Title: Identification of patients with Graves' disease who benefit from high-dose radioactive iodine therapy

Shiro Watanabe[1,2], Shozo Okamoto[3], Kazumasa Akikawa[4], Noriyuki Miyamoto[3], Miyuki Okamura-Kawasaki[5], Yuko Uchiyama[1,2], Junki Takenaka[1,2], Takuya Toyonaga[6], Kenji Hirata[1,2], Kohsuke Kudo [1,7]

Short title: High-dose RAI for Grave's disease

1. Department of Diagnostic Imaging, Hokkaido University Graduate School of Medicine, Kita 15 Nishi 7, Kita-Ku, Sapporo, Hokkaido, 060-8638, Japan.

2. Department of Nuclear Medicine, Hokkaido University Hospital, Kita 14 Nishi 5, Kita-Ku, Sapporo, Hokkaido, 060-8648, Japan

3. Department of Radiology, Obihiro Kosei Hospital, Minami 10-1, Nishi 14, Obihiro City, Hokkaido, 080-0024, Japan

4. Department of Internal Medicine, Hokkaido Medical Center of Rheumatic Diseases, 1-1-45, Kotoni 1-jo 3-chome, Nishi-ku, Sapporo, Hokkaido, 063-0811, Japan

5. Department of Radiology, Tomakomai City Hospital, 1-5-20 Shimizu-cho, Tomakomai, 053-8567, Japan

6. Positron Emission Tomography (PET) Center, Radiology and Biomedical Imaging, Yale School of Medicine, 801 Howard Ave., P.O. Box 208048, New Haven, CT 06520, United States

7. Global Station for Quantum Medical Science and Engineering, Global Institution for Collaborative Research and Education, Hokkaido University, Kita-14, Nishi-5, Kita-ku, Sapporo, 060-8648, Hokkaido

Corresponding author:

Shiro Watanabe, shirow@med.hokudai.ac.jp, TEL: +81-11-706-7779, FAX: +81-11-706-7408

Type of article: Original article

Sources of funding: None

ABSTRACT

Objective: Radioactive iodine (RAI) therapy is a useful treatment for Graves' disease (GD). Most RAI sessions administer ≤500 MBq of iodine (I)-131. Sometimes patients require repeated RAI, often for longer periods of remission. We investigated the characteristics of patients for whom high-dose (mostly 1110 MBq of I-131) RAI was effective as RAI therapy for GD.

Methods: We retrospectively analysed the cases of 79 patients who underwent RAI for GD in a multicenter setting. We divided the patients into two groups based on the I-131 dose administered: the low-dose (LD) group who received ≤500 MBq (n=44) and the high-dose (HD) group who received >500 MBq (n=35). The therapeutic effect was defined as achieving remission and reaching the point of participating in thyroid hormone replacement therapy within 1 year after RAI. We compared the LD and HD groups' remission rates and conducted a multivariate logistic regression analysis of predictive factors for remission. In a simulation, using the formula for predicting the probability of remission obtained from the analysis results, we estimated how much the remission rate would change if the I-131 dose is increased from 500 MBq to 1110 MBq.

Results: The mean ± standard deviation I-131 dose administered in the LD group was 480 ± 6 MBq, and that of the HD group was 1054 ± 265 MBq. Thirty-five patients (80%)

in the LD group and 26 patients (74%) in the HD group achieved remission; this difference in the remission rate was not significant. The multivariate analysis results demonstrated that the absorbed dose and thyroid-stimulating antibody (TSAb) were independent predictors of remission. Seven patients (8.9%) showed an increased probability of remission from <50% to >50% when the higher RAI dose was applied (1110 MBq instead of 500 MBq). The thyroid volume and TSAb values in these patients were relatively large at 54.7 ± 34.2 mL and 1378.4 ± 586.3%, respectively.

Conclusion: Although the overall remission rate was not significantly different between the patients who received high- or low-dose I-131, treatment with high-dose RAI may improve the probability of remission in patients with a massive thyroid volume and/or high-TSAb Graves' disease.

Keywords: Graves' disease, I-131, RAI, TSAb

Introduction

Graves' disease (GD) is the most common cause of hyperthyroidism, with an annual incidence of 20–50 per 100,000 individuals [1]; it is an autoimmune disease with high levels of thyroid-stimulating hormone (TSH)-stimulating antibodies [2, 3]. Radioactive iodine (RAI) therapy is widely used for the treatment of GD, along with antithyroid drugs (ATDs) and surgery. The dose of iodine (I)-131 administered as RAI is usually <555 MBq, and thyroid function normalizes within 3–12 months after RAI in 50%–90% of patients [4].

Biochemically severe thyrotoxicosis, large thyroid volume, male sex, and low RAI doses have been identified as predictors of RAI failure [5]. Patients with palpable and visible goiters often require multiple sessions of RAI [5, 6]. When repeated RAI treatment is required, there are disadvantages such as a long time to remission, repeated low-iodine diet restrictions, and temporary hyperthyroidism due to the discontinuation of an ATD at the pretreatment stage. High doses of I-131 (approx. 1,110 MBq) have been reported to achieve rapid effects [7]. It has also been reported that I-131 doses up to 740–1110 MBq improved the remission rate [8]. Thus, high-dose RAI can shorten the time to the resolution of hyperthyroidism and help reduce the disadvantages of repeated RAI.

Few reports have clarified the patient population for whom high-dose RAI (e.g.,

1110 MBq) should be applied. Unnecessary radiation exposure should be avoided, and it is excessive to provide high-dose RAI in all cases. We conducted the present study to compare the treatment efficacy of high-dose RAI with that of low-dose RAI in relation to well-known and possible clinical factors, and based on our findings we discuss the characteristics of the patients for whom high-dose RAI is useful.

Patients and Methods

Patients

This was a multicenter retrospective study approved by the ethics committee of each of our hospitals. We collected the patients' data by reviewing the clinical records of consecutive patients with GD who were referred to our hospitals for RAI therapy between 2011 and 2017. The cases of the total of 79 patients with GD who underwent RAI at two hospitals and could be followed for >1 year were analyzed; the patients' characteristics are summarized in Table 1.

