MEDIRAD

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Deliverable 2.17

Update of administered activity-to-organ-dose conversion factors for two commonly used radiopharmaceuticals

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1. Summary

MEDIRAD Subtask 2.3.2.2 was initially based on the processing of clinical data acquired within a clinical study. For various reasons – most of them being consequences of COVID - patient recruitment could not be done. In order to fulfil the objectives of the Subtask, it was decided to perform the analysis on data already available by consortium members. Tests were performed on a ^{18}F-labelled radiopharmaceutical (for PET studies) and a subset of patients treated with ^{131}I in WP3. A dosimetric software for patient-specific image-based dosimetry was developed and is freely available for use and upgrade (opensource). Results of the calculations are presented in that report and compared with conventional model-based results.

2. Introduction

Deliverable D2.17 “Update of administered activity-to-organ-dose conversion factors for two commonly used radiopharmaceuticals” concludes Subtask 2.3.2.2.

MEDIRAD Subtask 2.3.2.2 (Estimation of patient organ doses from two commonly used PET and SPECT tracers) aimed to collect state-of-the-art biodistribution data from both ^{99m}Tc-HMDP and ^{18}FDG (tracers identified in subtask 2.3.1) by means of sequential quantitative SPECT/CT and PET/CT acquisitions respectively. This was one of the rare prospective studies developed within the frame of MEDIRAD.

In a context of low irradiation, an estimate is usually sufficient to document the diagnostic procedure. According to the MIRD formalism, the absorbed dose $\bar{D}_k$ to a given target k is obtained by summing the contributions of all sources h to the target k:

$$\bar{D}_k = \sum_h \tilde{A}_h \times S_{(k \leftarrow h)}$$

Where $\tilde{A}_h$, the time-integrated activity, is the total sum of decays in source h, and $S_{(k \leftarrow h)}$ in Gy.Bq^{-1}.s^{-1} represents the absorbed dose delivered to target k per decay emitted in source h.

Then, following the IRCP formalism, the effective dose E for a given radiopharmaceutical can be obtained by combining the absorbed doses in selected organs with radiation (W_R) and tissue (W_T) weighting factors:

$$E = \sum_T W_T \sum_R W_R \times D_{T,R}$$

Then, assuming W_R=1 in the situation of most nuclear medicine radiopharmaceuticals (ie for photons, electrons/beta emissions), and combining the 2 equations:

$$E = \sum_k W_k \times \bar{D}_k$$

Usually, for effective dose determination, absorbed doses are obtained by combining pooled pharmacokinetics parameters (the time-integrated activities $\tilde{A}_h$) with reference S values ($S_{(k \leftarrow h)}$)

obtained from reference models according to IRCP recommendations. The models may vary (for example from ICRP 60 to ICRP 103) but the formalism remains the same: reference dosimetry is obtained from reference pharmacokinetics and reference anthropomorphic S values. The standardisation induced by model-based dosimetry is considered as more important than the potential gain in accuracy provided by more refined dosimetric approaches.

Yet, the relative uncertainty induced by implementing model-based dosimetry should be assessed. Evolutions in the clinical dosimetry methodology allow to compute patient-specific absorbed doses, for example using the growing availability of Monte Carlo modelling of radiation transport. Our project is to compare model-based dosimetry (using the latest ICRP recommendations and models) with patient-specific dosimetry.

Figure 1 presents a very simplified schema of the developments performed for the study. Monte-Carlo-based dosimetry was performed to provide patient-specific absorbed doses to all patients considered in the study (D_1, D_2, … D_n), where D_i represents the full dosimetric dataset obtained for patient i. In parallel, the pharmacokinetics for each patient was assessed, represented in Fig 1 by $\tilde{A}_i$. It is tempting to use a very simplified MIRD nomenclature to write that, for each patient $D_i=\tilde{A}_i \times S_i$. This only means that for each patient, 2 aspects are considered, the documentation of pharmacokinetics and the calculation of absorbed doses. Also, the dosimetric results can be averaged to provide D_{Av}.

In that context, the IRCP approach, that consists in using pooled pharmacokinetics for the n patients and a reference anthropomorphic dosimetric model for absorbed dose calculations can be represented as: $D_{Ref} = \tilde{A}_{Av} \times S_{Ref}$.

The average of the dosimetric results D_{Av} was computed. In parallel, Model-based dosimetry (ICRP 103) was be performed using pooled pharmacokinetics and reference dosimetry models (ICRP 110), thereby providing D_{Ref}.

D_{Av} and D_{Ref} were compared in order to assess the relevance of implementing refined dosimetric approaches in a context of diagnostic. In addition, the patient-specific approach also provided an idea of the variation around the average absorbed dose D_{Av}.

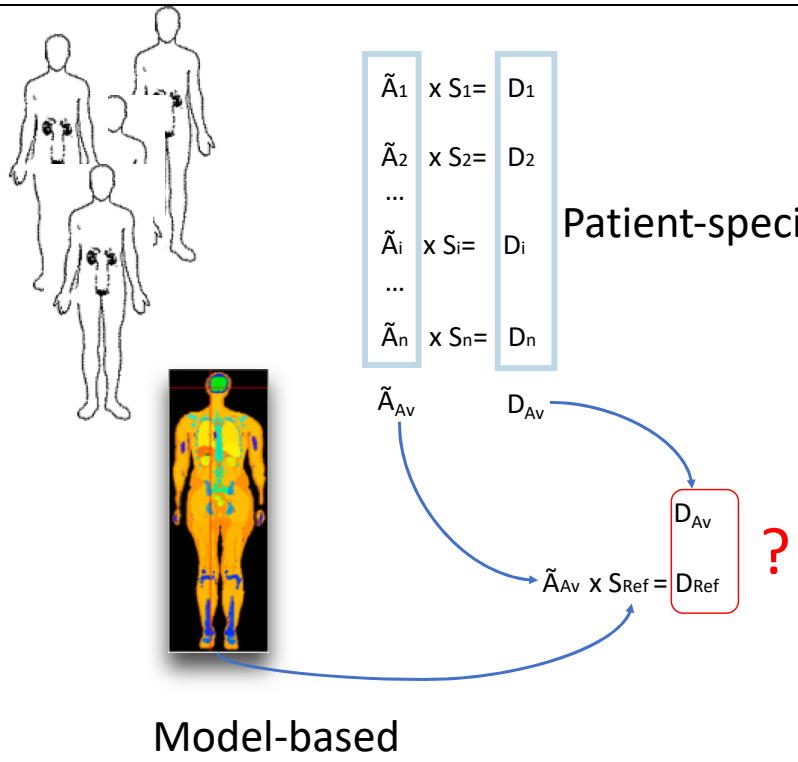

Fig 1: Comparative dosimetric study

3. Dosimetry software

Preparatory work for the patient-specific dosimetry simulations was conducted in anticipation, in order to speed up the overall process.

