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Long-term follow-up study of radioiodine treatment of hyperthyroidism

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Summary

OBJECTIVE To determine the cumulative incidence of hypothyroidism during long-term follow-up in patients treated for hyperthyroidism by radioactive iodine ^{131}I (RAI) therapy, the significance of clinical factors in predicting the development of hypothyroidism, and the outcome after a fixed 7 mCi (259 MBq) dose of RAI.

DESIGN Prospective cohort study of patients treated for hyperthyroidism by RAI.

PATIENTS AND MEASUREMENTS Since 1965, details on 2043 patients treated by RAI therapy in Tampere University Hospital were entered into a computerized register. Following RAI treatment, thyroid status was monitored every 1–3 months during the first year, and subsequently at 1–3-year intervals until June 2002 or until the patient died or moved out of the Tampere University Hospital district.

RESULTS The cumulative incidence of hypothyroidism in patients with Graves' disease and toxic multinodular goitre at 1, 10 and 25 years was 24% *vs.* 4%, 59% *vs.* 15% and 82% *vs.* 32%, respectively. In a Cox regression model, previous partial thyroidectomy [risk ratio (RR) = 1·63 in patients with Graves' disease and RR = 1·59 in those with toxic multinodular goitre] and age at the first RAI treatment (RR = 0·998 and RR = 0·996 per year) were statistically significantly associated with the development of hypothyroidism both in patients with Graves' disease and in those with toxic multinodular goitre. Antithyroid medication preceding RAI therapy (RR = 0·47) decreased and female gender (RR = 1·53) increased the risk of hypothyroidism only in patients with Graves' disease. Administration of a single dose of RAI resulted in the control of hyperthyroidism in 75% of patients, while two to six RAI treatments were needed in 25% of patients to achieve either a hypothyroid or a euthyroid state in both groups. None of the clinical factors studied was associated with the remission rate either in patients with Graves' disease or in those with toxic multinodular goitre. The remission rate did not differ between the patients who received a dose of RAI calculated according to the uptake of RAI and thyroid size and those who received an empirical dose of RAI. The fixed 7 mCi (259 MBq) dose of RAI cured 80% of patients.

CONCLUSION RAI treatment is effective in treating hyperthyroidism in patients with Graves' disease, but hypothyroidism will develop in 82% of patients in 25 years. Because the development of hypothyroidism seems to be inevitable and unpredictable by any clinical factors, the objective of RAI treatment should be to minimize the persistence of hyperthyroidism with the simplest possible form of treatment. We recommend a fixed 7 mCi dose of RAI to be used as the first empirical dose in the treatment of hyperthyroidism, at least in Graves' disease.

Hyperthyroidism affects approximately 2% of women and 0·2% of men (Tunbridge *et al*., 1977). Radioactive iodine ^{131}I (RAI) has been used to treat the condition for more than six decades (Chapman, 1983), and has proved clinically efficient, safe and cost-effective in comparison with other therapeutic alternatives, that is long-term antithyroid medication and surgery (Wartofsky, 1997). RAI has been used as a first-line therapy for hyperthyroidism, especially in the elderly (Gittoes & Franklyn, 1998), but the use of RAI is also increasing among younger patients, that is 18 years old or older (Wartofsky, 1996; Gittoes *et al*., 1998). However, RAI is contraindicated in children, in pregnancy and in breastfeeding mothers (Wartofsky, 1996; Gittoes *et al*., 1998). Administration of RAI to patients with active Graves' ophthalmopathy may cause an exacerbation of the eye symptoms, which might be prevented by the administration of glucocorticoids (Bartalena *et al*., 2000).

