Original Article

High Thyroid Stimulating Receptor Antibody Titre and Large Goitre Size at First-Time Radioactive Iodine Treatment are Associated with Treatment Failure in Graves' Disease

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Abstract

Introduction: Our study aimed to identify the factors associated with successful first-time radioactive iodine (RAI) treatment in patients with Graves' disease (GD). Materials and Methods: This is a retrospective study of patients with GD who were treated with RAI. Treatment success was defined as onset of permanent hypothyroidism or euthyroidism after 1 dose of RAI at 1-year follow-up. Results: There were 388 GD patients who underwent RAI treatment between January 2014 and December 2015. Of these, 74% achieved treatment success. Median time to achieve permanent hypothyroidism was 2 months. Male gender, smoking, higher antithyroid drug dosage, lower thyroid stimulating hormone (TSH) level, large goitre size and TSH receptor antibody (TRAb) titre at time of RAI were significantly associated with treatment failure. Multivariate analysis showed that larger goitre size and higher TRAb titre were associated with lower first-time RAI success. Conclusion: Larger goitre size and higher TRAb titre predict lower success of RAI therapy in GD patients. Treatment decisions and strategies should be customised for patients who present with these characteristics.

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Key words: Autoimmune thyroid disease, Hyperthyroidism, TSH receptor antibody

Introduction

Graves' disease (GD) is the most common cause of endogenous hyperthyroidism. Remission with medical therapy ranges from 20% to 60% after 1 to 2 years of treatment.[1] Definitive treatment options include radioactive iodine (RAI) and thyroidectomy, with the latter associated with complications of surgery and general anaesthesia. As such, the preferred mode of definitive therapy in uncomplicated GD is RAI.[2] The goal of RAI in GD is to render the patient hypothyroid or euthyroid. Ideally, 1 dose of RAI should achieve this goal in a predictable manner to allow timely initiation of thyroxine and to minimise symptoms associated with prolonged hypothyroidism. In most instances, post-RAI treatment hypothyroidism occurs from 4 weeks after treatment, most commonly between 2 to 6 months post-treatment.[3]

In the literature, the success of RAI therapy ranged from 61% (with 5.4 mCi) to 86% (with 15.7 mCi).[4] Although multiple studies have tried to determine the clinical or biochemical factors that influence the success of RAI treatment, current evidence is conflicting. The factors purported to be associated with reduced success of RAI treatment include younger age, antithyroid drug (ATD) pretreatment, male gender, higher thyroid stimulating hormone receptor antibody (TRAb) titre, higher free thyroxine (FT4) level and larger thyroid gland size.[1,4-7] Additionally, the specific role of TRAb in predicting RAI outcome is also not clear, unlike its role in medical therapy whereby a higher TRAb titre is associated with a lower likelihood of remission.[8]

Our study aimed to examine factors that may predict the success of first-time RAI in the treatment of GD to aid physicians to recommend more customised treatment options to their patients.

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Materials and Methods

Medical records of all GD patients treated with RAI between January 2014 and December 2015 in the Department of Nuclear Medicine and Molecular Imaging in our institution were retrospectively reviewed. The diagnosis of GD was based on elevated FT4 with suppressed thyroid stimulating hormone (TSH) level and clinical examination findings (such as diffusely enlarged goitre, thyroid eye disease and typical signs and symptoms of hyperthyroidism) with documented presence of thyroid autoantibodies. Cases were excluded when the underlying diagnosis was not clear or a patient has a concomitant toxic nodule. Patients who were not followed up for up to 1 year were also excluded.

The data included demographics, thyroid size at RAI, smoking status, GD duration, ATD dose before RAI, first incidence of GD or relapsed disease, presence of GD at time of RAI, use of steroid prophylaxis, empirical or calculated RAI dose, repeat RAI treatment and time to onset of permanent hypothyroidism. Biochemical data such as FT4 and TRAb titre at time of RAI were collected. FT4 was determined on UniCel DxI 800 Access immunoassay system (Beckman Coulter, Inc., Chaska, MN, USA; normal range, 8.8-14.4 μmol/L) using chemiluminescence detection methods. TRAb titre was measured using a second-generation TBII kit using recombinant human TSH receptor (B•R•A•H•M•S Diagnostics, Berlin, Germany; normal range, 0-1.5 IU/L).

