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Radioiodine Treatment of Hyperthyroidism—Prognostic Factors for Outcome

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There is little consensus regarding the most appropriate dose regimen for radioiodine (^{131}I) in the treatment of hyperthyroidism. We audited 813 consecutive hyperthyroid patients treated with radioiodine to compare the efficacy of 2 fixed-dose regimens used within our center (185 megabequerels, 370 megabequerels) and to explore factors that may predict outcome. Patients were categorized into 3 diagnostic groups: Graves' disease, toxic nodular goiter, and hyperthyroidism of indeterminate etiology. Cure after a single dose of ^{131}I was investigated and defined as euthyroid off all treatment for 6 months or T_4 replacement for biochemical hypothyroidism in all groups. As expected, patients given a single dose of 370 megabequerels had a higher cure rate than those given 185 megabequerels, (84.6% *vs.* 66.6%, $P < 0.0001$) but an increase in hypothyroidism incidence at 1 yr (60.8% *vs.* 41.3%, $P < 0.0001$). There was no difference in cure rate between the groups with Graves' disease and those with toxic nodular goiter (69.5% *vs.* 71.4%; *P*, not significant), but Graves' patients had a higher incidence of hypothyroidism (54.5% *vs.* 31.7%, $P < 0.0001$). Males had a lower cure rate than females (67.6% *vs.* 76.7%, $P = 0.02$), whereas younger patients (<40 yr) had a lower cure rate than patients over 40 yr old (68.9% *vs.* 79.3%, $P < 0.001$). Patients with more severe hyperthyroidism ($P < 0.0001$) and with goiters of medium or large size ($P < 0.0001$) were less likely to be cured after a single dose of ^{131}I. The use of antithyroid drugs, during a period 2 wk before or after ^{131}I, resulted in a significant reduction in cure rate in patients given 185 megabequerels ^{131}I ($P < 0.01$) but not 370 megabequerels. Logistic regression analysis showed dose, gender, goiters of medium or large size, and severity of hyperthyroidism to be significant independent prognostic factors for cure after a single dose of ^{131}I. We have demonstrated that a single fixed dose of 370 megabequerels ^{131}I is highly effective in curing toxic nodular hyperthyroidism as well as Graves' hyperthyroidism. Because male patients and those with more severe hyperthyroidism and medium or large-sized goiters are less likely to respond to a single dose of radioiodine, we suggest that the value of higher fixed initial doses of radioiodine should be evaluated in these patient categories with lower cure rates. (*J Clin Endocrinol Metab* 86: 3611–3617, 2001)

RADIOIODINE IS INCREASINGLY used as first line therapy for Graves' hyperthyroidism and is the treatment of choice for relapsed Graves' disease and toxic nodular hyperthyroidism (1). The aim of treatment is to destroy sufficient thyroid tissue to cure hyperthyroidism by rendering the patient either euthyroid or hypothyroid. Although it is highly effective, with a cure rate approaching 100% after one or more treatments (2), it has proved impossible to titrate doses for individual patients accurately to guarantee a euthyroid state (3). Despite more than half a century of experience, there is little agreement regarding the most appropriate dose regimen (1, 4). Several studies have attempted to determine the optimal dose of radioiodine for curing hyperthyroidism, while avoiding the development of permanent hypothyroidism. Regimens used have included low doses [80 megabequerels (MBq)] (2, 5, 6), various fixed doses (185, 370, and 555 mCi) (2, 6–8), and doses calculated on the basis of thyroid size, the uptake of radioiodine, or the turnover of radioiodine (^{131}I) (2, 8, 9). Most dosimetric methods have the benefit of including a measure of thyroid size in their formulas, thereby administering a dose of radioiodine proportional to size of the gland and theoretically increasing the probability of cure. In addition, the use of isotope uptake measurements, as part of the dose calculation protocol, can confirm the absence of thyroiditis and identify patients with extremes of isotope uptake or turnover, which may predict failure of radioiodine treatment (10). Despite these potential benefits of calculated doses, several studies have failed to demonstrate improvements in cure rate over fixed doses (8, 11, 12). Furthermore, there is little evidence that using a calculated dose has any advantage over a fixed-dose regimen, in terms of preventing hypothyroidism (13), so many centers use a single fixed dose (14).

