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Dosimetric methodology for ^{131}I therapy for benign thyroid diseases

Méthodologie pour la dosimétrie des traitements à l'iode 131 des maladies bénignes de la thyroïde

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Résumé

Le traitement à l'iode 131 fait partie des traitements de référence pour les maladies bénignes de la thyroïde. Habituellement, la dose prescrite est unique pour une même maladie. Inspirée de la radiothérapie externe, l'émergence de la dosimétrie personnalisée pré-thérapeutique dans les services de médecine nucléaire permet de s'adapter à la maladie et à la physiologie du patient ; plus particulière à sa cinétique de distribution de l'iode. En personnalisant l'activité prescrite, la dosimétrie permet de se conformer au principe ALARA en radiothérapie métabolique tout en préservant l'objectif thérapeutique. La dosimétrie post-traitement permet quant à elle de valider la méthodologie et, en relevant la dose réellement délivrée aux organes avoisinant le volume cible, de contribuer à la compréhension de la relation dose-effet. Après un rappel du formalisme du MIRD sur lequel s'appuie le calcul de dose, ce document recense la démarche à suivre en dosimétrie thyroïdienne. Définition de la sensibilité, calcul des facteurs S, estimation de l'activité cumulée et des temps de résidence puis calcul de la dose sont les différentes étapes présentées. La nécessité d'une bascule de la prescription en dose fixe à la prescription personnalisée semble aujourd'hui être une évidence. De nombreuses études en cours ainsi que l'émergence de nouveaux logiciels compilant l'ensemble des informations indispensables pour sa mise en œuvre permettent aux services de médecine nucléaire de se projeter plus facilement dans la démarche.

Dosimétrie personnalisée- Traitement à l'iode 131- Maladie bénigne de la thyroïde

Abstract

Treatment with ^{131}I is one of the standard treatments for benign thyroid disease. In most cases, the prescribed dose is specific for the same disease. Inspired by external radiotherapy, the emergence of personalized pre-therapeutic dosimetry in nuclear medicine departments makes it possible to adapt to the patient's diseases and physiology; more specific to its kinetics of iodine distribution. By personalizing the prescribed activity, dosimetry makes it possible to comply with the ALARA principle in metabolic radiotherapy while at the same time preserving the therapeutic objective. Post-treatment dosimetry permits to validate the methodology and, by recording the dose actually delivered to the organs surrounding the target volume, to contribute to the understanding of the dose-effect relationship. A re-reading of the MIRD formalism guidelines is important as this document lists the procedure to be followed in thyroid dosimetry. Defining the sensitivity, calculating the S factors, estimating the cumulative activity and residence times and then calculating the dose are the different steps presented. The need to switch from fixed dose prescription to personalized prescription seems to be evident. Several studies in progress as well as the emergence of new software compiling all the information essential for its implementation will permit nuclear medicine departments to involve themselves more easily into the process.

Personalized dosimetry- Radiodine therapy – Benign thyroid disease

1 Introduction

Treatment of hyperthyroidism including Graves' disease, toxic multinodular goiter and toxic solitary nodule with ^{131}I is routinely performed in nuclear medicine departments. The activity of administration can be determined using two approaches, empiric and dosimetry-based.

The current trend in France [1] and in many European countries is the administration of fixed activities, "one-size-fits all" or modulated by the clinical status of the patient (empiric approach). However, a more personalized approach, dosimetry-based, can also be proposed. This complies with EURATOM directive 2013/59 [2] from the Council of the European Union, which states that *for all medical exposure of patients for radiotherapeutic purposes, exposures of target volumes shall be individually planned (article 56 Optimization)*. Implementing patient specific dosimetry – and adapting the administered activity on a patient-specific base allows implementing the "ALARA" principle (*As Low As Reasonably Achievable*), while preserving the therapeutic objective (*...consistent with the intended radiotherapeutic purpose of the exposure*).

