the phantom were filled with ^{18}F-FDG mixed with pure water using an 800:1 sphere-to-background radioactivity concentration ratio. The radioactivity concentrations present in the torso cavity and six spheres were 0.00165 MBq/mL and 1.32 MBq/mL, respectively. The initial radioactivities of the torso cavity and six spheres (treated as source organs) were 15.9 MBq (torso cavity), 34.7 MBq (37 mm sphere), 15.1 MBq (28 mm sphere), 7.27 MBq (22 mm sphere), 3.26 MBq (17 mm sphere), 1.54 MBq (13 mm sphere), and 0.697 MBq (10 mm sphere). Eleven D-shuttle dosimeters were attached to the NEMA body phantom surface to obtain information on body surface dose and a mathematical NEMA body phantom has been modelled in the Heavy Ion Transport Code System (PHITS) Monte Carlo simulation code.

Results: Radioactivity was estimated in two minute intervals over a 110-min total dose time using our proposed technique. A significant correlation ($R^2 = 0.992$) was found between actual radioactivity and estimated radioactivity at every two minute interval for each source organ.

The estimated initial radioactivity (mean with standard deviation) was 16.5 ± 0.311 MBq (torso cavity), 33.0 ± 0.624 MBq (37 mm sphere), 15.7 ± 0.189 MBq (28 mm sphere), 7.11 ± 0.738 MBq (22 mm sphere), 4.17 ± 0.083 MBq (17 mm sphere), 1.48 ± 0.469 MBq (13 mm sphere), and 0.865 ± 0.313 MBq (10 mm sphere), which were very close to the actual initial radioactivity measurements for each source organ.

Conclusions: The phantom study showed that our technique worked successfully. This technique could be used to estimate internal radiation dosimetry in a clinical PET study.

Keywords: Internal radiation dose, D-shuttle dosimeter, PET, Monte Carlo simulation, MLEM algorithm

1. INTRODUCTION

Positron emission tomography (PET) is an important radioisotope imaging modality in nuclear medicine for the diagnosis, prognosis, staging, treatment response monitoring, and radiation therapy planning for a wide range of malignancies[1,2]. A large amount of radioactivity is administrated for the examinee when acquiring functional information on a patient during a PET examination, although the half-life of the radioactivity is very short[2,3]. Because of the harmful effect of ionizing radiation, a patient's radiation exposure is becoming a concerning issue during PET examinations[4]. Internal radiation dosimetry in nuclear medicine is a very important procedure for balancing the potential risks from radiation exposure during a PET examination against its benefits[5]. The Medical Internal Radiation Dose (MIRD) facilitates the problem of assessing internal radiation doses by providing models, methodologies, and schema. The MIRD computational method simplifies the calculation of radiation doses for specified target organs from the cumulative radioactivities in source organs and the so-called S-values from the source organ to the target organ[6]. The source organs are radioactive, and the target organ is the organ in which the dose is calculated, and the target and source organs can be the same organ. The S-value is the radiation dose in the target organ per unit of cumulative radioactivity in the source organ, which can be calculated using an MIRD reference phantom and a Monte Carlo simulation, and the cumulative radioactivity in a source organ is the total number of radioactive decays during the time the source organ is radioactive. For purposes of internal radiation dose calculation, and due to the required computational characteristics, family anthropomorphic mathematical phantoms associated with Monte Carlo simulations have been developed by the Oak Ridge National Laboratory (ORNL), and these phantoms are categorized as MIRD reference phantoms[7,8]. Finally, the radiation dose of the target organ can be estimated from the cumulative radioactivities in the source organs

by using computer software, such as the MIRDOSE software[9], OLINDA/EXM software[10], SPRIND Software [11], Hybrid Dosimetry software[12], etc.

There are a few conventional methods which have been applied to estimate cumulative radioactivities in the source organs of a patient in nuclear medicine. Cumulative radioactivities in source organs have been estimated using the classical tissue dissection method in animal species such as rodents, dogs, rabbits, and non-human primates; these estimates were later extended to humans[13,14,15,16]. After intravenously injecting animal species with a radiopharmaceutical, the animals were euthanized by cervical dislocation at several time points, and the major tissues have been harvested, weighed, and the tissue uptake is calculated as the percent injected dose per gram of tissue (%ID/g). Then, tissue uptake data has been extrapolated to a reference human body phantom using the %kg/gm method to estimate the cumulative radioactivity in human source organs[17] . This conventional ex vivo tissue dissection method requires a large number of animals to obtain cumulative radioactivities in source organs for dosimetry calculation[15,18]. Human data predicted on the basis of animal species data is also inaccurate. The large metabolic differences with respect to the administrated radiopharmaceuticals, interspecies differences in pharmacokinetics, differences in the amount of injected radioactivity, differences in anesthetic protocols, and methodological differences are the primary factors for the resulting inconsistencies between extrapolation from animal data and real human data in internal radiation dosimetry[19,20,21]. In the last decade, a repeated whole body PET imaging method was used to estimate the cumulative radioactivity in the source organ from internally administrated radioactivity in humans and has been widely applied in nuclear medicine[20,22,23]. Whole-body PET images have been reconstructed with attenuation and scattering corrections. Three-dimensional volumes of interest (VOIs) have been manually drawn on multiple slices of PET images, where the

organ is used to form time activity curves (TAC) for calculating cumulative radioactivity in the source organ. Because sophisticated imaging protocols and sufficient data are required to form TACs, a series of whole-body PET scans at different times are required to obtain an internal radiation dosimetry estimation, which is difficult to perform routinely and takes much longer than usual clinical PET studies; this can make the patient uncomfortable [22,24]. Therefore, TAC measurement for estimating cumulative radioactivities in a patient's source organs by repeated whole body PET scans is time consuming and expensive[25].

