


The prevalence and significance of nonuniform thyroid radioisotope uptake in patients with Graves' disease

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Abstract

Objective: To evaluate the prevalence and clinical significance of nonuniform technetium (^{99m}Tc) uptake among patients with Graves' disease (GD).

Design, Patients and Measurements: Patients with GD, referred between July 2005 and March 2018, had Tc^{99m}-uptake scans and TSH-receptor antibody (TRAb) measured before antithyroid drug (ATD) therapy. Risk of relapse after ATD cessation was monitored until June 2021 and compared between GD patients based on uptake patterns.

Results: Of the 276 GD patients (mean age, 49.8 years; 84% female), 25 (9.0%) had nonuniform Tc^{99m} uptake. At diagnosis, individuals with nonuniform uptake were older (mean age of 61.8 vs. 48.5 years, $p < .001$), had lower mean thyroid hormone levels (free thyroxine: 36.3 vs. 45.4 pmol/L, $p = .04$ and free triiodothyronine: 10.0 vs. 17.8 pmol/L, $p < .001$) and median TRAb levels (4.2 vs. 6.6 U/L, $p = .04$) compared with those with a uniform uptake. Older age was a significant predictor for the presence of nonuniform uptake in GD patients; odds ratio (95% confidence intervals) of 1.07 (1.03 – 1.10). The risk of relapse was similar in both groups after a median (IQR) follow-up of 41 (13–74) months after ATD cessation (56.0% vs. 46.3%, respectively); hazard ratio (95% confidence intervals) of 1.74 (0.96–3.15).

Conclusions: Nonuniform radio-isotope uptake is seen in 1 in 11 patients with GD which could be misdiagnosed as toxic multinodular goitre if TRAb levels are not measured. Treatment of GD patients with nonuniform radio-isotope uptake with ATD therapy as first-line appears to be equally effective as compared with those with uniform uptake. TRAb testing should be the main diagnostic test for patients with suspected GD with radio-labelled uptake scans being reserved for those who are TRAb negative.

KEYWORDS

^{99m}Tc uptake, Grave's disease, nonuniform uptake, TRAb

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1 | INTRODUCTION

Graves' disease (GD) and toxic multinodular goitre are the most frequent causes of hyperthyroidism. In iodine replete countries, GD is more prevalent with 20–30 annual cases per 100,000 individuals being reported.¹ GD is an organ-specific autoimmune disorder and its clinical manifestations are due to the stimulation of the thyrotropin (TSH) receptor by autoantibodies (TRAb) leading to hyperthyroidism and goitre. Similar to most autoimmune diseases, GD occurs more often in women with 3% of women and 0.5% of men developing the condition during their lifetime,² with the peak incidence being observed between the ages of 30 and 60 years.³

Distinguishing GD from other causes of hyperthyroidism is important as it influences the modality and duration of treatment. The aetiology of hyperthyroidism may not be clinically apparent in most patients and further diagnostic tests are required.⁴ The diagnosis of GD is confirmed by detecting raised TRAb levels which has a sensitivity and specificity of 97% and 99%, respectively, or the presence of uniform uptake of radio-labelled iodine or technetium.⁵ Before the advent of TRAb testing, the diagnosis of GD relied mainly on the presence of the characteristic clinical features and a uniform thyroid uptake on thyroid scintigraphy.⁶ Recent guidelines recommend measuring TRAb levels as the first-line diagnostic test followed by thyroid radionuclide scintigraphy if TRAb levels are low or unavailable.^{4,7,8} However, considerable variation exists in the use of diagnostic tests to determine the aetiology of hyperthyroidism with most clinicians undertaking thyroid ultrasound and/or radio-labelled scintigraphy in addition to TRAb determination.⁹ Measuring the percentage and pattern of administered radio-labelled tracer uptake by the thyroid gland using ^{99m}Tc-Technetium pertechnetate (^{99m}Tc) or ¹²³sodium iodide after a fixed interval is commonly used in the diagnostic pathway.⁴ ^{99m}Tc is an analogue of iodine and is trapped but not organified by the thyroid gland within 20 min of intravenous administration compared with ¹²³sodium iodide that first needs to be organified and then measured at 24 h. A uniform pattern of thyroidal uptake of the radio-labelled tracer is typical of GD but may be affected by the presence of a multinodular thyroid gland.¹⁰

