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Effectiveness of the selection of administered ^{131}I-iodide activity based on the thyroid "volume algorithm" approach for the therapy of Graves' disease

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ABSTRACT

Background: In the current clinical practice, radiometabolic therapy of Graves' disease is based on the administration of an amount of ^{131}I-iodide defined according to two different modalities: administration of a fixed activity (up to a maximum of 555 MBq allowed by many national legislations on an outpatient basis) or an ^{131}I-iodide activity individually defined so as to reach the certain fixed values of target thyroid-absorbed dose.

The aim of this study was to prove the effectiveness of a personalized approach to cure Graves' disease based on the administration of a ^{131}I activity defined according to the desired "optimal final thyroid mass." According to this model, one can predict the thyroid-absorbed dose following the administration of an activity as a function of the desired reduction of the baseline, pre-treatment mass of the gland.

Methods: A total of 217 patients with Graves' disease were included in this study. They were randomly divided into five groups, of which four groups were divided based on fixed thyroid-absorbed dose value of 100 (Group A, n = 29), 200 (Group B, n = 25), 300 (Group C, n = 51), and 400 (Group D, n = 25), respectively, whereas patients of the final thyroid mass (m_f) (Group V, n = 87) received a ^{131}I activity calculated based on the desired "optimal" final thyroid mass according to the so-called "volume algorithm" approach.

Results: At the 1-year follow-up, therapeutic success (i.e., a state of either hypothyroidism or euthyroidism) was achieved in 48% of patients in Group A (100 Gy), 64% in Group B (200 Gy), 78% in Group C (300 Gy), 96% in Group D (400 Gy), and 92% in Group V (m_f). A significantly higher proportion of patients were was cured in Groups D and V (m_f) than in Groups A, B, and C ($P < 0.01$). There was no statistical difference in cure rates between Groups D and V (m_f). The median thyroid-absorbed dose was 407 Gy for Group D (400 Gy), significantly higher than 296 Gy for Group V (m_f) ($P < 0.001$) and also significantly greater than the administered ^{131}I activity (494 *vs.* 345 MBq, $P < 0.001$).

Conclusions: This study indicates that the most effective thyroid-absorbed dose to be delivered for the radiometabolic therapy of patients with Graves' disease should not be based on a fixed dose but rather should be personalized. The new method based on thyroid mass reduction allows the optimization of ^{131}I-iodide therapy for Graves' disease on an individual basis, achieving a high therapeutic efficacy while at the same time avoiding the administration of unjustified greater activities of ^{131}I.

Keywords: Graves' disease, hyperthyroidism, radioiodine; ^{131}I-iodide, dosimetry in Graves' disease, "Volume algorithm" approach.

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Introduction

The hyperthyroidism of Graves' disease is treated by using antithyroid drugs (thionamides, such as propylthiouracil and methimazole) or by reducing the amount of functioning thyroid tissue either by surgery or radiometabolic therapy with ^{131}I-iodide. All such treatments are effective, but opinions vary regarding indications for the first-choice treatment. Antithyroid drugs are the predominant first-line therapy throughout Europe and Japan, whereas radioiodine is more often the first-line treatment in North America [1].

Therapy with ^{131}I-iodide, which is used for over 70 years, has largely replaced surgery for the treatment of Graves' disease because it is easy to perform and has proved to be effective. It causes a progressive destruction of thyroid cells due to the beta radiations emitted by ^{131}I; it can be employed either as an initial treatment or disease recurrence after antithyroid drugs. Its cure rate is close to 100% after one or more cycles. Some radiation safety precautions are recommended during the first 1–20 days after treatment although guidelines vary depending on local

protocols [2]. In general, the patients need to avoid close, prolonged contact with children and pregnant women for at least 20 days [2]. Rarely, there may be mild pain due to radiation thyroiditis in the anterior cervical region, about 1–2 weeks after treatment [3]. Furthermore, there is a small risk of a thyrotoxic crisis due to cytolysis of thyroid cells, which can be minimized by properly timed treatment with antithyroid drugs. Hyperthyroidism can persist for several months before radioiodine takes full effect (up to 6–8 months). In case of persistent hyperthyroidism, the patient can be treated with a second dose of radioiodine, usually not earlier than 8–12 months after the first dose [3].

