Original article

Predictive factors of success in the first radioactive iodine treatment for Graves' disease

Pinyaporn On-Ekkasit*

Department of Radiology, Hatyai Hospital, Songkhla 90110, Thailand

Background: Initial treatment options for Graves' disease are radioactive iodine (RAI) treatment, antithyroid drugs (ATDs), and surgery. RAI is effective and the definitive treatment for Graves' disease.
Objective: To evaluate factors associated with success in the first RAI treatment for Graves' disease.
Methods: A total of 89 patients who received the first RAI treatment for Graves' disease between September 2016 and January 2021 were retrospectively reviewed. Thyroid function outcome was evaluated within one year after RAI treatment. Logistic regression analysis was performed to identify factors associated with success after RAI treatment.
Results: The success rate of the first RAI treatment was 59.6%, including 15.7% of patients with euthyroidism (14 of 89) and 43.8% of patients with hypothyroidism (39 of 89). All patients were treated with ATDs before RAI treatment. The only factor associated with treatment outcome was the types of ATDs used before RAI treatment (P = 0.016). Logistic regression analysis showed that patients who used both methimazole (MMI) and propylthiouracil (PTU) before RAI treatment were less likely to achieve treatment success as compared to patients who solely used MMI before RAI treatment (odds ratio = 3.554, 95% confidence interval = 1.413 – 8.940, P = 0.007). There was no difference in the influence of MMI and PTU used before RAI treatment on treatment outcome.
Conclusion: The use of both MMI and PTU before RAI treatment reduced the success of the first RAI treatment as compared to solely use of MMI before RAI treatment.

Keywords: Antithyroid drugs, Graves' disease, I-131, radioactive iodine treatment.

Graves' disease is the most common cause of hyperthyroidism. The annual incidence is 20 to 50 cases per 100,000 persons with a lifetime risk of 3.0% for women and 0.5% for men.[1] It is an autoimmune disease causing thyrotropin receptor antibodies, which stimulate thyroid follicular cells, resulting in thyroid hormone overproduction.[1,2]

Initial treatment options for Graves' disease are radioactive iodine (RAI) treatment, antithyroid drugs (ATDs), and surgery.[3] RAI is the most preferred treatment by physicians in the United States, but there is a shift away from RAI and toward ATDs.[4] In Thailand, Japan, and Europe, ATDs are the most preferred treatment by physicians.[5,6]

RAI is safe, effective, and the definitive treatment for Graves' disease. It is incorporated into thyroid hormone and releases beta particles to damage thyroid follicular cells.[3,7] The goal of RAI treatment is to use sufficient activity of RAI to render the patient hypothyroid. The activity of RAI can be given orally as a fixed dose or by calculating the dose based on the size of the thyroid gland and its ability to trap RAI.[3]

Several factors were reported to be associated with the reduced success of the first RAI treatment in Graves' disease, such as age [8-11], male gender [12], longer duration of disease [13,14], use of ATDs before RAI treatment [8,15], larger thyroid gland [8-10,14,16-20], higher radioactive iodine uptake (RAIU) [8,13,15-16,20], more severe case of hyperthyroidism [8-12,16,18,21], higher TSH receptor antibody (TRAb) titer at diagnosis [19,22], longer time of ATDs withdrawal before RAI treatment [18], and lower dose of iodine-131 (I-131). [3,12,14,23] However, there was conflicting data in the literature about factors associated with RAI treatment outcomes and also limited studies on this field in Thailand. Thus, we aimed to evaluate factors associated with success in the first RAI treatment for Graves' disease to optimize the management of Graves' disease at our center in Thailand.

*Correspondence to: Pinyaporn On-Ekkasit, Department of Radiology, Hatyai Hospital, Songkhla 90110, Thailand.
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Materials and methods

This was a retrospective cohort study conducted at Hatyai Hospital, a tertiary care center in Southern Thailand. The study protocol has been approved by the Ethics Committee for Research on Human Subjects of Hatyai Hospital.

