Comparison of Different Thyroid Committed Doses in Radioiodine Therapy for Graves' Hyperthyroidism

Mariano Grosso,¹ Antonio Traino,² Giuseppe Boni,¹ Elena Banti,¹ Mauro Della Porta,¹ Gianpiero Manca,¹ Duccio Volterrani,¹ Serena Chiacchio,¹ Abedallatif AlSharif,¹ Elisa Borsò,¹ Rosanna Raschillà,¹ Fabio Di Martino,² and Giuliano Mariani¹

¹Regional Center of Nuclear Medicine, University of Pisa Medical School, Pisa, Italy

²Health Physics Unit, Section of Medical Physics, University Hospital, Pisa, Italy

ABSTRACT

Despite vast worldwide experience in the use of ¹³¹I for treating Graves' disease (GD), no consensus of opinion exists concerning the optimal method of dose calculation. In one of the most popular equations, the administered ¹³¹I dose is directly proportional to the estimated thyroid gland volume and inversely proportional to the measured 24-hour radioiodine uptake. In this study, we compared the efficiency of different tissue-absorbed doses to induce euthyroidism or hypothyroidism within 1 year after radioiodine therapy in GD patients. The study was carried out in 134 GD patients (age, 53 ± 14 year; range, 16–82 year; thyroid volume, 28 ± 18 mL; range, 6–95 mL; average 24-hour thyroid uptake, 72%) treated with ¹³¹I therapy. The average radioiodine activity administered to patients was 518 ± 226 MBq (range, 111–1110). The corresponding average thyroid absorbed dose, calculated by a modified Medical Internal Radiation Dose (MIRD) equation was 376 ± 258 Gy (range, 99–1683). One year after treatment, 58 patients (43%) were hypothyroid, 57 patients (43%) were euthyroid, and 19 patients (14%) remained hyperthyroid. The patients were divided into 3 groups: 150 Gy (n = 32), 300 Gy (n = 58) and >300 Gy (n = 44). No significant difference in the rate of recurrent hyperthyroidism was found among the 3 groups (150 Gy: 15%; 300 Gy: 14%; and >300 Gy: 14%; chi-square test, p = 0.72). Whereas, the rate of hypothyroidism in the 3 groups was significantly correlated with the dose (150 Gy: 30%; 300 Gy: 46%; >300 Gy: 71%; chi-square test, p = 0.0003). The results obtained in this study show no correlation between dose and outcome of radioiodine therapy (in terms of persistent hyperthyroidism) for thyroid absorbed doses ≥150 Gy, while confirming the relation between the thyroid absorbed dose and the incidence of hypothyroidism in GD patients.

Key words: Graves' disease, radioiodine therapy, clinical outcome, dosimetry

INTRODUCTION

Graves' disease (GD) is the most common cause of hyperthyroidism. Over the past 30 years, treat-

ment of GD has most commonly been performed using 1 or more of 3 modalities: medical therapy, total thyroidectomy, and radioiodine therapy.¹ All such treatments are effective, but opinions vary regarding their relative indications, as no single treatment guarantees permanent euthyroidism.^{2,3} Considerable disparity of opinion also exists among thyroid specialists around the world regarding the first-choice treatment for a "typical" GD patient.^{4–6} Radioiodine is being in-

Address reprint requests to: Mariano Grosso; Regional Center of Nuclear Medicine, University of Pisa Medical School; Via Roma 67, I-56126 Pisa, Italy; Tel.: +39-050-992115; Fax: +39-050-552100
E-mail: m.grosso@med.unipi.it

creasingly used as first-line therapy for GD patients. It is the treatment of choice for relapsed GD in the United States, while in Europe and Japan it usually represents the second-line therapy.

The goal of treatment with radioiodine is to destroy sufficient thyroid tissue to cure hyperthyroidism by rendering the patient either euthyroid or hypothyroid. Although this treatment is highly effective, with a cure rate approaching 100% after 1 or more cycles,⁷ no consensus of opinion exists concerning the optimal method of calculating the thyroid absorbed dose (Gy) or of establishing the ¹³¹I activity (MBq) to be administered.⁸

Therefore, debate is continuing in the scientific community as to the best way of estimating such parameters, either by fixed activity, fixed thyroid absorbed doses, and so forth. Several studies have attempted to determine the optimal dose or activity of radioiodine for curing hyperthyroidism while avoiding the development of permanent hypothyroidism. Regimens used have included low activities (80 MBq),^{9,10} various fixed activities (185, 370, and 555 MBq),^{11,12} and doses calculated on the basis of thyroid size, uptake of radioiodine, and turnover of ¹³¹I.¹³

In this study, we compared the efficacy of different tissue-absorbed doses to induce euthyroidism or hypothyroidism within 1 year after radioiodine therapy in an attempt to elucidate some of the still-open issues in the continuing debate over treatment parameters and to further optimize radioiodine treatment for individual patients with GD.

