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PREDICTORS OF EARLY-ONSET OVERT HYPOTHYROIDISM IN HYPERTHYROID PATIENTS TREATED WITH RADIOIODINE

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Abstract

Objectives: Radioiodine (RAI) treatment with iodine-131 is a safe and effective approach that is widely used for treating hyperthyroidism. Although euthyroidism is the optimal outcome of this treatment, some patients will eventually develop hypothyroidism requiring hormone replacement. In this context, we aimed to investigate the predictive factors for early-onset overt hypothyroidism developing within two months after the RAI treatment.

Materials and Methods: All hyperthyroid patients treated with RAI between March 2019 and March 2022 were screened retrospectively. Patients with thyroid function tests within two months after the treatment were included in the final analyses. Baseline clinical characteristics, including pre-treatment imaging modalities and laboratory tests, were retrieved from the institutional database. Predictors of early-onset overt hypothyroidism were determined with a multivariable logistic regression model.

Results: Seventy-two patients (44% female, median age 42 years) were included in the study. Twenty-four patients (33.3%) developed overt hypothyroidism within two months after the treatment. Multivariable logistic regression analysis revealed that the appearance of a diffuse goiter in ultrasound (OR= 4.33, 95% CI= 1.15–16.28, p= 0.030) and the dose of RAI per thyroid volume (OR= 4.30, 95% CI= 1.38–13.45, p= 0.012) were independently associated with the risk of early-onset hypothyroidism after RAI treatment.

Conclusion: The RAI dose per thyroid volume and the appearance of a diffuse goiter in ultrasound were significantly associated with an increased risk of early-onset overt hypothyroidism after RAI treatment. If validated in larger cohorts, these parameters could have a role in predicting the need for early hormone replacement in hyperthyroid patients treated with RAI.

Keywords: Hyperthyroidism, radioiodine, overt hypothyroidism.

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Introduction

Hyperthyroidism is a prevalent thyroid disorder seen in up to 2% of women (tenfold more than men) in iodine-replete communities.[1] The current therapeutic strategies for treating hyperthyroidism include antithyroid drugs (ATDs), radioiodine (RAI) and thyroidectomy. RAI treatment with iodine-131 (I-131) has been increasingly used as a safe and effective approach for treating hyperthyroidism ever since its introduction in 1941.[2-4] I-131 is a radioactive isotope of stable iodine that demonstrates thyroidal uptake with the same uptake mechanism and leads to cellular damage and volume reduction by emitting radioactive beta particles. These physical and biological features of I-131 make it an ideal radionuclide for treating all major causes of hyperthyroidism.[5]

The optimal dose of RAI should be high enough to cure hyperthyroidism and low enough to avoid the risk of RAI-induced hypothyroidism.[6] Empirical fixed-dose approach has been the most practical and the most common method for dose planning. Accordingly, I-131 is administered at a dose of 10-15 mCi in case of Graves' disease,[5] and the dose is increased to 15-30 mCi in cases of toxic nodular or multinodular goiter.[7] To date, empirical high-dose has been the most preferred approach in many centers to cure hyperthyroidism at the expense of developing hypothyroidism and to prevent the necessity of a second RAI treatment.[8,9] Maintaining stability with hormone replacement in case of RAI-induced hypothyroidism is a common and manageable practice. However, it makes the patient perpetually dependent on thyroid hormone replacement.

Regular follow-up after the RAI treatment involves periodical thyroid function tests (TFTs) and thyroid ultrasound (US). The practice guidelines by the Turkish Society of Endocrinology and Metabolism and the Turkish Society of Nuclear Medicine suggest the assessment of thyroid functions at two months following RAI treatment.[10,11] However, outcomes of the treatment can occasionally develop even sooner, and some patients may require early hormone replacement for improved management.

In this context, we sought to evaluate the frequency of overt hypothyroidism onsetting within two months after the RAI treatment and to investigate the predictors of this phenomenon.

Materials and Methods

Patient Selection

Hyperthyroid patients that received RAI treatment in our institution between March 2019 and March 2022 were screened retrospectively. Patients who underwent TFTs within two months (60 days) after the treatment were included in the study. Exclusion criteria were (a) receiving more than one episode of RAI treatment during the study period, (b) absence of TFTs within two months after treatment, and (c) failure to access baseline clinical characteristics. The records of thyroid ultrasonography, scintigraphy and radioiodine uptake (RAIU) test, as well as the levels of thyroid stimulating hormone (TSH), free thyroxine (fT4) and free triiodothyronine (fT3) within the two months after treatment was pulled from the institutional database. Informed consent was obtained from all participants included in the study. The institutional ethics committee approved the study (Approval no: E2-22-2069).

