Determination and Comparison of Radiation Absorbed dose to the Blood, by Applying Different Techniques, for Patients, Suffering from Differentiated Thyroid Cancer

Abstract

Background: Radiation absorbed dose to the red bone marrow, in the therapy of differentiated thyroid carcinoma (DTC) with 1311 (radioiodine), cannot be measured directly. The absorbed dose to the blood seems to be a good first- order approximation of the radiation absorbed dose to the hematopoietic system and a better means to quantify exposure from therapy than the total amount of activity administered. Objective: The aim of this research was to determine the radiation absorbed dose to the blood, for patients suffering from differentiated thyroid cancer. Materials and Methods: Twenty seven patients, 22 women and 5 men, suffering from DTC were enrolled in this study. We applied four formulas and we compared between the estimated values of absorbed dose that were obtained by three formulas and those that obtained by fourth (standard one). Results: All the values of absorbed dose that obtained by one of the techniques were regularly highly estimated, even though they have an excellent correlation (99%) with the standard value. Conclusions: Highly overestimated or highly underestimated results that can be obtained by certain method or technique are not desirable, because they tend to exaggerate, by increasing or decreasing, the radiation protection procedures. Conversion radiation Units: To convert the values of absorbed dose from S.I unit (mGy/MBq) to traditional unit (rad/mCi), we can simply multiply the values that expressed in S.I units by a factor of 3.7, and we don't need to apply complicated formulas, which were applied by other researches.

Keywords: ¹³¹*I* radioiodine, differentiated thyroid cancer, over and underestimated values, radiation absorbed dose

Introduction

Radiation absorbed dose to the red bone marrow, a critical organ in the therapy of differentiated thyroid carcinoma (DTC) with ¹³¹I (radioiodine), cannot be measured directly. As radioiodine concentration is comparable in blood and most organs,^[1] and is believed to be similar in red marrow,^[2] the absorbed dose to the blood seems to be a good first-order approximation of the radiation absorbed dose to the hematopoietic system and a better means to quantify exposure from therapy than the total amount of activity administered.

Blood dosimetry was introduced by Benua *et al.*^[3] in a study published in 1962. They found that radioiodine therapy is safe if the blood dose is restricted to <2 Gy (200 rad) while keeping the whole-body retention <4.4 GBq (120 mCi) at 48 h and the pulmonary uptake at 24 h <3 GBq (80 mCi).^[3,4]

Radiation exposure from fixed activities is very heterogeneous. Depending principally on the patient's size and renal clearance, the calculated blood absorbed dose per unit of activity administered can differ by more than a factor of 5.^[5] A low absorbed dose to the blood might predict reduced radioiodine availability for target tissue uptake and therefore, a low absorbed dose to the target tissue.

Individualized patient-specific therapy is ideally based on a pre-therapeutic dosimetry of both red marrow and target dose per activity administered and provides information on the activity necessary to eliminate all lesions or whether an effective tumor dose can be reached without exceeding the tolerable dose to the bone marrow.

Radioiodine therapy has proven to be a safe and effective method in the treatment of patients with DTC. The target dose is

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the determinant for successful therapy, and the decisive parameters are the therapeutic activity and retention of radioiodine in the target volume. There is no consensus on the activity of ¹³¹I to be administered. Usually, 1.1–3.7 GBq (30–100 mCi) is prescribed for the first radioiodine therapy after thyroidectomy in newly diagnosed DTC patients to ablate the remaining glandular tissue. Higher amounts of ¹³¹I are given in subsequent therapies or in case of metastatic disease. Usually, the activity is limited for safety to around 7.4 GBq (200 mCi).^[5]

However, not uncommonly, a higher administered activity is desired to achieve higher tumor doses. To avoid serious complications, the commonly used dose concept published by Benua *et al.*^[3] for radioiodine treatment of DTC restricts the blood dose to <2 Gy (200 rad). In their protocol, measurements of iodine retention in the blood and whole body with a tracer activity are required to estimate the blood dose before the radioiodine therapy; the method has been applied successfully.^[6,7]

The "Standard Operational Procedures for Pre-therapeutic Dosimetry" (SOP) gives recommendations on how to tailor the therapeutic activity to be administered for the systemic treatment of DTC so that the absorbed dose to the blood does not exceed 2 Gy and at 48 h after administration, the whole-body retention does not exceed 4.4 or 3 GBq in the absence or presence of iodine-avid diffuse lung metastases, respectively.^[3,4]

Several total body dosimetry formulas in the treatment of DTC have been developed and refined in a series of international multi-center trials,^[5,8,9] some of these methods use blood samples, whereas others prefer measuring radiation externally by the Geiger-Müller or gamma camera; in addition, measurements can be performed at different time intervals. To our knowledge, these methods have not been compared together or against standard in the medical literature previously.