In previous studies, 6–15% of patients given low doses (< 185 MBq) of RAI (Sridama *et al*., 1984; Turner *et al*., 1985; Goolden & Stewart, 1986; Watson *et al*., 1988) and 50–60% of those receiving high doses (> 350 MBq) became hypothyroid

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during the first post-treatment year (Kendall-Taylor *et al*., 1984; Ahmad *et al*., 2002). In the longest follow-up studies, the cumulative incidence of hypothyroidism 20–25 years after the first RAI therapy has been 42–72% (Holm *et al*., 1982; Franklyn *et al*., 1991). Over the past few decades, much attention has been focused on achieving euthyroidism and avoiding hypothyroidism by adjusting the RAI dose. However, while it is possible to deliver a relatively precise dose of radiation to the thyroid gland, the biological response of the gland remains unpredictable (Catargi *et al*., 1999). Despite the numerous associations found between hypothyroidism or cure rate and different pretreatment variables, no single variable or combination of variables has been shown to predict the outcome after RAI therapy with sufficient confidence to justify the use of a mathematical formula in determining the dose individually (Turner *et al*., 1985; Jarlov *et al*., 1995; Catargi *et al*., 1999; Leslie *et al*., 2003). Thus, hypothyroidism has become an expected outcome of RAI treatment. Many clinics prefer a fixed dose regimen in RAI treatment (Nordyke & Gilbert, 1991; Gittoes *et al*., 1998; Allahabadia *et al*., 2001; Kalinyak & McDougall, 2003). As concluded recently, no consensus exists regarding the ideal first dose of RAI in the treatment of hyperthyroidism (Kalinyak & McDougall, 2003).

The aims of our study were to provide data on the cumulative incidence of hypothyroidism during long-term follow-up after RAI treatment for hyperthyroidism, to determine the significance of different clinical factors in predicting development of hypothyroidism, and to evaluate the outcome after a 7 mCi (259 MBq) dose of RAI, which has been administered as a fixed dose to most hyperthyroid patients in our hospital since 1990.

Patients and methods

Patients

The data were collected between January 1965 and June 2002. The details of all patients treated for hyperthyroidism with RAI in Tampere University Hospital were entered into a computerized register. The follow-up period commenced at the time of the first RAI treatment and continued until June 2002 or until the patient died or moved out of the Tampere University Hospital district. Patients who did not participate in the follow-up in Tampere University Hospital after RAI treatment for at least 12 months were excluded due to missing follow-up data. The flow chart of the study is shown in Fig. 1. The ethics committee of the Pirkanmaa Hospital District approved the systematic gathering and presentation of the data. The study was undertaken in accordance with the Declaration of Helsinki.

Methods

Hyperthyroidism was diagnosed when classical symptoms and signs of hyperthyroidism coexisted with biochemical evidence,