The optimal activity of radioiodine to be administered to achieve euthyroidism, without a high incidence of relapse or progression to hypothyroidism, is still a matter of debate. Some patients inevitably relapse after a single treatment because the biologic effects of radiation vary among different individuals. However, the development of hypothyroidism is progressive, with an annual incidence of 2%–3% even many years after the therapy [4]. On the other hand, low-dose radioiodine treatment has a higher rate of failure; in these cases, further antithyroid drug therapy and additional ^{131}I therapies are needed [5].

According to the current guidelines, the goal of radioiodine therapy is to control hyperthyroidism by rendering the patient hypothyroid; this goal requires higher doses to achieve higher cure rates [6]. Nevertheless, there is still no consensus regarding the most appropriate dosing regimen. Although it is reasonable to assume that the effectiveness of such therapy depends on the administration of an appropriate radiation dose to the thyroid, there is no agreement on the optimal radiation dose to be delivered to the thyroid gland. A practical strategy followed in many centers is to administer a fixed activity of ^{131}I-iodide generally 5, 10, or 15 mCi (185, 370, or 555 MBq, respectively) based on clinical features, such as the severity of thyrotoxicosis, size of the goiter, and value of radioiodine uptake.

An additional approach employed in clinical practice is not based on dosimetric estimates (however, they might be derived) but rather on the target amount of radioactivity to be concentrated per mass of thyroid tissue. This method uses the thyroid gland size and the 24-hour radioiodine uptake value measurement to calculate the therapeutic activity of ^{131}I to be administered to achieve a certain concentration of ^{131}I in the thyroid gland. In particular, the suggested target is 3–8 MBq/g of thyroid tissue (or 80–220 μCi/g) [7], and 3 MBq/g is generally insufficient to achieve an acceptable cure rate if hypothyroidism is the ultimate goal of radiometabolic therapy. Some physicians choose to aim for a euthyroid state using a lower activity. Decreasing the administered therapeutic activity can lead to prolongation of hyperthyroidism, with the associated possible adverse clinical sequelae. On the other hand, an administered ^{131}I activity toward the upper end of this range, or even higher, is, especially, suitable for patients with rapid iodine turnover when 4-hour iodine uptake exceeds the 24-hour uptake.

Another strategy is to administer an activity individually calculated based on a fixed value of target absorbed dose (ranging 100–400 Gy in different guidelines) according to the Medical Internal Radiation Dose (MIRD) formula based on the size of the thyroid gland, 24-hour radioiodine uptake value [8], and measurement of effective radioiodine half-life in the thyroid gland [9].

In a previously published retrospective study, the effectiveness of different tissue absorbed doses to induce euthyroidism or hypothyroidism after radioiodine therapy in patients with Graves' disease was evaluated. No correlation was found between radiation dose and outcome of radioiodine therapy for thyroid absorbed doses of 150, 300, and >300 Gy, with a recurrence rate of hyperthyroidism of about 15% across all groups after the first radioiodine therapy [10]. These results raise a number of issues: why do some patients of the 15% failure group need a second therapy to be cured even if they have been treated with more than 300 Gy? Why for other patients only 100 Gy is sufficient to induce hypothyroidism? Perhaps, a general value of thyroid-absorbed dose does not fit for all patients? And, which features of this heterogeneous disease could impact on outcomes after radioiodine therapy?

It is now known that some factors influence the success of radioiodine therapy such as age, severity of hyperthyroidism, thyroid volume at presentation, and radioiodine uptake [11,12]. It is a common observation that the optimal thyroid dose varies from patient to patient according to some yet unknown features specific for the individual patient and that the efficacy of radioiodine therapy translates into a certain reduction in the final thyroid volume after therapy. In this regard, a relationship has been demonstrated between outcomes and final thyroid volume after radioiodine therapy. Chiovato et al. [13] showed that the early outcome of thyroid function after ^{131}I therapy was mainly related to the pre-treatment thyroid volume and degree of its reduction after therapy. According to Haase et al. [14], post-therapeutic thyroid volumes correlated significantly with clinical outcome 6 months after therapy, thus providing a rationale for adjusting the target doses based on thyroid volumes before therapy to induce an appropriate reduction of thyroid volumes. Gómez-Arnaiz et al. [15] showed that the ultrasonographic thyroid volume at 3 and 6 months after low-dose ^{131}I treatment could be a reliable prognostic factor of thyroid function outcome in the 1st year after treatment.