The aim of this study is to calculate blood radiation absorbed dose in patients with DTC treated with radioactive iodine using modified Benua method (SOP) as standard and to compare between the estimated values obtained by three formulas and those obtained by standard SOP method. In addition, we propose a simple conversion method for absorbed dose from S.I unit (mGy/MBq) to traditional unit (rad/mCi).

Materials and Methods

Twenty-seven patients, 22 women and 5 men, suffering from DTC were enrolled in this study.

The information and data concerning these patients (weight, height, retention function, and residence time), are taken from.^[5]

Calibrated probes or survey meters with a linear range up to a minimum of 100 μ Gy/h and a resolution

of $<0.1 \mu$ Gy/h or corresponding counting rates were used for the probe measurements. All measurements for an individual patient were conducted with the same probe as conjugate (anterior and posterior) counts at a distance of 2 m using a reproducible measuring geometry. Every probe measurement of the patient was accompanied by measurements of a calibration standard and the actual background counting rate.

The well counters to quantify the blood activity concentrations at each site were calibrated for ¹³¹I and quality checked with *in vitro* standards of well-known activities.

All scintillation camera images of the patient were acquired with the same dual-head camera system and the same set of high-energy ¹³¹I collimators. The camera settings (width of the energy window, 15%; acquisition matrix, 256×256 for static neck images and 1024×256 for whole-body scans; scan speed of whole-body acquisitions, 20 cm/min) were identical for all patients. Before the first imaging of every patient, the camera system was checked to meet the uniformity specifications of the National Electrical Manufacturers Association.^[10]

The data extraction was performed by drawing regions of interest at each site according to a dosimetry operational manual with detailed instructions that was distributed to all participating centers before the beginning of the study.

Whole-body probe measurements and blood collections (2 ml whole-blood samples) were conducted 2, 6, 24, 48, 72–96, and 96–168 h after the administration of ¹³¹I to obtain time-activity curves.

Scintigraphic imaging is the most precise tool to quantify radioiodine in the remnant and the whole body. In contrast to diagnostic investigations, scintillation camera systems cannot be used to quantify the activity in a patient within the first hours after the administration of therapeutic ¹³¹I activities because of uncertainties introduced through dead-time characteristics. On the other hand, scintillation camera measurements are expected to be more precise at later time points when the whole-body activity is small. Therefore, the geometric mean values of the anterior and posterior net counts of probe and camera measurements were combined to evaluate the decay curve of the activity in the whole body. The value obtained in the first probe count nominally 2 h after administration with no interim excretion was used to normalize all successive measurements to fraction of administered activity (activity at 2 h = 100%).

The time–activity functions used to calculate the residence times in the whole body and blood were assumed to be biexponential, unless the slowly decaying component was negligible.

The following SOP equation based on the generally accepted formalism of the Medical International Radiation

Dose Committee was used to determine mean blood absorbed dose.

(D blood) per unit of administered activity (A_0) :^[8]

$$\frac{\mathbf{D}_{\cdot\text{blood}}}{\mathbf{A}_{0}} \left(\frac{\mathbf{G}\mathbf{y}}{\mathbf{G}\mathbf{B}\mathbf{q}}\right) = 108 \times \tau_{\text{mlof blood}}\left(\mathbf{h}\right) + \left(\frac{0.0188}{\left(\text{wt}\left(\text{kg}\right)\right)^{2/3}}\right) \times \tau_{\text{total body}}(\mathbf{h})$$
(1)

where $\tau_{total \ body}$ total body residence time; $\tau_{ml \ of \ blood}$ residence time in a ml of whole blood; and wt, patient's weight in kg.

The first addend in Equation 1 accounts for the contribution from β radiation assuming energy absorption of 187 keV per decay in the blood. The second addend accounts for decays outside the blood contributing to the blood dose by penetrating radiation with an S-value (mean absorbed dose) depending on the patient's weight.

