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RESEARCH ARTICLE

Radioactive Iodine Treatment of Graves' Disease: Predictors of Time Interval Greater than 90 Days for Treatment Success

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Abstract

Objective: **Radioactive iodine (RAI) is often used for treating Graves' disease. We study predictors for a time interval greater than 90 days between RAI treatment and success.**

Methods: **This was a retrospective study of 106 patients with Graves' disease seen at a public hospital in suburban New York City. Predictor variables were from demographics, prior treatment history, iodine 131 RAI treatment, and thyroid function prior to RAI treatment.**

Results: **There were 62.3% that had a time interval greater than 90 days between RAI treatment and success. Only the thyroid function prior to RAI treatment variable of free thyroxine (FT4) had statistically significantly increased odds for time interval greater than 90 days between RAI treatment and success (OR:1.28, 95% CI:1.02, 1.61, p = 0.03). Demographics, prior treatment history, and iodine 131 RAI treatment variables were not significantly associated with time interval greater than 90 days between RAI treatment and success.**

Conclusion: **Thyroid function measured by FT4 was significantly associated with time interval greater than 90 days between RAI treatment and success. We suggest that the thyroid function variable of FT4 levels at initial diagnosis is most helpful for understanding the prognosis and success rate for using RAI treatment in patients with Graves' disease.**

Keywords: Graves disease, Hyperthyroidism, Autoimmune diseases, Therapeutics

1. Introduction

Graves' disease is the most common cause of hyperthyroidism.[1] As an autoimmune disease, the pathogenesis of Graves' disease is the production of thyrotropin receptor antibodies (TRAbs), including thyroid stimulating immunoglobulin (TSI), which target and stimulate thyroid stimulating hormone (TSH) receptors in the thyroid gland leading to excess thyroid hormone.[2] The American Thyroid Association recommends three effective modalities to treat Graves' disease of anti-thyroid drugs, radioactive iodine (RAI), and surgery.[3] Although anti-thyroid drugs are the first-line treatment modality, RAI is often favored over anti-thyroid drugs due to the undesired adverse effects of anti-thyroid drugs on hematologic or liver function.[3]

With regard to demographic variables and RAI treatment success, most studies report age is not associated with treatment success.[4-8] while one study reports that RAI success was associated with a lower mean age than RAI failure.[9] With regard to sex, most studies report sex is not associated with treatment success.[4,6-9] while one study reports that women had greater treatment success than men.[5] With regard to race/ethnicity, whites, Blacks, and Hispanics did not differ for RAI success.[5] Body mass index was not associated with RAI success.[10]

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There are mixed findings regarding prior treatment history. One study reports that prior antithyroid drug (ATD) therapy of propylthiouracil was associated with RAI treatment failure while methimazole was not associated with RAI treatment failure.[8] However, other studies do not report any association of any prior ATD therapy with RAI treatment failure.[5,7] Patients receiving the surgical procedure of thyroidectomy often have high treatment success with one study reporting 99% success.[5] Patients who had unsuccessful thyroidectomy had increased RAI treatment success.[4] One study reports 38.4 days as the mean number of days from the time of diagnosis to RAI treatment but did not include this variable in their multivariate analysis for RAI treatment success.[5]

Regarding the iodine 131 RAI treatment process, larger thyroid size is associated with treatment failure.[6,7,11] There are mixed findings for RAI 24 h uptake. One study reports a greater percentage of update associated with treatment success[10] while others report that RAI 24 h uptake is not associated with treatment success.[7-11,] Higher RAI dose is associated with increased treatment success.[12] Higher initial FT4 levels are associated with increased RAI failure[7,13] Also, a meta-analysis reported that FT3, TSH, and TSI were each not associated with RAI failure.[13]

Among the many studies determining variables associated with RAI treatment success in Graves' disease patients, only one study mentioned days from the time of diagnosis to treatment but did not include this variable in their multivariate analysis.[5] It is possible that delay in obtaining treatment can worsen the disease process and negatively impact treatment options. Also, many of the studies do not comprehensively include in a multivariate analysis the variables from all four factors of demographics, prior treatment history, iodine 131 RAI treatment process, and thyroid function prior to RAI treatment. We are aware of only one study that includes variables from these four factors and was conducted in a Chinese sample.[7] Our study focused on variables from these four factors and their association with a time interval greater than 90 days between RAI treatment and success in a diverse multi-racial/ethnic sample from the United States.