Over several years of clinical experience with patients undergoing radiometabolic therapy for the treatment of Graves' disease, we have observed that there is a threshold value of thyroid gland volume after treatment that guarantees success of therapy (i.e., achievement of euthyroidism or hypothyroidism). This final post-therapy thyroid

volume is not only a fixed value across patients but also instead related in each patient to baseline thyroid mass and the value of radioiodine maximum uptake (usually 24 hours after therapy administration). Based on this observation, we have developed a new algorithm (the so-called "volume algorithm") aimed at personalizing the amount of ^{131}I activity to be administered to cure patients from hyperthyroidism: According to this approach, the activity of ^{131}I to be administered is calculated using a relatively simple equation, in which the only unknown variable is "activity" as a function of the desirable (optimal) target post-therapy thyroid volume that guarantees success of treatment, whereas the baseline thyroid mass and radioiodine uptake are experimentally measured [16–20].

We present, here, the results of a prospective study, in which we compared the cure rates of Graves' disease patients treated with the "volume algorithm" with the cure rates of patients receiving therapy according to different fixed thyroid-absorbed doses (100, 200, 300, and 400 Gy).

Materials and Methods

A total of 217 Graves' disease patients, with ages ranging from 19 to 82 years (mean 53 ± 18 years), who were referred to the department for first radioiodine therapy from 2004 to 2014, were enrolled in the study. According to the approved protocol, all the patients signed an informed consent form, before enrollment in the study.

Grave's disease had been diagnosed in all cases by typical clinical symptoms and laboratory tests (suppressed TSH levels associated with increased fT3 and fT4 levels) and typical ultrasound finding (diffusely hypoechoic and hypervascularized thyroid). The presence of anti-TSH receptor autoantibodies (DASIT-Brahms, Italy, sensitivity 0.3 IU/mL) confirmed the diagnosis.

The exclusion criteria included patients with ophthalmopathy, concomitant steroid treatment when administering therapeutic ^{131}I, age younger than 18 years, suspicion of pregnancy, presence of any suspicions thyroid nodule on ultrasound, and thyroid volume greater than 80 mL.

Before ^{131}I therapy, patients were recommended to stay on a generic low-iodine diet for at least 2 weeks [21]. Furthermore, antithyroid drugs were discontinued before radioiodine therapy, at least 6 days for methimazole and at least 21 days for propylthiouracil. Antithyroid drug treatment was restarted after a minimum of 7 days following ^{131}I therapy and progressively suspended when a state of ipo- or euthyroidism is reached.

All patients underwent full clinical evaluation, thyroid scintigraphy, measurement of thyroid volume by high-resolution ultrasound, and measurement of radioiodine uptake to evaluate the retention kinetics of iodine in the thyroid gland (effective half-life and time to maximum uptake).

Ultrasound was performed using a Logiq7 echograph (GE Healthcare, Milwaukee, WI, USA) equipped with a 5–13 MHz array transducer. Thyroid volume was calculated using the ellipsoid model for each lobe and isthmus; thyroid mass was estimated assuming a thyroid density of 1 g/mL (similarly as water).

^{131}I-iodide uptake and kinetics were evaluated based on a set of measurements performed at 4, 24, 48, and 96 hours after the administration of a diagnostic activity (1.85 MBq) of ^{131}I-iodide, compared to reference measurements of the administered activity placed in a thyroid phantom. All measurements were performed using a shielded 2-inch NaI(Tl) probe (Biodex Medical Systems, New York, NY) properly collimated and calibrated (distance from the patient's thyroid to the probe: 27 cm). Twenty-four hours after administration of the ^{131}I tracer activity, all patients underwent scintigraphy.

The patients were randomly divided into five groups:

- Group A (29 patients): the administered ^{131}I activity was determined so as to deliver a thyroid-absorbed dose of 100 Gy.
- Group B (25 patients): the administered ^{131}I activity was determined so as to deliver a thyroid-absorbed dose of 200 Gy.
- Group C (51 patients): the administered ^{131}I activity was determined so as to deliver a thyroid-absorbed dose of 300 Gy.
- Group D (25 patients): the administered ^{131}I activity was determined so as to deliver a thyroid-absorbed dose of 400 Gy.
- Group V (m_f) (87 patients): the administered ^{131}I activity was determined so as to achieve an "optimal" desired final thyroid mass according to the "volume algorithm."

As previously described, the optimal thyroid final mass (m_f), i.e., the desirable target of radiometabolic therapy, was estimated in the individual patients using the following equation:

$$m_f = 0.24 \times m_0/U_0 \quad (1)$$

where m_0 is the basal mass of the thyroid and U_0 is the maximum ^{131}I uptake in the gland [14,15].