The prevalence of nonuniform uptake in patients with GD that has previously been quoted has varied substantially: ranging between 0.3% and 56%,^{11–15} reflecting differences in how the diagnosis of GD was established. First- and second-generation TRAb assays had much lower sensitivity and specificity than current third-generation assays.⁵ Similarly, factors that may affect thyroid nodule formation such as iodine intake, tobacco smoking habits and age may have also contributed to the wide variation reported. The prevalence and clinical course of nonuniform thyroid uptake among patients with GD diagnosed with contemporary TRAb assays in an iodine replete area of Europe remain unclear. We therefore analysed baseline and follow-up data from patients with newly diagnosed GD who had both TRAb levels measured and ^{99m}Tc uptake scans performed to determine the prevalence and clinical course based on their uptake patterns.

2 | MATERIALS AND METHODS

2.1 | Patients

Consecutive patients referred to an out-patient clinic with biochemically proven first episode of hyperthyroidism were prospectively studied between July 2005 and March 2018. Of these, only those patients that were diagnosed with GD were included in this analysis. In addition, those who were pregnant, breastfeeding or refused uptake scans were also excluded ($n = 31$). Serum samples were obtained before the commencement of antithyroid drugs (ATD). All patients also underwent a thyroid ^{99m}Tc-uptake scan before commencement of ATD. The diagnosis of GD was confirmed by an endocrinologist based on the typical biochemical features of hyperthyroidism (raised free thyroid hormones with suppressed TSH levels) and either elevated TRAb levels or uniform radio-isotope uptake. Patients with raised TRAb levels and nonuniform radio-isotope uptake were deemed to have GD as the underlying cause of their hyperthyroidism. As this analysis utilizes routinely collected clinical data, no informed consent was obtained nor was ethical approval required. The presence of Graves orbitopathy (GO) was diagnosed based on clinical recommendations.¹⁶ Smoking status, based on patient self-reporting, was classed as nonsmoking, ex-smoking (if stopped more than 3 months ago) or current smoker (at least one cigarette per day or the use of e-cigarettes). Patients with GD are usually treated with carbimazole unless there are plans for pregnancy or the patient specifically expressed a wish for propylthiouracil treatment. In our centre, patients with GD are treated with ATD until TRAb levels are (or are close to) normal (TRAb < 1.8 U/L), with some degree of flexibility based on clinician and/or patient preference. Similarly, the choice of treatment strategy between titration of ATD dose (based on thyroid hormone levels) or block-replacement is left to the clinician and/or patient preference.

The prevalence of nonuniform uptake on ^{99m}Tc-uptake scanning was calculated from the baseline investigations. The average daily dose of ATD was calculated as the total cumulative dose divided by the number of days of treatment. For patients treated with propylthiouracil, the equivalent daily dose was calculated based on 10:1 propylthiouracil-carbimazole equivalence ratio.¹⁷ Some patients were not included in the follow-up analysis due to being lost to follow-up, becoming pregnant after ATD cessation, not being treated with ATD therapy due to having subclinical hyperthyroidism, having had definitive therapy with either thyroidectomy or radioactive iodine, or having died before 12 months of follow-up was completed. Relapse of GD was defined as recurrent hyperthyroidism (low serum TSH with high thyroid hormone levels and raised TRAb concentration) after cessation of ATD therapy. The date of ATD therapy cessation was considered the first date of follow-up and the last date of follow-up was the date of relapse, date of death or date of the most recent thyroid function assessment, whichever came first.

2.2 | Laboratory analyses

Thyroid function tests (TSH, free thyroxine and free triiodothyronine) and a third-generation TRAb were analysed by using the Roche Elecsys electrochemiluminescence immunoassay on the Cobas e602 analytical platform. The reference ranges were: TSH (0.4–4.5 mIU/L), free thyroxine (10–23 pmol/L), free triiodothyronine (3.0–6.8 pmol/L) and TRAb (<1.8 U/L).

2.3 | ^{99m}Tc scanning

Anterior views of the thyroid were obtained with the patient in supine position using a gamma camera (low energy planar high-resolution collimator) 20 min after 80 MBq ^{99m}Tc pertechnetate was injected intravenously. The ^{99m}Tc scans were graded by two nuclear medicine specialists who were unaware of the TRAb status of the patient. Uptake of the radio-labelled tracer by the thyroid gland was described as uniform or nonuniform following local clinical protocol. The pattern of radio-labelled tracer distribution (homogenous or heterogenous) was utilized to define uniform or nonuniform uptake, respectively. The pattern of scans that had an ambiguous uptake was resolved after mutual discussion.