A method to estimate blood dose from external whole-body counting without blood sampling was proposed by Thomas *et al.*^[11] The authors found in a study with 49 dosimetric assessments that 14–17% (14% ± 4%, 14% ± 4% and 17% ± 5% for three groups) (range 3%–25%) of the whole-body residence time can be attributed to the blood. This percentage was consequently confirmed by Hänscheid *et al.* in two papers; 13% ± 3% (range 7%–21%) and 14% ± 3% (range 8%–24%).^[5,12]

The relation can be expressed as:

$$\tau_{\text{mlof blood}}\left(h\right) = \left(\frac{0.14}{\text{BLV}(\text{ml})}\right) \times \tau_{\text{total body}}(h)$$
(2)

The individual blood volume (BLV) can be estimated from the patient's weight wt (kg) and height ht (cm),^[13] to be BLV = $31.9 \times ht + 26.3 \times wt - 2402$ for males and BLV = $56.9 \times ht + 14.1 \times wt - 6460$ for females.

Equations 1 and 2 can be combined to equation 3 being applicable to estimate the blood dose from the whole-body residence time:

$$\frac{D_{\cdot blood}}{A_0} \left(\frac{mGy}{MBq}\right) = \left(\frac{15.12}{BLV(ml)} + \frac{0.0188}{\left(wt(kg)\right)^{2/3}}\right) \times \tau_{total body}(h)$$
(3)

Sisson *et al.*^[14] proposed to use the 48 h whole-body retention measured in a diagnostic assessment to adapt the activity in the subsequent radioiodine therapy in case of markedly low or high 48 h whole-body uptake. As a step further, a blood dose estimate from a single measurement of the whole-body retention can be deduced if the retention R (t) at t hours after the radioiodine administration is taken to be representative for the total-body residence time according to:

$$\tau_{\text{total body}}\left(\mathbf{h}\right) = -\frac{\mathbf{t}}{\ln(\mathbf{R}\left(\mathbf{t}\right))} \tag{4}$$

The blood absorbed dose becomes:

$$\frac{D_{\text{*blood}}}{A_0} \left(\frac{\text{mGy}}{\text{MBq}} \right) = - \left(\frac{15.12}{\text{BLV(ml)}} + \frac{0.0188}{\left(\text{wt}(\text{kg}) \right)^{2/3}} \right) \times \frac{t(\text{h})}{\ln(R(t))}$$
(5)

or in traditional units:

$$\frac{D_{\text{blood}}}{A_0} \left(\frac{\text{rad}}{\text{mCi}}\right) = -\left(\frac{56}{\text{BLV(ml)}} + \frac{0.7}{\left(\text{wt}(\text{kg})\right)^{2/3}}\right) \times \frac{\text{t(h)}}{\ln(R(t))}$$
(6)

The absorbed dose to the blood was calculated with a modified method deduced from a procedure originally described by Thomas *et al.*^[11] This refined method was applied by Hänscheid *et al.*^[5] using the following equation:

$$\frac{D_{\text{blood}}}{A_0} \left(\frac{mGy}{MBq} \right) = 116 \times \tau_{\text{mlof blood}} (h) + \left(\frac{0.104}{(\text{wt}(\text{kg}))^{0.86}} \right) \times \tau_{\text{total body}} (h)$$
(7)

or in traditional units:

$$\frac{D_{\cdot blood}}{A_0} \left(\frac{rad}{mCi}\right) = 429 \times \tau_{mlof blood}(h) + \left(\frac{0.385}{(wt(kg))^{0.86}}\right) \times \tau_{total body}(h)$$
(8)

This latter approach is based on the formalism of the Committee on Medical Internal Radiation Dose of the Society of Nuclear Medicine. Published S values,^[15-17] were used to account for contributions of activity in the blood and the remainder of the body to the blood dose.

In our study, retention was calculated by normalization of the geometric mean of background corrected anterior and posterior counts to the initial measurement which was made 2 h after administration without interim micturition or defecation. The patients were asked to empty their urinary bladder before subsequent whole-body counts. Blood activity concentrations were measured in a calibrated well counter. Data integrity was assured by adequate quality control procedures as recommended in Lassmann *et al.*^[8]

The residence times in whole body $\tau_{total \ body}$ and blood $\tau_{ml \ of \ blood}$ were determined by integrating biphasic decay curves fitted to the whole-body retention and blood activity concentration data, respectively, and actual blood dose values were calculated with Equation 1.

