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Radioiodine (^{131}I) treatment for Graves' disease: Geant4 Monte Carlo simulation for patient personalized dose estimation

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▸ ***Original article***

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ABSTRACT

Background: Reliable estimation of radiation-absorbed dose is necessary to evaluate the benefits and the risks of radiopharmaceuticals used for diagnostic or therapeutic purposes in nuclear medicine. ***Materiel and Methods:*** This study included 47 patients treated with iodine-131 for Graves' disease. A comparative study between Geant4 Monte Carlo simulation and MIRD formalism was carried out to evaluate the dose received by each patient. Patients' thyroids and internal radiation were modeled using Geant4. Geant4 simulations were compared to experimental measurements performed with TLDs placed inside an ellipsoidal Thyroid phantom. MIRD was used to determine the beta doses received by the different patients. ***Results:*** The average difference between MIRD and Geant4 considering only beta emitted radiation was approximately 5.6%; this difference is justified by the fact that, Geant4, contrary to MIRD, considers all particle energies of the ^{131}I spectrum, the shape of the thyroid and the heterogeneity of the dose deposited in the modeled volume. A good agreement was found between experiment and Geant4 simulations. The total dose received by patients varies between 176Gy and 359Gy. After 9 month, 74% of treated patients were rendered hypothyroid. ***Conclusion:*** This study showed the necessity of determining the specific activity of each patient considering the thyroid volume and the iodine fixation. It also revealed that the Geant4 toolis appropriate for accurate internal dosimetry calculations, particularly for the case of Graves' disease treatment. GEANT4 can be used as a standard for the comparison of experimental measurements.

Keywords: *^{131}I, MIRD, Geant4 simulations, TLD.*

INTRODUCTION

131I has been in use since 1941 in the treatment of thyroid cancer and hyperthyroidism. The effectivenessof internal radiotherapy with radioactive iodine results from the high level of the absorbed dose delivered to thyroid cells, the relative tissue specificity of irradiation and its appropriate half-life (8.05d) and beta- and gamma-ray energies (1, 2, 3).

A reliable estimation of the radiation-absorbed dose is necessary to evaluate the benefits and the risks of radiopharmaceuticals used for diagnostic or therapeutic purposes in nuclear medicine.

Consequently, accurate assessment of the dose into the thyroid has recently gained significant importance. In hyperthyroidism treatment, the goal is to accurately determine the optimal 131I activity to cure hyperthyroidism while avoiding a permanent secondary hypothyroidism.

While it has been used in the clinic for many years, the optimum administered activity of iodine for ablation remains controversial (1, 4, 5, 6).

Two methods are used: the most commonly known is the administration of a fixed activity (the mean value used in this study is 518MBq); an alternative method is the administration of an activity individually calculated to deliver a prescribed absorbed dose based on MIRD (Medical Internal Radiation Dosimetry). However, these two approaches are based on a theoretical model that could underestimate or overestimate the dose received by the patient (7, 8).

Monte Carlo simulations are able to overcome theoretical model problems. They also provide an accurate value of radiation absorbed doses into different target organs. Monte Carlo simulations use statistical methods employing random numbers and statistical sampling experiments.

In particular, the Monte Carlo method can accurately model any complex physical system. It can also model interactions within the physical system based on known probabilities of occurrence.

There has been an increasing interest in the use of Monte Carlo simulations in studying the beta and gamma emitting radionuclides used for diagnostic and therapeutic purposes.

Multiple Monte Carlo codes are available, such as PENELOPE, FLUKA, MCNP, Geant4 and EGSnrc (9).

Geant4 is a toolkit for the simulation of the passage of particles through matter. It was initially developed by the European Nuclear Research Center with the collaboration of hundreds of physicists and computer scientists. It aims to provide a complete, precise and robust simulator for various applications.

Geant4 covers all relevant physics processes, including electromagnetic, hadronic, decay, and optical, for both long and short-lived particles, over a wide range of energy.

It has been applied in particle physics, nuclear physics, accelerator design, space engineering and medical physics (10).

This work presents the results of the development of Geant4 Monte Carlo code for the simulation of energy deposition induced by β− and gamma radioactivity into ellipsoidal volumes. A Geant4 model was developed to calculate the absorbed doses in a polyamide thyroid phantom having the same dimensions, and this polyamide thyroid phantom was used for the experiments. Six TLD type 100 dosimeters were placed on the phantom surface filled with ^{131}I. Increasing activities of 7.4, 11.1, 18.5,37, 74, and 111 MBq were then administered for 22 h.