The concept of treatment planning is very well accepted in external beam radiotherapy (EBRT). It is tempting to establish a parallel with targeted radionuclide therapy (TRT), even though radiation delivery is very different – which may impact the radiobiology and therefore the clinical outcome of the treatment.

In EBRT, the process is to simulate the treatment by calculating a dose distribution map, verify it and then assess how the treatment plan is implemented during the therapy. This means comparing post-treatment dosimetry with pre-treatment dosimetry.

In TRT, the aims associated with dosimetry can be different, as pre-therapeutic and post-therapeutic dosimetry can be implemented with different purposes:

- Pre-therapeutic dosimetry aims at tailoring the treatment according to a dosimetric index. The concept of treatment planning in TRT relies on the assumption that pharmacokinetics obtained from a pretherapeutic procedure can predict that of the actual treatment. In addition, administering a given activity based on a dosimetric parameter (the absorbed dose to the clinical target, or that to a critical organ) relies on the knowledge of the absorbed dose – effect relationship (as is the case in EBRT).
- Post-therapeutic dosimetry can be implemented to document the radiotherapeutic procedure, even when routine activities are administered. The assessment of absorbed doses delivered after activity administration allow understanding the clinical outcome. In addition, like in EBRT, post-therapeutic dosimetry can be implemented to verify the delivered treatment after pre-therapeutic dosimetry.

For the treatment of benign thyroid disease, several journals reported an absorbed dose-related outcome after radioiodine treatment [3; 4] and a correlation has been identified between hypothyroidism and absorbed dose, while the irradiation of non-target tissues has also emerged as a factor that needs careful consideration [5].

In consequence, for the benefit of patients it might be suitable to tailor the administrated activity according to their biokinetics and thus avoid under- or over treatment. That is why developments are oriented on personalized dosimetry to improve the quality and outcome of radionuclide therapy [6; 7]. In this context, personalized treatment should be particularly encouraged for children who have a higher risk than adults to develop radiation-induced cancer.

By exposing an overview of dosimetry approaches, the aim of this document is to provide information to help implementing dosimetry procedures in nuclear medicine departments.

2 Dosimetric Methodology

We will present the basics of radiopharmaceutical dosimetry, and then see how they can be applied to the specific situation of the therapy of thyroid benign disease with ^{131}I as presented in the European Association of Nuclear Medicine (EANM) guidelines [8; 9].

2.1 Radioisotopes for dosimetry

For pre-therapeutic dosimetry, a low activity of ^{131}I can be used [10]. Alternatively, the distribution of ^{131}I can be estimated indirectly using a surrogate isotope like ^{123}I , with similar biological and chemical characteristics, but better suited to scintigraphic imaging (gamma emission of 159 keV and physical half-life of 13.2 hours) [11].

Recent studies proposed using ^{124}I with positron emission tomography (PET) for pretherapeutic dosimetry [11; 12] and compared ^{124}I and ^{131}I uptake in patients. ^{124}I is 511 keV gamma emitter with a half-life of 4.18 days.

For post-therapeutic dosimetry, ^{131}I administrated for the treatment is used. Iodine 131 is a beta-emitting radionuclide with a physical half-life of 8.02 days. The maximum energy of the main beta emission is 610 keV (average beta energy of 192 keV), which corresponds to an average range of 0.4 mm in soft tissues thereby assessing localized irradiation as is desirable in TRT. The principal gamma ray of 364 keV makes it possible (albeit not optimal) to visualize and quantify activity in the patient [13].

2.2 Phantom and calibration measurements

The quantification of activity present in patient body requires implementing calibration procedures. Calibration should be made for each isotope used in clinical practice.

Series of phantom measurements including known activities are performed and used for quantitative studies. Aside from the determination of camera sensitivity, acquisitions performed in phantoms that mimic the clinical situation allow implementing attenuation, scatter or partial volume effect corrections.

