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Note

Dose Assessment on the Mean Absorbed Estimates Derived from the Simple Approach Method Applying Marinelli-Quimby's Formula for Ambient Risk Organs to Thyroid Uptake in the Administered ^{131}I Radiopharmaceutical of Graves' Disease Using PHITS and ICRP Reference Computational Voxel Phantom

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This study aimed to report a simple approach dosimetric tool for ambient risk organs/tissues (targets) to thyroid uptake (source) for ^{131}I radiopharmaceutical of Graves' disease. The dosimetric tool introduced in this study is based on the mean absorbed dose estimates and calculations by the Monte-Carlo code in radiation transport of particle heavy ion transport code system (PHITS), which is incorporated with Marinelli-Quimby's formula in clinical use on therapeutic nuclear medicine using the International Com-mission on Radiological Protection (ICRP) reference adult male computational voxel phantom. More-over this feature can perform those dose estimates without fully calculating specific absorbed fractions (SAFs) or S-values relative to the radiation transport and energy deposition from source within targets, in-stead using the main absorbed dose (334.5500 Gy) of thyroid uptake determined by Marinelli-Quimby's formula and precomputed dose ratio tables derived from PHITS between the thyroid uptake and ambient risk targeted organs/tissues (spleen, liver, pancreas, and thymus) and also easily working on 2D and 3D display procedure for radiation transport and energy deposition distribution mappings on ParaView and ANGEL (the latter is installed in PHITS) applications. To investigate the validation of our proposed simple approach dosimetric tool, we have compared it with different methods (PHITS direct method, ICRP Pub.53, IDAC-Dose2.1, and OpenDose) to the mean absorbed dose estimates in the thyroid gland and those ambient risk targeted organs/tissues. We have found that it is in generally good agreement with those dose estimate results obtained in our proposed simple approach and others, and also represents that the PHITS calculation coupled with the Marinelli-Quimby's formula is quite reliable enough to with-stand an absorbed dose estimate tool for other uptake organs/tissues working on sources themselves. It would seem that the proposed dosimetric tool has allowed any attending physician and medical physicist to provide easy and simply absorbed dose estimates for every normal and risk ambient organs/tissues to thyroid uptake in the administrated ^{131}I radiopharmaceutical in therapeutic nuclear medicine on Graves' disease.

Key words: PHITS (Particle Heavy Ion Transport code System), Reference ICRP computational voxel phantom, Mean absorbed dose, Thyroid gland on Graves' disease, ^{131}I radiopharmaceutical, S-value

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1. Introduction

In radionuclide therapy with radiopharmaceuticals in nuclear medicine, several beta- and alpha-emitters are generally used well to date. Typical beta-emitters in clinical use including ^{131}I, ^{89}Sr, and ^{90}Y have been utilized for the treatment of pain of thyroid cancer and bone metastases and non-Hodgkin's lym-phoma on the radionuclide therapy so far. Particularly, as of ^{131}I in radiation therapy of Graves' disease, it is known that the proportion of treated cases in the United States is 60% to 70%[1]. In Japan, the pro-portion of cases, for example, iodine capsule of Na^{131}I, is not so high as in the United States but has been increasing recently. Moreover, regarding outpatient treatment for residual thyroid destruction (ablation) with ^{131}I (1,110 MBq), which have been highlighted recently, the radioactivity intensity handled by this treatment has reached extremely high levels, and the exposure dose assessment control surrounding the internal therapy of ^{131}I is becoming more important, as indicated by strict guidelines[2] supervised by the Japanese Society of nuclear medicine and others.

In contrast, recently, by the clinical fulfillment involved in advances in the alpha-targeted delivery of radionuclides and radionuclide conjugation chemistry techniques and increased availability of alpha-emitters appropriate for clinical use, we have led the alpha-radionuclide therapy to the treatments and patient trials of radiopharmaceuticals labeled with alpha-particle emitters[3], such as ^{223}Ra, ^{217}At. For several years, clinical treatments for bone metastasis in castration resistant prostate cancer are performed through radionuclide therapy of ^{223}Ra alpha-emitter for the first time from June, 2016 in Japan[4].

It is necessary to control the internal absorbed doses appropriately to normal tissues (risk organs; these are also collectively called "target(s)" in the case) to each minimum level, while maximizing the radiation damage and advantages of high potency and localized energy deposition to targeted tumors and immunodeficiency organs (these tissues/organs are also collectively called "source(s)" in the case), which uptake those radiopharmaceuticals in the radionuclide therapy during such a tidal current relative to radiation therapy, and the adequacy of the absorbed dose evaluation involved in their radiation properties of beta- and alpha-emitters becomes more important in the future[5-7].

For early-stage standardized internal absorbed dose estimate (dose calculation) in patients for diag-nostic nuclear medicine, including the radiopharmaceutical of ^{131}I, ICRP Publication 53[8] has been a basic and well-established radiation dose estimate method and a well known textbook-like model even now. The treatise titled "Radiation Dose to Patients from radiopharmaceuticals" in 1987 has been based on a biokinetic model providing quantitative estimations for the distribution and metabolism of the ra-diopharmaceutical on each compartment model for a specific target organ/tissue of interest with each inherent mass in the human body without radiation hazard. Moreover, the ICRP Publication 128[9] in 2015 has been published for diagnostic nuclear medicine, included a compendium of revised information relating to internal absorbed dose for widely used radiopharmaceuticals, and provided new information for ^{82}Rb with the same biokinetic model and using a dosimetry application software code named "MIRDOSE" (renamed "OLINDA/EXM"[10] and has been well known today in nuclear medicine.) to facilitate automated and standardized internal dose calculations for nuclear medicine with improve-ment in computer performance. The model of kinetic behavior of iodine on the ICRP Publication 53[8] described that the administered radiopharmaceutical (^{131}I) introduced into the human body has a distri-bution ration inherent to each organ/tissue on thyroid uptake set at various compartment levels based on the biokinetic model, and each serves as a source to radiation dose (absorbed dose) on the organ/tissue itself, whereas OLINDA/EXM on the ICRP Publication 128[9] has allowed the calculation method that extends this basic concept with the biokinetic model to be estimated to the absorbed radiation doses for ambient risk organs/tissues (as targets) of the human model body (as a standardized phantom) from source organs/tissues (in this study, it corresponds to the thyroid gland) distributed with administration of a certain amount of ^{131}I.