MATERIALS AND METHODS

Patients

A total of 134 patients (102 women and 32 men, with a mean age of 53 ± 14 year; range, 16–82 year) were enrolled in this study comparing the clinical effectiveness of different thyroid-committed doses in radioiodine therapy. All patients included had proven thyrotoxicosis from GD, as confirmed by suppressed basal thyroid-stimulating hormone (TSH), increased serum tri-iodothyronine, and thyroxine serum levels and on the presence of TSH receptor antibodies and/or evidence of ophthalmopathy.

Clinical Assessment

Before ¹³¹I therapy, each patient underwent a full clinical evaluation, determination of thyroid vol-

ume (by high-resolution ultrasound examination), serum analysis (TSH, fT₄, fT₃, and anti-thyroid autoantibodies including TSH-receptor antibodies), 4-hour and 24-hour radioiodine uptake, and a thyroid scan. Besides possible refusal of radioiodine therapy by the patient, exclusion criteria included an age younger than 18 years, suspicion of pregnancy, and the presence of any suspicious thyroid nodule on ultrasound examination. All patients were advised to stay on a generic, low-iodine diet for at least 2 weeks prior to measurements, and were taken off antithyroid drug therapy prior to radioiodine administration (average, 7.5 days; range, 5–30 days). Antithyroid drug treatment was restarted at least 7 days following ¹³¹I therapy.

Assessment by Investigation

Radioiodine uptake (RAIU) and determination of ¹³¹I kinetics

The RAIU and ¹³¹I kinetics in the patients were evaluated as follows:

1. the radioactivity count rate from a diagnostic dose of ¹³¹I (1.85 MBq) placed in a thyroid phantom was measured using a properly collimated and calibrated NaI(Tl) probe (reference measurement);
2. thyroid uptake at 4 hour and 24 hour post-administration of the diagnostic ¹³¹I dose was measured in each patient in the upright position, with the anterior surface of the neck at 25 cm from the same NaI(Tl) probe (120 second counting time);
3. the patterns of ¹³¹I kinetics in the thyroid were identified after calculating the 4-hr (U_4) and the 24-hour (U_{24}) fractional thyroidal uptake, by deriving from such uptake values estimates of the half-time of ¹³¹I in the thyroid (T_{eff}). Based on *a priori* assumptions derived from literature data for the expected T_{eff} values, patients were divided into 4 subgroups:
 - slow kinetics: $T_{eff} = 169$ hour; $T_{max} = 4$ hour with $U_{24}/U_4 > 0.92$;
 - normal kinetics: $T_{eff} = 121$ hour; $T_{max} = 24$ hour with $U_{24}/U_4 > 1$;
 - normal kinetics with fast uptake: $T_{eff} = 121$ hour; $T_{max} = 4$ hour with U_{24}/U_4 between 0.88–0.92; and
 - fast kinetics: $T_{eff} = 107$ hour; $T_{max} = 4$ hour with $U_{24}/U_4 < 0.88$,

where T_{max} is the time at which fractional thyroidal uptake is maximum.

This method for predicting activity and dose to the gland has some disadvantages because it does not accurately follow radioiodine kinetics in a patient's thyroid by sequential measurements (other than the 4-hour and 24-hour time points) during the uptake and clearance phase following tracer administration. Thus, the calculated predicted dose and activity are approximately $\pm 40\%$, which is considered acceptably accurate for internal dosimetry estimates. On the other hand, this method has the advantage of being not time-consuming, thus fitting very well with the scheduling requirements of a busy department of nuclear medicine.

Thyroid ultrasound examination

Ultrasound examination was performed using an AU-4 echograph (ESAOTE; Florence, Italy), equipped with an array 7.5-Hz transducer, with all measurement being carried out by the same operator. Volume was determined by the ellipsoid model ($\text{length} \times \text{width} \times \text{depth} \times \pi/6$) for each lobe and isthmus; thyroid mass was estimated assuming thyroid density being equal to 1 g/mL.

Thyroid scintigraphy

Twenty-four (24) hours after receiving the ^{131}I tracer dose (1.85 MBq), all patients underwent ^{131}I scintigraphy immediately after performing the 24-hour RAIU measurement before receiving the therapeutic dose, to confirm the GD diagnosis.

