TITLE: POST-**RA**DIOIODINE **G**RAVES' **MA**NAGEMENT: THE **PRAGMA** STUDY

SHORT RUNNING TITLE: Graves' disease management post-radioiodine

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SUMMARY

Objective. Thyroid status in the months following radioiodine treatment for Graves' disease can be unstable.Our objective was to quantify frequency of abnormal thyroid function post-radioiodine and compare effectiveness of common management strategies.

Design. Retrospective, multi-centre, observational study.

Patients. Adult patients with Graves' disease treated with radioiodine with 12 months' follow-up.

Measurements. Euthyroidism was defined as both serum thyrotropin (TSH) and free thyroxine (FT4) within their reference ranges or, when only one was available, it was within its reference range; hypothyroidism as TSH ≥ 10 mu/L, or subnormal FT4 regardless of TSH; hyperthyroidism as TSH below and FT4 above their reference ranges; dysthyroidism as the sum of hypo- and hyperthyroidism; subclinical hypothyroidism as normal FT4 and TSH between the upper limit of normal and <10 mu/L; subclinical hyperthyroidism as low TSH and normal FT4

Results. Of 812 patients studied post-radioiodine, hypothyroidism occurred in 80.7% and hyperthyroidism in 48.6% of patients. Three principal post-radioiodine management

strategies were employed: (a) anti-thyroid drugs alone, (b) levothyroxine alone and (c) combination of the two. Differences among these were small. Adherence to national guidelines regarding monitoring thyroid function in the first 6 months was low (21.4–28.7%). No negative outcomes (new-onset/exacerbation of Graves' orbitopathy, weight gain, cardiovascular events), were associated with dysthyroidism. There were significant differences in demographics, clinical practice, and thyroid status post-radioiodine between centres.

Conclusions. Dysthyroidism in the 12 months post-radioiodine was common. Differences between post-radioiodine strategies were small , suggesting these interventions alone are unlikely to address the high frequency of dysthyroidism.

CLINICAL TRIAL REGISTRATION: Clinical.trials.gov (identifier No. NCT01885533).

KEY WORDS: Graves' disease, thyroid, radioiodine, hypothyroidism, hyperthyroidism

CONFLICT OF INTEREST STATEMENT: The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT: The data that support the findings of this study are available on request from the corresponding author.

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ABBREVIATIONS: ATDs, anti-thyroid drugs**;** B&R, block and replace**;** FT3, free tri-iodothyronine**;** FT4, free thyroxine**;** L-T4, levothyroxine**;** GD, Graves' disease; GO, Graves' orbitopathy; Q, quarter**;** RI, radioiodine**;** TFTs, thyroid function tests**;** TSH, thyroid stimulating hormone.

INTRODUCTION

Radioiodine (RI) is a safe and effective treatment for Graves' disease (GD) [1]. The aim of RI therapy is to cure the hyperthyroidism [2,3]. Attempts to calculate a dose of RI that eliminate hyperthyroidism yet prevent hypothyroidism have not produced reliable results, and have been abandoned in the UK and other countries in favour of larger, fixed doses [2,4-6]. As a consequence, the majority of patients develop thyroid hormone dependence within the first year after RI[7].

Whether hypothyroidism should be allowed to occur post-RI before thyroid hormone replacement is introduced, or be prevented, is an important question, which has received little attention in recent years. The argument in favour of allowing hypothyroidism to develop is to ensure that life-long treatment with levothyroxine (L-T4) is necessary. The case against is based on associations between hypothyroidism with impaired quality of life[8], weight gain[9] and Graves' orbitopathy (GO) [10-12]. Surveys performed more than 20 years ago revealed a wide variation among clinicians agreeing with the proposition that transient hypothyroidism with subsequent introduction of replacement therapy is an acceptable practice [13-15]. A more recent UK-based survey [6] and large published series [11,16] indicate that such variations in practice persist. Strategies used by clinicians to bridge the transition from hyperthyroidism to euthyroidism on stable L-T4 therapy following RI include a short course of anti-thyroid drugs (ATDs) alone, the combination of ATDs with L-T4 known as "block and replace" (B&R), or watchful monitoring with the introduction of L-T4 when needed [2,3,6,10].

MATERIALS AND METHODS

Objectives

The primary objectives were to document the frequency of dysthyroidism in the first 12 months following RI and compare the impact of different post-RI management strategies on thyroid status. Secondary objectives were to identify potential drivers for post-RI dysthyroidism, relationships between post-RI dysthyroidism, and clinical outcomes and differences between participating centres.

Study design

Retrospective, observational, multi-centre, secondary care study.

Inclusion Criteria

Age ≥ 18 years at the time of RI; diagnosis of GD; treatment with RI; 12 months follow-up after RI; most recent RI dose administered 1 or more years before enrolment.

Participating centres

Investigators were invited to participate through the *Society for Endocrinology* website and its newsletters (https://www.endocrinology.org/). Thirty-one NHS hospitals / centres participated in the study (https://web.archive.org/web/20210329111703/https://www.mapcustomizer.com/map/PRAGMA%20centres).

Enrolment and data collection

Patients were identified from registries of RI administration and endocrine departmental databases at each institution. Following enrolment, the medical records were used to extract relevant information. All paper records were pseudo-anonymized and entered in a central electronic database. Recruitment commenced in March 2013 and ended in February 2015.

Definitions

Patients were considered to have GD when there was biochemical evidence of thyrotoxicosis (low serum TSH with elevated serum FT3 and / or FT4 levels) and one or more of the following: (a) Diffuse uptake on thyroid isotope scan, (b) elevated serum TSH receptor antibody levels, (c) clinical evidence of GO, (d) diffuse goitre by palpation and positive thyroid peroxidase antibodies. Patients were considered to have GO if they had eye features class II or greater according to the NOSPECS classification [17]. Exacerbation of GO was defined as recorded evidence of worsening symptoms and / or eye signs.

Based on the results of TFTs performed in local laboratories, patients were classified as:

- **Hypothyroid:** serum TSH above and FT4 below the reference range, or serum TSH $\geq$10 mU/l associated with a normal serum FT4, or TSH $\geq$10 mU/l without an available FT4 level, or serum FT4 less than the reference range regardless of the serum TSH concentration
- **Hyperthyroid**: serum TSH below and serum FT4 above the reference ranges
- **Subclinical hypothyroid:** serum TSH above the reference range but <10 mU/L and serum FT4 within the reference range
- **Subclinical hyperthyroidism:** serum FT4 within and serum TSH below the reference range
- **Euthyroid:** both serum TSH and FT4 within the reference range or, when only one was available, within the reference range.