Most patients received an empirical RAI dose based on estimated thyroid volume measured by clinical palpation according to the World Health Organization's classification of goitre: small (Grade 0, no palpable or visible goitre), moderate (Grade 1, a mass in the neck that is consistent with an enlarged thyroid which is palpable but not visible when the neck is in the normal position) and large (Grade 2, a swelling in the neck that is visible when the neck is in the normal position and is consistent with an enlarged thyroid when the neck is palpated).[9] Generally, the RAI dose for these 3 goitre sizes are 10-15 mCi, 15-20 mCi and 20-30 mCi, respectively. A small number (n = 25) of patients received a calculated dose using ultrasound for thyroid volumetry and subsequent RAI doses were based on the Marinelli formula with fixed assumptions for maximum thyroid uptake ratios.[10] RAI was ordered in the form of liquid sodium iodide (GE Healthcare, Amersham Place, UK; ANSTO, Sydney, Australia; and POLATOM, Otwock, Poland).

Titrations of RAI dose were performed in our nuclear medicine laboratory by an experienced clinician who measured radioactivity levels using an Atomlab™ 500 Dose Calibrator (Biodex Medical Systems, NY, USA) with an error acceptance rate of ± 5%. This was fed to patients via ingestion using a straw with more water for top-up.

The presence of GD is considered if eyelid retraction occurs in association with thyroid dysfunction, exophthalmos, optic nerve dysfunction or extraocular muscle involvement and when other confounding causes such as idiopathic orbital inflammation are excluded.[11] Steroid prophylaxis is defined as at least 2 weeks of treatment with a pharmacological dose of glucocorticoids. Patients with pre-existing GD or risk factors for GD progression and those with large goitres were given steroid prophylaxis to reduce the risk of GD progression and post-RAI thyroiditis, respectively. ATDs available in our institution are carbimazole, thiamazole and propylthiouracil. ATDs were titrated to equivalent dosage of carbimazole which is 10:1 for propylthiouracil to carbimazole and 2:3 for thiamazole to carbimazole.[1,12] In our institution, ATDs are routinely discontinued 4 to 7 days prior to RAI treatment and restarted after 3 days at the discretion of the treating nuclear medicine physician. Additionally, patients were instructed to strictly follow a diet low in iodine for up to 1 week following the same period of discontinuation of ATDs for RAI treatment.

Successful RAI outcome was defined as achievement of permanent hypothyroidism (requiring thyroxine initiation) or euthyroidism (cessation of all ATDs) after 1 dose of RAI at 1-year follow-up. As such, individuals who had transient hypothyroidism (initially hypothyroid after RAI but became euthyroid or hyperthyroid at 1 year after RAI) had treatment failure.

Statistical analysis was performed using SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as mean ± standard deviation or median (interquartile range) for continuous variables and as count (percentage) for categorical variables. The primary outcome of interest was successful RAI after first-time RAI treatment. Univariate test of factors associated with outcomes were done using Mann-Whitney U test and chi-square test for continuous and categorical data types, respectively. Significant results were defined as $P < 0.05$.

Logistic regression analysis was used to identify factors that predict success of RAI therapy. The dependent variable includes successful RAI outcome after first-time RAI treatment. The independent variables include age at RAI, gender, smoking status, pre-existing GD, duration of diagnosis, TSH and TRAb titre at RAI, ATD pretreatment, ATD dose, steroid prophylaxis, goitre size and RAI dose.

The study was approved by SingHealth Institutional Research Ethics Committee.

Results

There were 388 patients with GD who were treated with RAI during the study period. The main indication for RAI treatment was relapsed GD in 68.3% of patients. Other indications include patient's treatment choice, allergy to ATDs and definitive treatment due to complications from thyrotoxicosis such as thyroid storm or thyrocardiac disease.