Recently, from 2015, with expansion from diagnostic to therapeutic nuclear medicine applications, a wide variety of computational dosimetry systems based on standardized phantoms, such as OLINDA/EXM version 2.0[11], IDAC-Dose 2.1[12], PARaDIM[13] and OpenDose[14], have been released and are becoming widespread in the radiopharmaceutical industry and research community for internal dose cal-culations of radiopharmaceuticals, in particular, by the attending nuclear medicine physician and medical physicist. They have been certainly well-established in every field and also benefited clinical users at pro-viding user-friendly operations and accurate absorbed dose estimates in any organ/tissue of interest as either the target or source, however, they have some matters of concern for the attending physician and medical physicist because not all nuclear medicine physician and medical physicist users who use them necessarily understand the complex and detailed computational dosimetry system leading up to dose calculations, and also have fairly depended on their dose estimates which are obtained and displayed through their user-friendly interface. Moreover, they have some shortcomings when applied to 3D visu-alization functions of radiation trajectories and distribution map of those

absorbed dose in the internal dosimetry system.

In this study, to simplify the implementation of absorbed dose calculations using a male reference voxel phantom, the research group for radiation transport analysis at JAEA has promoted to develop the Monte-Carlo-based PHITS[15-17] and establish one of the standard calculation codes for risk as-sessment and research field of diagnostic and therapeutic nuclear medicine. We have collaborated with the PHITS research group to work on the pertinent improvement of the PHITS code which is specialized for nuclear medicine in clinical use. Therefore, this study has introduced our proposed simple approach method to the absorbed dose estimates together with directly PHITS calculation data in comparison with ever conventional applications of ICRP Publication 53, IDAC-Dose 2.1, and OpenDose and also those absorbed doses and trajectories on 3D visual distribution mappings to the ambient risk targeted organs/tissues from the source organ of thyroid gland with uptakes of ^{131}I by PHITS in conjunction with the ICRP male reference voxel phantom (ICRP voxel-based model)[18] due to radiation hazards with ad-ministration of ^{131}I in Graves' disease in therapeutic nuclear medicine. Thus, based on the normalization of those absorbed dose estimates in the ICRP voxel phantom, we have proposed and verified the simple approach method to simplify the implementation of the absorbed dose calculations for the ambient risk organs/tissues applying Marinelli-Quimby's formula[19, 20] generally in clinical use.

2. Materials and Methods

Presently, the last version 3.24 of PHITS is available for implementations of internal absorbed dose estimates of thyroid gland and ambient organs/tissues of ^{131}I $\beta(\gamma)$ nuclides delivered on radiopharma-ceuticals in therapeutic nuclear medicine. The EGS5 mode installed in PHITS was used for photon and electron transport. In geometrical modeling of a complex structure, such as the human body, the PHITS can provide valuable insight and assistance for internal dosimetry of organs/tissues of interest, including the thyroid gland. This original voxel modeling in PHITS virtual space described based on the "Uni-verse" and "Lattice" functions and easily exchanged to initial input data with a binary format for PHITS using the software named dicom2phits allow collection of numerical and computational voxel reference phantom data of the adult male licensed under ICRP Publication 110[18], in which the content provides shapes and masses of organs/tissues and elemental composition of the adult Male in general. PHITS mesh tallies in terms of visualization were used to graphically display the dose and track in voxels for the ICRP reference phantom model using ParaView and ANGEL applications. These unit sizes of the voxel phantom data on the adult male in PHITS space are rectangles of $2.137 \times 2.137 \times 8.000$ mm^3 and $1.775 \times 1.775 \times 4.840$ mm^3, respectively. For the source modeling of beta particles and photons orig-inating from $\beta(\gamma)$-decaying ^{131}I nuclides, the beta-particle and gamma-ray response functions (electron and photon sources) as energy spectra are available on providing their spectrum data based on the dataset of MIRD Decay Schemes 2nd Edition[21, 22] and the dataset (the revised data of ICRP Publication 38)[23] of RI source generation function in PHITS. As for photon response function of ^{131}I decaying nuclides, it is also available to adopt only the latter dataset because it would be insufficient to provide the gamma-ray spectrum of ^{131}I on the former dataset on MIRD Decay Schemes[21, 22]. On the course of the present PHITS calculations of the absorbed dose for the targeted thyroid gland with Graves' dis-ease, it has revealed that the absorbed dose and dose distribution on the ICRP computational reference male voxel phantom[18] are obtained from the total scoring number of history of 2.0000E + 8 (200,000,004) corresponding to the details of 5,263,158 per batch by 38 batches. 3D simulation data are selected for those output providing the absorbed dose on a deposit tally mode and electron and photon tracks on a user-defined tally mode; in the case, it is usually called "Trajectory" tally mode in PHITS visualization function. In this user-defined tally setting for the trajectory, we have computed it up to the maximum number limit of 99999 to make it easy to distinguish between those electron and photon tracks. Those trajectory calculation data were exported into this visualization toolkit (VTK) format. This VTK format is generally in use, and a versatile format for a graphical user interface-based application for data analysis and visualization is called "Paraview". All calculation processes were executed by using both openMP and MPI parallel computing calculations properly because PHITS, which is significantly better compared to other codes, provides environment in which those parallel calculations can be easily executed with the default settings. We have utilized our new workstations of Mac Pro 2019 installed with AMD Radeon Pro 560X (2.5 GHz 28-core Intel Xeon W, this machine score capability is approximately 1305 GFlops) and also PC-Linux machine (Ubuntu 18.04.5 LTS) equipped with NVIDIA Tesla K20 (2.1 GHz 20-core Intel Xeon Gold 5218R, its score capability is approximately 626 GFlops). It is likely that those GPU performance greatly contributes to the 3D drawing function of VTK format and trajectory tally mode.