The absorbed dose in the polyamide phantom was compared to the dose simulated in the ellipsoidal model created in Geant4.

Various dimensions and ellipticities of the ellipsoidal thyroid volumes of 47 patients treated for Graves' disease were used. Patient's thyroids were then simulated using ellipsoidal volumes.

To evaluate the effect of thyroid mass and thyroid uptake on the dose delivered to the thyroid, the simulation results of each patient were compared (11).

The aim of this work is to demonstrate the importance of determining the personalized dose for each patient during the treatment of Graves' disease with iodine-131.

Through this study, we wish to demonstrate the effectiveness of the Monte Carlo simulation by Geant4 in calculating the personalized patient dose.

MATERIALS AND METHODS

A simplified MIRD Formula

The MIRD formalism was proposed in 1968 by Loevinger and Berman to establish a general equation of the absorbed dose calculation, by integrating the relation set of the Marinelli method defined by the type of ionizing radiation (12).

A simplified MIRD formula is given by assimilating the thyroid kinetics to a curve of monoexponential decay. This formula is written as equation 1 (12).

$$D(\beta) = \frac{(A \times \Delta\beta \times \Phi)}{M} \quad (1)$$

Where

Dβ (in Gy) is the absorbed dose;

A (in Bq.s) is the cumulated activity;

Δβ (in J.Bq-1.s-1) is the average energy of beta emitted per second [(1)].

Φ is the absorbed fraction equal to 1 for betas; andM (in kg) is the mass of the target volume (the phantom).

Patient study

The simplified MIRD formula was applied to determine the dose received by 47 patients (8 men and 39 women) treated for hyperthyroidism in Clinic El Manar of Tunis with 518MBq of administered activity.

Thyroid uptake

A ^{131}I uptake test was carried out with a double-headed gamma camera from the Siemens brand in Clinic El Manar, in conjunction with a thyroid phantom.

The thyroid phantom is a polyamide phantom with two ellipsoidal lobes simulating the thyroid. The thyroid phantom was created in the laboratory of the Faculty of Medicine of Tunisia.

This phantom was used to determine the counts for the administered activity.

The ^{131}I uptake measurement was made at a separation distance of 12.5cm, between the gamma camera collimator and the polyamide phantom, with 0.5 MBq.

^{131}I activity was administered 24 h before. The same separation distance was kept between the collimatorand the anterior neck of the patients. Special care was then taken while measuring the separation distances and the activity.

Neck counts, thigh counts, standard calibration counts for a thyroid phantom and background counts were recorded. Radioactive iodine uptake (IU) was calculated using the equation 2:

$$\mathrm{IU} = \left(\frac{(I1-I2)}{(I0-IB)}\right) \times 100 \quad (2)$$

Where I1 is the counts per minute at the neck level of patient, I2 is the counts per minute at the thigh level, I0 is the standard calibration counts per minute for a thyroid phantom and IB is the background counts per minute [(13)].

Thyroid mass calculation

The mass of the different thyroids was determined by ultrasound.

Experiment

For the experimental measurement, a polyamide thyroid phantom was used. The same phantom used for the thyroid uptake calculation was used for the patient study. A thyroid phantom having the same dimensions and characteristics as the one used in the experiment that was performed in the Geant4.A comparison study was developed by comparing the numerical results with the experimental measurements (see 2.4).

The experimental measurements were carried out using three passive dosimeters (TLD-100) (Thermo Fisher Scientific, France) placed in each thyroid lobe at the surface of the thyroid phantom.

TLD-100 dosimeters are composed of lithium fluoride, which is doped with magnesium and titanium (LiF: Mg, Ti) and commonly applied for the detection of beta and gamma radiation. The TLDs employed in this work have the nominal dimensions of 4.5 mm (diameter) and 0.8 mm (thickness). The lower dose limit, spatial resolution and atomic mass equivalent tissue for the TLDs are 10 pGy, 2 mm and 8.2.TLD100, respectively. Calibration was performed using cobalt 60 from Saleh Azeiz Institute of Tunisia.

Prior to each irradiation, the TLDs were annealed, at 400°C and for 1 h, in a regeneration oven type FIMEL present in the Radioprotection Center of Tunisia.

This heating was followed by rapid cooling using two aluminum plates. The readout of the TLDs was performed using the 4500 Harshaw reader model. The TLDs were heated to 300°C using a heating rate of 10°C/sin to optimize the thermo-luminescent signal-to-background ratio in the high-temperature region. Continuous nitrogen flow was used to reduce

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chemiluminescence and spurious signals that were not related to the irradiation (14, 15).