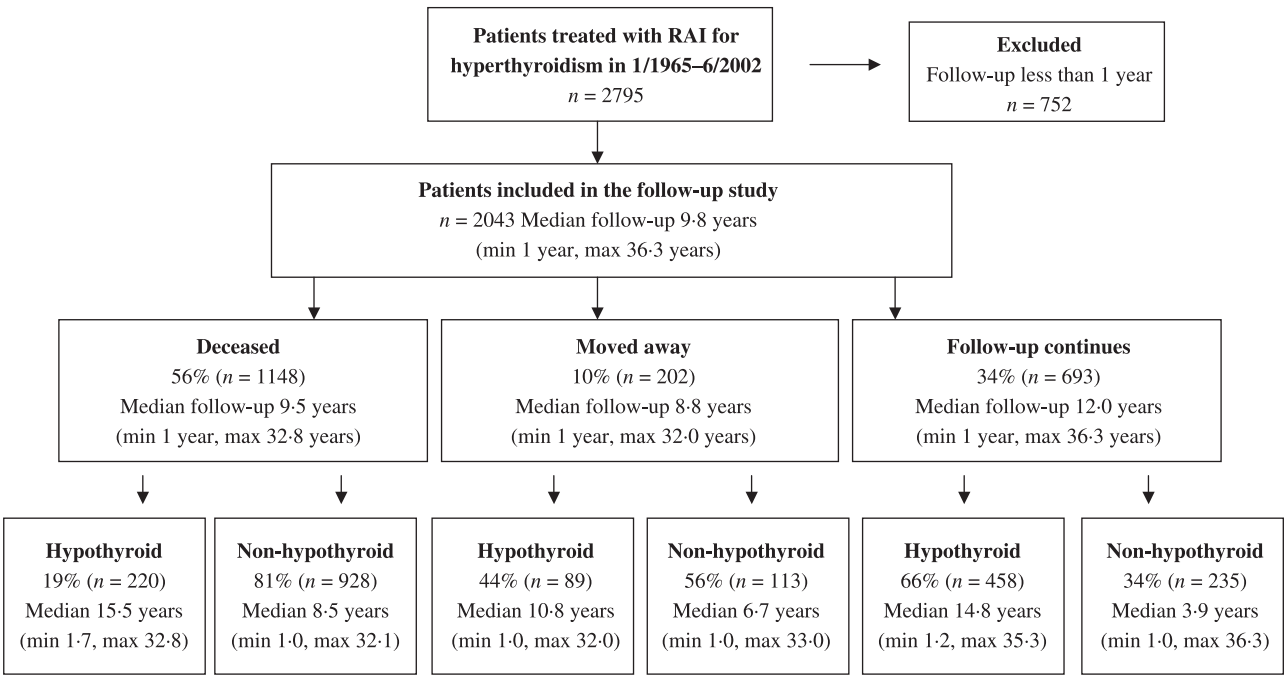


Fig. 1 Flow chart and follow-up times of patients.

that is high total T4 or free T4 associated with decreased levels of TSH (Gittoes *et al*., 1998). The aetiology of hyperthyroidism was determined by clinical examination. The diagnosis of Graves' disease was made if a diffuse goitre was present. The diagnosis of toxic nodular goitre was made if examination of the neck revealed nodularity within an enlarged thyroid. Toxic thyroid adenoma was diagnosed if a solitary nodule within an otherwise normal thyroid gland was present. If the cause of hyperthyroidism was not apparent by clinical examination, thyroid antibodies were measured. Furthermore, the aetiology was verified by thyroid scintigraphy in 72% of cases. The aetiology of hyperthyroidism was classified according to the Finnish version of the ICD (International Classification of Diseases) codes into three classes: Graves' disease, toxic multinodular goitre and toxic adenoma.

According to a common policy in Tampere University Hospital, most patients were given antithyroid drug therapy in order to achieve euthyroidism before treatment with RAI. The drug of choice was carbimazole unless the patient was allergic to it. The RAI treatment was given for most patients unless they were pregnant or breastfeeding or had severe eye symptoms of Graves' disease. Young patients as well as patients with eye symptoms of Graves' disease usually received long-term antithyroid drug therapy, and RAI was chosen only for those who suffered a relapse of Graves' disease after long-term antithyroid treatment. Surgical treatment was chosen if a patient had a very large multinodular or diffuse goitre causing symptoms of compression in the neck, or if there was a suspicion of a malignancy in the thyroid gland. Patients were informed to discontinue antithyroid drug therapy 4 days before RAI treatment and continue it again 4 days after RAI treatment. Subsequently, they gradually reduced the dose of antithyroid medication according to instructions until they discontinued it 4 weeks after RAI treatment.

Following the RAI treatment, the thyroid status of the patients was monitored by blood samples every 1–3 months during the first year, and subsequently at 1–3-years intervals. In addition, the patients completed a questionnaire on the symptoms of hypo- or hyperthyroidism, and reported their present medication for the thyroid illness (thyroxine or antithyroid drugs) and when the medication had been started. Patients were classified as hypothyroid when symptoms and biochemical evidence (i.e. low total T4 or free T4 associated with an elevation of TSH) suggested hypothyroidism and resulted in the initiation of thyroxine replacement therapy. Transient hypothyroidism after RAI therapy was not recorded. Patients were classified as having relapsed hyperthyroidism when symptoms and biochemical evidence (i.e. high total T4 or free T4 associated with decreased levels of TSH) necessitated repeated RAI therapy or continuous antithyroid medication lasting more than 1 year after the RAI therapy. The remission rate was determined as the proportion of patients who became euthyroid and hypothyroid after a single RAI treatment.