The corrected-MIRD formalism was used to calculate the ^{131}I activity to be administered (A_0) in Groups A, B, C, and D. The activity to achieve the optimal thyroid final mass (m_f) [Eq (1)] was calculated by using the same corrected-MIRD formalism for patients in Group V (m_f) [13].

After ^{131}I treatment, all the patients were reassessed every 3 months with clinical examination and fT4, fT3, and TSH assays. Therapeutic success was classified as euthyroidism or hypothyroidism (i.e., serum TSH > 0.3 μIU/mL) at the 1-year follow-up.

The Mann–Whitney statistical test was performed to evaluate the differences in baseline mass between Group A (100 Gy), Group B (200 Gy), Group C (300 Gy), and Group D (400 Gy) versus Group V (m_f). The same test was performed to evaluate the differences in the maximum thyroid uptake among all different groups.

The *z*-test was employed to compare the cure rates in Group A (100 Gy), Group B (200 Gy), Group C (300 Gy), and Group D (400 Gy) versus Group V (m_f).

The two-tailed unpaired *t*-test was employed to evaluate the statistical significance of differences in the administered activities and thyroid-absorbed doses between Groups D (400 Gy) and V (m_f).

Results

Baseline characteristics are shown in Table 1. There were no differences in age and uptake values among the groups, and similarly, there were no statistically significant differences regarding main clinical features, anti-TSH receptor autoantibodies, gender distribution, and type/duration of treatment with antithyroid drugs before radioiodine administration. The only statistical difference in baseline thyroid mass was found between Groups A (100 Gy) and V (m_f) (median value of m_0 29 g versus 20 g, respectively, $P = 0.03$).

The cure rates among the five different groups using different levels/types of therapeutic approach are shown in Table 2. None of the patients developed ophthalmopathy after treatment with ^{131}I-iodide.

A significantly higher cure rate was achieved in Groups D and V (m_f) than in Groups A, B, and C ($P < 0.001$, statistical *z*-test), whereas there was no significant difference in cure rate between Groups D and V (m_f) (Figure 1).

The median thyroid-absorbed dose was 407 Gy for Group D (400 Gy), significantly higher than 296 Gy for Group V (m_f) ($P < 0.001$) (Table 2 and Figure 2B) and also significantly greater than the administered ^{131}I activity (494 *vs.* 345 MBq, $P < 0.001$) (Table 2 and Figure 2A).

Among the cured patients at the 1-year follow-up, 17/80 (21%) patients of Group V (m_f) were euthyroid

Table 1. Main baseline features in the five groups of patients treated.

	N	GENDER MEN/WOMEN	THYROID BASAL MASS (M_0) MEDIAN (5^{TH}–95^{TH})	MAX. UPTAKE (U_0) MEDIAN (5^{TH}–95^{TH})
Group A (100 Gy)	29	12/17	29 g (13-63)	0.68 (0.46-0.92)
Group B (200 Gy)	25	9/16	22 g (12-35)	0.72 (0.49-0.92)
Group C (300 Gy)	51	9/42	24 g (10-64)	0.76 (0.50-0.87)
Group D (400 Gy)	25	8/17	16 g 9-40)	0.62 (0.44-0.67)
Group V (m_f)	87	17/70	20 g (10-53)	0.70 (0.41-0.56)

The data report the median value and the 5th and 95th percentiles for thyroid basal mass (m_0) and maximum uptake (U_0).

Table 2. Results of treatment in the five groups of patients.

GROUPS	THYROID ABSORBED DOSE (Gy) MEDIAN 5^{TH} –95^{TH}	ADMINISTERED ^{131}I ACTIVITY (MBq) MEDIAN 5^{TH} –95^{TH}	CURE RATE
Group A (100 Gy)	100 (96–133)	185 (100–376)	48% (14/29)
Group B (200 Gy)	204 (189–224)	257 (133–386)	64% (16/25)
Group C (300 Gy)	300 (279–320)	370 (185–824)	78% (40/51)
Group D (400 Gy)	407 (387–430)	494 (288–863)	96% (24/25)
Group V (m_f)	296 (148–368)	345 (185–733)	92% (80/87)

The data report the median value and the 5th and 95th percentiles for the thyroid absorbed Dose (Gy) and administered ^{131}I activity (MBq).

