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Absorbed Dose Evaluation in Radioiodine Therapy with Different Approaches

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Abstract: The main approach to differentiated thyroid cancer (DTC) therapy is still empiric, consisting of the administration of fixed activities. Repeated treatments, however, may have a stunning effect. An individualized dosimetric study may represent an important tool to determine the best activity to prescribe, in particular for patients with distant metastases or when therapy with recombinant human thyroid-stimulating hormone (rhTSH) stimulation is deemed necessary. This study provides a practical operational example for carrying out a dosimetric study, according to the European Directive EURATOM/59/13. Starting from the case of a patient who underwent rhTSH stimulation before radioiodine ablation, we illustrate the necessity of measuring both red marrow (RM) and blood (BL) absorbed dose during the treatment in order to not exceed the dose limit of 2 Gy to the RM, so as to avoid repeating radioiodine treatment several times. Dosimetry to the RM and BL was performed during the treatments, after administration of therapeutic activity without modifying the fixed activity schema, using different approaches. The results suggest the possibility of restricting the number of treatments, reducing thus the risk of stunning effect and, where possible, eliminating an additional source of stress and dejection for patients.

Keywords: DTC; dosimetry; I-131; bone marrow

1. Introduction

Radioiodine therapy is a standard procedure in the treatment of differentiated thyroid cancer (DTC). Iodine choice is justified by the specific irradiation of the cancerous tissue due to the metabolic capacity to simulate the behavior of iodine in the thyroid hormone synthesis.

Currently, dosimetric study is rarely performed, and in most care centers the therapy is based on the administration of the empirical fixed activity of ^{131}I. The choice of empiric activity quantity should depend on patient classification. Two groups of patients can be identified as follows [1]:

(1) high-risk group, patients with documented persistent disease or at high risk of persistent or recurrent disease. Postoperative ^{131}I administration reduces the recurrence rate and possibly prolongs survival; it also permits early detection of persistent disease. A high activity of radioiodine is indicated, following the prolonged withdrawal of thyroid hormone treatment, since the use of recombinant human thyroid-stimulating hormone (rhTSH) stimulation has not yet been approved for this indication;
(2) low-risk group, includes all other patients. Benefits are controversial and there are still uncertainties as to whether it should be administered to all patients or only to selected patients.

Many clinicians perform ablation in this setting where completeness of thyroidectomy is uncertain; there is no consensus on when surgery has been complete because in this setting benefits are not demonstrated. Whether a low or a high activity should be administered and whether preparation should be achieved by prolonged withdrawal or following rhTSH stimulation are still uncertain and need further studies.

The choice of ^{131}I activity to be administered for the ablation of thyroid residues is a controversial subject; the use of high activity (3.7 GBq or 100 mCi) increases the probability of treatment success, especially in cases with relatively high volume thyroid residues, and could allow a greater efficacy of the therapy at the level of occult micrometastases. The administration of low activity (1.1 GBq or 30 mCi) is effective in most patients and has the advantage of reducing the incidence of undesirable effects and limiting the duration of hospitalization. Higher amounts of ^{131}I in subsequent therapies or in the case of metastatic disease are given. Usually the activity is limited for safety reasons to around 7.4 GBq (200 mCi) [2]. It is appropriate to modulate the activity administered based on the subject's risk factors. In subjects with low-risk of Differentiated Thyroid Carcinoma (CTD) and low thyroid residue, it is appropriate to consider the low-activity of ^{131}I for ablative purposes.

In our center, we presently administer an activity equal to 1.1 GBq for patients at low risk and 3.7 GBq for patients classified as high risk or after preparation by rhTSH for low-risk patients, with possible repeated treatments. In fact, if for low-risk patients the success rate after the first treatment is greater than 70%, in the case of high-risk patients this percentage is drastically lowered (about 30%). Problems related to this treatment modality are definitely the stress for the patient and the ineffectiveness of the protracted treatments.

