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Technical note

Treatment of hyperthyroidism with radioiodine targeted activity: A comparison between two dosimetric methods

Ernesto Amato [a,*], Alfredo Campennì [a], Salvatore Leotta [b], Rosaria M. Ruggeri [c], Sergio Baldari [a]

[a] Section of Radiological Sciences, Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy
[b] School of Medicine and Surgery, University of Palermo, Palermo, Italy
[c] Section of Endocrinology, Department of Clinical and Experimental Medicine and Pharmacology, University of Messina, Messina, Italy

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ABSTRACT

Radioiodine therapy is an effective and safe treatment of hyperthyroidism due to Graves' disease, toxic adenoma, toxic multinodular goiter. We compared the outcomes of a traditional calculation method based on an analytical fit of the uptake curve and subsequent dose calculation with the MIRD approach, and an alternative computation approach based on a formulation implemented in a public-access website, searching for the best timing of radioiodine uptake measurements in pre-therapeutic dosimetry. We report about sixty-nine hyperthyroid patients that were treated after performing a pre-therapeutic dosimetry calculated by fitting a six-point uptake curve (3–168 h). In order to evaluate the results of the radioiodine treatment, patients were followed up to sixty-four months after treatment (mean 47.4 ± 16.9). Patient dosimetry was then retrospectively recalculated with the two above-mentioned methods. Several time schedules for uptake measurements were considered, with different timings and total number of points. Early time schedules, sampling uptake up to 48 h, do not allow to set-up an accurate treatment plan, while schedules including the measurement at one week give significantly better results. The analytical fit procedure applied to the three-point time schedule 3(6)–24–168 h gave results significantly more accurate than the website approach exploiting either the same schedule, or the single measurement at 168 h. Consequently, the best strategy among the ones considered is to sample the uptake at 3(6)–24–168 h, and carry out an analytical fit of the curve, while extra measurements at 48 and 72 h lead only marginal improvements in the accuracy of therapeutic activity determination.
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1. Introduction

Radioiodine therapy is an effective and safe treatment of hyperthyroidism due to Graves' disease (GD), toxic adenoma (TA), toxic multinodular goiter (TMNG) [1–4].

Several studies throughout the years have pointed out the importance of personalizing the therapeutic activity of ^{131}I to be administered in order to achieve the clinical outcome, while minimizing radiation exposures to healthy organs and tissues [5–8].

The personalization of radioiodine activity necessary to impart a prescribed radiation dose to target tissues (autonomous nodules or the entire thyroid) is accomplished through a simple pre-therapeutic dosimetry consisting in multiple measurements of radioiodine uptake after administration of a tracer activity of either ^{131}I or ^{123}I isotopes [9,10].

Different research groups have compared dosimetric methods and measurement time schedules, building scientific evidence about the superiority of multiple uptake measurements sampling both the early and the late phases with respect to dosimetric methods based on early measurements only and fixed effective half lives [11–16].

Aim of the present study was to compare the outcomes of a traditional calculation method based on an analytical fit of the uptake curve and subsequent dose calculation with the MIRD approach, and an alternative computation approach based on a formulation described in Ref. [17] and implemented in a public-access website [18].

This comparison was carried out by retrospectively analyzing the possible deviations in therapeutic activity determination that would arise assuming several simplified measurement time schedules and subsequent activity determinations in the two methods, with the aim of optimizing timing of ^{131}I activity measurements in pre-therapeutic dosimetry of benign hyperthyroidism.

* Corresponding author.
E-mail address: eamato@unime.it (E. Amato).

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2. Patients and methods

2.1. Patient enrollment and pre-treatment dosimetry

Sixty-nine consecutive patients referred to the Nuclear Medicine Unit of our University Hospital for radioiodine therapy were enrolled in the study. Among these patients (44 females and 25 males, mean age at recruitment 64.2 ± 12.6 years), 43 were affected by single TA, 13 by TMNG and 13 by GD. Thyroid disorders were diagnosed according to the current rules [19].

All but 17 patients (75%) were overtly hyperthyroid (i.e. serum TSH value under the correspondent normal range and serum FT4 and/or FT3 value over the correspondent normal range). Forty-one (59.4%) patients had received anti-thyroid drugs (namely, methimazole), which were withdrawn 5–10 days before radioiodine thyroid uptake (RAIU) and radioiodine therapy (RaIT). Twenty patients had positive anti-thyroglobulin antibody (TgAb) and/or anti-tireoperoxidase antibody (TPOAb). RAIU measurement was performed as elsewhere described [20].

