Internal Dose Estimation of Human Subjects on Intakes of Radiopharmaceuticals in PET studies

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INTRODUCTION

Internal dosimetry resulting from nuclear medicine is important in comparing the benefit of a procedure with its potential risk. A method for the estimation of internal dose due to intake of radioisotopes has been established by the Medical Internal Radiation Dose (MIRD) committee of the Society of Nuclear Medicine. In the MIRD method, the absorbed doses in target organs are estimated from the activities accumulated in source organs. The usual methods for obtaining the cumulated activities are: (i) direct measurements by Positron Emission Tomography (PET) and Single Photon Emission Tomography (SPECT); (ii) extrapolation from animal data; and (iii) calculations based on the mathematical biokinetic model. Among these methods, extrapolation of animal data to humans includes inevitable inaccuracy due to large interspecies metabolic differences with regard to the administered radiochemical. Biokinetic modeling requires adequate knowledge of various kinetic parameters, which is based on some biological assumptions. Direct measurements can provide cumulated activity distributions with fewer biological assumptions. But direct measurements of PET/SPECT are difficult to perform routinely. Since cumulated activity estimation requires the activity measurements of all source organs as a function of time, the repeated dynamic scans take much longer time than the usual clinical study.

In our succeeding studies, a new method has been developed to obtain the cumulated activities of organs of interest through the use of TLDs (1-3). In this TLD method a number of TLDs are placed on the body surface, just above the source organs during the clinical PET study, and the cumulated activities of source organs can be calculated by a mathematical inverse transformation method. Without impeding clinical studies, this method is suitable for calculating the cumulated activities of organs for the administered radiopharmaceutical.

We first investigated the accuracy of this method by calibration studies using a water phantom in which several gamma-ray volume sources containing known activities were arranged to simulate source organs (3). We then applied this method to estimate the organ cumulated activities and absorbed doses of subjects to whom ^{15}O- and ^{11}C-labelled radiopharmaceuticals were administered (2,3,4). We further investigated the accuracy of this TLD method by using the body surface dose measurements with TLDs simultaneously with the whole body PET experiments (5,6) for ^{18}F-FDG injection, on six normal volunteers, since ^{18}F-FDG is one of the most popular and important radiopharmaceuticals used worldwide in clinical study.

MATERIALS AND METHODS

1. Subjects

Six normal volunteers were participated in the ^{18}F-FDG PET study (all male, age: 22 -56 years, average 30 ± 13 years, average weight 64.5 ± 9.9 kg) at the Cyclotron and Radioisotope Center (CYRIC), Tohoku University. None of them had a prior history of any major physical illness. Body surface dose measurements with TLDs were done simultaneously with the PET study. All volunteers were asked to refrain from eating and drinking for 4 hrs before the PET study. All subjects gave their written consent and the Ethics Committee for Clinical Radioisotope Research of Tohoku University approved the study protocol.

The measurements of body-surface doses with TLDs were also done in clinical PET studies using ^{11}C-Doxepin, ^{11}C-Benzotropin and ^{11}C-YM09151-2. For each of these three radiopharmaceuticals the subjects were four normal volunteers, twelve subjects in total (all male, age 22 to 56 years, average age 30 ± 13 years, average weight 60 ± 5 kg).

During successive continuous inhalation of O-15 labeled gases ($C^{15}O_2$, $^{15}O_2$ and $C^{15}O_2$), two independent studies were carried out to estimate radiation doses. One study measured the percentage uptake of inhaled gases; the other estimated the body surface doses with TLDs. The uptake percentage measurements were done on 10 subjects and body surface doses were measured on another 7 subjects. The ages of the subjects were 13 to 30 years. The flow rates were 370 to 740 MBq/min for $C^{15}O_2$ and $^{15}O_2$ and 259 to 481 MBq/min for $C^{15}O$, and the rates were controlled by a radio gas controller (Hokusan, Ltd., Japan). The subjects inhaled the gases sequentially (first; $C^{15}O_2$, second; $^{15}O_2$ and third; $C^{15}O$) under their own control. The inhalation periods for $C^{15}O_2$ and $^{15}O_2$ were 10 to 15 minutes and for $C^{15}O$ was 2 to 5 minutes. For the measurements of the body surface doses with TLDs, five subjects were adult and two were (13 years old) children.

2. Whole body PET and body surface dose measurements with TLD

Body surface dose measurements by TLDs were done during the PET study with a whole body PET scanner (SET-2400W, Shimadzu Co. Ltd., Kyoto, Japan) at CYRIC. The scanner provides 63 continuous transaxial slices with a resolution of 3.9 mm FWHM in the plane and 4.5 mm axially. The transaxial field of view is 59 cm and the axial field of view is 20 cm.