For the experimental measurements, TLDs were covered with plastic before placing them at the surface of the phantom. The goal was to prevent leakage of fluoride into the phantom (figure1). The activities administered to the phantom were 7.4, 11.1, 18.5, 37, 74 and 111 MBq).

Figure 1. TLD deposited in the phantom.

An activimeter was used to measure the activity. TLDs were placed in the phantom filled with ^{131}I for 22 h, and then, the radiation was read with a Harshaw 4500 reader. The procedure was repeated for each activity. The phantom implemented in Geant4 has the same characteristics as the real phantom. Similar to the real phantom, we put detectors having the same characteristics as the TLD100 at the surface of the model.

In experimental measurement of the phantom, two comparisons were made: The experimental results were compared to Geant4 simulations for each activity. We considered only gamma rays as in the experimental measurements the plastic that covered the TLD stopped the beta rays. The MIRD formula was applied to calculate the absorbed dose in the phantom, and the calculated result was compared to the Geant4 simulations. We only considered beta rays.

Geant4 simulation

The Geant4 code considers all physical processes governing particle interactions. In addition, it stores and tracks event data. It also permits the tracking of energy and dose in a selection of target regions (10). In this study, the Geant4 code, version 4.9.5, was used to model an ellipsoidal thyroid, considered as a volumetric source, in which ^{131}I is distributed uniformly. The energy deposited by beta radiation into the thyroids of treated patients was then computed using the developed Geant4 model. For the purpose of comparison with experimental study performed in the polyamide phantom, only gamma radiations were computed in Geant4.

The Configuration of the developed Geant4 model

A volume composed of air was surrounding the phantom, which was modeled using parallelepiped polyamide. It included two hollow ellipsoids that reproduce the two thyroid lobes. Six cylindrical dosimeters, composed of lithium fluoride, were also modeled and inserted into the surface of the phantom. The same characteristics of the dosimeters that used during the experiment were applied for their definition. Inside the model, the dosimeters were defined as "Sensitive Detectors", for the energy scoring. The resulting geometry (implemented in Geant4 model) is illustrated in figure 2.

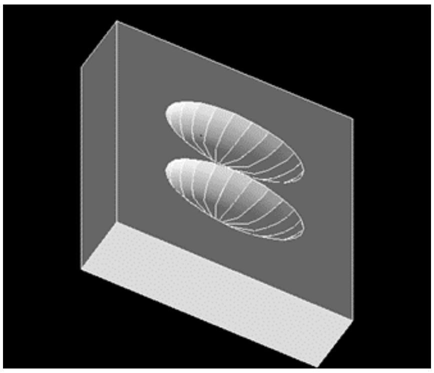

Figure 2. Phantom modelling.

The physics process generated by each type of radiation used in Geant4 had to be defined in the appropriate Physics List class. Since our model was considering transport of low energy beta and gamma rays within the phantom, the processes that were taken for the electrons are the following: bremsstrahlung, multiple scattering and ionization. The induced electromagnetic radiations undergo the effects of

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Compton scattering and photoelectric effect. In our model, the Cut Value (corresponding to the particle stop range) was set to 10μm.

The description, including the type, energy, position and direction of each primary particle, had to be defined in the model.The production of the particle position and direction were performed randomly inside the ellipsoid. For the particle type and energy, the eight decay possibilities of the ^{131}I were implemented with the related probability for each decay. Table 1 illustrates the principles of emissions of beta and gamma rays for ^{131}I with a percentage greater than 1%.

Table 1. The principles of emissions of beta and gamma rays for 131I (1).

Principals of emission	Energies (keV)	Percentage of Emissions (%)
Electrons	45.6	3.5
	329.6	1.5
Betas	247.9	2.1
	333.8	7.2
	606.3	89.9
Gammas	80.18	2.6
	284.3	6.2
	364.48	81.6
	639.97	7.1
	722.89	1.8
RayonsX	29.4	1.5
	29.7	1.8

The computation convergence was checked by varying the generated primary particle number for each configuration of the model. The simulated dose rate was calculated using equation 3:

$$D = \frac{(A \times E \times C)}{(N \times M)} \qquad (3)$$

Where D is the absorbed dose rate in Gy/h, A is the source activity in Bq, N is the number of histories/primary particles generated, and M is the mass in kg, E is the deposited energy in Joule (J) given by the Geant4 model and C is a conversion time factor [9].

