Original Article

# Predictive value of pyramidal lobe, percentage thyroid uptake and age for ablation outcome after 15 mCi fixed dose of radioiodine-131 in Graves' disease

**Maseeh uz Zaman, Nosheen Fatima[1], Unaiza Zaman[2], Zafar Sajjad, Areeba Zaman[2], Rabia Tahseen[2]**

Department of Radiology, Section of Nuclear Medicine, Aga Khan University Hospital, [1]Department of Nuclear Medicine, Dr. Ziauddin Hospital, [2]Dow Medical College, Dow University of Health Sciences, Karachi, Pakistan

ABSTRACT

**Purpose:** The purpose was to find out the efficacy of fixed 15 mCi radioactive iodine-131 (RAI) dose and predictive values of various factors for inducing hypothyroidism in Graves' disease (GD). **Materials and Methods:** Retrospective study conducted from January 2012 till August 2014. Patients with GD who had a technetium-99m thyroid scan, thyroid antibodies, received fixed 15 mCi RAI and did follow endocrine clinics for at least 6 months were selected. RAI was considered successful if within 6 months of RAI therapy patients developed hypothyroidism. **Results:** Of the 370 patients with GD who had RAI during study period, 210 (57%) qualified study criteria. Mean age of patients was 48 ± 15 years with female: male ratio of 69:31, positive thyroid antibodies in 61%, means thyroid uptake of 15.09 ± 11.23%, and presence of pyramidal lobe in 40% of total population. Hypothyroidism was achieved in 161 (77%) patients while 49 (23%) patients failed to achieve it (remained either hyperthyroid or euthyroid on antithyroid medication). Patients who became hypothyroid were significantly younger with higher proportion of presence of thyroid antibodies and pyramidal lobe and lower percentage thyroid uptake than those who failed. Multiple logistic regression analysis revealed that age (odds ratio; OR = 2.074), pyramidal lobe (OR = 3.317), thyroid antibodies (OR = 8.198), and percentage thyroid uptake (OR = 3.043) were found to be significant prognostic risk factors for post-RAI hypothyroidism. Gender was found to have nonsignificant association with the development of hypothyroidism. Receiver operating characteristic analysis revealed age <42 years and thyroid uptake <15% as threshold values for the development of post-RAI hypothyroidism. **Conclusion:** We conclude that fixed (15 mCi) RAI dose is highly effective in rendering hypothyroidism in patients with GD. Age (≤42 years), thyroid uptake (≤15%) and presence of pyramidal lobe are strong predictors of hypothyroidism and must be considered for selecting optimal RAI dose.

**Keywords:** Fixed dose, Graves' disease, pyramidal lobe, radioiodine-131, thyroid uptake

## INTRODUCTION

Graves' disease (GD) is the most common cause of hyperthyroidism accounting for about 90% of cases with a female preponderance.[1] It is an autoimmune disorder heralded by circulating thyrotropin receptor antibodies (TRAbs) stimulating the thyroid stimulating hormone (TSH) receptors resulting in excessive production of thyroid hormones.[2] Treatment of GD comprised of antithyroid drugs (methimazole and propylthiouracil), radioactive iodine-131 (RAI), and thyroidectomy. RAI is the therapy of choice in the USA, being selected by 60% of thyroid specialists who responded to a survey in 2011, but only 13% of European thyroid specialists[3] and even lower selection in United Kingdom and Australia as well.[4,5]

The primary objective of RAI is to render the patient euthyroid, with hypothyroidism considered as a disadvantage. However, the most effective dose of RAI to achieve euthyroid in GD is debatable. Literature is flooded with studies comparing adjusted dose approaches and fixed dose protocols with no superiority of either to achieve euthyroid status and rate of hypothyroidism is high with either approach.[1] Due to these inconsistent results, American Thyroid Association (ATA) and American Association of Clinical Endocrinologists (AACE) in its 2011 guidelines has

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**Address for correspondence:**
Dr. Maseeh uz Zaman, Department of Radiology, Aga Khan University Hospital, Karachi, Pakistan. E-mail: maseeh.uzzaman@aku.edu

recommended (recommendation number 8) 10–15 mCi of I-131 with a goal to control hyperthyroidism by rendering patients hypothyroid.[2]

There has been ample evidence that apart from RAI dose, there are various risk factors such as age, gender, severity of GD, size of goiter, and presence of TRAbs and thyroid antibodies associated with ablation outcome in GD.[1] Data are conflicting about the effect of antithyroid drugs on the efficacy of RAI therapy.[6] Similarly, data are scanty about the values of independent risk factors to estimate the probability of post-RAI hypothyroidism.[7] Such estimates would help the treating physicians to select lower or higher fixed dose of RAI in patients with higher or lower probabilities for hypothyroidism, respectively.

