The definitive version of this article is published as:
Vaidya B, Abraham P, Williams GR, Pearce SHS. National survey of radioiodine use in benign thyroid disease. *Clin Endocrinol* 2008, 68, 814-20.

Radioiodine Treatment for Benign Thyroid Disorders: Results of A Nationwide Survey of the UK Endocrinologists

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Word count (text): Text 2678, Abstract 258, Tables 5, Figures 3

Abbreviated title: Radioiodine for benign thyroid disorders

Key words: radioiodine, thyroid, thyroid eye disease, subclinical hyperthyroidism, goitre

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Summary

Background: The first UK survey of physicians' practice relating to radioiodine administration for hyperthyroidism was carried out over 15 years ago and showed wide variations in patient management. This led to the development of National guidelines for the use of radioiodine in hyperthyroidism. As there have been significant advances in the field since that survey, we carried out another survey to study the prevalent practices relating to radioiodine therapy for benign thyroid disorders across the UK.

Subjects and methods: We mailed 698 UK consultant endocrinologists a questionnaire on radioiodine treatment based on three patient scenarios, hyperthyroid Graves' disease, subclinical hyperthyroidism and non-toxic goitre.

Results: The response rate was 40%. For the case of an initial presentation of Graves' disease, 80%, 19% and 0.4% of respondents preferred thionamide, radioiodine or thyroidectomy, respectively. There were inconsistencies in respondents' recommendations on radioiodine dose, the use of pre- and post-radioiodine supplementary treatments, timing of a repeat dose, and the use of radioiodine in thyroid eye disease. For the case of subclinical hyperthyroidism, one-third of respondents would generally initiate treatment. The majority were more likely to treat subclinical hyperthyroidism in the presence of paroxysmal atrial fibrillation or osteoporosis. If a decision were made to treat subclinical hyperthyroidism, 63%, 35%, 1% and 0.4% would recommend radioiodine, thionamide, beta-blocker and thyroidectomy, respectively. For the case of non-toxic goitre, 62%, 21%, 13% and 5% favoured observation, thyroidectomy, radioiodine and thyroxine, respectively.

Conclusions: There remain significant differences in several aspects of clinical practice relating to the use of radioiodine treatment for benign thyroid disorders in the UK.

Introduction

Radioiodine has been used routinely in the treatment of various forms of thyrotoxicosis, including Graves' disease, toxic nodular goitre and solitary toxic nodule, for over 60 years.[1] Over this time it has proved a safe, efficacious and relatively inexpensive therapy. Approximately 10,000 doses of radioiodine therapy are administered annually in the UK.[2] Despite the longstanding and widespread use, there remains a lack of consensus on several aspects of radioiodine therapy.[3] The first nationwide survey in the UK, carried out more than 15 years ago, showed wide variations in the clinical practice surrounding the radioiodine treatment in thyrotoxicosis.[4] That survey led to the development of the UK guidelines for the use of radioiodine in the management of thyrotoxicosis.[5, 6] Since the first UK radioiodine survey, there have been significant advances in the knowledge relating to the safety and efficacy of radioiodine treatment,[1, 3, 7-9] and its applications in the management of different thyroid disorders,[10] with important clinical implications. Therefore, we have carried out another nationwide survey of UK endocrinologists to study the prevalent current practices with regards to radioiodine therapy for benign thyroid disorders, including thyrotoxicosis, subclinical hyperthyroidism and non-toxic goitre, across the country. In addition, we aimed to assess changes in the clinical practice since the first UK radioiodine survey, and to compare the current clinical practices in the UK with those in the other parts of the world.

Materials and methods

A questionnaire survey was mailed to 698 endocrinologists, who were listed on the web-based directory of UK consultants (http://www.specialistinfo.com) as practicing consultants in the field of endocrinology and diabetes in the UK, in November 2006.