Pre-treatment dosimetry was carried out by orally administering 1.85 MBq of ^{131}I and building up an uptake-washout curve through scintillation probe measurements taken at 3, 6, 24, 48, 72 or 96, and 168 h. Time-activity curve was then analytically fitted with the equation:

$$U(t) = \frac{\lambda_i U_{MAX}}{\lambda_o - \lambda_i}\left(e^{-\lambda_i t} - e^{-\lambda_o t}\right) \quad (1)$$

where $U(t)$ is the ^{131}I uptake at time t, U_{MAX} is the percentage of administered iodine which is transferred to the thyroid, λ_i and λ_o are the intake and washout rates, respectively. Mean RAIU was 49.1 ± 13.8%.

Planar scintigraphy was performed 24 h after radioiodine administration by using a double-headed gamma camera (Millennium VG, GE Medical System) equipped with high-energy low resolution parallel hole collimators (HELRPAR). Images (magnification: 1.4; matrix: 256 × 256; frame time: 900 s), obtained with the neck in hyperextension position, were performed with and without a jugular radioactive mark employed to better define the gland position with respect to the upper mediastinum.

Planar scintigraphy at 24 h was also used to quantify the relative per cent uptake of each nodule in TMNG patients, and to ascertain the full suppression of thyroid parenchyma in TA disease.

Thyroid ultrasonography (TU) was performed using a real-time 2D apparatus (General Electric Healthcare, USA) with a 7.5–10 MHz linear transducer. The volume of thyroid lobes, as well as the volume of thyroid nodules(s), was calculated with the ellipsoid formula ($\pi/6 \times$ height $\times$ width $\times$ depth, each diameter being expressed in cm). In TMNG and TA, the "net" volume of the hot nodule(s) was calculated by subtracting the volume of involution area(s).

The activity to be administered in MBq, A_0, was then calculated as:

$$A_0 = 5.829 \cdot \frac{Dm}{U_{MAX} T_{1/2\mathrm{eff}}} \quad (2)$$

where D is the prescribed dose in cGy, m is the target mass in g obtained multiplying the volume by a density of 1.04 g cm^{-3}, U_{MAX} is the percentage of administered iodine which is transferred to the thyroid, and $T_{1/2\mathrm{eff}}$ is the effective half-life of the nuclide in hours obtained from Eq. (1).

2.2. Patient treatment and follow-up

All but one patient were treated in outpatient modality. Hospitalization was necessary only for a female patient with a very large TA (52 mm of maximum diameter), whose radioiodine administered activity was higher than the limit allowed for outpatient treatment.

The first clinical and laboratory evaluation (TSH, FT3, FT4) was performed 2–3 months after treatment, while the subsequent evaluations were established in each patient on the basis of the laboratory results ("targeted follow-up"). Mean follow-up was 47.4 ± 16.9 months.

Thirty-five patients with nodular toxic disease (either TA or TMNG) underwent TU six months after RAIT. Subjects were examined by the same trained ultra-sonographer, who had carried out the US before RAIT.

2.3. Comparative analysis of dosimetric methods

The dosimetry of each patient was then retrospectively recalculated with two methods: the analytical fit of Eq. (1) and subsequent therapeutic activity determination as in Eq. (2), referred afterwards as *fit*, and the calculation approach presented in Ref. [17] implemented in a website accessible at Ref. [18], referred afterwards as *website*.

The *website* calculation approach describes the radioiodine kinetics using a nonlinear mixed-effects mathematical model that relies on the proper characterization of a reference population (for which 41 patients treated for GD were retrospectively analyzed). In Ref. [17], the Authors showed that choosing appropriate measurement times one can optimize probabilistic bounds on the accuracy of the corresponding estimates.

For each method, several time schedules were considered, taking into account that a maximum of three time points are allowed in the website approach, and that the traditional fit approach do not allow convergence with only one-time point, or without at least one measurement in the decay phase (after 24 h).

Consequently, both approaches were tested and compared with 24–48 h, 24–96 h, 3–24–48 h, 3–24–96 h, 3–24–168 h and 6–24–168 h time schedules. The website approach was also employed using 3 h, 3–24 h, and 168 h measurement times. Finally, the fit procedure was tested with the four-point time schedules 3–24–48–168 h and 6–24–48–168 h, and with the five-point schedules 3–24–48–72–168 h and 6–24–48–72–168 h.

The obtained therapeutic activities were compared with the actual therapeutic activity that had been administered following the calculation procedure described above, i.e. a fit approach which exploits all the measurement points available. Relative per cent errors of the therapeutic activity calculated by the approach under test, A_i, with respect to the actual administered activity, A_0, were calculated as:

$$\varepsilon = 100 \cdot \frac{A_i - A_0}{A_0} \quad (3)$$

3. Results

3.1. Patient treatment and follow-up

The mean "net" volumes of the hot nodule(s) or the whole gland were 15.0 ± 7.6 (TA), 11.9 ± 7.4 (TMNG) and 23.6 ± 6.6 (GD) milliliters.

Mean administrated activity was 303 ± 135 MBq and mean adsorbed dose, as estimated from pre-therapeutic dosimetry, was

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