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Graves’ disease radioiodine-therapy: Choosing target absorbed doses for therapy planning

J. Willegaignon,a) M. T. Sapienza, and G. B. Coura-Filho
Cancer Institute of São Paulo State (ICESP), Clinical Hospital, School of Medicine, University of São Paulo, São Paulo 01246-000, Brazil and Nuclear Medicine Service, Department of Radiology, School of Medicine, University of São Paulo, São Paulo 01246-000, Brazil

T. Watanabe
Nuclear Medicine Service, Department of Radiology, School of Medicine, University of São Paulo, São Paulo 01246-000, Brazil

A. C. Traino
Unit of Medical Physics, Azienda Ospedaliero-Universitaria Pisana, Pisa 56126, Italy

C. A. Buchpiguel
Cancer Institute of São Paulo State (ICESP), Clinical Hospital, School of Medicine, University of São Paulo, São Paulo 01246-000, Brazil and Nuclear Medicine Service, Department of Radiology, School of Medicine, University of São Paulo, São Paulo 01246-000, Brazil

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Purpose: The precise determination of organ mass ($m_{th}$) and total number of disintegrations within the thyroid gland ($\tilde{A}$) are essential for thyroid absorbed-dose calculations for radioiodine therapy. Nevertheless, these parameters may vary according to the method employed for their estimation, thus introducing uncertainty in the estimated thyroid absorbed dose and in any dose–response relationship derived using such estimates. In consideration of these points, thyroid absorbed doses for Graves’ disease (GD) treatment planning were calculated using different approaches to estimating the $m_{th}$ and $\tilde{A}$.

Methods: Fifty patients were included in the study. Thyroid 131I uptake measurements were performed at 2, 6, 24, 48, 96, and 220 h postadministration of a tracer activity in order to estimate the effective half-time ($T_{eff}$) of 131I in the thyroid; the thyroid cumulated activity was then estimated using the $T_{eff}$ thus determined or, alternatively, calculated by numeric integration of the measured time-activity data. Thyroid mass was estimated by ultrasonography (USG) and scintigraphy (SCTG). Absorbed doses were calculated with the OLINDA/EXM software. The relationships between thyroid absorbed dose and therapy response were evaluated at 3 months and 1 year after therapy.

Results: The average ratio (±1 standard deviation) between $m_{th}$ estimated by SCTG and USG was 1.74 (±0.64) and that between $\tilde{A}$ obtained by $T_{eff}$ and the integration of measured activity in the gland was 1.71 (±0.14). These differences affect the calculated absorbed dose. Overall, therapeutic success, corresponding to induction of durable hypothyroidism or euthyroidism, was achieved in 72% of all patients at 3 months and in 90% at 1 year. A therapeutic success rate of at least 95% was found in the group of patients receiving doses of 200 Gy ($p = 0.0483$) and 330 Gy ($p = 0.0131$) when $m_{th}$ was measured by either USG or SCTG and $\tilde{A}$ was determined by the integration of measured 131I activity in the thyroid gland and based on $T_{eff}$, respectively. No statistically significant relationship was found between therapeutic response and patients’ age, administered 131I activity (MBq), 24-h thyroid 131I uptake (%) or $T_{eff}$ ($p \geq 0.064$); nonetheless, a good relationship was found between the therapeutic response and $m_{th}$ ($p \leq 0.035$).

Conclusions: According to the results of this study, the most effective thyroid absorbed dose to be targeted in GD therapy should not be based on a fixed dose but rather should be individualized based on the patient’s $m_{th}$ and $\tilde{A}$. To achieve a therapeutic success (i.e., durable euthyroidism or hypothyroidism) rate of at least 95%, a thyroid absorbed dose of 200 or 330 Gy is required depending on the methodology used for estimating $m_{th}$ and $\tilde{A}$. © 2014 American Association of Physicists in Medicine. [http://dx.doi.org/10.1118/1.4846056]

Key words: Graves’ disease, radioiodine therapy, dosimetry, target dose, therapy planning

1. INTRODUCTION

For more than six decades, radioactive iodine ($^{131}$I) has been successfully applied in the treatment of Graves’ disease (GD). However, controversy has persisted regarding the optimum $^{131}$I activity to be administered and the thyroid absorbed dose (Gy) to be delivered to thyroid, and the latter determined computationally based on the patients...
thyroid mass ($m_{th}$) and total cumulated activity within the gland ($\tilde{A}$).