Medical records of patients aged 18 years and older who were referred to received the first RAI treatment for Graves' disease and followed up at the outpatient department of Hatyai Hospital between September 2016 and January 2021 were retrospectively collected and reviewed. Graves' disease was diagnosed based on clinical presentation and biochemical evidence of hyperthyroidism. If thyroid nodularity is present, diagnostic testing such as a thyroid scan, ultrasonography of the neck, or fine needle aspiration was performed to determine the definite diagnosis.

All patients were referred to receive the first RAI treatment at Songklanakarin Hospital, a university hospital in Southern Thailand. The dose of I-131 was decided based on the fixed activity approach by nuclear medicine physicians at Songklanakarin Hospital. Patients were instructed to discontinue ATDs 3 to 7 days before RAI treatment. The reason for the prescribed doses and the exact duration of ATD withdrawal before RAI treatment were not documented in medical records. Thyroid function outcome was evaluated within one year after RAI treatment. We defined euthyroidism and hypothyroidism as treatment success and persistent hyperthyroidism as treatment failure.

The data including gender, age at RAI treatment, types and duration of ATDs used before RAI treatment, size of the thyroid gland, presence of Graves' ophthalmopathy, pre-RAI FT4 level, dose of I-131, duration of outcome evaluation, and thyroid function outcome after RAI treatment were recorded. Patients with missing data were excluded from the study.

Statistical analysis

Data collected were analyzed using the Statistical Package for Social Sciences software version 21. Continuous variables were presented as median and range or mean and standard deviation (SD). Categorical variables were presented as numbers and percentages. The unpaired *t* - test or the Mann-Whitney U test was used to compare continuous variables between groups. The Chi-square test or the Fisher exact test was used to compare categorical variables between groups. Pearson's correlation coefficient or Spearman's rank correlation coefficient was used to analyze the correlation between continuous variables. Logistic regression analysis was performed to identify factors associated with success after RAI treatment using odds ratio (OR) and 95% confidence interval (CI). The forward stepwise (conditional) method was used for variable selection. A $P < 0.05$ was considered statistically significant.

Results

A total of 244 patients were assessed for study eligibility, 155 patients were excluded from the study due to missing data; and 89 patients were recruited for final analysis. The clinical characteristics of patients are described in Table 1. More than two-thirds of patients (n = 61, 68.5%) were females with a mean age at RAI treatment of 42.0 ± 13.7 years. All patients (n = 89) were treated with ATDs before RAI treatment and the median duration of ATDs used was 24 months. About half of patients used methimazole (MMI) before RAI treatment (n = 46, 51.7%) and the median duration of MMI used was 26.5 months. More than one-third of the patients were initially treated with or propylthiouracil (PTU) and switched to the other ATD before RAI treatment (n = 36, 40.4%). The median duration of both MMI and PTU used was 20.8 months and the median duration of each drug used in this subgroup was 8 months for MMI and 6 months for PTU. Few patients used PTU before RAI treatment and the mean duration of PTU used was 21.6 months. The dose of I-131 ranged from 5 to 30 millicuries (mCi) with a median dose of 10 mCi. However, there was a moderate correlation between the size of the thyroid gland and the dose of I-131 ($r = 0.567$, $P = < 0.001$).

The median duration of the overall outcome evaluation was seven months. The median duration of outcome evaluation for success and failure groups was 7 and 6.5 months, retrospectively. Success after the first RAI treatment was achieved in 59.6% of patients (53 of 89), including 15.7% of patients with euthyroidism (14 of 89) and 43.8% of patients with hypothyroidism (39 of 89). Failure after the first RAI treatment was found in 40.4% of patients who had persistent hyperthyroidism (36 of 89).

The comparison of clinical characteristics of patients between success and failure after the first RAI treatment is shown in Table 2. The only factor associated with treatment outcome was the types of ATDs used before RAI treatment ($P = 0.016$).

Table 1. Clinical characteristics of 89 Graves' disease patients.