A patient-specific radiopharmaceutical dosimetry package was built within CRCT (INSERM). This software is at the intersection of WP2 and WP3. First, both WP include radiopharmaceutical dosimetry studies, in Subtask 2.3.2.2 and Task 3.3. Second, the development of the imaging and radiation dose biobank – IRDBB - (Task 2.4) triggered fructuous discussions between consortium members. The nuclear medicine dosimetry software developed, OpenDose3D (OD3D), was based on an *open-source* software platform for medical image informatics, image processing, and three-dimensional visualization, 3D Slicer (www.slicer.org). The added value of basing the dosimetry software on 3D Slicer is that some of the steps included in a clinical dosimetry procedure, such as data import (in the DICOM format), image registration or segmentation are already present, documented and validated.

This led to the development of missing modules such as:

- Calculation of absorbed dose (rate) from 3D maps of density and cumulated activity (activity) according to different algorithms (local energy deposition & convolution, with or without density correction and Monte Carlo with GATE[1]),

[1] http://www.opengatecollaboration.org/

- Integration of time-dependant parameters such as activity (to provide cumulated activity or time-integrated activity) or absorbed dose rates (to provide the absorbed dose).

In addition, the *assembly of modules in a structured way* led to a global application that allows considering the calibration step as part of the dosimetry procedure (*a missing feature in all existing software*), and the storage and possible input/output of intermediary stages of de dosimetry procedure. This will not only allow processing data in different sessions if needed, but also to compare the intermediary results obtained using different approaches/software.

Last, export of results and relevant dosimetric variables in the IRDBB was tested, thereby populating the database and allowing further retrospective analysis of the results based on a range of dosimetric parameters.

The development of the software (OpenDose3D) has been structured from the start as an open source project and participates to the OpenDose collaboration (www.opendose.org). This means free access to the sources via a gitlab project (https://gitlab.com/opendose/opendose3d), and association of partners for the development, debugging and validation. It is believed that this is a way to ensure sustainable development – and provide the software a life expectancy that goes beyond the MEDIRAD project duration.

The development phase is globally completed and the software was validated on test-cases provided by clinical centres (Fig. 2). The preliminary results were presented at the EANM congress in October 2020[2].

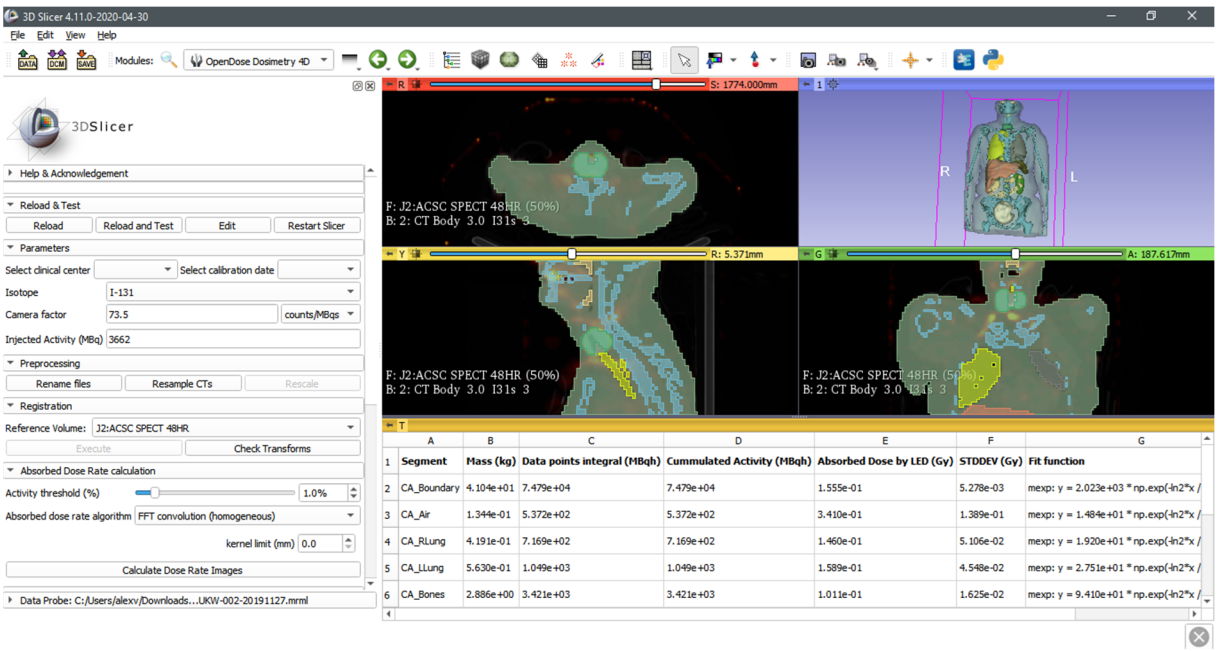

Fig 2: Presentation of the dosimetric software interface for a MEDIRAD WP3 patient.

[2] A. Vergara Gil, E. Amato, L. Auditore, M. Brenet, M. Chauvin, et al.. OpenDose3D: A free, collaborative 3D Slicer module for patient-specific dosimetry. *European Journal of Nuclear Medicine and Molecular Imaging*, Springer Verlag (Germany), 2020, 47 (SUPPL 1), pp.S314-S315. ⟨hal-03095450⟩

4. Clinical scenario considered

4.1 ^{18}F-labeled diagnostic radiopharmaceutical for PET-based dosimetry

In order to progress and perform Subtask 2.3.2.2 work without waiting for patient recruitment, it was considered to process clinical data used in a previous study [1]. In that study, 6 patients received an injection of a fluorinated brain tracer, and underwent sequential quantitative PET imaging to derive pharmacokinetics and dosimetry. The initial study was performed using OLINDA (basically complying with ICRP 60 recommendations). Our work aimed at comparing that model-based dosimetry study with patient-specific approaches, using a vendor-specific software (STRATOS) designed for molecular radiotherapy or direct monte Carlo modelling (GEANT4). The conclusion was that accurate diagnostic dosimetry required specific software able to compute absorbed doses at a distance from radioactive sources.

The decision was taken to reprocess the data according to the procedure presented in Figure 1, perform patient-specific dosimetry using OpenDose3D and Monte Carlo modelling, then perform dosimetry according to ICRP 103 recommendations using IDAC-Dose 2.1[3]

The comparison of the results helps in appraising how *administered activity-to-organ-dose conversion factors* vary from one approach to the other, at least in the case of a ^{18}F-Labelled tracer.

The patient-specific dosimetry software (OpenDose3D) was updated to allow processing of ^{18}F dosimetry. An illustration is presented in Figure 3.