The aim of this study was to find out the efficacy of a fixed 15 mCi RAI dose and predictive values of various factors for inducing hypothyroidism in patients with GD.

## MATERIALS AND METHODS

This was a retrospective study conducted at Nuclear Medicine sections of Aga Khan University Hospital, Karachi, Pakistan (January 2012 to August 2014) and Dr. Ziauddin Hospital Karachi, Pakistan (April 2013 to August 2014). Records of all patients with GD who were treated with RAI during the study period were evaluated. Patients who had a technetium-99m ($^{99m}$Tc) pertechnetate thyroid scan, thyroid antibodies, have had 15 mCi fixed dose of RAI and had followed endocrine clinics for at least 6 months were selected as the study cohort. Patients with GD, who did not meet these criteria were excluded. RAI was considered successful if within 6 months of fixed dose patients developed hypothyroidism (TSH >4.2 uIU/ml and/or FT4 <0.9 ng/ml) with definitive discontinuation of antithyroid medications.

Thyroid scintigraphy was performed with 3–5 mCi of $^{99m}$Tc pertechnetate injected intravenously and after 20 min multiple static images were acquired under single or dual head gamma cameras fitted with low energy high resolution collimators (ECAM, Siemens, Germany). Thyroid uptake was calculated using commercial software and a value of 0.5–3.5% was considered normal. All scans were reported by qualified nuclear physicians having more than 6-years of experience.

Serum TSH was measured using chemiluminescent assays with analytical sensitivity of 0.008 uIU/ml, functional assay sensitivity of 0.008 uIU/ml, and reportable range of 0.008–150 uIU/ml. Thyroid antibodies (antithyroglobulin [aTg] and antithyroid peroxidase [aTPO]) were measured using chemiluminescent assays with analytical assay sensitivity of 2.2 IU/ml, inter-assay precision of 4.6–5.8%, and intra-assay precision of 3.2–4.9% with reportable range of 20–3000 IU/ml and normal range of <40 IU/ml for aTg and <35 IU/ml for aTPO.

Radioiodine-131 treatment was administered in liquid form in a 15 mCi fixed dose as per ATA and AACE guidelines[2] (with a primary goal to render patients hypothyroid). As per department protocol patients were advised to stop antithyroid medication at least 3–5 days prior the RAI and restart 5 days later (as per physician's advice) and follow the measures to minimize radiation exposure to general public and family members.

### Statistical analysis

Data were analyzed using commercially available packages such as the MedCalc statistical software (MedCalc Software, Ostend, Belgium), version 11.3.10, and the Statistical Package for Social Sciences (SPSS version 17; SPSS Inc., Chicago, Illinois, USA). Comparisons between patient groups were made using the Student's *t*-test for continuous variables and the Chi-square test for categorical variables. Continuous variables were described by mean ± standard deviation. Receiver-operating characteristic curves (ROCs) were plotted to threshold for percentage thyroid uptake and age to discriminate between RAI treatment outcomes. For regression analysis, age, gender, thyroid uptake, and the presence of thyroid antibodies and pyramidal lobe were used as covariates. $P < 0.05$ were considered significant.

## RESULTS

During study period, 370 patients with GD had received RAI at two nuclear medicine departments and out of these, 210 (57%) patients qualified the study criteria. The mean age of the total study cohort was 48 ± 15 years with female: male ratio of 69:31 with positive thyroid antibodies in 61% of the total population. Thyroid scintigraphy revealed a mean thyroid uptake of 15.09% ± 11.23% and presence of pyramidal lobe in 40% of the total population [Table 1]. At 6 months after RAI therapy, 161 (77%) patients developed hypothyroidism (TSH >4.2 uIU/ml and/or FT4 <0.9 ng/ml) while 49 (23%) patients failed to achieve it (remained hyperthyroid or euthyroid on antithyroid medication). Inter-group analysis using Chi-square test revealed that patients who became hypothyroid were significantly younger with higher proportion of presence of thyroid antibodies and pyramidal lobe and lower percentage thyroid uptake on thyroid scan than those who failed to achieve hypothyroidism at 6 months after 15 mCi fixed dose of RAI. No significant difference was observed for female gender preponderance in either group [nonsignificant *P* value; Table 1]. Multiple logistic regression analysis revealed that age (odds ratio; OR = 2.074), pyramidal lobe (OR = 3.317), thyroid antibodies (OR = 8.198), and percentage thyroid uptake (OR = 3.043) were found to be significant prognostic risk factors for post-RAI hypothyroidism within 6 months. Gender was not found to have any significant association with the development of post-RAI hypothyroidism [Table 2].

Receiver operating characteristic analysis revealed age <42 years (sensitivity = 55.3%; specificity = 61.5%) and thyroid uptake <15% (sensitivity = 65.8%; specificity = 76.5%) as threshold values for the development of post-RAI hypothyroidism [Figures 1 and 2].