Our focused Marinelli-Quimby's formula[19, 20] of ^{131}I in clinical use is expressed as follows:

Absorbed dose of uptake thyroid gland (Gy)

$$= \frac{135 \times A \times U \times T_{eff}}{3.7 \times W \times 8 \times 100} \quad (1)$$

where A (MBq) in general case of 300 (MBq) is the prescription radioactivity of ^{131}I, U (%) is an uptake rate on 24 h and that is 70%[24] in general on the formula, T_{eff} (day) is the effective half-life of ^{131}I (6.3 day)[25], and W (g) is expressed as the mass for the source region of the thyroid gland in which the ^{131}I radiopharmaceutical has been accumulated on the therapeutic nuclear medicine and the mass is set to 20 g, whose volume is a segmented volume of 19.2 cm^3 of the thyroid gland at the adult male reference voxel phantom, resulting in the value described in ICRP Publication 110[18]. As is well known, it would be empirically considered for attending physicians and medical physicists that the Marinelli-Quimby's formula shown here only requires the mean absorbed dose at the thyroid gland uptake of 70% with administration of ^{131}I radiopharmaceutical. We have inferred that our proposed simple approach method enables us to deduce the mean absorbed doses of the ambient targeted risk organs/tissues based on the normalization of the obtained absorbed dose to the source organ of the thyroid gland by Marinelli-Quimby's formula. If the absorbed dose in other ambient organs/tissues can be linearly interpolated only by taking the relative ratio calculated by PHITS and also be multiplied by the normalization factor of the obtained mean absorbed dose of thyroid of Marinelli-Quimby's formula on the proposed method, this simple approach method can be easily performed in clinical scenes of attending physicians and medical physicists.

Generally, regardless of which dosimetry calculation system and computational codes are used for the internal absorbed dose estimates in nuclear medicine, the absorbed doses are calculated using the MIRD formalism with the time-independent formulation as follows, which is defined at MIRD Pamphlet No.21[26]:

$$D_{(Target,T_D)} = \sum_{Source} \{\tilde{A}_{(Source,T_D)} \times S_{(Target \leftarrow Source)}\} \text{ [Gy]} \quad , \quad (2)$$

where $D_{(Target,T_D)}$ is the mean absorbed dose (Gy) delivered to ambient risk organs/tissues due to source radiation hazards in a reference human body phantom. That is, in the ICRP Publication 53, targeted risk organs/tissues with the distribution ration inherent to a source organ/tissue (in case of thyroid uptake of ^{131}I) have been set at various compartment levels based on the biokinetic model and the mean deposit en-ergy with $S_{(Target\ within\ itself)}$, which is called "S-value", has been imparted to each individual organ/tissue within itself. In contrast, in IDAC-Dose 2.1, OpenDose, and PHITS (in this study), $S_{(Target \leftarrow Source)}$, which is also corresponding to "S-value", is the mean absorbed dose to a given ambient target per nuclear disin-tegration in the source (thyroid uptake) after depositing a part of the disintegration energy of beta particle or photon within itself. $\tilde{A}_{(Source,T_D)}$ is the total number of time-integrated or cumulated radioactivities on the uptake radiopharmaceutical in the source (thyroid gland) (Bq·s) over the integration period T_D. In this study, in IDAC-Dose 2.1, OpenDose, and PHITS, by making the consistent period T_D to calculate and investigate their $S_{(Target \leftarrow Source)}$ (S-value) values respectively, we have adopted the integration time of four times the effective half-life (6.3 day×4) because it is assumed that it corresponds to the adequate time required for the cumulative radioactivity of ^{131}I, which is also common in Marinelli-Quimby's for-mula. The calculation of S-values requires a clear definition of the geometry of the model in this case of the ICRP male reference voxel phantom (ICRP voxel-based model) and ^{131}I decay characteristics:

$$S_{(Target \leftarrow Source)} = \sum_i E_i Y_i \Phi_{i\,(Target \leftarrow Source,\ Ei)} \quad \text{[Gy/Bq]} \quad , \quad (3)$$

where $\Phi_{i(Target \leftarrow Source,\ E_i)}$ is the specific absorbed fraction (kg^{-1}), which is the so-called "SAF value"[27] in the field of radiopharmaceutical dosimetry of the i-th emitted radiation of the radionuclide (in the case ^{131}I). That is, the fraction of the E_i[22, 23] emitted in source region of *Source* to the target organ/tissue *Target* divided by the mass of the target organ/tissue in kilograms. E_i and Y_i are the mean energies (or part of the energy distribution of electrons and photons associated with β-decay in this case ^{131}I radiopharmaceutical) in joules and the product yield of the i-th nuclear transition of the radiopharmaceutical radionuclide in (Bq^{-1}· s^{-1}).