The directory does not allow those with sub-speciality practices (i.e. 100% diabetes) to be distinguished. The survey was based on 3 clinical case scenarios (Table 1), and asked questions about the clinical practices related to radioiodine for the treatment of thyrotoxicosis, subclinical hyperthyroidism and non-toxic goitre. A full copy of the questionnaire is available on request from the authors. This survey was carried out on behalf of the British Thyroid Association.

All frequencies were adjusted on a 100% basis excluding the non-responders. Results are predominantly presented as percentages, rounded up to a whole number in the text and up to one decimal point in the tables. We used chi-square and Mann-Whitney U tests for statistical comparisons (SPSS version 11.5, SAS Institute, Cary, NC, USA).

Results

Characteristics of respondents

We received 279 responses (response rate 40%). Sixteen respondents were not involved in treating thyroid disorders; therefore only 263 responses were included in the analysis. The respondents represented endocrinologists from all regions of the UK including Scotland (n=36), Wales (n=15) and Northern Ireland (n=11). The percentages of respondents treating >100, 51-100, 10-50 and <10 patients with thyroid disorders annually were 63%, 25%, 11% and 1%, respectively.

Radioiodine treatment for thyrotoxicosis

For the treatment of an initial presentation of Graves' thyrotoxicosis (case 1), 80%, 19% and 0.4% of respondents preferred thionamide, radioiodine or thyroidectomy,

respectively (Figure 1). Of those favouring thionamide, 66% used thionamide alone, whilst 34% used thionamide in combination with thyroxine (block & replace).

In general, respondents were more likely to use radioiodine in recurrent thyrotoxicosis, older age group, patients with cardiac diseases, and patients with poor compliance or intolerance to antithyroid drugs (Figure 2). They were less likely to use the treatment in the presence of thyroid eye disease (TED) or in those with young children at home. The majority of respondents (46%) would avoid radioiodine in active TED but use in inactive TED *with* steroid cover; although 26% of respondents would avoid radioiodine in active TED but use in inactive TED *without* steroid cover (Figure 3).

Seventy percent of respondents used a fixed dose of radioiodine for treatment of thyrotoxicosis. The activity of radioiodine used in the fixed dose was variable (median 420 MBq, range 200-800MBq), although 99% of the respondents favouring a fixed dose regime used an activity over 350 MBq (9.5 mCi). Thirty percent of respondents used variable doses of radioiodine based on a variety of clinical factors, including the size of goitre on palpation (30%) or ultrasound (9%), level of uptake on isotope scan (32%), thyroid nodularity on palpation (25%) or ultrasound/uptake scan (23%), severity of hyperthyroidism (19%), and the presence of atrial fibrillation (25%), exertional angina (26%) and cardiac failure (26%). Only one respondent used a precise dosimetric method to determine the dose of radioiodine.

Most respondents (77%) routinely used thionamide – alone or with thyroxine – as a supplementary treatment before radioiodine (Table 2). If a patient has been treated

with a thionamide before radioiodine, respondents stopped the drug at variable durations prior to the radioiodine therapy (carbimazole vs. propylthiouracil: median 7 days vs. 7 days, range 0-28 days vs. 0-45 days, p= 0.85). The majority (66%) of respondents did not routinely use any supplementary treatment after radioiodine (Table 2).

If hyperthyroidism persisted after a dose of radioiodine, respondents would wait the following durations before recommending a repeat dose: at least 6 weeks, 0.4%; at least 3 months, 15%; at least 6 months, 66%; at least 9 months, 8%; at least 12, 11%, months; and variable duration depending upon the severity of thyrotoxicosis, 1%.

As compared to the first UK radioiodine survey, this survey showed an increased trend to use a fixed dose of radioiodine and to use thionamide as a pre-radioiodine supplementary treatment, and showed a decreased trend to use thionamide as a post-radioiodine supplementary treatment and to wait over 12 months for a repeat dose (Table 3).

Radioiodine treatment for subclinical hyperthyroidism

With regards to the patient with subclinical hyperthyroidism (case 2), most respondents would see and assess such a patient if referred; however, the investigations carried out by respondents were inconsistent (Table 4). One-third of respondents stated that they would generally treat the patient for thyrotoxicosis. Respondents were more likely to treat subclinical hyperthyroidism in the presence of paroxysmal atrial fibrillation or osteoporosis (Figure 4).