Opinions also vary about the need for larger doses of radioiodine in toxic nodular goiter, as compared with Graves' disease (15, 16). Patients with toxic nodular hyperthyroidism are perceived to be relatively radioresistant, compared with those with Graves' disease (15), although evidence is conflicting. Studies report the use of relatively large, but varying, quantities of radioiodine (555–1850 MBq) in patients with toxic nodular goiter (17, 18); and some studies suggest that persistent hyperthyroidism is more common in patients with Graves' disease (16).

The influence of antithyroid drugs on outcome of radioiodine treatment has also received attention. Some studies have suggested relative radioresistance in those prescribed antithyroid drugs before or after radioiodine (19, 20), but others have shown no effect (9) or an effect confined to propylthiouracil (21).

The ideal radioiodine dose regimen remains elusive, and uncertainties persist regarding the influence of underlying disease processes and treatment with antithyroid drugs

Abbreviations: CI, confidence interval; MBq, megabequerel.

upon outcome. In the present study, we have audited the treatment of hyperthyroidism within our large clinical practice to explore these and other clinical factors that may predict outcome, in an attempt to resolve the continuing debate and to further optimize radioiodine treatment for individual patients with hyperthyroidism.

Materials and Methods

Patients

Our cohort comprised 813 consecutive patients with hyperthyroidism treated with ^{131}I at the Thyroid Clinic at the Queen Elizabeth Hospital, Birmingham, between 1985 and 1999. Data were retrieved from our thyroid clinic database, which has been used in other studies (3), and case notes were also reviewed. Patients were categorized, by simple clinical and immunological criteria, into three diagnostic groups: Graves' disease, toxic nodular hyperthyroidism, and hyperthyroidism of indeterminate etiology. Graves' disease was defined as the presence of biochemical hyperthyroidism (raised serum free T_4 concentration and undetectable TSH) together with the presence of two of the following: a palpable diffuse goiter, a significant titer of thyroid peroxidase and/or Tg autoantibodies (a titer of 1:100 was considered significant), and/or the presence of dysthyroid eye disease. Toxic nodular hyperthyroidism was defined as hyperthyroidism in the presence of a palpable nodular goiter. Patients who did not fulfill either of these strict criteria were designated to the indeterminate group (these patients would represent a mixed group with Graves' disease, toxic nodular hyperthyroidism, or both). The size of this group reflected our policy of not performing radionuclide imaging in patients presenting with hyperthyroidism. Thyroid function and thyroid autoantibodies were measured as described elsewhere (22).

The size and type of goiter at diagnosis was categorized on the basis of physical examination by M. C. Sheppard or J. A. Franklyn: none (gland impalpable or normal size), small (thyroid palpably enlarged but not visible), and medium or large (palpable and visible goiter). Eye disease was defined according to the presence of eye signs in categories 2–6 of the NOSPECS classification (23). The following factors were defined at diagnosis (before initiation of treatment) and recorded in the database: gender; age at diagnosis; the presence of eye disease; the presence, size, and type of goiter; autoantibody status and titer, and serum concentrations of free T_4. Information regarding dose and duration of antithyroid drugs, dose, and timing of radioiodine and outcome after radioiodine was also recorded.

Our policy, over the period of the study, was to offer a single fixed first dose of ^{131}I to patients, over the age of 40 yr, presenting with hyperthyroidism for the first time and to all patients with relapsed Graves' disease. The size of dose was initially 185 MBq but was increased to 370 MBq in 1995. This change in dose regimen was based on a prospective study performed within the clinic, which demonstrated a low cure rate with 185 MBq (16). Antithyroid drugs, if given, were withdrawn a week before radioiodine therapy and not recommenced for a minimum of 1 wk after therapy. Thyroid status was assessed at monthly intervals after radioiodine administration. Patients were judged to be euthyroid if serum free T_4 concentrations off antithyroid drug therapy were within the normal range (9.0–20 pM); patients were classified as persistently hyperthyroid if free T_4 remained elevated, and hypothyroid if serum free T_4 was below the normal range and serum TSH was elevated (3). In those with normal serum free T_4 and elevated serum TSH (subclinical hypothyroidism) and in those with only modest reduction in free T_4 and elevation of serum TSH, T_4 replacement therapy (if commenced) was later withdrawn and thyroid status reassessed to exclude cases of transient hypothyroidism. Patients who remained hyperthyroid at 6 months were retreated with a second dose of radioiodine.