Fixed activity administration does not take account of the patient's individuality (mass of tissue, weight, height, radioiodine kinetics), neglecting thus the absorbed dose to critical organs; in the specific case, the hematopoietic red marrow (RM) is the organ at risk (OAR). Furthermore, multiple empiric fixed activities may not be equivalent to the same total radioiodine absorbed dose calculated due to dosimetric study and given in a unique administration. Repeated treatments could actually induce the stunning effect, usually defined as the inhibition or suppression of iodide trapping by remnant thyroid tissue or by functioning metastases [3,4].

Dosimetric methods are often reserved for patients with distant metastases or unusual situations such as renal insufficiency or when therapy with rhTSH stimulation is deemed necessary [5–7].

A successful ablation is strongly dependent on the absorbed dose to the thyroid remnant. Dosimetry-based personalized treatment can prevent both sub-optimal administrations, which entails further radioiodine therapy, and excessive administration of radioactivity, which increases the potential for radiation toxicity. In fact, radioiodine therapy for well-differentiated thyroid cancer (WDTC) is associated with increased risk of myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPNs) [8]. Moreover, these patients had an increased early risk of developing acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), although no other second hematologic malignancies (SHMs) have been highlighted [9]. The therapy with ^{131}I use in patients with WDTC should be limited to patients with high-risk disease features, and patients with WDTC treated with adjuvant radioiodine therapy should be monitored for myeloid malignancies as part of cancer surveillance. Therefore, attention to the amount of activity to be administered to the patient is of fundamental importance.

The treatment of DTC considers two different dosimetric approaches. The first one, used in the present study, is centered on the RM dose limit. This concept, described by Benua et al. [10] and subsequently applied to a greater number of patients by Benua and Leeper [11], sets a limit of 2 Gy for the absorbed dose to blood, as surrogated of red marrow, to avoid serious myelotoxicity. Moreover, a pre-treatment dosimetry is required to define the maximum tolerated activity (MTA), which they considered the most effective one. The second approach takes into account the dose to lesion, that is, the thyroid remnant. Dosimetric study, originated by Maxon [12], has the aim of

improving the effectiveness of the treatment by providing an absorbed dose threshold of 300 Gy to remnant and of 80 Gy to metastases.

As aforementioned, the rationale for using a dosimetric approach in DTC treatment is to replace the conventional fixed activity regimen by a modern setting, which allows the administered therapeutic activity to be increased while avoiding undesired side effects. Using this strategy, the absorbed dose to remnants and metastases can be optimized, without inducing potential toxicity.

This work was carried out at ARNAS Garibaldi - Nesima in Catania, within the framework of the therapeutic scheme which involves the administration of fixed activity (1.1 or 3.7 GBq). It shows the clinical case of a woman of 69 years old, affected by DTC with metastasis in the cranial and costal position, prepared using rhTSH before radioiodine therapy. RM absorbed dose was calculated by using formulations suggested by the red marrow dosimetry protocol produced by the Internal Dosimetry Group of the Italian Association of Medical Physics (AIFM) [13,14] and by Traino et al. [15]. The blood absorbed dose was estimated by applying formulations from Benua and Leeper [11] and the European Association of Nuclear Medicine (EANM) [6,7].

The specific goal of this study was to provide a practical example of dosimetric protocol to modify the current method of therapy in our institute. In this way, values of personalized activity exceeding 3.7 GBq may be administered in a single treatment, in respect of the MTA to red marrow.

2. Materials and Methods

2.1. Dosimetry in DTC: Red Marrow and Blood Absorbed Dose Calculations

Internal dosimetry aims to determine the amount and the spatial and temporal distribution of the absorbed dose inside organs and tissues of the human body, after the administration of a known activity (Bq or Ci) of a radioactive substance.

In nuclear medicine, the method usually employed to estimate the internal dose was developed by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine, that provides a systematic approach of calculation, called the "MIRD schema" [12]. Through a particular mathematical formalism, the MIRD schema takes into account the variables concerning the physical process of energetic deposition from ionization radiation, as well as those associated with the biological system to which the dose is calculated.