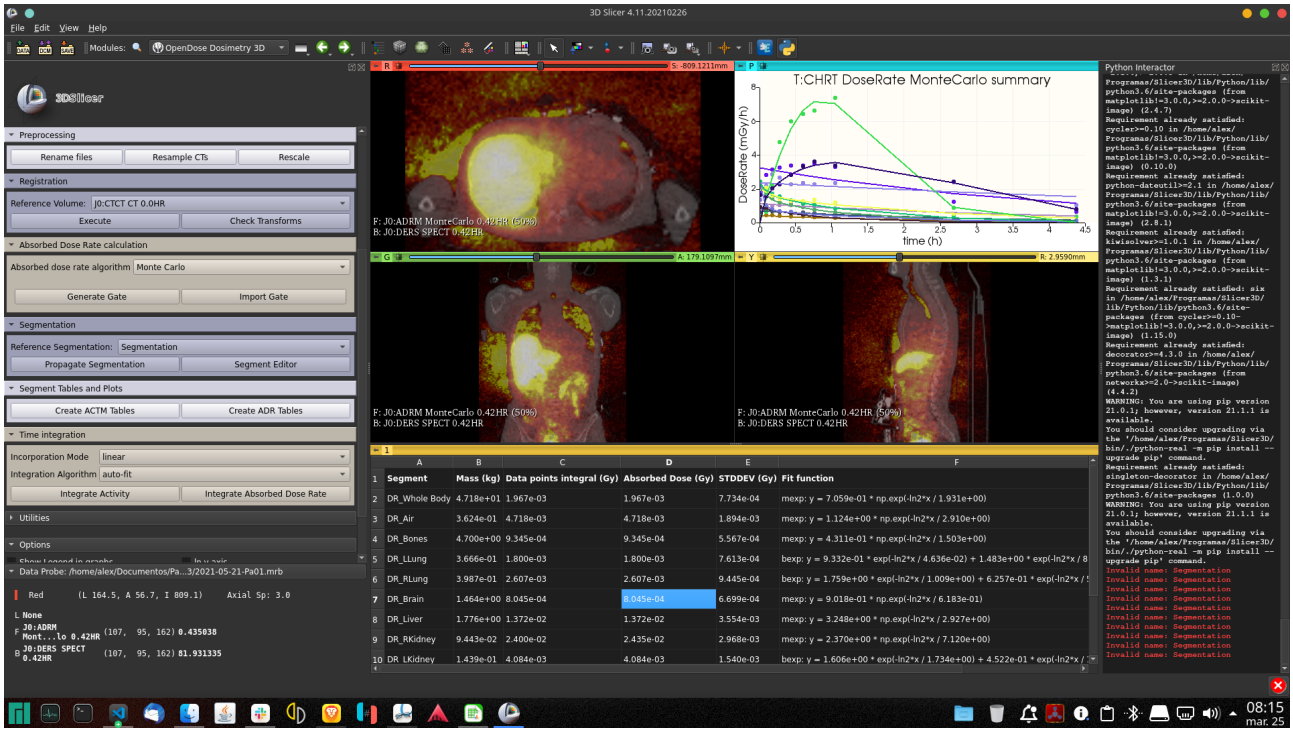

Fig. 3: Preliminary dosimetry results for a ^{18}F-labelled diagnostic tracer, using Monte Carlo (GATE).

[3] https://www.idac-dose.org

4.2 ^{131}I for SPECT-based dosimetry

As no ^{99m}Tc-labelled tracer imaging dataset was available, it was decided to analyse a subset of the patients included in WP3 (T3.3). Within the 25 patients enrolled at RMH for post thyroid ablation therapy dosimetry, 13 who benefited from 3 time-points image acquisitions were included in the Subtask 2.3.2.2 study.

It is acknowledged that the radiopharmaceutical is not administered in a context of diagnostic, however the absorbed doses at a distance from the main source (in the neck region) are low and can be used for the sake of the comparison between patient-specific and model-based reference dosimetry. The values obtained may therefore be taken to demonstrated the added value of the approach.

The patient-specific dosimetry software (OpenDose3D) was used with ^{131}I SPECT/CT images to perform dosimetry and obtain cumulated activities and residence times (time-integrated activities and time-integrated activity coefficients), i.e. pharmacokinetics parameters of interest to IDAC-Dose.

4.3 Diagnostic dosimetry ^{18}F comparative study

4.3.1 Methodology

The data consisted in a series of PET/CT. Basically 8 acquisitions were performed in a single dynamic PET/CT, followed by two single PET/CT after 2 and 4 hours respectively. All CT images were calibrated and expressed in HU units. All PET images were quantitative and expressed in Bq/ml. The acquisition started at the time of the tracer injection, therefore there was no incorporation time to consider. Table 1 shows the relevant patient data.

Subject ID	Sex	Age	Race	Height (cm)	Weight (kg)	BMI (kg/m2)	Injected Activity (MBq)
Patient 1	M	73	Caucasian	165	63	23.1	95.8
Patient 2	M	73	Caucasian	172	70	23.7	97.2
Patient 3	F	71	Caucasian	153	58	24.8	139.1
Patient 4	M	73	Caucasian	160	71	27.7	143.9

Table 1: Patient data considered in this report.

The dosimetry was performed using OpenDose3D (OD3D). As PET images were expressed in Bq/ml. Multiplying activity concentrations by the voxel volume yield activity-indexed images. Similarly, the CT image was transformed into a density-indexed image by the use of the Schneider curve [2].

Voxel-based absorbed dose rates at all time points were calculated for the whole FOV, using Monte Carlo simulation with voxelized source and density map generated directly from patient data. Absorbed dose rates (ADR) were obtained using dockerized Gate 9.1. Simulations took 3 days per patient in a workstation (AMD Ryzen2700X 16 cores, 32GB RAM) as the number of time points was very large (10) and taking over 30GB of RAM in total. The ADR were then imported back to OD3D. Since ADR calculation is performed voxel-wise, this step requires no *a priori* segmentation.

The segmentation was performed using tools available in Slicer3D. Depending on the situation, manual or threshold-based segmentation was made on the density map (CT) or the activity map (PET). This provided both ADR and activity in organs at different time points.

Time integration was performed using mono-exponential fit function. ADR were integrated into absorbed doses in VOI and, in addition the cumulated activities (time-integrated activities) were also integrated from the activities, for comparison with the original study.

For the bladder, the absorbed dose computed in the bladder contents was divided by a factor 2 to estimate the absorbed dose to the bladder wall (approximation of semi-infinite medium).

Equivalent doses were obtained based on the ICRP60[3] and ICRP103 [4] recommendations, manually on Excel using the absorbed doses calculated in identified VOI. For target organs not segmented the absorbed dose in remainder of the body (considered homogeneous) was used and multiplied by the recommended tissue weighting factors (Wt). In parallel, effective doses were also calculated using IDAC 2.1 [5], based on patient-averaged residence times in VOI, with no mass

correction (reference dosimetry). This allowed the comparison of effective doses based on patient specific dosimetry with effective doses based on average residence times in reference models.

4.3.2 Results

Table 2 shows the results for the volumes of interest (VOI) on the patients evaluated.