Whole body transmission scans at nine positions were performed with a ^{68}Ge rod source for attenuation correction of the emission data. Nine bed positions covered the length of 168.5 cm. The duration of scan at each position was 4 min. After the transmission scan, the TLDs were placed on the body surface near the source organs. These organs are the brain, thyroid, heart, lung, liver, spleen, kidney, pancreas and the bladder. After bolus injection of ^{18}F-FDG three repeated whole body emission scans were performed. Whole body emission scan at nine positions covered the length of the whole body and the duration of scan in each position was 3 min. The average injected dose was 120 MBq (from 78 MBq to 196 MBq). After the last emission scan the TLDs were removed from the body surface and TLD doses were measured by a TLD reader (Panasonic-UD-512P).

For four normal volunteers clinically treated with ^{11}C-labeled Doxepin, YM09151-2 and Benzotropin, the injected activities and the TLD attachment periods of Doxepin were 270 to 490 MBq and 91 to 96 min, those of YM09151-2 were 350 to 530 MBq and 70 to 95 min, and those of Benzotropin were 360 to 760 MBq and 86 to 98 min, respectively.

3. Basic theory of TLD method

In the MIRD method, the absorbed dose in a target organ is expressed by the sum of contributions from several source organs, as follows,

$$D_i = \sum_j S(i \leftarrow j)\tilde{A}_j = \sum_j S_{i,j}\tilde{A}_j \qquad (1)$$

where D_i is the absorbed dose in the i-th target organ, $\tilde{A}_j$ is the cumulated activity in the j-th source organ, and $S_{i,j}$ is the absorbed dose in the i-th target organ per unit cumulated activity in the j-th source organ, which means the transmission fraction of radiation.

In our new TLD method, the term "target organ" is replaced by the term "TLD position", as follows,

$$C_i = \sum_j R_{i,j} X_j \qquad (2)$$

where C_i is the absorbed dose in the i-th TLD position, X_j is the integrated activity in the j-th source organ during the TLD attachment on the body surface, and $R_{i,j}$ is the absorbed dose at the i-th TLD position per unit cumulated activity in the j-th source organ. The $\boldsymbol{C}$ vector can be obtained by the TLD measurements, and the $\boldsymbol{R}$ matrix can be calculated by using the MIRD mathematical phantom (7) and the VADMAP code (8) based on the point kernel method, so that one can obtain the $\boldsymbol{X}$ vector by performing the inverse transform of the above matrix equation with the unfolding technique.

4. Estimation of cumulated activity by unfolding

From the measured body-surface doses (the component of the $\boldsymbol{C}$ vector) and the calculated response of the body-surface dose at each position per unit cumulated activities (the component of the $\boldsymbol{R}$ matrix), cumulated activities in source organs can be estimated by the slightly modified SAND-2 unfolding code (9) based on the successive iterative method. This unfolding method starts from the initial guess values and the unfolded results are influenced by the initial guess values. In order to investigate the effect of the initial guess, three types of initial guess were considered. The first guess is selected to be equal to the results obtained from the whole body PET, which is probably the most accurate guess. The second guess is a uniform distribution assuming that the activity concentration is uniform throughout the body, which is generally used in the absence of a-priori information. In the third case the SAND-2 unfolding is repeated twice. In the first unfolding the initial guess is set to be uniform as in the second case, and the repeated unfolding starts with the initial guess of the first unfolding results.

This calculation proceeds under the constraint condition that the sum of cumulated activity in each source organ must be equal to the total accumulation of administered activity, such as

$$X_{total} = X_1 + X_2 + X_3 + \ldots = \int_0^t A_0 e^{-\lambda t} dt = \frac{A_0}{\lambda}(1 - e^{-\lambda t}) \qquad (3)$$

where A_0 is the injected activity, λ is the decay constant of radionuclide, and t is the measuring time period.

TLD measurements could be done only during the usual 1 h course of a clinical PET procedure, although it is desirable to carry TLDs on subjects during at least three half-lives of the radiotracer. Therefore the estimation of the cumulated activities was obtained only for that 1 h period. The contribution of residual cumulated activities after the TLD measurement can be estimated, assuming that biological clearance is negligible and only physical decay dominates, by the use of the following parameter,

$$\tilde{A}_i(\infty) = X_i(t)\frac{\int_0^\infty e^{-\lambda t}dt}{\int_0^t e^{-\lambda t}dt} \qquad (4)$$

This assumption which was introduced owing to limited biological disappearance data results in a conservative dose estimate. It is noted that the bladder activity is not applicable to Eq.(4) because patients urinate immediately after TLD (or PET) measurements. We therefore estimated that the cumulated activity of the bladder, $\tilde{A}_{bladder}(\infty)$, is equal to the integrated activity for measuring time, $X_{bladder}(t)$, with the assumption that the radiopharmaceutical is no longer accumulated in the bladder after urination.

5. Measurement of activity concentrations of the organs using whole body PET

The organs having a higher uptake of ^{18}F-FDG were considered as the source organs in this study. These organs are brain, heart, lung, liver, spleen, kidney, pancreas, bladder and the remainder of the body. ROI analysis was carried out with a built-in PET image analysis software running on a workstation. The radioactivities in the organs were obtained as cps/ml (counts per second per unit of volume) from reconstructed PET images by averaging the activities of several ROIs in one organ with attenuation correction of the emission data. To obtain quantitative radioactivity data for every clinical session the PET system was calibrated by doing the phantom experiment including ^{18}F-FDG solution of known radioactivity. Thus, the pixel counts of PET image in cps/ml could be converted to activity concentration as MBq/ml.