Radiation absorbed dose to the RM cannot be measured directly. It is necessary to quantify the absorbed dose to the blood (BL) due to the total activity administered. Therefore, we must know both the cumulated activity to blood and to the rest of the body (RoB). In fact, RM and BL absorbed doses are calculated as being the sum of both direct irradiation due to activity located within them and indirect irradiation due to activity located in the RoB, as shown in Equations (1) and (2):

$$D_{RM} = \widetilde{A}_{BL} \cdot S_{RM \leftarrow BL} + \widetilde{A}_{RoB} \cdot S_{RM \leftarrow RoB}\,, \tag{1}$$

$$D_{BL} = \widetilde{A}_{BL} \cdot S_{BL \leftarrow BL} + \widetilde{A}_{RoB} \cdot S_{BL \leftarrow RoB}\,, \tag{2}$$

where $\widetilde{A}_{BL}$ is the cumulated activity in the blood, $\widetilde{A}_{RoB}$ is the activity cumulated in the rest of the body, $S_{RM \leftarrow BL}$ and $S_{RM \leftarrow RoB}$ are the MIRD S-values representing the mean dose absorbed by target tissue (red marrow) per unit activity present in source tissue (blood and rest of the body, respectively), and $S_{BL \leftarrow BL}$ and $S_{BL \leftarrow RoB}$ are the MIRD S-values representing the mean dose absorbed by blood and delivered per unit activity present in blood and RoB, respectively.

The maximum tolerated activity (MTA), delivering to the RM the maximum allowed dose of 2 Gy [10], is given by Equation (3):

$$\mathbf{MTA[GBq]} = \frac{\mathbf{2\ Gy}}{\mathbf{D_{RM}[Gy]}} \mathbf{A_0[GBq]}, \tag{3}$$

where A_0 represents the administered therapeutic activity and D_{RM} represents the consequent dose delivered to the RM.

In order to perform BL and RM dosimetry with the aforementioned methods, one needs whole-body (WB) measurements and data about radioiodine concentration in blood [7].

2.1.1. EAMN Method: Blood Dosimetry

The EANM method calculates the absorbed dose to blood according to the Benua approach [10,11], as follows:

$$D_{BL} = A_0\left(\frac{0.0188}{m_{WB}^{2/3}}\tau_{WB} + 108\ \tau_{BL}^{1\ ml}\right)[Gy], \quad (4)$$

where A_0 is the administered activity expressed in GBq, m_{WB} is the patient's mass expressed in kg, τ_{WB} is the residence time in the WB and is expressed in h, and $\tau_{BL}^{1\ ml}$ is the residence time in 1 ml of blood and is expressed in h g^{-1} (or h ml^{-1}).

2.1.2. AIFM and Traino Method: Red Marrow Dosimetry

The AIFM method for RM absorbed dose calculation is based on the linear scaling of S-factors with the patient's WB mass. The formulae used for male (Equation (5)) and female (Equation (6)) patients are as follows:

$$D_{RM} = A_0\left(\frac{0.105}{m_{WB}}\tau_{WB} + 61\ \tau_{BL}^{1\ ml}\right)[Gy], \quad (5)$$

$$D_{RM} = A_0\left(\frac{0.0945}{m_{WB}}\tau_{WB} + 65\ \tau_{BL}^{1\ ml}\right)[Gy]. \quad (6)$$

The Traino method is based on non-linearly scale S-values to patient-specific RM mass. Starting from the S-values and S-values mass correction factors tabulated in OLINDA/EXM software (version 1.0, Michael Stabin PhD, CHP, Vanderbilt University, Nashville, TN, USA), Traino proposes for the RM dose calculation the following equations, for male (7) and female (8) patients, respectively:

$$D_{RM} = A_0\left[55.89\ \tau_{BL}^{1\ ml} m_{WB}^{0.026} + \left(\tau_{WB} - 15.2\ \tau_{BL}^{1\ ml}\ m_{WB}\right)\left(\frac{0.6967}{m_{WB}^{1.331}} - \frac{4.1683}{m_{WB}^{1.984}}\right)\right][Gy], \quad (7)$$

$$D_{RM} = A_0\left[58.97\ \tau_{BL}^{1\ ml} m_{WB}^{0.028} + \left(\tau_{WB} - 22.8\ \tau_{BL}^{1\ ml}\ m_{WB}\right)\left(\frac{0.5427}{m_{WB}^{1.302}} - \frac{3.4074}{m_{WB}^{1.944}}\right)\right][Gy]. \quad (8)$$