For all of the patients, the radioactive iodine uptake (RAIU) in the thyroid was measured at 24 hr after an oral administration of 3.7 MBq of I-123 with anterior neck counts measured with a probe placed 25 cm from the patient. Before the administration of I-131, each patient's thyroid volume was measured with the use of ultrasound and the

following equation:

$$\text{Thyroid volume (mL)} = \frac{4}{3}\pi \times \frac{\text{height (cm)} \times \text{width (cm)} \times \text{depth (cm)}}{8}$$

For each patient, the absorbed dose for the thyroid was calculated using the following Marinelli-Quimby formula [9]:

$$\text{Absorbed dose (Gy)} = \frac{135 \times \text{I} - 131 \text{ dose (MBq)} \times \text{RAIU (\%)} \times \text{EHL (day)}}{3.7 \times \text{thyroid volume (mL)} \times 8 \times 100}$$

where EHL indicates the effective half-life in the thyroid gland of the GD patients, which depends on various factors such as the RAIU, the use of ATDs, thyroglobulin antibodies, thyroid peroxidase antibodies, TSH receptor antibodies, and more. Based on earlier studies [10, 11], we defined the EHL as 5.5 days.

RAI therapy

All patients were treated with RAI according to the European Thyroid Association (ETA) guidelines, American Thyroid Association (ATA) guidelines, and Japanese treatment guidelines [2, 3, 12]. The patient was placed on a low-iodine diet for ≥1 week before and for 3 days after the I-131 administration. In addition, ATDs were discontinued as much as possible for ≥7 days before and 3 days after the I-131 administration. The dose was aimed at hypothyroidism in all cases and was usually fixed at 500 MBq or 1110 MBq. In Japan, up to 500 MBq can be administered as an outpatient. Depending on the

patient's condition, a higher dose was selected when hypothyroidism needs to be achieved reliably or in a short period of time, for example, heart failure due to hyperthyroidism, significant weight loss, or patient requests due to social circumstances, while a normal dose was selected when side effects, radiation exposure, or outpatient treatment are considered. After the RAI therapy, ATDs were resumed and continued until the patient's thyroid function was normalized clinically and biochemically. Thyroid hormone replacement therapy was initiated if hypothyroidism was identified without an ATD during the follow-up.

Thyroid function measurement

Serum free triiodothyronine (fT3), free thyroxine (fT4), and TSH were measured in the clinical laboratories of each hospital on the day of the patient's I-131 administration. The reference values at Hospitals A and B were fT3 2.1–3.8 ng/mL and 1.88–3.18 ng/mL; fT4 0.82–1.63 μg/dL and 0.70–1.48 μg/dL; and TSH 0.38–4.31 μIU/mL and 0.35–4.94 μIU/mL, respectively. The detection limits of fT3 and fT4 at Hospitals A and B were 25.0 and 30.0 ng/mL, and 8.0 and 6.0 μg/dL, respectively. The detection limits of TSH were 0.01 and 0.003 μIU/mL at the two hospitals. TSH receptor (TR) antibodies (TRAb) and thyroid-stimulating (TS) antibodies (TSAb) were measured before the patients' RAI

treatment. The reference values were TRAb 0–2.0 IU/L and TSAb 0%–120% at both hospitals.

Statistical analyses

Continuous data are presented as the mean ± SD (standard deviation). We defined the therapeutic effect as a patient achieving remission who reached the point of participating in thyroid hormone replacement therapy within 1 year after the first RAI therapy during follow-up; i.e., the remission group. The non-remission group was comprised of the patients who did not reach the milestone of participating in thyroid hormone replacement therapy after the first RAI therapy and those who underwent a second session of RAI therapy within 1 year after the first RAI therapy.

We divided the 79 patients with GD into two groups according to the I-131 dose administered: the low-dose (LD) group who received ≤500 MBq (n=44) and the high-dose (HD) group who received >500 MBq (n=35). The remission rates are expressed as the percentages of the total group within each category. The remission rate, thyroid volume, I-123 thyroid uptake rate, absorbed dose, and thyroid function test values were compared between the remission and non-remission groups and between the LD and HD groups using Fisher's exact test and the Wilcoxon signed rank test. For all analyses, a

probability (p)-value <0.05 was considered significant. Success after RAI treatment was defined as an "event," and time to remission was calculated by the Kaplan-Meier method.

We performed a multivariate logistic regression analysis of potential predictors of remission. A receiver operating characteristic (ROC) analysis was applied to determine the thresholds for the parameters that predict remission. In a simulation, using the model and optimized parameters that were indicated to be independent predictors of remission in the multivariate analysis, we calculated the probability of remission for 500 MBq and 1110 MBq doses in all patients by using the same formula that we applied for the prediction of the probability of remission.

Results

The patient population consisted of 73 (92.4%) females and 6 (7.6%) males. The mean age and thyroid size were 42.5 ± 13.2 years and 61.7 ± 88.2 mL, respectively. The 24-hr RAIU was 59.9 ± 14.7%. Sixty-one patients (77.2%) were in remission at 1 year after RAI (Table 1). Eighteen patients failed the first RAI therapy, and five of these patients' developed hypothyroidism after their second RAI therapy. No serious side effects of radioiodine (e.g., flare-up of hyperthyroidism, thyrotoxic heart disease, significant thyroid eye disease) were recorded.

There was no significant difference in the remission rate, thyroid volume, baseline TSH, baseline fT4, or RAIU between the LD and HD groups (Table 2). In the LD group, 35 of the 44 patients (80%) reached remission within 1-year post-RAI, whereas 26 of the 35 patients (74%) in the HD group achieved remission. The remission rates were not significantly different between the LD and HD groups (p=0.60).

In the 61 patients who achieved successful ablation after the first RAI treatment, the mean time to remission was 121.1 ± 104.0 days. The Kaplan-Meier analysis showed no significant difference in time to remission between the LD and HD groups (p=0.11, Fig. 1).