Data on weight gain were extracted from medical records.

Each centre used local laboratories and reference ranges upon which the above classifications were based.

Data handling

The 12-month follow-up period after RI was split into 3-month blocks or quarters (Qs): Q1=0-91 days, Q2=92-182, Q3=183-274 days, Q4=275-365 after RI treatment.

For further analyses each Q for each patient was coded as:

- **"Hyperthyroid"** when one or more TFTs showed hyperthyroid biochemistry
- **"Hypothyroid"** when one or more TFTs showed hypothyroid biochemistry
- **"Euthyroid"** when TFTs showed euthyroid biochemistry
- **"Subclinical hypothyroid"** when one or more TFTs showed subclinical hypothyroid biochemistry
- **"Subclinical hyperthyroid"** when one or more TFTs showed subclinical hyperthyroid biochemistry

An assumption was made that, following detection of hypo- or hyperthyroid TFTs, the abnormal biochemistry would be correctable within 3 months, therefore a similarly classified thyroid profile within 3 months of the previous was not counted. When multiple sets of TFTs were available in the same Q showing either hypo- or hyperthyroidism, only the most abnormal result was included. When there were episodes of both hypo- and hyperthyroidism in the same Q, they were both counted. From the above, the total number of hypo-, hyper- and dysthyroid episodes for each patient were calculated (dysthyroid was the sum of hypo- and hyperthyroid episodes).

Missing data

For the analyses pertaining to thyroid status during the 12 months following RI, 27 patients were excluded because they had no TFTs available. For other analyses (not involving TFTs) data from all 812 patients were included.

Biochemical assays

Biochemical data on thyroid function were derived from the local laboratories. The assay platforms used were: Siemens Advia Centaur XP, Siemens Vista, Roche Cobas 800, Roche Modular, Centaur, Abbott Architect, Beckman Coulter DxI. The most commonly used reference ranges for TSH (0.35-4.5 mU/L) and FT4 (10-22 pmol/L) were used for normalisation of all TSH and FT4 data, so as to make them comparable for statistical analyses. Validated formulas for normalisation were used[18] . To calculate values from laboratory x to laboratory y according to the following formula (y represents a normalized value from laboratory x to laboratory y, x is a measured concentration at laboratory x, Uy is the upper reference level for laboratory y and Ux is the upper reference level for laboratory x):

$$y = x\frac{U_y}{U_x}$$

It has been reported that patients on L-T4 for primary hypothyroidism have a higher mean FT4 serum concentration than healthy euthyroid people[19] and this fact may need to be taken into account when interpreting TFTs of such patients. However, for the purposes of this study the same normalised reference range for FT4 was used for all patients.

Statistical analyses

Statistical analyses were undertaken using STATA (STATA Corp LLC, College Station, TX, USA. Version 16) for primary and secondary outcomes. Parametric and non-

parametric tests, linear and logistic regression analyses were used. All *p* values are two-sided and a value of 0.05 considered to indicate statistical significance. The effects of post-RI treatment strategies were examined using a linear mixed model. The model included age, gender, smoking habit, dose of RI, and centre ID. Logistic regression was used to examine: (a) associations between new-onset and exacerbation of GO and age, gender, smoking, time from diagnosis of GD, dose of RI, prophylactic steroid use and thyroid status post-RI; (b) associations between changes in body weight and age, gender, smoking, thyroid status post-RI, use of prophylactic steroids, centre ID; (c) associations between cardiovascular events and age, gender, smoking, dose of RI, thyroid status post-RI. A linear mixed model was used to explore differences between centres using age, gender, smoking, proportion of patients who had previously been treated with ATDs with curative intent, GO prior to RI, use of prophylactic steroids, dose of RI, weight change and thyroid status in the model.

Regulatory approvals

Ethical approval was granted from the National Research Ethics Service (IRAS reference 110269). The study was adopted by the National Institute of Health Research Clinical Research Network, and received Research and Development and Caldicott Guardian approval from each of the sites.

RESULTS

A total of 812 patients were included from 31 UK centres. The baseline characteristics are shown in Table 1.

Thyroid function tests

A total of 3,951 sets of TFTs (3,616 paired TSH and FT4, 328 TSH only, 7 FT4 only) were recorded over 12 months following RI treatment in 785 patients. The TSH and FT4 values across time are shown in Figure 1. Categorisation of the data shown in Figure 1 into thyroid status were, euthyroid 23.9% (945/3951), hypothyroid 31.9% (1262/3951), hyperthyroid 12.0% (475/3951), subclinical hypothyroid 8.3% (328/3951), subclinical hyperthyroid 20.7% (816/3951), The median number of tests per patient per Q was 1 (range 0-7) for Q1, 2 (range 0-5) for Q2, 1 (range 0-6) for Q3, and 1 (range 0-7) for Q4. Hypothyroidism peaked in Q2 (61.8%) and declined to 17.8% in Q4. Hyperthyroidism was highest in Q1 (26.3%) and reached a trough in Q4 (13.4%). Hypothyroidism was most prevalent in Q2 (60.2%) and lowest in Q4 (18.6%), while euthyroidism was lowest in Q2 (11.3%) and highest in Q4 (33.0%). Subclinical hyper- and hypothyroidism varied between 9.1-23% and 3.9-11.4% respectively (Figure 2). The overall risk of patients experiencing at least one episode of hypo- or hyperthyroidism in the 12 months following RI (calculated from a subgroup of 358 patients who had at least one set of TFTs for every Q), was 80.7% and 48.6% respectively (Table 2). Conversely, only 9.2% of patients avoided dysthyroidism during the 12 months post-RI. TSH values peaked in Q2 and were lowest in Q4. There were no differences in serum FT4 levels across Qs (Table 3). It may be argued that hyperthyroidism in Q1 is to be expected and that a single episode of hypothyroidism is acceptable in order to confirm the need for life-long thyroid hormone replacement, however, 26.8% of patients experienced more than one episode of hypothyroidism and 54.8% of the hyperthyroid episodes occurred after Q1 (Figures 1 and 2).