Accuracy in thyroid absorbed-dose calculation depends on the $m_{th}$ and $\tilde{A}$; however, the values of these parameters vary according to the methods employed for their estimation. Whereas the thyroid mass can be measured by means of ultrasonography (USG) or scintigraphy (SCTG), $\tilde{A}$ can be obtained by either the integration of $^{131}$I activity measured in the thyroid gland over time or by considering the $^{131}$I effective half-time ($T_{eff}$) in the gland. Therefore, for the various method-dependent values of $m_{th}$ and $\tilde{A}$ thus determined, different thyroid absorbed doses (Gy/MBq $^{131}$I administered) and, consequently, dose–response relationships will result. To date, no optimum thyroidal absorbed dose for treatment of GD has been identified. Although a large range of doses, from 100 to over 400 Gy, has been indicated to treat thyroid disease,4–10 including the often-cited value of 300 Gy,11 this has not been “validated” for the dosimetry methodology used.

To address this point, the current prospective study of $^{131}$I therapy of GD correlates different methodology-dependent thyroid absorbed doses with the therapeutic response at 3 months and 1 year post-therapy and thereby derives a target dose for treatment planning.

2. METHODS

Fifty patients (44 women and 6 men), with ages ranging from 20 to 72 years (average 42 ± 12), were included in the study. Prior approval was obtained from the local institutional ethics committee (Protocol number: 0744/07). Each patient signed their informed consent, after receiving an explanation of study aims.

For each patient, GD was confirmed through evaluation of clinical symptoms as well as laboratory tests of serum thyroid receptor antibodies (TRAb), thyroid-stimulating hormone (TSH), thyroxine (free T4), and total tri-iodothyronine (T3) levels, and T4 concentration in the blood, together with elevated thyroidal $^{131}$I uptake.

Thyroid masses were estimated by USG and SCTG using the Philips iU22 system and a gamma-camera (Model ECAM Gantry Dual Head Extended, SN: 7086, Siemens Medical System, USA), respectively. The volume of each thyroid lobe from ultrasonography was estimated with an ellipsoid model and the formula: volume (ml) = $\pi / 6 \times$ height (cm) $\times$ depth (cm) $\times$ width (cm). The thyroid mass was calculated assuming a mass density of 1 g/ml. Following 0.37 MBq (10 $\mu$Ci) of $^{131}$I test activity administration, thyroid $^{131}$I uptake measurements were made at intervals of 2, 6, 24, 48, 96, and 220 h. Estimation of individual thyroid mass was performed by scanning with an activity of 370 MBq (10 mCi) of $^{99m}$Tc-pertechnetate and application of the Allen formula:12

Thyroid mass (g)

= area of the frontal contour of the gland (cm$^2$) $\times$ height of the gland (cm) $\times$ 0.323

Thyroid gland radiiodine uptake was assessed with a precalibrated Captus 600 Thyroid Uptake System (Capintec Inc.). $T_{eff}$ values were calculated for each patient, by fitting a monoexponential function to thyroid $^{131}$I uptake data as follows: thyroid $^{131}$I uptake ($%$) = $a e^{-\lambda_{eff} t}$, where $\lambda_{eff} = 0.693 / T_{eff}$, $a$ is the initial value for the thyroid $^{131}$I uptake, and $\lambda_{eff}$ is the effective clearance constant of the $^{131}$I in the gland.

This study was performed under dietary iodine restriction for at least 15 days for all the patients. Antithyroid drug medication, such as propylthiouracil and methimazole, was suspended for at least 7 days prior to initiation of therapy.

Total thyroid gland $^{131}$I cumulated activity of each patient was determined by three methods. The first is based on the integration of thyroidal $^{131}$I activity measured up to 220 h after activity administration ($A_1$). The second is based on the $T_{eff}$ in the gland, by determining cumulated $^{131}$I activity with the equation $\tilde{A} = 1.443 \times f \times A_0 \times T_{eff}$, where $f$ is the fraction of administered activity ($A_0$) resident in the thyroid gland at 24 h post-$^{131}$I administration ($A_2$). The third focused on the integration of resident $^{131}$I activity measured in the thyroid gland up to 24 h plus the equation $\tilde{A} = 1.443 \times f \times A_0 \times T_{eff} (A_3)$ beyond this period. The three methods mentioned above are illustrated in Fig. 1.

