

Graves' Disease Patients with Large Goiters Respond Best to Radioactive Iodine Doses of at Least 15 mCi: a Sonographic Volumetric Study

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Background and Objectives: Radioactive iodine therapy (RAI) is an important treatment modality of Graves' disease (GD), but there is still not a consensus on the optimal dosage regimen. We studied the treatment success rate of different RAI doses, and examined which clinical markers were useful for determining the optimal RAI dosage for successful therapy in Korean patients. **Materials and Methods:** We retrospectively studied 123 patients with GD treated with RAI between 2004 and 2014 at Chonnam National University Hwasun Hospital. The responder group was defined as patients who developed hypothyroidism requiring levothyroxine replacement following RAI, regardless of the RAI dosage. **Results:** A total of 54 patients (43.9%) became hypothyroid after the first dose, and 31 needed two to four additional doses to achieve hypothyroidism. In the responder group as a whole (85 patients), the mean total dose of RAI was 15.5 ± 7.0 mCi and the mean thyroid volume (TV) was 35.4 ± 23.4 mL. When divided into low dose (< 15 mCi, $n=46$) and high dose (≥ 15 mCi, $n=39$) responder groups, TV was significantly lower in the low-dose responder group (25.7 ± 11.4 vs. 48.4 ± 31.3 , $p < 0.001$). The optimal cut-off TV for the low-dose responder group was < 32.37 mL (sensitivity 80.9%, specificity 76.7%). **Conclusion:** TV had significant effects on the outcome of RAI in GD patients. The optimal fixed RAI dose for Korean GD patients with a large goiter (≥ 33 mL) should be at least 15 mCi to achieve the best outcome.

Key Words: Graves' disease, Radiotherapy, Iodine-131, Diagnostic imaging

Introduction

Graves' disease (GD) is the most common cause of hyperthyroidism in iodine-replete areas. There are several treatment options including the use of antithyroid drugs (ATDs), thyroidectomy, and radioactive iodine therapy (RAI). RAI was introduced as a treatment for GD by Henry Plummer in 1923, and since then, has become an important treatment modality for GD.¹⁾ When radioactive iodine is introduced into the body, it concentrates in thyroid cells that take up iodine and destroys the thyroid gland, with little effect on other

parts of the body. RAI is an efficient and safe treatment for GD with a relapse rate of 10–50% after the first dose.¹⁾

Lowering RAI dose was preferred because of reducing restrictions on behavior of out-patients after RAI and decreasing risk of radiation induced malignancies.²⁾ However, it is not easy to determine the appropriate dose because the failure rate increases if the dose is low. Despite more than a 70 years' history of RAI treatment, some controversies still remain, and here is not a consensus on the best dosage.³⁾ Lewis et al.⁴⁾ and Gupta et al.⁵⁾ preferred fixed doses of 15 mCi RAI for GD, which resulted in

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a 78% and 79.5% cure rate, respectively. Turner et al.⁶⁾ concluded that a calculated dose has no advantage over a fixed dose of 5 mCi. On the other hand, Farrar and Toft⁷⁾ proposed individualizing the dose according to the Quimby–Marinelli formula, which includes thyroid volume (TV) and 24-hour RAI uptake. Peters et al.⁸⁾ recommended activity-calculated RAI rather than standard fixed doses of 15mCi RAI. Jarlov et al.⁹⁾ found that a semiquantitative approach (5, 10, or 15 mCi depending on thyroid gland size) was as effective as more elaborate calculations. In a recent 2011 American Thyroid Association and American Association of Clinical Endocrinologists guideline, a single dose of 10–15 mCi RAI is recommended.¹⁰⁾ A fixed dose regimen is simple, but in cases of a large goiter or severe hyperthyroidism, this may result in treatment failure. Calculated-dose regimens are individualized; however, the additional measurements used for this approach intensify the complexity of the procedure and increase the cost.

Although ATD is the preferred first-line therapy for GD in Korea, RAI is a viable option for GD patients who desire early definitive therapy, and is also used in cases of relapse, drug refractoriness, or severe side effects from ATD. There is no consensus on the optimal dose of RAI for GD in Korea. Therefore, we studied the success rate of various RAI doses, and examined the clinical markers that may predict an optimal dose for successful therapy in Korean patients.