Estimation of Pre-treatment Thyroid Volume

The volume of each lobe of the thyroid gland was estimated according to the previously suggested formula:[12]

[Volume (mL) = Length (cm) × Depth (cm) × Width (cm) × $\pi/6$] by using the dimensions derived from pre-treatment US. The total thyroid volume was found by adding the volumes of both lobes, with the isthmus not being taken into account. The RAI dose per thyroid volume was calculated by dividing the total administered dose by the volume of the thyroid gland.

Administration of Radioiodine

The dose of RAI was determined empirically for each patient and varied between 7 and 25 mCi, with a median (IQR) of 15 (10 – 20) mCi. The most frequently administered dose was 10 mCi (n=31, 43.06%), followed by 15 mCi (n=28, 38.89%). Patients were placed on an iodine-restricted diet starting two weeks before the treatment to ensure adequate RAI uptake. Pharmaceuticals that could potentially affect the accumulation of RAI in the thyroid tissue were discontinued before the treatment (e.g., ATDs, corticosteroids, iodized compounds). Patients were tried to be made euthyroid before the treatment to prevent a possible thyroid storm that may develop due to RAI-induced cell damage. All patients fasted for 4-6 hours before the treatment. RAI was administered orally and patients were released from the hospital after two hours.

Treatment Outcomes

The primary outcome was the onset of overt hypothyroidism according to levels of TSH, fT4 and fT3 within two months after RAI treatment. Overt hypothyroidism was defined as the presence of clear hypothyroidism

characterized by an increase in TSH level along with a decrease in fT3 and fT4 levels. All TFTs were performed using the same immunoassay system throughout the study period. The limit of detection for TSH was 0.008 mU/L. The results below this value were assigned the value of 0.008 for the sake of statistical analyses. The accepted normal ranges for TSH and fT4 were 0.55 – 4.78 mU/L and 0.89 – 1.76 ng/dL, respectively. None of the patients had undergone multiple TFTs within the study period, so the selection of a particular assay was not required.

Statistical Analyses

Continuous variables are expressed as median (interquartile range, IQR), and categorical variables as frequency (percentage). The two samples T-test was used to compare independent means. A multivariable logistic regression model was built using the variables that demonstrated substantial association in the univariable analysis. Statistical analyses were performed using the R statistical package (R Foundation for Statistical Computing, Vienna, Austria) and Stata/MP 16 (Stata Corporation, College Station, Texas, USA) software. A p-value below 0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 72 patients (61% female) were included in the final analyses. The median (IQR) age was 42 (36–55) years. The characteristics of the study population are presented in Table 1. The median (IQR) values of baseline TSH, fT4 and fT3, were 34 (8 – 662) mU/L, 1.14 (0.96 – 1.31) ng/dL and 3.40 (3.02 – 3.93) ng/dL, respectively.

All patients had undergone thyroid US within 12 months before the RAI treatment. The median (IQR) time between the US and the RAI treatment was 90 (56 – 172) days. Baseline thyroid volume ranged between 5.09 and 88.61 mL, with a median (IQR) of 17.31 (12.94 – 22.75) mL. According to baseline US findings, 33 patients (45.83%) had diffuse goiter, while 16 patients (22.22%) had a solitary nodular goiter and 23 patients (31.95%) had a multinodular goiter.

Thyroid scintigraphy was performed in 47 patients (65.28%) within 12 months before RAI treatment. The median (IQR) time between the scintigraphy and the RAI treatment was 56 (24 – 124) days. Accordingly, 25 patients had a diffusely active gland, four had toxic adenoma, and 11 had a multinodular goiter. Twenty-five patients (34.72%) had undergone a radioiodine uptake test (RAIU) within two months before the treatment. The median (IQR) time between RAIU and the treatment was 17 (13 – 25) days. The median (IQR) values of RAIU at 4- and 24-hours were 46% and 67%, respectively.