In the series of all 79 patients, the absorbed dose, thyroid volume, TRAb, and TSAb values were found to be significant predictors of remission (Table 3). Since we excluded the parameters that were significantly correlated with each other (Table 4), two model analyses were performed — one for TRAb and the absorbed dose and the other for TSAb and the absorbed dose — to avoid the problem of multicollinearity in the multivariate logistic regression analysis (Table 5). The results demonstrated that the absorbed dose and TSAb were independent predictors of remission.

An ROC analysis for remission was performed using the absorbed dose and TSAb, and the threshold values were determined from the Youden Index. The area under the

curve (AUC) of 0.90 for the dose was 234.6 Gy, and the AUC of 0.81 for TSAb was 951% (Fig. 2).

From these results, we established the following equation to calculate the remission rate from logistic regression:

$$\text{logit(p)} = \text{Abosrbed Dose (Gy)} \times 0.0150 - \text{TSAb(\%)} \times 0.00206 - 0.441$$

where p is the probability of remission. The probability of remission was calculated for all patients with the hypothetical doses of 500 MBq and 1110 MBq.

We defined three groups: (*i*) the response group consisting of patients with a remission probability >50% for both doses (n=62); (*ii*) the resistance group consisting of the patients with a remission probability <50% for both the 500 MBq and 1110 MBq doses (n=10); and (*iii*) the conversion group of patients with a remission probability <50% for the low dose and >50% for the high dose (n=7). The distributions of thyroid volume and TSAb values are depicted in Figure 3 for the three groups.

In the simulation study, when the RAI dose was virtually increased from 500 MBq to 1110 MBq the remission rates increased from 88.0 ± 11.8% to 98.8 ± 3.3% in the response group, from 5.5 ± 5.3% to 9.3 ± 7.3% in the resistance group, and from 38.0 ± 11.8% to 89.8 ± 10.7% in the conversion group. The changes in the remission rate per TSAb and thyroid volume in each patient are illustrated in Figure 4. In the conversion

group, the thyroid volume was 54.7 ± 34.2 mL and TSAb was 1378.4 ± 586.3%. The ROC analysis of the resistance group using the thyroid volume and TSAb showed an AUC of 0.99 for a thyroid volume at 124.5 mL and 0.90 for TSAb at 1120% (Fig. 5).

Discussion

The results of our present retrospective analyses of the cases of 79 patients with GD demonstrated that the absorbed dose and the TSAb level are independent predictors of remission following I-131 treatment for GD. A virtual comparison of the effects of high (1110 MBq) and low (500 MB) doses showed that an increase in the administered RAI may improve the remission rate, especially in cases with a low predicted dose (<234.6 Gy) and a high TSAb level (>961%). Using the high-dose RAI regimen may help reduce the time to relieve hyperthyroidism in these patients by reducing the number of RAI doses. However, if a patient's thyroid volume is >124.5 mL or the TSAb is >1120%, it can be difficult to achieve remission of the hyperthyroid state even with high doses of RAI (1110 MBq), and the patient's therapy should be managed with extra care.

Higher RAI doses have been reported to improve remission rates. In light of the high failure rates at low RAI doses, many experts advocate radioiodine doses that result in hypothyroidism [3]. The ATA guidelines for the management of Graves'

hyperthyroidism recommend a dose sufficient to cause hypothyroidism (typically 370–555 MBq) [3], and the ETA guidelines also recommend fixed activity values such as 185, 370, and 555 MBq [2]. However, factors such as large thyroid size, low iodine uptake, and low absorbed doses can reduce the remission rate. Another approach is to individualize the radioiodine dose based on the patient's thyroid size and 24-hr radioiodine intake, in which the dose is calculated based on the MBq/mL of the thyroid tissue to be accumulated.

Some reports have recommended an absorbed dose of 120–150 Gy or higher for the remission of GD [13, 14]. Calculated doses require multiple visits to the hospital to measure the 24-hr iodine uptake rates, which is burdensome for hyperthyroid patients whose ATDs have been reduced or discontinued. The use of fixed-dose radioiodine has been shown to be less expensive than individually calculated doses. Prospective randomization studies showed that a semi-quantitative fixed-dose regimen could produce effects comparable to those of elaborately calculated individual doses [15, 16].

Some studies used higher absorbed doses of I-131 for patients with giant goiters compared to patients with smaller thyroid volumes [17, 18], which is consistent with the results of the present study; for example, Hernández-Jiménez et al. reported that remission of autoimmune hyperthyroidism was achieved with doses of 740–1110 MBq and was

more likely than when ≤555 MBq was administered [8]. Although that report did not mention the patients' thyroid volumes, our present findings revealed a relationship between remission and thyroid volume.

In the present series, all but one of the patients with a thyroid volume >100 mL were in the resistance group. This may have occurred because the absorbed dose is lower as the volume increases. We observed that when we used a thyroid volume of 124.5 mL as a threshold, the treatment with 1110 MBq showed a reliable distinction between remission and non-remission. If the absorbed dose is low with a thyroid volume of ≤124.5 mL, increasing the dose to 1110 MBq may be considered. The treatment at 1110 MBq in the present patient series was also free of serious adverse events. Our results indicate that selecting a higher dose of RAI in certain cases may result in fewer total treatment cycles, but further investigation is needed to confirm this.

We also observed that patients had relatively low remission rates at the common doses described above and higher remission rates at higher doses (>234.6 Gy). A possible reason for this may be that the study included many patients with very large goiters. In this study, 16 patients (20.3%) had a thyroid volume >50 mL, with a maximum volume of 439 mL. In Japan, almost all patients with GD receive pretreatment with an ATD, and RAI treatment is generally indicated when patients show side effects or resistance to an

ATD. The use of an ATD induces resistance to RAI treatment [19], which may be another reason for the low remission rate observed herein.