Outcome after radioiodine was defined as the number of doses of radioiodine required to result in cure of hyperthyroidism (euthyroid off all treatment for 6 months or T_4 replacement for biochemical hypothyroidism). The incidence of hypothyroidism was determined at 1 yr after the administration of radioiodine. The use of antithyroid drugs was determined for the period 2 wk before or after radioiodine administration.

Statistical analysis

The chi-square test was used to test for association between two categorical factors. The unpaired *t* test was used to assess the relationship between continuous and dichotomous categorical factors; and ANOVA, for categorical variables with three or more levels. The results of *t* tests and ANOVA were confirmed using Mann Whitney for continuous data that were not normally distributed. These analyses were performed using STATVIEW Version 4.5 (Abacus Concepts, SAS Institute Inc., Cary, NC). Logistic regression was used to determine which factors contributed to the prediction of outcome of treatment using MINITAB 12 (Minitab, Inc.).

Results

The demographic, clinical, and laboratory characteristics at presentation of the cohort are summarized in Table 1. Of the 813 patients, 321 were classified as having Graves' disease, 126 as cases of toxic nodular hyperthyroidism, and 366 were assigned to the group of hyperthyroidism of indeterminate etiology. Four hundred and forty three patients were treated with a first dose of 185 MBq, and 370 received a 370-MBq dose. As expected, patients with Graves' disease presented with hyperthyroidism at an earlier age than those

TABLE 1. Clinical details of patients with toxic nodular hyperthyroidism, Graves' hyperthyroidism and hyperthyroidism of indeterminate etiology treated with radioiodine

	Graves' disease n = 321	Toxic nodular disease n = 126	Indeterminate etiology n = 366	Statistical significance (*P*) of difference between groups (by χ^2/*t* test)
Females	252 (78.5%)	113 (89.7%)	278 (75.4%)	$P = 0.005$
Males	69 (21.5%)	13 (10.3%)	88 (24.6%)	
Mean age and range (yr)				
Females	38.4 (11–80)	59.0 (19–84)	47.0 (13–88)	$p < 0.0001$
Males	38.6 (14–80)	62.1 (39–75)	46.4 (15–85)	
Palpable goiter				
None	57 (17.8%)	0 (0%)	197 (53.8%)	$P < 0.0001$
Small	182 (56.7%)	98 (77.7%)	96 (26.2%)	
Medium/large	82 (25.5%)	28 (22.3%)	73 (20%)	
Ophthalmopathy				
Yes	132 (41.1%)	0 (0%)	0 (0%)	$P < 0.0001$
No	189 (58.9%)	126 (100%)	366 (0%)	
Mean free T_4 at diagnosis (pM)				
Mean ± SEM	56.8 ± 1.8	41.5 ± 2.2	50.4 ± 1.8	$P < 0.0001$
Range	21.3–150	20.6–136.9	21.1–150	

with toxic nodular goiter and were also found to have more severe hyperthyroidism, as determined by serum free T_4 concentration. Relationships of dose regimen, cause of hyperthyroidism, and other factors (including gender, age of onset, and other clinical and laboratory parameters), with outcome of treatment, are discussed below.

Radioiodine dose regimen

Age, gender, and other pretreatment variables (including goiter size and type, serum free T_4 concentrations, and the use of antithyroid drugs) were similar for patients in the two radioiodine dose groups. There was a significantly higher cure rate for patients treated with a first dose of 370 MBq, compared with those given 185 MBq (84.6% *vs.* 66.6%, $P < 0.0001$) (Table 2). Assessment of thyroid status, at 1 yr after treatment, demonstrated a greater incidence of hypothyroidism in patients given the larger dose of radioiodine (370 MBq *vs.* 185 MBq, 60.8% *vs.* 41.3%, $P < 0.0001$). After treatment with a second dose of radioiodine, however, there was little difference in the total incidence of hypothyroidism, at 1 yr, between the two dose regimens (71.4% *vs.* 66.4%, $P = 0.13$). The association between size of the first dose administered and the requirement for more than one dose of radioiodine was, in addition to association with a number of other variables (see below), determined using logistic regression analysis [estimated odds ratio, 3.9; 95% confidence interval (CI), 2.4–6.3; $P < 0.0001$] (see Table 5). Radioiodine dose was also a significant contributing factor for the development of hypothyroidism, after adjusting for cause of hyperthyroidism (estimated odds ratio, 2.4; 95% CI, 1.8–3.3; $P < 0.0001$).