Materials and Methods

The clinical outcomes of 123 patients with GD treated with RAI between April 2004 and December 2014 at Chonnam National University Hwasun Hospital were analyzed retrospectively. All patients were initially treated with ATDs. We choose RAI as a second line therapy excepting patients with thyroid nodule suspected cancer or complaining of compressive symptom. ATD and intake of iodine-rich foods were discontinued 5 days before RAI treatment, and this discontinuation was maintained for 1 week after RAI treatment. The doses of I-131 were empirical (fixed doses of 8–20 mCi). The responder group was de-

fined as patients who developed hypothyroidism requiring levothyroxine replacement following RAI treatment, regardless of the dosage. A subset of responders achieved this status within 6 months after the first RAI therapy, and was classified as the primary responder group (n=54). All other patients (those who responded after multiple RAI treatments plus those who did not respond) were classified as non-primary responders (n=69). Patients whose hyperthyroidism was not controlled 6 months after the first RAI treatment were treated a second time. Thyroid hormone assays were performed in all patients before RAI and at follow-up using the following reference ranges: Thyroid stimulating hormone (TSH), 0.4–4.8 uIU/mL; free T4, 0.8–1.71 ng/dL; and total T3, 0.6–1.6 ng/mL. Thyrotropin-binding inhibitory immunoglobulin (TBII) was analyzed using radioreceptor assays that measured inhibition of binding of labeled TSH to TSH receptors by patient immunoglobulins; the reference range was 0–1.5 IU/L.¹¹⁾

TV was measured using high-resolution ultrasonography with a 5–13 MHz linear transducer (Logiq9, GE Medical system, Milwaukee, WI, USA or ACUSON Antares, Siemens Medical Solutions, Malvern, PA, USA). Longitudinal and transverse scans were performed to obtain width, depth, and length of each lobe in centimeters. The total TV was calculated as the sum of the left and right lobe volumes. The TV was assessed with sonography using the ellipsoid formula: volume (mL)=width of lobe (cm)×height of lobe (cm)×length of lobe (cm)× $\pi/6$. This study was reviewed and approved by the Institutional Review Board of Chonnam National University Hwasun Hospital, Hwasun, Korea. IBM SPSS Statistics 21.0.0 was used for all statistical analyses.

A p value less than 0.05 was considered statistically significant. Student's unpaired t-tests were used to assess mean differences between two groups. The chi-square test was used to determine associations between two groups. Pearson's correlation coefficients were used to assess the correlations between variables. To determine the best threshold for TV to discriminate success and failure of RAI, the receiver operator characteristic (ROC) curve was used.

Results

Outcome of RAI

Our study included 123 patients (42 [33.9%] male, 81 [66.1%] female) with a mean age of 43.85 ± 13.9 years. The median duration of GD was 4.28 years (0.1–18.0) and the mean TV was 39.9 ± 24.6 mL, with a large proportion of TVs in the 20–40 mL range. A total of 74 patients (60.2%) received a single RAI treatment, 41 (33.3%) received two treatments, 6 (4.9%) received three treatments, and 2 patients (1.6%) received four treatments. In all, 54 patients (43.9%) achieved hypothyroidism after the first treatment (primary responders), and 31 patients achieved hypothyroidism after additional treatments. Together, these patients were defined as the overall responder group (85 patients); the mean total dose of RAI was 15.5 ± 7.0 mCi and the mean TV was 35.4 ± 23.4 mL.

Factors Associated with RAI Success

TV was significantly associated with treatment success. The 54 patients who achieved hypothyroidism after the first RAI treatment (primary responder group) had significantly lower TVs than the non-primary responder group (25.1 ± 8.8 vs. $52.8 \pm$

28.2 mL; $p < 0.001$; Table 1), and achieved hypothyroidism after one treatment despite receiving lower doses than the non-primary responder group (11.1 ± 2.7 vs. 20.7 ± 9.4 mCi; $p < 0.001$). TV < 20 mL was associated with a high rate of hypothyroidism (75%), and as TV increased, the treatment response rate decreased. Strikingly, the response rate of patients with TV of 20–40 mL was 60.9%, whereas that of patients with TV of 40–60 mL was 21.1%. None of the patients with a TV greater than 60 mL responded to the first RAI treatment. TBII levels were higher in the non-primary responder group than in the primary responder group; however, this was not statistically significant. Treatment success was not associated with age, sex, or duration of the disease. Mean total RAI dose of the overall responder group (who became hypothyroid after RAI) was 15.6 mCi. When divided into a low-dose responder group (< 15 mCi, $n = 46$) and a high-dose responder group (≥ 15 mCi, $n = 39$) based on total accumulated RAI doses, there were no differences in age, sex, or disease duration, but TV was significantly lower in patients treated with low-dose RAI (25.7 ± 11.4 vs. 48.4 ± 31.3 , $p < 0.001$) (Table 2). TBII was significantly higher in the high-dose responder group. Univariate regression analyses showed that TV was the most important factor affecting the overall responder group by a factor of 0.976