The Monte-Carlo-based PHITS simulation we have utilized for this study, like any other Monte-Carlo simulation code, such as MCNP6.0 (IDAC-Dose2.1), EGSnrc (OpenDose), and GEANT4 (OpenDose), can derive the mean absorbed doses at target and source organs/tissues directly generating the SAF values while considering a description of human geometry in a simulation space of interest and involving every transport process of radiations in various substances in the adult male reference ICRP model. These mean absorbed dose estimates obtained directly of the thyroid gland (source organ) and four ambient organs (targets) of the spleen, liver, pancreas, and thymus are provided in detail to be the mean absorbed dose rate in Gy/s on PHITS and OpenDose and Gy/Bq on IDAC-Dose2.1 and ICRP Pub.53 from the administered radiopharmaceutical of ^{131}I. The ICRP Pub.53 is not in the category of Monte-Carlo sim-ulation method and has been classified with various compartment levels based on the biokinetic model by the

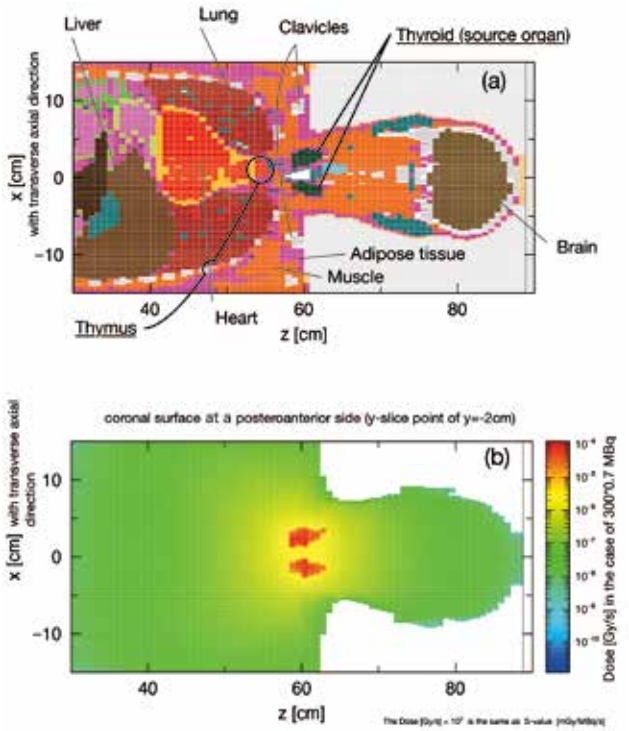

Fig. 1. Absorbed dose distribution on the coronal cross-section (as a rearward side view) of the upper half of voxel phantom.

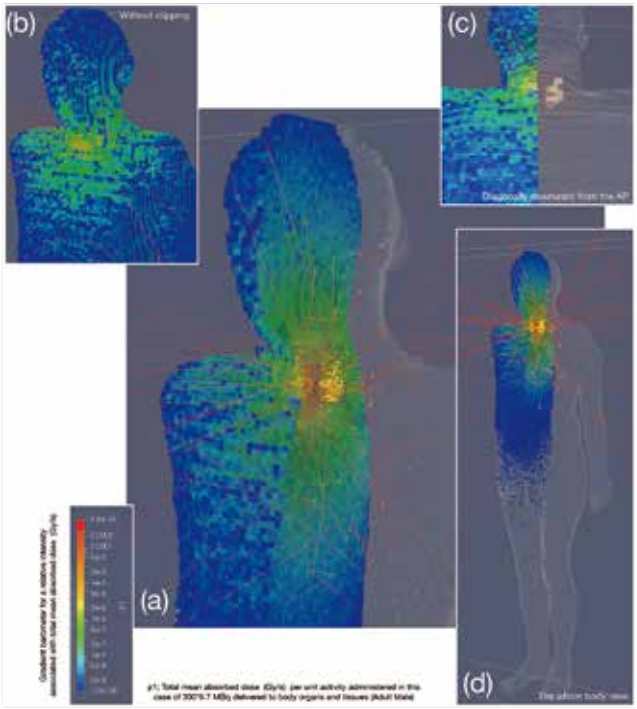

Fig. 2. Voxelized 3D mean absorbed dose distribution map and the limited number of trajectories (ra-diation tracks as represented by small dots and thin lines) map of electrons and photons on the adult male ICRP computational voxel phantom visualized for the VTK format data by ParaView. The Voxelized map shows the PHITS calculated relative mean absorbed dose distribution on the zoomed-up sagittal view (a) with clipping of the focused region including the ambient organs around the thyroid gland. The mapping data were obtained by the total scoring number of history of 2E + 8 (200,000,004 in detail). Those views of (b), (c), and (d) represent without clipping, diagonally downward from the AP direction with clipping, zoomed-out sagittal view of the Voxelized whole body, respectively. The gradient barome-ter in which S-value is involved stands for our PHITS calculated relative mean absorbed dose rate (Gy/s) from 1.0000E-08 to 5.8000E-04.