2.1.3. BL and WB Measurements and Calculations

Dosimetry to the RM and BL was performed during the treatments, after the administration of nominal therapeutic activity of ^{131}I equal to 3.7 ± 0.2 GBq, without modifying the fixed activity schema.

Dosimetric calculations were carried out on blood samples of 3 ml at 2, 6, 24, 48, and 144 h after administration of the therapeutic activity. The activity of each sample was measured using a dose calibrator ATOMLAB 100Plus (Biodex Medical Systems, Inc., Shirley, New York, NY, USA), working in the energy domain 25 keV to 3 MeV and measuring activity ranging from 0.01 μCi to 9999 mCi (or from 0.001 mBq to 399.9 GBq) of ^{99}Tc with an accuracy of about 5%.

Moreover, the patient underwent WB measurements at 2, 6, 24, 48, and 144 h after therapeutic administration, with a full bladder, using an environmental ionization chamber LUDLUM 9DP (ELSE Solutions s.r.l., Trezzano, IT, Milano). This chamber is suitable for performing total body radioactivity measurements, mainly revealing γ rays and X-rays in the energy range of 25 keV–2 MeV, with an accuracy of ± 10%. The first data after 2 h correspond to the effective administered activity A_0.

Three measures were carried out at a distance of 1 m, in particular at the neck, abdomen, and legs, both in the front position (AP) and in the posterior position (PA), as shown in Figure 1 for the abdomen

case. Then, for each set of values, the geometric mean was calculated, to which the background was subtracted. The WB measurement was obtained by running an additional geometric mean. The error associated with each measurement using the propagation of uncertainly was estimated, considering that the activity values are affected by an error associated with instruments.

Figure 1. Setup for radioactivity measurements: (**a**) front position (AP) and (**b**) anterior position (PA) positions to the abdomen, at the distance of 1 m.

Measurements are given in terms of ambient dose equivalent rate (μSv/h), so the results have to be expressed in activity. The calibration factor is obtained from the ratio of the therapeutic activity administered (A_0) and the WB measurement 2 h after administration.

In order to determine the residence times for the WB and for the concentration of activity in the BL, τ_{WB} [h] and $\tau_{BL}^{1\ ml}$ [h/g], the fraction of injected activity (FIA) is considered, expressed by the following equation [14]:

$$FIA_{WB}(t) = \frac{A_{WB}(t)}{A_0}. \tag{9}$$

A bi-exponential fit is adequate to describe the kinetics of the whole body, as follows:

$$FIA_{WB}(t) = A\ \exp(-Bt) + C\ \exp(-Dt), \tag{10}$$

where A, B, C, and D are fit parameters.

The uncertainty associated with the whole-body activity, A_{WB}, is related to the accuracy of the ionization chamber (10%). Consequently, the error on the FIA is obtained by summing the relative errors of the individual quantities.

The WB resident time is calculated by integrating Equation (10), as follows:

$$\tau_{WB} = \int_0^\infty FIA_{WB}(t)\ dt = A/B + C/D. \tag{11}$$

The BL retention is assumed to be a mono-exponential curve [16], so the Equations (9)–(11) become the following:

$$FIA_{BL}(t) = A_s(t)/A_0, \tag{12}$$

$$FIA_{BL}(t) = A\ \exp(-Bt), \tag{13}$$

$$\tau_{BL} = \int_0^\infty FIA_{BL}(t)\ dt = A/B, \tag{14}$$

where $A_s(t)$ is the specific activity per ml (or gram) in blood and A and B are the fit parameters.