A total of 273 (70.4%) patients became permanently hypothyroid and 14 (3.6%) were euthyroid at 1-year follow-up. As such, 73.7% of GD patients in our study had a successful RAI outcome after the first treatment. Median time to onset of hypothyroidism in patients who achieved permanent hypothyroidism after first-time RAI treatment was 2 months (95% confidence interval, 1.9-2.1) as shown in Figure 1. In patients who failed first-time RAI, 24 (6.2%) remained on long-term ATDs and 77 (19.8%) underwent a second RAI treatment. A total of 73 patients became permanently hypothyroid after the second RAI treatment. Of the remaining 4 patients who underwent the second RAI treatment, 1 was euthyroid and 3 were placed on long-term ATDs. Table 1 shows the baseline characteristics of patients who had a successful outcome after first-time RAI treatment (achievement of euthyroidism or permanent hypothyroidism) against those who remained hyperthyroid after 1 treatment.

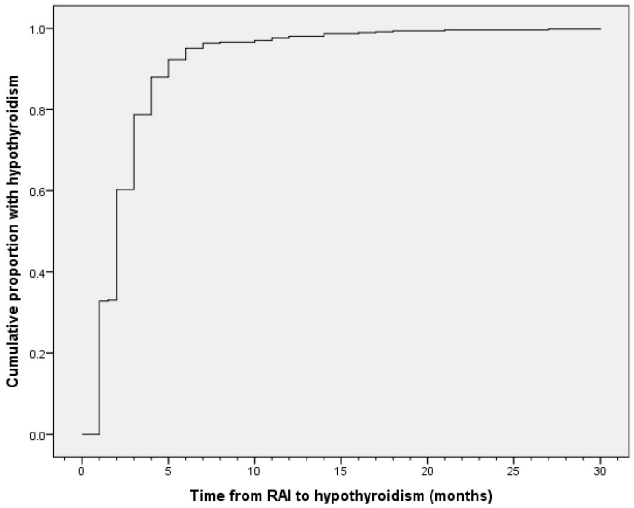

Fig. 1. Cumulative incidence of hypothyroidism seen in patients after first-time RAI therapy. RAI: Radioactive iodine.

Male gender, smoking, higher ATD dosage, large goitre size, lower TSH and higher TRAb titre at RAI treatment were significantly associated with RAI treatment failure (Table 1). There were significantly more male than female smokers (68.4% vs 31.6%, P <0.001). The proportion of patients on each ATD who had a successful outcome after first-time RAI treatment against those who remained

Table 1. Baseline Characteristics of Patients after First-Time RAI Therapy

Variable	Euthyroid or Hypothyroid (n = 286)	Remained Hyperthyroid (n = 102)	*P* Value
Age at diagnosis (years, mean ± SD)	45 ± 14	45 ± 13	0.928
Male gender (%)	67 (23.4)	35 (34.3)	0.032
Smoker (%)	35 (15.7)	22 (24.2)	0.037
Median duration of diagnosis (months, IQR)	65 (34 – 117)	81 (37 – 125)	0.319
Relapsed Graves' disease (%)	192 (67.1)	73 (71.6)	0.433
Pre-existing Graves' ophthalmopathy (%)	53 (18.5)	28 (27.5)	0.057
ATD pretreatment (%)	263 (92.0)	99 (97.1)	0.077
ATD dose (mg/day, mean ± SD)	10.8 ± 9	13.2 ± 9	0.025
Duration of ATD treatment before RAI (months, mean ± SD)	12 ± 5.34	18 ± 5.37	0.238
RAI dosing (%)			
Empirical dosing	265 (92.7)	95 (93.1)	-
Calculated dosing	18 (6.3)	7 (6.9)	0.860
Goitre size (%)			
Small	175 (61.2)	42 (41.2)	-
Moderate	80 (28.0)	34 (33.3)	-
Large	29 (10.1)	25 (24.5)	<0.001
Steroid prophylaxis (%)	68 (23.8)	33 (32.4)	0.090
Median dose of first RAI (mCi, IQR)	18 (15 – 20)	20 (16 – 23)	0.056
Median TSH at RAI (IU/L, IQR)	0.050 (0.015 – 1.000)	0.026 (0.010 – 0.345)	0.013
Median TRAb titre at RAI (IU/L, IQR)	5.9 (2.5 – 16.4)	11.9 (5.3 – 29.8)	<0.001

ATD: Antithyroid drug; IQR: Interquartile range; RAI: Radioactive iodine; SD: Standard deviation; TRAb: Thyroid stimulating hormone receptor antibody; TSH: Thyroid stimulating hormone

hyperthyroid were, respectively, 80.8% versus 82.2% for carbimazole, 4.5% versus 3.0% for thiamazole and 6.6% versus 11.9% for propylthiouracil. The remaining patients (6.7%) were either on non-ATD drugs such as lithium and cholestyramine or not on any form of treatment. The comparison of usage of ATD types between groups did not reach statistical significance. A total of 21 (5.4%) patients had transient hypothyroidism.