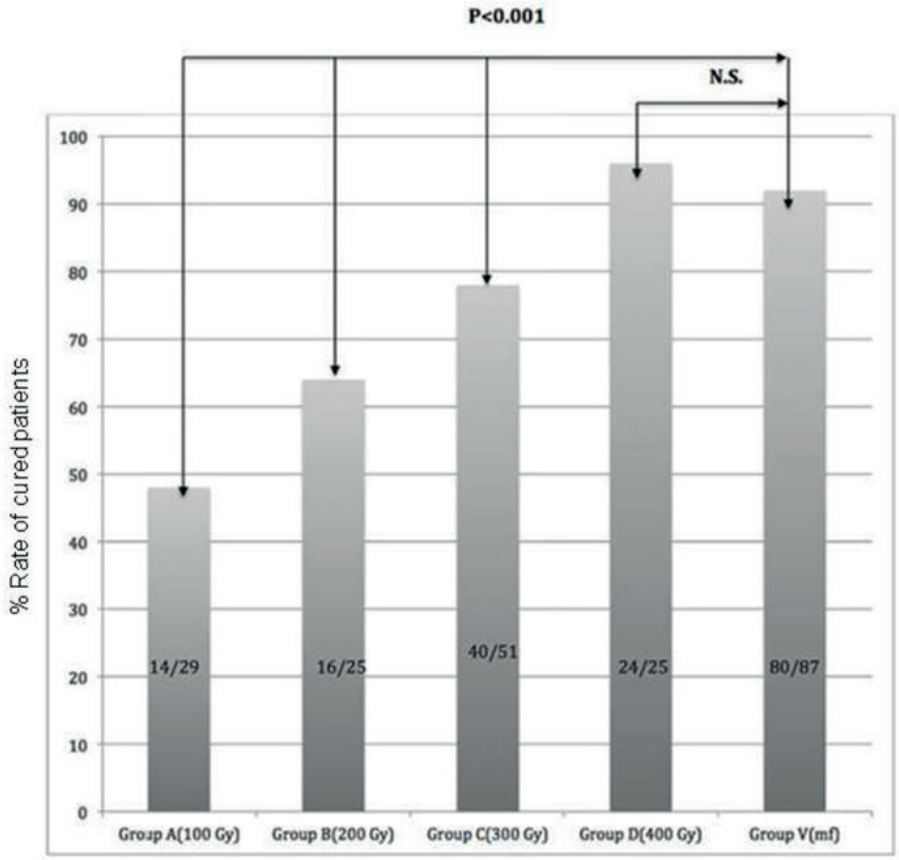

Figure 1. *Comparison among cure rates in the five groups. The effectives cure rate for Groups A, B, C is much lower than groups D and V. In base of percentage of cure rate the effectiveness treatment of the Group D is comparable to the Group V (m_f).*

compared to 1/24 (4%) of Group D, whereas the remaining patients in each group were hypothyroid.

Dicussion

The ^{131}I activity to be administered to patients with Graves' disease is currently based either on the empirical fixed-activity approach or the fixed-thyroid-absorbed dose approach.

The fixed-activity approach does not take into account the individual patient-related parameters (such as thyroid volume/mass, maximum radioiodine uptake, and kinetics). Therefore, the amount of ^{131}I administered is often unnecessarily high, thus conveying an unjustified radiation dose to the patient and environment (immediate family and caretakers). On the other hand, the activity administered might be too low, thus missing the therapeutic target of either euthyroidism or hypothyroidism. For practical reasons, in many centers, patients receive the maximum activity that can be administered on an outpatient basis (600 MBq in Europe).

The approach based on a fixed-thyroid-absorbed dose is more tailored, and the administered ^{131}I activity depends on patient-specific parameters (m_0, U_0, or iodine kinetics), which can be evaluated before therapy. However, the definition of the optimum thyroid-absorbed dose value is still an open issue, and there is no general consensus on the best method to be employed in the clinical routine [22–24].

According to the European Association Nuclear Medicine (EANM) guidelines, a thyroid-absorbed dose of 150 Gy is sufficient to cure hyperthyroidism, whereas 200–300 Gy is required for the complete ablation of thyroid tissue in patients with ophthalmopathy [25]. On the other hand, according to the Society of Nuclear Medicine and Molecular Imaging (SNMMI) guidelines, it is reasonable to base ^{131}I therapy on the radiation dose delivered to the thyroid gland rather than on administered activity. Nevertheless, the SNMMI panel concluded that there are only few publications validating this assumption unequivocally and that dosimetry for the treatment of thyrotoxicosis with ^{131}I has still not been sufficiently standardized [5].