VOI	Modality	Segmentation Mode	Patient 1		Patient 2		Patient 3		Patient 4	
			Volume (cm3)	Mass (kg)	Volume (cm3)	Mass (kg)	Volume (cm3)	Mass (kg)	Volume (cm3)	Mass (kg)
Whole Body	CT	Threshold	4.84E+04	4.72E+01	4.99E+04	4.53E+01	4.66E+04	4.42E+01	5.15E+04	5.07E+01
Left lung	CT	Threshold	1.22E+03	3.67E-01	1.44E+03	4.44E-01	7.11E+02	1.94E-01	1.46E+03	5.50E-01
Right lung	CT	Threshold	1.24E+03	3.99E-01	1.92E+03	5.30E-01	8.43E+02	2.26E-01	1.55E+03	5.19E-01
Bones	CT	Threshold	3.20E+03	4.70E+00	4.59E+03	5.42E+00	2.52E+03	3.29E+00	3.86E+03	4.56E+00
Liver	CT	Manual	1.79E+03	1.78E+00	1.28E+03	1.30E+00	1.21E+03	1.22E+00	1.62E+03	1.61E+00
Right kidney	CT	Manual	9.92E+01	9.44E-02	1.18E+02	1.15E-01	1.49E+02	1.49E-01	1.73E+02	1.64E-01
Left kidney	CT	Manual	1.49E+02	1.44E-01	1.49E+02	1.45E-01	8.43E+01	8.46E-02	2.62E+02	2.51E-01
Spleen	CT	Manual	1.62E+02	1.61E-01	1.06E+02	1.05E-01	7.88E+01	7.80E-02	1.04E+02	9.78E-02
Bladder	PET	Threshold – Manual	1.11E+02	1.06E-01	1.69E+02	1.57E-01	1.07E+02	1.06E-01	1.22E+02	1.19E-01
Brain	PET	Threshold – Manual	1.42E+03	1.46E+00	1.27E+03	1.33E+00	1.41E+03	1.46E+00	1.39E+03	1.43E+00

Table 2. Segmented VOI.

Table 3 shows the absorbed doses (AD) for each organ calculated by Monte Carlo (GATE).

Segment	Patient 1	Patient 2	Patient 3	Patient 4
	Absorbed Dose (mGy)	Absorbed Dose (mGy)	Absorbed Dose (mGy)	Absorbed Dose (mGy)
Whole Body	1.97	2.06	2.84	2.57
Left lung	1.80	2.89	2.47	3.86
Right lung	2.61	3.54	4.78	6.96
Bones	0.94	1.18	1.73	1.81
Liver	13.70	4.79	17.28	10.85
Right kidney	24.40	3.56	5.11	6.82
Left kidney	4.08	4.53	5.49	3.32
Spleen	1.38	8.29	2.35	3.11
Bladder	6.00	13.55	6.05	3.20
Brain	0.81	0.75	0.89	1.15
Remainder	1.47	1.90	2.48	2.24

Table 3: Absorbed dose for the selected patients in the segmented ROI.

Table 4 presents the equivalent/effective doses derived from calculated AD from table 3 and calculated following the ICRP 60 [3] recommendations. Equivalent doses were calculated by multiplying absorbed doses per administered activity by the radiation weighting factor (W_R=1 here). Then, for each organ/tissue k listed in ICRP 60, the product $W_k \times \overline{D}_k$ was performed.

For example the equivalent dose presented for patient 1 in the liver (7.15E-3 mSv/MBq) is obtained by dividing the absorbed dose to the liver (13.70 mGy) by the administered activity (95.8 MBq) and multiplying with the liver tissue weighting factor (0.05).

Equivalent Dose ICRP 60 (mSv/MBq)							
Organ	*Wt*	*Patient 1*	*Patient 2*	*Patient 3*	*Patient 4*	*Average*	*StdDev*
Bone-marrow (red)	0.12	1.81E-06	2.29E-06	2.09E-06	1.83E-06	2.00E-06	2.28E-07
Colon	0.12	1.81E-06	2.29E-06	2.09E-06	1.83E-06	2.00E-06	2.28E-07
Lung	0.12	2.78E-03	4.00E-03	3.20E-03	4.47E-03	3.62E-03	7.64E-04
Stomach	0.12	1.81E-06	2.29E-06	2.09E-06	1.83E-06	2.00E-06	2.28E-07
Breast	0.05	7.53E-07	9.54E-07	8.70E-07	7.64E-07	8.35E-07	9.49E-08
Remainder	0.05	4.07E-03	2.73E-03	1.63E-03	1.53E-03	2.49E-03	1.19E-03
Gonads	0.2	3.01E-06	3.81E-06	3.48E-06	3.06E-06	3.34E-06	3.48E-07
Bladder	0.05	6.26E-03	6.97E-03	2.17E-03	1.11E-03	4.13E-03	2.92E-03
Oesophagus	0.05	7.53E-07	9.54E-07	8.70E-07	7.64E-07	8.35E-07	9.49E-08
Liver	0.05	7.15E-03	2.46E-03	6.21E-03	3.77E-03	4.90E-03	2.16E-03
Thyroid	0.05	7.53E-07	9.54E-07	8.70E-07	7.64E-07	8.35E-07	9.49E-08
Bone	0.01	9.76E-05	1.21E-04	1.24E-04	1.25E-04	1.17E-04	1.31E-05
Skin	0.01	1.51E-07	1.91E-07	1.74E-07	1.53E-07	1.67E-07	1.90E-08
Effective Dose (mSv/MBq)		2.04E-02	1.63E-02	1.33E-02	1.10E-02	1.53E-02	4.04E-03

Table 4: Effective dose calculated following ICRP 60 [3]

Table 5 presents the equivalent/effective doses derived from calculated AD from table 3 and calculated following the ICRP103 [4] recommendations. The principles remain the same as for the previous results, but the absorbed dose calculation is performed based on the more recent reference adult males/female models (presented in ICRP 110), by averaging the equivalent doses obtained separately for male and female and by using an updated tissue radiation weighting factor dataset. Notice that radiation weighting factors are the same in this situation.