The uncertainty associated with A_s is related to the accuracy of the activity calibrator (5%). Before the measurements, it is necessary to verify this accuracy as well as the linearity of the instrument. In addition, during the long measurement period, it is advisable to also carry out a stability test.

With the suggested acquisition time (last measurement on the whole body and blood at 96 h), the underestimation of residence times due to undetected body compartments induces an error in the calculation of the dose lower than 10% [14].

As the dosimetry measurement is performed during treatment, the patient's stay in the protected department allows a greater number of measurements, obtaining greater accuracy in determining the curve. A further reduction of error can come from a careful measurement of the environmental background (BKG), mainly due to the presence of other patients in neighboring rooms or of contaminated residues of any type.

Uncertainty about retention times and calculated dose values is obtained through the theory of error propagation in agreement with the EAMN guidelines [17] on the calculation of the uncertainties associated with the cumulative activity and, consequently, with the absorbed dose.

The experimental fits were carried out by LABFIT software (version 7.2.50, Wilton and Cleide Pereira da Silva, Universidade Federal de Campina Grande, DF/CCT, Campina Grande, Brasil, Paraiba) [18], whereas dosimetric estimations were performed by using a specially created Excel spreadsheet (version 16.0, Microsoft Corporation, Redmond, WA, USA).

3. Results and Discussion

The registered WB and BL activity data and the corresponding values of FIA are shown in Tables 1 and 2, useful both for the calculation of τ_{WB} (h) and $\tau_{BL}^{1\ ml}$ (h/g).

Table 1. Whole-body (WB) activity and associated fraction of injected activity (FIA) values.

Time (h)	A_{WB} (GBq)	FIA_{WB}
2 (full bladder)	3.70 ± 0.18	1.00 ± 0.08
2 + 10 minutes (empty bladder)	3.54 ± 0.35	0.96 ± 0.14
6	2.93 ± 0.29	0.79 ± 0.12
24	1.48 ± 0.15	0.40 ± 0.06
48	0.86 ± 0.09	0.23 ± 0.03
96	0.44 ± 0.04	0.12 ± 0.02

Table 2. Blood (BL) specific activity per gram and calculated FIA values.

Time (h)	A_s (GBq/g)	FIA_{BL} (g^{-1})
2 (full bladder)	$4.85 \times 10^{-2} \pm 0.17 \times 10^{-2}$	$1.31 \times 10^{-2} \pm 0.11 \times 10^{-2}$
6	$4.59 \times 10^{-2} \pm 0.16 \times 10^{-2}$	$1.24 \times 10^{-2} \pm 0.10 \times 10^{-2}$
24	$3.34 \times 10^{-2} \pm 0.12 \times 10^{-2}$	$9.03 \times 10^{-3} \pm 0.77 \times 10^{-3}$
48	$2.29 \times 10^{-2} \pm 0.08 \times 10^{-2}$	$6.20 \times 10^{-3} \pm 0.53 \times 10^{-3}$
96	$4.37 \times 10^{-3} \pm 0.15 \times 10^{-3}$	$1.18 \times 10^{-3} \pm 0.10 \times 10^{-3}$

The BL were calculated fitting the experimental data, according to Equations (9) and (10), as shown in Figures 2 and 3, respectively.