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Blood dose estimates according to Equations 3,5, and 7 from measured whole-body retentions at nominal 2 h, 6 h, 24 h, 48 h, 72–96, and 96–168 h after administration are compared with the values that obtained by applying Equation 1.^[12]

Results

The relations and the correlations between the values of absorbed dose obtained by the "standard " method (represented by Equation 1) and those obtained by each of the other methods (2nd, 3rd and 4th methods that represented by equations 3, 5, and 7) are plotted in Figures 1-6.

The blood absorbed dose values deduced with the standard procedures, Equation 1, and the other methods, Equations. 3, 5, and 7, respectively, are listed in Table 1.^[5]



Figure 1: Correlation between the values of radiation absorbed doses obtained by applying equations 1 and 3



Figure 3: Correlation between the values of radiation absorbed doses obtained by applying equations 1 and 7

It is worth to indicate and mention that, to convert the values of absorbed dose from S.I unit (mGy/MBq) to the traditional unit (rad/mCi), we can simply multiply directly the values that expressed in S.I units by a factor of 3.7.

Discussion

Radioiodine ablation of DTC has long been associated with a lower rate of recurrence and distant metastases, as well as a reduced risk of cancer mortality.^[18-22] While some physicians favor low radioiodine levels approximating 1.11



Figure 2: Correlation between the values of radiation absorbed doses obtained by applying equations 1 and 5



Figure 4: (A) Relationship between the values of radiation absorbed doses obtained by applying equations 1 and 3, (B) Coincidence line represents the ideal relationship between them, this relationship is represented by a ratio of 1: 1



Figure 5: (A) Relationship between the values of radiation absorbed doses obtained by applying equations 1 and 5, (B) Coincidence line represents the ideal relationship between them, this relationship is represented by a ratio of 1: 1

GBq, others prefer higher amounts of up to 7.4 GBq^[23-25] Physicians in most centers often use a predetermined and fixed radioiodine level from 1.11 to 7.4 GBq rather than accurate radiation doses based on bio-kinetic properties of patients.^[26-28]

From a historical point of view, it has long been accepted that a single administration of a higher radioiodine level results in a more successful ablation. This was based on the hypothesis that the larger the amount of radioiodine, the more likely it is than lower levels to ablate remnants and destroy residual micrometastases.^[29]

Fatholahi et al.[30] evaluated whether higher activities of administered radioactive iodine would necessarily increase the absorbed dose to the blood in treating patients with DTC. The study revealed that absorbed dose to the blood of patients with DTC administrated with 5.55 GBq radioiodine is significantly higher than that of patients administrated with 3.7 GBq of radioiodine. However, there is no significant difference in the absorbed dose to patients' blood when treated with 7.4 GBq of radioiodine compared to 5.55 GBq. Given that the absorbed dose to the blood is a better predictor of ablation success than overall radioiodine administered,^[31] these findings suggest that 5.55 GBq would be the most favorable dose compared to 3.7 GBq and 7.4 GBq of radioiodine in thyroid ablation. Dosage of 5.55 GBq is not only more advantageous therapeutically but it also causes fewer therapeutic problems than a dose of 7.4 GBq. These results are in contradiction with results of Mazzaferri^[21] on 1004 DTC patients undergoing radioiodine ablation of thyroid remnant. That study categorized patients into two groups: those treated with 1-1.85 GBq (mean 1.74 GBg) of radioiodine and those treated with 1.89-7.4 GBq (mean 4.1 GBq). That study observed no significant difference in recurrence rates between the two groups of patients.^[21] Using administered radioactive iodine activity