Cause of hyperthyroidism

The mean age, at presentation, was lowest in patients with Graves' disease and greatest in the group with toxic nodular hyperthyroidism. In contrast, patients with Graves' disease had significantly more severe hyperthyroidism at diagnosis than those with toxic nodular disease ($P < 0.0001$). As might be expected from a mixed group comprising patients with Graves' disease and/or toxic nodular hyperthyroidism, the mean age and mean serum free T_4 concentrations for patients in the indeterminate group were intermediate between the other two groups. A significantly greater proportion of males was present in the group with Graves' disease, compared with those with toxic nodular disease ($P < 0.01$). A goiter was palpable in all patients with toxic nodular hyperthyroidism (by definition) and in 82.2% of patients with Graves' disease. In subjects with hyperthyroidism of indeterminate etiology, however, more than 50% of patients had no palpable goiter. There was no significant difference in the cure rate, after one dose of radioiodine, between Graves' disease and toxic nodular goiter; but Graves' patients had a significantly higher incidence of hypothyroidism ($P < 0.0001$) (Table 3). Patients with hyperthyroidism of indeterminate etiology had a significantly higher rate of cure after one dose of radioiodine, compared with patients with Graves' disease and toxic nodular goiter. Logistic regression analysis did not demonstrate significant association between the underlying cause of hyperthyroidism and cure after one dose of radioiodine; but it did show the diagnosis of Graves' disease to be a contributing factor to the development of hypothyroidism, after adjusting for the effect of radioiodine dose (estimated odds ratio, 2.5; 95% CI, 1.5–3.9; $P < 0.0001$).

Gender

Characteristics of males and females at presentation of hyperthyroidism were similar, although males had nonsignificantly higher serum free T_4 concentrations at diagnosis (males, 55.2 ± 2.3 pM (mean ± SE); females, 50.2 ± 1.3 pM; $P = 0.06$). In contrast, females had a significantly higher prevalence of palpable goiter, compared with males (71.2% *vs.* 60.6%, $P < 0.01$) and a nonsignificantly larger proportion of goiters classified clinically as medium or large in size (23.3% *vs.* 19.4%, $P = 0.3$). Males had a significantly lower cure rate, after one dose of radioiodine, than females ($P = 0.02$) (Table 4). This difference was even greater when the underlying diagnosis was Graves' disease (52.2% *vs.* 74.2%, $P < 0.001$). The incidence of hypothyroidism did not vary significantly between females and males (50.5% *vs.* 49.4%, $P = 0.9$). An association between male sex and requirement for more than one dose of radioiodine was, in addition to association with a number of other variables (see below), determined using logistic regression analysis (estimated odds ratio, 1.9; 95% CI, 1.1–3.2; $P = 0.03$) (Table 5).

Age of onset

For analysis, patients were divided into those less than 40 yr old at presentation and those greater than 40 yr old. Younger patients more frequently had palpable goiter (82.2% *vs.* 58.8%, $P < 0.0001$) and were more likely to have goiters judged clinically to be medium or large in size (38.1% *vs.* 10.5%, $P < 0.0001$). Likewise, younger patients had more severe hyperthyroidism at presentation (<40 yr, mean free T_4 at presentation, 59.8 ± 2.0 pM; >40 yr, 46.8 ± 1.3; $P < 0.0001$). Patients in the younger age group were more likely to fail to respond to a single dose of radioiodine than patients in the older group ($P < 0.001$) (Table 4). The incidence of hypothyroidism did not vary significantly between the younger and older age groups (51.4% *vs.* 49.9%, $P = 0.7$). Similar

TABLE 2. Outcome for a single fixed first dose of radioiodine at 1 yr for patients with all causes of hyperthyroidism treated with 185 MBq and 370 MBq