Table 1. Primary responders vs. non-primary responders

	Primary responder (n=54)	Non-primary responder (n=69)	p-value
Male	19 (35.2%)	23 (32.9%)	0.786
Age (year)	45.0 ± 14.6	42.9 ± 13.5	0.410
GD duration (year)	4.3 ± 4.5	4.3 ± 4.0	0.986
ATD	MMI 41 (19.7 ± 15.4 mg) CMZ 1 PTU 8 (225.0 ± 88.6 mg)	MMI 57 (17.9 ± 10.1 mg) CMZ 0 PTU 10 (320.0 ± 141.8 mg)	0.477
TSH (uIU/mL)	0.56 ± 1.49	0.52 ± 1.35	0.887
RAI dose (mCi)	11.1 ± 2.7	20.7 ± 9.4	< 0.001
TBII (IU/L)	6.1 ± 6.0	8.8 ± 11.3	0.116
Thyroid volume (mL)	25.1 ± 8.8	52.8 ± 28.2	< 0.001
0–20 mL	15 (31.9)	5 (8.5)	
20–40 mL	28 (59.6)	18 (30.5)	
40–60 mL	4 (8.5)	15 (25.4)	
60–80 mL	0 (0)	13 (22.0)	
>80 mL	0 (0)	8 (13.6)	

ATD: antithyroid drug, CMZ: carbimazole, GD: Graves' disease, MMI: methimazole, PTU: propylthiouracil, RAI: radioactive iodine, TBII: thyrotropin-binding inhibitory immunoglobulin, TSH: thyroid stimulating hormone

Table 2. Low-dose responders vs. high-dose responders

	< 15 mCi (n=46)	≥ 15 mCi (n=39)	p-value
Male	16 (34.8%)	12 (30.8%)	0.695
Age (year)	46.2±14.8	40.5±11.8	0.053
GD duration (year)	4.2±4.7	4.1±4.0	0.932
ATD	MMI 35 (19.4±16.4 mg)	MMI 31 (19.1±11.2 mg)	0.929
	CMZ 1	CMZ 0	
	PTU 6 (166.7±81.6 mg)	PTU 6 (325.0±61.2 mg)	0.003
TSH	0.58±1.5	0.46±1.2	0.697
TBII (IU/L)	5.1±4.4	10.9±12.7	0.006
Thyroid volume (mL)	25.7±11.4	48.4±31.3	<0.001
0–20 mL	13 (33.3)	3 (8.6)	
20–40 mL	22 (56.4)	16 (45.7)	
40–60 mL	3 (7.7)	8 (22.9)	
60–80 mL	1 (2.6)	4 (11.4)	
>80 mL	0 (0)	4 (11.4)	

ATD: antithyroid drug, CMZ: carbimazole, GD: Graves' disease, MMI: methimazole, PTU: propylthiouracil, RAI: radioactive iodine, TBII: thyrotropin-binding inhibitory immunoglobulin, TSH: thyroid stimulating hormone

Table 3. Odds ratios and confidence intervals obtained from the logistic regression model to find the factors affecting treatment success (overall responders vs. non-responders)

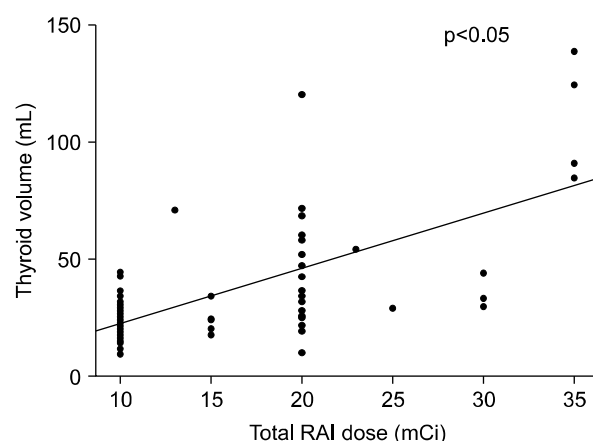
Predictor variable	Odds ratio	Confidence interval	p-value
Age	0.996	0.969–1.024	0.789
GD duration	0.980	0.896–1.071	0.656
TBII	1.008	0.965–1.054	0.712
TSH	0.981	0.749–1.284	0.889
Thyroid volume	0.976	0.959–0.994	0.007
Total iodine dose	0.964	0.924–1.006	0.096