It has been reported that TRAb antibody titers measured at the time of RAI treatment are significantly associated with treatment failure of initial RAI [6], and we speculate that the functional thyroid cells remaining after RAI treatment are still stimulated by TRAb, which may contribute to persistent hyperthyroidism. However, aging has also been reported to alter the effects of TRAb [20, 21], and aging may increase the proportion of TRAb biologic activity that is non-stimulating antibody. Our present findings showed that, unlike TRAb, TSAb is an independent predictor of remission. This may be because the detection of TSAb allows for a more selective activity assessment since it can distinguish thyrotropin receptor antibody subtypes (blocking/neutral/stimulating). TSAb values have been shown to be superior to TRAb assays in predicting GD relapse after ATD discontinuation [22, 23], and in light of the background of similar mechanisms, a relapse or residual activity of GD after RAI treatment can also be evaluated with TSAb measurements. In this study, we observed that high activity at the time of RAI treatment is a predictor of persistent hyperthyroidism, and it was evident that especially in cases with very high activity (>1120%), even a dose escalation to 1110 MBq is likely to not lead to remission. A careful follow-up of thyroid

function may be warranted in patients with high TSAb levels.

A limitation of this study is its retrospective design; selective bias thus cannot be avoided. However, there was no significant difference in thyroid volume between the low- and high-dose groups (Table 2), although the dosage may have been adjusted according to the thyroid size. It is in an iodine-rich region and may not be generalizable to different iodine supplementation situations. In addition, the follow-up period was a relatively short period (1 year), and some patients with GD achieve remission after >1 year [24]. However, at our hospitals, patients with giant goiters tend to have high fT3 and fT4 levels and are unable to receive an ATD due to side effects or the development of hyperthyroidism under maximal ATD treatment. These patients are at risk of a thyroid crisis and may require rapid remission. If remission is not achieved within approx. 6 months, re-treatment should be considered, and thus 1 year is sufficient for a follow-up period.

In conclusion, single-dose remission may be achieved with high-dose RAI in Graves' disease patients with a low predicted absorbed dose or a high TSAb level. In addition, in patients with a high predicted dose and low TSAb, a standard RAI dose may be sufficient to both achieve a therapeutic effect and avoid the extra radiation exposure.

References

1. Smith TJ, Hegedüs L. Graves' Disease. N Engl J Med. United States; 2016;375:1552–65.

2. Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, Pearce SH. 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. Eur Thyroid J. 2018;7:167–86.

3. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid. United States; 2016;26:1343–421.

4. Bonnema SJ, Hegedüs L. Radioiodine therapy in benign thyroid diseases: effects, side effects, and factors affecting therapeutic outcome. Endocr Rev. United States; 2012;33:920–80.

5. Allahabadia A, Daykin J, Sheppard MC, Gough SC, Franklyn JA. Radioiodine treatment of hyperthyroidism-prognostic factors for outcome. J Clin Endocrinol Metab. United States; 2001;86:3611–7.

6. Tay WL, Chng CL, Tien CS, Loke KS, Lam WW, Fook-Chong SM, et al. High Thyroid Stimulating Receptor Antibody Titre and Large Goitre Size at First-Time

Radioactive Iodine Treatment are Associated with Treatment Failure in Graves' Disease. Ann Acad Med Singapore. Singapore; 2019;48:181–7.

7. Neto AM, Tambascia MA, Brunetto S, Ramos CD, Zantut-Wittmann DE. Extremely high doses of radioiodine required for treatment of Graves' hyperthyroidism: a case report. Cases J. 2009. p. 8479.

8. Hernández-Jiménez S, Pachón-Burgos A, Aguilar-Salinas CA, Andrade V, Reynoso R, Ríos A, et al. Radioiodine treatment in autoimmune hyperthyroidism: analysis of outcomes in relation to dosage. Arch Med Res. United States; 2007;38:185–9.

9. MARINELLI LD, QUIMBY EH, HINE GJ. Dosage determination with radioactive isotopes; practical considerations in therapy and protection. Am J Roentgenol Radium Ther. United States; 1948;59:260–81.

10. Eschmann SM, Thelen MH, Dittmann H, Bares R. Influence of short-term interruption of antithyroid drugs on the outcome of radioiodine therapy of Graves' disease: results of a prospective study. Exp Clin Endocrinol diabetes Off journal, Ger Soc Endocrinol [and] Ger Diabetes Assoc. Germany; 2006;114:222–6.

11. Zhang R, Zhang G, Wang R, Tan J, He Y, Meng Z. Prediction of thyroidal (131)I effective half-life in patients with Graves' disease. Oncotarget. 2017;8:80934–40.

12. Misaki T. [Therapeutic guidelines:progress in diagnosis and treatment. 2. Internal

131-I therapy of Basedow's disease]. Nihon Naika Gakkai Zasshi. Japan; 2010;99:741–6.

13. Howarth D, Epstein M, Lan L, Tan P, Booker J. Determination of the optimal minimum radioiodine dose in patients with Graves' disease: a clinical outcome study. Eur J Nucl Med. Germany; 2001;28:1489–95.

14. Grosso M, Traino A, Boni G, Banti E, Della Porta M, Manca G, et al. Comparison of different thyroid committed doses in radioiodine therapy for Graves' hyperthyroidism. Cancer Biother Radiopharm. United States; 2005;20:218–23.

15. Jarløv AE, Hegedüs L, Kristensen LO, Nygaard B, Hansen JM. Is calculation of the dose in radioiodine therapy of hyperthyroidism worth while? Clin Endocrinol (Oxf). England; 1995;43:325–9.

16. Leslie WD, Ward L, Salamon EA, Ludwig S, Rowe RC, Cowden EA. A randomized comparison of radioiodine doses in graves' hyperthyroidism. J Clin Endocrinol Metab. 2003;88:978–83.

17. Gomi Y, Hamada N, Yoshimura H, Ishikawa N, Momotani N, Ito K, et al. [The outcome of adjusted accumulation dose of treatment of Graves' disease]. Kaku Igaku. Japan; 1997;34:1131–8.

18. Kaplan MM, Meier DA, Dworkin HJ. Treatment of hyperthyroidism with

radioactive iodine. Endocrinol Metab Clin North Am. United States; 1998;27:205–23.

19. Walter MA, Briel M, Christ-Crain M, Bonnema SJ, Connell J, Cooper DS, et al. Effects of antithyroid drugs on radioiodine treatment: systematic review and meta-analysis of randomised controlled trials. BMJ. 2007;334:514.