Basically, the calibration should be performed using a phantom with a geometry and a composition as close as possible to that of the human neck, to replicate radiation absorption and scatter in the patient's thyroid [14].

Simple thyroid phantoms (such as simple cylinders) have been routinely used in clinical practice, but present limitations due to their simplistic geometry [15]. More recently, some teams have proposed more realistic and low cost thyroid phantoms based on 3D printing [16-18]. These efforts may lead to improved calibrations of the imaging devices or thyroid counters.

The tracer activity used for dosimetry should be measured in the phantom prior to the administration. Image/counting acquisitions should be performed with a phantom placed at the same distance to the camera than the patient's neck. The resulting count rate value represents a 100 % uptake, and the count rate divided by the activity should be used as a constancy check for the sensitivity of the device [9].

The system volume sensitivity, which is the conversion factor used for calculating radioactivity from SPECT counts, can be obtained according to the method described by Frey *et al.* [19].

Verifying the constancy of detector sensitivity for a reproducible geometry is recommended and its periodicity should be defined in each nuclear medicine department as a function of activity. Ideally, the sensitivity should be evaluated by measuring the activity to be administered before each administration, in both by the measuring device and by an activimeter [9].

2.3 SPECT/CT: acquisition and correction

SPECT/CT is used to perform the uptake measurements. With ^{123}I , a low energy collimator with a high resolution is used for acquisition. For iodine 131, possibly used for pre and post-therapeutic dosimetry, a high energy collimator is used for scintigraphy to reduce septal penetration. If available, a camera with a thick NaI(Tl) crystal should be selected to increase detection sensitivity and count rate. Such cameras can be expected to record enough counts, about 50 counts per second per mega Becquerel for ^{131}I in a 15 % window centered on the main emission peak at 364 keV [9]. The distance between camera and patient should be as small as possible to improve spatial resolution.

To improve image quality and allow activity quantification, different corrections must be made like a background correction in planar imaging, attenuation correction using CT in hybrid SPECT/CT systems, scatter correction, partial volume effect correction and dead time [20; 21].

Periodic checks must be carried out on the SPECT/CT to ensure the constancy of imaging performances.

2.4 Thyroid mass assessment

The determination of thyroid volume is essential, as the absorbed dose is inversely proportional to the mass of the volume of interest. Thyroid volume is most often assessed via 2D or 3D ultrasonography (US) [22-24]. Magnetic resonance imaging or computed tomography [25-27] have also been proposed.

Ultrasound measurements were compared with reference MRI measurements and found to correlate well, provided that the ellipsoid formula [9] used in ultrasonography is corrected. When comparing US measured volumes with surgically removed volume, mean differences of 13% and 22% were found by Hussy *et al.* [28] and Miccoli *et al.* [29], respectively.

Comparing 2D and 3D US measurements, [30] found that 2D overestimated the volume by 17%. Even if the overall accuracy of US might be acceptable for absorbed dose assessment [31], the experience of observers is an important factor affecting the precision of measurements [23; 30; 32].

2.5 MIRD formalism

According to the MIRD formalism, consistent with the ICRP formalism, the absorbed dose delivered to a given target k is the sum of the contributions of every source h present in the patient:

$$\overline{D}_k = \sum_h \overline{A}_h \times S_{(k \leftarrow h)} \quad (1).$$

\bar{A}_h is the cumulated activity in the source (or time integrated activity, which means residence time) and represents the number of nuclear disintegrations occurring in the source h (in MBq.s or equivalent).

$S_{(k \leftarrow h)}$ is called the “S-factor” and gives the absorbed dose delivered in target k per nuclear disintegration in the source h. It is more convenient to express S in Gy.MBq⁻¹.days⁻¹.

2.6 Thyroid S-factors

For thyroid dosimetry following ¹³¹I administration, the previous equation can be simplified since (i) most of the up taken activity stays in the thyroid, and (ii) the fraction of photon energy emitted in the thyroid and absorbed in the thyroid (self-absorbed) is extremely small, whereas (iii) most of the electrons/beta energy emitted in the thyroid is absorbed in the thyroid.