Multivariate analysis showed that large gland size and higher TRAb titre at RAI treatment had an odds ratio (OR) of 0.244 (P = 0.003) and 0.969 (P = 0.004), respectively, and were associated with a lower probability of successful first-time RAI treatment outcome after controlling for other factors (Table 2).

Discussion

Our study demonstrated that RAI is effective in 73.7% of patients who achieved a successful outcome (permanent hypothyroidism or euthyroidism) after receiving a first-time median RAI dose of 19 mCi. The onset of post-RAI treatment hypothyroidism is often unpredictable in clinical practice. As such, the duration of follow-up after RAI is often dependent on the attending physician. It has been recommended that assessment of FT4 should be performed between 2 to 6 weeks after RAI therapy to avoid GD exacerbation.[13,14] In our study, the median time to hypothyroidism was 8 weeks after RAI therapy and this finding concurred with that of other studies.[3] This suggests that patients who are treated with RAI should be followed up within 2 months for development of hypothyroidism.

We have demonstrated that TRAb titre—measured at RAI treatment—was significantly associated with treatment failure of first-time RAI. Notably, every 1 IU/L increase in TRAb was associated with a 3.1% reduction in treatment success. This association persisted even after adjustment for multiple factors had been made. Some studies have proposed a link between higher TRAb titre and failure of RAI treatment (Table 3). It has been postulated that functioning thyroid cells that remained after RAI treatment are still being stimulated by TRAb which contributes to the persistence of hyperthyroidism.[15,16]

One finding of our study is that larger goitre size is associated with treatment failure and this finding remained significant in multivariate analysis. Several studies have shown that a larger thyroid gland is associated with a higher risk of treatment failure (Table 3). Although it is difficult to ascertain the exact cause of failure due to differences in dosage in various studies and the complex interactions between thyroid size and other disease risk factors, a larger thyroid gland intuitively implies a higher burden of autonomously functioning thyroid tissue and greater resistance to RAI therapy.

In our study, there were fewer male patients who became euthyroid or hypothyroid after first-time RAI treatment. Male smokers with GD have a poorer response to ATD treatment.[1] There were significantly more male smokers than female smokers in our study. It is plausible that smoking can impact on the treatment outcome of RAI therapy. Smoking may promote immune activation and increase TRAb levels which can lead to resistance to RAI.[17] While the 2 large series by Alevizaki et al and Boelaert et al had demonstrated that male gender was associated with reduced response to RAI treatment, this finding has not been replicated in other studies.[18,19]

Table 2. Multivariate Logistic Regression of Factors that Predict Successful First-Time RAI Therapy

Factor	Odds Ratio (95% Confidence Interval)	*P* Value
Age at RAI (years)	0.990 (0.969 – 1.011)	0.345
Male	0.679 (0.358 – 1.289)	0.237
Smoker	0.651 (0.311 – 1.365)	0.256
Pre-existing Graves' ophthalmopathy	0.634 (0.309 – 1.302)	0.215
Duration of diagnosis (months)	1.001 (0.998 – 1.004)	0.572
TSH at RAI	1.203 (0.994 – 1.456)	0.057
ATD pretreatment	0.393 (0.094 – 1.637)	0.200
ATD dose	0.999 (0.969 – 1.031)	0.958
Steroid prophylaxis	1.379 (0.671 – 2.835)	0.382
Goitre size at RAI		
Small	1.000	-
Medium	0.582 (0.299 – 1.132)	0.111
Large	0.244 (0.097 – 0.611)	0.003
First RAI dose (mCi)	1.042 (0.961 – 1.130)	0.314
TRAb titre at RAI (IU/L)	0.969 (0.948 – 0.990)	0.004