20. Lu L, Gao C, Zhang N. Age moderates the associations between TRAbs, free T3 and outcomes of Graves' disease patients with radioactive iodine treatment. Clin Endocrinol (Oxf). 2021;94:303–9.

21. Bano A, Gan E, Addison C, Narayanan K, Weaver JU, Tsatlidis V, et al. Age May Influence the Impact of TRAbs on Thyroid Function and Relapse-Risk in Patients With Graves Disease. J Clin Endocrinol Metab. United States; 2019;104:1378–85.

22. Kwon H, Kim WG, Jang EK, Kim M, Park S, Jeon MJ, et al. Usefulness of Measuring Thyroid Stimulating Antibody at the Time of Antithyroid Drug Withdrawal for Predicting Relapse of Graves Disease. Endocrinol Metab (Seoul, Korea). 2016;31:300–10.

23. Da Silva Santos T, Oliveira JC, Freitas C, Couto de Carvalho A. Thyroid-Stimulatory Antibody as a Predictive Factor for Graves' Disease Relapse. Cureus. 2022;14:e22190.

24. Sridama V, McCormick M, Kaplan EL, Fauchet R, DeGroot LJ. Long-term follow-

up study of compensated low-dose 131I therapy for Graves' disease. N Engl J Med. United States; 1984;311:426–32.

Acknowledgments

We thank the radiologic technologists Keiichi Magota, Hiroshi Arai, Daisuke Inotsume, and Hiroaki Ono for their excellent technical assistance with the radioisotope management, and the nurses Asuka Tamura, Yuko Ohara, Miki Oshima for the careful support of patients regarding the low-iodine diet.

The authors have no potential conflicts of interest to disclose.

Figures and Figure Legends

Fig. 1. Kaplan-Meier curves for the remission of Grave's disease after RAI therapy in the low-dose (LD) group who received ≤500 MBq (n=44) and the high-dose (HD) group who received >500 MBq (n=35).

Fig. 2. The results of the ROC analysis for remission using the absorbed I-131 dose and thyroid-stimulating antibody (TSAb).

Fig. 3. Distribution of thyroid volume and TSAb values in the response (n=62), resistance (n=10), and conversion (n=7) groups.

Fig. 4. Changes in the remission rate per TSAb and thyroid volume in Graves' disease. **a:** Changes in the remission rate per TSAb. **b:** Changes in the remission rate per thyroid volume.

Fig. 5. The results of the ROC analysis for predicting resistance using the thyroid volume and TSAb.

Table 1. Characteristics of the patients with Grave's disease (n=79)

Parameter	Non-Remission				Remission				p-value
	n	%	Mean	SD	n	%	Mean	SD	
Hospital:									
A	9	11.4			30	37.8			1
B	9	11.4			31	39.2			
Gender:									
Female	15	19.0			58	73.4			0.13
Male	3	3.8			3	3.8			
Age	18	22.7	42.3	11.2	61	77.3	42.5	13.8	0.99
fT3, pg/dL	18	22.8	15.0	8.3	61	77.2	14.9	10.2	0.77
fT4, ng/dL	18	21.1	3.3	2.4	61	78.9	3.6	2.1	0.38
TSH, μIU/mL	18	2.6	0.0	0.0	61	97.4	0.1	0.4	0.86
TRAb, IU/L	17	56.2	71.0	120.9	61	43.8	15.4	21.3	**<0.01***
TSAb, %	17	41.0	1496.1	947.5	60	59.0	610.1	567.5	**<0.01***
Uptake	18	23.7	62.4	9.4	61	76.3	59.2	15.9	0.74
Volume	18	58.8	159.3	132.2	61	41.2	32.9	38.2	**<0.01***
Oral dose, mCi	18	24.8	21.6	8.9	61	75.2	19.3	9.1	0.25
Absorbed dose, Gy	18	8.7	136.1	90.9	61	91.3	420.2	276.3	**<0.01***

TRAb: thyrotrophin receptor antibody, TSAb: thyroid-stimulating antibody, TSH: thyroid stimulating hormone.

Table 2. Remission rate in the low-dose (LD) and high-dose (HD) groups

Parameter	Low dose				High dose				p-value
	n	%	Mean	SD	n	%	Mean	SD	
Gender:									
Female	41	51.9			32	40.5			1.00
Male	3	3.8			3	3.8			
Age	44	55.5	42.3	12.2	35	44.5	42.7	14.5	0.72
fT3, pg/dL	44	63.6	17.1	10.3	35	36.4	12.3	8.3	**0.02***
fT4, ng/dL	44	52.6	3.4	1.7	35	47.4	3.8	2.6	0.98
TSH, μIU/mL	44	33.8	0.1	0.3	35	66.2	0.1	0.4	**<0.01***
TRAb, IU/L	43	27.4	13.7	16.2	35	72.6	44.5	89.6	0.20
TSAb, %	42	54.4	804.0	735.0	35	45.6	807.8	797.3	0.94
Uptake	44	53.1	57.1	11.7	35	46.9	63.5	17.3	**<0.01***
Volume	44	47.0	52.1	84.0	35	53.0	73.8	93.0	0.12
Oral dose, mCi	44	36.5	13.0	0.2	35	63.5	28.5	7.2	**<0.01***
Absorbed dose, Gy	44	40.4	257.7	133.8	35	59.6	478.3	348.2	**<0.01***
Outcome:									
Remission	35	44.3			26	32.9			0.60
Non-remission	9	11.4			9	11.4			

TRAb: thyrotrophin receptor antibody, TSAb: thyroid-stimulating antibody, TSH: thyroid stimulating hormone.