MIRD Dose Estimate Report No.5[28] because, to compare with the dose estimate of Marinelli-Quimby's formula in this study, thyroid uptake of 70% and other ambient organ uptakes (except for the thymus) in response to its condition were reproduced by extrapolating the range of 0% (thyroid blocked)-to 55% uptake as described in ICRP Pub.53. The IDAC-Dose2.1 (Windows version), which was written in MATLAB, can be obtained for free from the website (https://www.idac-dose.org/#/), but it re-quires the MATLAB runtime compilation and would possibly be unable to work on calculating the mean absorbed dose estimates unless it works well depending on the individual computer OS environment. In fact, it could not work in our macOS version 11 (Big Sur) environment. (In supplement, OLINDA/EXM version 2.0[11] program is expensive and charged, so the calculation could not be executed.) The OpenDose website framework (https://www.opendose.org/home), in whose database SAFs already calculated by many Monte Carlo simulation codes have been stored is quite available and informative for us to calculate the mean absorbed dose estimates to validate ours using the simple approach method based on Marinelli-Quimby's formula and directly deriving the dose estimates from PHITS calculations) in comparison with them.

3. Results and Discussion

Figure 1 shows PHITS calculated dose distribution mapping data of the ICRP reference male computational voxel phantom regarding the mean absorbed dose rate together with the Voxelized 2D view also displayed in response to the location of organs/tissues. The data involved the energy deposition in the organs/tissues of the adult male ICRP Voxelized phantom on the coronal cross-sectional surface (from rearward side view) around the upper half of the phantom, which was calculated by PHITS, with the total number of 2.0000E + 8 (200,000,004 in detail) histories. The average computational time required with scoring those histories was approximately 5 h for the transport calculation for all radiations of electron and photon from the thyroid gland (source) in the Monte Carlo simulation space with the description ge-ometry of the voxel phantom. This result shows that

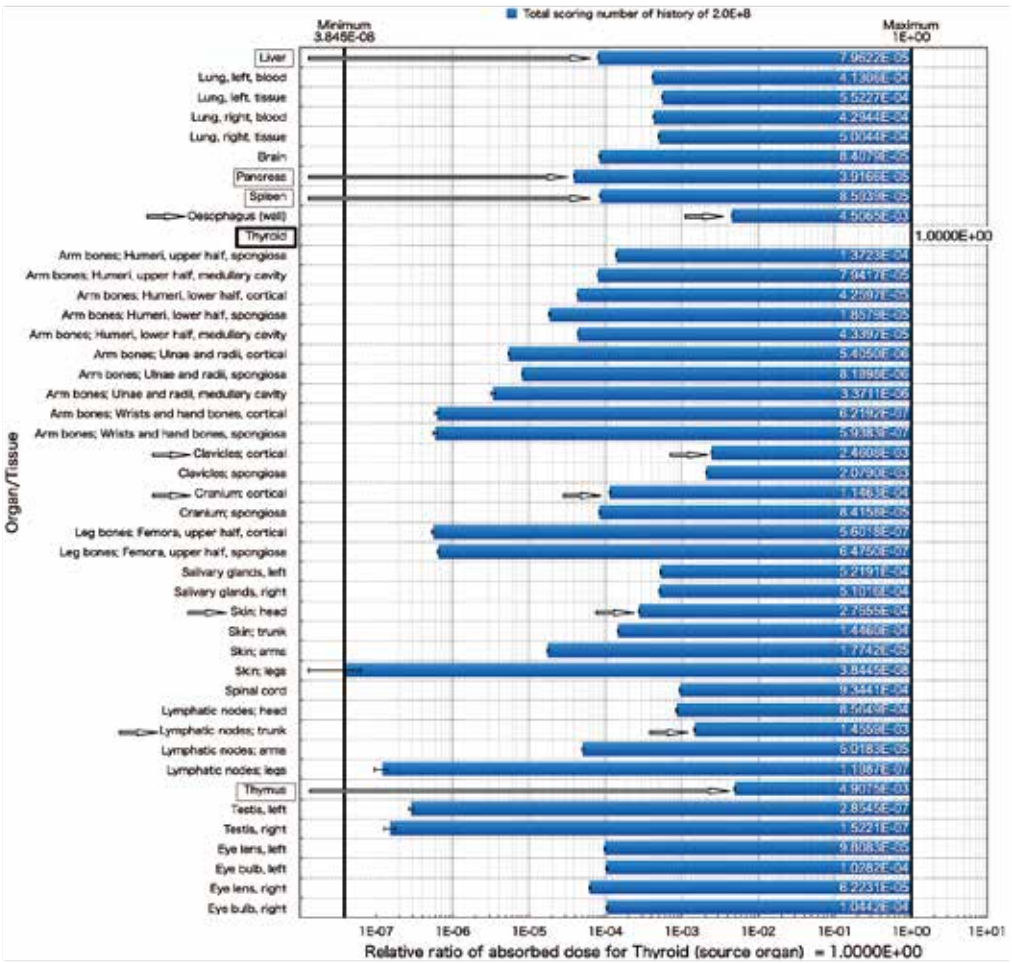

Fig. 3. Comparing ratios between PHITS calculated mean absorbed doses (Gy/s) corresponding to S-value for the ambient organs/tissues and that of thyroid uptake (^{131}I) set to the normalized value of 1.0000E+00.

the absorbed dose of thyroid gland becomes higher compared comparison with that of the ambient organs/tissues because its calculation has shown that the radiopharmaceutical labeled with an $\beta(\gamma)$ emitter of ^{131}I is certainly accumulated into the thyroid gland on the radionuclide therapy of Graves' disease. The outline part, which shows the highest absorbed dose distribution has been represented clearly corresponding to the shape of thyroid gland upon the internal exposure of radiation hazards of administered radiopharmaceutical ^{131}I. Notably, it has been conjectured that the absorbed dose distribution of more ambient organs that encloses the thyroid gland become higher than that of organs/tissues which are located far from its source organ. Conversely, the absorbed dose estimates of organs/tissues, which are approximately ≥ 20 cm from the thyroid gland, suddenly decrease, and it has been expected that the potential of the absorbed doses become fairly lower to the radiation hazards associated with administration of therapeutic amounts of ^{131}I.