Ultimate and penultimate TFTs before commencement of L-T4 treatment

In a subset of patients (61.7%, 484/785), dates were available for starting L-T4 treatment. For this group of patients, it was possible to explore: (a) thyroid status before starting L-T4, (b) how promptly L-T4 was started after the blood test, (c) whether dysthyroidism in the last (ultimate) set of TFTs before commencing L-T4 could have been predicted by the previous (penultimate) set of TFTs. At the time of the ultimate TFTs before starting L-T4, 77% (373/484) of patients were hypothyroid. Hypothyroid patients were commenced on L-T4 treatment within a median of 7.8 days (range 0-161) from the date of the ultimate hypothyroid TFTs. In 67.8% (328/484) of patients penultimate TFTs were available. Penultimate TFTs were taken a median of 48 days (range 2-203) before the ultimate TFTs, and a median of 60 days (range 1-342) since RI. Of these 328 patients the penultimate TFTs showed: subclinical hyperthyroidism in 37.5% (123/328), euthyroidism in 23.8% (78/328), hypothyroidism in 18.3% (60/328), hyperthyroidism in 18.0% (59/328) and subclinical hypothyroidism in 2.4% (8/328). The probability of hypothyroidism in the ultimate TFT was highest (90%) if the penultimate TFT was also hypothyroid, and lowest (75.6%) if the penultimate TFT was euthyroid.

Post-RI management strategies and thyroid status outcomes

Of the 785 patients who had follow-up TFTs after RI, the post-RI treatment strategy was recorded in 91.6% of cases (719/785): 35.5% (255/719) received ATDs alone, 15.2% (109/719) B&R, and 49.4% (355/719) L-T4 alone. There were some differences in baseline characteristics between the three management strategy categories (Supplementary Table 1). Table 3B shows the frequencies in thyroid status for the entire cohort and by treatment strategy for each Q. Using a liner mixed model that included age, gender, smoking habit, dose of RI, and centre ID, and considering thyroid status as

a categorical variable (hypothyroid, hyperthyroid or dysthyroid), the only difference between the management strategy groups was a lower risk of hyperthyroidism associated with the use of L-T4 alone compared to other treatment strategies ($p<0.02$, Figure 3).

Efficacy of RI treatment

Hyperthyroid thyroid function tests in Q4 were used as a surrogate measure of failure of RI treatment. Using this criterion (and data from 516/785 patients with available TFTs in Q4), RI failed in 13.4% (69/516) of patients.

Changes in body weight

Data on body weight were available in 74.0% (601/812) of patients. The majority (73.9%) gained weight within a year of being treated with RI by a mean of 3.0 kg (SD 4.3). This amount of weight seems modest compared to that reported by other studies [9], however most patients in PRAGMA had relapsed thyrotoxicosis and were probably not as thyrotoxic. Multiple linear regression showed no association with demographic variables, smoking status, post-RI thyroid status, use of prophylactic steroids for GO, or post-RI treatment strategy, after adjusting for centre ID.

Graves' orbitopathy

A minority of patients (18.2%, 148/812) had GO prior to treatment with RI. The median time from diagnosis of GD to RI for patients with GO was 31.9 months (range 0.9-226.5) and not statistically different to patients without GO. Current smoking was associated with a greater risk of GO prior to RI (28.3%) compared to non-smokers (14.5%) ($p<0.001$). New-onset GO after RI developed in 3.5% (23/664), while exacerbation of pre-existing GO in 41.9% (62/148) of patients. Logistic regression showed that current

smoking status and a lower dose of most recent RI were the only two factors that were predictive of new-onset of GO (p=0.029 and p=0.027 respectively). Prophylactic steroids were administered in 47.3% (70/148) of patients with pre-existing GO, and in 0.3% (2/664) patients without GO. The rate of exacerbation of GO after RI in patients with pre-existing GO who received prophylactic steroids (24.3%, 17/70) was no different to those who did not receive steroids (17.9%, 14/78, p=NS). The rates of referral to Ophthalmology were 82.6% (19/23) for new-onset and 41.9% (26/62) for exacerbation of pre-existing GO. Specific treatments for GO were administered in 13.4% (23/172) of patients after RI and all took place after referral to Ophthalmology. The commonest treatment was steroids (47.8%, 11/23) followed by surgical orbital decompression (26.1%, 6/23), lid surgery (17.4%, 4/23), radiotherapy (4.3%, 1/23) and squint surgery (4.3%, 1/23).

Cardiovascular events post-RI

Data on cardiovascular events were available in 97% (788/812) of patients and occurred in 1.2% (10/788) after RI (atrial fibrillation 1.0%, atrial fibrillation associated with acute coronary syndrome 0.1%, stroke 0.1%). Logistic regression showed no associations between age, gender, smoking, dose of RI, thyroid status post-RI or treatment strategy post-RI.

Adherence to guidelines

Adherence to the 2007 national guidelines[20] was high in relation to dose of RI (93.1%), timing of initiation of ATDs after RI when indicated (93.8%), measurement of both FT4 and TSH (91.7%), and measurement of TFTs at 7-9 months (75.0%) and 9-12 months

(84%). Adherence was low to the recommendations that TFTs should be measured at about 6 weeks post-RI (21.4%), 12-14 weeks (28.7%) and 24-26 weeks (21.4%).

Differences between centres

Differences between centres were noted in patient age ($p<0.001$), gender ($p<0.05$), current smoking status ($p<0.05$), previous treatment with ATDs with curative intent ($p<0.001$), prevalence of GO prior to RI ($p<0.001$), use of prophylactic steroids for prevention of exacerbation or new-onset of GO ($p<0.001$), dose of RI administered ($p<0.001$), weight change ($p<0.001$), and number of hypothyroid ($p<0.05$), hyperthyroid ($p<0.05$) and dysthyroid episodes ($p<0.05$) (Supplementary Figure 1).

DISCUSSION

One of the main findings of PRAGMA was the high frequency of dysthyroidism in the first 12 months post-RI. Only 9.2% of patients avoided dysthyroidism, while 80.7% and 48.6% experienced at least one episode of biochemical hypo- or hyperthyroidism respectively. Hypothyroidism was most likely to occur in Q2, while hyperthyroidism was commonest in Q1; thus, the first 6 months after RI define the time window of the highest risk of dysthyroidism. More than a quarter (26.8%) of patients suffered two or more hypothyroid episodes. These findings suggest that management of many patients may be suboptimal. Paradoxically, one of the contributors to the high frequency of hypothyroidism may be misinterpretation of professional guidelines. The American Thyroid Association guidelines [2] state *"The goal of radioiodine therapy in Graves' disease is to control hyperthyroidism by rendering the patient hypothyroid".* This statement was probably intended to emphasise the futility of striving to achieve