Table 1. Characteristics of the study population (n=72)*

Sociodemograhics (n=72)	
Age, *years*	42 (36 – 55)
Sex	
Male	28 (38.89)
Female	44 (61.11)
Baseline Thyroid Functions (n=72)	
TSH, *mU/L*	34 (8 – 662)
Free T4, *ng/dL*	1.14 (0.96 – 1.31)
Free T3, *ng/dL*	3.40 (3.02 – 3.93)
Baseline Ultrasound (n=72)	
Thyroid Volume, *mL*	17.31 (12.95 – 22.76)
Diffuse Goiter	33 (45.83)
Solitary Nodular Goiter	16 (22.22)
Multinodular Goiter	23 (31.94)
Number of Nodules	1 (0 – 2)
Baseline Scintigraphy (n=47)	
Normal	7 (14.89)
Diffuse Active	25 (53.19)
Toxic Adenoma	4 (8.51)
Multinodular Goiter	11 (23.40)
Baseline Radioiodine Uptake Test (n=25)	
Uptake at 4 hours, *%*	46 (43 – 60)
Uptake at 24 hours, *%*	67 (59 – 86)

*Continuous variables are presented as median (interquartile range) and categorical variables are presented as frequency (percentage).

Treatment Outcomes

An overview of dosimetric parameters and treatment outcomes is presented in Table 2. The median (IQR) levels of TSH, fT4 and fT3 within two months after the RAI treatment were 28.71 (4.64 – 438.51) mU/L, 1.05 (0.69 – 1.36) ng/dL and 2.67 (2.07 – 3.68) ng/dL, respectively. The early outcome of RAI treatment was specified as overt hypothyroidism in 24 patients (33.33%), subclinical hypothyroidism in 28 patients (38.89%), euthyroidism in 4 patients (5.56%), subclinical hyperthyroidism in 3 patients (4.17%) and overt hyperthyroidism in 6 patients (8.33%). Seven patients could not be classified as any of these clinical conditions, as 5 of them had a low fT4 and normal TSH, while two had elevated values for both fT4 and TSH.

Table 2. Dosimetric parameters and early treatment outcomes*

Dosimetric Parameters (n=72)	
RAI Dose, *mCi*	15 (7 – 25)
RAI Dose per Volume, *mCi/mL*	0.77 (0.52 – 1.08)
Post-treatment Thyroid Functions (n=72)	
TSH, *mIU/L*	28.71 (4.63 – 438.51)
Free T4, *ng/dL*	1.05 (0.69 – 1.35)
Free T3, *ng/dL*	2.67 (2.07 – 3.68)
Early Treatment Outcomes (n=72)	
Overt Hypothyroidism	24 (33.33)
Subclinical Hypothyroidism	28 (38.89)
Euthyroidism	4 (5.56)
Subclinical Hyperthyroidism	3 (4.17)
Overt Hyperthyroidism	6 (8.33)
Other	7 (9.72)

*Continuous variables are presented as median (interquartile range) and categorical variables are presented as frequency (percentage).

Predictors of Early-Onset Overt Hypothyroidism

Table 3 shows the comparison of parameters between the patients that did and did not develop overt hypothyroidism within two months after the RAI treatment. The mean RAI dose per thyroid volume was significantly higher in patients with early-onset overt hypothyroidism (1.11 vs. 0.79 mCi, p=0.023). Other parameters, including the total RAI dose or the thyroid volume alone, were not significantly different across the two groups.

A multivariable logistic regression model was built using the parameters that could hypothetically have an impact on the treatment outcomes (Table 4). The scintigraphic uptake pattern and RAIU test were excluded from the model due to a large amount of missing data. Accordingly, the RAI dose per thyroid volume (OR= 4.345, 95% CI= 1.382 – 13.664, p= 0.012) and the appearance of a diffuse goiter in the baseline US (OR= 3.680, 95% CI= 1.003 – 13.505, p= 0.030) were independently associated with increased risk of early-onset overt hypothyroidism after the RAI treatment.

Table 3. Comparison of patients that did and did not develop overt hypothyroidism within the study period.*

	Early-Onset Overt Hypothyroidism		p-value
	Yes (n=24)	No (n=48)	
Age, *years*	44 (37.5 – 54)	42 (35 – 58)	0.620
Male	8 (33)	20 (42)	0.490
RAI Dose, *mCi*	15 (10 – 15)	15 (10 – 15)	0.460
Thyroid Volume, *mL*	21.11 (21.17)	20.45 (10.62)	0.860
RAI Dose per Volume, *mCi/mL*	1.11 (0.78)	0.79 (0.41)	0.023*
Diffuse Goiter in Ultrasound	14 (58)	19 (40)	0.130
Uptake at 4 hours, *%*	54.11 (17.06)	48.01 (18.88)	0.450
Uptake at 24 hours, *%*	73.17 (16.76)	70.00 (18.52)	0.680

* Continuous variables are presented as median (min-max) and categorical variables are presented as frequency (percentage).