Statistical analysis

We used statistical software Stata 7·0 to calculate the incidence of hypothyroidism according to person-years after the first RAI treatment for hyperthyroidism. Other statistical analyses were performed using SPSS for Windows, version 11·0. A *P*-value less than 0·05 was considered statistically significant. The cumulative incidence of hypothyroidism was determined by Kaplan–Meier life-table analysis. Normality of the distribution of the variables studied was tested by Kolmogorov–Smirnov test. The distribution of all continuous variables was skewed. The values of continuous variables are expressed as median (minimum, maximum). Categorical variables are expressed as frequencies. Association between two continuous variables was estimated with Spearman's correlation coefficient. According to the number of categorical variables, the Mann–Whitney test or Kruskal–Wallis test was used to assess the relationship between continuous and categorical variables. The χ^2-test was used to determine whether an association seen between two categorical variables was statistically significant. Cox regression analysis was performed to evaluate the significance of different clinical factors in predicting hypothyroidism. An event was the development of hypothyroidism and the covariates were gender, the aetiology of hyperthyroidism (Graves' disease, toxic multinodular goitre or toxic adenoma), previous partial thyroidectomy (yes or no), preceding antithyroid treatment (yes or no), duration of antithyroid treatment (< 3 months, 3 – 6 months or > 6 months), remission of hyperthyroidism after the first dose of RAI (yes or no), age at the first RAI treatment (years), 24-h uptake in thyroid scintigraphy (%), and the first dose of RAI (MBq). Patients who did not develop hypothyroidism were censored in June 2002 or when they died or moved out of the Tampere University Hospital district.

Results

During the past 37 years (January 1965 to June 2002) a total of 2795 patients suffering from hyperthyroidism were treated with RAI in Tampere University Hospital and included in the computerized register. Twenty-seven per cent of these patients did not participate in the follow-up for 1 year and were excluded. Figure 1 shows the number and follow-up times of the remaining 2043 patients according to different end-point groups. During the follow-up, hypothyroidism was diagnosed and treated in 38% of the patients. The median time to the development of hypothyroidism was 2 years (minimum 1 month, maximum 25·4 years).

The clinical characteristics of the patients according to different aetiological groups are presented in Table 1. In the whole population, the most common cause of hyperthyroidism was Graves' disease (53%). However, the distribution of the aetiology varied according to the decade studied. In the 1960s, toxic multinodular goitre was the most common cause of hyperthyroidism

Table 1 Clinical characteristics of the patients according to different aetiological groups

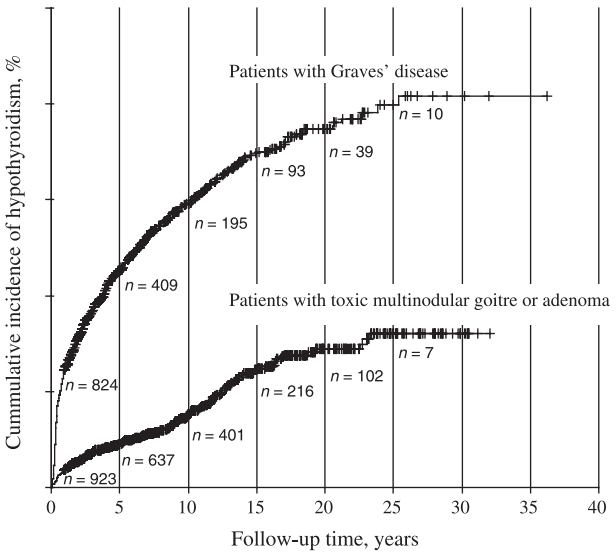
	Graves' disease (53%, *n* = 1086)	Toxic multinodular goitre (37%, *n* = 749)	Toxic adenoma (10%, *n* = 208)	All (*n* = 2043)
Gender*				
Male	18 (199)	13 (94)	16 (33)	16 (326)
Female	82 (887)	87 (655)	84 (175)	84 (1717)
Antithyroid drug*				
Yes	88 (958)	82 (616)	75 (156)	85 (1730)
No	8 (91)	15 (111)	22 (45)	12 (247)
Duration of antithyroid treatment*				
< 3 months	34 (373)	31 (230)	36 (75)	33 (678)
3–6 months	34 (365)	23 (170)	19 (39)	28 (574)
> 6 months	26 (286)	33 (249)	27 (57)	29 (592)
Post-operative				
Yes	12 (127)	12 (90)	13 (26)	12 (243)
No	78 (849)	81 (603)	83 (173)	80 (1625)
Remission after first dose of RAI				
Yes	76 (827)	74 (555)	77 (161)	75 (1543)
No	24 (259)	26 (194)	23 (47)	25 (500)
First dose of RAI (MBq)*	222 (55, 555)	259 (56, 740)	222 (55, 555)	222 (55, 740)
Total dose of RAI (MBq)*	259 (55, 2664)	259 (56, 2368)	259 (55, 1443)	259 (55, 2664)
Age at first RAI (years)*	56 (13, 90)	67 (25, 93)	65 (36, 84)	62 (13, 93)
24-h uptake in thyroid scintigraphy (%)*	68 (8, 99)	57 (12, 99)	49 (13, 87)	61 (8, 99)