Using the thyroid $^{131}$I cumulated activity thus determined, the thyroid absorbed dose (in mGy) was determined using the OLINDA/EXM software,13 and taking into account the patient’s thyroid $m_{th}$. The absorbed dose (in mGy) was converted to absorbed dose (in Gy/MBq) by dividing by the administered activity (in MBq). It was assumed that the radiiodine biokinetics for the therapy administration were the same as those for the tracer administration. Due to uncertainty in $m_{th}$ measurement (USG technique) and thyroid $^{131}$I uptake estimated by a probe, uncertainties of at least ±10% to the calculated dose should be considered.14

The $^{131}$I activity administered to patients for therapy was based on a fixed amount, 35 patients receiving 555 MBq (15 mCi) and 15 receiving 1.11 GBq (30 mCi). $^{131}$I was administered orally on an outpatient basis.

The relationship between thyroid absorbed dose and therapy response was evaluated at 3 months and 1 year after therapy administration. Therapy–outcome evaluation was based on clinical parameters and laboratory testing, as follows: Euthyroidism (Eu)—normal clinical and laboratory parameters of euthyroidism, without antithyroid drug medication or thyroxine (T4); Hyperthyroidism (Hyper)—clinical criteria (e.g., fatigue, palpitations, insomnia, trembling hands, etc.), introduction of antithyroid drug medication after three months of therapy or TSH level less than 0.25 $\mu$IU/ml and high dosage of free T4; and Hypothyroidism (Hypo)—clinical parameters of hypothyroidism or replacement of thyroid hormone after three months of therapy or TSH level greater than 4.0 $\mu$IU/ml and low dosage of free T4. This form of classification was based on the criteria and cutoff values defined by the Central Clinical Laboratory of the Hospital. It was considered a successful outcome when patients reached the euthyroid or hypothyroid status at 1 year post-$^{131}$I therapy.

Where appropriate, data were expressed as average values ± 1 standard deviation (SD), and minimum and maximum
values, $p$ values of less than 0.05 were considered statistically significant.

3. RESULTS

The average ($\pm$SD) values of thyroid $^{131}$I uptake at 2, 6, 24, 48, 96, and 220 h were 41 ($\pm$21)%, 62 ($\pm$22)%, 65 ($\pm$15)%, 57 ($\pm$13)%, 46 ($\pm$10)%, and 28 ($\pm$6)% of administered $^{131}$I activity, respectively. The data set used for $T_{eff}$ calculation was that measured at 24, 48, 96, and 220 h post-$^{131}$I administration. The overall $T_{eff}$ was 6.95 ($\pm$0.81) days, ranging from 4.99 to 8.0 days. Our group has already reported the calculation method for a previous study.\textsuperscript{15}

Figure 1 presents the various methods employed for $\bar{A}$ calculation, and their mutual ratios in all 50 patients.

The thyroid mass measured by ultrasound, 30 ($\pm$19) g, was different from that measured scintigraphically, 47 ($\pm$25) g, with an average ultrasound-to-scintigraphy mass ratio of 1.74 ($\pm$0.64) (Fig. 2). This, of course, translates to a 70% higher thyroid absorbed dose on average based on the ultrasound-versus scintigraphy-derived thyroid mass. Table I presents the physical characteristics and radiometric data of all 50 patients studied. In this table all patients were divided into two groups, (Hyper) and (Eu + Hypo), according to therapeutic outcome evaluated at 3 months and 1 year post-treatment and several dosimetric parameters are presented for each group, such as

![Figure 1. Total cumulated thyroid gland $^{131}$I activity of each patient based on three methods: (a) integration of resident $^{131}$I activity measured up to 220 h after activity administration ($\bar{A}_1$); (b) determined with the equation $\bar{A} = 1.443 \times f \times A_0 \times T_{eff}$; and (c) focused on the integration of resident $^{131}$I activity measured in the gland up to 24 h plus the equation $\bar{A} = 1.443 \times f \times A_0 \times T_{eff}(\bar{A}_3)$ beyond this period. The ratios $\bar{A}_3/\bar{A}_1$ and $\bar{A}_3/\bar{A}_2$ for all the 50 studied patients are presented in the graph (d).](image-url)

![Figure 2. Bland–Altman graphic showing the relationship between thyroid mass determined when using the USG and SCTG techniques.](image-url)
Table I. Physical characteristics and radiometric data of all the 50 patients.