2. Methods

2.1. Setting

This was a retrospective study of 106 patients of the 129 patients with Graves' disease seen from September 2010 through September 2022 at a public hospital located in suburban New York City. The 23 patients who did not follow up for treatment and were excluded consisted of 18 without health insurance, 3 with public insurance, and 2 with private insurance. Inclusion criteria were those diagnosed with Graves' disease and successfully treated with RAI. Patients who failed RAI treatment were excluded. Patients with previous thyroid malignancies, successful treatment without RAI, and those lost to follow-up were excluded. Diagnosis criteria used to classify Graves' disease were elevated free thyroxine (FT4) (≥1.8 ng/dl), elevated total triiodothyronine (FT3) (≥182 pg/mL), suppressed thyroid stimulating hormone (TSH) (<0.55 uIU/mL), and elevated TSI (≥140%). Patient's thyroid weight (as estimated by the clinician based upon physical examination and sonographic findings), dose factor, and radiation uptake equation algorithm (weight of thyroid gland in grams X 100–120 uCi per gram/24 h RAI uptake expressed as decimal X 1000) were used to calculate RAI dose for each treatment. Successful RAI treatment was defined as patient follow-up visit with normal FT4 (0.8–1.79 ng/dL) and normal FT3 (60–181 pg/mL) levels. This study was ethically conducted and received approval from the Nassau Health Care Corporation Institutional Review Board (#22–414). A waiver for informed consent was obtained due to the retrospective nature of the study.

2.2. Variables

Patient demographic variables were age (years), sex (male/female), race/ethnicity (white, black, Hispanic, other), body mass index (kg/m^2), and insurance (private, public, self-pay). Patient prior treatment history variables were ATD (no/yes), prior thyroid surgery (no/yes), and time interval between diagnosis and RAI treatment (days). Patient iodine 131 RAI treatment variables were thyroid size (grams), RAI uptake in 24 h (percentage), and iodine dose (mCi). Patient thyroid function prior to RAI treatment variables were TSI (%), TSH [uIU/mL], FT3 [pg/ml], and FT4 (ng/dl). The outcome variable was time interval greater than 90 days between RAI treatment and success (no/yes). Success required both FT4 and FT3 levels to be within normal range. This cutoff value was chosen based upon a priori clinical experience for determining if RAI treatment for Graves' disease is successful for a patient.

2.3. Statistical analysis

Mean and standard deviation described the continuous variables. Frequency and percentage

described the categorical variables. Univariate logistic regression was performed for each of the predictor variables. All p-values were two tailed with alpha level for significance at $p < 0.05$. IBM SPSS Statistics version 29 was used for the analyses (IBM Corporation, Armonk, NY, 2022).

3. Results

Table 1 shows the sample characteristics for the 106 patients. Demographic variables consisted of a mean age of 49 years, more than three-quarters were female, more than half were Hispanic race/ethnicity, mean BMI was below 30, and almost three-quarters used self-pay insurance. Prior treatment history variables consisted of more than one-third with anti-thyroid medication, only one person had prior thyroid surgery, and the mean time interval between diagnosis and RAI treatment was 241 days. Iodine 131 RAI treatment variables consisted of mean thyroid size of 63.1 g, mean RAI uptake percentage at 24 h of 59.4, and mean iodine dose of 11.1 mCi. Thyroid function prior to RAI treatment variables consisted of mean TSI of 313.7%, TSH of 0.01 uIU/mL, FT3 of 359.0 pg/mL, and FT4 of 3.3 ng/dL. There were 62.3% that had a time interval greater than 90 days between RAI treatment and success.

Table 2 shows univariate logistic regression analyses for the outcome of time interval greater than 90 days between RAI treatment and success. None of the demographic, prior treatment history, or iodine 131 RAI treatment variables were significantly associated with the outcome. The thyroid function prior to RAI treatment variable of FT4 had statistically significantly increased odds for time interval greater than 90 days between RAI treatment and success (OR:1.28, 95% CI:1.02, 1.61, $p = 0.03$). FT4 as a categorical variable with abnormal of 1.8 and higher was also statistically significantly associated with increased odds for time interval greater than 90 days between RAI treatment and success (OR: 2.75, 95% CI: 1.16, 6.51, $p = 0.02$). None of the other thyroid function prior to RAI treatment variables of TSI, TSH, or FT3 were significantly associated with time interval greater than 90 days between RAI treatment and success.