The actual cumulated activities of nine source organs were obtained from the time-activity curves by fitting which has been described in our previous studies(6,10). The activity remaining in the organ after the last measurement is also assumed to decrease only by physical decay as in Eq. (4).

6. TLD dose

The TLDs used in this study are BeO (Matsushita Electric Co. Ltd., Osaka, Japan). Since the *R* matrix calculation procedure by the VADMAP code is independent of energy, the TLD sensitivity to photons for the body surface dose measurement should also be independent of energy. Therefore, we selected BeO which is almost independent of photon energy.

Before the intravenous injection of ^{18}F-FDG, ^{11}C-Doxepin, ^{11}C-Benzotropin and ^{11}C-YM09151-2, the TLDs were placed on the body surface at nine positions close to the centers of the above nine source organs to measure the body surface dose at those positions during the PET study. At each TLD position a set of five TLDs were placed under the directions of the medical doctors to get the average dose. The TLDs were attached directly to the skin surface with adhesive tape under the clothes and on the bladder, since the TLDs are much influenced by geometrical ambiguities such as air gaps. The coordinates of the positions for adults were calculated from the MIRD phantom and the TLD positions are shown as Cartesian coordinates together with nearby source organs in Fig. 1, although the thyroid is not targeted as a source organ. The remainder of the body was treated as a single source organ in which the activity was uniformly distributed.

For ^{15}O-labeled gas inhalation study, the TLDs were placed on the body surface at eleven positions close to the previous source organs and the two new source organs, nasal cavity and major airway. Among the TLD positions, the positions near the brain, nasal cavity, thyroid and upper respiratory tract are very close to the face gas mask. These TLDs receive a remarkable amount of background radiation from the gas mask. Hence, the body surface doses obtained by these TLDs are the doses due to the internal radiation transmitted through the body from the source organs and the external background radiation from the gas mask, inlet and outlet pipes. The estimation and subtraction of external background radiation is important in obtaining the real body surface dose due to the internal radiation. Practically the background subtraction is very difficult and we have done it by simulation described in our previous paper (2).

When the TLD dose at the j-th TLD position during the total inhalation period for these three gases is $C_{t,j}$, the TLD dose at the j-th position for individual gas flow (either CO_2 or O_2, or CO) can be given by the following equation:

$$C_{g,j}(t) = \frac{fA_g}{A_0} \times C_{t,j} \quad (5)$$

where g is a variable for CO_2, O_2 and CO; A_g is the corresponding supplied activity; A_0 is the total activity of three gases; fA_g is the absorbed activity of the g-th gas; and f is the percentage uptake. The internal dose on the body surface of the j-th TLD due to a single g-th gas supply can be calculated as follows:

$$T_{g,j}(t) = C_{g,j}(t) - C_{g,j}(bg) \quad (6)$$

where $C_{g,j}(bg)$ is the external background dose.

7 Absorbed dose calculations

By using the cumulated activities $\tilde{A}$ thus obtained, absorbed doses in target organs, D, can be calculated by the MIRD method from Eq.(1). The **S** matrix in Eq.(1) consists of the component of penetrating radiation (gamma ray) and that of non-penetrating radiation (positron particles). The gamma-ray component was calculated by the VADMAP code, in just the same way as in the calculation of the **R** matrix, for nine source organs for intravenous injection, and two additional source organs, nasal cavity and major airway, for continuous inhalation. For the non-penetrating radiation component, the positron energy emitted in an organ is assumed to be fully absorbed in this organ, i.e., the self absorption is unity and the contribution to other target organs is zero, with the exception, to be on the safe side, that the positron energies emitted in the heart or bladder contents are absorbed entirely in the organ walls. The self doses due to positrons in eight organs, i.e., brain, heart, lung, liver, kidney, spleen, pancreas and bladder, can easily be calculated as the cumulated activities are already known. As for other organs contained in the rest of the body, we considered that cumulated activity in an organ and that in the remainder were proportional to their volume, because the concentration in the rest of the body was assumed to be uniform.

According to ICRP 60 (11), the effective dose was calculated from the following formula

$$H_E = \sum_i w_i H_i = \sum_i w_i D_i Q = \sum_i w_i D_i \quad (7)$$

where H_i is the dose equivalent of the i-th target organ, D_i is the absorbed dose of i-th target organ, Q is the quality factor (Q =1 for β and γ-rays) and w_i is the tissue weighting factor. To calculate the effective dose, in ICRP 60, the colon includes only LLI (Lower Large Intestine). According to the suggestion of Zankle and Drexler (12), we defined the colon as both LLI and ULI (Upper Large Intestine) and its weighting factor was divided equally on ULI and LLI. An equal tissue weighting factor was applied for all target organs in the remainder of the body.