euthyroidism without thyroid hormone substitution by using small doses of RI, and the inevitability of thyroid failure, rather than encourage clinicians to allow patients to become hypothyroid. The UK national guidelines available at the time of the study state *"hypothyroidism in the first six months after treatment may be transient in over half of the patients, and long-term thyroxine replacement should not be given unless it is clear that hypothyroidism is permanent"* [20]. This recommendation is based on a cited study by Aizawa *et al* (1997) [21], whereby relatively small calculated doses of RI were used (ranging from 171-219 MBq), in contrast to current practices in the UK, the rest of Europe and North America, which range between 400 and 800 MBq [2,4,5]. PRAGMA shows that when 400-800 MBq of RI is used, the probability of a hypothyroid episode in the first 6 months being persistent, if not treated, is 90%. An important question is whether dysthyroidism can be prevented in the year following RI. Some studies have shown that it is possible to achieve lower rates of dysthyroidism than PRAGMA in the first year after RI [10,12,22] (incidence of hypothyroidism and subclinical hypothyroidism less than 5.5% and 14% respectively), though it is unclear which are the important components that determine success and how much different strategies (use of ATDs alone, B&R or L-T4 alone) contribute. There were no major differences between the three main post-RI strategies (although a non-significant trend of an association between the use of B&R and greater rates of euthyroidism achieved was noted (Table 3B)), suggesting that these interventions alone are unlikely to address the high frequency of dysthyroidism. Probable contributors to dysthyroidism post-RI include: (a) suboptimal level of biochemical monitoring, especially in the first 6 months; (b) non-

adherence by patients with treatment; (c) and reluctance by physicians to introduce full replacement doses of L-T4; (d) rapid change in biochemical status post-RI.

New-onset of GO after RI was uncommon in the PRAGMA cohort and similar to one of the largest published series [23]. The negative association between the dose of the most recent RI and new-onset of GO is an interesting observation and may relate to the hypothesis that “total thyroid ablation” is beneficial in GO [24]. Prophylactic steroids did not seem to prevent exacerbations of pre-existing GO, which has been noted in other studies [25,26], and may be related to the dose and route of administration [27]. In the majority of patients, new-onset and exacerbation of pre-existing GO triggered referrals to Ophthalmology (79.2% and 86.7% respectively), and subsequently most referred patients received treatment. This contrasts to a European survey conducted in 2006 which showed a reluctance among endocrinologists to refer patients to Ophthalmology [28] and suggests that the management of GO in the UK may be improving, possibly in response to the efforts of TEAMeD (Thyroid Eye Disease Amsterdam Declaration Implementation Group, UK) [29,30]. Cardiovascular events after RI were reassuringly uncommon after RI and similar to that reported for the background population in England [31]. Significant differences in patient outcomes were noted between centres, which may be explained partly by differences in patient demographics and therefore case-mix, and requires further attention. Despite the high frequency of dysthyroidism in the first 12 months post-RI, there were no discernible negative effects on patient outcomes, such as increased risk of GO, or cardiovascular events.

The principal strength of PRAGMA is the large number of patients and multi-centre participation. Based on available UK data [32, 33, 34], it is estimated that the PRAGMA cohort represented about 10% of the UK population of patients with GD treated with RI per year. Given the participation of 31 centres and their wide geographical distribution across the UK, it can be inferred that the findings of PRAGMA are likely to be representative of UK patients and practises. The fact that most of the PRAGMA cohort had previously been treated with ATDs with curative intent concurs with current practices in Europe [6,35], and the USA [36]. In view of the above, and the fact that the number of patients included in PRAGMA is one of the largest in the literature, this suggests that the findings generated by PRAGMA are also likely to be of relevance to other European and North American populations of adult patients with GD treated with RI. The study is also subject to weaknesses. The data are retrospective, there are likely to be selection biases, there were missing data, and it was not possible to validate the data independently due to limited resources.

Based on the findings of PRAGMA, some simple measures may reduce the frequency of post-RI dysthyroidism: (a) adherence to the recent NICE guidelines which recommend monitoring of TSH, FT4 and FT3 6 weekly during the first 6 months following RI until TSH is in the reference range[37]; (b) patient engagement (patients being informed of the high risk of dysthyroidism, the importance of adherence to medication, the importance of frequent monitoring and need to modify their medication following results of blood tests); (c) initiation of L-T4 treatment when thyroid biochemistry shows subclinical hypothyroidism or hypothyroidism; (d) use of full

replacement doses of L-T4 from the outset as recommended by NICE [37]. Additional prospective studies are required to define the efficacy and cost effectiveness of other strategies for the post-RI management of patients with GD.

In conclusion, dysthyroidism in the first 12 months after RI, especially hypothyroidism, is very common and often recurrent, suggesting suboptimal management. The findings of PRAGMA indicate that guidance from professional organizations on whether avoidance of dysthyroidism after RI should be pursued rigorously by clinicians for all patients with GD post-RI, would be valuable.

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ADDITIONAL INFORMATION

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Data availability: The datasets generated during and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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LEGENDS FOR FIGURES AND TABLES

FIGURE 1

The distribution of serum TSH (left panel) and FT4 (right panel) across time is shown for all patients with recorded thyroid function tests (n=785). The y axes show the serum TSH and FT4 concentrations. The x axis shows time. The reference ranges for normalized TSH and FT4 were 0.30-45 mU/L and 9-22 pmol/L respectively.

FIGURE 2

Thyroid status across time for all 785 patients with available thyroid function tests after radioiodine. The y axis shows frequency ofeuthyroidism, hypothyroidism hyperthyroidism , subclinical hypothyroidism and subclinical hyperthyroidism. The x axes show time across 3-month blocks (quarters Q1-Q4). The horizontal brackets denote statistically significant pairs ($p<0.05$, chi-squared tests).

FIGURE 3

Thyroid status for patients treated with anti-thyroid drugs alone post-radioiodine (dark grey columns), block and replace (white columns) and levothyroxine alone (light grey columns). The x axes show time across 3-month blocks (quarters Q1-Q4). Use of L-T4

alone was associated with a lower risk of hyperthyroidism compared to other treatment strategies ($p<0.02$, linear mixed model). ATDs: anti-thyroid drugs; B&R: block and replace. L-T4: levothyroxine

SUPPLEMENTARY FIGURE 1

Differences between centres. The vertical axes indicate the parameters of interest (mean and 95% CI). The horizontal axes denote the centre identification numbers. All parameters shown in the figure were statistically different when tested by centre to the level of $p<0.05$. The upper panel shows differences in the primary outcomes. A: number of hypothyroid episodes RI; B: number of hyperthyroid episodes post-RI; C: number of episodes post-RI. The lower panel shows differences between centres in baseline characteristics. RI: radioiodine; GO: Graves' orbitopathy; centre ID: centre identification number.

TABLE 1

Baseline characteristics of patients.

TABLE 2

Cumulative rates of euthyroidism and dysthyroidism progressing through quarters.