4. Discussion

The only pre-RAI treatment variable which we found to be associated with time interval greater than

Table 1. Sample characteristics of the 108 Graves' disease patients.

Variables	M (SD) or Frequency (%)
Demographics	
Age (years) [mean]	49.1 (13.98)
Sex (female)	83 (78.3)
Race/ethnicity	
White	14 (13.2)
Black	25 (23.6)
Hispanic	59 (55.7)
Other	8 (7.5)
Body mass index (kg/m^2) [mean]	29.7 (6.69)
Insurance	
Private	15 (14.2)
Public	14 (13.2)
Self-pay	77 (72.6)
Prior Treatment History	
Anti-thyroid drug (yes)	36 (34.0)
Prior thyroid surgery (yes)	1 (0.9)
Time interval between diagnosis and RAI treatment (days) [mean]	241.2 (230.40)
Iodine 131 RAI Treatment	
Thyroid size (grams) [mean]	63.1 (26.29)
RAI uptake 24 h (percentage) [mean]	59.4 (17.83)
Iodine dose (mCi) [mean]	11.1 (4.98)
Thyroid Function Prior to RAI Treatment	
Thyroid stimulating immunoglobulin (TSI) [mean of the %]	313.7 (161.73)
Thyroid stimulating hormone (TSH) (uIU/mL) [mean]	0.01 (0.03)
Total triiodothyronine (FT3) (pg/mL) [mean]	359.0 (207.76)
Free thyroxine (FT4) (ng/dL) [mean]	3.3 (2.03)
Outcomes	
Time interval between RAI treatment and success greater than 90 days (yes)	66 (62.3)

Note: RAI = radioactive iodine. Anti-thyroid medication of methimazole. No one used propylthiouracil.

Table 2. Univariate logistic regression analyses for time interval more than 90 days between radioactive iodine treatment and success.

Variables	OR (95% CI)	p-value
Demographics		
Age (years) [mean]	0.98 (0.96, 1.01)	0.23
Sex (female)	1.36 (0.53, 3.47)	0.52
Race/ethnicity		
White	1.00	
Black	0.99 (0.25, 3.87)	0.99
Hispanic	0.87 (0.26, 2.92)	0.82
Other	0.93 (0.15, 5.61)	0.93
Body mass index (kg/m^2)	1.05 (0.99, 1.12)	0.14
Insurance		
Private	1.00	
Public	4.19 (0.82, 21.40)	0.09
Self-pay	1.89 (0.62, 5.76)	0.26
Prior Treatment History		
Anti-thyroid drug (yes)	0.65 (0.29, 1.48)	0.31
Prior thyroid surgery (yes)	9.9×10^8 (—, —)	1.00
Time interval between diagnosis and RAI treatment (days)	1.001 (0.999, 1.003)	0.23
Iodine 131 RAI Treatment		
Thyroid size (grams)	1.00 (0.99, 1.02)	0.97
RAI uptake 24 h (percentage)	1.01 (0.99, 1.03)	0.52
Iodine dose (mCi)	0.99 (0.91, 1.07)	0.74
Thyroid Function Prior to RAI Treatment		
Thyroid stimulating immunoglobulin (TSI) (%)	1.001 (0.999, 1.004)	0.32
Thyroid stimulating hormone (TSH) (uIU/mL)	65.23 (<0.001, 1.2×10^8)	0.57
Total triiodothyronine (FT3) (pg/mL)	1.001 (0.999, 1.003)	0.18
Free thyroxine (FT4) (ng/dL)	1.28 (1.02, 1.61)	0.03

Note: OR = odds ratio, CI = confidence interval, RAI = radioactive iodine. Free thyroxine as a categorical variable with abnormal of 1.8 and higher was also statistically significant (OR: 2.75, 95% CI: 1.16, 6.51, p = 0.02).

90 days between RAI treatment and success was the measure of thyroid function by FT4. Increased FT4 was significantly associated with time interval greater than 90 days between RAI treatment and success. None of the demographic, prior treatment history, iodine 131 RAI treatment variables, or other measures of thyroid function of TSI, TSH, and FT3 were significantly associated with time interval greater than 90 days between RAI treatment and success.

