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Fixed Dose Radioactive Iodine Therapy in Hyperthyroidism: Outcome and Factors Affecting it in a Region in South India

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Abstract. **Objective:** Radioactive iodine-131 (RAI or ^{131}I) has been established as effective in the treatment of patients with various etiologies of hyperthyroidism. However, the short-term and long-term clinical outcome of patients receiving RAI differs in various studies. The aim of this study was to assess the clinical outcome one year after RAI therapy and identify factors associated with a good response. **Methods:** In this experimental study, 164 patients were included. They were randomly selected from patients referred to the Nuclear Medicine Department for Graves' disease, multinodular goiter, or toxic adenomas, which are indications for RAI therapy. The radioiodine dose was calculated based on the size of the thyroid gland by physical examination. Patients with normal thyroid glands were administered less than 10 mCi; patients with large thyroid glands or thyroid nodularity were administered a dose of greater than 10 mCi (approximately 15 mCi). Patients were monitored closely clinically and with blood investigations after treatment for one year. **Results:** Among 158 patients who completed follow up, 98.8% recovered and 1.2% remained thyrotoxic. Among patients who recovered, 74.2% became hypothyroid and 22.6% euthyroid. The incidence of hypothyroidism was 23% in first trimester, 43.7% in second trimester, 4.4% in third trimester, and 3.1% in forth trimester. **Conclusion:** In our study, a good result was seen in more patients than in other studies. The better outcome may be related to higher absorption of radioactive iodine in our region. The highest incidence of hypothyroidism was in the second trimester, so we recommend that patients should be carefully followed in this posttreatment period.

Keywords • Hyperthyroidism • Graves' disease • Radioiodine therapy • Outcome • Hypothyroidism

Introduction

Radioiodine therapy has enjoyed increasing popularity since its initial use in the 1960s for hyperthyroidism. Its popularity is based on its efficacy and low incidence of side effects.

Hyperthyroidism is a state of increased function of the thyroid gland leading usually to a clinical state of thyrotoxicosis. The most common cause of hyperthyroidism is Graves' disease, an autoimmune disease caused by an antibody (thyroid stimulating immunoglobulin) that is active against thyroid stimulating hormone receptors. Graves' disease accounts for 60%-to-80% of all cases of hyperthyroidism. Other common causes include toxic multinodular goiter and toxic adenomas.[1]

The main treatment options for persistent hyperthyroidism are antithyroid drugs, radioactive iodine (RAI), and surgery.[2,4,5] RAI-131, a radioactive isotope of iodine, is the treatment of choice for most patients with Graves' diseases and toxic nodular goiter. It is inexpensive, highly effective, easy to administer, tissue specific, and its safety has been proven in all age groups.[1]

Objectives of RAI Treatment. The primary goal of radioiodine therapy in Grave's disease is to cure the hyperthyroidism. It is controversial, however, whether radioiodine should be given in a dose sufficient to induce hypothyroidism or in a dose low dose in an attempt to provide the patient with a euthyroid state. Controversy exists also regarding the optimal dosing regimen of radioiodine to ablate the thyroid gland.

However, it is clear that most patients ultimately

develop hypothyroidism after therapy. Administration of relatively low doses of RAI-131 are designed to avoid hypothyroidism and to restore euthyroidism. But the low doses may simply delay hypothyroidism or fail to cure the hyperthyroidism.[2,3] Most patients who become euthyroid soon after radioiodine therapy eventually develop hypothyroidism at a rate of approximately 5% per year.[4]

The aim of treatment is to destroy sufficient thyroid tissue to cure hyperthyroidism by rendering the patients euthyroid or hypothyroid in the long term. The treatment is highly effective with a cure rate approaching 100% after one or more treatments, depending on the dose administered and various other factors.[6]

Potential Complications of RAI Treatment. Some complications from RAI treatment have been reported. These include delayed control of symptoms; transient neck soreness; flushing and decreased taste; and posttreatment hypothyroidism in the majority of Graves' patients (82% after 25 years) regardless of dosage. In addition, radiation thyroiditis occurs in 1% of patients. Because Graves' ophthalmology may be exacerbated, pretreatment with antithyroid drugs is required for older or cardiac patients.[1]

Previously, there was concern that this form of therapy might also produce thyroid carcinoma, leukemia, or an increase in mutation rates. However, in more than seven decades in which RAI has been in use, no increased prevalence of thyroid or other carcinoma in treated patients has been noted.[7,8]

Table 1. Characteristics of study patients.