2.4 | Statistical analysis

Variables with a continuous distribution were compared using unpaired *t* test whereas categorical variables were compared by χ^2 test. Continuous variables that had nonparametric distribution (TRAb at diagnosis, TRAb at ATD cessation and duration of treatment with ATD therapy) were compared by Mann–Whitney *U* test. Significant predictors for nonuniform uptake were analysed using binary logistic regression analysis. Cox proportional hazard model was used to assess the association of type of thyroidal uptake (uniform or nonuniform) with risk of relapse after adjusting for potential confounders. Follow-up interval was calculated from the date of ATD cessation until the date of relapse or the date of the most recent thyroid function test if still euthyroid or hypothyroid. All analyses were tested for potential effect modification by several factors. We separately added product interaction terms of TRAb with age, sex, presence of GO and smoking status. Potential confounders were selected based on biological plausibility and previous literature. All analyses were adjusted for age, sex, smoking status, presence of GO, average daily dose of ATD therapy, duration of treatment with ATD and TRAb levels (at baseline and at ATD cessation, separately). We also performed a secondary analysis using baseline variables only (age, sex, smoking status, presence of GO and TRAb levels at presentation) in the Cox-proportional hazard model. The assumption of normally distributed residuals was checked and met. The proportional hazards assumption was assessed by Schoenfeld test and plots. No violation of the proportional hazards assumption was observed. No sample size estimation was performed before

conducting the analyses. A *p* value < .05 was deemed to indicate statistical significance. Statistical analyses were conducted by using the statistical software SPSS version 27 (IBM Corp.).

3 | RESULTS

Twenty-five out of the 276 GD patients showed a nonuniform ^{99m}Tc uptake (9.0%) (Figure 1). Individuals with nonuniform uptake were significantly older (mean age of 61.8 vs. 48.6 years) and presented with lower levels of thyroid hormones at diagnosis (free thyroxine: 36.3 vs. 45.5 pmol/L and free triiodothyronine: 10.0 vs. 17.9 pmol/L) compared with those with a uniform uptake. TRAb levels were significantly lower in those with nonuniform uptake (median of 4.2 vs. 6.6 U/L, *p* < .05) compared with patients with uniform uptake (Table 1). The median daily dose of ATD was also consequently lower in the nonuniform uptake group compared with those with uniform uptake (10.2 vs. 20 mg/day, *p* = .01). Median (interquartile range) TRAb levels at the point of ATD cessation were also similar in both groups: 1.41 U/L (0.82–2.38) vs. 1.08 U/L (0.62–2.37), *p* = .27, in the nonuniform and uniform uptake groups, respectively. Sixteen (5.8%) patients had negative TRAb levels but, by definition, had uniform ^{99m}Tc uptake. The TRAb negative GD patients were older (58.1 vs. 49.2 years, *p* = .02) and had less severe biochemical hyperthyroidism (free thyroxine: 30.5 vs. 45.5 pmol/L, *p* < .01 and free triiodothyronine: 10.2 vs. 17.6 pmol/L, *p* < .01) than the TRAb-positive patients.

On multivariable binary logistic regression analysis, older age was the only significant independent predictor of having a nonuniform uptake with odds ratio (95% confidence interval) of 1.07 (1.03–1.10). None of the other variables in the model were significantly associated with the risk of having a nonuniform uptake including sex, smoking status, presence of GO and TRAb levels at diagnosis (data not shown).

Follow-up data were available for 269 patients with GD. Seven patients were excluded from this analysis due to loss to follow-up (*n* = 2), proceeding to radioactive iodine therapy (*n* = 1) or thyroidectomy (*n* = 1), not being treated with ATD as they had subclinical hyperthyroidism (*n* = 2), or due to death of the individual (*n* = 1). The median (interquartile range) duration of treatment with ATD was 13 (12–16) months. Most patients were treated with carbimazole (95.3%) and the rest with propylthiouracil. Over a median follow-up of 41 (13–74) months after ATD cessation, 127 (47.2%) patients relapsed, of which 14 (56.0%) relapsed in the nonuniform uptake group and 113 (46.3%) relapsed in those with uniform uptake. Individuals with nonuniform uptake had a nonsignificantly higher risk of relapse with a hazard ratio (95% confidence interval) of 1.74 (0.96–3.15), *p* = .07 (Figure 2). When TRAb at ATD cessation was substituted for TRAb at baseline in this analysis, nonuniform uptake pattern still had a nonsignificantly higher risk of relapse with a hazard ratio (95% confidence interval) of 1.38 (0.74–2.57), *p* = .31. In the secondary analysis, when only baseline variables were used, the risk of relapse remained nonsignificantly raised in the patients with nonuniform uptake with a hazard ratio (95% confidence interval) of 1.79 (0.98–3.24), *p* = .06.