RESULTS AND DISCUSSIONS

1. ^{18}F-FDG

(1)Cumulated activities of source organs

The mean cumulated activities of six subjects, obtained by the TLD method with the initial guesses resolved from the whole body PET values, are shown in Table 1 and compared with the reference cumulated activities directly obtained from the whole body PET. The effect of three types of initial guesses on the cumulated activities is shown in Fig. 2 with the reference cumulated activities obtained from the whole body PET (A). The initial guesses were the initial guess from PET (B), the uniform initial guess considering the uniform radioactivity distribution throughout the body (C) and the initial guess of the results unfolded with uniform initial guess (D) as described before.

In Table 1, the mean cumulated activities of the source organs for six subjects obtained by the TLD method and whole body PET agree well within around 90% except for the results of the pancreas and the heart. In the TLD method, the R-matrix was obtained simply by correcting the MIRD organ sizes with a factor related to individual total weight as given by Yamaguchi (13), however actual individual organ sizes may practically deviate from organ sizes corrected in this manner. It may also happen that the TLD positions used to measure the individual body surface doses and those positions used for calculation of R matrices are different. All these effects introduce some variations between the results of the TLD method and whole body PET, especially for small source organs. The cumulated activity of the heart in the PET study (Table 1) is 2.6 times lower than the result obtained by the TLD method. The reason for this big difference is not clear, but may be partly due to some contribution to the TLD dose from the highly concentrated blood activity through the heart just after the FDG injection which could not be measured by the whole body PET owing to the delayed scanning time.

It is clearly seen that the cumulated activities obtained with the initial guess from the PET data, (B), give the best fit to the direct PET data, compared with other two initial guesses, (C) and (D). The TLD results for the initial guess (D) show better agreement with the PET results than for the initial guess (C).

For radiopharmaceuticals with known organ biodistribution of cumulated activities, the initial guess

for unfolding with the TLD data must be adjusted to that of a-priori values. But for new radiopharmaceuticals this study shows that the unfolding should be performed twice; the first unfolding with the uniform initial guess and second unfolding with the initial guess of results of the first unfolding, and that results thus-obtained will provide the agreement with the PET reference results within about 15% difference for organs of higher cumulated activities and within a factor of 1.6 for organs (pancreas) of lower activity. Even when we perform only one unfolding with the uniform initial guess, however, we can get comparatively good results to within about 40% difference for highly accumulating organs.

(2) Absorbed doses in target organs

The mean absorbed doses to some major organs with their standard deviations for six subjects are shown in Table 2. These results are compared with the data published in ICRP 53 (14). In the TLD method the target organs receiving the highest absorbed doses are bladder wall, brain and kidney; those values are 3.7×10^{-1}, 4.1×10^{-2} and 2.6×10^{-2} mGy/MBq, respectively, in this descending order.

The mean absorbed doses for six individuals (Table 2) obtained from the TLD method with an initial guess from PET (B) and whole body PET show good agreement with each other. The TLD results agree with the PET results to within 20%, except for the pancreas and heart wall, similarly as in the previous section. Our results are also compared with the ICRP 53 results. Our TLD results are higher by a factor of 2.2 for bladder, 1.6 for liver, 1.7 for lung, 3 for pancreas and 1.6 times for brain, but lower (0.5) for heart wall than the ICRP 53 data. For other organs, both results agree to within about 30%. The ICRP-53 data are summarized from the reported values extrapolated from animal data except for brain and bladder. These underestimated results in ICRP-53 may be partly attributed to the metabolic difference between humans and animals.

2. ^{11}C-labeled radiotracers

(1) Cumulated activities in source organs

Figure 3 shows the cumulated activities as kBq h per 1MBq injection of ^{11}C-labeled YM09151-2 in nine source organs averaged for all subjects with standard deviations, as an example. In the figure the TLD result only in brain is compared with the PET result. This comparison reveals that the cumulated activity estimated with the TLD method again gives rather good agreement with that estimated with PET. From the obtained results, it is found that the lungs and the remainder of the body accumulate much of the radioactivity, and the cumulated activities of these two organs are higher for Doxepin, Benzotropin and YM09151-2 in this descending order. The cumulated activity in the brain for Doxepin is about twice that for YM09151-2 and Benzotropin, and for other organs the cumulated activities have similar values for these three radiopharmaceuticals, excluding a slightly higher value in bladder for YM09151-2.

(2) Absorbed dose

The results averaged for all subjects are given as mGy per 1MBq injection in Table 3 for ^{11}C-YM09151-2 as an example, with standard deviations in parenthesis. No other comparative data exist for these ^{11}C labeled radiopharmaceuticals. The table gives that the target organs which receive the higher absorbed doses are pancreas, spleen, kidney and heart wall in this descending order.

From the obtained results, the effective doses for intakes of ^{11}C-Methionine, ^{11}C-Doxepin, ^{11}C-YM09151-2 and ^{11}C-Benzotropin are 5.0×10^{-3}, 6.92×10^{-3}, 7.08×10^{-3} and 7.65×10^{-3} mSv MBq^{-1}, respectively.