As an alternative to these aforementioned conventional methods, Matsumoto et al.[5] has proposed a method to estimate internal dosimetry through the external measurements with thermoluminescent dosimeters (TLDs). In this method, a number of TLD are attached to the patient' body surface during a PET study to obtain information on body surface doses, as these doses are connected to cumulative radioactivities in multiple source organs considering gamma ray contributions. The R-matrix (i.e., S-value) is then calculated by a Monte Carlo simulation[26] with an MIRD mathematical phantom. Cumulative radioactivities of the source organs have been estimated by solving the dose-radioactivity equation from the R-matrix and the body surface dose by using the mathematical inverse transform method[27]. Recently Cheng-Chang Lu et al.[25] have proposed an advanced TLD method to obtain TAC data from fractional cumulative radioactivities in a source organ, and they performed validation studies on physical phantoms. In this method, serial body surface dose measurements at different time periods with several sets of TLDs are placed on the body surface and used to estimate the fractional cumulative radioactivities in each organ for each time period using Monte Carlo simulation, a patient-specific dosimetry system (SimDOSE)[28], and the Jacobi linear inverse method. In their validation study, body surface doses have been measured three times at three time periods by using three sets of TLDs. This study is impractical and time consuming.

Because TLD measurements can usually be obtained during a one-hour clinical PET study, cumulative radioactivities have only been estimated for that time period. The contribution of residual cumulative radioactivities for an infinite time period have been extrapolated by assuming that biological excretion and uptake is negligible, and only physical decay dominates. This TLD measurement dose data based on a single time point is not sufficient for estimating realistic cumulative radioactivities in source organs.

Here, we propose a technique for estimating cumulative radioactivity in the source organ of a patient using D-shuttle dosimeters. D-shuttle is a semiconductor dosimeter which has been used for purposes of continuous long-term personal dose monitoring of residents in the area affected by the Fukushima Daiichi nuclear power plant accident in 2011, which was caused by the great east Japan earthquake and tsunami[29,30,31]. A small number of D-shuttle dosimeters will be attached to the patient body surface to obtain dose information from several source organs. Radioactivities in the source organs will be calculated by solving the dose-radioactivity formula iteratively using body surface doses as measured by the D-shuttle dosimeter and R-matrix. We utilized the maximum-likelihood expectation-maximization (MLEM) algorithm[32] to solve the dose-radioactivity formula. Since a D-shuttle dosimeter gives data every two minutes and can be read out by a computer interface[31], the radioactivity in a source organ at two minute intervals can be easily estimated by our proposed technique. The cumulative radioactivity in a source organ then can be calculated from the radioactivity at two minute intervals. Moreover, we can easily obtain sufficient data from the D-shuttle dosimeter measurement during the PET study, and then these data can be extrapolated for the required time period to estimate the residual cumulative radioactivity in the organs.

In the present study, we validate our proposed method using a NEMA body phantom experiment with ^{18}F-FDG PET radiotracer.

2. MATERIALS AND METHODS

2.A. D-shuttle Dosimeter

D-shuttle is a simple, reliable, durable, low-priced, and user friendly personal gamma ray dosimeter which was produced by Chiyoda Technol Corporation, Japan[29,30] (Figure 1). This new dosimetry system includes a Si diode-based dosimeter, a pocket reader, a table reader connectable via USB cable to a PC, and a complementary software application. It is capable of logging the integrated dose every hour in an internal memory with time stamps. Dose measurements (the personal dose equivalent at a depth of 10 mm, $H_p(10)$) can displayed on a computer, and a dedicated workstation displays the dose graphically for easy analysis[31] . One should note that the manufacturer has customized the dosimeter for obtaining sufficient dose data in two minute intervals. Various D-shuttle dosimeter features described by the manufacturer are listed in Table 1[29,30,31]. Z Čemusová et al.[30] tested the dosimetric characteristics of D-shuttle related to Hp(10) measurements, energy dependency, angular dependency, etc., and reported that most of the results were in agreement with the manufacturer's specifications.

2.B. Medical Internal Radiation Dose (MIRD) method

The internal radiation dosimetry formulation has been adopted by the MIRD computational methodology and simplifies radiation dose calculations for specified target organs (Figure 2) [5,6]. Doses due to radioactive decay in source organs are expressed by the following formula:

$$D_i = S_{i,1}.\tilde{A}_1 + S_{i,2}.\tilde{A}_2 + S_{i,3}.\tilde{A}_3 + \cdots$$
$$= \sum_j S_{i,j}.\tilde{A}_j. \quad (1)$$

The cumulative radioactivity in the jth source organ[33] is

$$\tilde{A}_j = \int_0^\infty A(t)\, dt. \quad (2)$$

A(t) is the present radioactivity in the jth source organ, D_i is the radiation dose in the ith target organ, and $S_{i,j}$ is the radiation dose in the ith target organ per unit cumulative radioactivity in the jth source organ. This equation can also be expressed by the following matrix equation:

$$\begin{bmatrix} D_1 \\ D_2 \\ \vdots \\ D_i \end{bmatrix} = \begin{bmatrix} S_{1,1} & S_{1,2} & \cdots & S_{1,j} \\ S_{2,1} & S_{2,2} & \cdots & S_{2,j} \\ \vdots & \vdots & \ddots & \vdots \\ S_{i,1} & S_{i,2} & \cdots & S_{i,j} \end{bmatrix} \begin{bmatrix} \tilde{A}_1 \\ \tilde{A}_2 \\ \vdots \\ \tilde{A}_j \end{bmatrix} \quad (3)$$