We found that the measure of thyroid function by FT4 was significantly associated with time interval greater than 90 days between RAI treatment and success. This pattern occurred for the continuous variable of increased FT4 and for the categorical variable of abnormal FT4 of 1.8 and higher. However, none of the other measures of thyroid function of TSI, TSH, and FT3 were significantly associated with time interval greater than 90 days between RAI treatment and success. We are unaware of any literature studying measures of thyroid function and time interval greater than 90 days between RAI treatment and success. A meta-analysis of RAI treatment failure reports for measures of thyroid function that higher initial FT4 levels are associated with increased RAI failure while FT3, TSH, and TSI were each not associated with RAI failure.[13] Our study has a similar pattern and shows that FT4 is associated with the outcome and not the other measures of thyroid function of FT3, TSH, and TSI. Circulatory FT4 hormone is a prohormone that is converted to the active form of FT3 by deiodination.[14] Genetic polymorphism has been shown to both increase (Type 1) and (decrease Type 2) conversion of FT4 to FT3.[15,16] We speculate that deiodinase activity at the cellular level may impact why FT4 is associated with our outcome but not FT3. Our findings for FT4 also suggest that those with abnormal FT4 levels take longer time for treatment success. Clinicians should be aware of this point when considering treatment options.

We did not find any association of demographic variables with time interval greater than 90 days between RAI treatment and success. We are unaware of any literature studying demographic variables and time interval greater than 90 days between RAI treatment and success. Previous literature typically does not report any association of demographic variables with RAI treatment failure.[4-8] Our study has a similar pattern. We suggest that demographic variables do not impact treatment prognosis since the thyroid gland is not altered by demographic variables of age, sex, or race/ethnicity.

We did not find any association of prior treatment history with time interval greater than 90 days

between RAI treatment and success. We are unaware of any literature studying prior treatment history and time interval greater than 90 days between RAI treatment and success. Previous literature for prior treatment history has mixed findings of ATD treatment prior to RAI therapy where some report ATD are beneficial while others report that ATD are not beneficial.[5,7,8] Our study has findings similar to those showing no association of ATD. We speculate that if ATD treatments are discontinued appropriately prior to the RAI treatment, their inhibitory action on intrathyroidal metabolism is eliminated and thus does not impact the success in any manner including the time interval from treatment to success.

We did not find any association of iodine RAI treatment variables with time interval greater than 90 days between RAI treatment and success. We are unaware of any literature studying iodine 131 RAI treatments with time interval greater than 90 days between RAI treatment and success. Previous literature for iodine 131 RAI treatment has mixed findings on RAI 24-h uptake where one study reports a greater percentage of uptake associated with treatment success[10] while others report RAI 24-h uptake is not associated with treatment success.[7-11] Our study has findings similar to those showing no association of RAI 24-h uptake with treatment success. We suggest that although RAI 24-h uptake indicates the efficiency of the thyroid gland trapping iodine, it is not informative for prognosis for time interval greater than 90 days between RAI treatment and success.

A strength of this study is the diverse racial/ethnic sample. This study has several limitations. First, we excluded certain patients from our sample since they did not return for a follow-up post RAI dose and this may suggest bias in our sample. Second, our diverse racial/ethnic sample may have certain characteristics that are not generalizable to a non-diverse racial/ethnic sample.

In conclusion, we found measurement of thyroid function by FT4 was significantly associated with time interval greater than 90 days between RAI treatment and success. We suggest that the thyroid function variable of FT4 levels at initial diagnosis is most helpful for understanding the prognosis and success rate for using RAI treatment in patients with Graves' disease.

Ethics information

This study was ethically conducted and received approval from the Nassau Health Care Corporation Institutional Review Board (#22-414).

Author contributions

Luis E. Joya: data acquisition, data interpretation, manuscript drafting, approval of final version; Joshua Fogel: study design, data analysis, data interpretation, manuscript critically reviewing for important intellectual content, approval of final version; Kaushik Mandal: study design, data acquisition, manuscript critically reviewing for important intellectual content, approval of final version; David S. Rosenthal: study design, data interpretation, manuscript critically reviewing for important intellectual content, approval of final version.

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Conflicts of interest

The authors have no conflicts of interest.

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