GD: Graves' disease, TBII: thyrotropin-binding inhibitory immunoglobulin, TSH: thyroid stimulating hormone

(95% CI: 0.959–0.994, $p=0.007$) (Table 3). In the overall responder group, total RAI dose was correlate with the TV (ρ 0.575, $p<0.05$) (Fig. 1). ROC analyses to determine the cut-off for TV were performed for total RAI dose. The area under the ROC curve (AUC), which indicates the value for the low-dose responder group ($\text{RAI}<15$ mCi), was 0.835 (95% CI: 0.76–0.91, $p<0.05$). The optimal cut-off for TV for the low-dose responder group was <32.37 mL (sensitivity 80.9%, specificity 76.7%).

Discussion

GD is the most common cause of hyperthyroidism. ATDs are used as initial treatments for this disease in 97.1% of patients in Korea.¹²⁾ However, if patients are unresponsive to ATDs or have associated side effects,

**Fig. 1.** Spearman correlation between thyroid volume and total RAI dose. RAI: radioactive iodine therapy

other treatment modalities are needed including RAI and total thyroidectomy. Sundaresh et al.¹³⁾ reported 75% of patients opted RAI compared with 15.9% se-

lected thyroidectomy as a second line therapy after ATD failure, also Korean Endocrinologists choose RAI of 48.4% compared with thyroidectomy of 4.7% as a second line therapy.¹²⁾ RAI is preferred because it is inexpensive, relatively safe, convenient, noninvasive, and efficient. Surgery is usually preferred when the patient complains of compression symptoms or has combined suspicious cancerous nodules. However, several factors affecting the outcome of RAI have been suggested. Pretreatment thyroid status, thyroid uptake of iodine, and use of ATDs can influence the outcome.¹⁴⁾ The sex and age of the patient have also been considered.^{15,16)}

TV can also have a considerable impact on the therapeutic effects of RAI. Goolden and Fraser¹⁷⁾ first reported a relationship between treatment failure and high TV. Markovic and Eterovic¹⁸⁾ showed that normoechogenic, larger thyroid glands are associated with increased radioresistance. Rivkees and Cornelius¹⁹⁾ recommended more than 0.3 mCi/g is needed to treat thyroid glands larger than 60 g in children. De Jong et al.²⁰⁾ recommended that patients with TV greater than 50 mL require 0.2 mCi/mL. Santos et al.²¹⁾ recommended a 10 mCi fixed dose for all GD patients, except those with large palpable goiters (>60 g), who should receive 15 mCi. Moura-Neto et al.²²⁾ found that a 15 mCi fixed dose was effective, but high failure rates were observed in larger goiters (>62 g). In accordance with these previous findings, our study revealed that TV is an important predictor of the success of RAI. We found that a fixed RAI dose of at least 15 mCi should be administered to GD patients with larger goiters (≥ 33 mL) to achieve the best outcome.

In our dataset, TV was smaller than that in previous studies, but the RAI dose necessary to achieve hypothyroidism was similar or higher. This may be explained by race differences. High iodine intake in Korea is a likely explanation for the higher RAI dose.²³⁾ However, measures of urine iodine before RAI are necessary to test this explanation.

There were several limitations to our study. First, this was a retrospective study. The patients were not controlled, and some data on clinical characteristics were

missing. At the first RAI treatment, the RAI doses were not uniform and the treatments were not randomized, so there may be imbalances in outcomes. Second, we did not measure radioiodine uptake or urine iodine before RAI, so we could not evaluate the effects of individual iodine pooling on response to RAI. To mitigate this limitation, all patients underwent RAI treatment after TSH levels were restored to normal using ATDs. Further, ATD was discontinued 5 days prior to RAI treatment, and a low iodine diet was prescribed to all patients.

In conclusion, TV had a significant effect on the outcome of RAI in GD patients. The optimal fixed RAI dose for GD patients with larger goiters (≥ 33 mL) should be at least 15 mCi to simplify treatment and achieve the best outcome in iodine-replete Korea.

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