**Table 1: Patients' demographic with GD (*n*=210/370)**

| Variables | Total (*n*=210/370) 57% | Postablation hypothyroid (*n*=161/210) 77% | Ablation failure (*n*=49) 23% | $\chi^2$/*t*-test values ±95% CI | *P* |
|---|---|---|---|---|---|
| Age in years | | | | | |
| Mean±SD | 48±15 | 45±10 | 49±13 | 2.277 (0.5-7.5) | 0.023* |
| Female:Male (%) | 145:65 (69:31) | 114:47 (71:29) | 31:18 (63:37) | 0.783 (−7-24.5) | 0.376 |
| Pyramidal lobe (%) | 84 (40) | 74 (46) | 10 (20) | 9.531 (10-38.9) | 0.002* |
| Thyroid uptake (%) | | | | | |
| Mean±SD (range) | 15.09±11.23 (02-48) | 13.05±9.47 (02-45) | 16.19±10.47 (04-48) | 1.982 (0.01-6.26) | 0.048* |
| Thyroid antibodies (%) | | | | | |
| Positive | 129 (61) | 117 (73) | 12 (24) | 36.07 (32-61) | <0.0001* |
| Negative | 81 (39) | 44 (27) | 37 (76) | | |

*$P$<0.05. SD: Standard deviation, CI: Confidence interval, GD: Graves' disease

**Table 2: OR for postablation hypothyroidism against different variables in patients with GD treated with single fixed 15 mCi dose of I-131**

| Variables | Postablation hypothyroid (*n*=161) | Ablation failure (*n*=49) | OR (95% CI) | *Z* statistics | *P* |
|---|---|---|---|---|---|
| Age years | | | | | |
| ≤42 years:>42 years | 98:63 | 21:28 | 2.074 (1.08-3.96) | 2.205 | 0.027* |
| Female:Male | 114:47 | 31:18 | 1.408 (0.72-2.76) | 0.997 | 0.318 |
| Pyramidal lobe | | | | | |
| Present:Absent | 74:87 | 10:39 | 3.317 (1.55-7.09) | 3.089 | 0.002* |
| Thyroid uptake % | | | | | |
| ≤15%:>15% | 106:55 | 19:30 | 3.043 (1.57-5.89) | 3.302 | 0.001* |
| Thyroid antibodies | | | | | |
| Positive:Negative | 117:44 | 12:37 | 8.198 (3.92-17.14) | 5.591 | <0.0001* |

*$P$<0.05. CI: Confidence interval, GD: Graves' disease, OR: Odds ratio

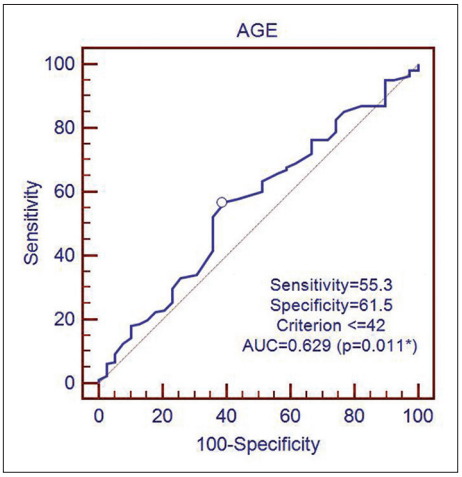


**Figure 1:** Receiver operating characteristics curve for age as a predictor of post-ablation hypothyroidism in patients with Graves' disease treated with single fixed 15 mCi dose of I-131

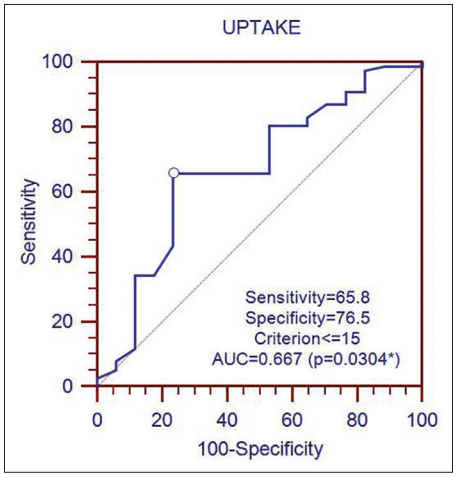


**Figure 2:** Receiver operating characteristics curve for camera based thyroid uptake as predictor of post-ablation hypothyroidism in patients with Graves' disease treated with single fixed 15 mCi dose of I-131

## DISCUSSION

For GD optimal dose of RAI has been a matter of controversy for decades for reasons of the direct relation between RAI dose and radiation exposure and goal to achieve euthyroidism rather than hypothyroidism.[7] Although the proponents of lower or calculated RAI dose have been successful in reducing the incidence of early onset hypothyroidism, but incidence of late onset hypothyroidism was disappointingly high.[8,9] For these reasons, ATA and AACE in its recent guidelines have emphasized upon a fixed dose of 10–15 mCi with primary goal to render GD patients hypothyroid.[2] In this study, we have evaluated the efficacy of a fixed 15 mCi dose of RAI for rendering patients with GD hypothyroid within 6 months (successful ablation) and also evaluated various predictors for this outcome as well.