Values are % (*n*) or median (min, max). *Statistically significant difference between the aetiological groups. The χ^2-test was used for two categorical variables, and the Kruskal–Wallis test for continuous and categorical variables.

(70%), while the proportion of diffuse goitre increased to be the major cause of hyperthyroidism in the 1990s (73%, aetiological group *vs.* decade studied, $P < 0{\cdot}001$). The patients with Graves' disease were slightly younger than the patients with toxic multinodular goitre or adenoma (Table 1). In the whole population, the proportion of patients who were treated before or at the age of 40 increased during the decades studied: 3% of the patients were less than 40 years old at the 1960s, 5% at the 1970s, 14% at the 1980s and 19% at the 1990s. Only 11 patients were less than 20 years old, and all of them had Graves' disease.

The incidence of hypothyroidism

Summarized follow-up times of all patients studied resulted in 15 251 person-years at risk of hypothyroidism after RAI treatment. The incidence of hypothyroidism was 50/1000 person-years at risk in all patients. In patients with Graves' disease the incidence of hypothyroidism was 103/1000 person-years at risk, in patients with toxic multinodular goitre 18/1000 and in patients with toxic adenoma 17/1000. In Fig. 2 the cumulative incidence of hypothyroidism and the number of patients at risk at 5-year intervals are shown in different aetiological groups. The cumulative incidence of hypothyroidism in patients with Graves' disease and those with toxic multinodular goitre or toxic adenoma were 24% *vs.* 4%, 59% *vs.* 15% and 82% *vs.* 32% at 1, 10 and 25 years, respectively.



n = Number of patients at risk at five years' intervals

Fig. 2 The cumulative incidence of hypothyroidism after RAI treatment for hyperthyroidism in patients with Graves' disease and in patients with toxic multinodular goitre or toxic adenoma.

Table 2 Clinical factors influencing the development of hypothyroidism after RAI treatment

	Graves' disease (n = 1086)			Toxic multinodular goitre or adenoma (n = 957)		
Factors	RR	95% CI	P-value	RR	95% CI	P-value
Gender						
Male	1·00			1·00		
Female	1·53	1·13–2·08	0·007	0·65	0·39–1·01	0·101
Antithyroid drug						
No	1·00			1·00		
Yes	0·47	0·33–0·68	< 0·001	1·43	0·61–3·36	0·411
Duration of treatment						
> 6 months	1·00			1·00		
3–6 months	0·92	0·70–1·22	0·571	1·05	0·70–1·58	0·808
< 3 months	0·99	0·77–1·28	0·954	1·18	0·76–1·82	0·469
Post-operative						
No	1·00			1·00		
Yes	1·63	1·24–2·14	0·001	1·59	1·04–2·42	0·031
Remission with first RAI dose						
No	1·00			1·00		
Yes	0·99	0·82–1·26	0·969	1·00	0·66–1·54	0·985
Age at first RAI therapy, RR per year	0·971	0·964–0·979	< 0·001	0·950	0·934–0·967	< 0·001
First dose of RAI, RR per MBq	0·998	0·998–1·001	0·467	0·996	0·994–0·999	0·003
24-h uptake (%) RR per %	1·004	0·996–1·012	0·308	1·002	0·989–1·014	0·809

Cox regression analysis. Method: enter.