Presuming that a decision were made to treat subclinical hyperthyroidism, the percentages of respondents favouring different treatment modalities were: radioiodine 63%, thionamide 35%, beta-blocker alone 1%, and thyroidectomy 0.4%.

Radioiodine treatment for non-toxic goitre

For the patient with non-toxic goitre (case 3), the majority of respondents (62%) favoured observation without any treatment, whilst 13% of respondents recommended radioiodine (Table 5).

Of the respondents recommending radioiodine for non-toxic goitre, 86% would use a single fixed dose (median dose 550 MBq, range 367-800 MBq), whilst 14% favoured variable calculated dose. One respondent (3%) stated that he/she would use recombinant human TSH with radioiodine.

Comparison of clinical practice amongst endocrinologists with varying levels of thyroid workload

A comparison of clinical practice of the endocrinologists treating over 50 thyroid patients a year with those treating a lesser number of thyroid patients showed that the latter group used a fixed dose of radioiodine for Graves' thyrotoxicosis less frequently (72% vs. 52%, $p=0.04$) and had a greater tendency to avoid radioiodine in patients with any degree of TED (4.9% vs. 26.7%, $p<0.001$). There were no significant differences in any other practices between the two groups.

Discussion

This nationwide survey of the UK endocrinologists shows diversity in the prevailing clinical practices regarding radioiodine treatment for benign thyroid disorders across the country. The majority of respondents preferred thionamide for the initial presentation of Graves' disease (case scenario 1), although 19% favoured radioiodine (Figure 1). Previous surveys have highlighted international differences in the preferred treatment option for such a patient (Figure 1). Radioiodine treatment usually results in permanent remission from thyrotoxicosis, and is comparable to thionamide in the treatment of Graves' disease in terms of quality of life and superior in cost effectiveness.[16, 17] However, for the majority of the UK endocrinologists, radioiodine remains a second line treatment for Graves' disease. Furthermore, although male sex, young age of onset (<40 years) and the presence of a large goitre have been shown to be predictors of failure of long-term remission with thionamide in Graves' disease,[7] these factors appear not to influence most respondents' decision to treat thyrotoxicosis with radioiodine (Figure 2).

This survey has shown striking differences amongst the UK endocrinologists with regards to the radioiodine dose, use of pre- and post-radioiodine supplementary treatment, timing of a repeat dose and the use of radioiodine in the presence of TED. In addition, there were noticeable changes in the practice over the last 15 years (Table 3). There was an increased trend to use a fixed dose regime, in line with recent randomised controlled studies showing a lack of better clinical outcome with precise dosimetric methods,[18-20] and with the UK radioiodine guidelines, which recommend the use of single fixed doses rather than precise dosimetric methods.[6] There was a general trend to use a larger ablative dose with 99% of respondents using the dose

above 350 MBq (9.5 mCi), which is supported by the finding of a significantly higher cure rate of thyrotoxicosis with a fixed single dose of 370 MBq (10 mCi) than with a dose of 185 MBq (5 mCi).[8] Most respondents discontinued thionamide before radioiodine; however, the timing of discontinuation was variable. Although treatment with propylthiouracil before radioiodine has been shown to have a more prolonged radio-protective effect,[22, 23] there was no significant difference in respondents' reported timings of discontinuation of carbimazole and propylthiouracil. There was a general trend amongst UK endocrinologists to avoid radioiodine in patients with TED, particularly if the eye disease is active (Figures 2, Table 4). The concomitant use of steroids with radioiodine in patients with TED was also common. These are consistent with prospective randomised controlled studies showing a small but significant risk of the development of TED or the worsening of pre-existing TED,[24, 25] which could be prevented by a concomitant treatment with corticosteroids.[25] A recent prospective observational study has suggested that the risk of deterioration of TED following radioiodine is very small if the eye disease is inactive and post-radioiodine hypothyroidism is avoided, and a routine use of prophylactic steroids is unnecessary for such patients.[26] In line with these findings, a quarter of respondents used radioiodine in patients with inactive TED without steroid cover (Table 3).