Figure 6: (A) Relationship between the values of radiation absorbed doses obtained by applying equations 1 and 7, (B) Coincidence line represents the ideal relationship between them, this relationship is represented by a ratio of 1: 1

rather than proper dosimetric approach may be, at least in part, be responsible for different treatment outcomes among patients with DTC receiving different radioactive iodine administered activities. Factors affecting blood absorbed dose are the renal and gastrointestinal functions (urine and stool frequency), fluid intake, presence and extent of metastases, and other physiological and pathological iodine uptakes,^[31,32] different lesion uptakes due to the different biological half-life of each patient, and perspiration level. One of the most obvious reasons for increasing blood dose of a patient in comparison with other patients with the same administration activity is high-level residence time activity to blood and whole body that produce the area under the time-activity curve and the blood dose. Many studies have been performed to find the proper administrated activity of radioiodine for the treatment of DTC.[19,22,33] Some studies found that radioiodine therapy is safe if the blood dose is confined to <2 Gy while keeping the whole-body retention less than 4.4 GBq at 48 h, and the pulmonary uptake at 24 h <3 GBq.^[3] Although other studies have different recommendations for radioiodine levels from 1.11 up to 7.4 GBq.^[26-28,34]

In our paper, we compared between four different methods in calculating blood absorbed dose in patients with DTC undergoing radioactive iodine treatment; to our knowledge, no papers have been published previously comparing between these dosimetric approaches.

Furthermore, we compared our results of absorbed dose, that were obtained by applying four methods, with those that were obtained by Albornoz-Castañeda *et al.*^[35] For low activities administered (3.20 GBq), the average values of absorbed dose (for 27 patients) were 0.39 Gy, 0.39 Gy, 0.40 Gy, and 0.54 Gy respectively, whereas the average value obtained by Albornoz-Castañeda *et al.*^[35] (10 patients) was 0.33 Gy, with differences of 0.06 Gy, 0.06 Gy, 0.07 Gy, and 0.21 Gy. For high activities administered (4.95 GBq), the average values obtained by applying the four methods (for 27 patients) were 0.61 Gy, 0.60 Gy,

Table 1: Values of the radiation absorbed doses obtained by applying four equations							
Patient number	Α	В	С	D	B/A	C/A	D/A
1	0.061	0.077	0.07	0.088	1.262295082	1.147540984	1.442622951
2	0.07	0.078	0.074	0.101	1.114285714	1.057142857	1.442857143
3	0.076	0.084	0.078	0.104	1.105263158	1.026315789	1.368421053
4	0.082	0.08	0.084	0.108	0.975609756	1.024390244	1.317073171
5	0.089	0.105	0.104	0.125	1.179775281	1.168539326	1.404494382
6	0.091	0.106	0.078	0.126	1.164835165	0.857142857	1.384615385
7	0.1	0.115	0.14	0.141	1.15	1.4	1.41
8	0.104	0.112	0.115	0.142	1.076923077	1.105769231	1.365384615
9	0.095	0.148	0.097	0.149	1.557894737	1.021052632	1.568421053
10	0.107	0.121	0.111	0.154	1.130841121	1.037383178	1.439252336
11	0.113	0.132	0.122	0.157	1.168141593	1.079646018	1.389380531
12	0.12	0.104	0.101	0.164	0.866666667	0.841666667	1.366666667
13	0.117	0.129	0.126	0.174	1.102564103	1.076923077	1.487179487
14	0.131	0.102	0.098	0.177	0.778625954	0.748091603	1.351145038
15	0.144	0.116	0.122	0.185	0.805555556	0.847222222	1.284722222
16	0.127	0.179	0.157	0.186	1.409448819	1.236220472	1.464566929
17	0.138	0.109	0.108	0.189	0.789855072	0.782608696	1.369565217
18	0.178	0.115	0.119	0.223	0.646067416	0.668539326	1.252808989
19	0.154	0.158	0.173	0.218	1.025974026	1.123376623	1.415584416
20	0.19	0.169	0.198	0.25	0.889473684	1.042105263	1.315789474
21	0.2	0.18	0.24	0.27	0.9	1.2	1.35
22	0.28	0.22	0.28	0.36	0.785714286	1	1.285714286
23	0.071	0.072	0.092	0.099	1.014084507	1.295774648	1.394366197
24	0.093	0.085	0.083	0.127	0.913978495	0.892473118	1.365591398
25	0.091	0.102	0.104	0.133	1.120879121	1.142857143	1.461538462
26	0.12	0.121	0.104	0.168	1.008333333	0.866666667	1.4
27	0.18	0.14	0.17	0.24	0.77777778	0.94444444	1.3333333333
Average \pm	0.123037037	0.120703704	0.124	0.168814815	1.026698648	0.10154827	1.387978142
S.D	0.049022351	0.036128845	0.050672402	0.061337049	0.342605471	0.14361094	0.07727943
Median	0.113	0.115	0.108	0.157	1.020029267	1.045992714	1.387978142
Max	0.18	0.14	0.17	0.24	1.262295082	1.147540984	1.442622951
Min	0.061	0.072	0.07	0.088	0.77777778	0.94444444	1.3333333333