3. O-15 labeled gases

(1) Uptake fractions of O-15 labeled gases

The $C^{15}O_2$, $^{15}O_2$ and $C^{15}O$ gases produced from the AVF cyclotron at CYRIC were supplied to the subjects for inhalation through the mask under their own control. To measure the activity of the outlet gas, a collimated NaI(Tl) scintillation detector and a gas flow meter were placed along the outlet pipe. During the PET study, the outlet flow rate due to exhalation and the corresponding activity were measured with these instruments. The inhalation rate of the gas was considered to be equal to the flow rate from the controller. The difference between the radioactivities of the supply gas and outlet gas measured with the NaI(Tl) detector gave the uptake ratio of the inhaled gas. The average percentages of uptake for $C^{15}O_2$, $^{15}O_2$ and $C^{15}O$ gases were given as 68 ± 6%, 54 ± 8% and 72 ± 7%, respectively.

(2) Cumulated activities of source organs

Using the body surface dose measured by TLDs and the unfolding technique, the mean cumulated activities of 11 source organs due to uptake of O_2, CO_2 and CO for two 13 year-old and five adult subjects are shown in Table 4 together with their standard deviations. The highest accumulation organs are the remainder of the body, lung and heart content, in descending order, both for the 13 year-old and adult subjects. For CO_2 and CO, the next high accumulation organs in adults are liver, brain and major airway content, whereas for O_2, those

organs are the liver, major airway content and brain. In the 13 year-old subjects, for all three gases, the next highest accumulation organ is the major airway content, and the nasal cavity, liver and brain have almost the same accumulation. For adults, the accumulation of the ^{15}O radioactivities to lung, brain and heart is higher than that for the 13 year-old subjects, whereas for the major airway it is the reverse.

(3) Absorbed dose

The absorbed dose estimates in the 23 target organs due to uptake of O_2 gas are shown in Table 5, as an example. Our results are compared with the values reported by ICRP 53 (14). As the ICRP report does not give the absorbed doses for 13 year-old subjects, we interpolated those values from the data for 10 and 15 year-old children.

Among the target organs, the nasal cavity and major airway receive highest absorbed doses and these doses in decending order are CO_2, CO and O_2. For all gases, the critical organs are the nasal cavity and major airway, which includes the pharynx, larynx and trachea. For all gases, the next highest absorbed dose is in the lung both for 13 year-old children and adult subjects. The ICRP doses of lung for O_2 and CO are close to our estimated dose for both 13 year-old and adult subjects, but for CO_2, our result is about 4 times higher than the dose reported by ICRP. Our result for the heart dose for O_2 is very close to the ICRP value, whereas for CO, our result is about 4 times lower than the ICRP value, both for 13 year-old and adult subjects. The doses to pancreas, kidney and spleen in this study are much higher than the ICRP values for all gases, although their cumulated activities show a good agreement. The pancreas is a small organ and lies between liver and spleen; thus it receives the dose from these two larger organs in addition to its own dose, which contributes to the higher total dose. The doses of the other target (non source) organs were estimated from the cumulated activity of the remainder of the body, considering their mass proportion, and are relatively lower than those of the 10 source organs. The doses of those organs in this study agree with the ICRP reported values within a factor of 2.

The effective doses of $C^{15}O_2$, $^{15}O_2$ and $C^{15}O$ gas inhalation studies are 7.33×10^{-4}, 6.60×10^{-4}, 6.14×10^{-4} mSv MBq^{-1} for adults and 1.26×10^{-3}, 1.02×10^{-3}, 1.21×10^{-3} mSv MBq^{-1} for 13 year-old children, respectively. The effective doses for children are about 50 to 100% higher than for adults.

CONCLUSION

It can be concluded from these results that the new TLD method for estimating organ cumulated activities in humans from the surface dose measured with TLDs gives sufficiently good results considering experimental errors. This TLD method has great advantages, in that cumulated activities in several human organs can easily be estimated, in contrast with the PET study that requires many procedures to estimate biodistribution, and that the TLD measurements can be done simultaneously with medical study without interrupting it. After the body surface dose measurement of a subject, the dose of the target organs can be calculated with a good accuracy within a very short time (4 hrs), whereas PET and its associated procedures required a relatively longer time (several days). Thus, this method would be useful for estimating the personal dose from medical procedures because of the easy handling of TLDs.

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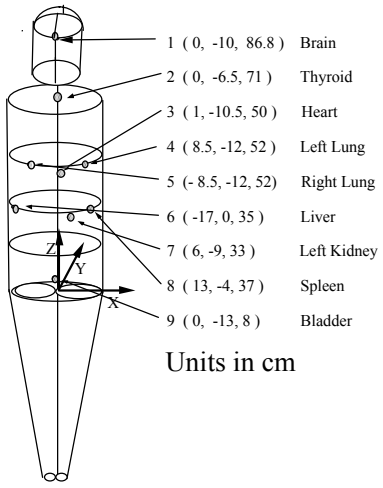

Figure 1. TLD position on the body surface near to the source organs on an adult MIRD phantom with the Cartesian coordinate