TABLE 3

Thyroid function tests by quarter (3-month blocks, or Qs) (A) and thyroid status by post-radioiodine treatment strategy (B).

SUPPLEMENTARY TABLE 1

Baseline characteristics of all patients and in patients and in patients treated with anti-thyroid drugs, block and replace and L-T4 alone post-radioiodine (RI).

616

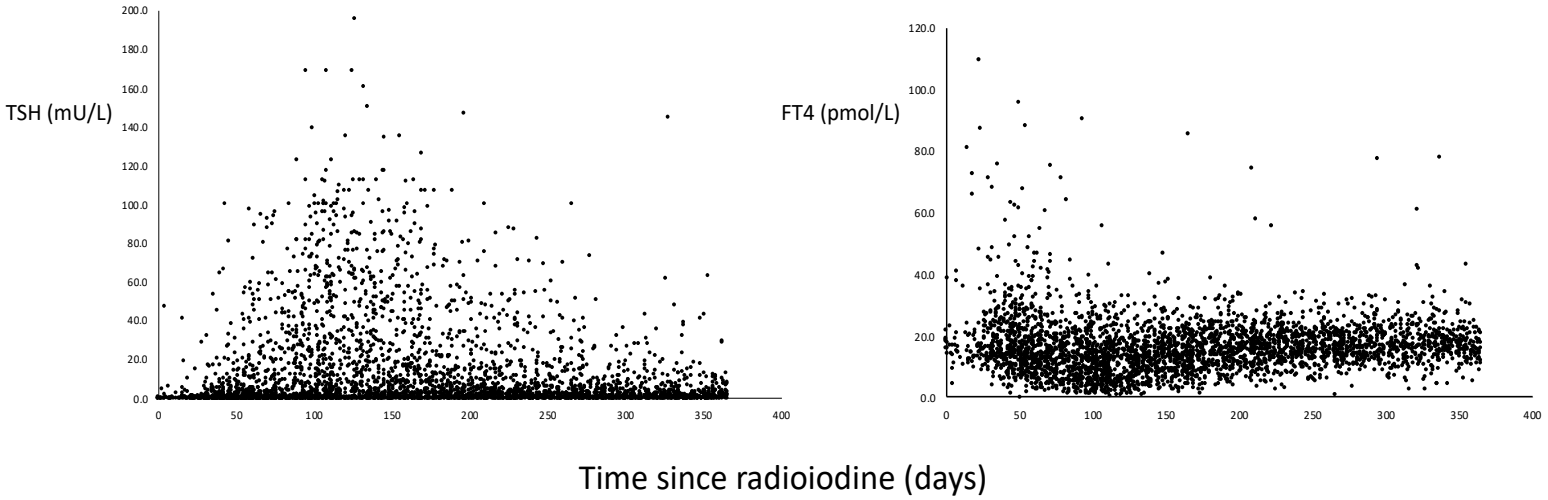


Figure 1

617

618

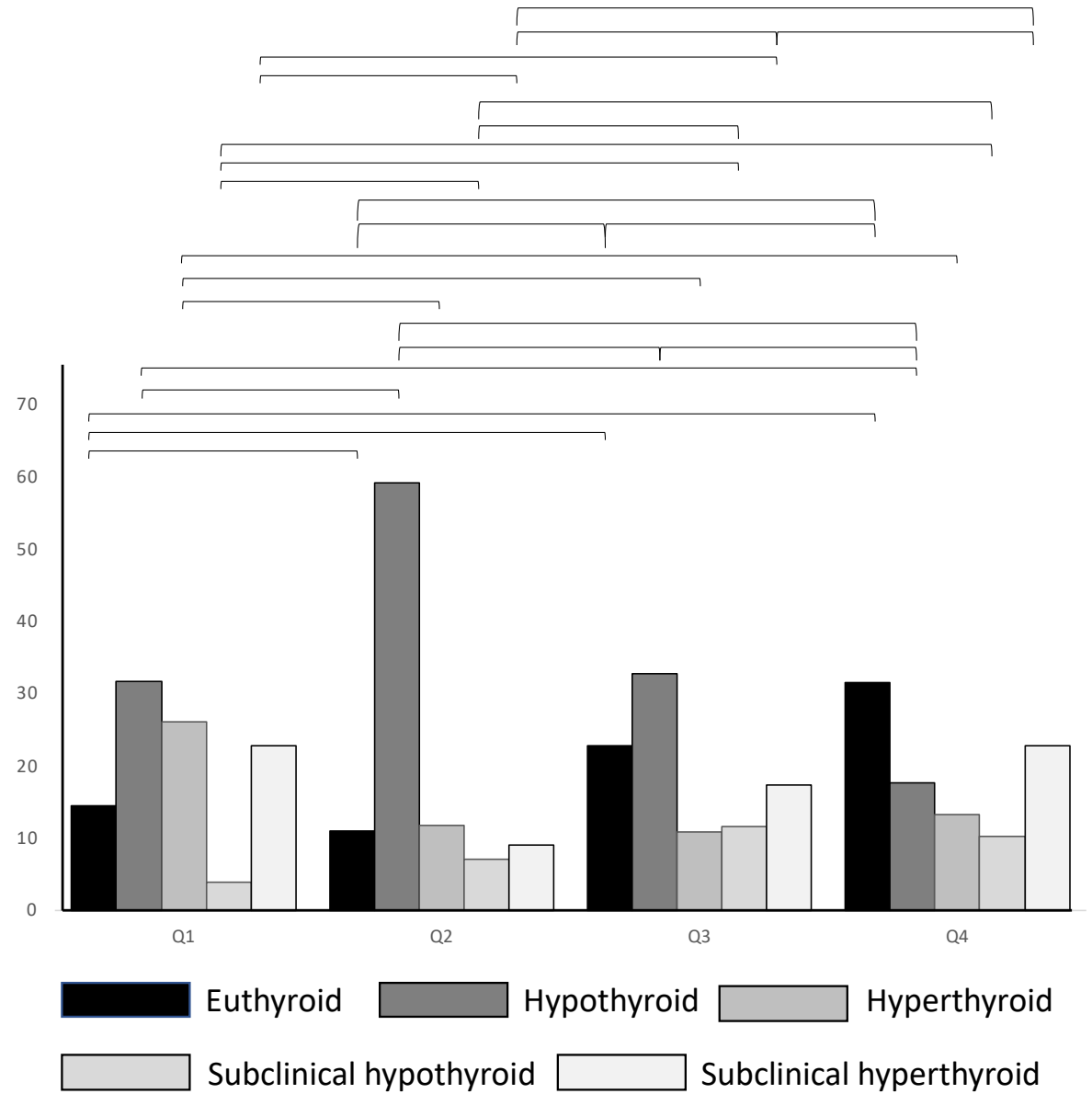

70
60
50
40
30
20
10
0
Q1
Q2
Q3
Q4
Euthyroid
Hypothyroid
Hyperthyroid
Subclinical hypothyroid
Subclinical hyperthyroid