In order to evaluate the significance of different clinical factors in predicting the development of hypothyroidism, Cox regression analysis was undertaken with hypothyroidism as an event and the clinical characteristics presented in Table 1 as covariates. The risk ratios are shown in Table 2 separately in patients with Graves' disease and those with toxic multinodular goitre or adenoma. Previous partial thyroidectomy and age at the first RAI treatment were statistically significantly associated with the development of hypothyroidism both in patients with Graves' disease and in those with toxic multinodular goitre. Antithyroid medication preceding RAI therapy decreased and female gender increased the risk of hypothyroidism only in patients with Graves' disease. The first dose of RAI did not affect the risk of hypothyroidism in patients with Graves' disease. Surprisingly, in patients with multinodular goitre or adenoma, hypothyroidism developed more easily in the patients receiving lower doses of RAI than in those receiving higher doses of RAI; that is the risk ratio was 0·996 per MBq.

There was an inverse correlation between age at the first RAI treatment and the uptake of RAI in thyroid scintigraphy (Spearman's correlation coefficient was −0·21 (P < 0·001) and −0·12 (P < 0·001) in patients with Graves' disease and in those with toxic multinodular goitre or adenoma, respectively). In patients with Graves' disease the uptake of RAI did not differ between patients who received antithyroid drugs and those who did not (P = 0·168). In patients with toxic multinodular goitre or adenoma the median uptake of RAI was slightly higher in patients who received antithyroid drugs than in those who did not (P < 0·001, 57% *vs.* 47%, respectively).

If the cumulative dose of RAI was included in the Cox regression analysis instead of the first dose of RAI, the cumulative dose had no influence on the risk of hypothyroidism in patients with Graves' disease [risk ratio (RR) 0·999 per 1 MBq, 95% confidence interval (CI) 0·998–1·000, P = 0·092]. However, in patients with toxic multinodular goitre or adenoma there was an inverse correlation between the cumulative dose and the development of hypothyroidism; that is, the higher the dose needed to cure hyperthyroidism the lower the risk of hypothyroidism (RR 0·998 per 1 MBq, 95% CI 0·996–0·999, P = 0·006).

Remission rate after RAI treatment

To achieve either a hypothyroid or a euthyroid state, two RAI treatments were needed in 373 (18%) patients, three in 69 (3%) cases, four in 26 (1%), five in seven (0·3%) and six in four (0·2%) cases. One per cent (n = 21) of patients received antithyroid treatment for more than 1 year after the first RAI treatment to maintain a euthyroid state. The second RAI dose was given for persistent hyperthyroidism after a median of 10 months (minimum

4 months, maximum 33 years). The number of RAI treatments needed to achieve remission did not differ between the aetiological groups ($P = 0{\cdot}819$).

Administration of a single dose of RAI resulted in the control of hyperthyroidism in 76% of the patients with Graves' disease, 74% of the patients with toxic multinodular goitre and 77% of the patients with toxic adenoma ($P = 0{\cdot}484$) (Table 1). In patients with Graves' disease ($n = 1086$), the distribution of gender ($P = 0{\cdot}581$), antithyroid medication preceding RAI therapy ($P = 0{\cdot}158$), duration of antithyroid medication ($P = 0{\cdot}236$) and surgical treatment ($P = 0{\cdot}504$) did not differ between those patients who were cured with a single dose of RAI and those who needed more than one dose of RAI or prolonged antithyroid treatment to achieve remission. Neither did the first dose of RAI ($P = 0{\cdot}360$) nor the age at the first RAI treatment ($P = 0{\cdot}826$) differed between the cured patients and those with persistent hyperthyroidism. The 24-h uptake in thyroid scintigraphy was slightly lower in patients who achieved remission with a single dose of RAI than those who needed several doses or prolonged antithyroid therapy (median 67% *vs.* 72%, $P = 0{\cdot}001$). The results were similar in patients with toxic multinodular goitre or adenoma.