Equivalent Dose ICRP 103 (mSv/MBq)							
Organ	*Wt*	*Patient 1*	*Patient 2*	*Patient 3*	*Patient 4*	*Average*	*StdDev*
Bone-marrow (red)	0.12	1.84E-06	2.34E-06	2.14E-06	1.86E-06	2.05E-06	2.39E-07
Colon	0.12	1.84E-06	2.34E-06	2.14E-06	1.86E-06	2.05E-06	2.39E-07
Lung	0.12	2.78E-03	4.00E-03	3.20E-03	4.47E-03	3.62E-03	7.64E-04
Stomach	0.12	1.84E-06	2.34E-06	2.14E-06	1.86E-06	2.05E-06	2.39E-07
Breast	0.12	1.84E-06	2.34E-06	2.14E-06	1.86E-06	2.05E-06	2.39E-07
Remainder	0.12	9.76E-03	6.55E-03	3.90E-03	3.67E-03	5.97E-03	2.85E-03
Gonads	0.08	1.23E-06	1.56E-06	1.43E-06	1.24E-06	1.36E-06	1.59E-07
Bladder	0.04	5.01E-03	5.58E-03	1.74E-03	8.89E-04	3.30E-03	2.33E-03
Oesophagus	0.04	6.13E-07	7.80E-07	7.14E-07	6.22E-07	6.82E-07	7.97E-08
Liver	0.04	5.72E-03	1.97E-03	4.97E-03	3.02E-03	3.92E-03	1.73E-03
Thyroid	0.04	6.13E-07	7.80E-07	7.14E-07	6.22E-07	6.82E-07	7.97E-08
Bone	0.01	9.76E-05	1.21E-04	1.24E-04	1.25E-04	1.17E-04	1.31E-05
Brain	0.01	8.40E-05	7.72E-05	6.37E-05	8.01E-05	7.62E-05	8.81E-06
Salivary glands	0.01	1.53E-07	1.95E-07	1.78E-07	1.55E-07	1.71E-07	1.99E-08
Skin	0.01	1.53E-07	1.95E-07	1.78E-07	1.55E-07	1.71E-07	1.99E-08
Effective Dose (mSv/MBq)		2.35E-02	1.83E-02	1.40E-02	1.23E-02	1.70E-02	5.00E-03

Table 5: Effective doses calculated following ICRP 103 [4]

Table 6 presents the comparison of effective doses obtained using different approaches.

Effective Dose per Unit Administered Activity (mSv/MBq)		
Subject	ICRP60	ICRP103
Patient 1	2.04E-02	2.35E-02
Patient 2	1.63E-02	1.83E-02
Patient 3	1.33E-02	1.40E-02
Patient 4	1.10E-02	1.23E-02
Mean	**1.53E-02**	**1.70E-02**
StdDev	**4.04E-03**	**5.00E-03**
Maximum	2.04E-02	2.35E-02
Minimum	1.10E-02	1.23E-02

Table 6: Comparison of effective doses: ICRP60 [3] vs. ICRP103 [4] recommendations.

Table 7 presents residence times (OD3D) and effective doses calculated with IDAC 2.1 [5]

Effective Dose IDAC 2.1	Average residence time (h)		
Organ	Male (3 pat)	Female (1 pat)	Average (4 pat)
Whole Body	2.321	2.408	2.343
Bones	0.088	0.067	0.083
LLung	0.032	0.013	0.027
RLung	0.059	0.025	0.051
Brain	0.044	0.048	0.045
Liver	0.429	0.605	0.473
RKidney	0.038	0.009	0.031
LKidney	0.017	0.010	0.015
Spleen	0.003	0.002	0.003
Bladder	0.086	0.044	0.076
Effective Dose ICRP60 (mSv/MBq)	--		***1.49E-02***
Effective Dose ICRP103 (mSv/MBq)	**1.57E-02**		--

Table 7: Effective dose calculations using IDAC 2.1[5].

Figure 4 shows a graphical comparison of this work against results obtained using IDAC 2.1.

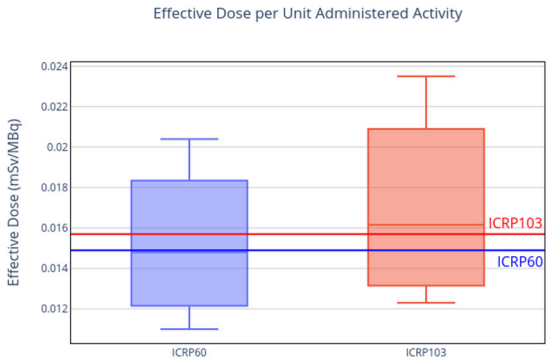

Figure 4. Box plot of the effective dose compared with IDAC 2.1 (horizontal lines).

4.4. "pseudo-diagnostic" dosimetry 131I comparative study

4.4.1 Methodology

The data consisted in a series of SPECT and SPECT/CT. Basically 3 acquisitions were performed, 1 SPECT at 24h, 1 SPECT/CT at 48h and 1 SPECT at 96h. The CT was used in all time points, after registration, for attenuation correction. All CT images were calibrated and expressed in HU units. All SPECT images were expressed in counts.

For these patients, the field of view (FOV) is from head to torso, so no abdominal structures could be segmented. Table 8 shows the relevant patient data.

Patient	Time points	FOV	Sex	Height (cm)	Weight (kg)	Activity Injected	Observations
RMH-006	3	Head, Torso	Male	171	61	3591	low statistics in 72h
RMH-011	3	Head, Torso	Female	167	60.2	3132	
RMH-013	3	Head, Torso	Male	174.7	106.3	3604	
RMH-014	3	Head, Torso	Female	164	59.2	3669	
RMH-015	3	Head, Torso	Male	189.5	133.6	3736	very large volume in neck incorporation
RMH-016	3	Head, Torso	Male	175	65.1	3685	low statistics in 72h
RMH-018	3	Head, Torso	Male	188	181.6	3803	weird patient position
RMH-020	3	Head, Torso	Female	163.5	55.6	3564	Low neck activity
RMH-021	3	Head, Torso	Female	160	93.5	1060	
RMH-022	3	Head, Torso	Female	157	90.7	3583	very large volume in neck incorporation
RMH-023	3	Head, Torso	Female	166.5	122	3537	very large volume in neck incorporation
RMH-024	3	Head, Torso	Female	158	102.8	3653	
RMH-025	3	Head, Torso	Female	161	59.7	3811	

Table 8: Patient data considered in this report.

The dosimetry was performed using OpenDose3D (OD3D), a patient-specific dosimetry software based on 3D SLICER, specifically developed for the MEDIRAD project.

All SPECT images were expressed in counts and converted to activity using the SPECT sensitivity of 62.4 cps/MBq given by the clinical centre (RMH). Similarly, the CT image was transformed into a density-indexed image by the use of the Schneider curve [1].

Voxel-based absorbed dose rates *at all time points* were calculated for the whole FOV, using Monte Carlo simulation with voxelized source and density map generated directly from patient data.

The CT was propagated to each time point following the same registration procedure as for attenuation correction. Absorbed dose rates (ADR) were obtained using dockerized Gate 9.1. Simulations took 8 hours per patient in a workstation (AMD Ryzen2700X 16 cores, 32GB RAM). As the number of time points was 3, the simulation took around 5GB of RAM in total. The ADR were imported back to OD3D.

The segmentation was then performed using tools available in Slicer3D. Depending on the situation, manual or threshold-based segmentation was made on the density map (CT) or the activity map (PET). Since patients were scanned from neck to torso, segmented (visualised) structures can differ, from one patient to the next. Structures considered are the lungs (left/right), the salivary glands, the bones visible in the field of view (FOV) and the neck region (even though the functional volume defined may hide high activity gradients in microscopic regions). The total body mass was documented for each patient before the imaging sessions. The remainder was defined as the total body minus all defined volumes of interest. This provided both ADR and Activity in organs at different time points.