FIGURE 2

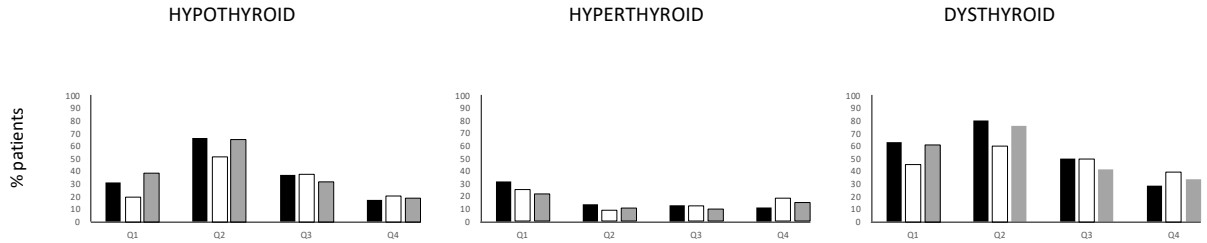

HYPOTHYROID
HYPERTHYROID
DYSTHYROID
% patients
100
90
80
70
60
50
40
30
20
10
0
Q1
Q2
Q3
Q4

FIGURE 3

TABLE 1

Baseline characteristics of patients.

Patients enrolled		
	Total	812
	Per centre	
	Mean (SD)	26.1 (16.0)
	Median (range)	21 (5-66)
	95% CI	20.3-32.0
Age at time of most recent RI treatment		
	Mean (SD) (years)	49.8 (14.2)
	Median (range)	50 (18-89)
	95% CI	48.8-50.8
	Missing data (%, n)	2.0 (16/812)
Female		
	% (n)	75.6 (615/812)
	Missing data (%, n)	0 (0/812)
Activity of most recent RI		

	Mean (SD) (MBq)	481.8 MBq (101.8)
	Median (range)	416 (330-809)
	95% CI	474.7-488.9
	Missing data (%, n)	2.0 (17/812)
Cumulative activity of RI		
	Mean (SD) (MBq)	527.0 (196.0)
	Median (range)	424.0 (330-1750)
	95% CI	513.3-540.7

TABLE 2

Rates of euthyroidism and dysthyroidism progressing through quarters (Qs) 1-4 in a subgroup of 358 patients who had at least one set of thyroid function tests in each Q. Each Q represents a 3-month block from the date of radioiodine (RI) treatment.

	CUMULATIVE RATES			
	Q1*	**Q2***	**Q3***	**Q4***
Euthyroidism (%, n)	18.4 (66/358)	5.0 (18/358)	5.0 (18/358)	5.0 (18/358)
Hypothyroidism (%, n)	26.5 (95/358)	72.9 (261/358)	79.3 (284/358)	80.7 (289/358)
Hyperthyroidism (%, n)	31.3 (112/358)	39.1 (140/358)	45.3 (162/358)	48.6 (174/358)
Subclinical hypothyroid (%, n)	22.3 (8/358)	0.3 (1/358)	2.0 (7/358)	2.0 (7/358)
Subclinical hyperthyroID (%, n)	26.0 (93/358)	7.0 (25/358)	2.2 (8/358)	2.2 (8/358)
Missing data (%, n)	0 (0/358)	0 (0/358)	0 (0/358)	0 (0/358)

**The sum of the rows in all Qs is greater than 100% because some patients had both hypo- and hyperthyroid episodes in*

TABLE 3

Thyroid function tests by quarter (3-month blocks, or Qs) (A) and thyroid status by post-radioiodine treatment strategy (B).

A

	Q1	**Q2**	**Q3**	**Q4**
Serum TSH (mu/L)				
Mean (SD)	8.9 (18.5)*	29.7 (36.0)*	11.3 (19.1)*	5.3 (11.4)
Median (range)	0.3 (0.0-122.9)	13.1 (0.0-195.9)	2.6 (0.0-146.8)	1.2 (0.0-144.7)
95% CI	7.5-10.2	27.0-32.3	9.9-12.8	5.3-6.4
n	724	713	647	455
Serum FT4 (pmol/L)				
Mean (SD)	18.0 (13.2)	12.5 (9.1)	16.6 (7.1)	18.1 (7.5)
Median (range)	14.4 (1.2-109.7)	10.7 (0.4-90.2)	15.8 (0.8-74.4)	17.4 (2.5-77.9)
95% CI	17.0-19.0	11.8-13.2	16.0-17.2	17.5-18.8
n	689	689	597	456

B**

	Q1	Q2	Q3	Q4
All patients (%, n)				
Euthyroid	14.5 (105/723)	11.0 (79/715)	22.7 (147/648)	31.5 (165/524)
Hypothyroid	31.7 (229/723)	59.2 (423/715)	32.7 (212/648)	17.7 (93/524)
Hyperthyroid	26.1 (189/723)	11.7 (84/715)	10.8 (70/648)	13.2 (69/524)
Subclinical hypothyroid	3.9 (28/723)	7.0 (50/715)	11.6 (75/648)	10.3 (54/524)
Subclinical hyperthyroid	22.8 (165/723)	9.0 (64/715)	17.3 (112/648)	22.7 (119/524)
Other§	1.0 (7/723)	2.1 (15/715)	4.9 (32/648)	4.6 (24/524)
Missing data	0.1 (1/724)	0 (0/715)	0 (0/648)	0 (0/524)
Anti-thyroid drugs alone (%, n)				
Euthyroid	15.5 (37/239)	6.6 (16/242)	19.3 (43/223)	34.1 (63/185)
Hypothyroid	29.7 (71/239)	63.2 (153/242)	36.3 (81/223)	17.8 (33/185)
Hyperthyroid	30.1 (72/239)	13.2 (32/242)	12.6 (28/223)	10.8 (20/185)
Subclinical hypothyroid	2.9 (7/239)	7.9 (19/242)	12.1 (27/223)	11.4 (21/185**)**
Subclinical hyperthyroid	20.1 (48/239)	8.3 (20/242)	17.5 (39/223)	22.7 (42/185)
Other§	1.7 (4/239)	0.8 (2/242)	2.2 (5/223)	3.2 (6/185)
Missing data	0 (0/239)	0 (0/242)	0 (0/223)	0 (0/185)
Block and replace (%, n)				
Euthyroid	20.5 (17/83)	24.2 (22/91)	21.9 (21/96)	32.5 (26/80)