Table 3. Logistic analysis of remission after RAI

Parameter	p-value	OR	95%CI
Gender	0.12	0.26	0.047–1.413
Age	0.94	1	0.962–1.043
fT3	0.99	1	0.947–1.056
fT4	0.55	1.08	0.838–1.397
TRAb	**0.0044***	0.975	0.959–0.992
TSAb	**0.0005***	0.998	0.998–0.999
Uptake	0.41	0.983	0.946–1.023
Thyroid volume	**0.0017***	0.977	0.963–0.991
Oral dose	0.35	0.97	0.921–1.030
Absorbed dose	***0.0001**	1.015	1.008–1.023

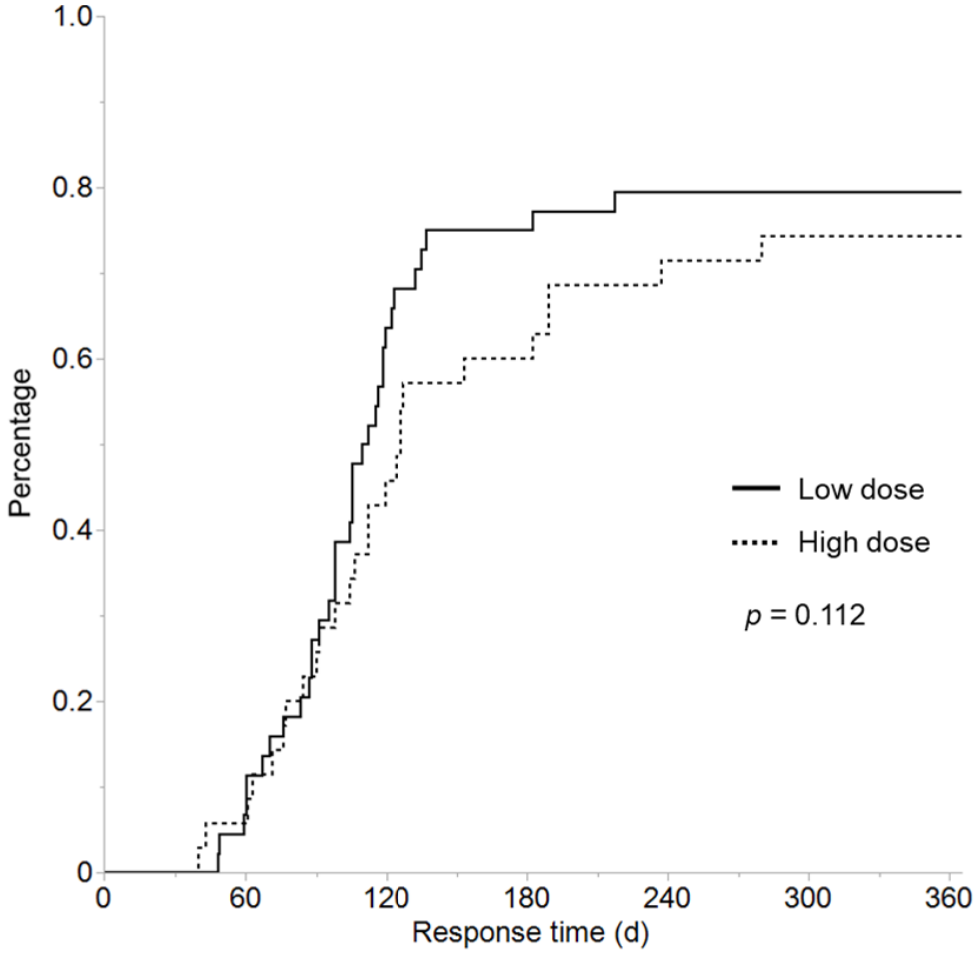
Table 4. Correlation coefficients of various parameters

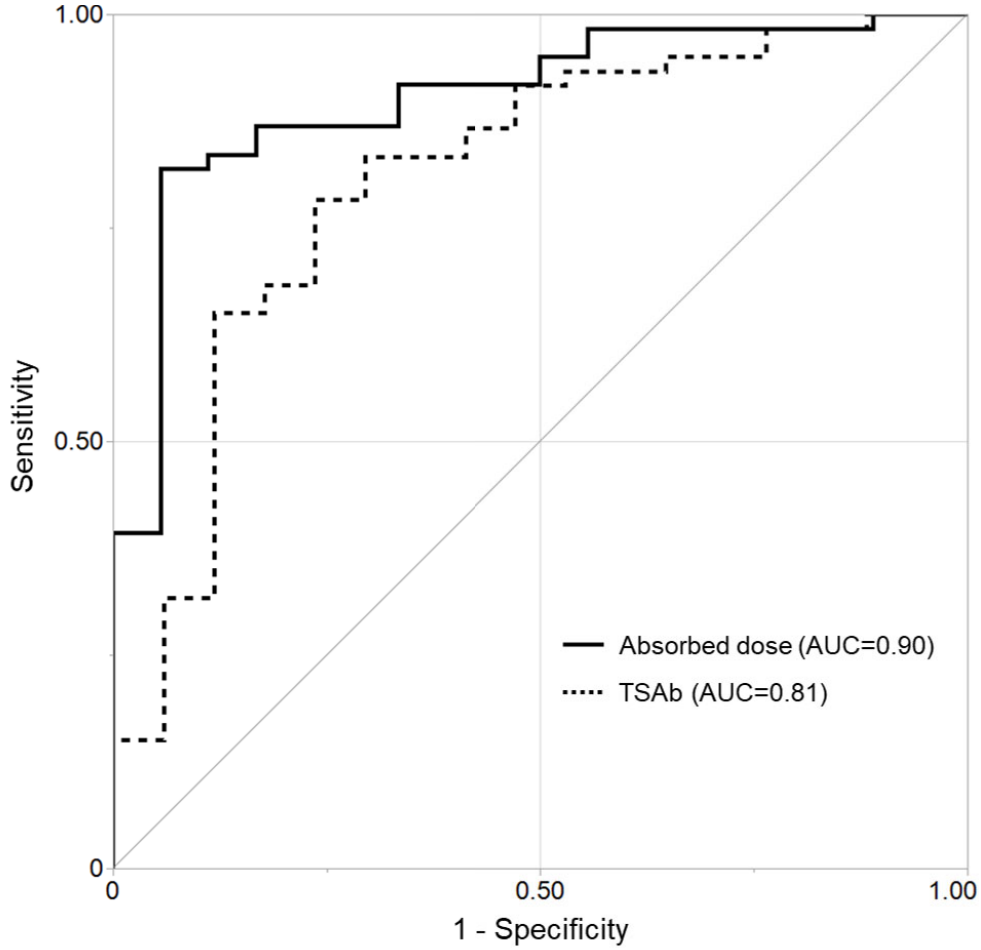
	TRAb, IU/L	**TSAb, %**	**Absorbed dose, Gy**	**Thyroid volume, mL**
TRAb	–	0.487, **p<0.001***	−0.106, p=0.376	0.319, **p=0.006***
TSAb	–	–	−0.155, p=0.178	0.409, **p<0.001***
Absorbed dose	–	–	–	−0.450, **p<0.001***