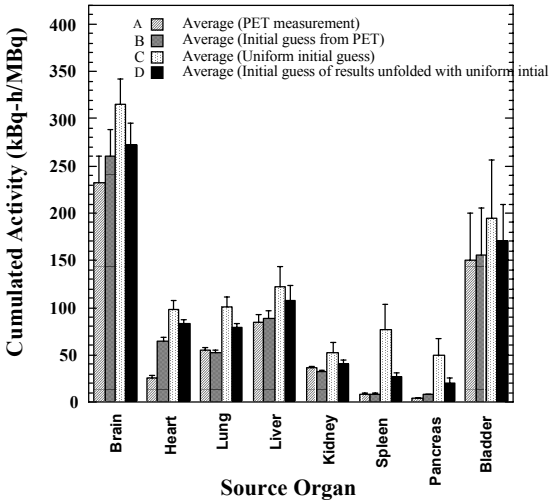

Figure 2. Average cumulated activities of source organs for ^{18}F-FDG injection obtained from the TLD method for three initial guesses of (B) initial guess from PET, (C) uniform initial guess, (D) initial guess from the unfolded results of uniform initial guess and comparison with the results of whole body PET(A).

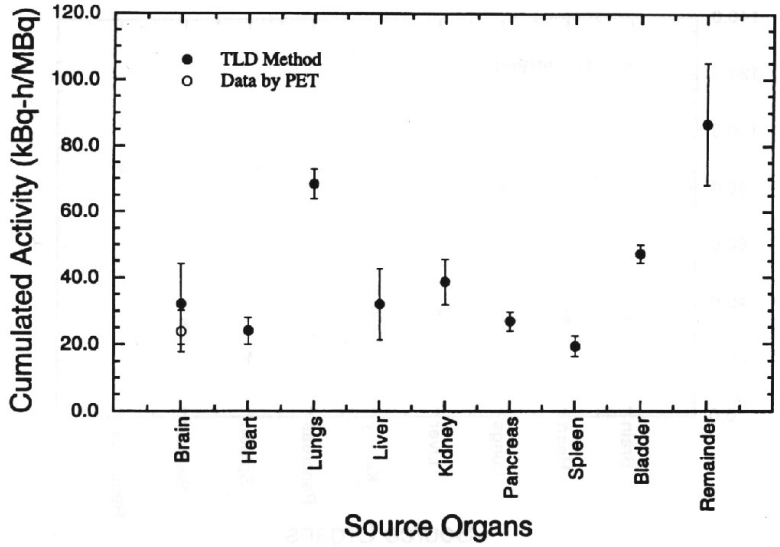

Figure 3 Average cumulated activities of source organs for ^{11}C-YM09151-2 obtained from the TLD method and comparison with the PET result only for brain

Table 1. Average (for six subjects) cumulated activities (kBq-hr MBq^{-1}) of the source organs with standard deviation obtained by the TLD method and whole body PET

Source Organs	*Average TLD*	*Average PET*	*TLD/PET*	*Source Organs*	*Average TLD*	*Average PET*	*TLD/PET*
Brain	260±29	230±40	1.13	Spleen	8.4±2	7.9±3	1.06
Heart	65±4	25±7	2.64	Pancreas	7.5±2.7	4.1±3	1.83
Lung	52±4	55±8	0.95	Bladder	156±49	151±39	1.03
Liver	88±10	84±16	1.05	Remainder of the body	1966±46	1975±97	1.00
Kidney	32±4	36±19	0.89				

Table 2. Absorbed dose estimates (mGy MBq^{-1}) (mean ± standard deviation) to the target organs in this study and compared with ICRP 53 (11).