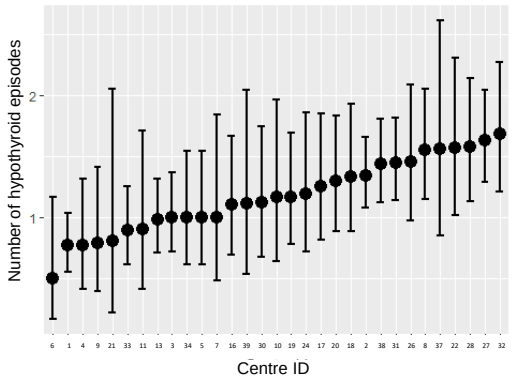
	Hypothyroid	19.3 (16/83)	49.4 (45/91)	36.4 (35/96)	20.0 (16/80)
	Hyperthyroid	26.5 (22/83)	8.9 (8/91)	11.5 (11/96)	17.5 (14/80)
	Subclinical hypothyroid	3.6 (3/83)	6.6 (6/91)	11.5 (11/96)	8.7 (7/80)
	Subclinical hyperthyroid	26.5 (22/83)	6.6 (6/91)	13.5 (13/96)	16.3 (13/80)
	Other§	3.6 (3/83)	4.3 (4/91)	5.2 (5/96)	5.0 (4/80)
	Missing data	0 (0/83)	0 (0/91)	0 (0/96)	0 (0/80)
L-T4 alone (%, n)					
	Euthyroid	11.8 (44/373)	10.7 (38/356)	24.5 (74/302)	28.0 (67/239)
	Hypothyroid	37.8 (141/373)	62.4 (222/356)	31.5 (95/302)	18.5 (44/239)
	Hyperthyroid	22.5 (84/373)	11.0 (39/356)	9.9 (30/302)	14.6 (35/239)
	Subclinical hypothyroid	4.6 (17/373)	6.2 (22/356)	11.6 (35/302)	10.1 (24/239)
	Subclinical hyperthyroid	23.3 (87/373)	7.3 (26/356)	15.2 (46/302)	23.4 (56/239)
	Other§	(0/373)	2.4 (9/356)	7.3 (22/302)	5.4 (13/239)
	Missing data	0 (0/373)	0 (0/356)	0 (0/302)	0 (0/239)

**TSH in Q1 vs Q2, p<0.001); Q1 vs Q3, p<0.001, Q2 vs Q3, p<0.001, Q4 vs Q4, p<0.001 (Kruskal-Wallis test).*

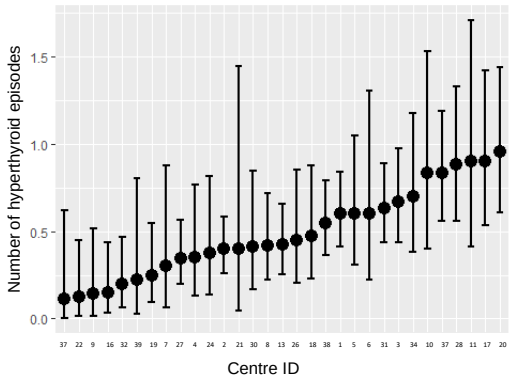
*** The definitions of categories in B were: hypothyroid: serum TSH above and FT4 below the reference range, or serum TSH >10 mU/l associated with a normal serum FT4, or TSH >10 mU/l without an available FT4 level, or serum FT4 less than the reference range regardless of the serum TSH concentration; hyperthyroid: serum TSH below and serum FT4 above the reference ranges; subclinical hypothyroid: serum TSH above the reference range but <10 mU/L and serum FT4 within the reference range; subclinical hyperthyroidism: serum FT4 within and serum TSH below the reference range; euthyroid: both serum TSH and FT4 within the reference range or, when only one was available, within the reference range.*

§TSH and FT4 did not conform to any of the listed categories (both elevated or both reduced).

A



B



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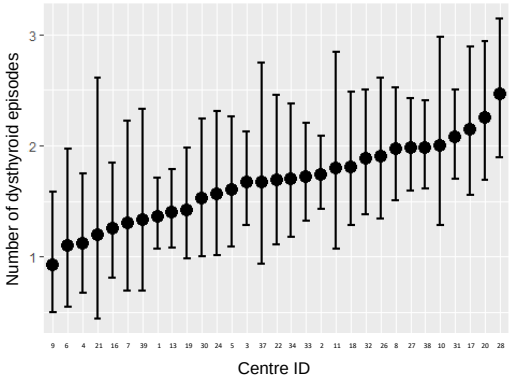
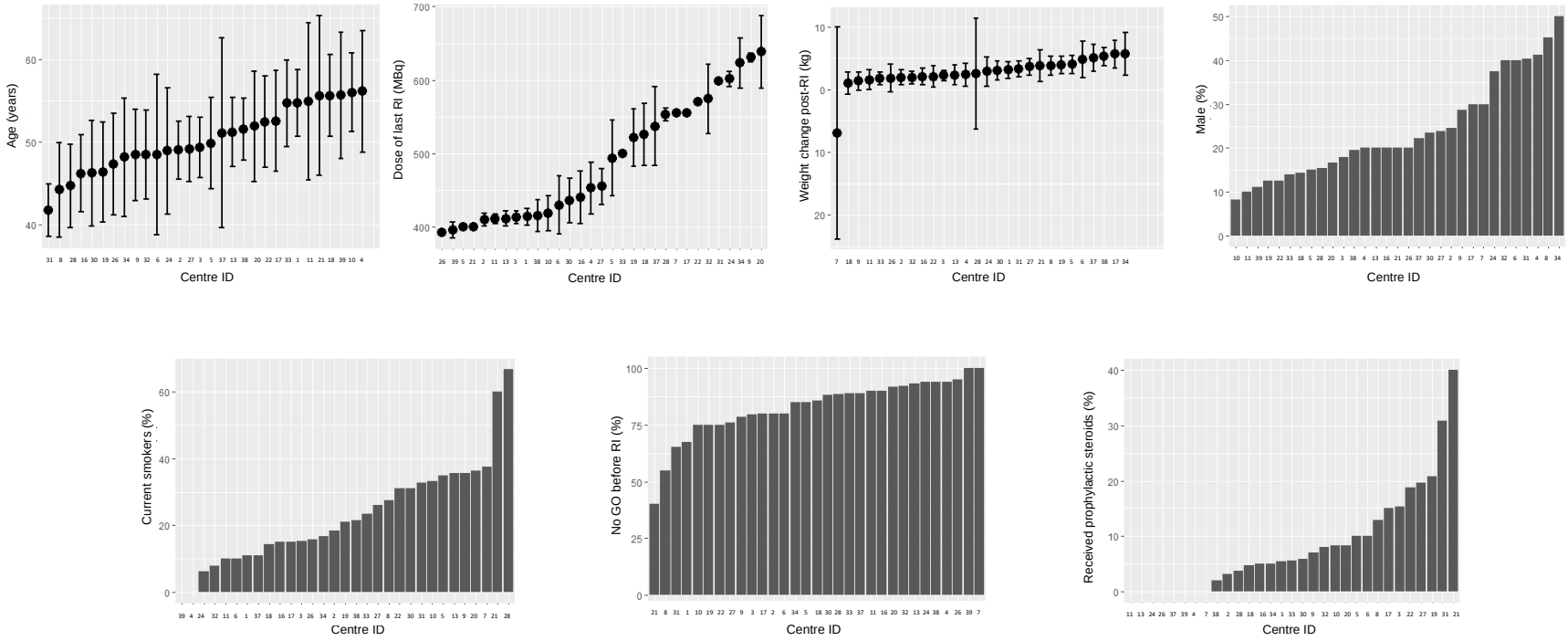