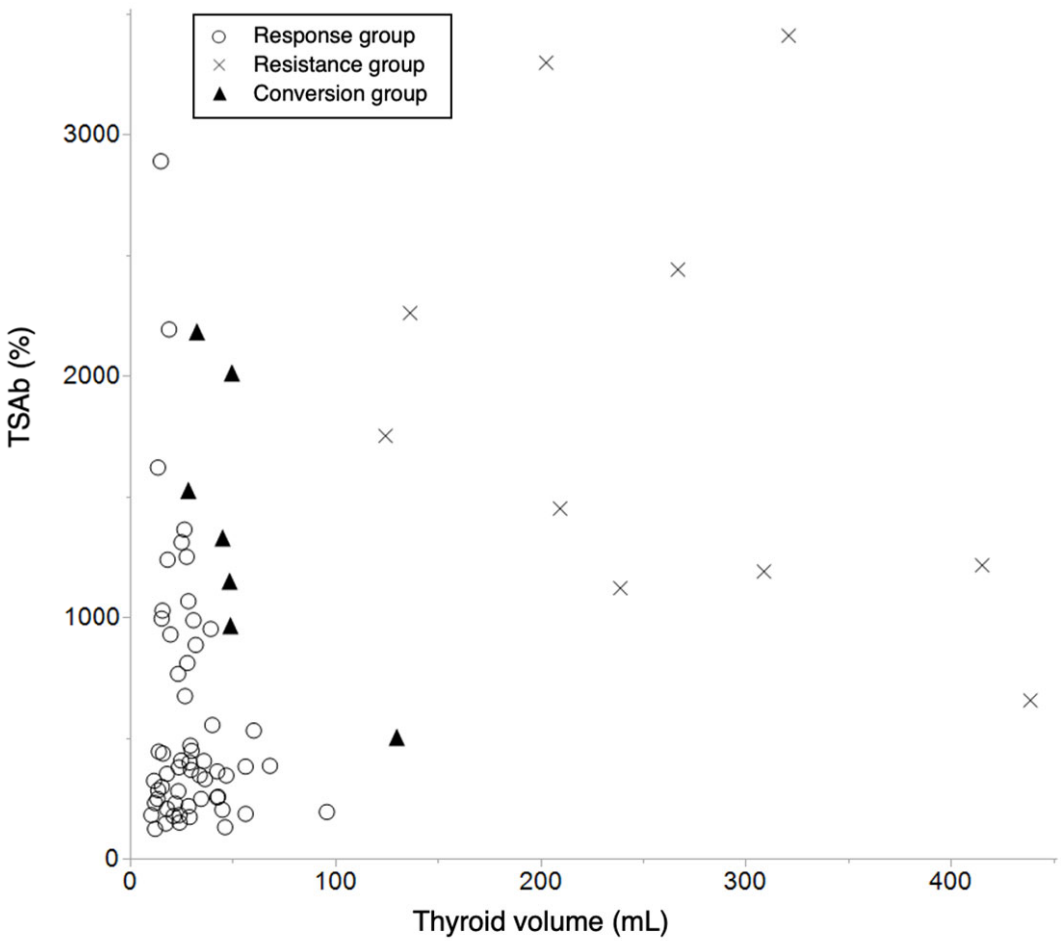
Table 5. Multivariate analysis of remission factors after RAI for GD