The value of the energy deposited within each dosimeter was calculated by a predefined function of Geant4 (G4 Kinetic Energy). For good statistical results, 400,000,000 histories were generated for each measurement, and each measurement was repeated three times.

Statistical analysis

For the comparison of the results, we introduced the data inExcel, and we created the corresponding charts for a visual comparison. Then, to find the difference in percentage between the calculation and the measurement as well as the calculation and the simulation, we calculated the average of the results found by calculation and those by simulation and by measurement.

RESULTS

The inter-comparison of the dose received by the different patients using MIRD

The inter comparison between the dose received by the patients showed important dissimilarities due to the differences in the mass and the iodine uptake for each patient. The thyroid mass varied between 0.0197 Kg and 0.035Kg. The thyroid uptake varied between 30% and 47%. The absorbed dose varied from 176Gy to 359Gy.

After 9 month of iodine treatment, 74.5% of the patients enrolled in our study were rendered hypothyroid (35 patients); a euthyroid state was achieved in eight patients (17%), and four patients (8%) remained hyperthyroid (4 patients) [8].

Patient study: Comparison between Geant4 and MIRD

The absorbed dose results using MIRD and Geant4 simulations for 47 patients treated for Graves' disease(s) are shown in figure 3. These results consider only beta effects produced by ^{131}I after 24 h in the treated thyroid patients. The results show that a good agreement is found. The comparison between MIRD and Geant4 results is presented by the difference D1 (%) in equation 4.

$$D1\ (\%) = \left(\frac{(DM - DG1)}{DG1}\right) \times 100 \qquad (4)$$

DM is the dose determined by MIRD, and DG1 is the dose determined by Geant4, considering only beta energy. The average relative difference found was 5.6%.

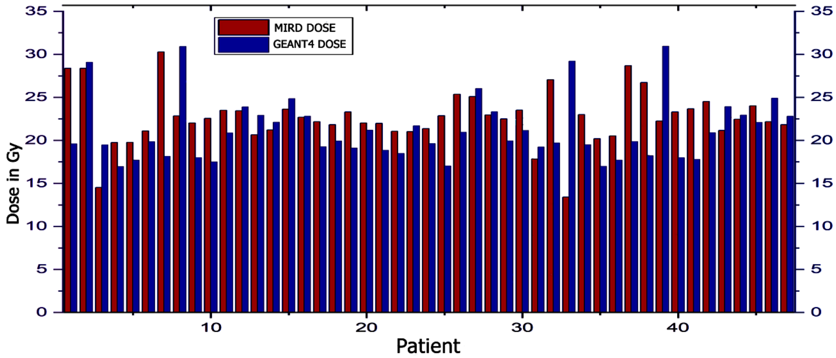

Figure 3. Comparison between the dose determined by MIRD and Geant4 of 47 patients

Phantom model comparison

Comparison between MIRD and Geant4 considering only beta energy

The results of the dose value for various activities administered to the phantom using MIRD and Geant4 simulations are shown in figure 4.

The comparison between the MIRD and Geant4 results is presented as the percentage the relative difference calculated by the difference D1 (%). Only beta energy of ^{131}I was considered in the comparison between MIRD and Geant4.

The maximum relative difference between the MIRD and the Geant4 simulated results was 3.67%.

Comparison between experiment and Geant4 considering only gamma energy

The comparison between experimental measurement and Geant4 is presented as a percentage relative difference calculated by the difference D2 (%) in equation 5. It is shown in figure 5.

Only gamma energy of ^{131}I was considered as betas were stopped by the plastic that covers the TLD (19).

$$D2\ (\%) = \left(\frac{(DE - DG2)}{DG2}\right) \times 100 \qquad (5)$$

DG2 is the dose determined by Geant4 considering gamma energy. DE is the dose determined by experimental measurement. Figure 5 shows that a good agreement was found between the experimental measures and the Geant4 simulation. DG1 and DG2 present the average of the dose delivered by the six TLDs deposited at the surface of the phantom.DE is the average of the dose delivered by the six TLDs deposited at the surface of the thyroid phantom. The maximum relative difference between experimental and Geant4 is 5.2%.

Homogeneity and TLD size influence

The size of the dosimeter used in the experiment and simulated in Geant4 may influence the precision of the dose delivered to the phantom. The number of dosimeters used can be considered small. The number of dosimeters increased to 7 in each axis. Twenty-one TLDS of a smaller size were used in the Geant4 model to evaluate the TLD volume effect on the dose and the dose deposition homogeneity in the ellipsoid.