2.C. Proposed Technique

A flow chart of our proposed technique for estimating internal radiation dose in PET studies is shown in Figure 3. Replacing the term target organ by the D-shuttle dosimeter position, we proposed a similar technique for estimating cumulative radioactivities in a patient's source organs (Figure 4). The body surface dose at the D-shuttle dosimeter position can be facilitated by the sum of contributions from each source organ and is expressed by

$$d_i(t) = R_{i,1}.A_1(t) + R_{i,2}.A_2(t) + R_{i,3}.A_3(t)$$
$$= \sum_j R_{i,j}.A_j(t). \quad (4)$$

where $d_i(t)$ is the body surface dose at the ith D-shuttle dosimeter position at time *t*, $A_j(t)$ is the radioactivity at time *t* in the jth source organ, and $R_{i,j}$ is radiation dose at the ith D-shuttle dosimeter position per unit cumulative radioactivity in the jth source organ. This equation can also be expressed by the following matrix equation:

$$\begin{bmatrix} d_1(t) \\ d_2(t) \\ \vdots \\ d_i(t) \end{bmatrix} = \begin{bmatrix} R_{1,1} & R_{1,2} & \cdots & R_{1,j} \\ R_{2,1} & R_{2,2} & \cdots & R_{2,j} \\ \vdots & \vdots & \ddots & \vdots \\ R_{i,1} & R_{i,2} & \cdots & R_{i,j} \end{bmatrix} \begin{bmatrix} A_1(t) \\ A_2(t) \\ \vdots \\ A_j(t) \end{bmatrix} \quad (5)$$

The body surface doses at time *t* at the ith D-shuttle dosimeter position $d_i(t)$ can be obtained from the D-shuttle dosimeter attachment on the patient body surface, and $R_{i,j}$ can be calculated by a Monte Carlo simulation. The R-value can be determined based on the photon energy fluence and the mass energy absorption coefficient as expressed by the following formula[34]:

$$R = \Sigma\psi(E)\left(\frac{\mu_{en}(E)}{\rho}\right) \quad (6)$$

$\psi(E)$ is the photon fluence as a function of energy per unit cumulative radioactivity in the source organ, and $\mu_{en}\rho^{-1}$ is the mass energy absorption coefficient. The mass energy absorption coefficient can be taken from the International Commission on Radiation Units and Measurements (ICRU) Report 44 (1989)[35], and the photon fluence can be obtained from a Monte Carlo simulation.

Radioactivity *A(t)* at time *t* in a source organ can be estimated from $R_{i,j}$ values and D-shuttle dosimeter measurements to solve Eq. (4) iteratively using the maximum-likelihood expectation-maximization (MLEM) algorithm. The MLEM algorithm can be expressed by the following equation[32,36].

$$A_j(t)^{(n+1)} = A_j(t)^{(n)} \cdot \frac{1}{\sum_i R_{i,j}} \cdot \sum_i R_{i,j} \cdot \frac{d_i(t)}{\sum_k R_{i,k} \cdot A_k(t)^{(n)}} \quad (7)$$

Analyzing equation (7), the MLEM algorithm can be described in three steps:

(a) Start with an initial estimation of $A_j(t)^{(0)}$, where $A_j(t)^{(0)}>0$ for j = 1, 2, 3…

(b) If $A_j(t)^{(n)}$ denotes the estimate of $A_j(t)$ at the nth iteration, calculate a new $A_j(t)^{(n+1)}$ using Eq. (7)

(c) If the resulting estimation offers an acceptable result then stop. Otherwise, return to (b).

2.D. Phantom Study

To validate our proposed technique, we performed a phantom study to estimate radioactivities in fillable compartments embedded in the NEMA body phantom. This phantom consists of a body phantom, a lung insert, and an insert with six spheres of various diameters (10, 13, 17, 22, 28, and 37 mm) [37]. The fillable compartments (torso cavity and six spheres) of the NEMA body phantom were filled with ^{18}F-FDG mixed with pure water using an 800:1 sphere-to-background radioactivity concentration ratio. Radioactivity concentrations present in the torso cavity and six spheres were 0.00165 MBq/mL and 1.32 MBq/mL, respectively. The lung insert was not used in this experiment. Eleven D-shuttle dosimeters were attached to the NEMA body phantom surface to obtain information on body surface doses (see Figure 5). Another D-shuttle dosimeter was placed inside the experiment room but away from the NEMA body phantom to obtain a natural background radiation measurement.

The inner volume of the torso cavity and each sphere were measured using their weights (filled with water) and wall thicknesses, and the radioactivity concentration of the ^{18}F-FDG PET radiotracer was measured with a dose calibrator (CRC®-55t Well counter, Capintec, inc). The initial radioactivity of the torso cavity and each sphere (treated as source organs) were calculated from the radioactivity concentration and measured inner volumes. Radioactivity was measured for each fillable compartment (torso cavity and six spheres) over the course of 110 min in two minute intervals from their initial radioactivity.

A mathematical NEMA body phantom has been modeled using PHITS (Heavy Ion Transport Code System) Monte Carlo simulation code and was used to compute the R-values in Eq. (4) [37,38,39]. PHITS is a general-purpose Monte Carlo particle transport code written in Fortran, and the recommended compiler is Intel Fortran 11.1 (or, later versions). PHITS was developed under collaboration between the Japan Atomic Energy Agency (JAEA), the

Research Organization for Information and Technology (RIST), the High Energy Accelerator Research Organization (KEK), and several other institutes in Japan. PHITS can deal with the transport of all particles (nucleons, nuclei, mesons, photons, and electrons) over wide energy ranges. D-shuttle dosimeter positions in Cartesian co-ordinates on the body surface of the mathematical NEMA body phantom in PHITS were determined according to the original positions of the D-shuttle dosimeters on the body surface of the NEMA body phantom during the phantom study. We performed a Monte Carlo simulation using 511 keV primary energy, 60 keV-700 keV energy range, 100 energy bins, and 10^7 history number. PHITS simulation yields the photon energy fluence at each D-shuttle dosimeter position for each source organ. We calculated R-values at every D-shuttle dosimeter position for each source organ from the obtained photon energy fluence using Eq. (6).