	185 MBq n = 443	370 MBq n = 370	Statistical significance (P) of difference between ^{131}I groups (by χ^2 test)
Hypothyroid	41.3%	60.8%	$P < 0.0001$
Euthyroid	25.3%	23.8%	$P = 0.6$
Euthyroid + hypothyroid (cure)	66.6%	84.6%	$P < 0.0001$
Treated with 2nd dose of ^{131}I	33.4%	15.4%	$P < 0.0001$

TABLE 3. Outcome of a single fixed dose (185 MBq or 370 MBq) of radioiodine for patients with Graves' disease, toxic nodular hyperthyroidism, and hyperthyroidism of indeterminate etiology

	Hypothyroid	Euthyroid	Hypothyroid + euthyroid	Treated with 2nd dose ^{131}I
Toxic nodular hyperthyroidism n = 126	31.7%	39.7%	71.4%	28.6%
Graves' disease n = 321	54.5%	15%	69.5%	30.5%
Hyperthyroidism of indeterminate etiology n = 366	53.0%	27.6%	80.6%	19.4%

TABLE 4. The relationship of clinical factors with outcome of radioiodine treatment

	Cure with 1 dose of radioiodine	Cure with >1 dose of radioiodine	Statistical significance (P) of difference between ^{131}I outcome groups (by χ^2/t test)
Sex			
Males (%)	67.6	32.4	$P = 0.02$
Females (%)	76.7	23.3	
Age			
<40 yr (%)	68.9	31.1	$P < 0.001$
>40 yr (%)	79.3	20.7	
Goiter			
None (%)	86.1	13.9	$P < 0.0001$
Small (%)	75.7	24.3	
Medium/large (%)	57.4	42.6	
Antithyroid drugs			
Yes (%)	70.4	79.1	$P = 0.02$
No (%)	29.6	20.9	
Free T_4 at diagnosis (pM; mean ± SE)	47.9 ± 1.2	61.4 ± 2.3	$P < 0.0001$

TABLE 5. Factors predictive of an unsuccessful response to one dose of radioiodine using logistic regression analysis

	Adjusted odds ratio of successful response	95% Confidence interval	Statistical significance P-value
Male sex	1.9	1.1–3.2	0.03
Free T_4 concentration at presentation	1.03	1.02–1.04	<0.0001
Medium/large goiter	6.6	3.2–13.6	<0.0001
Radioiodine dose (185 MBq)	3.9	2.4–6.3	<0.0001

findings were evident when age was analyzed as a continuous variable. Using logistic regression, the contribution of age to outcome of radioiodine treatment was statistically nonsignificant because of strong association between serum free T_4 concentration at presentation and goiter size.

Other clinical and laboratory factors

Goiter size at presentation was strongly associated with mean free T_4 at presentation ($P < 0.0001$) and age at onset of hyperthyroidism ($P < 0.0001$). The presence of a palpable goiter (in particular, a goiter judged to be medium or large) was associated with failure to respond to a single dose of radioiodine ($P < 0.0001$) (Table 4). Patients who required more than one dose of radioiodine also had higher serum mean free T_4 at presentation (61.4 ± 2.3 *vs.* 47.9 ± 1.2 pM, $P < 0.0001$) than patients who were cured with one dose (Table 4). The use of antithyroid drugs within 2 wk before or after radioiodine administration was significantly associated with failure to respond to one dose of radioiodine ($P = 0.02$) (Table 4). Further analysis of antithyroid drugs, in the two radioiodine regimens used, demonstrated a significant association with failure to respond to a fixed dose of 185 MBq ($P < 0.01$) but not with 370 MBq ($P = 0.3$). Logistic regression analysis showed the presence of palpable goiter (estimated odds ratio, 6.6; 95% CI, 3.2–13.6; $P < 0.0001$) and the severity of hyperthyroidism (estimated odds ratio, 1.03; 95% CI, 1.02–1.04; $P < 0.0001$) to be significant contributing factors to failure to respond to a single dose of radioiodine, after adjusting for gender, dose administered, and age of onset of hyperthyroidism (Table 5).