A correlation between the absorbed-thyroid dose value and the cure rate of hyperthyroidism has already been reported [26,27]. In these reports, the cure rate for patients whose thyroid absorbed dose is 100 and 400 Gy is consistent with the data obtained in this study for the patients of Groups A and D, respectively [24].

On the other hand, Bajnok et al. [28] reported a higher success rate 6 months after therapy for thyroid-absorbed doses ranging 70–100 Gy. Nevertheless, the success of therapy was inversely related to the pre-treatment thyroid

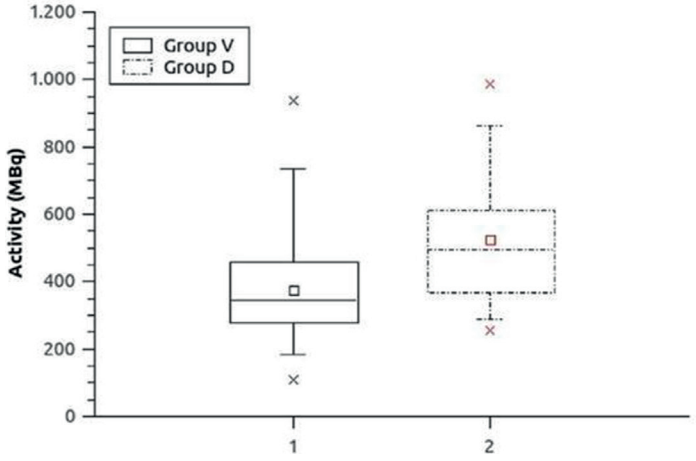

Figure 2A. *Whisker box-plot diagrams representing comparison between administered ^{131}I-iodide activity (MBq) in Group D (400 Gy) and Group V(m_f).*

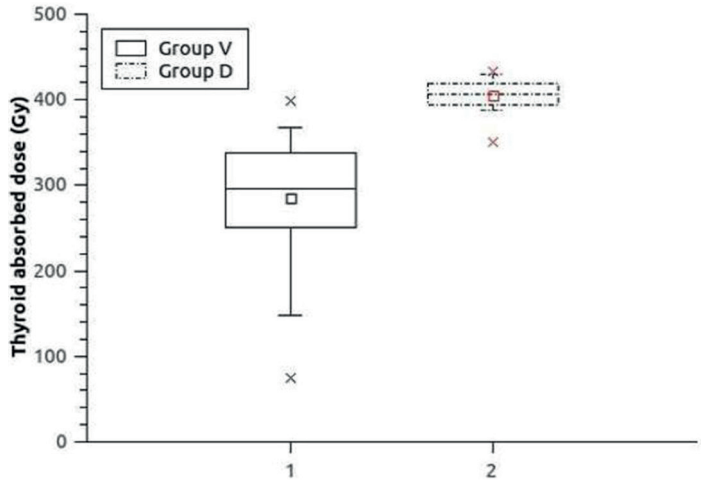

Figure 2B. *Whisker box-plot diagrams representing comparison between thyroid abdsorbed dose in Group D (400 Gy) and Group V (m_f).*

volume; in fact, the cure rate for the subgroups with small and medium thyroid mass was around 81%, whereas it was around 53% in the patients with a large thyroid mass larger than 50 g.

Haase et al. [14] recently showed how therapeutic success is associated with different target doses depending on the baseline thyroid volume (mass) [14]. In particular, they observed that different thyroid-absorbed doses were required to achieve the same cure rate, i.e., 150 Gy for thyroid volumes < 15 mL, 220 Gy for thyroid volumes in the 15–25 mL range, and 260 Gy for thyroid volumes > 25 mL. Furthermore, these authors observed a significant correlation between post-therapeutic thyroid volume (mass) and clinical outcome, i.e., smaller thyroid glands after therapy were observed in patients who achieved euthyroidism or hypothyroidism following radiometabolic therapy.