The radioactivity *A(t)* at each two minute interval in each source organ was estimated using the MLEM algorithm based on body surface doses as measured by D-shuttle dosimeters and the R-values obtained by PHITS simulation. A Python script was used to solve Eq. 7 iteratively. An initial guess of 10^{15} Bq and a total of 50 iterations were used in the MLEM algorithm for estimating the radioactivity in each source organ.

We also investigated the effect of the MLEM algorithmic response by increasing the number of iterations to validate our proposed technique. Hence, the actual cumulative radioactivity in each source organ over a 110-min dose measurement was calculated from the initial radioactivity of each source organ. The cumulative radioactivity from each source organ was estimated over 110 min from the radioactivity values obtained through our proposed technique.

3. RESULTS

3.A. Simulation by PHITS

Computational reconstruction of a NEMA body phantom is presented in Figures 6 and 7. These figures correspond with the experimental set up in this study (see Figure 5). Figure 6 also depicts the eleven D-shuttle dosimeter (D) positions in Cartesian co-ordinates on the mathematical NEMA body phantom. Figure 7 (a) depicts the coronal (XZ plane) view at Y=0 cm in the mathematical phantom where regions 7 through 11 represent the bottom, the superior, the top lid, the phantom wall, the and torso cavity, of the NEMA body phantom, respectively. Figure 7 (b) also depicts the lateral (XY plane) view at Z=13.5 cm in the mathematical phantom, where regions 1 through 6 represent the six spheres with 37 mm, 28 mm, 22 mm, 17 mm, 13 mm, and 10 mm inner diameters, respectively. The color schemes in Figure 7 depict the experimental configuration in PHITS, where red, yellow, and blue colors represent the radioactive sources, background, and polymethylmethacrylate (PMMA) phantom material, respectively. After performing the PHITS simulation, R-values in mGy/MBq.s at eleven D-shuttle dosimeter positions have been calculated from the photon energy fluence and mass energy absorption coefficients by solving the Eq. (6), which are summarized in Table 2.

3.B. Radioactivity Estimation

The actual initial radioactivities of the source organs were 34.7 MBq (37 mm sphere), 15.1 MBq (28 mm sphere), 7.27 MBq (22 mm sphere), 3.26 MBq (17 mm sphere), 1.54 MBq (13 mm sphere), 0.697 MBq (10 mm sphere), and 15.9 MBq (torso cavity). Radioactivity was calculated from the actual initial radioactivity in each source organ at each two-minute interval (see Figure 8). The estimated initial radioactivity (mean with standard deviation,

n=55) with the present technique in each source organ is tabulated in Table 3. The lowest and the highest % CV values (1.21% and 36.2%) were obtained from the 28-mm sphere and 10 mm sphere, respectively. As shown in Figure 8, the regression line was y=0.944x+0.468, and significant correlation (R^2 = 0.992) was found between the actual radioactivity and the estimated radioactivity at each two-minute measurement interval.

The actual and estimated cumulative radioactivities in each source organ were 21.1 MBq.h (torso cavity), 45.9 MBq.h (37 mm sphere), 20.0 MBq.h (28 mm sphere), 9.61 MBq.h (22 mm sphere), 4.31 MBq.h (17 mm sphere), 2.04 MBq.h (13 mm sphere), 0.921 MBq.h (10 mm sphere), and 22.4 MBq.h (torso cavity), 44.2 MBq.h (37 mm sphere), 21.1 MBq.h (28 mm sphere), 9.51 MBq.h (22 mm sphere), 5.57 MBq.h (17 mm sphere), 2.00 MBq.h (13 mm sphere), 1.17 MBq.h (10 mm sphere), respectively. The number of iterations and its effect on the estimated cumulative radioactivity in each source organ are shown in Figure 9. At first, the MLEM output increased with the number of iterations. After a certain iteration (approximately 25), the MLEM results showed a consistent cumulative radioactivity estimation for each source organ.

4. DISCUSSION

We proposed a new technique for estimating the internal radiation dosimetry in PET studies using multiple D-shuttle dosimeters attached on the patient body surface, and we performed a phantom study to validate our new technique by estimating the radioactivities while the fillable compartments were placed in a NEMA body phantom. Although we found some errors in the estimated radioactivity, as high as 28% in the 17 mm sphere and 24% in the 10 mm sphere, the phantom study overall showed a good correlation (R^2=0.992) between the estimated and actual radioactivity, as shown in Figure 8. The average estimated and actual

radioactivities were well-matched in this study (see Table 3). Therefore, the effective dose can be reasonably estimated using our method if we consider the common tissue weighting factor for all seven source organs.

Z Čemusová et al.[30] reported that the $H_p(10)$ measurements showed linear behavior regarding the dose response with the actual dose in the range of 0.12mSv to 121 mSv and dose rate linearity up to 1 mSv/h (Our study was within these ranges). Their study also showed the angular variability of D-shuttle dosimeter. In this study, we omit the angular variability of the D-shuttle dosimeter in the Monte Carlo simulation, assuming a point detector in the center of the D-shuttle dosimeter. Further improvement may be achieved if we include the geometry of the D-shuttle dosimeter in the Monte Carlo simulation. Moreover, the error associated with Monte Carlo simulation is a function of the number of histories and will be propagated to the estimated cumulative radioactivity. By increasing the number of histories in the Monte Carlo simulation, these errors can be reduced, although it requires more computing resources.