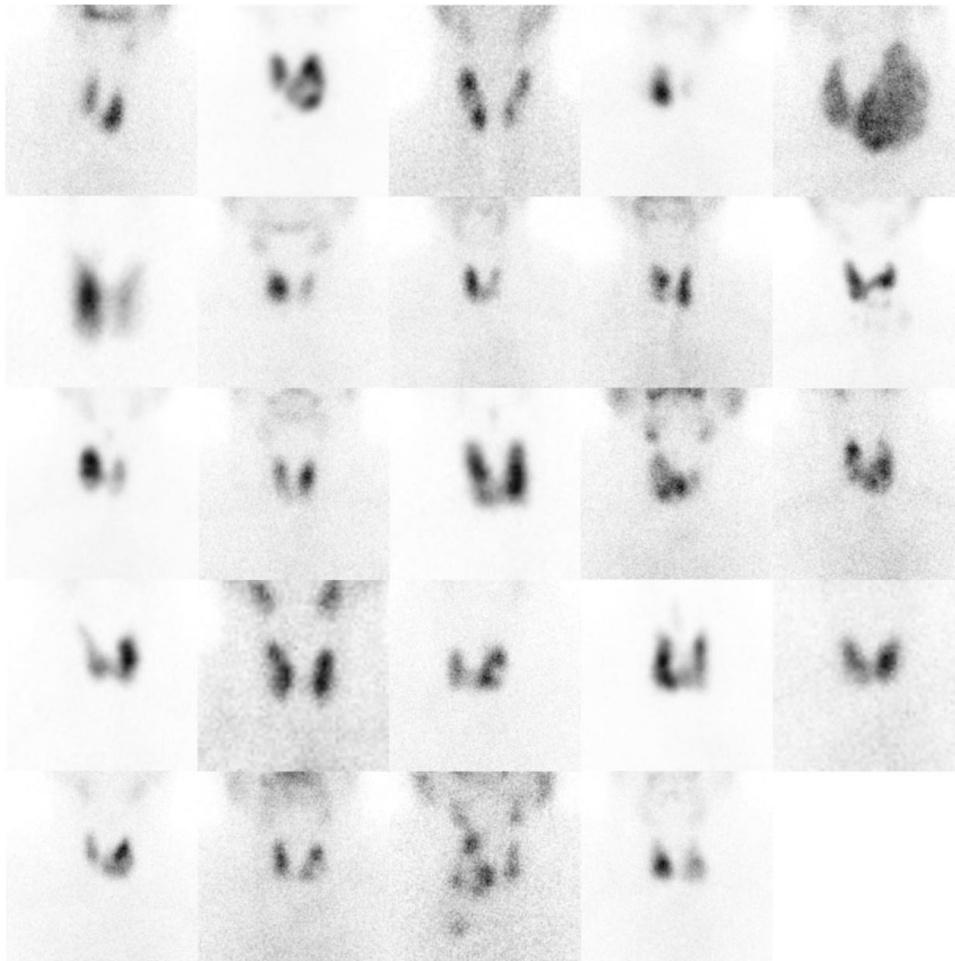


FIGURE 1 Nonuniform thyroid ^{99m}Tc uptake scans among patients with Graves' disease. Scans were available for 24 of the 25 patients with Graves' disease and nonuniform uptake of ^{99m}Tc pertechnetate. For the remaining patients the uptake film is no longer available

4 | DISCUSSION

To our knowledge there are limited data describing the prevalence and clinical outcomes of nonuniform thyroid uptake among patients with GD. Our analysis demonstrates that almost 1 in 11 patients with GD have nonuniform uptake on ^{99m}Tc isotope scan and that these patients are usually older and tend to have lower elevation in thyroid hormone levels. Furthermore, older age appears to be the only significant independent risk factor for the development of nonuniform uptake in GD patients. However, the risk of relapse in these patients with nonuniform uptake remains similar to those with a uniform uptake. Thus, TRAb assessment at baseline should be the mainstay for diagnosing GD and radio-labelled uptake or ultrasound scans should be reserved for those patients who are biochemically hyperthyroid and TRAb negative.