Target Organs	*TLD method**	*Whole Body PET*	*TLD/PET*	*ICRP 53*
Adrenal	$1.4\times10^{-2}\pm2.0\times10^{-3}$	$1.6\times10^{-2}\pm2.8\times10^{-3}$	0.88	1.4×10^{-2}
Major Airway (wall)	$1.9\times10^{-2}\pm2.2\times10^{-3}$	$2.2\times10^{-2}\pm3.5\times10^{-3}$	0.86	
Nasal Cavity (wall)	$2.1\times10^{-2}\pm1.8\times10^{-3}$	$2.2\times10^{-2}\pm2.8\times10^{-3}$	0.95	
Bladder (wall)	$3.7\times10^{-1}\pm3.2\times10^{-1}$	$3.1\times10^{-1}\pm1.8\times10^{-1}$	1.19	1.7×10^{-1}
Stomach (wall)	$1.4\times10^{-2}\pm1.8\times10^{-3}$	$1.2\times10^{-2}\pm1.2\times10^{-3}$	1.17	1.2×10^{-2}
Small Intestine	$1.4\times10^{-2}\pm1.9\times10^{-3}$	$1.5\times10^{-2}\pm2.1\times10^{-3}$	0.93	1.3×10^{-2}
ULI (wall)	$1.4\times10^{-2}\pm1.9\times10^{-3}$	$1.5\times10^{-2}\pm2.4\times10^{-3}$	0.93	1.3×10^{-2}
LLI (wall)	$1.4\times10^{-2}\pm1.9\times10^{-3}$	$1.5\times10^{-2}\pm2.2\times10^{-3}$	0.93	1.6×10^{-2}
Kidney	$2.6\times10^{-2}\pm5.2\times10^{-3}$	$2.8\times10^{-2}\pm8.9\times10^{-3}$	0.93	2.1×10^{-2}
Liver	$1.9\times10^{-2}\pm3.7\times10^{-3}$	$1.8\times10^{-2}\pm4.5\times10^{-3}$	1.06	1.2×10^{-2}
Lung	$1.9\times10^{-2}\pm4.3\times10^{-3}$	$1.8\times10^{-2}\pm1.6\times10^{-3}$	1.06	1.1×10^{-2}
Pancreas	$3.6\times10^{-2}\pm1.8\times10^{-2}$	$2.6\times10^{-2}\pm2.3\times10^{-2}$	1.38	1.2×10^{-2}
Spleen	$1.6\times10^{-2}\pm3.8\times10^{-3}$	$1.4\times10^{-2}\pm2.1\times10^{-3}$	1.14	1.2×10^{-2}
Testes	$1.4\times10^{-2}\pm1.9\times10^{-3}$	$1.5\times10^{-2}\pm2.2\times10^{-3}$	0.93	1.5×10^{-2}
Thymus	$1.3\times10^{-2}\pm1.8\times10^{-3}$	$1.2\times10^{-2}\pm1.6\times10^{-3}$	1.08	
Thyroid	$1.3\times10^{-2}\pm1.6\times10^{-3}$	$1.3\times10^{-2}\pm2.4\times10^{-3}$	1.00	9.7×10^{-3}
Breast	$1.0\times10^{-2}\pm1.4\times10^{-3}$	$1.0\times10^{-2}\pm1.3\times10^{-3}$	1.00	
Brain	$4.1\times10^{-2}\pm6.1\times10^{-3}$	$3.7\times10^{-2}\pm3.0\times10^{-3}$	1.11	2.6×10^{-2}
Heart Wall	$3.2\times10^{-2}\pm1.1\times10^{-2}$	$1.7\times10^{-2}\pm5.4\times10^{-3}$	1.88	6.5×10^{-2}
Red Marrow	$5.7\times10^{-3}\pm5.5\times10^{-4}$	$5.6\times10^{-3}\pm7.7\times10^{-4}$	1.02	1.1×10^{-2}
Bone Surface	$8.0\times10^{-3}\pm8.4\times10^{-4}$	$8.0\times10^{-3}\pm1.0\times10^{-3}$	1.00	1.0×10^{-2}
ED (mSv/MBq)	$3.2\times10^{-2}\pm1.7\times10^{-2}$	$2.9\times10^{-2}\pm9.2\times10^{-3}$	1.10	2.7×10^{-2}

ED=effective dose; ULI=upper large intestine; LLI=lower large intestine

* the data with initial guess from PET

Table 3. Absorbed doses in target organs and effective dose with standard deviations in parenthesis for 1MBq injection of ^{11}C-YM09151-2 obtained from the TLD method.

Target Organ	*Absorbed Dose (mGy/MBq)*	*Standard Deviation*
Adrenal	4.34×10^{-3}	(0.063)
Bladder	2.30×10^{-2}	(0.515)
Stomach (wall)	3.33×10^{-3}	(0.078)
Small intestine (wall)	1.45×10^{-3}	(0.097)
ULI (wall)	1.46×10^{-3}	(0.083)
LLI (wall)	8.90×10^{-4}	(0.107)
Kidney	4.82×10^{-2}	(0.148)
Liver	9.67×10^{-3}	(0.102)
Lung	2.78×10^{-2}	(0.193)
Ovary	1.39×10^{-3}	(0.228)
Pancreas	6.89×10^{-2}	(0.205)
Spleen	5.47×10^{-2}	(0.081)
Testes	9.05×10^{-4}	(0.232)
Thymus	2.18×10^{-3}	(0.173)
Thyroid	9.31×10^{-4}	(0.155)
Uterus	2.36×10^{-3}	(0.358)
Breast	1.59×10^{-3}	(0.147)
Ribs	1.77×10^{-3}	(0.084)
Skull	3.13×10^{-3}	(0.197)
Spine	2.19×10^{-3}	(0.063)
Pelvis	9.65×10^{-4}	(0.125)
Arm bone	9.52×10^{-4}	(0.079)
Leg bone	3.80×10^{-4}	(0.151)
Brain	1.30×10^{-2}	(0.214)
Heart (wall)	3.99×10^{-2}	(0.237)
Red marrow	1.14×10^{-3}	(0.072)
Bone surface	1.08×10^{-3}	(0.067)
Effective Dose	7.08×10^{-3} mSv/MBq	(0.049)

Table 4. Cumulated activities of $^{15}O_2$, $C^{15}O_2$ and $C^{15}O$ for various source organs (kBq-hr MBq $^{-1}$) obtained from the TLD method