The TLD dimensions were 1.3 mm in diameter and 0.1mm in thickness. Figure 6 represents the variation of the absorbed dose (beta and gammas) for each dosimeter position.

The dosimeters 1 and 7 were placed at the phantom extremities. They receive the lowest doses. The dosimeters 2 and 6 were placed slightly further away from these extremities. The dosimeters 3, 4 and 5 illustrate the highest dose values because they were placed at the center of the phantom. Figure 6 shows these dose value results for 7.4 MBqof administered activity. The dose values are given along the 3 axes and for the twenty-one individual TLDs.

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Homogeneity is deduced by subtracting the highest dose value from the lowest and then dividing by the lowest value. This value must be less than 0.3 for the homogeneous medium. The dose homogeneities along the XX'axis (H1 [%]), the YY'axis (H2 [%]), and the ZZ'axis (H3 [%]) were found to be equal to 18%, 57% and 3%, respectively.

The deposition of iodine is not 100% homogeneous throughout the volume. At the phantom extremity, some of the simulated particles will be lost and will interact with the external relatively low-density surroundings, which explains the drop in the dose. Figure 6 shows that the closer you get to the center, the higher the dose values are. The deposition of iodine is homogeneous in the middle of the phantom, and only particles at the extremities are partially lost. The dose deposition is not homogenous in the volume.

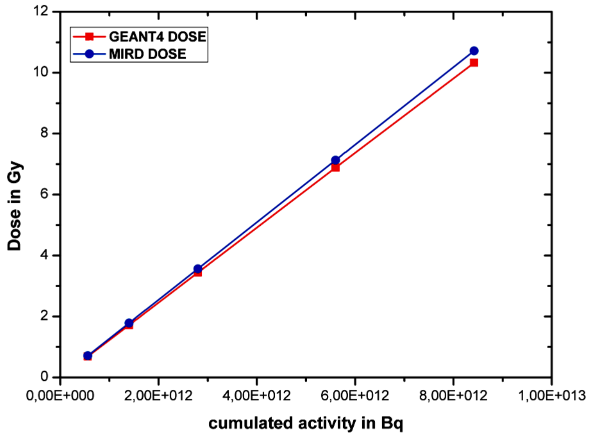

Figure 4. Comparison between MIRD and Geant4: Phantom Case.

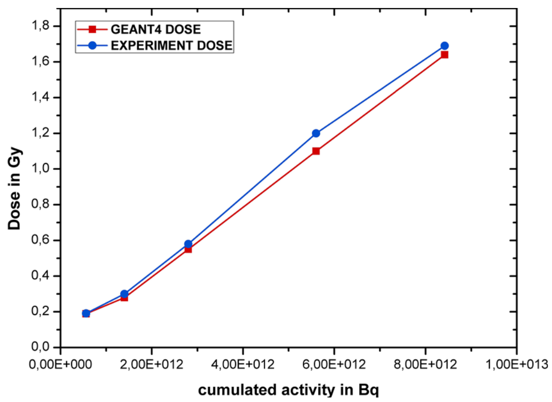

Figure 5. Comparison between experiment and Geant4: Phantom Case.

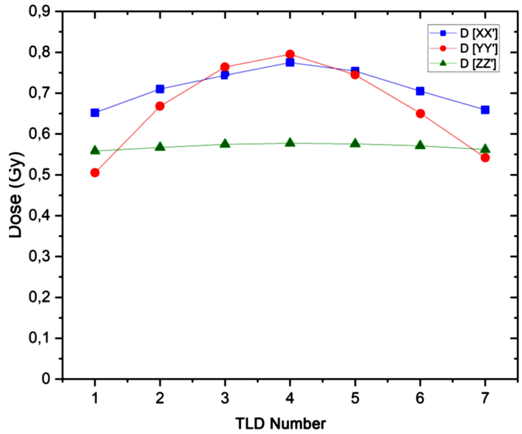

Figure 6. Dose distribution for smaller dosimeters in the three axes.

DISCUSSION

The inter comparison between the total clinical doses received by the different patients using MIRD shows important dissimilarities. These dissimilarities are due to the differences in the mass and the iodine uptake for each patient.