Before the advent of reliable TRAb assays, clinical judgement and the presence of uniform uptake of a radio-labelled tracer were predominantly relied on to make a diagnosis of GD, the argument being that clinical and biochemical features of hyperthyroidism, diffuse goitre and presence of GO was sufficient to make a

diagnosis.⁶ However, diffusely enlarged goitre is not observed or palpable in all patients and only a fifth of GD patients have eye involvement.¹⁸ Despite the high sensitivity and specificity of third-generation TRAb levels in diagnosing GD, clinical practice remains variable.⁸ Differences in clinical practice with regard to using TRAb testing to diagnose GD are probably due to multiple factors including clinician preferences, availability and costs of TRAb assays, particularly in healthcare systems where the patient pays, and lack of TRAb tests across all laboratory platforms. Recommendations from the United Kingdom suggest that TRAb should be measured to determine the aetiology of all cases of hyperthyroidism and that technetium scanning be considered if the TRAb result is negative.⁸ The American Thyroid Association guidelines recommend that TRAb tests should be measured where the aetiology of hyperthyroidism is unclear from their presentation and biochemistry.⁴ The European Thyroid Association recommends the measurement of TRAb in patients with hyperthyroidism to aid rapid and accurate diagnosis and suggests that radio-labelled thyroid uptake scanning is reserved for those with co-existing thyroid nodularity.⁷ Reflecting the differences in guidelines, wide variation in clinical practice has been reported.⁹ Almost

90% of clinical members of the European Thyroid Association stated that they use TRAb tests to assess underlying aetiology of hyperthyroidism whereas just more than 30% stated that they request thyroid isotope uptake scans.⁸ This practice is in marked

TABLE 1 Baseline characteristics of patients with Graves' disease based on pattern of ^{99m}Tc thyroid uptake scan results

	Nonuniform (n = 25)	Uniform (n = 251)	p value
Age, years	61.8 ± 12.4	48.5 ± 15.5	<.001
Females, n (%)	23 (92)	210 (83.7)	.24
Ethnicity, n (%)			
Caucasian	23 (92)	241 (96)	.76
Asian/Indian	1 (4)	6 (2.4)	
Other	1 (4)	4 (1.6)	
Smoking, n (%)			
Current	6 (24)	79 (31)	.59
Ex-smoker	7 (28)	51 (20)	
Nonsmoker	12 (48)	123 (49)	
GO, n (%)	3 (12)	45 (17.9)	.47
FT4, pmol/L	36.3 ± 21.8	45.4 ± 21.2	.04
FT3, pmol/L	10.0 ± 3.6	17.8 ± 9.8	<.001
TRAb, U/L	4.2 (2.6– 7.7)	6.6 (3.4–13.6)	<.05
Average daily dose of ATD (mg/day)	10.2 (5.8–37.5)	20 (12.4–40)	.01
Duration of treatment with ATD, months	13 (12–14)	13 (12–16)	.90

Note: Data are provided as mean ± SD or median (interquartile range). Abbreviations: ATD, antithyroid drug; FT3, free triiodothyronine; FT4, free thyroxine; GO, Graves' orbitopathy; TRAb, TSH receptor antibody.

contrast to that undertaken by counterparts in North America where TRAb measurements are less frequently requested (54%) and isotope scans are requested in 45% of patients.¹⁹

The results of this analysis have several implications. Firstly, making a diagnosis of GD may be missed or misdiagnosed as toxic multinodular goitre if radio-labelled isotope scans alone are utilized in trying to elucidate the aetiology of hyperthyroidism. This may lead the clinician to opt for radioactive iodine or surgery as first-line treatment options rather than ATD therapy. Secondly, ageing is a significant predictor of detecting nonuniform uptake of radio-labelled isotope by the thyroid gland. This is not unexpected as nonuniform uptake likely reflects underlying nodular thyroid anatomy and nodular thyroids are more commonly observed in older people.²⁰ The older age and lower TRAb levels observed in GD patients with nonuniform uptake likely explain the less severe biochemical hyperthyroidism in this group.²¹ The third inference of our analysis is that the detection of a nonuniform uptake in patients with GD has no clinical consequence with regard to risk of relapse and thus should not determine treatment options. It should, however, be borne in mind that this analysis was not powered to detect a statistical difference in relapse outcomes between the two GD groups. Furthermore, our results provide data to reinforce existing guidelines that thyroid scintigraphy or ultrasound scanning is reserved for those GD patients with borderline or low TRAb levels. However, a larger study may be required to confirm this finding as the risk of relapse was borderline in the relatively small number of patients with nonuniform uptake included in this analysis.