<table>
<thead>
<tr>
<th>Follow-up period</th>
<th>3 months</th>
<th>1 year</th>
<th>Statistical significance (t test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic response</td>
<td>Hyper (Eu + Hypo)</td>
<td>Hyper (Eu + Hypo)</td>
<td>Total</td>
</tr>
<tr>
<td>Patients (n)</td>
<td>14 (28%)</td>
<td>5 (10%)</td>
<td>50 (100%)</td>
</tr>
<tr>
<td>Gender (female/male)</td>
<td>12/2</td>
<td>4/1</td>
<td>44/6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>43 ± 12</td>
<td>49 ± 13</td>
<td>42 ± 12</td>
</tr>
<tr>
<td>Thyroid mass—USG (g)</td>
<td>40 ± 24</td>
<td>48 ± 30</td>
<td>28 ± 17</td>
</tr>
<tr>
<td>Thyroid mass—SCTG (g)</td>
<td>61 ± 32</td>
<td>69 ± 47</td>
<td>45 ± 20</td>
</tr>
<tr>
<td>Administered $^{131}$I activity (MBq)</td>
<td>674 ± 236</td>
<td>740 ± 265</td>
<td>555 ± 0</td>
</tr>
<tr>
<td>24-h thyroid $^{131}$I uptake (%)</td>
<td>69 ± 14</td>
<td>76 ± 9</td>
<td>65 ± 15</td>
</tr>
<tr>
<td>Administered $^{131}$I activity per thyroid mass—USG (MBq/g)</td>
<td>26 ± 25</td>
<td>16 ± 10</td>
<td>33 ± 22</td>
</tr>
<tr>
<td>Administered $^{131}$I activity per thyroid mass—SCTG (MBq/g)</td>
<td>15 ± 12</td>
<td>11 ± 6</td>
<td>20 ± 12</td>
</tr>
<tr>
<td>24-h $^{131}$I uptake per thyroid mass—USG (MBq/g)</td>
<td>16 ± 12</td>
<td>12 ± 6</td>
<td>21 ± 14</td>
</tr>
<tr>
<td>24-h $^{131}$I uptake per thyroid mass—SCTG (MBq/g)</td>
<td>9 ± 6</td>
<td>8 ± 4</td>
<td>13 ± 8</td>
</tr>
<tr>
<td>Thyroid $^{131}$I effective half-life—$T_{eff}$ (days)</td>
<td>7.14 ± 0.87</td>
<td>6.87 ± 0.78</td>
<td>6.88 ± 1.18</td>
</tr>
</tbody>
</table>

*Statistical significance of relationship between characteristic and therapeutic response evaluated at 1 year post-therapy.

Based on data from Table I, the therapeutic planning should be performed considering 200 Gy as the minimum dose to be targeted when the thyroid mass is estimated by USG and cumulated $^{131}$I activity by the $\tilde{A}_1$ method and 330 Gy when provided by either the $\tilde{A}_2$ or $\tilde{A}_3$ method. If the thyroid mass is determined by the SCTG technique, the target dose should be 200 Gy in association to the $\tilde{A}_1$ method and 300 Gy for either the $\tilde{A}_2$ or $\tilde{A}_3$ method. The positive agreement between absorbed doses to be targeted in therapy planning, when thyroid masses are estimated with either USG or SCTG, is noteworthy. Nonetheless, when using SCTG, it has been shown through statistical analysis that this technique is potentially less reliable in predicting therapeutic response in relation to thyroid absorbed dose (Table II).

### 4. DISCUSSION

The minimum $^{131}$I thyroid absorbed dose for effectively treating GD and the optimum approach to deriving the thyroid absorbed dose, including estimation of gland mass and cumulated activity, remain controversial. It is important, therefore, that any study of dose–response relationship for $^{131}$I therapy of GD explicitly describe the dosimetry employed, as different methodological approaches will yield numerically different estimates of the absorbed dose.

Otherwise, reaching a consensus on the optimum dose will remain problematic. For example, according to the widely cited study by Willemsen et al., a fixed dose of 300 Gy is required to effectively treat all GD patients. However, the methodology for deriving this dose value was not described. Likewise, although, according to the EANM guideline, an absorbed dose of 150 Gy is indicated for restoring the euthyroid status and a dose range of 200–300 Gy for ablating the thyroid gland, this guideline does not describe the methodology to be used for deriving the thyroid absorbed dose.
Furthermore, and contrary to the results presented in this work, EANM guidelines indicate an identical dose for GD therapy targeting regardless of the methods used either for estimating gland size (palpation, ultrasonography, or scintigraphy) or $^{131}$I thyroid cumulated activity.