Factors	Number (%)
Gender	
Male	28 (31.5)
Female	61 (68.5)
Age at RAI treatment (years), mean ± SD	42.0 ± 13.7
Types of ATDs used	
MMI	46 (51.7)
PTU	7 (7.9)
Both MMI and PTU	36 (40.4)
Duration of ATDs used (months), median (range)	24.0 (2.6 - 290)
Size of the thyroid gland (g), median (range)	45.0 (20 - 150)
Graves' ophthalmopathy	
Yes	11 (12.4)
No	78 (87.6)
FT4 (ng/dL), median (range)	1.5 (0.5 - 4.7)
Dose of I-131 (mCi), median (range)	10.0 (5 - 30)

SD = standard deviation, ATDs = antithyroid drugs, g = gram, MMI = methimazole,
PTU = propylthiouracil, FT4 = free thyroxine, ng/dL = nanograms per deciliter,
I-131 = iodine-131, mCi = millicurie

Table 2. Comparison of clinical characteristics of patients between success and failure after the first radioactive iodine treatment.

Factors	Outcome after RAI treatment		*P* - value
	Success (n = 53) number (%)	Failure (n = 36) number (%)	
Gender			
Male	18 (34.0)	10 (27.8)	0.537
Female	35 (66.0)	26 (72.2)	
Age (years), mean ± SD	42.7 ± 13.2	40.9 ± 14.6	0.555
Types of ATDs used			
MMI	33 (62.3)	13 (36.1)	0.016
PTU	5 (9.4)	2 (5.6)	
Both MMI and PTU	15 (28.3)	21 (58.3)	
Duration of ATDs used (months), median (range)	23 (2.6 – 290.0)	18 (7.0 – 103.0)	0.670
Size of the thyroid gland (g), median (range)	45 (35.0 – 80.0)	45 (30.0 – 150.0)	0.419
Graves' ophthalmopathy			
Yes	6 (11.3)	5 (13.9)	0.480
No	47 (88.7)	31 (86.1)	
FT4 (ng/dL), median (range)	1.4 (0.5 - 4.7)	1.6 (0.8 - 3.6)	0.087
Dose of I-131 (mCi), median (range)	10 (7.0 – 30.0)	9 (6.0 – 25.0)	0.915

RAI = radioactive iodine, SD = standard deviation, ATDs = antithyroid drugs, MMI = methimazole,
PTU = propylthiouracil, g = gram, FT4 = free thyroxine, ng/dL = nanograms per deciliter, I-131 = iodine-131, mCi = millicurie

Factors associated with success after the first RAI treatment based on logistic regression analysis are demonstrated in Table 3. The types of ATDs used before RAI treatment were the selected variable to use in logistic regression analysis. MMI was used as a reference because the 2016 American thyroid association guidelines recommended that MMI should be used in almost all patients who choose ATD treatment for Graves' disease.[3] Patients who used both MMI and PTU before RAI treatment were less likely to achieve treatment success as compared to patients who solely used MMI before RAI treatment (OR = 3.554, 95% CI = 1.413 – 8.940, $P = 0.007$). There was no difference in the influence of MMI and PTU used before RAI treatment on treatment outcome.

Table 3. Factors associated with success after the first radioactive iodine treatment based on logistic regression analysis.

Factors	OR (95% CI)	*P*-value
ATDs		
MMI	Ref.	
PTU	1.015 (0.175 - 5.907)	0.986
Both MMI and PTU	3.554 (1.413 – 8.940)	0.007

OR = odds ratio, CI = confidence interval, ATDs = antithyroid drugs, MMI = methimazole, PTU = propylthiouracil, Ref. = reference category

Discussion

The success rate of the first RAI treatment for Graves' disease in our study was 59.6%. All patients were treated with ATDs before RAI treatment. The only factor associated with treatment outcome was the types of ATDs used before RAI treatment. Patients who used both MMI and PTU before RAI treatment were less likely to achieve treatment success as compared to patients who solely used MMI before RAI treatment.