Discussion

The use of radioiodine in hyperthyroidism is increasing, particularly as first line therapy for Graves' disease (where the likelihood of success with antithyroid drugs is modest). Furthermore, younger patients are now offered radioiodine earlier in the course of their disease (24), because evidence suggests that onset of Graves' hyperthyroidism at a young age is associated with increased likelihood of relapse after medical treatment (3, 25, 26). Over the last 30 yr, much attention has focused on achieving euthyroidism by adjusting the dose of radioiodine. Regimens used have included various fixed doses and doses calculated on the basis of the size of the thyroid gland by means of ultrasonography or

isotope scans, these methods being superior to assessment of thyroid size by palpation alone (27). Some formulas also incorporate measurements of isotope uptake or turnover. Most dosimetric methods incorporate thyroid size in their formulas, because this has been considered to be an important prognostic factor for success after radioiodine treatment. Measures of isotope uptake or turnover have the additional advantages of confirming the presence or absence of thyroiditis and identifying patients with values at the extreme ends of the reference range, which are likely to indicate subsequent failure of radioiodine treatment (10). Despite this, the evidence from several studies is that calculated doses of radioiodine do not have any benefit over fixed doses, in terms of improving cure rates (8, 11, 12) or in preventing the development of hypothyroidism (9); so many clinicians prefer the use of a fixed-dose regimen (1). Although low fixed doses (185 MBq) are associated with a reduced early incidence of hypothyroidism, they often result in unacceptably low cure rates. Moreover, the development of long-term hypothyroidism seems to be inevitable, irrespective of the amount of radioiodine administered, with an annual incidence of 2–3% many years after therapy (2, 24). Some clinicians now prefer to give a large ablative dose (555 MBq and upwards), which results in early hypothyroidism, so that the need for long-term follow-up of thyroid function in euthyroid patients is obviated. Concerns about the possible long-term effects of radioiodine and T_4 replacement therapy (28), however, suggest the need for caution in increasing the amount of radioiodine administered to achieve an acceptable cure rate. It may be possible to improve cure rates using a single fixed-dose regimen without increasing the dose in all patients. This might be achieved by the identification of subjects with poor prognostic factors who are unlikely to respond to standard doses and by administering larger doses only to these individuals.

Several factors have been considered to influence the outcome of radioiodine treatment. Many studies have demonstrated that patients with larger-volume thyroid glands (6, 7, 29) and severe hyperthyroidism (7, 9, 16, 30) are more likely to fail to respond to a single dose of radioiodine. In addition to the amount of radioiodine administered, these two clinical factors are widely regarded as the most reliable predictors of response to treatment. Patients with toxic nodular goiter have often been stated to be more resistant to radioiodine than those with Graves' disease and have consequently received larger doses (15). Our own previous findings, however, have not shown an excess of persistent hyperthyroidism in patients with toxic nodular hyperthyroidism (16), suggesting this view needs reconsideration. Although antithyroid drugs are known to confer a degree of radioresistance, results have been conflicting, with some (19, 20), but not all (31), studies reporting a reduction in response rates to radioiodine if patients have received pretreatment with antithyroid drugs. Furthermore, some studies have shown an effect only with propylthiouracil alone (21).

In the present study, we have compared outcome of treatment with two single fixed-first-dose regimens of radioiodine (185 MBq and 370 MBq), used within our center, in hyperthyroid patients with Graves disease' and toxic nodular hyperthyroidism. Outcome after radioiodine treatment was defined as the number of doses of radioiodine required to result in cure of hyperthyroidism (euthyroid off all treatment for 6 months or T_4 replacement for biochemical hypothyroidism). Euthyroidism was defined in accord with our previous studies (3, 16) and those of others (32, 33). It should be noted that serum TSH concentrations remained suppressed in a number of subjects assigned to the cured group. It is well recognized that TSH suppression can persist for several months, or even years, after successful treatment of hyperthyroidism with thionamide drugs or radioiodine (34). Whether such patients should be considered euthyroid or considered for further antithyroid treatment is controversial and a subject for debate (35). Our data from the present study demonstrated a significantly greater response to a single fixed dose of radioiodine of 370 MBq, compared with a 185-MBq dose, with only 15% of patients who were given the former dose requiring treatment with a second dose to achieve cure of hyperthyroidism. In contrast, twice as many subjects required a second treatment after a first dose of only 185 MBq. The cure rates determined for these two fixed doses of radioiodine are in accord with our own previous findings (16) and those of others (6). As expected, there was an increase in incidence of hypothyroidism, at 1 yr, using the larger dose. When second or further doses were administered to achieve cure in those with persistent hyperthyroidism, the total incidence of hypothyroidism at 1 yr was similar for the two groups divided according to the size of the first fixed dose (370 MBq *vs.* 185 MBq, 71.4% *vs.* 66.4%), so that any advantage in terms of development of hypothyroidism for the low-dose regimen was lost.