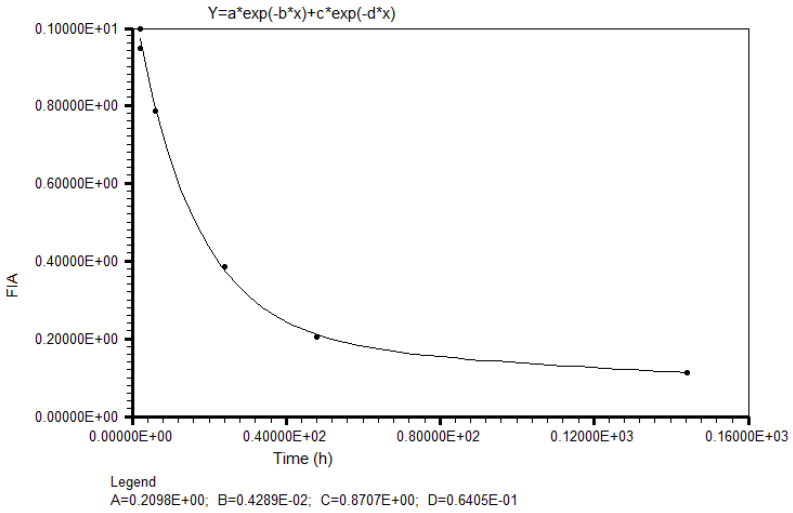

Figure 2. Bi-exponential fit of FIA_{WB} values vs. time after administration.

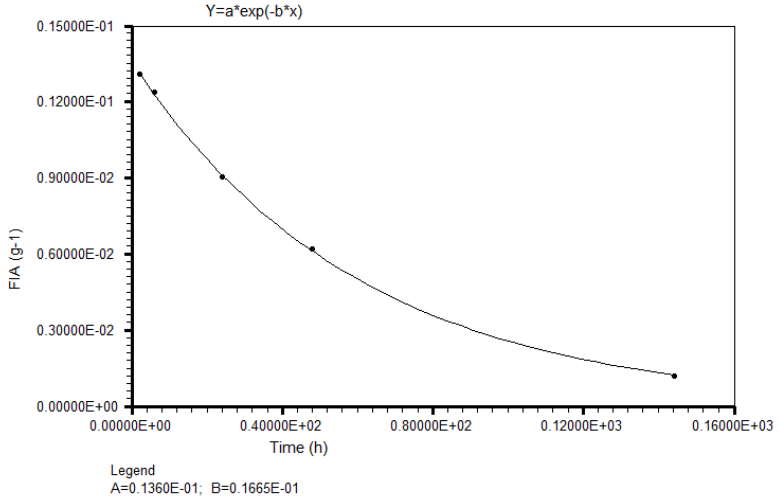

Figure 3. Mono-exponential fit of FIA_{BL} values vs. time after administration.

The estimated dose to BL (EANM formula) and RM (AIFM and Traino dosimetric formulae), normalized to the administered activities, is reported in Table 3, with τ_{WB} and $\tau_{BL}^{1\ ml}$.

Table 3. WB and BL retention time, dose to BL, and red marrow (RM) calculated, respectively, from the European Association of Nuclear Medicine (EAMN), the Italian Association of Medical Physics (AIFM), and Traino methods.

τ_{WB} (h)	$\tau_{BL}^{1\ ml}$ (h/g)	D_{BL} (Gy/GBq) EAMN	D_{RM} (Gy/GBq) AIFM	D_{RM} (Gy/GBq) Traino
18.48 ± 3.31	$3.43 \times 10^{-4} \pm 0.64 \times 10^{-4}$	$3.69 \times 10^{-2} \pm 1.25 \times 10^{-2}$	$2.20 \times 10^{-2} \pm 0.77 \times 10^{-2}$	$2.74 \times 10^{-2} \pm 0.96 \times 10^{-2}$

According to Equation (3), the MTA resulting from the calculation of the blood absorbed dose is reported in Table 4, for different approaches.

Table 4. Maximum tolerated activity (MTA) values derived from the different dosimetric approaches using 2 Gy as the limit for blood or red marrow absorbed dose.

	EAMN	**AIFM**	**Traino**
MTA (GBq)	14.65 ± 5.13	24.57 ± 8.60	20.02 ± 7.00

The EANM method can be applied over a wide range of tracer and therapeutic activities [19]; therefore, in Table 5, we report the dose calculation differences between AIFM and Traino methods from the EAMN approach. For completeness, the differences between the AIFM and Traino methods are also shown.

Table 5. Percentage difference between different calculation methods.