The strengths of our analysis include the relatively large number of GD patients, confirmed by a contemporary third-generation TRAb assay, studied in a systematic prospective manner and the long period of follow-up to detect relapse. One of the major limitations of our study is the lack of ultrasound data to assess thyroid anatomy and confirm if indeed nonuniform uptake correlates with a nodular thyroid gland. However, a previous study using ultrasound demonstrated that

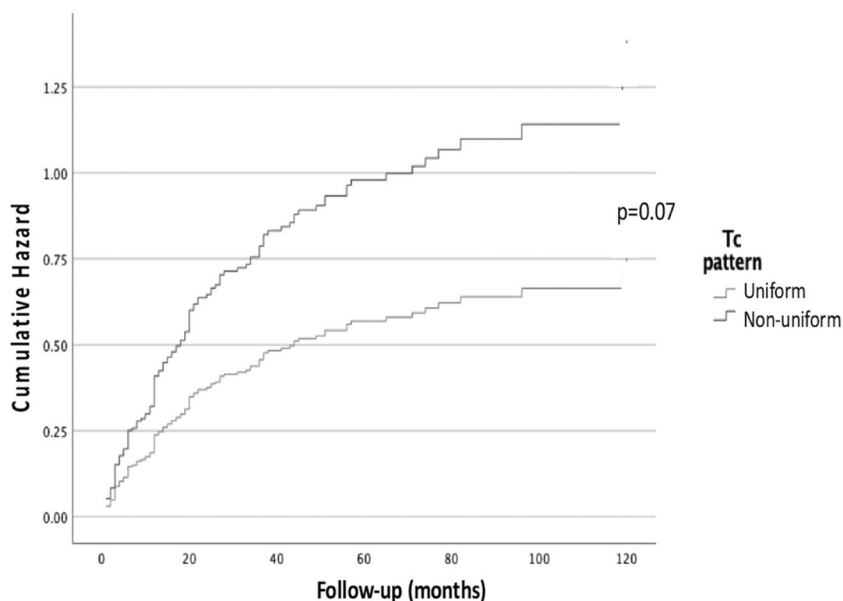


FIGURE 2 Hazard plot of risk of relapse by pattern of thyroidal ^{99m}Tc uptake at baseline. The hazard ratio (95% confidence interval) for risk of relapse in patients with Graves' disease and nonuniform uptake was 1.74 (0.96–3.15), adjusted for age, sex, smoking status, presence of GO, average daily dose of antithyroid drug therapy, duration of treatment with antithyroid drugs, and baseline TRAb levels. GO, Graves orbitopathy; TRAb, TSH receptor antibody

there was no significant difference in the number of thyroid nodules or thyroidal volume between TRAb-positive or -negative hyperthyroid patients with nonuniform uptake.¹³ The other limitation is the lack of standard practice or guidelines to define uniform or nonuniform uptake of radio-labelled tracer and thus reporting may have been subjective. However, all thyroid uptake scans in our analysis were reported by one nuclear medicine expert and subsequently verified by another. Finally, not all patients with hyperthyroidism had both TRAb levels and radiolabel isotope scanning with ^{99m}Tc tests and may have led to a selection bias, particularly with individuals with borderline TRAb levels being more likely to be included or those who declined radioisotope scanning being excluded.

In summary, our analysis provides an insight into the prevalence, determinants and clinical consequences of nonuniform thyroid radio-isotope uptake in patients with GD. This study suggests that almost 1 in 11 patients with GD are likely to have a nonuniform uptake on thyroid scintigraphy and that age is an independent predictor of this finding. Treatment of this group of GD patients with ATD appears to be as effective as in those with GD and uniform uptake of the radio-labelled compound. Therefore, TRAb measurement should be undertaken as the first-line diagnostic test in all patients with hyperthyroidism and radio-isotope scans should be undertaken in those who are TRAb negative. Studies with larger number of patients and/or longer duration of follow-up are required to confirm the risk of relapse in these patients which could then influence clinical decision making with regard to the best treatment modality.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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