H M Deloar et al.[40] has estimated cumulative radioactivities in source organs and internal radiation doses in target organs by the TLD method and conventional whole body PET imaging, and the obtained results from both methods have been compared to validate the TLD method. The obtained TLD results agree with the PET results, except in the pancreas and the heart. In their study, TLD only gives the total dose over a period of time during the experiment, thus they calculated the TLD dose for an infinite time period using the equation below. The following equation assumes that biological excretion and uptake is negligible, and only physical decay dominates.

$$T_k(\infty) = \frac{\int_0^{\infty} e^{-\lambda t}\, dt}{\int_0^{t_0} e^{-\lambda t}\, dt} T_k(t_0) \tag{8}$$

$T_k(\infty)$ is the body surface dose for infinite time at the k'th TLD position, and $T_k(t_0)$ is the body surface dose at the k'th TLD position during the measuring time period t_0. Since the D-shuttle dosimeter gives a TAC, we are able to estimate the cumulative radioactivity in a source organ more precisely. The residual cumulative radioactivity in a source organ can be estimated by extrapolating the measured dose data of the D-shuttle dosimeters during clinical PET study by utilizing a compartment model[41] or using exponential fitting of the TAC[42]. Moreover, their study reported that the obtained cumulative radioactivity in the heart using the TLD method was 2.64 times higher than the results obtained from conventional PET imaging. This large inconsistency was due to a TLD dose response from the heart due to highly concentrated blood radioactivity just after the FDG injection. This radioactivity signal from blood could not be measured using the whole body PET because of the delayed scanning time. Since a D-shuttle dosimeter gives us measurements in two minute intervals during the entire experiment, it is possible to detect the early phase of injected radioactivity that could not be measured in a PET study due to the delayed scanning time.

Their study also reported that the obtained cumulative radioactivity in the pancreas from the TLD method was 1.83 times higher than the result obtained from the conventional PET imaging method. The authors concluded the reasons for this extensive inconsistency were 1) actual individual organ sizes had partially deviated from the MIRD organ sizes with a factor related to individual total weight, and 2) the TLD positions used for measurement of the individual body surface doses during the PET study and their positions used for the R-matrix calculation were different. Actually, the MIRD reference phantoms are mainly established using statistics on Caucasians. But human geometries considering height, weight, organ shape, and volume varies between ethnicities because of diverse dietary habits, lifestyles, and geographic environments. In our phantom study, the mathematical NEMA body

phantom was modelled in Monte Carlo PHITS simulation using the geometry described in IEC standard 61675-1[39] and the data spectrum's NEMA IEC body phantom manual[37]. Therefore, there was no geometric inconsistency between the experimental set up and simulated results by PHITS[38], and D-shuttle dosimeter positions on the surface of a physical NEMA body phantom and their positions on the surface of a mathematical NEMA body phantom used for R-value calculation were the same (see Figures 5, 6, and 7). Hence, we obtained good results in all variants. But the R-value calculation using Formula 6 based on the MIRD reference phantom may produce bias in estimated internal dosimetry due to the mismatch of D-shuttle dosimeter positions and organ geometries if we apply our technique in a real patient. Therefore, a personalized phantom is ideal for estimating realistic internal dosimetry for R-value calculations from the Monte Carlo simulation. Anatomical data can be obtained by performing computed tomography (CT) or magnetic resonance imaging (MRI) measurements, and a voxel phantom based on digital images recorded from CT or MRI is then utilized in PHITS (Heavy Ion Transport Code System) Monte Carlo simulation. Alternatively, we may choose any one of the following procedures if CT or MRI procedures are not available. First procedure: We may redesign the regional reference phantom (Japanese[44], Korean[45], or Taiwanese[46] reference phantom) by modifying the equations of the outer body and the internal organs. The outer body dimensions can be obtained by scaling the measurements of the patient's body. Based on the outer dimensions of the patient's body, we may reconstruct the internal structure of the phantom using the same volumes of the internal organs of the regional phantom. Second procedure: As WAZA-ARI[47] does, we may prepare several voxel phantoms that vary with age, weight, and height. H M Deloar et al.[40] utilized a common mathematical phantom to compute R-values at each TLD position for all six normal volunteers (age 22-56 years) in their study. They found that the highest and lowest inter subject variation

of the absorbed dose estimate were 86% and 8.57%, for the bladder wall and nasal cavity wall, respectively. We may obtain less variable results for the internal radiation doses of a patient in the clinical PET study by modeling the phantom in the Monte Carlo simulation using any of the above-mentioned procedures. It should be noted that PHITS has already been used for various medical applications, such as patient dose estimation for radiotherapy and computed tomography examination[47,48,49].

The number of D-shuttle dosimeters must be greater than the number of source organs to stably estimate cumulative radioactivity. We placed the D-shuttle dosimeters randomly on the surface of the NEMA body phantom and determined the positions of the D-shuttle dosimeter carefully against the source organ, as shown in Figure 5. However, the inaccurate determination of D-shuttle dosimeter positioning on the patient body surface may lead to inaccuracies in internal radiation dosimetry estimation in clinical PET studies. These may be addressed using the following ideas. First: We may use an apron or jacket that will be adjusted with the patient's body. The location of the D-shuttle dosimeters will be marked on the apron or jacket, and then D-shuttle dosimeters will be attached to the identified locations on the apron or jacket. Second: The three-dimensional positions of D-shuttle dosimeters will be determined using an optical tracking system[50].