Time integration was performed using mono-exponential fit function (3 time points only). ADR were integrated into absorbed doses in VOI, and in addition the activities were also integrated to allow the use of model-based reference dosimetry (IDAC-Dose v2.1 [5]).

Equivalent doses were obtained following ICRP60[3] and ICRP103 [4] recommendations, manually on Excel using the absorbed doses calculated in identified VOI. For target organs not segmented the absorbed dose in remainder of the body considered homogeneous was used and multiplied by the recommended tissue weighting factors (Wt).

In parallel, effective doses were also calculated using IDAC, based on patient-averaged residence times in VOI, with no mass corrections. It was then possible to compare effective doses based on patient specific dosimetry with conventional effective doses based on average residence times in reference models.

4.4.2 Results

Table 9 shows the results for the volumes of interest (VOI) of the organs/tissues considered

Patient	Mass (kg)								
	Body FOV	Left Lung	Right Lung	Bones FOV	Salivary Glands	Neck	Remainder FOV	Remainder	Total Body
RMH-006	1.40E+01	1.07E-02	2.95E-01	3.54E-01	2.12E+00	4.08E-02	3.98E-02	1.12E+01	5.81E+01
RMH-011	9.98E+00	6.59E-01	3.53E-01	2.89E-01	1.56E+00	8.57E-02	3.25E-02	7.00E+00	5.72E+01
RMH-013	1.58E+01	8.80E-03	1.95E-01	2.38E-01	1.43E+00	3.28E-02	6.75E-02	1.39E+01	1.04E+02
RMH-014	1.28E+01	1.84E-02	3.18E-01	3.33E-01	1.67E+00	1.94E-02	3.03E-02	1.04E+01	5.68E+01
RMH-015	2.67E+01	1.35E-02	2.24E-01	3.05E-01	2.47E+00	7.17E-02	4.30E-02	2.36E+01	1.30E+02
RMH-016	1.44E+01	1.39E-02	2.90E-01	3.21E-01	1.90E+00	3.71E-02	2.86E-02	1.18E+01	6.25E+01
RMH-018	4.60E+01	1.40E-02	2.66E-01	3.07E-01	3.20E+00	3.03E-02	9.00E-02	4.21E+01	1.78E+02
RMH-020	1.22E+01	9.83E-03	3.01E-01	3.25E-01	1.53E+00	1.15E-02	9.22E-03	1.00E+01	5.34E+01
RMH-021	2.11E+01	7.50E-03	2.35E-01	2.88E-01	1.77E+00	1.41E-02	3.69E-02	1.87E+01	9.12E+01
RMH-022	2.66E+01	7.33E-03	1.28E-01	1.53E-01	1.64E+00	8.67E-03	1.63E-01	2.45E+01	8.86E+01
RMH-023	2.88E+01	8.49E-03	1.91E-01	2.69E-01	2.08E+00	1.65E-02	6.61E-02	2.62E+01	1.19E+02
RMH-024	2.99E+01	5.87E-03	2.45E-01	2.06E-01	1.80E+00	2.14E-02	3.49E-02	2.76E+01	1.00E+02
RMH-025	1.62E+01	1.25E-02	2.12E-01	2.54E-01	1.56E+00	3.21E-02	3.45E-02	1.41E+01	5.55E+01

Table 9. Segmented VOI. Remainder is an extrapolation, patient total body mass is reported

Table 10 shows the absorbed doses (AD) for each organ calculated by Monte Carlo.

Patient	Absorbed Dose (mGy/MBq)								
	Body FOV	Left Lung	Right Lung	Bones FOV	Salivary Glands	Neck	Remainder FOV	Remainder	Total Body
RMH-006	5.59E-02	1.59E-01	1.55E-01	2.93E-02	1.56E-01	2.29E-01	5.42E-02	5.42E-02	5.46E-02
RMH-011	2.60E-02	6.34E-02	7.80E-02	2.93E-02	1.17E-01	9.20E-02	2.23E-02	2.23E-02	2.29E-02
RMH-013	2.39E-02	4.45E-02	5.10E-02	2.47E-02	6.91E-02	8.10E-02	2.27E-02	2.27E-02	2.29E-02
RMH-014	2.60E-02	8.31E-02	6.77E-02	2.88E-02	1.50E-01	1.21E-01	2.20E-02	2.20E-02	2.28E-02
RMH-015	3.09E-02	4.29E-02	5.16E-02	2.45E-02	7.51E-02	5.09E+00	6.19E-03	6.19E-03	1.11E-02
RMH-016	4.18E-02	1.02E-01	1.15E-01	2.14E-02	7.59E-02	1.36E+00	3.83E-02	3.83E-02	3.91E-02
RMH-018	2.48E-02	5.00E-02	5.95E-02	2.64E-02	5.52E-02	3.00E-01	2.38E-02	2.38E-02	2.41E-02
RMH-020	2.25E-02	4.77E-02	4.23E-02	2.33E-02	1.15E-01	5.37E-02	2.17E-02	2.17E-02	2.19E-02
RMH-021	2.25E-02	4.77E-02	4.23E-02	2.33E-02	1.15E-01	5.37E-02	2.17E-02	2.17E-02	2.19E-02
RMH-022	5.40E-02	9.10E-02	9.39E-02	5.77E-02	2.34E-01	4.75E+00	2.20E-02	2.20E-02	3.14E-02
RMH-023	2.66E-02	4.89E-02	4.84E-02	2.67E-02	1.11E-01	1.37E+00	2.28E-02	2.28E-02	2.37E-02
RMH-024	3.40E-02	7.60E-02	7.30E-02	3.47E-02	1.85E-01	1.24E-01	3.30E-02	3.30E-02	3.33E-02
RMH-025	4.30E-02	1.14E-01	7.86E-02	3.98E-02	2.62E-01	5.99E-01	3.98E-02	3.98E-02	4.07E-02

Table 10: Absorbed dose for the selected patients in the segmented ROI.

Table 11 shows the calculated equivalent/effective doses using the ICRP60 [2] recommendations derived from the calculated AD from table 3.