Radioiodine therapy

The following equation was used to calculate the required ^{131}I activity to achieve the target dose:

$$D_T = \frac{\Delta_{np} U A_0}{m_0}$$

$$\left\{ \frac{T_{\max}}{2} + \frac{1}{\gamma A_0} \left[1 - \left(1 - 2\gamma \frac{A_0 T_{\text{eff}}}{\ln(2)} \right)^{\frac{1}{2}} \right] \right\} \quad (1)$$

where $\Delta_{np} = 0.032 \text{ mGy} \times \text{g} \times \text{MBq}^{-1} \times \text{s}^{-1}$ is the equilibrium dose constant for nonpenetrating radiations;¹⁴ A_0 (MBq) is the ^{131}I activity administered to the patient; T_{eff} (hour) is the effective half-life of radiiodine in the thyroid; $U = A_m/A_0$ is the fractional thyroidal uptake (A_m is the maximum activity in the gland expressed in MBq); $T_{\max}$ (hour) is the time to maximum uptake; m_0 (g) is the pretherapy mass of the gland; U is the maximum fractional thyroidal uptake

(whether it is U_4 or U_{24}). Equation 1 is a predictive equation which allows for a calculation of the radiation dose to the thyroid, taking into account the change of thyroid mass during the clearance phase of ^{131}I from the gland.¹⁵

Based on calculations obtained with Equation 1, patients were retrospectively divided into 3 groups according to the absorbed target dose: group I included 32 patients (24%) whose thyroid average absorbed dose was 150 Gy (148 ± 26 Gy); group II included 58 patients (43%) whose thyroid average absorbed dose was 300 Gy (295 ± 52 Gy); and group III included 44 patients (33%) whose thyroid average absorbed dose was greater than 300 Gy (649 ± 281 Gy). The patients included in groups I and II were randomly chosen; the patients included in group III were treated before, by a fixed value of radioiodine activity (range, 470–586 MBq), based on our experience.

The average radioiodine activity administered to patients was 518 ± 226 MBq, with a range of 111–1110 (14 ± 6.1 mCi; range, 3–30 mCi). The corresponding average thyroid absorbed dose, as calculated by the Medical Internal Radiation Dose (MIRD) equation (as modified by Traino et al.¹⁵), was 376 ± 258 Gy (range, 99–1683) (see Table 1).

Follow-up

The clinical outcome 1 year after ^{131}I treatment was evaluated on the basis of a regular follow-up. Therapeutic success (i.e., elimination of hyperthyroidism demonstrated at the 1-year follow-up evaluation) resulted in either euthyroidism or hypothyroidism.

RESULTS

One year after ^{131}I treatment, a euthyroid state was achieved in 57 patients (43%) and a hypothyroid state in 58 patients (43%), while 19 patients (14%) remained hyperthyroid.

Of the 32 patients receiving an average thyroid tissue dose of 150 Gy, 27 patients (85%) had a favorable response to radioiodine therapy, with 19 patients (60%) being euthyroid and 8 patients (25%) being hypothyroid. The remaining 5 patients (15%) had persistent hyperthyroidism.

Of the 58 patients receiving an average thyroid tissue dose of 300 Gy, 50 patients showed a response to therapy, with 27 patients (46%) being euthyroid and 23 patients (40%) being hypothy-

Table 1. Baseline Characteristics of the 134 GD Patients Subdivided According to Three Different Committed Target Dose Levels

	150 Gy	300 Gy	>300 Gy	Total
Patients (no.)	32	58	44	134
Age (years)	61 ± 13	54 ± 14	48 ± 15	53 ± 14
Thyroid volume (mL)	38 ± 24	26 ± 14	23 ± 13	28 ± 18
Radioiodine uptake (%)	56 ± 22	69 ± 19	74 ± 20	72 ± 20
Activity administered (MBq)	455 ± 250	444 ± 181	663 ± 193	518 ± 226

GD, Graves' disease; Gy, absorbed dose.

roid. The remaining 8 patients (14%) had persistent hyperthyroidism.

In the group of 44 patients receiving an average thyroid tissue dose greater than 300 Gy, 27 patients (85%) responded favorably to therapy, with 11 patients (25%) being euthyroid and 27 patients (61%) being hypothyroid. The remaining 6 patients (14%) remained hyperthyroid (see Fig. 1).

No significant difference in the rate of persisting or recurrent hyperthyroidism was found among the three groups (group I, 15%; group II, 14%, and group III, 14%; chi-square test, $p = 0.72$). On the other hand, a significant difference in the rate of hypothyroidism was found between the cured (euthyroid or hypothyroid) patients of the 3 groups (150 Gy, 30%; 300 Gy, 46%; >300 Gy, 71%; chi-square test, $p = 0.0003$).

When analyzing other factors which might further affect therapeutic outcome, no statistically significant correlation was found between baseline thyroid volume and outcome (average thy-

roid volume in persisting or recurrent hyperthyroid patients was 27 ± 14 mL; range, 10–52 mL versus 28 ± 18 mL in hypothyroid and euthyroid patients; range, 6–95 mL; t test, $p = 0.78$).