In that context, the S-factor $S_{(Thyroid \leftarrow Thyroid)}$ for ¹³¹I in Gy.MBq⁻¹.day⁻¹ can be given by:

$$S_{(Thyroid \leftarrow Thyroid)} = \frac{2.808}{M(g)} \quad (2).$$

For a thyroid weight less than 90 g this simple relation gives error less than 5% [9]. A more precise expression is:

$$S_{(Thyroid \leftarrow Thyroid)} = \frac{2.5}{M} + 0.139M^{-0.75} \quad (3)$$

Alternative expressions for the S-factors are provided in [34; 35] but they do not represent significant change to those presented here.

2.7 Biokinetic model for the thyroid

To calculate the number of nuclear disintegration in a given organ (\bar{A}) one needs a biokinetic model describing the thyroid activity content along time. The biokinetic model adopted by the EANM [9] is reproduced in **Figure 1**.

In this simple model the activity in the thyroid is described by three transfer rates, the blood to thyroid transfer rate (k_t), the renal clearance (k_r), the thyroid hormone clearance (k_h). The physical decay constant is noted k_p . For consistency with the previous relations the transfer rates and physical decay constant must be expressed in days⁻¹. The transfer rates are patient dependent but the physical decay depends on the radio-iodine isotope, the biokinetic model is thus not specific of ¹³¹I.

The biokinetic model enables the calculation of the fractional Radio-Iodine Uptake (RIU) in the thyroid at a given time, i.e. the fraction of the administrated activity (A_a) that is in the thyroid at a time t :

$$RIU(t) = \frac{A_{Thyroid}(t)}{A_a} \quad (4)$$

The advantage of the simple biokinetic model is that $RIU(t)$ can be calculated as follows:

$$RIU(t) = \frac{k_t}{k_B - k_T} (e^{-k_T t} - e^{-k_B t}) \quad (5)$$

The parameters k_B and k_T are defined as follows:

$$k_B = k_p + k_r + k_t \quad (6a)$$

$$k_T = k_p + k_h. \quad (6b)$$

At this stage it can be noticed that the long-term trend of $RIU(t)$ is given by the first time in parenthesis of **Eq. 5** and it thus enables to define the effective half-live of radio-iodine in thyroid as follows:

$$T_{eff} = \frac{\ln(2)}{k_p + k_h} \quad (7)$$

The cumulated activity is the integral of $RIU(t)$ multiplied by the administrated activity:

$$\bar{A}_{Thyr} = A_\alpha \frac{k_t}{k_p \cdot k_T} = A_\alpha \cdot \tau_{Thyr} \quad (8).$$

The last term τ_{Thyr} stands for the residence time (or time integrated activity coefficient) in the thyroid. It is the integral of $RIU(t)$ and has units of days.

2.8 Residence time assessment from measurements and activity prescription

It is assumed that activity measurements in the thyroid are taken at early (t_e) and/or late (t_l) time after administration of a tracer activity of ^{131}I .

Once τ_{Thyr} is determined, the activity to administer to obtain the therapeutic absorbed dose can be calculated using **Eq. 9** described below. **Table 1** gives approximations for τ_{Thyr} assessment.

2.9 Pre-therapeutic dosimetry and prescription of administrated activity A_α

To deliver a given therapeutic absorbed dose to the thyroid (\bar{D}_{Thyr}) one thus needs:

- The S-factor $S_{(Thyrr-Thyr)}$ that is easily calculated from the thyroid mass (cf section above);
- The biokinetic parameters describing the thyroid uptake (k_t , k_T , k_B) or an estimate of the resident time (τ_{Thyr})

Then the activity A_a required to reach a given absorbed dose \bar{D}_{Thyr} is given by:

$$A_a = \frac{\bar{D}_{Thyr}}{S_{(Thyrr-Thyr)} \cdot \tau_{Thyr}} \quad (9)$$

Depending on the time (after tracer activity administration) and on the numbers of thyroid uptake measurements different approximation can be given for τ_{Thyr} , as presented in the previous paragraph that summarizes the EANM guidelines.