Figure 2 shows some views in different angular directions and from zooming on 3D fusion drawings between the absorbed dose distribution on a deposit tally mode and radiation tracks on a user-defined tally mode of trajectory tally mode for electrons and photons (gamma-rays) due to the disintegration of ^{131}I are presented in the 3D visualization plot of the standardized phantom of adult male using the ParaView software. The present sophisticated and fusion 3D figure obtained in the ParaView application allowed us to elucidate how primary photons (the red thin lines shown in Fig. 2) emitted inside the thyroid gland region have been transported in detail. The yellow small dots have mainly represented the electrons generated by photoelectric effect and Compton scattering associated with those photon transports and energy depositions, and the locations where they are strongly concentrated are deduced to be the shape of thyroid gland, and it can be fairly visually confirmed that the concentrated electrons have deposited their own energies at each location according to the shape of the source organ for the thyroid gland. It has been found that the influence of source radiation hazards

Table 1. PHITS S-value ratios of the spleen, liver, pancreas, and thymus to the normalization of the mean absorbed dose estimate of thyroid uptake, which is obtained from the Marinelli-Quimby's formula in comparison with ICRP Pub.53[8], IDAC-Dose2.1[12], and OpenDose[14]

	This work	ICRP Pub.53	IDAC-Dose2.1	OpenDose
Monte Carlo simulation or biokinetic model	PHITS	Biokinetic behavior model with compartment model	MCNP6.0	EGSnrc/EGS++, FLUKA, GATE, Geant4, MCNP/ MCNPX, PENELOPE
Adult male computa- tional reference type model	ICRP voxel-based model	Mathematical phantoms representing a male (MIRD-5 phantom)	ICRP voxel-based model	ICRP voxel-based model
<Organ>				
Thyroid (Source)	1.0000E+00	1.0000E+00	1.0000E+00	1.0000E+00
Spleen (Target)	8.5939E-05	5.5799E-05	1.1600E-04	9.9186E-05
Liver (Target)	7.9622E-05	4.5052E-05	1.0800E-04	9.2068E-05
Pancreas (Target)	3.9166E-05	6.4183E-05	5.3900E-05	4.5899E-05
Thymus (Target)	4.9075E-03	no data	6.4700E-03	5.5110E-03

due to the administered ^{131}I radiopharmaceutical of thyroid gland has been noted from the top of the head to the lower abdomen in the adult male body in the range of our PHITS calculated relative mean absorbed dose rate (Gy/s) from 1.0000E-08 to 5.8000E-04.

Figure 3 summarized the ratios of the calculated absorbed doses for main normal (or risk) ambient organs/tissues, for example thymus and oesophagus, around the thyroid gland to that of the thyroid gland set to a normalized value of 1.0000E + 00. These calculated ratio data reveal that all absorbed doses of the ambient risk organs/tissues are double or fairly less rather than the value of the thyroid gland, and also from the present PHITS calculations it can be observed from this figure that their absorbed doses of risk organs will be trending with extremely lower ratios between 10^{-8} and 10^{-3} with few health influence even if those values take the well-known sublethal damage recovery of a cell into consideration. Based on the normalization by Marinelli-Quimby's formula in our proposed simple approach method, at first we have confirmed that the mean absorbed dose estimate of the thyroid gland (source organ) was determined to be 334.55 Gy. As a result, we have obtained the mean absorbed dose estimate of each organ/tissue (target) from the relative ratio of the standardized one on the thyroid uptake (70%), and when focusing on the six organs/tissues that are classified, as shown in Figure 3, as having relatively high absorbed dose group, that is, the thymus, oesophagus (wall), clavicles (cortical), lymphatic nodes (trunk), skin (head), and cranium (cortical) , they can be estimated to be 1.6418, 1.5076, 0.8232, 0.4871, 0.0922, and 0.0384 Gy, respectively.

To validate our simple approach method of the mean absorbed doses for ambient risk organs/tissues by considering the relative ratio with that of a source organ (thyroid gland), which is obtained using Marinelli-Quimby's formula and PHITS, we have compared our approach with different methods (PHITS direct method, ICRP Pub.53, IDAC-Dose2.1, and OpenDose). That is, the organs to be compared and verified were the thyroid gland (source), spleen (target), liver (target), pancreas (target), and thymus (target) in the adult male computational reference voxel phantom, which are also commonly used as subjects (benchmarks) by these other methods. Table 1 shows the ratio of respective ambient organs to those S-value with four significant figures, assuming that the mean absorbed dose estimates related to the normalized S-value in the thyroid uptake (70%) of administered ^{131}I radiopharmaceutical. Obviously, even if the ratio of the thymus for which the ICRP Pub.53 has not been reported is excluded in Table 1, it can be confirmed that the result trends of all ratios decrease in that order from the normalization value of thyroid gland to the thymus, spleen, liver, and pancreas in our proposed approach method including PHITS, ICRP Pub.53, IDAC-Dose2.1, and OpenDose. The ratios of any organs in our suggested method provided intermediate values between the minimum value group on ICRP Pub.53 and the maximum one on IDAC-Dose2.1. Our results showed almost the same ratios of any organs as that of OpenDose. Thus, it has been found that the validity of the PHITS calculation in this study is fairly apparent compared with other widely used Monte Carlo codes, such as Geant4 and MCNP/MCNPX, which are offered in the dosimetry system of OpenDose. Table 2 compares the mean absorbed dose estimates of the thy-roid gland (source)