The results obtained in this study show that the effectiveness of the method based on the "volume algorithm" is comparable to that of the fixed 400-Gy thyroid-absorbed method. However, the cure of Graves' disease in the fixed 400-Gy group was achieved at the expense of a significantly greater administered activity than in the thyroid mass reduction method (494 *vs.* 345 MBq, $P < 0.001$). Therefore, the "volume algorithm" approach allows the administration of a lower ^{131}I activity, thus implying a lower radiation burden to the thyroid itself (296 *vs.* 407 Gy, $P < 0.001$) and, more notably, to the remainder of the body.

Figure 3 shows the individually administered ^{131}I activity in the patients of Group V (m_f) who were cured, clearly showing that several patients were cured with a much lower activity (118 MBq) than the mean value (376 MBq), whereas other patients needed much greater activities (892 MBq). The two extremes correspond to two different pathophysiologic conditions, i.e., small initial thyroid volume combined with high radioiodine uptake for the patient treated with 118 MBq of ^{131}I versus large initial

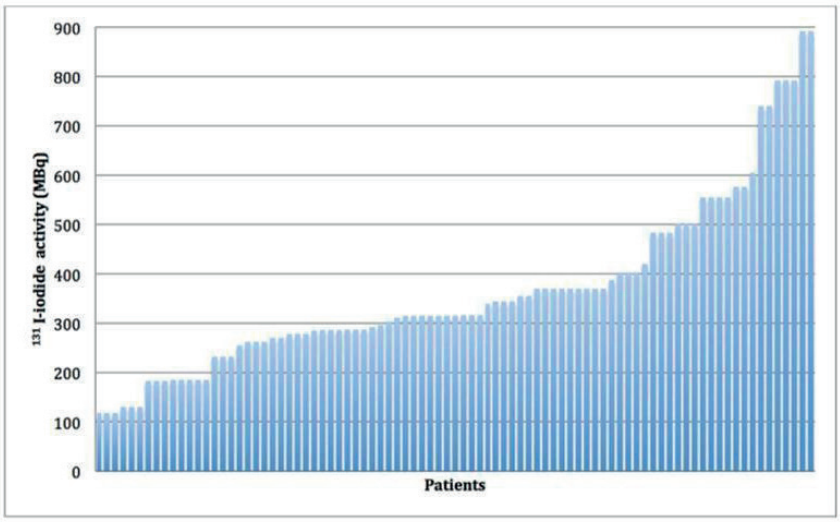

Figure 3. *Individually administered ^{131}I-iodide activity (MBq) in the 87 patients of Group V(m_f).*

thyroid volume combined with relatively low uptake in the patient treated with 892 MBq. This observation confirms that the patient-specific activity of ^{131}I is necessary to cure Graves' disease. The present study shows that the "volume algorithm" best guarantees tailoring of therapy adjusted to the individual patient's pathophysiologic features while at the same time permitting to administer a lower amount of activity versus the thyroid-absorbed dose method to achieve the same cure rate.

This feature of the "volume algorithm" approach (which does not imply any relevant additional burden to the healthcare staff in terms of time dedicated to each patient) results in associated advantages to the patient (e.g., by reducing the radiation burden to the whole body, as well as the prescription of time off work of following treatment with radioiodine), to the environment (by reducing the risk of contamination for family members and/or caretakers in general), and to the hospital staff (by reducing professional exposure linked to daily handling of radioactive materials).

Finally, the "volume algorithm" approach achieves the same cure rates obtained with the fixed-activity method (555 MBq of ^{131}I-iodide) or the thyroid-absorbed dose method guaranteeing maximum effectiveness (400-Gy group). The average net cost of purchasing ^{131}I-iodide for therapy was EUR 110/patient for the group treated with the "volume algorithm," whereas it was much higher for the 400-Gy group (EUR 158, or 44% higher); the corresponding cost would be EUR 178/patient for treatment with a fixed activity of 555 MBq (62% higher than for the "volume algorithm" group).

List of Abbreviations

A_0	activity to be administered
EANM	European Association of Nuclare Medicine
EUR	euro
fT3	free Triiodothyonine
fT4	free Thyroxine
g	grams
Gy	Gray
I	Iodine
MBq	Megabequerel
m_f	final mass
mL	millilitre
m_0	initial mass
MHz	Megahertz
MIRD	Medical Internal Radiation Dose
mCi	milliCurie
Na	Sodium
SNMMI	Society of Nuclear Medicine and Molecular Imaging
Tl	Tallium
TSH	Thyroid-stimulating hormone
U_0	initial uptake
µlU	micro Internation Unit

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Consent for publication

Informed consent was obtained from all individual participants included in the study.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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