The effect of an empirical 7 mCi dose vs. other doses of RAI on outcome after RAI treatment

Until the end of the 1980s, thyroid scintigraphy with measurement of RAI uptake and the weight of the thyroid gland estimated by palpation were used to calculate the dose of RAI in Tampere University Hospital. Thereafter, the dose has been chosen empirically. The remission rate did not differ between the patients who received a dose of RAI calculated according to the uptake of RAI and thyroid size ($n = 1477$) and those who received an empirical dose of RAI ($n = 566$) either in patients with Graves' disease ($P = 0{\cdot}128$) or in those with toxic multinodular goitre or adenoma ($P = 0{\cdot}337$).

Since 1990, a fixed 7 mCi (259 MBq) dose of RAI has been recommended as the first dose for all hyperthyroid patients. A total of 364 patients received the recommended 7 mCi dose. However, other empirical doses were also used: 61 patients received 5 mCi (185 MBq), 29 patients received 10 mCi (370 MBq) and 112 patients received other empirical doses; median 6 mCi (222 MBq), minimum 1·5 mCi (55 MBq) and maximum 15 mCi (555 MBq). The clinical characteristics of the patients in the different dose groups are presented in Table 3. The remission rate did not differ statistically significantly between the dose groups (80% in patients who received 7 mCi, 77% in patients who received 5 mCi and 69% in patients who received 10 mCi).

The cumulative incidence of hypothyroidism 1 year and 25 years after RAI treatment was 23% *vs.* 15% *vs.* 13% and 59% *vs.* 57% *vs.* 46% in patients given 7 mCi, 5 mCi or 10 mCi as the first empirical dose of RAI, respectively. The patients given 5 mCi as the first empirical dose of RAI had lower risk and those given 10 mCi similar risk of hypothyroidism compared with those given the recommended 7 mCi dose, when adjusted for the other clinical characteristics by Cox regression analysis.

Table 3 Clinical characteristics of patients given 7 mCi and those given other empirical doses

	7 mCi	5 mCi	10 mCi	*P*-value
Gender, % (*n*)				0·482
Male	16 (60)	12 (7)	21 (6)	
Female	84 (304)	88 (54)	79 (23)	
Aetiology of hyperthyroidism, % (*n*)				0·275
Graves' disease	81 (296)	72 (44)	86 (25)	
Toxic multinodular goitre	16 (58)	26 (16)	14 (4)	
Toxic adenoma	3 (10)	2 (1)	0 (0)	
Antithyroid drug, % (*n*)				0·030
Yes	97 (338)	95 (57)	86 (25)	
No	3 (12)	5 (3)	14 (4)	
Duration of antithyroid treatment, % (*n*)				0·171
< 3 months	47 (168)	37 (22)	50 (14)	
3–6 months	36 (131)	36 (21)	43 (12)	
> 6 months	17 (60)	27 (16)	7 (2)	
Post-operative, % (*n*)				0·525
Yes	9 (28)	10 (6)	3 (1)	
No	91 (270)	90 (51)	97 (28)	
Remission after first dose of RAI, % (*n*)				0·354
Yes	80 (291)	77 (47)	69 (20)	
No	20 (73)	23 (14)	31 (9)	
Age at first RAI, years, median (min, max)	59 (13, 88)	65 (21, 83)	53 (27, 84)	0·051

The χ^2-test was used for two categorical variables, and the Kruskal–Wallis test for continuous and categorical variables.