Comments: A: Radiation absorbed dose (mGy/MBq) obtained by applying the standard method, B: Radiation absorbed dose (mGy/MBq) obtained by applying the 2^{nd} method, C: Radiation absorbed dose (mGy/MBq) obtained by applying the 3^{rd} method, D: Radiation absorbed dose (mGy/MBq) obtained by applying the 3^{rd} method, D: Radiation absorbed dose (mGy/MBq) obtained by applying the 4^{th} method, B/A, C/A and D/A are the ratios between the values of absorbed dose that obtained by the 2^{nd} , 3^{rd} , 4^{th} methods and the standard one. SD: Standard deviation

0.61 Gy, and 0.84 Gy, whereas the average value obtained by Albornoz-Castañeda *et al.*^[35] (8 patients) was 0.48 Gy, with differences of 0.13 Gy, 0.12 Gy, 0.13 Gy, and 0.36 Gy. We notice that our results, that were obtained by applying 1st, 2nd, and 3rd methods are in very good agreement with those that were obtained by Albornoz-Castañeda *et al.*^[35] Taking into account that, the number of patients included in the research conducted by Albornoz-Castañeda *et al.*^[35] was 10 and 8 patients, whereas the sample of our research includes 27 patients, we applied the four methods for low- and high-activities administered on all the patients of the sample.

Figure 1 demonstrates that excellent correlation between the values of absorbed dose obtained by applying the 2^{nd} method and those obtained by applying the standard method, r = 90%, we also found that 9 of 27 of the cases (33.3%) have underestimated values and 18 of 27 of the cases (66.7%) of the cases have overestimated values compared with those obtained by the standard method.

Figure 2, demonstrated that 11 cases from 27 of the cases (40.7%) have underestimated values of absorbed dose, whereas 16 cases from 27 of the cases (59.3%) have overestimated values, and have a very good correlation coefficient (r = 83%), compared with those obtained by standard technique (Equation 1).

From Figure 3, we notice that all the estimated values are over the coincidence line, which means that all the estimated values that are calculated by applying equation 7 are all greater than those obtained by standard technique, even though the correlation coefficient between them is excellent (r = 99%).

From Table 1, we notice that the ratio between the standard values (equation 1), and estimated values (equation 7),

ranges from 1.25 to 1.57, with maximum overestimated value by 57% and minimum overestimated value by 25%.

All the values obtained by equation 7 are regularly highly estimated, which is not realistic, even though they have an excellent correlation (99%) with the standard value.

Highly overestimated or highly underestimated results obtained by certain method or technique are not desirable, because they tend to exaggerate, by increasing or decreasing, the radiation protection procedures which is in the two cases become far from the realistic or recommended procedures.

From the three methods, we believe that the estimated values (results) that are obtained by applying equation 3 are better than those obtained by equations 5 and 7. They are more realistic (66.7% of the cases are overestimated) and have excellent correlation (r = 90%) compared with those obtained by standard value.

It is worth to indicate and mention that, to convert the values of absorbed dose from S.I unit (mGy/MBq) to traditional unit (rad/mCi), in equations 6 and 8, we can simply multiply directly equations 5 and 7 by a factor of 3.7, and we do not need to use the complicated formulas, equations 6 and 8 which are applied by Hänscheid *et al.*,^[5] they applied equation 6, and by Hänscheid *et al.*,^[12] they applied equation 8.

Conclusions

- 1. From the three methods applied in this research, we believe that the estimated values (results) that are obtained by the 2^{nd} method (by applying equation 3) are better than those that obtained by the other two methods (by applying equations 5 and 7). They are more realistic (66.7% of the cases are overestimated) and have excellent correlation (r = 90%) compared with those obtained by standard value
- 2. Highly overestimated or highly underestimated results obtained by certain method or technique are not desirable, because they tend to exaggerate, by increasing or decreasing, the radiation protection procedures which is in the two cases become far from the realistic or recommended procedures.

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Conflicts of interest

There are no conflicts of interest.

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