Table 2 presents numerical examples for the cases described in **Table 1**. Starting from the thyroid mass the S factor is calculated with **Eq. 2**. The residence time is calculated from Table 1. The administrated activity required to reach a given therapeutic absorbed dose is obtained from **Eq. 9**.

2.10 Post-therapeutic dosimetry

Even if low activity of ^{131}I is administrated in the pre-therapeutic phase it cannot be ruled out that thyroid stunning might occur, and even if stunning is not induced by the pre-therapy administration the administrated therapy activity might modify the thyroid uptake parameters [36; 37]. Similarly, the time elapsed since anti-thyroid drug withdrawal might induce change in thyroid uptake [38-40], thus thyroid uptake during the pre-therapy and therapy phase are not necessarily the same.

Consequently, post-therapy dosimetry is useful to adjust following treatments if the current one fails and to document at best the patient records.

The methods exposed in the previous sections for pre-therapeutic dosimetry remains valid for post-therapeutic dosimetry. Uptake measurements can be obtained to check that the administered activity A_a actually led to the prescribed absorbed dose \bar{D}_{Thy} . A study by Fujita et al. investigated post-therapeutic imaging for dosimetry [14]. The absorbed dose delivered was calculated based on quantitative SPECT/CT, on the basis of the guidelines proposed by the MIRD committee for voxel dosimetry. Patient SPECT images were acquired 24 h after oral administration to confirm iodine uptake in the thyroid, and at various time intervals to determine time activity curve.

We exposed pre-therapeutic and post-therapeutic implementation of ^{131}I dosimetry for the treatment of benign thyroid disease. The most important point is the assessment of patient-specific biokinetic parameters, which can be done also with other radio-iodine isotopes [12; 41]. To adapt the method to other radio-iodine isotopes with shorter half-live it would be needed to:

- Administer enough activity so that late measurements are not under detection limits;
- Perform a physical decay correction to transform the *RIU* to the ^{131}I equivalent.

Other iodine biokinetic models are available [42]. If such models were used it is not guaranteed that the residence time assessment presented in the EANM guidelines would remain strictly valid. In that situation, an alternate way to assess the residence time would be needed to grant a correct dosimetric prescription.

3 Perspectives

This document provide an overview of the dosimetric approaches for radiodine treatment of benign thyroid diseases.

The relevance of dosimetry is not questioned in external beam radiotherapy, where treatment planning has been routinely performed for decades. A number of justifications are frequently presented to avoid dosimetry in nuclear medicine therapy [43; 44], like the prohibiting cost, the uncertainties associated with absorbed dose determination [45] or the difficulty to make evident the absorbed dose-effect relationship [46].

Studies are necessary to improve the correlations between the administered activity and the clinical outcome and enable better understanding of the absorbed dose-response relationship. Different groups are working to reach this goal.

As described, both pre-therapeutic and post-therapeutic dosimetry are performed using the MIRD formalism.

The concept of S value implicitly refers to model-based dosimetry, where tables of precomputed S values are calculated for anthropomorphic dosimetric models. Codes like the well-known OLINDA/EXM implements this model-based approach [47; 48]. Interestingly, S values can be adapted when the mass of organs/tissues differ from that of the reference model [49]. A new generation of voxel-based and more realistic human models was proposed by various authors [50] and implemented in more recent software like OLINDA/EXM 2.0 [51] or IDAC [52]. The recently created OpenDose collaboration aims at providing open access resources (including S values) for nuclear medicine dosimetry [53].