In contrast to our study, two retrospective studies reported no association between treatment outcomes and the types of ATDs used (MMI or PTU) before RAI treatment.[17, 20] However, patients in these studies did not use both MMI and PTU before RAI treatment, which is different from our study population. The retrospective study by Kwak JJ, et al. reported that the use of ATDs before RAI treatment, the exclusively used of MMI, and the use of MMI > 3 months were associated with treatment failure.[15] However, this study compared the treatment outcome between patients who used ATDs before RAI treatment and ATDs-naïve patients, and a relatively small number of patients in this study used both MMI and PTU. Meanwhile, our study compared the treatment outcome among patients who were treated with ATDs and used MMI as a reference. More than one-third of the patients in our study used both MMI and PTU. Therefore, the difference in methods and study population could affect the results. The meta-analysis of 14 randomized controlled trials by Walter MA, *et al*. showed increased treatment failures if ATDs are given in the week before or after RAI treatment, and there was no difference in the influence of MMI and PTU on RAI treatment outcome.[24] However, patients in randomized controlled trials that were included in this meta-analysis did not use both MMI and PTU before RAI treatment. Further studies are required to investigate the relationship between RAI treatment outcomes and the use of both MMI and PTU before RAI treatment.

The size of the thyroid gland and the dose of I-131 showed no significant association with RAI treatment outcome, which is different from several studies that showed lower success rates in patients with larger thyroid glands [8 - 10, 14, 16 - 20] and lower doses of I-131.[3, 12, 14, 23] This could be explained by the moderate correlation between the size of the thyroid gland and the dose of I-131. Patients with larger thyroid glands tended to receive higher doses of I-131, which may reduce the effect of these factors on treatment outcomes.

The pre-RAI FT4 level showed no significant association with RAI treatment outcome. On the contrary, the retrospective study by Aung ET, *et al*. showed a lower success rate in patients with higher pre-RAI FT4 levels.[21] The pre-RAI FT4 level represents the severity of the disease. However, all patients in our study were initially treated with ATDs before RAI treatment to achieve euthyroidism and control the disease severity. Thus, the use of ATDs is an important confounder that could affect the results.[25]

The impact of age on the effect of RAI treatment is controversial. Our study found that there was no significant association between age and RAI treatment outcome, which is similar to several studies.[12 - 21, 23, 26] Some studies reported lower success rates in older patients [9, 10], whereas other studies showed lower success rates in younger patients.[8 , 11] The different findings may be due to other factors confounding the results, such as the severity of the disease, use of ATDs, and size of the thyroid gland.[25]

Gender showed no significant association with RAI treatment outcome, which is similar to most studies.[8 - 11, 14, 15, 17 - 21, 23, 26, 27] However, the retrospective study by Allahabadia A, *et al*. reported a lower success rate in the male gender.[12] There is no specific reason to explain the difference in the biological response to RAI treatment between males and females.[25]

The presence of Graves' ophthalmopathy and the duration of ATDs used before RAI treatment showed no significant association with RAI treatment outcome, which is similar to previous studies.[9, 12, 14, 16 - 19, 22, 23]

Our study has some limitations. First, this is a retrospective study based on medical records review. Data of other potential predictive factors such as duration of disease, RAIU, TRAb, and duration of ATD withdrawal before RAI treatment are not available. Furthermore, some data were incompletely recorded. Second, the influence of MMI used before RAI treatment on treatment outcome cannot be evaluated because our study compared the treatment outcome among patients who were treated with ATDs and used MMI as a reference.

Conclusion

The use of both MMI and PTU before RAI treatment reduced the success of the first RAI treatment as compared to solely use of MMI before RAI treatment.

The use of higher activities of RAI may offset the reduced treatment success after the use of both MMI and PTU.

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Conflicts of interest statement

The authors have each completed an ICMJE disclosure form. None of the authors declare any potential or actual relationship, activity, or interest related to the content of this article.

Data sharing statement

The present review is based on the references cited. Further details, opinions, and interpretation are available from the corresponding authors on reasonable request.

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