ATD: Antithyroid drug; RAI: Radioactive iodine; TRAb: Thyroid stimulating hormone receptor antibody; TSH: Thyroid stimulating hormone

Table 3. Studies of Goitre Size and TRAb on Outcome of RAI Therapy

First Author (Year)	Number of Patients	Study Design	Goitre Size	TRAb
Davies et al (1982)*	43	Retrospective	ND	+
Marcocci et al (1990)†	274	Retrospective	+	ND
Kung et al (1990) ‡	827	Retrospective	+	ND
Kaise et al (1991) §	109	Retrospective	+	+
Murakami et al (1996)‖	52	Prospective	ND	+
Chiovato et al (1998)¶	31	Prospective	+	+
Sabri et al (1999)#	207	Prospective	–	–
Howarth et al (2001)**	58	Prospective	+	ND
Allahabadia et al (2001)††	813 (321 with GD)	Retrospective	+	ND
Andrade et al (2001)‡‡	61	Prospective	+	–
Alexander and Larsen (2002)§§	261	Retrospective	+	ND
Zantut-Wittmann et al (2005)‖‖	82	Retrospective	+	ND
Boelaert et al (2009)¶¶	1278 (543 with GD)	Cohort	+	ND
Zheng et al (2012)##	796	Retrospective	+	+
Sapienza et al (2015)***	91	Prospective	+	ND
Sfiligoj et al (2015) †††	724	Retrospective	+	ND
Yang et al (2018)‡‡‡	325	Retrospective	+	–

GD: Graves' disease; ND: Not determined; RAI: Radioactive iodine; TRAb: Thyroid stimulating hormone receptor antibody
+: An association was observed between RAI treatment failure and larger goitre size and/or high TRAb.
–: No association was observed between RAI treatment success and goitre size and/or TRAb.
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##Zheng W, Jian T, Guizhi Z, Zhaowei M, Renfei W. Analysis of ^{131}I therapy and correlation factors of Graves' disease patients: a 4-year retrospective study. Nucl Med Commun 2012;33:97-101.
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However, in our study, subsequent multivariate analysis showed that male gender and smoking did not predict treatment outcome of RAI therapy after accounting for other clinical factors.

Patients who remained hyperthyroid after RAI treatment were on a much higher dose of ATDs and had lower serum TSH at RAI treatment compared to those who became euthyroid or hypothyroid after RAI (Table 1). Lower TSH at RAI treatment likely reflects increased disease severity and lesser likelihood of treatment success. TSH at time of RAI was not significant on multivariate analysis (OR, 1.203; $P = 0.057$). It is postulated that this is because patients with lower TSH and more severe disease are more likely to have higher TRAb titres.

The main limitation of our study is its retrospective design. While we acknowledge that transient hypothyroidism has previously been demonstrated as a potential marker of treatment failure, its low incidence of 5.4% in our study made it improbable as a predictor of treatment failure.[20] Our institution does not routinely perform radioiodine uptake or measure the iodine status of all patients before RAI treatment. The absence of this information prior to the determination of empirical RAI treatment dose could potentially affect treatment outcome in our patients. However, a recent study had demonstrated that the efficacy of RAI therapy in GD was not compromised by iodine nutritional status even when patients presented with urinary iodine excretion that is compatible with mildly excessive iodine ingestion.[21]

Another limitation of our study is the lack of uniform strategies in the selection of RAI dosage to treat patients. Many institutions in Europe prefer the use of empirical over calculated RAI dosing strategies.[22] Our institution generally follows similar principles and only a small number (<5%) of patients are treated using a calculated RAI dosage strategy. Studies have shown that estimation of goitre size by manual palpation demonstrates a good correlation with ultrasonographic measurements when it is performed by experienced clinicians.[23] More importantly, both empirical and calculated RAI dosing strategies have achieved comparable outcomes.[23,24]

Conclusion

Our study demonstrated that larger goitre size and higher TRAb titre are associated with failure of first-time RAI therapy. Identification of the predictors of RAI treatment failure will help to moderate the expectations of patients and physicians on the response and outcome of RAI therapy. This information can also guide treatment selection in GD patients such as recommending thyroidectomy or long-term ATDs over RAI in patients with large goitre size or high TRAb titre.

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