Matsumoto et al.[5] has used the mathematical inverse transform method (unfolding code SAND -II)[27], which does not consider the statistical features of TLD measurements when estimating cumulative radioactivities in the source organs, and Deloar et a.l[40] reported that this method is highly dependent on the initial guess. Lu et al.[25] has used the Jacobi linear inverse method to estimate the cumulative radioactivities in source organs. The Jacobi method can generally be used for solving a linear system where the coefficient matrix is diagonally dominant. This iterative method works fine with a well-conditioned linear system,

but it will fail to converge for an ill-conditioned linear system. In our proposed technique, the maximum-likelihood expectation-maximization (MLEM) algorithm[32] was used to solve the dose radioactivity formula iteratively. The MLEM algorithm is widely utilized as a PET image reconstruction method as the observed data follows a Poisson distribution. Because a D-shuttle dosimeter counts the number of photons and follows Poisson distributions, the MLEM algorithm is expected to be more stable provide a better internal dosimetry estimate than the unfolding method or the Jacobi method. In this phantom experiment, nine D-shuttle dosimeters were attached to the front side of the phantom, and two D-shuttle dosimeters were attached to the back side of the phantom. Each % CV (see Table 3) was obtained from the estimated radioactivity data in two-minute intervals over a 110-min total dose measurement (n=55), and each estimated radioactivity in a source organ was calculated using data from eleven D-shuttle dosimeters. In general, less bias and % CV value were observed for larger source organs in the present study (see Table 3). Interestingly, the lowest % CV value obtained in this study occurred for the 28 mm sphere, although the 37 mm sphere had the highest radioactivity. Because of the internal radioactivity and geometric dependency, the 28 mm sphere contributed to a larger D-shuttle dosimeter response. The % CV value for the 22 mm sphere was larger than the expected value. This phenomenon may have occurred because the distance from the D-shuttle dosimeters attached the backside of the phantom to the 22 mm sphere was the largest. It is clearly seen in Figure 9 that the estimated result for each source organ was almost consistent after 25 iterations in the MLEM calculations. Further studies are required to determine how many iterations and how many D-shuttle dosimeters will be needed when the MLEM method is applied in a clinical PET study.

In this phantom study, we validated our proposed technique for estimating internal dosimetry in a PET study using ^{18}F-FDG PET radiotracer. Our new technique for

internal dosimetry may be also useful for other nuclear imaging modalities, such as single photon emission computed tomography (SPECT), planar scintigraphy, etc. Generally, PET radiotracers (^{11}C, ^{13}N, ^{15}O, ^{18}F etc.) emit higher energy gamma rays (511 keV). D-shuttle dosimeters were originally intended for use in the Fukushima Daiichi nuclear power plant accident and were optimized to detect 661.7 keV gamma rays emitted from ^{137}Cs, which are close to PET annihilation photon energy of 551 keV. Moreover, Z Čemusová et al.[30] tested the energy dependency of the D-shuttle dosimeter and reported that maximum Hp(10) underestimation of 38% and 40% was detected for radiation qualities of N-150 and N-250, respectively. Therefore, to use our proposed technique on SPECT radiotracers (usually less than 300 keV gamma rays), we may need to optimize the energy response of the D-shuttle.

5. CONCLUSION

In this paper, we proposed a convenient, novel, and non-invasive technique to estimate the internal dosimetry in a PET study using multiple D-shuttle dosimeters attached to the body surface of a patient. To validate our proposed technique, we performed a phantom study using a NEMA body phantom that contained six spherical radioactive sources and background radioactivity. The phantom study showed a good overall correlation between estimated and actual radioactivity.

ACKNOWLEDGMENTS

This study was supported by Grants-in-Aid for Scientific Research No. 16K15342 from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japanese Government.

DISCLOSURE OF CONFLICTS OF INTEREST

The authors have no relevant conflicts of interest to disclose.

REFERENCES

1. Quinn B, Dauer Z, Pandit-Taskar N, Schoder H, Dauer LT. Radiation dosimetry of ^{18}F-FDG PET/CT: Incorporating exam-specific parameters in dose estimates. *BMC Med Imaging*. 2016;16:41.
2. Xie T, Zaidi H. Development of computational pregnant female and fetus models and assessment of radiation dose from positron-emitting tracers. *Eur J Nucl Med Mol Imaging*. 2016;43:2290-2300.
3. Yamaguchi Y, Sasaki T, Onishi S, Baba M. Basic Study on the Estimation of Medical Exposure Dose Using Monte Carlo Simulation. *J Nucl Sci Technol*. 2008;(Supplement 5):p.191-193.
4. Kaushik A, Jaimini A, Tripathi M, et al. Estimation of radiation dose to patients from ^{18}FDG whole body PET/CT investigations using dynamic PET scan protocol. *Indian J Med Res*. 2015;142:pp 721-731.
5. Matsumoto M, Nakamura T, Watabe H, Itoh M, Hatazawa J. Estimation of organ biodistribution and absorbed dose from external measurement with TLDs in PET studies. *Med Biol Eng Comput*. 1993;31:151-156.
6. Bolch WE, Eckerman KF, Sgouros G, Thomas SR. MIRD Pamphlet No. 21: A Generalized Schema for Radiopharmaceutical Dosimetry-Standardization of Nomenclature. *J Nucl Med*. 2009;50:477-484.
7. Snyder WS, Ford RM, Warner GG. MIRD Pamphlet No. 5, revised: Estimates of specific absorbed fractions for photon sources uniformly distributed in various organs of a

heterogeneous phantom. *J Nucl Med*. 1978;40:1-67.

8. Cristy M. Mathematical phantoms representing children of various ages for use in estimates of internal dose. *Oak Ridge Natl Lab*. 1980;Report no.:ORNL/NUREG/TM-367.