	AIFM-EAMN	**Traino-EAMN**	**AIFM-Traino**
% diff.	40	26	20

This result confirms that the choice of the calculation method is fundamental, in order to reduce the uncertainties due to a last or underlying dose.

4. Conclusions

The aim of this study was to investigate the possibility of restricting the number of treatments and, consequently, to reduce the risk of the stunning effect that causes a decrease in iodine uptake by cancerous tissue. In particular, in the presence of metastatic Differentiated Thyroid Carcinoma (CDT), Chiesa et al. [3] demonstrated that repetition of treatment on a lesion drastically reduces its uptake, with a loss of therapeutic efficacy along the sequence of fixed activity administrations. Furthermore, Klubo-Gwiezdzinska et al. [20] underlined a higher efficacy of dosimetry-based prescribed activity with a similar safety profile compared to the standard approach, and supports the rationale for employing individually prescribed activity in high-risk patients with DTC.

Thanks to the dosimetric study, it was thus highlighted that it is possible to administer individualized activities for DTC patients, higher than the standard ones, but which produce an absorbed dose to critical organs still lower than the maximum allowed value. In order to personalize the treatment and estimate the maximum tolerable activity (MTA), a pre-treatment dosimetry is necessary. This can be performed by administering a tracer activity (about 15–20 MBq) before the treatment and adopting the measurement procedure shown in this work. The availability of a previsional instrument radically changes the methodological approach, introducing an a priori quantitative evaluation criterion. This could have a significant impact on the therapeutic strategy (reduction of multiple treatments) and on the quality of life of the treated patient. The benefits of the individual forecast dosimetry are however counterbalanced by costs relative to man time versus machine time, as well as pertaining to the patient's logistics. The availability of simplified methods, however, makes a forecast dosimetric study feasible in order to administer the desired dose to the residue, limiting the exposure of the critical organs.

Even if clinical data have not yet demonstrated the therapeutic effectiveness of higher activities, some authors have suggested that high-activity single therapy may result in a higher efficacy than multiple low-activity treatments, because of the potential for smaller fractionated doses to increase the radio-resistance of metastatic tumors [2]. Moreover, Giostra et al. [21] found that the administered therapeutic activity could be safely increased compared to the current prescribed activities (from 7.4 GBq to 11.1 GBq). Dorn et al. [22] combined red marrow and lesion dosimetry showing that high-activity administrations with less than 3 Gy to the red marrow are a safe and more effective method with respect to fixed activity administrations. They performed a range of activities from 7.4 to 38.5 GBq in order to deliver the most curative dose to the lesions.

The most appropriate dosimetric calculation methodology is still a subject of discussion, as it appears to be fundamental in order not to underestimate or overestimate the bone marrow dose. However, the choice of the best approach is not the purpose of this work. The estimation of the MTA in all approaches is affected by considerable uncertainty. In our case, the associated error is greater than 30% and this is certainly related to the uncertainties derived from the calculation of the absorbed blood and red marrow dose. This value represents a significant error, and it is known that errors about the estimate of the internal dose exceed those of the external beam radiation therapy (EBRT) by an order of size.

The administration of such high activities certainly raises problems. If, on the one hand, a better therapeutic result could be obtained by avoiding the treatment of the patient several times, the use of high activities on the other hand would involve the extension of the number of days of the protected stay (at least one week). This would surely be a source of stress for the patient. Furthermore, the rate of exposure measured at discharge would certainly be higher than in the case of low activity. This would lead to the prescription of conductive indications that are certainly more restrictive and durable during the patient's discharge. Suffice it to say that in our center, as of today, protected shelter is provided for only two days. This would lead to a modification in the patient management protocol currently in use in our center, involving the use of a greater number of resources in terms of nursing staff and doctors and a greater number of medical physicists dedicated to personalized dosimetry.

Patient specific dosimetry could lead to an effective optimization of the treatment with regard to the organs at risk, but further implementations are necessary, such as the dosimetry of the lesions and the definition of dose–effect curves for OARs and targets.

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