Despite previous reports of lower response rates in toxic nodular goiter (15), we found almost identical cure rates in patients with toxic nodular hyperthyroidism and Graves' disease. Patients with toxic nodular hyperthyroidism were predictably less likely to develop hypothyroidism, presumably because uptake of radioiodine was restricted mainly to hyperfunctioning autonomous areas within the gland. Although radioiodine is clearly successful in curing hyperthyroidism in such patients, surgery should be discussed as a treatment option because of the small risk of malignancy within residual nonfunctioning thyroid nodules (36); surgical treatments include hemithyroidectomy (with ultrasound) for patients with unilateral toxic nodular goiter or total thyroidectomy for multinodular toxic goiter. The group of indeterminate etiology comprised patients with both Graves' disease and toxic nodular disease, although a majority of these patients would be expected to have Graves' disease because of a significantly higher prevalence of this condition in the United Kingdom (37, 38). In this group, we found the highest cure rate, with a single dose of radioiodine, of the three diagnostic groups. This probably reflected the low prevalence of palpable goiter and lower proportion of patients with goiters of medium or large size. The prevalence of hypothyroidism was, however, similar to the Graves' disease group of patients.

Male patients had a significantly worse outcome after treatment than females, despite a reduced prevalence of palpable goiter in males. This observation was even more marked in those with Graves' disease, where the cure rate with a single dose of radioiodine was only 50%. Gender has

not previously been demonstrated to be a significant prognostic factor for response to radioiodine treatment of hyperthyroidism, other than in Graves' disease by ourselves (3); although one previous smaller study, using several different dose regimens, did show a nonsignificant trend (6). Patients who developed hyperthyroidism at an early age responded poorly to treatment, compared with older patients, but this finding was attributable to a strong association with goiter and severity of hyperthyroidism, such that age became nonsignificant after logistic regression analysis. Our findings for goiter and severity of hyperthyroidism are in agreement with other studies (6, 7, 9, 16, 29, 30). The use of antithyroid drugs within 2 wk of radioiodine administration was a significant predictor of failure to respond to a 185-MBq dose of radioiodine but did not have a significant effect in those given a higher dose. The contribution of antithyroid drugs, therefore, seems to be clinically relevant at lower doses and may be overcome by the administration of a larger amount of radioiodine.

Factors that influence the response to radioiodine treatment have previously been reported by ourselves in a study of outcome of medical and radioiodine treatment in Graves' disease (3). In the present study, we have expanded our previous cohort of Graves' disease patients treated with radioiodine, with longer follow-up of subjects in whom outcome was not previously determined and also by the inclusion of new patients. The present findings confirm the results of our earlier study in Graves' disease (3) and demonstrate similar effects in patients with toxic nodular goiter, in terms of cure of hyperthyroidism after a single fixed dose of radioiodine. These findings are also evident in a large mixed group of patients, where it is not possible to determine the underlying diagnosis by clinical examination and immunological investigation, providing further evidence that the approach to treatment with radioiodine should be the same for patients with Graves' disease and toxic nodular goiter.

The results of the present study of a large cohort of patients with hyperthyroidism demonstrate that a single fixed dose of 370 MBq of radioiodine is highly effective in curing toxic nodular hyperthyroidism as well as Graves' hyperthyroidism. In contrast to previous studies, we have not demonstrated any difference in response to treatment between these two categories of patients; and therefore, treatment protocols for these groups should be identical. Although the cure rate for this regimen is good, potential for improvement exists by taking into account poor prognostic factors in individual patients. The striking findings that male sex, high serum free T_4 concentrations at diagnosis before the initiation of treatment, and presence of medium-sized or large goiter do influence the response to treatment determine that these factors should be taken into consideration when planning treatment. If such factors are present, the present retrospective review suggests that the initial dose should be increased, although this would need to be addressed in a prospective study. The present findings also highlight the value of clinical databases in allowing investigation of factors associated with adverse outcomes of treatment and recognition of clinical factors that have not previously been regarded as important determinants of outcome.

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