9. Stabin MG. MIRDOSE: personal computer software for internal dose assessment in nuclear medicine. *J Nucl Med*. 1996;37:538-546.

10. Stabin MG, Sparks RB, Crowe E. OLINDA/EXM: The Second-Generation Personal Computer Software for Internal Dose Assessment in Nuclear Medicine. *J Nucl Med*. 2005;46:1023-1027.

11. Visser E, Postema E, Boerman O, Visschers J, Oyen W, Corstens F. Software package for integrated data processing for internal dose assessment in nuclear medicine (SPRIND). *Eur J Nucl Med Mol Imaging*. 2007;34:413-421.

12. Mirzaei S, Sohlberg A, Knoll P, Zakavi R, Diemling M. Easy-to-use online software package for internal dose assessment after radionuclide treatment in clinical routine. *Clin Nucl Med*. 2013;38(9):686-690.

13. Toyohara J, Sakata M, Hatano K, et al. Preclinical and first-in-man studies of [^{11}C]CB184 for imaging the 18-kDa translocator protein by positron emission tomography. *Ann Nucl Med*. 2016;30:534-543.

14. Liu S, Vorobyova I, Park R, Conti PS. Biodistribution and Radiation Dosimetry of the Integrin Marker ^{64}Cu-BaBaSar-RGD$_2$ Determined from Whole-Body PET/CT in a Non-human Primate. *Front Phys*. 2017;5:Article 54.

15. Zhou X, Elsinga PH, Khanapur S, Dierckx RAJO, de Vries EFJ, de Jong JR. Radiation Dosimetry of a Novel Adenosine A_{2A}Receptor Radioligand [^{11}C]Preladenant Based on PET/CT Imaging and Ex Vivo Biodistribution in Rats. *Mol Imaging Biol*. 2017;19:289-297.

16. Sakata M, Oda K, Toyohara J, Ishii K, Nariai T, Ishiwata K. Direct comparison of radiation

dosimetry of six PET tracers using human whole-body imaging and murine biodistribution studies. *Ann Nucl Med*. 2013;27:285-296.

17. Kirschner AS, Ice RD, Beierwaltes WH. Radiation dosimetry of ^{131}I-19-iodocholesterol: the pitfalls of using tissue concentration data—reply. J Nucl Med. 1975;16:248–9.

18. McParland BJ. Nuclear medicine radiation dosimetry. In: The biodistribution I—preclinical. Springer. 2010; pp 519-532

19. Zanotti-fregonara P, Innis RB. Suggested pathway to assess radiation safety of ^{11}C-labeled PET tracers for for first-in-human studies. *Eur J Nucl Med Mol Imaging*. 2012;39(3):544-547.

20. Bretin F, Bahri MA, Bernard C, et al. Biodistribution and Radiation Dosimetry for the Novel SV2A Radiotracer [^{18}F]UCB-H: First-in-Human Study. *Mol Imaging Biol*. 2015;17:557-564.

21. Fueger BJ, Czernin J, Hildebrandt I, et al. Impact of animal handling on the results of ^{18}F-FDG PET studies in mice. *J Nucl Med*. 2006;47:999-1006.

22. Garg PK, Lokitz SJ, Nazih R, Garg S. Biodistribution and Radiation Dosimetry of ^{11} C-Nicotine from Whole-Body PET Imaging in Humans. *J Nucl Med*. 2017;58:473-478.

23. Herrmann K, Lapa C, Wester H-J, et al. Biodistribution and Radiation Dosimetry for the Chemokine Receptor CXCR4-Targeting Probe ^{68}Ga-Pentixafor. *J Nucl Med*. 2015;56(3):410-416.

24. Cropley VL, Fujita M, Musachio JL, et al. Whole-body biodistribution and estimation of radiation-absorbed doses of the dopamine D_1 receptor radioligand ^{11}C-NNC 112 in humans. *J Nucl Med*. 2006;47(1):100-104.

25. Lu CC, Dong SL, Lin HH, Ni YC, Jan ML, Chuang KS. Noninvasive measurement of radiopharmaceutical time-activity data using external thermoluminescent dosimeters

(TLDs). *Phys Med Biol*. 2017;62:N58-N72.

26. Yamaguchi Y, Togawa O and Honma T. The VADMAP code to calculate the SAF of photon - code description and the performance -. Japan Atomic Energy Research Institute. 1987; JAERI Report: M87-186.

27. McElroy WN, Berg S, Crockett T and Hawkins RG. A computer-automated iterative method for neutron flux spectra determination by foil activation. Air Force Weapons Laboratory.1967; AFWL-TR-67-41.

28. Chuang KS, Lu JC, Lin HH, et al. Improvements on a patient-specific dose estimation system in nuclear medicine examination. *Radiat Prot Dosimetry*. 2014;158(1):1-7.

29. Naito W, Uesaka M, Kurosawa T, Kuroda Y. Measuring and assessing individual external doses during the rehabilitation phase in Iitate village after the Fukushima Daiichi nuclear power plant accident. *J Radiol Prot*. 2017;37:606-622.

30. Čemusová Z, Ekendahl D, Judas L. Testing of the D-Shuttle personal dosemeter. *Radiat Meas*. 2017;106:214-217.

31. Adachi N, Adamovitch V, Adjovi Y, et al. Measurement and comparison of individual external doses of high-school students living in Japan, France, Poland and Belarus - The “D-shuttle” project -. *J Radiol Prot*. 2016;36:49-66.

32. Gaitanis A, Kontaxakis G, Spyrou G, Panayiotakis G, Tzanakos G. PET image reconstruction: A stopping rule for the MLEM algorithm based on properties of the updating coefficients. *Comput Med Imaging Graph*. 2010;34:131-141.