Table 2. Comparing the mean absorbed dose estimates (Gy) of thyroid uptake and targeted ambient risk organs (spleen, liver, pancreas, and thymus), which were derived from Marinelli-Quimby's formula and directly calculated dose results by PHITS with those obtained dose estimates from ICRP Pub.53[8], IDAC-Dose2.1[12], and OpenDose[14], respectively

<Organ>	Marinelli-Quimby's formula [this work] (Gy)	Directly derived from PHITS [this work] (Gy)	ICRP Pub.53 (Gy)	IDAC-Dose2.1 (Gy)	OpenDose (Gy)
Thyroid (Source)	334.5500	336.1726	300.5606	303.3140	291.5699
Spleen (Target)	0.0288	0.0289	0.0168	0.0350	0.0289
Liver (Target)	0.0266	0.0268	0.0135	0.0328	0.0268
Pancreas (Target)	0.0131	0.0132	0.0193	0.0163	0.0134
Thymus (Target)	1.6418	1.6497	no data	1.9600	1.6068

and ambient risk organs for the normalization of Marinelli-Quimby's formula on our proposed simple approach method and also derived directly from PHITS, and then that of other dosime-try systems (ICRP Pub.53, IDAC-Dose2.1 and OpenDose) as already described above. In Table 2, the mean absorbed dose estimate of the thyroid gland (source) itself has been determined to be 336.1726 Gy by PHITS directly calculated result on the cumulative radioactivity of four times the effective half-life at the administered radioactivity (300 MBq) of ^{131}I and uptake (70%) in clinical use for the treatment of Graves' disease. The PHITS calculation shown here was fairly identical to the mean absorbed dose estimate method based on Marinelli-Quimby's formula in general clinical use, and also represents that the PHITS calculation is quite reliable to withstand an absorbed dose estimate tool for other uptake or-gans/tissues working on sources themselves, for instance, the small intestine, kidneys, and bladder in ^{131}I administration in therapeutic nuclear medicine. However, it exhibited that there was no problem and its calculation was only slightly higher than the values derived from other evaluated methods of thyroid up-take. Conversely, when comparing them with other estimate methods of IDAC-Dose2.1 and OpenDose (within a similar category of Monte-Carlo-based calculation) with respect to those ambient risk targeted organs, as shown in Table 2, it was found that our proposed simple approach method with normalization-based on the Marinelli-Quimby's formula, these obtained data are quite consistent with them, especially in OpenDose, indicating the validity of our proposed method. Then, focusing on those dose estimates derived from ICRP Pub.53 in comparison with Monte-Carlo based mean absorbed estimates of ours (the Marinelli-Quimby's formula coupled with PHITS), IDAC-Dose2.1 and OpenDose, their energy deposi-tions of those uptake organs of ^{131}I as radiation sources are given to themselves without affecting each other, having the distribution ratio inherent to each organ/tissue on thyroid uptake set at various com-partment levels based on the biokinetic model. Thus, the integrated mean absorbed dose estimates of these organs can be determined by adding the deposition energies (as external effect) transported from source (thyroid) to targeted organs (spleen, liver, pancreas and thymus) derived from the Monte-Carlo-based estimations, including our proposed approach method and others (IDAC-Dose2.1 and OpenDose) to that (internal effect) of ICRP Pub.53 based on biokinetic compartment model. As shown in Table 2, it has been confirmed that both the external and internal effects under the hazard radiations (electrons and photons) due to the administered ^{131}I radiopharmaceutical are almost the same level compared with their dose estimate methods. Therefore, so far, the general view is that, even if the external effect due to the radiations originating from ^{131}I thyroid uptake of 300 MBq on dose to ambient risk organs (spleen, liver, pancreas and thymus) has possibly negligible influence, but it cannot be ignored because the effect on the dose corresponds to the same dose effect in response to uptake condition themselves for the organs even more close to the thyroid gland.

4. Conclusion

In this study, from the implementation of the absorbed dose calculations for that combined with the PHITS code and Marinelli-Quimby's formula in general clinical use, it can be concluded that our pro-posed simple approach method will be validated to obtain the mean absorbed dose estimates of not only the source organ of the thyroid gland with Graves' disease but also the targeted ambient risk organs, which are the spleen, liver, pancreas, and thymus, considering such as benchmarks in common by com-paring PHITS direct method, ICRP Pub.53, IDAC-Dose2.1, and OpenDose. For our proposed approach, despite only normalizing our obtained mean absorbed dose estimate of the source organ of the thyroid gland in the administered ^{131}I radiopharmaceutical by Marinelli-Quimby's formula in response to those relative ratios of the S-values to those organs derived from PHITS calculation, we have found that the dose evaluation capability for clinical use is comparable to other

calculations. Moreover, the 3D visual-ization function on PHITS coupled with the ParaView application have really benefited nuclear medicine physician and medical physicist and also support them in evaluating the mean absorbed dose distribution to ambient risk organs/tissues in the ICRP reference computational voxel phantom. Finally, we believe our proposed simple approach method based on Marinelli-Quimby's formula will easily provide practi-cal and clinical dose understanding on those ambient risk organs/tissues.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Reference