In the recent years, subclinical hyperthyroidism has been shown to be associated with several adverse health outcomes, including an increased risk of cardiovascular mortality,[28, 29] atrial fibrillation,[30-32] and loss of bone mineral density and fractures.[33, 34] However, there is as yet no randomised controlled trial evidence to show that treatment of subclinical hyperthyroidism improves these adverse outcomes, apart from the prevention of bone loss.[35-37] Recent expert panel guidelines recommend to

consider treatment of subclinical hyperthyroidism (TSH <0.1mU/l) in patients, who are elderly, have symptoms of thyrotoxicosis or at increased risk of cardiac disease or osteoporosis.[38] In response to the vignette of an older woman in sinus rhythm, only one-third of respondents of this survey stated that they would generally treat subclinical hyperthyroidism (Table 4); this is in contrast to the finding of survey of members of ATA, which showed that two-thirds of respondents preferred to treat a similar (but not congruent) patient.[39] The UK endocrinologists were more likely to treat subclinical hyperthyroidism in the presence of paroxysmal atrial fibrillation or osteoporosis (Figure 4); however, only 8% and 26% of respondents routinely investigated such patients to identify these complications (Table 4). If a decision were made to treat subclinical hyperthyroidism, the UK respondents, in common with North American thyroidologists,[39] favoured radioiodine over thionamide, although there are no studies comparing these two treatment modalities in this condition.

There is a lack of consensus amongst the UK endocrinologists with regards to the treatment of benign non-toxic goitre. Such discrepancy between clinicians on treatment recommendations for non-toxic goitre has been found in the previous surveys in other countries, using the identical case (Table 5).[12, 40-42] The majority of the UK endocrinologists preferred no active treatment for non-toxic goitre; however, an important minority (13%) favoured radioiodine. The proportion of respondents recommending observation only or recommending radioiodine was significantly higher in this survey as compared to the previous surveys (Table 5). In contrast, thyroxine treatment was favoured less by the UK endocrinologists. These findings may be a reflection of changing practice due to the emerging evidence that radioiodine is more effective and better tolerated than TSH suppression with

thyroxine in non-toxic goitre.[3, 43-45] Of the UK endocrinologists who favoured radioiodine treatment for non-toxic goitre, most (86%) used a single fixed dose of moderate activity (median activity 550 MBq [15 mCi]), although there is evidence to suggest that higher and repeated doses of radioiodine may be necessary in patients with non-toxic goitre, particularly if the goitre is huge.[47, 48] Pre-treatment with recombinant human thyrotropin has been shown to augment the effect of radioiodine in non-toxic goitre;[49] however, the use of recombinant human thyrotropin in this context is not currently licensed in the UK and rarely used.

A limitation of this survey is the low response rate (40%), although the absolute number of respondents was high (n=279) compared to other national surveys,[11, 12] and respondents were spread uniformly across all geographical regions of the UK. Over 20% of consultant endocrinologists in the UK have a subspecialty practice in diabetes and are rarely involved in treating thyroid disorders (personal communication, Medical Workforce Unit, Royal College of Physicians). Most of the endocrinologists who responded to the survey have a substantial workload in the management of thyroid disorders, 88% treating over 50 patients with thyroid diseases each year. Therefore, despite being cautious of the relatively low response rate, we believe that this survey fairly represents the current trends in clinical practice amongst active UK thyroidologists. The other limitation of the survey is that it does not take an account of patients' preference in the choice of treatment modalities, which often carries a significant influence in the real life clinical practice.

In conclusion, this survey has highlighted diverse clinical practices relating to radioiodine treatment for benign thyroid diseases. It also demonstrates the changes in

practice in the country over the last decades since the first UK radioiodine survey, and the influence of the UK radioiodine guidelines in promoting these changes. It is hoped that the recently published updated UK radioiodine guidelines and further studies in the field will continue to promote a consistent, evidence-based clinical practice.