Table 4. Multivariable logistic regression model for identifying the predictors of early-onset overt hypothyroidism after the RAI treatment

Parameter	Odds Ratio	95% Confidence Interval	p-value
Age	1.011	0.963 – 1.060	0.664
Sex	1.039	0.270 – 3.993	0.755
RAI Dose per Volume, *mCi/mL*	4.345	1.382 – 13.664	0.012*
The appearance of Diffuse Goiter in US	3.680	1.003 – 13.505	0.049*
Diffuse Active Gland in Scintigraphy	2.179	0.608 – 7.811	0.232
Baseline fT4, *ng/dL*	0.107	0.010 – 1.103	0.060

Discussion

In this study, we investigated the predictive factors for overt hypothyroidism developing within two months after the RAI treatment and found that the RAI dose per thyroid volume and the appearance of a diffuse goiter in US were independently associated with this phenomenon. Other characteristics, including age, sex and baseline TFTs, did not demonstrate significant association with the study outcome.

RAI treatment is a long-known, safe and effective approach that is widely used for treating hyperthyroidism through radiation-induced volume reduction.[5] Although higher doses of RAI will necessarily improve treatment success by leading to better volume reduction. An increased dose is also associated with the risk of RAI-induced hypothyroidism.[13] According to our results, the RAI dose alone or the baseline thyroid volume

alone were not associated with the development of early overt hypothyroidism. Instead, an alternative measure, the RAI dose per unit volume of the thyroid gland, was significantly associated with an increased risk of early-onset overt hypothyroidism. This parameter was derived by dividing the total RAI dose by the volume of the thyroid gland in an attempt to have a better insight into the radiation burden of the thyroid gland. There have been previous studies reporting the separate roles of higher RAI dose and smaller thyroid volume in the development of post-treatment hypothyroidism.[14] To the best of our knowledge, this is the first study incorporating the relative RAI dose with respect to thyroid volume as a parameter for predicting post-treatment hypothyroidism.

The appearance of a diffuse goiter in the pre-treatment US was yet another predictive parameter for the early development of overt hypothyroidism after the RAI treatment. Diffuse goiter is defined as the uniform enlargement of the thyroid gland and differs from multinodular goiter by the absence of nodules. In the literature, data revealing the effect of diffuse goiter and nodularity on the outcome of hypothyroidism are not sufficient. Generally, the relationship between nodule volume and treatment success or the effect of RAI treatment on nodule volume has been investigated. Schiavo et al. reported that nodule volume was inversely correlated with the treatment efficacy.[15]

According to our results, the baseline levels of TSH and fT4 were not associated with the risk of early-onset overt hypothyroidism after the RAI treatment. These findings are in line with previous studies investigating the association between baseline TFTs and treatment outcomes.[16-18] There are several other factors that could potentially have an impact on the outcome of the RAI treatment, e.g., use of ATDs, corticosteroids, age of onset, adherence to low-iodine diet or smoking habits. These covariates will usually be influenced by the clinical condition and the age of the patient. Nevertheless, further studies are needed to investigate their independent impact on early treatment outcomes.

Almost one-fourth of the patients in our cohort (n=20, 27.7%) did not develop overt or subclinical hypothyroidism within the study period. However, it has been previously shown that the transition to hypothyroidism may continue in the following months. Ahmad et al. shared that the overall cumulative incidence of hypothyroidism following the RAI treatment was 38.2% after six months and increased to 55%, 66%, 69% and 86% after 1, 3, 5 and 10 years, respectively.[19] A gradual increase in the incidence of post-RAI hypothyroidism was reported in several other studies.[13,20,21] Further studies may focus on developing clinical nomograms to predict the time of onset for the treatment outcomes.

Our results should be interpreted in the context of some limitations. Firstly, the relatively small size of the study population may fail to represent the true nature of the general population. These results should be validated with larger multi-centric cohorts. Secondly, we were unable to include scintigraphic findings and RAIU values

in the prediction model due to a substantial amount of missing data. Lastly, this was a retrospective, observational study that could be prone to recall bias.

In conclusion, our results indicate that the RAI dose per thyroid volume and the appearance of a diffuse goiter in baseline US were significantly associated with an increased risk of developing overt hypothyroidism within two months after the RAI treatment. If validated in larger cohorts, these parameters could have a role in predicting the need for early hormone replacement in hyperthyroid patients treated with RAI.

Ethical Considerations: Informed consent was obtained from all individual participants included in the study. The institutional ethics committee approved the study (Approval no: E2-22-2069).

Conflict of Interest: The authors declare no conflict of interest.

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