Equivalent Dose ICRP 60 (mSv/MBq)														
Organ	*Bone-marrow (red)*	*Colon*	*Lung*	*Stomach*	*Breast*	*Remainder*	*Gonads*	*Bladder*	*Oesophagus*	*Liver*	*Thyroid*	*Bone*	*Skin*	*Effective Dose (mSv/MBq)*
Wt	0.12	0.12	0.12	0.12	0.05	0.05	0.2	0.05	0.05	0.05	0.05	0.01	0.01	1
RMH-006	6.50E-03	6.50E-03	1.88E-02	6.50E-03	2.71E-03	2.71E-03	1.08E-02	2.71E-03	2.71E-03	2.71E-03	1.15E-02	2.93E-04	5.42E-04	7.50E-02
RMH-011	2.68E-03	2.68E-03	8.48E-03	2.68E-03	1.12E-03	1.12E-03	4.46E-03	1.12E-03	1.12E-03	1.12E-03	4.60E-03	2.93E-04	2.23E-04	3.17E-02
RMH-013	2.72E-03	2.72E-03	5.73E-03	2.72E-03	1.14E-03	1.14E-03	4.54E-03	1.14E-03	1.14E-03	1.14E-03	4.05E-03	2.47E-04	2.27E-04	2.86E-02
RMH-014	2.64E-03	2.64E-03	9.05E-03	2.64E-03	1.10E-03	1.10E-03	4.40E-03	1.10E-03	1.10E-03	1.10E-03	6.05E-03	2.88E-04	2.20E-04	3.34E-02
RMH-015	7.43E-04	7.43E-04	5.67E-03	7.43E-04	3.10E-04	3.10E-04	1.24E-03	3.10E-04	3.10E-04	3.10E-04	2.55E-01	2.45E-04	6.19E-05	2.65E-01
RMH-016	4.60E-03	4.60E-03	1.30E-02	4.60E-03	1.92E-03	1.92E-03	7.66E-03	1.92E-03	1.92E-03	1.92E-03	6.80E-02	2.14E-04	3.83E-04	1.13E-01
RMH-018	2.86E-03	2.86E-03	6.57E-03	2.86E-03	1.19E-03	1.19E-03	4.76E-03	1.19E-03	1.19E-03	1.19E-03	1.50E-02	2.64E-04	2.38E-04	4.14E-02
RMH-020	2.60E-03	2.60E-03	5.40E-03	2.60E-03	1.09E-03	1.09E-03	4.34E-03	1.09E-03	1.09E-03	1.09E-03	2.69E-03	2.33E-04	2.17E-04	2.61E-02
RMH-021	2.60E-03	2.60E-03	5.40E-03	2.60E-03	1.09E-03	1.09E-03	4.34E-03	1.09E-03	1.09E-03	1.09E-03	2.69E-03	2.33E-04	2.17E-04	2.61E-02
RMH-022	2.64E-03	2.64E-03	1.11E-02	2.64E-03	1.10E-03	1.10E-03	4.40E-03	1.10E-03	1.10E-03	1.10E-03	2.38E-01	5.77E-04	2.20E-04	2.67E-01
RMH-023	2.74E-03	2.74E-03	5.84E-03	2.74E-03	1.14E-03	1.14E-03	4.56E-03	1.14E-03	1.14E-03	1.14E-03	6.85E-02	2.67E-04	2.28E-04	9.33E-02
RMH-024	3.96E-03	3.96E-03	8.94E-03	3.96E-03	1.65E-03	1.65E-03	6.60E-03	1.65E-03	1.65E-03	1.65E-03	6.20E-03	3.47E-04	3.30E-04	4.25E-02
RMH-025	4.78E-03	4.78E-03	1.16E-02	4.78E-03	1.99E-03	1.99E-03	7.96E-03	1.99E-03	1.99E-03	1.99E-03	3.00E-02	3.98E-04	3.98E-04	7.45E-02
Average	3.24E-03	3.24E-03	8.89E-03	3.24E-03	1.35E-03	1.35E-03	5.39E-03	1.35E-03	1.35E-03	1.35E-03	5.47E-02	3.00E-04	2.70E-04	8.60E-02
Std dev	1.42E-03	1.42E-03	3.95E-03	1.42E-03	5.91E-04	5.91E-04	2.36E-03	5.91E-04	5.91E-04	5.91E-04	8.80E-02	9.72E-05	1.18E-04	8.47E-02

Table 11: Effective dose calculated with ICRP 60 [2] approach.

Table 12 shows the calculated equivalent/effective dose using the ICRP103 [3] recommendations derived from the calculated AD from table 3.

Equivalent Dose ICRP 103 (mSv/MBq)																
Organ	*Bone-marrow (red)*	*Colon*	*Lung*	*Stomach*	*Breast*	*Remainder*	*Gonads*	*Bladder*	*Oesophagus*	*Liver*	*Thyroid*	*Bone*	*Brain*	*Salivary glands*	*Skin*	*Effective Dose (mSv/MBq)*
Wt	*0.12*	*0.12*	*0.12*	*0.12*	*0.12*	*0.12*	*0.08*	*0.04*	*0.04*	*0.04*	*0.04*	*0.01*	*0.01*	*0.01*	*0.01*	*1*
RMH-006	6.50E-03	6.50E-03	1.88E-02	6.50E-03	6.50E-03	6.50E-03	4.34E-03	2.17E-03	2.17E-03	2.17 E-03	9.16E-03	2.93E-04	5.42E-04	1.56E-03	5.42E-04	7.43E-02
RMH-011	2.68E-03	2.68E-03	8.48E-03	2.68E-03	2.68E-03	2.68E-03	1.78E-03	8.92E-04	8.92E-04	8.92 E-04	3.68E-03	2.93E-04	2.23E-04	1.17E-03	2.23E-04	3.19E-02
RMH-013	2.72E-03	2.72E-03	5.73E-03	2.72E-03	2.72E-03	2.72E-03	1.82E-03	9.08E-04	9.08E-04	9.08 E-04	3.24E-03	2.47E-04	2.27E-04	6.91E-04	2.27E-04	2.85E-02
RMH-014	2.64E-03	2.64E-03	9.05E-03	2.64E-03	2.64E-03	2.64E-03	1.76E-03	8.80E-04	8.80E-04	8.80 E-04	4.84E-03	2.88E-04	2.20E-04	1.50E-03	2.20E-04	3.37E-02
RMH-015	7.43E-04	7.43E-04	5.67E-03	7.43E-04	7.43E-04	7.43E-04	4.95E-04	2.48E-04	2.48E-04	2.48 E-04	2.04E-01	2.45E-04	6.19E-05	7.51E-04	6.19E-05	2.15E-01
RMH-016	4.60E-03	4.60E-03	1.30E-02	4.60E-03	4.60E-03	4.60E-03	3.06E-03	1.53E-03	1.53E-03	1.53 E-03	5.44E-02	2.14E-04	3.83E-04	7.59E-04	3.83E-04	9.98E-02
RMH-018	2.86E-03	2.86E-03	6.57E-03	2.86E-03	2.86E-03	2.86E-03	1.90E-03	9.52E-04	9.52E-04	9.52 E-04	1.20E-02	2.64E-04	2.38E-04	5.52E-04	2.38E-04	3.89E-02
RMH-020	2.60E-03	2.60E-03	5.40E-03	2.60E-03	2.60E-03	2.60E-03	1.74E-03	8.68E-04	8.68E-04	8.68 E-04	2.15E-03	2.33E-04	2.17E-04	1.15E-03	2.17E-04	2.67E-02
RMH-021	2.60E-03	2.60E-03	5.40E-03	2.60E-03	2.60E-03	2.60E-03	1.74E-03	8.68E-04	8.68E-04	8.68 E-04	2.15E-03	2.33E-04	2.17E-04	1.15E-03	2.17E-04	2.67E-02
RMH-022	2.64E-03	2.64E-03	1.11E-02	2.64E-03	2.64E-03	2.64E-03	1.76E-03	8.80E-04	8.80E-04	8.80 E-04	1.90E-01	5.77E-04	2.20E-04	2.34E-03	2.20E-04	2.22E-01
RMH-023	2.74E-03	2.74E-03	5.84E-03	2.74E-03	2.74E-03	2.74E-03	1.82E-03	9.12E-04	9.12E-04	9.12 E-04	5.48E-02	2.67E-04	2.28E-04	1.11E-03	2.28E-04	8.07E-02
RMH-024	3.96E-03	3.96E-03	8.94E-03	3.96E-03	3.96E-03	3.96E-03	2.64E-03	1.32E-03	1.32E-03	1.32 E-03	4.96E-03	3.47E-04	3.30E-04	1.85E-03	3.30E-04	4.32E-02
RMH-025	4.78E-03	4.78E-03	1.16E-02	4.78E-03	4.78E-03	4.78E-03	3.18E-03	1.59E-03	1.59E-03	1.59 E-03	2.40E-02	3.98E-04	3.98E-04	2.62E-03	3.98E-04	7.12E-02
Average	3.24E-03	3.24E-03	8.89E-03	3.24E-03	3.24E-03	3.24E-03	2.16E-03	1.08E-03	1.08E-03	1.08 E-03	4.38E-02	3.00E-04	2.70E-04	1.32E-03	2.70E-04	7.64E-02
Std dev	1.42E-03	1.42E-03	3.95E-03	1.42E-03	1.42E-03	1.42E-03	9.45E-04	4.73E-04	4.73E-04	4.73 E-04	7.04E-02	9.72E-05	1.65E-03	6.36E-04	1.18E-04	6.75E-02