Acknowledgements

The authors wish to thank all respondents for completing the questionnaire, the executive committee members of the British Thyroid Association for comments on the design and results of the survey, the British Thyroid Foundation and Medical Research Council for funding, Prof. John Lazarus for providing us with the original questionnaire from the first UK radioiodine survey, and Betty Nevens for administrative assistance.

Figure legends

Figure 1. Preferred treatment modalities of the UK endocrinologists for a 43-year-old woman with initial presentation of Graves' thyrotoxicosis, as compared to those of respondents of the European Thyroid Association (ETA) and American Thyroid Association (ATA), and other national surveys.

Figure 1

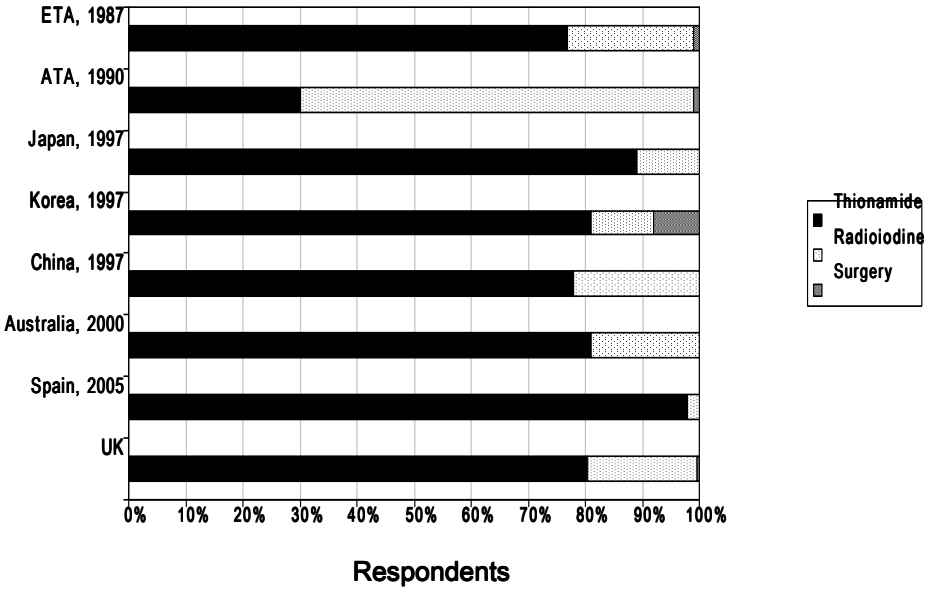

Figure 2. Factors influencing the decision to treat thyrotoxicosis with radioiodine.