SUPPLEMENTARY FIGURE 1 (UPPER PANEL)



SUPPLEMENTARY FIGURE 1 (LOWER PANEL)

SUPPLEMENTARY TABLE 1

Baseline characteristics of all patients and in patients and in patients treated with anti-thyroid drugs, block and replace and L-T4 alone post-radioiodine (RI).

	ALL ENROLLED PATIENTS	**PATIENT GROUPS BY POST-RI MANAGEMENT STRATEGY**		
		Anti-thyroid drugs alone	**Block and replace**	**L-T4 alone**
n	812	255	109	355
Age at time of most recent RI treatment				
Mean (SD) (years)	49.8 (14.2)	48.3 (13.8)*	52.1 (13.6)*	50.0 (14.6)
Median (range)	50 (18-89)	49.0 (19-83)	50.0 (22-86)	50.0 (18-89)
95% CI	48.8-50.8	46.5-50.0	49.5-54.6	48.4-51.5

	Missing data (%, n)	2.0 (16/812) (8/355)	2.0 (5/255)	0 (0/109)	2.2
Female					
	% (n)	75.6 (615/812)	72.2 (184/255)	74.3 (81/109)	78.3 (278/355)
	Missing data (%, n)	0 (0/812)	0 (0/255)	0 (0/109)	0 (0/355)
Activity of most recent RI					
	Mean (SD) (MBq)	481.8 MBq (101.8) (97.5)	508.0 (111.0)**	459.9 (91.4)***	472.0
	Median (range)	416 (330-809) (330-800)	531 (364-809)	400.0 (390-800)	410.5
	95% CI	474.7-488.9 482.2	494.2-521.8	442.5-477.3	461.7-
	Missing data (%, n)	2.0 (17/812) (7/355)	2.0 (5/255)	0.9 (1/109)	2.0
Time from diagnosis of Graves'					

disease to most recent RI					
Mean (SD) (months)	38.3 (43.7)	36.4 (35.8)	37.4 (31.4)	41.3 (49.3)
Median (range)	26.9 (-8.9-458.0)§	27.3 (-8.9-283.1)	27.2 (1.0-186.0)	28.3 (0-464.1)
95% CI	35.3-41.3	32.0-40.8	31.4-43.3	36.1-46.5
Missing data (%, n)	1.2 (10/812)	0 (0/255)	0 (0/109)	1.1 (4/355)
Smoking status				
Never smoked (%, n)	52.3 (401/767)	47.8 (122/243)	59.6 (62/104)	50.6 (174/336)
Ex-smoker (%, n)	26.1 (200/767)	26.3 (64/243)	22.1 (23/104)	26.8 (90/336)
Current smoker (%, n)	21.6 (166/767)	23.5 (57/243)	18.3 (19/104)	21.4 (72/336)

	Missing data (%, n)	5.5 (45/812)	2.4 (12/255)	4.6 (5/109)	5.4 (19/355)
Treatment with curative intent for hyperthyroidism prior to most recent radioiodine treatment					
	No treatment (%, n)	14.9 (121/812)	1.1 (28/255)	10.1 (11/109)	20.3 (72/355)[a]
	Course of anti-thyroid drugs (%, n)	75.1 (610/812)	78.4 (200/255)	79.8 (87/109)	69.6 (247/355)[a]
	Thyroidectomy (%, n)	0.6 (5/812)	0.8 (2/255)	1.8 (2/109)	0.3 (1/355)
	Radioiodine (%, n)	9.4 (76/812)	9.8 (25/255)	8.2 (9/109)	9.9 (35/355)
	Missing data (%, n)	0 (0/812)	0 (0/255)	0 (0/109)	0 (0/355)
Graves' orbitopathy before RI (%, n)		18.2 (148/812)	20.8 (53/255)	28.4 (31/109)[b]	13.2 (47/355)[c]
	Missing data (%, n)	0 (0/812)	0 (0/255)	0 (0/109)	0 (0/355)

**The mean age of patients treated with block and replace was significantly greater than patients treated with anti-thyroid drugs alone (unpaired t-test p=0.017); all other comparisons of age between groups were statistically insignificant.*

***Patients treated with anti-thyroid drugs had received a higher dose of RI than the entire group (p=0.000), than the groups treated with block and replace (p=0.000), and the group treated with L-T4 (p=0.000).*

****Patients treated with block and replace had received a lower dose of RI than the entire group (p=0.028).*

§In a single case, the diagnosis of Graves' disease as the cause of thyrotoxicosis was made after the RI.

[a]Patients treated with L-T4 were less likely to have received definitive treatment before RI compared to patients treated with anti-thyroid drugs alone (p=0.02, Chi-squared test) and patients treated with block ad replace (p=0.02, Chi-squared test).

[b]Patients treated with block and replace had a higher frequency of Graves' orbitopathy before RI treatment than the rest of the cohort (p=0.014) and patients treated with L-T4 (p=0.000, Chi-squared test)..

[c]Patients treated with L-T4 had a lower frequency of Graves' orbitopathy before RI treatment than the rest of the cohort (p=0.04, Chi-squared test), than patients treated with anti-thyroid drugs alone (p=0.015, Chi-squared test), and lower than patients treated with block and replace (p=0.000, Chi-squared test).