According to Kobe et al., when using a similar method for dose calculation, overall therapeutic success is greater than 95% when doses of 200 Gy are delivered to the thyroid. Moreover, Reinhardt et al. and Willensen et al. when using $T_{eff}$, a fixed dose of 300 Gy and Marinelli’s formula, also encountered a similar therapeutic response (92% and 95%, respectively) and (100% and 95%, respectively), although 21% of the patients included in the Willemsen study had already undergone previous radioiodine therapy with 150 Gy. However, as stressed by Sisson, a possible failure rate of 5%–10% at 1-year post-radioiodine therapy should not be neglected. Furthermore, $T_{eff}$ determined with thyroid $^{131}$I uptake measured at 24, 48, and 72 h postactivity administration, as indicated in Willemsen’s study, may differ by as much as 50% from those determined with late activity measurements.

![Figure 3: Dose–response relationship presented by patients at 1 year after $^{131}$I therapy, according to the method used for estimating $m_{th}$ and $\tilde{A}$.](image)
The optimum absorbed dose for GD therapy depends on the methodology employed for \( m_{th} \) and \( \bar{A} \) estimation. However, a minimum dose of 200 or 330 Gy is recommended for GD therapy planning when \( m_{th} \) is estimated by USG or SCTG technique, and \( \bar{A} \) is based on the integration of resident \( 131I \) activity in the gland and on considering the \( 131I \) \( T_{eff} \) in this organ, respectively.

Table II. The best relationships between thyroid absorbed dose, calculated according to the radiometric data used for dose calculation, and to the therapeutic response evaluated at 1 year after \( 131I \) therapy.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of patients</th>
<th>Success</th>
<th>Failure</th>
<th>( p ) value (Fisher test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USG</td>
<td>( \bar{A}_1 ) ≤203 Gy</td>
<td>10</td>
<td>7 (70%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td></td>
<td>&gt;203 Gy</td>
<td>40</td>
<td>38 (95%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td></td>
<td>( \bar{A}_2 ) ≤331 Gy</td>
<td>13</td>
<td>9 (69%)</td>
<td>4 (31%)</td>
</tr>
<tr>
<td></td>
<td>&gt;331 Gy</td>
<td>37</td>
<td>36 (97%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td></td>
<td>( \bar{A}_3 ) ≤366 Gy</td>
<td>13</td>
<td>9 (69%)</td>
<td>4 (31%)</td>
</tr>
<tr>
<td>SCTG</td>
<td>( \bar{A}_1 ) ≤202 Gy</td>
<td>29</td>
<td>24 (83%)</td>
<td>5 (17%)</td>
</tr>
<tr>
<td></td>
<td>&gt;202 Gy</td>
<td>21</td>
<td>21 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>( \bar{A}_2 ) ≤301 Gy</td>
<td>29</td>
<td>24 (83%)</td>
<td>5 (17%)</td>
</tr>
<tr>
<td></td>
<td>&gt;301 Gy</td>
<td>21</td>
<td>21 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>( \bar{A}_3 ) ≤327 Gy</td>
<td>29</td>
<td>24 (83%)</td>
<td>5 (17%)</td>
</tr>
<tr>
<td></td>
<td>&gt;327 Gy</td>
<td>21</td>
<td>21 (100%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

(e.g., up to 220 h), with a probable impact on dose/activity calculation.\(^{15}\)

As illustrated by the results presented, lack of consensus on the optimum \( 131I \) thyroid absorbed dose for treatment of GD is no doubt related, at least in part, to the different dosimetry methodologies employed.

### 5. CONCLUSIONS

The optimum absorbed dose for GD therapy depends on the methodology employed for \( m_{th} \) and \( \bar{A} \) estimation. However, a minimum dose of 200 or 330 Gy is recommended for GD therapy planning when \( m_{th} \) is estimated by USG or SCTG technique, and \( \bar{A} \) is based on the integration of resident \( 131I \) activity in the gland and on considering the \( 131I \) \( T_{eff} \) in this organ, respectively.

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