Figure 2

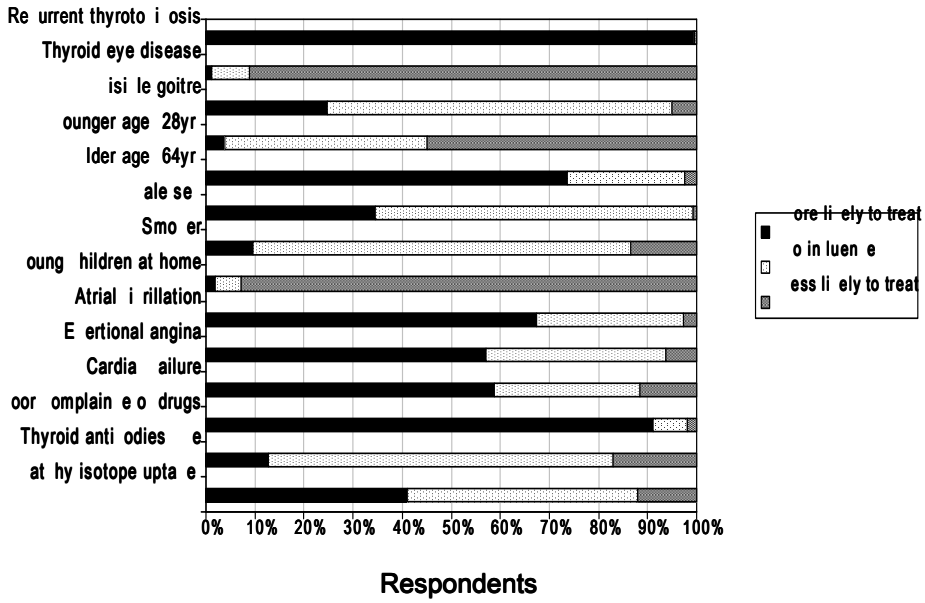

Figure 3. Current clinical practices of respondents with regards to the use of radioiodine in the presence of thyroid eye disease (TED).

Figure 3

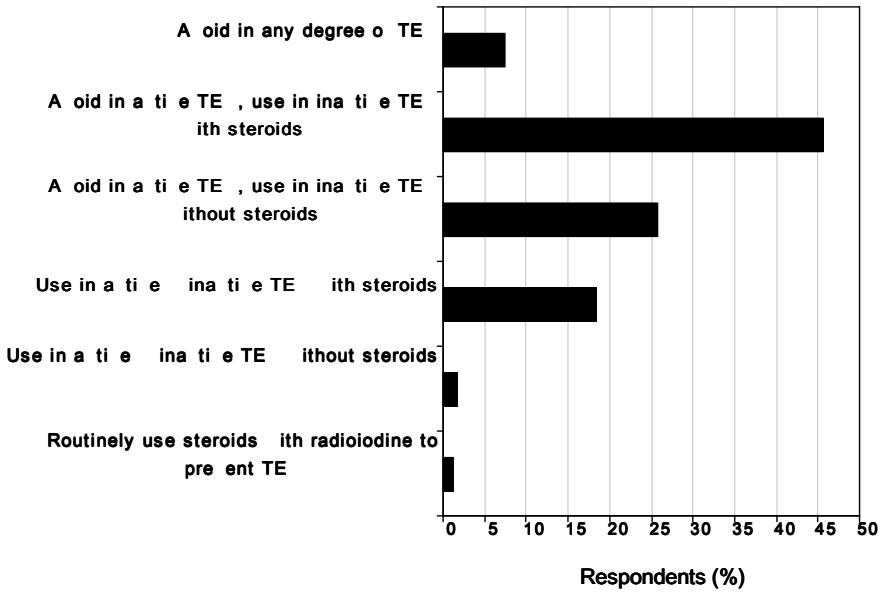

Figure 4. Factors influencing the decision to treat subclinical hyperthyroidism.

Figure 4

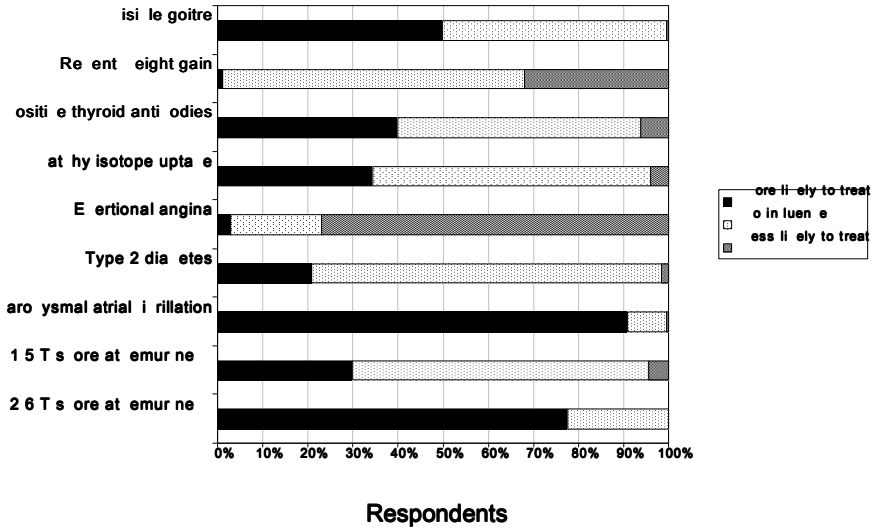

Table 1. Clinical case scenarios

Case 1: Initial presentation of Graves' thyrotoxicosis

A 43-yr-old woman presents with symptoms of thyrotoxicosis. She has sinus tachycardia and a small diffuse goitre, but no evidence of thyroid eye disease. She has no plans for being pregnant. TSH is fully suppressed with high free T4 45pmol/l (normal range 12-24) and positive thyroid antibodies.