Discussion

The relationship of clinical factors to the outcome after RAI treatment

There are only a few previously published long-term follow-up studies regarding RAI treatment of hyperthyroidism. In the present study, most patients with Graves' disease eventually developed hypothyroidism. Our results are consistent with an earlier long-term follow-up study (Holm *et al*., 1982). In the patients with toxic multinodular goitre, however, the cumulative incidence of hypothyroidism seemed to level off at 30% 15 years after RAI treatment. The differences in the development of hypothyroidism in long-term follow-up might result from the different nature of Graves' disease and toxic multinodular goitre. The higher rate of hypothyroidism in patients with Graves' disease than in patients with toxic multinodular goitre might result from the protection of the suppressed normal extranodular tissue by its inability to concentrate RAI in patients with toxic multinodular goitre (Holm *et al*., 1982; Ahmad *et al*., 2002). Furthermore, Graves' disease is an autoimmune disease of the thyroid gland caused by anti-thyrotrophin receptor antibodies, which may subside in the course of time and in some cases may also cause hypothyroidism (Akamizu, 2001). In fact, approximately 15% of patients who receive only antithyroid medication for Graves' disease develop hypothyroidism after discontinuation of the treatment, reflecting the autoimmune nature of Graves' disease (Gittoes *et al*., 1998).

The present long-term follow-up study did not verify earlier reports of a dose–response relationship between the radioactive dose and the rate of hypothyroidism or a positive correlation between the cure rate and hypothyroidism (Doi *et al*., 2001). The associations between clinical factors and the risk of hypothyroidism found in our study were not strong enough to justify the use of individually adjusted doses of RAI for treatment of hyperthyroidism. The reliability of predicting the development of hypothyroidism after RAI treatment for hyperthyroidism has also been poor (50–60% by multivariate logistic regression models) in previous studies (Turner *et al*., 1985; Kung *et al*., 1990). Thus, the objective of RAI treatment should be to achieve and maintain long-term remission with the simplest possible form of treatment.

The effect of an empirical 7 mCi dose vs. other doses of RAI on outcome after RAI treatment

Administration of empirical doses of RAI has been preferred to calculated doses in many clinics, because the need to measure the size and the RAI uptake of the thyroid gland involves considerable inconvenience to the patient and additional costs. The preparation of doses of RAI of varying sizes also means extra work. In a few randomized clinical trials, a fixed dose and a calculated dose of RAI have been compared directly in the treatment of hyperthyroidism (Smith & Wilson, 1967; Jarlov *et al*., 1995; Peters *et al*., 1997; Leslie *et al*., 2003). The advantages of a variety of dose calculation methods have been few and of little clinical significance (Smith *et al*., 1967; Jarlov *et al*., 1995; Peters *et al*., 1995; Leslie *et al*., 2003). Our results were consistent with these earlier studies: the remission rate did not differ between the patients who received a calculated dose of RAI and those who received an empirical dose.

There has been no consensus concerning the ideal fixed dose to be used. In previous literature doses of RAI varying between 5 and 10 mCi (185–370 MBq) have been recommended as the standard fixed dose in RAI treatment for hyperthyroidism (Watson *et al*., 1988; Allahabadia *et al*., 2001). A fixed 7 mCi (259 MBq) dose has been used as a standard treatment for hyperthyroidism since 1990 in Tampere University Hospital. In earlier studies remission rates of 67–72% with a 5 mCi dose of RAI and 85% with a 10 mCi dose have been reported (Watson *et al*., 1988; Allahabadia *et al*., 2001). There are no previous data on the remission rate after a fixed 7 mCi dose of RAI. In our study the remission rate achieved with the fixed 7 mCi dose of RAI was 80%. There seem to be no clinically significant differences in the outcome after the fixed 7 mCi dose selected in our clinic and the 10 mCi dose preferred in several clinics. However, to confirm this a randomized study comparing different empirical doses would be needed.

We conclude that RAI treatment is effective in treating hyperthyroidism in patients with Graves' disease, but hypothyroidism will develop in 82% of patients in 25 years. Because the development of hypothyroidism seems to be inevitable and unpredictable by any clinical factors, the objective of RAI treatment should be to minimize the persistence of hyperthyroidism with an easily manageable treatment scheme with minimal costs. We recommend a fixed 7 mCi dose of RAI to be used as the first empirical dose in the treatment of hyperthyroidism, at least in Graves' disease.

Acknowledgements

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