The clinical dose varies between 176Gy and 359Gy. These high doses delivered to patients increased the therapeutic effect, but at the expense of an increased rate of hypothyroidism (74.5% of patients). An Australian study performed under the auspices of the International Atomic Energy Commission reports a relatively poor response to therapeutic doses of up to 90 Gy and concluded that doses in excess of 90 Gy are required to achieve a rapid and complete response to radioiodine (16). This same study, carried out on 55 patients, shows that to achieve a faster therapeutic effect at the expense of an increased rate of hypothyroidism, doses in excess of 120 Gy may be required. The study also indicates that patients with a larger thyroid mass have a greater likelihood of efficacious therapy, if treated with higher dose radioiodine. Hence, there is a need to determine the thyroid volume before the treatment. A German prospective randomized study of 205 Graves' disease patients estimated that a thyroid tissue dose of 200 Gy is required to achieve 80% treatment success (16, 21, 22).

In the patient study considering only beta energy, the doses determined by MIRD and by Geant4 are different, on average, by 5.6%. This difference could be explained by the disparity between the energy spectra of the primary ionizing particles that were used. The spectrum used for the MIRD Committee's calculation corresponds only to the average of the beta energies used. While the ^{131}I spectrum, in Geant4, is much more accurately representative of the beta energies, as given by IRSN [1]. The difference in beta energies between the two systems can also be explained by the fact that in MIRD the thyroid tissue is simulated by water. In Geant4, the thyroid tissue is considered as given in NIST (National Institute of Standards and Technology), which is more precise [11, 17].

In this study, a simple experiment was performed by modifying the density of the thyroid by the water in a single test. We found a difference of 5% for gamma rays and 0.6% for beta rays. These values agree with those of the Rahman et al study.

In a Geant 4 simulation study performed using an anthropomorphic phantom; Rahman et al demonstrated that there is a difference in the absorbed fraction values for soft tissue and water. This difference can go up to 7.2% for gamma rays and up to 0.4% for beta rays.

In the MIRD formula, we can over- or underestimate the dose delivered to the patient knowing that the total energy deposition per transformation increases with the volume [9]. Another reason is that the absorbed fraction is equal to one in MIRD, but in Geant4, this factor is affined.

In terms of absorbed doses, Geant4 gives more accurate results than the MIRD formula for the studied cases.

For the experimental measurements made in the polyamide phantom, good agreements were found.

Considering only gamma rays, the maximum difference between the Geant4 and the experimental measures is 5.2%. One of the reasons for the observed difference between the experimental results and the Geant4 simulated results in the phantom is that in Geant4 only gamma ray radiation was considered. However, TLDs detect X-rays that exist in small percentages in the emission of ^{131}I.

A maximum difference of 3.67% between Geant4and MIRD was registered. This difference could be explained by several explanations that were detailed in the patient study. Ingo Wolf *et al*., in their study, compared S values in individual voxel phantoms in EGS4 Monte Carlo Code and MIRD. The study showed that the individual S values calculated are greater than the MIRD values, which agrees with our study (figure 5). Ingo Wolf *et al.* showed also that the deviation ranges are between 0% and 14%. Those deviations are higher than ours. This difference can be explained by the fact that in this study we did not consider other organs surrounding the thyroid [18]. We have demonstrated in this work that the dose deposition is not 100% homogeneous throughout the thyroid volume and that the dose increases significantly when approaching the center.

Those results are aligned with the literature. Rahman et al showed that the energy deposited in a thyroid model in Geant4 is not homogenous in a comparison between large and small thyroids [17, 20]. By comparing the average dose value along the XX' axis with the value found with 3 TLDs of the same size in the same axis, we find a difference of 3%. The information obtained by the simulation is more resolute and more accurate because of the dosimeter size and the increased number of dosimeters (which was multiplied by 7). Hence, there was a difference between the measured and simulated values.

CONCLUSION

This study has proven the importance of the determination of the specific dose for each patient when treating Graves' disease. As 74.5% of patients developed hypothyroidism after treatment, the doses delivered are considered high and should be revised. All the methods detailed in this work (experimental measurement, MIRD or Geant4 simulation) can be used to determine the radiation dose absorbed by the thyroid. Nonetheless, GEANT4 remains the best method of estimation as it can consider more accurately all particle energies, thyroid density and volume, and the heterogeneity of the dose deposition in the volume. This study concludes that Geant4 is a suitable tool for internal dosimetry, especially for hyperthyroidism treatment. Geant4 can be used in nuclear medical centers to predetermine the radiation activity that should be administered to each patient.

Conflicts of interest: *Declared none.*

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