Similarly, no statistically significant correlation was found between maximum thyroid uptake and outcome (average thyroid uptake in persisting or recurrent hyperthyroid patients was $72\% \pm 23\%$, versus $67\% \pm 21\%$ in hypothyroid and euthyroid patients; t test, $p = 0.45$).

Finally, no statistically significant correlation was found between age and outcome (average age in persisting or recurrent hyperthyroid patients was 48 ± 12 years; range, 21–68 years versus 54 ± 15 years; range, 16–82 years) in hypothyroid and euthyroid patients (t test, $p = 0.07$) (Table 2).

DISCUSSION

Radioiodine therapy is a well-established treatment for Graves' hyperthyroidism. The use of ra-

Figure 1. Response of patients to thyroid doses.

Table 2. Final Outcome 12 Months After Radioiodine Therapy in 134 GD Patients According to Intended Target Doses

	150 Gy	300 Gy	>300 Gy	Total
Patients (n)	32	58	44	134
Hypothyroidism (%)	25%	40%	61%	43%
Euthyroidism (%)	60%	46%	25%	43%
Hyperthyroidism (%)	15%	14%	14%	14%
Thyroid dose (Gy)	148 ± 26	295 ± 52	649 ± 281	376 ± 258

GD, Graves' disease; Gy, absorbed dose.

radioiodine in hyperthyroidism is increasing, particularly as first-line therapy for GD patients in whom the likelihood of success with antithyroid drugs is limited. Especially in the United States, young adult patients are now offered radioiodine earlier in the course of their disease,¹⁶ because onset of GD at a young age has been reported to be associated with an increased likelihood of relapse after medical treatment alone.^{17,18}

Despite widespread use of ¹³¹I therapy for GD patients, no consensus of opinion exists concerning the optimal method of dose calculation. This is owing to several factors, including varying goals of treatment (hypothyroidism versus euthyroidism), and the lack of comprehensive studies relating the efficacy of different treatment protocols to outcomes.⁸ Because of the excellent clinical results achieved with levothyroxine replacement therapy, hypothyroidism following ¹³¹I therapy is not considered a complication by the majority of nuclear medicine and endocrinology specialists. Thus, therapy outcome is considered to be favorable also for the patients reaching permanent hypothyroidism after ¹³¹I therapy.

Several factors have been considered to influence the outcome of radioiodine treatment. Many studies have demonstrated that patients with larger-volume thyroid glands¹⁰ and severe hyperthyroidism are more likely to fail to respond to a single dose of radioiodine. In our series, all the 9 patients with a thyroid volume of more than 60 mL responded favorably to radioiodine therapy (3 patients became hypothyroid and 6 patients became euthyroid). Treatment with antithyroid drugs has been reported to confer a certain degree of radioresistance, although with conflicting reports (some studies showing an effect only with propylthiouracil alone).

Given the need to prevent persistent hyperthyroidism and the high likelihood of possible hypothyroidism after any protocol of ¹³¹I ther-

apy,^{19,20} ablative radioiodine therapy with a 300-Gy absorbed dose is considered to be an effective treatment of hyperthyroidism in GD patients.²¹

In this study, we have compared the outcome of treatment with 3 calculated dose regimens of radioiodine (150 Gy, 300 Gy, and >300 Gy) in patients with GD. The percentage of hypothyroid patients 1 year after ¹³¹I therapy administration increased with the thyroid absorbed dose (Fig. 1): 25% in group I (150 Gy), 40% in group II (300 Gy), and 61% in group III (>300 Gy), while the percentage of hyperthyroid patients (~15%) was similar in 3 groups. This means that the favorable response (percentage of euthyroid and hypothyroid patients) to ¹³¹I therapy was relatively independent from the actual thyroid-committed doses. Consistent with prior reports, our results confirm the efficacy of radioiodine therapy in 85% of the patients treated at the 1-year follow-up evaluation.²²

CONCLUSIONS

In conclusion, our experience suggests no correlation between the thyroid-committed dose and the outcome of radioiodine therapy for thyroid absorbed doses ≥150 Gy in GD patients, while confirming the relationship between the thyroid absorbed dose and the incidence of hypothyroidism. Thus, it seems to confirm that:

- It is not useful for the thyroid to absorb a dose over 150 Gy, except in the case of ophthalmopathy and high immunity.
- It is important to perform a personal dosimetry, to avoid giving activities too high.
- A fixed-activity administration is a convenient and cost-effective method but not patient-specific, and the results cannot be predicted unless a very high amount of activity is administered;

but, in that case, the therapy is not optimized with respect to radiation safety (ALARA principle).

We are currently assessing the possible relation between the outcome of radioiodine therapy in GD and the reduction of thyroid volume as a consequence of such therapy. This is to optimize the individual calculation of ^{131}I activity to administer to the patient.

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