Case 2: Subclinical hyperthyroidism

A 75 year old woman, reportedly in sinus rhythm, is referred with a persistently low serum TSH of <0.1mU/l, with normal range free T4 (17pmol/l) and free T3 (5.5pmol/l).

Case 3: Non-toxic goitre

A 42-year-old woman presents with a nontender bilateral moderate sized goitre (50-80gm) of 3-5 years duration. She is clinically and biochemically euthyroid, and thyroid antibodies are negative. Thyroid ultrasonography shows features of a multinodular goitre. Two fine needle aspirations show benign thyroid cells. She complains of moderate local neck discomfort, but no objective evidence of tracheal compression.

Table 2. Routine use of supplementary treatment pre- and post-radioiodine

Supplementary treatment	**Respondents using pre-radioiodine (%)**	**Respondents using post-radioiodine (%)**
None	42 (16.6)	162 (65.6)
Beta-blocker alone	15 (5.9)	3 (1.2)
Thionamide ± beta-blocker	167 (66)	63 (25.5)
Thionamide & thyroxine (block & replace)	27 (10.7)	15 (6.1)
Thyroxine alone	-	4 (1.6)
Others	2 (0.8)*	-
Total	**253 (100)**	**247 (100)**

***Lithium (n=2)

Table 3. Comparison of trends in clinical practice relating to radioiodine treatment for thyrotoxicosis between the first UK radioiodine survey and the current survey

	First UK radioiodine survey	**This survey**
Respondents using a fixed dose of radioiodine	50%	70%
Activity range used in a fixed dose of radioiodine	111-740 MBq	200-800 MBq
Respondents using thionamide routinely before radioiodine	16%	77%
Respondents using thionamide routinely after radioiodine	50%	32%
Respondents awaiting at least 12 months before a repeat dose of radioiodine	78%	11%

Table 4. Respondents' approaches for the management of a patient with subclinical hyperthyroidism

Statement	No of respondents (%)
Would see and assess if referred	253 (96.2)
Would routinely order thyroid autoantibodies	159 (62.1)
Would routinely arrange an isotope thyroid uptake scan	90 (34.2)
Would routinely arrange a 24hr heart rhythm tape	22 (8.4)
Would routinely perform a bone density scan	67 (25.5)
Would generally treat such a patient for thyrotoxicosis	89 (33.8)

Table 5. Treatment preferences for non-toxic goitre amongst the UK endocrinologists, and members of European Thyroid Association (ETA), American Thyroid Association (ATA) and Latin American Thyroid Association (LATS) [40-42]

Treatment	UK	ETA (2000)		ATA (2002)		LATS (2005)	
	N (%)	N (%)	*P*	N (%)	*P*	N (%)	*P*
Observation only	157 (61.8)	34 (28.4)	<0.001	50 (35.7)	<0.001	58 (39.2)	<0.001
Thyroxine	12 (4.7)	62 (51.6)	<0.001	79 (56.4)	<0.001	31 (20.9)	<0.001
Radioiodine	32 (12.6)	7 (5.8)	0.036	2 (1.4)	<0.001	10 (6.7)	0.0499
Surgery	53 (20.9)	12 (10)	0.006	9 (6.4)	<0.001	42 (28.4)	0.13
Total	**254 (100)**	**120 (100)***		**140 (100)**		**148 (100)***	

The *P* values after the ETA, ATA and LATS data refer to comparisons of the respective data with the UK data (this survey).

*As not all treatment options are included, the values do not add up to 100%.

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