1. Kasagi H, Iwata M, Omae T, oKnishi J, Hanbara H. Jpn J Rad (in Japanese). 2000;60:729–37.
2. Japanese guideline manual ver. 3 of outpatient treatment for residual thyroid destruc-tion (ablation) with iodine-131 (1,110 MBq), The Japanese Society of Nuclear Medicine and others 2013. Available from: http://jsnm.org/wp_jsnm/wp-content/themes/theme_jsnm/doc/i_ 131tekiseishiyoumanual_3.pdf
3. Washiyama K. An approval of Ra-223 as an alpha particle-emitting radiopharmaceutical for the treatment of patients with castration-resistant cancer and metastases. Houshakagaku (Radiochemistry). 2016;34:38–42.
4. Yoshida K, Kaneta T, Takano S, Sugiura M, Kawano T, Hino A, *et al*. Pharmacokinetics of single dose radium-223 dichloride (BAY 88-8223) in Japanese patients with castration-resistant prostate cancer and bone metastases. Ann Nucl Med. é016;30(7):453–60.
5. Hobbs R F, Song H, Watchman C J, Bolch W E, Aksnes A K, Ramdahl T, *et al*. A bone marrow toxicity model for ^{223}Ra alpha-emitter radiophamaceutical therapy. Phys Med Biol. 2012;57(10):3207–22.
6. Szumowski P, Mojsak M, Abdelrazek S, Sykała M, Amelian-Fiłonowicz A, Jurgilewicz D, *et al*. Calculation of therapeutic activity of radioiodine in Graves' disease by means of Marinelli's formula, using technetium (^{99}mTc) scintigraphy. Endocrine. 2016; 54(3):751–6.
7. Sato T, Furuta T, Liu Y, Naka S, Nagamori S, Kanai Y, *et al*. Individual dosimetry system for targeted alpha therapy based on PHITS coupled with microdosimetric kinetic model. EJNMMI phys. 2021;8(1):4.
8. Annals of the ICRP. Radiation Dose to Patients from Radiopharmaceuticals, ICRP Publication 53, 1987;18:1–4.
9. Annals of the ICRP. Radiation dose to patients from radiopharmaceuticals: a compendium of current information related to frequently used substances, ICRP publication 128. 2015;44(2S).
10. Stabin MG, Sparks RB, Crowe E. OLINDA/EXM: the second-generation personal computer soft-ware for internal dose assessment in nuclear medicine. J Nucl Med. 2005;46(6):1023–7.
11. Stabin MG, Siegel JA. RADAR dose estimate report: a compendium of radiopharmaceutical dose estimates based on OLINDA/EXM Version 2.0. J Nucl Med. 2018;59(1):154–60.
12. Andersson M, Johansson L, Eckerman K, Mattsson S. IDAC-Dose 2.1, an internal dosimetry pro-gram for diagnostic nuclear medicine based on the ICRP adult reference voxel phantoms, EJNMMI Research. 2017;7(1):88.
13. Carter LM, Crawford TM, Sato T, Furuta T, Choi C, Kim C H, *et al*. PARaDIM: a PHITS-based Monte Carlo tool for internal dosimetry with tetrahedral mesh éomputational phantoms. J Nucl Med. 2019;60(12):1802–11.
14. Chauvin M, Borys D, Botta F, Bzowski P, Dabin J, Denis-Bacelar A M, *et al*. OpenDose: open access resources for nuclear medicine dosimetry. J Nucl Med. 2020;61:1514–9.
15. Sato T, Niita K, Matsuda N, Hashimoto S, Iwamoto Y, Noda S, *et al*. Particle and heavy ion transport code system, PHITS, version 2.52. J Nucl Sci Tech. 2013;50(9):913–23.
16. Sato T, Niita K, Matsuda N, Hashimoto S, Iwamoto Y, Furuta T, *et al*. Overview of particle and heavy ion transport code system PHITS. Ann Nucl Energy. 2015;82:110–5.
17. Sato T, Iwamoto Y, Hashimoto S, Ogawa T, Furuta T, Abe S, *et al*. Features of particle and heavy ion transport code system (PHITS) version 3.02. J Nucl Sci Tech. 2018;55(6):684–90.
18. The International Comission on Radiological Protection Adult Reference Computational Phantoms ICRP Publication 110. Ann ICRP. 2009;39(2).
19. Stelson A, Watson E, Cloutier R. A history of medical internal dosimetry. Health Phys. 1995;69(5):766–82.
20. Traino A, Di Martino F, Lazzeri M. A dosimetric approach to patient-specific radioiodine treat-ment of Graves' disease with incorporation of treatment-induced changes in thyroid mass. Med Phys. 2004;31(7):2121–7.
21. Ackerman K, Endo A. MIRD Decay Schemes 2nd Edition, Society of Nuclear Medicine and Molec-ular Imaging. Ed. 2008 Virginia, US.
22. Eckerman K, Endo A. Nuclear decay data for dosimetric calculations. ICRP Publication 107. Ann ICRP. 2008;38:7–96.
23. Endo A, Yamaguchi Y, Eckerman K. Nuclear decay data for dosimetry calculation - Revised data of ICRP Publication JAERI. 2005;38:1347.
24. Stabin MG, Watson EE, Marcus CS, Salk RD. Radiation dosimetry for the adult female and fetus from iodine-131 administration in Hyperthyroidism, J Nucl Med. 1991;32(5):808–13.
25. Draft Regulatory Guide DG-8015, US Nuclear Regulatory Commission, April 1997.
26. Bolch WE, Eckerman KF, Sgouros G, Thomas SR. MIRD Pamphlet No. 21: A general-ized schema for radiopharmaceutical dosimetry-standardization of nomenclature, J Nucl Med. 2009;50(3):477–84.
27. Computational framework for internal dose assessment for reference adults: specific absorbed fractions, ICRP Publication 133. Ann ICRP. 2016;45(2):174.
28. MIRD Dose Estimate Report No.5., Summary of current radiation dose estimates to human from ^{123}I, ^{124}I, ^{125}I, ^{126}I, ^{130}I, ^{131}I and ^{132}I as sodium iodine, J Nucl Med. 1975;16:857–60.