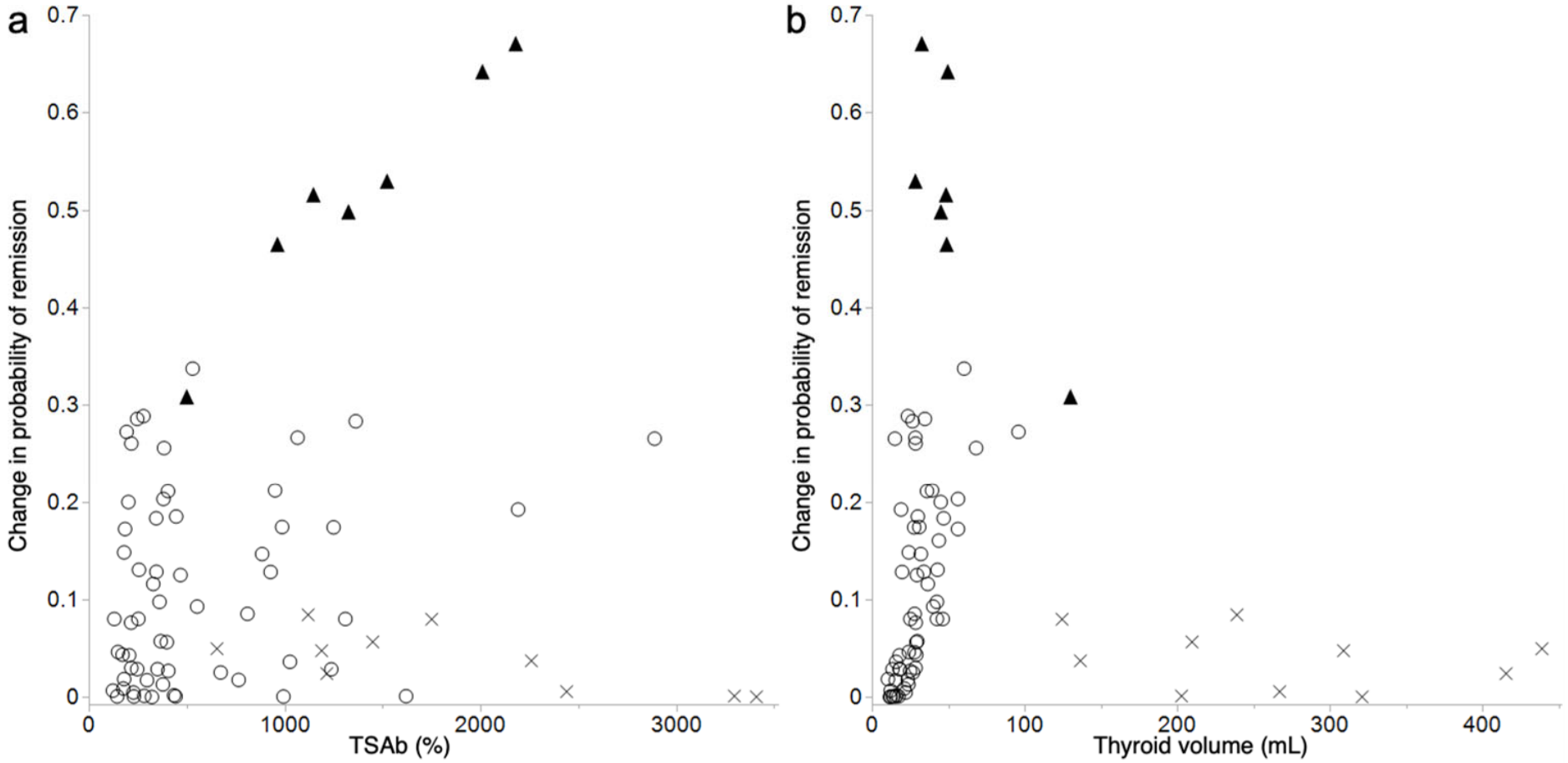
Model	Parameter	p-value	OR	95%CI
1	Absorbed dose	**0.0008***	1.016	1.007–1.026
	TRAb	0.165		
2	Absorbed dose	**0.0008***	1.015	1.006–1.024
	TSAb	**0.0036***	0.998	0.997–0.999

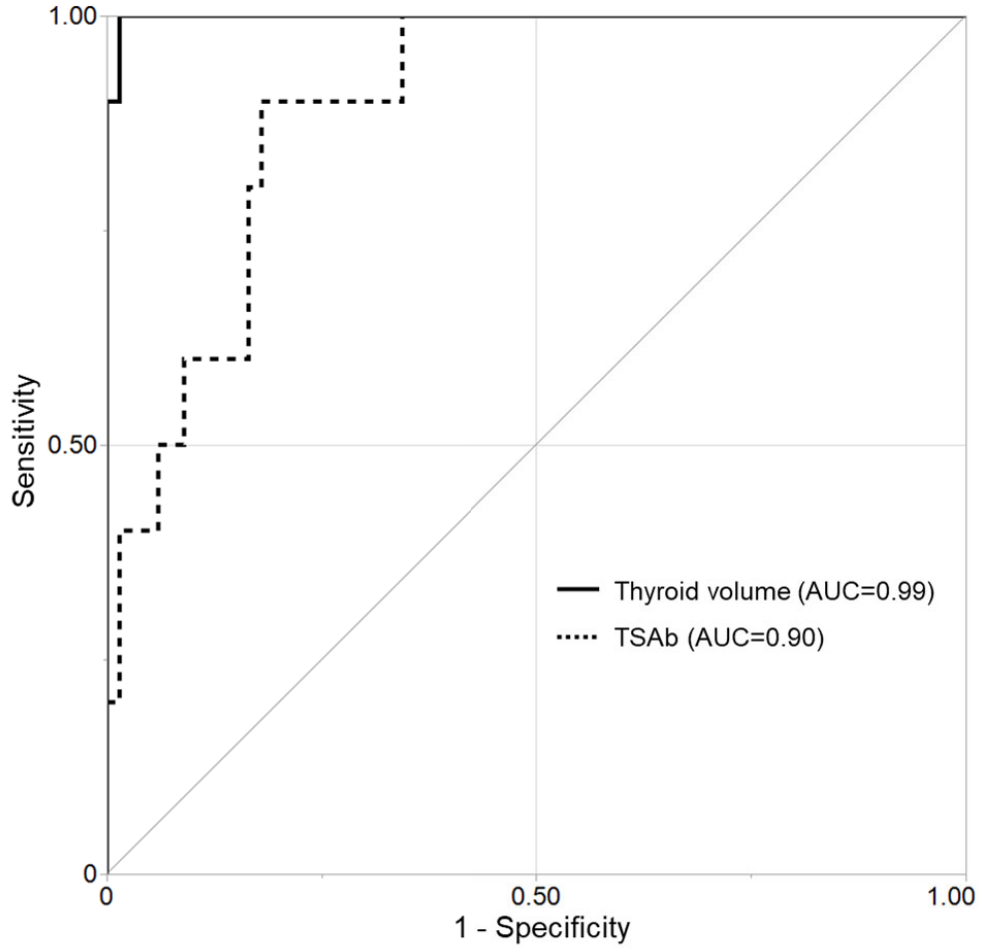
GD: Grave's disease, OR: odds ratio, RAI: radioactive iodine therapy.


1.0
0.8
0.6
0.4
0.2
0
Percentage
0
60
120
180
240
300
360
Response time (d)
Low dose
High dose
p = 0.112


1.00
0.50
0
Sensitivity
0
0.50
1.00
1 - Specificity
Absorbed dose (AUC=0.90)
TSAb (AUC=0.81)


Response group
Resistance group
Conversion group
TSAb (%)
3000
2000
1000
0
0
100
200
300
400
Thyroid volume (mL)


a
b
Change in probability of remission
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
1000
2000
3000
TSAb (%)
0
100
200
300
400
Thyroid volume (mL)


1.00
0.50
0
Sensitivity
0
0.50
1.00
1 - Specificity
Thyroid volume (AUC=0.99)
TSAb (AUC=0.90)