Source Organ	*$^{15}O_2$ (13 yr.)*	*$^{15}O_2$ (adult)*	*$C^{15}O_2$ (13 yr.)*	*$C^{15}O_2$ (adult)*	*$C^{15}O$ (13yrs)*	*$C^{15}O$ (adult)*
Major-airway (content)	2.15± 0.07	1.98± 0.52	2.47± 0.39	2.14± 0.83	2.55± 0.22	2.30± 0.10
Nasal Cavity (content)	1.10± 0.15	1.40± 0.40	1.65± 0.64	1.45± 0.31	1.30± 0.29	1.61± 0.77
Bladder (content)	0.97± 0.32	0.69± 0.41	1.2± 0.35	0.74± 0.55	1.30± 0.56	0.82± 0.31
Kidney	0.51± 0.41	0.43± 0.25	0.75± 0.22	0.53± 0.24	0.77± 0.24	0.42± 0.03
Liver	1.40± 0.21	2.20± 0.51	1.58± 0.10	2.54± 0.35	1.68± 0.12	3.50± 1.29
Lung	4.83± 0.21	5.64± 1.85	5.80± 0.23	5.94± 1.21	5.50± 0.56	6.22± 1.80
Pancreas	0.23± 0.06	0.16± 0.11	0.20± 0.02	0.21± 0.11	0.24± 0.04	0.13± 0.03
Spleen	1.98± 0.04	0.29± 0.17	0.25± 0.05	0.36± 0.13	0.27± 0.05	0.26± 0.03
Heart (content)	2.45± 0.69	2.90± 0.49	2.73± 0.38	3.12± 0.55	2.67± 0.47	3.60± 1.00
Brain	1.01± 0.36	1.64± 0.44	1.46± 0.76	2.34± 1.44	1.78± 0.70	2.90± 1.89
Remainder of the body	9.5± 1.62	8.21± 1.16	14.1± 0.98	12.9± 1.36	13.48± 3.7	11.35± 2.2

Table 5. Absorbed dose estimates to target organs for $^{15}O_2$ (mGy MBq^{-1}) and compared with ICRP53 (11)

Target Organ	*Adults*		*13-yr-old children*	
	Present work	ICRP 53	Present work	ICRP 53*
Adrenal	2.17×10^{-4}	1.7×10^{-4}	3.51×10^{-4}	2.85×10^{-4}
Major airway (wall)	9.98×10^{-3}		1.99×10^{-2}	
Nasal Cavity (wall)	1.34×10^{-2}		1.89×10^{-2}	
Bladder (wall)	5.98×10^{-4}	6.9×10^{-5}	1.22×10^{-3}	1.06×10^{-4}
Stomach (wall)	1.73×10^{-4}	9.2×10^{-5}	3.04×10^{-4}	1.40×10^{-4}
Small intestine (wall)	1.35×10^{-4}	7.4×10^{-5}	2.63×10^{-4}	1.21×10^{-4}
ULI (wall)	1.38×10^{-4}	7.6×10^{-5}	2.64×10^{-4}	1.20×10^{-4}
LLI (wall)	1.21×10^{-4}	7.1×10^{-5}	2.48×10^{-4}	1.12×10^{-4}
Kidney	7.93×10^{-4}	1.5×10^{-4}	1.4×10^{-3}	2.40×10^{-4}
Liver	8.20×10^{-4}	1.3×10^{-4}	9.12×10^{-4}	2.15×10^{-4}
Lung	3.47×10^{-3}	2.6×10^{-3}	5.11×10^{-3}	5.00×10^{-3}
Ovary	1.32×10^{-4}	6.9×10^{-5}	2.6×10^{-4}	1.15×10^{-4}
Pancreas	1.61×10^{-3}	1.1×10^{-4}	1.61×10^{-3}	1.65×10^{-4}
Spleen	9.20×10^{-4}	2.6×10^{-4}	1.36×10^{-3}	4.35×10^{-4}
Testes	1.18×10^{-4}	6.8×10^{-5}	2.43×10^{-4}	1.00×10^{-4}
Thymus	2.29×10^{-4}		3.72×10^{-4}	
Thyroid	1.78×10^{-4}	1.2×10^{-4}	3.22×10^{-4}	2.05×10^{-4}
Uterus	1.45×10^{-4}	6.8×10^{-5}	2.89×10^{-4}	1.14×10^{-4}
Breast	1.68×10^{-4}	1.2×10^{-4}	2.87×10^{-4}	1.65×10^{-4}
Brain	6.76×10^{-4}		8.06×10^{-4}	
Heart (wall)	5.00×10^{-4}	3.9×10^{-4}	6.45×10^{-4}	6.10×10^{-4}
Red marrow	6.72×10^{-5}	1.0×10^{-4}	7.18×10^{-5}	1.80×10^{-4}
Bone surface	6.03×10^{-5}	8.5×10^{-5}	9.50×10^{-5}	1.60×10^{-4}
ED (mSv/MBq)	6.6×10^{-4}	3.86×10^{-4}	1.015×10^{-3}	7.2×10^{-4}

*Interpolated values between data from 10- and 15-yr-old children.