33. Bevelacqua J J. Health Physics: Radiation-Generating Devices, Characteristics, and Hazards. In: Part VII- Appendix D: Internal Dosimetry. 2016; pp 689-712.

34. Büermann L, Grosswendt B, Kramer HM, et al. Measurement of the x-ray mass energy-absorption coefficient of air using 3 keV to 10 keV synchrotron radiation. *Phys Med Biol*.

2006;51:5125-5150.

35. White DR, Booz J, Griffith RV, Spokas JJ, Wilson IJ. Tissue Substitutes in Radiation Dosimetry and Measurement, the International Commission on Radiation Units and Measurements (ICRU), Report 44. 1989;os23:pages NP.

36. Słomski A, Rudy Z, Bednarski T, et al. 3D PET image reconstruction based on the maximum likelihood estimation method (MLEM) algorithm. *Bio-Algorithms and Med-Systems*. 2014;10(1):1-7.

37. Greer K, Perry T. Data Spectrum's NEMA IEC Body Phantom Set User's Manual. National Electrical Manufacturers Association. 2006, Product ID: PET/IEC-BODY/P, Manual Number: PET/IEC-BODY/UM.

38. Sato T, Iwamoto Y, Hashimoto S, et al. Features of Particle and Heavy Ion Transport code System (PHITS) version 3.02. *J Nucl Sci Technol*. 2018;3131:1-7.

39. Performance Measurements of Positron Emission Tomographs (PETs), National Electrical Manufacturers Association. *NEMA Stand Publ*. 2001; NU 2.

40. Deloar HM, Fujiwara T, Shidahara M, Nakamura T, Yamadera A, Itoh M. Internal absorbed dose estimation by a TLD method for ^{18} F-FDG and comparison with the dose estimates from whole body PET. *Phys Med Biol*. 1999;44:595-606.

41. Watabe H, Ikoma Y, Kimura Y, Naganawa M, Shidahara M. PET kinetic analysis-compartment model. *Ann Nucl Med.* 2006;20(9):583-588.

42. Deloar HM, Fujiwara T, Shidahara M, Nakamura T, Watabe H, et al. Estimation of absorbed dose for 2-[F-18] fluoro-2-deoxy-D-glucose using whole-body positron emission tomography and magnetic resonance imaging. *Eur J Nucl Med*. 1998;25(6):565-574.

43. Cristy M and Eckerman K F. Specific absorbed fractions of energy at various ages from

internal photon sources. *Oak Ridge Natl Lab*. 1987;Report no.: ORNL/TM-8381/V1.

44. Cristy M. Mathematical phantoms for use in reassessment of radiation doses to Japanese atom-bomb survivors. *Oak Ridge Natl Lab*. 1985;Report no.:ORNL/TM-9487.

45. Park S, Lee JK, Lee C. Development of a Korean adult male computational phantom for internal dosimetry calculation. *Radiat Prot Dosimetry*. 2006;121(3):257-264.

46. Chang SJ, Hung SY, Liu YL, Jiang SH. Construction of taiwanese adult reference phantoms for internal dose evaluation. *PLoS One*. 2016;11(9):1-14.

47. Ban N, Takahashi F, Sato K, et al. Development of a Web-Based CT Dose Calculator : WAZA-ARI. *Radiat Prot Dosimetry*. 2011;147(1):333-337.

48. Sato T, Niita K, Matsuda N, et al. Overview of the PHITS code and its application to medical physics. *Prog Nucl Sci Technol*. 2014;4:879-882.

49. Ohta M, Nakao N, Kuribayashi S, Miyashita T, Shigematsu N, Hayashizaki N. Evaluation of radiation exposure in Ir-192 brachytherapy for treatment of keloids. *Energy Procedia*. 2017;131:363-370.

50. S.-K. Woo, H. Watabe, Y. Choi, K. M. Kim, C. C. Park, and P. M. Bloomfield, Sinogram-based motion correction of PET images using optical motion tracking system and list-mode data acquisition. IEEE Trans. Nucl. Sci. 2004; 51(3):782–788.

FIGURE LEGENDS

Figure 1. D-shuttle dosimeters which are capable to record every two-minute dose data in the internal memory and can be later read out by a computer interface.

Figure 2. Concept of the MIRD method. Radiation dose in ith target organ is connected to radioactive decay in each source organ and the so-called S-values from source organ to target organ.

Figure 3. Flow chart of the proposed technique for estimating internal radiation dose in PET studies.

Figure 4. Concept of the proposed technique. The body surface dose at the D-shuttle dosimeter position is connected to gamma decay in each source organ and R-values from the source organ to the D-shuttle dosimeter position.

Figure 5. Experimental set up and eleven D-shuttle dosimeter (D) positions in Cartesian co-ordinates on the surface of a NEMA body phantom for obtaining body surface doses; a) front side of the phantom and b) back side of the phantom.

Figure 6. Simulated mathematical NEMA body phantom with eleven D-shuttle dosimeter (D) positions in Cartesian co-ordinates; a) front side of the phantom and b) back side of the phantom.

Figure 7. a) Coronal view at Y=0 cm and b) lateral view at Z=13.5 cm of the mathematical NEMA body phantom in PHITS; there are six spheres, with inner diameters of 1) 37 mm, 2) 28 mm, 3) 22 mm, 4) 17 mm, 5) 13 mm, and 6) 10 mm.

Figure 8. Correlation between actual radioactivity and estimated radioactivity over 110 min of dose measurements (n=55) in the source organs.

Figure 9. Number of iterations versus the cumulative radioactivity in each source organ.