Table 12: Effective dose calculated with ICRP 103 [3] approach.

Table 13 shows the comparison of effective dose using the different approaches.

Effective Dose (mSv/MBq)		
Subject	ICRP60	ICRP103
RMH-006	0.075	0.074
RMH-011	0.032	0.032
RMH-013	0.029	0.029
RMH-014	0.033	0.034
RMH-015	0.265	0.215
RMH-016	0.113	0.100
RMH-018	0.041	0.039
RMH-020	0.026	0.027
RMH-021	0.026	0.027
RMH-022	0.267	0.222
RMH-023	0.093	0.081
RMH-024	0.043	0.043
RMH-025	0.075	0.071
Average	8.60E-02	7.64E-02
Std dev	8.47E-02	6.75E-02

Table 13: Comparison of effective dose using tissue weighting factors accordingly to ICRP60 [2] and ICRP103 [3] publications.

Table 14 shows the residence times obtained (OD3D) and the effective doses (IDAC 2.1 [4])

Effective Dose IDAC 2.1	Average residence time (h)		
Organ	Male (5 pat)	Female (8 pat)	Average (13 pat)
Body FOV	2.69	3.30	3.06
Lungs	0.09	0.10	0.10
Bones FOV	0.26	0.27	0.27
Salivary Glands	0.03	0.03	0.03
Neck	0.52	0.77	0.67
Remainder	15.25	14.54	14.81
Effective Dose ICRP60 (mSv/MBq)	--		***1.53E-01***
Effective Dose ICRP103 (mSv/MBq)	**1.24E-01**		--

Table 14: Effective dose calculations using IDAC 2.1[4].

Figure 5 shows the graphical comparison of the results obtained (OD3D vs. IDAC 2.1).

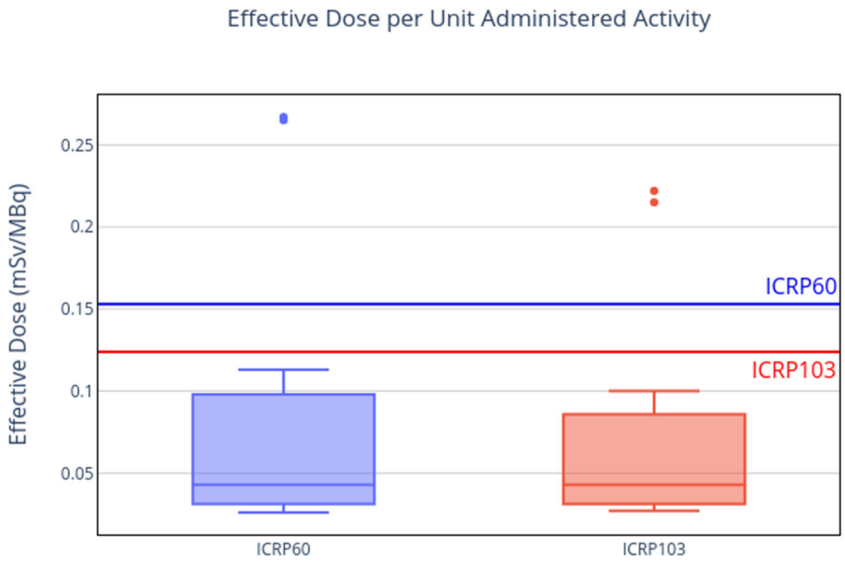

Figure 5. Box plot of the effective dose dispersion per patient calculated in this work and compared to the results obtained with IDAC 2.1 (horizontal lines).

5. Discussion

For the ^{18}F-labelled diagnostic tracer considered in this study, it is noted that the effective doses reported by IDAC2.1 match the calculated values for both ICRP60 (RD=2.4%) and ICRP103 (RD=7.7%) approaches. However, the patient-specific calculation allows the appraisal of the dispersion around mean absorbed doses.

For the ^{131}I "pseudo-diagnostic" tracer considered in this study, it is noted that the effective doses reported by IDAC2.1 are higher (200%) than the median of our calculated values. This requires further investigations, but an explanation may be related to the variability of the geometries considered. As the irradiation varies with distance according to the inverse square law, the Monte Carlo calculation explicitly takes morphology variations into account, contrary to the reference dosimetry approach based on a single geometry (reference model). This may impact mostly absorbed doses at a distance of the source.

Here, the main irradiation source is the neck region. In fact, since the remnants cannot be delineated, the "neck" region is defined using an activity threshold (functional volume), which is debatable. The absorbed dose results to the neck region should therefore be taken with care.

6. Conclusions

- The feasibility of patient-specific dosimetry was established, even in a diagnostic context.
- This allows the appraisal of inter-patient variability, and therefore adds relevant dosimetric information thus far not taken into account
- This does not put in question, but rather complement the conventional model-based reference dosimetry. For new radiopharmaceuticals, a dosimetric approach combining patient-specific and model-based approaches would bring useful extra information.

The average results are contrasted.

- For the ^{18}F-labelled radiopharmaceutical studied here, and despite the low number of patient considered, the results in terms of absorbed dose coefficients agree well between specific study and reference dosimetry.
- For ^{131}I, a high inter-patient variability was observed, but furthermore the average results differ between patient-specific dosimetry and model-based dosimetry. There are many possibilities to explore and further analysis and verification will have to be performed.

7. References

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