We have found that 15 mCi fixed RAI dose was effective in rendering 77% of hyperthyroid patients with GD within 6 months. The selection of this dose was based on experience of other researchers who showed no superiority of calculated dose over a fixed approach due to its cumbersomeness, complexity, and expense.[10] The sole reason for selecting a 15 mCi dose rather than 10 mCi as per ATA and AACE guideline was our goal to achieve hypothyroidism with a single dose of RAI, which has

a better chance with higher RAI dose. There are studies which have shown higher treatment failure rate with lower fixed doses of RAI.[2] Our success rate is comparable with a study from United Kingdom, which did show a success rate of 72% with 15 mCi and 57% with 10 mCi RAI dose.[7] Our success rate is significantly higher than other published studies using a 15 mCi fixed dose making 62% of recipients hypothyroid,[1] 10 mCi with 49%[11] and 5 mCi with 59–61%[6] success rates. The selection of 6 months to decide about the success or failure of RAI treatment was according to ATA and AACE guidelines.[2]

Our data revealed a significant association between younger age and RAI-induced hypothyroidism and ROC curve showed a threshold age of ≤42 years for achieving this goal. The possible explanation for this association could be lack of fibrosis in goiters of younger which is expected in long-standing diffuse goiters.[12] However, data are conflicting about the association of age and outcome to RAI treatment in GD as some show poor response in younger patients[13,14] or no significant age-related response.[15,16] Gender was not found to have any significant association with ablation outcome in our study and this is in concordance with other published data.[14,15,17] However, there are some published studies elucidating male gender as a risk factor for ablation failure.[12,13,18]

In this study, higher Tc-99m uptake on thyroid scan did show a significant negative correlation with successful ablation (RAI-induced hypothyroidism) and ROC curve did show that tracer uptake <15% on thyroid scan has better predictive value for RAI-induced hypothyroidism. This important finding is contradictory to the conventional understanding that higher thyroid $^{99m}$Tc pertechnetate or radioiodine uptake ensure better ablation outcome with a lower dose of RAI to achieve hypothyroidism. The explanation for this observation could be a higher iodide turnover resulting in shorter residence of RAI in thyroid cells and suboptimal delivery of radiation to thyroid cells.[1] Our finding is in concordance with various published studies[1,6,11] and guides the treating physicians to select higher doses of RAI in GD patients with Tc-99m pertechnetate uptake values >15% to overcome the possibility of ablation failure.

This study also revealed that the presence of thyroid antibodies has a significant association with RAI-induced hypothyroidism and regression analysis also demonstrated its presence as a significant predictor for the development of hypothyroidism after RAI. This important observation is consistent with other published data as well[7] although many studies deny any significance correlation between them.[8,19] The possible explanation is triggering of RAI-induced humoral and cell-mediated autoimmune response within the thyroid gland and presence of thyroid antibodies being a marker of co-existing chronic inflammatory process contributes to the progressive development of hypothyroidism.[7]

Another important observation of our study was a significant association of the presence of pyramidal lobe on thyroid scintigraphy with post-RAI-induced hypothyroidism. More interestingly, regression analysis revealed pyramidal lobe as a significant predictor of hypothyroidism as well. This is a unique observation and we could not find any other study in literature showing correlation between pyramidal lobe and RAI-induced hypothyroidism. We have no plausible explanation for this relationship and strongly feel that it is an area of future research.

Significant limitations of our study include its retrospective nature and no data about the size of goiter, presence and severity of ophthalamopathy, which were primarily due to inconsistent data collection. Another limitation is a lack of data revealing patients who became euthyroid after RAI and this was again due to inconsistent follow-up of patients after RAI. In this study, we did not study the impact of antithyroid medication on RAI outcome as we had no control group (treatment naïve). Another potential limitation is use of $^{99m}$Tc thyroid uptake rather than iodine uptake (as former is taken up but has no organification as later) but despite of this discrepancy various studies have shown that $^{99m}$Tc imaging and uptake is a convenient alternative.[11]

We conclude that fixed (15 mCi) RAI dose is highly effective in rendering hypothyroidism in patients with GD. Age (≤42 years), thyroid uptake (≤15%) and presence of pyramidal lobe are strong predictors of hypothyroidism and must be considered for selecting optimal RAI dose.

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