At the same time, research work and clinical needs have stimulated the emergence of commercial software enabling to directly compute patient-specific, image-based absorbed dose (rate) maps at the voxel level, from anatomic/functional data derived from hybrid imaging technologies. As is current practice in EBRT, absorbed dose volume histograms can be generated from these new software. Biological Equivalent Dose (BED) and a range of dosimetry-related indexes can be obtained, even though it remains to be seen if voxel-based dosimetry can provide a better appraisal of clinical response [54].

These softwares may have an FDA/EAM approval or CE marking as medical device, making them a viable option to implement dosimetry in clinical routine. Studies are in progress to identify “dosimetry-based biomarkers of response” for TRT, and the availability of user-friendly software is a further motivation for deploying personalized dosimetry in nuclear medicine departments.

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CONFLICT OF INTEREST

The authors confirm that there is no conflict of interest

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Figure 1

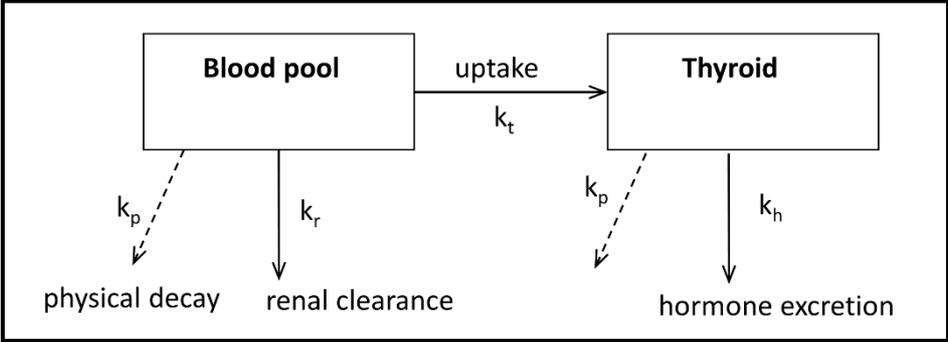


Table 1

Three or more uptake measurements	
<p>Measurements should be at least three and around 4-6 hours, 1-2 days and 5-8 days. Measurements are used to fit RIU(t) and deduce k_t, k_B, k_T from which τ_{Thyr} is assessed. An example is provided in [9].</p>	
Two uptake measurements : early and late	
Conditions	τ_{Thyr} approximation
$1 \leq t_e \leq 2$ days $4 \leq t_l \leq 8$ days $t_l - t_e \geq 3$ days	$T_{eff} = \frac{\ln(2)(t_l - t_e)}{\ln(RIU(t_l)) - \ln(RIU(t_e))}$ <p>If T_{eff} is more than 8 days, it is set to 8 days</p> $\tau_{Thyr} = 1.4 RIU(t_l) \cdot 2^{t_l / T_{eff}} \cdot T_{eff}$
One late uptake measurement	
Conditions	τ_{Thyr} approximation
$4 \leq t_l \leq 8$ days	$\tau_{Thyr} = 2.8 RIU(t_l) \cdot t_l$
One early uptake measurement	
Conditions	τ_{Thyr} approximation
$1 \leq t_e \leq 3$ days	$\tau_{Thyr} = 1.4 RIU(t_e) \cdot 2^{t_e / T_{est}} \cdot T_{est}$ <p>T_{est} is the estimated effective half-life.</p>

Table 2

Case	Thyroid mass (g)	Therapeutic absorbed dose \bar{D}_{thy} (Gy)	t_e (days)	t_l (days)	RIU(t_e)	RIU(t_l)	A_a (MBq)
Two uptake measurements	20	300	1.5	6	0.4	0.25	491.6
Two uptake measurements. $T_{eff} > 8$ days	10	300	1	4	0.35	0.3	224.8
One late measurement	20	150		7		0.2	272.5
One early measurement $T_{eff} = 5.5$ days	15	250	2		0.45		299.5