Variable		Number	Percentage
Sex	Female	113	71.5%
	Male	45	28.5%
Cause of hyperthyroidism	Graves' disease	134	84.8%
	Toxic multinodular goiter	13	8.2%
	Toxic adenoma	11	6.9%
Duration of pretreatment antithyroid drug therapy	Less than 1 year	38	24.1%
	More than 1 year	120	75.9%
Recurrences of disease before RAI	1 time	82	52%
	2 times	11	7%
	More than 2 times	19	1.2%
RAI dose	Less than 10 mCi	72	45.6%
	More than 10 mCi	86	54.4%

The most important side effect is hypothyroidism. Many treating physicians state that this is the inevitable outcome. Many reports have documented that the incidence of hypothyroidism is significant during the first year or two after treatment with RAI, and thereafter, the incidence continues to increase at a rate of approximately 5% per year. Studies have reported the incidence of post-RAI hypothyroidism at 5 years to be between 30% and 50%, depending on dosage and geographical factors. However, values as high as 70% have been reported.[9]

About 1% of patients who undergo RAI may experience radiation thyroiditis 5-to-10 days later. These patients usually experience pain over the thyroid area of the anterior neck. Some have thyroiditis-associated hyperthyroidism due to the release of stored thyroid hormone, and an occasional patient may progress to posttreatment thyroid storm.[10] Also, there has been reluctance to use RAI in women of childbearing years because of potential genetic damage in future offspring. Long-term follow up of patients has not validated this concern.[11,12]

There is concern, then, over the long-term effects of RAI treatment. The aim of this study was to address the concerns by assessing the outcome 1 year after patients had received RAI therapy.

Material and Methods

Our study had the approval of the institutional review board and ethics committee of our Institute.

The study was carried out in accordance with the Declaration of Helsinki. Informed consent was obtained from all participating patients.

Patients who participated in the study were hyperthyroid patients referred to the Nuclear Medicine Department for RAI therapy for Graves' disease, multinodular goiter, or toxic adenoma. Among referred patients, 164 were randomly selected to take part in the study. (See Table 1 for characteristics of study patients.) Exclusion criteria were pregnancy, breast feeding, severe Graves' ophthalmopathy, and age under 20 years.

Iodine-containing medications were discontinued several weeks before RAI therapy and antithyroid-drugs were withdrawn at least 5 days before therapy. Most patients were put on pretreatment β-blockers that patients continued for approximately 2 weeks post therapy.

Doses of ^{131}I were calculated on the basis of the size of a patient's thyroid gland determined by physical examination. Patients with normal thyroid glands were given less than 10 mCi of ^{131}I; patients with large thyroid glands, and those with nodules as in toxic adenomas and toxic multinodular goiters, received more than 10 mCi. Most received approximately 15 mCi. Patients were advised to avoid physical contact and transfer of secretions to others for several days after treatment.

For one year after therapy, patients were monitored closely clinically and biochemically at frequent outpatient visits. After RAI therapy, a good result was considered either euthyroidism or hypothyroidism.

Statistical Analysis. For statistical analysis, categorical variables were compared with chi-square and the Fisher Exact test. Continuous variables that are normally distributed were expressed as mean ± SD. Statistical calculation was performed using a commercial computer package (Statistical Package for Social Sciences [SPSS], version 13.0) for Windows.

Results

At the beginning of the study, 164 subjects were selected but only 158 patients completed follow up. Of the 158 subjects, 134 (84.8%) had Graves' disease, 13 (8.2%) had multinodular goiter, and 12 (7.6%) had toxic adenomas. Before RAI therapy, 97.4% of the patients received antithyroid drugs. Of these patients, 75.5% were treated for more than one year. Before RAI therapy, 52% of the patients had one recurrence, 7% had two recurrences, and 1.2 % had three recurrences.

Among these patients, 98.8% recovered from hyperthyroidism and were either euthyroid or hypothyroid; 1.2% remained hyperthyroid. Among patients who recovered, 22.6% became euthyroid and 74.2% became hypothyroid.

The incidence of hypothyroidism was 23% in the first trimester, 43.7% in the second trimester, 4.4% in the third trimester, and 3.1% in the forth trimester (Table 3). A good result was obtained in 96.3% of Graves' disease patients and 100% of patients with toxic adenomas and multinodular goiters. Only 3.7% of Graves' disease patients did not achieve the desired result. Pleasant results were reported by 96.5% of women and 97.7% of men. Unpleasant results (hyperthyroidism) were reported by 3.5% of women and 2.3% of men.

No significant association was observed between sex and cure rate (P = 0.9). Significant pleasant results were observed in 93.2% of subject aged less than 35 years and 100% of subjects more than 35 years (P = 0.02). In subjects who received antithyroid medication, 96.7% obtained a good result and 3.2% obtained an unpleasant result, but this association was not significant (P = 0.9). A pleasant result was reported by 97.4% of patients who received antithyroid medications for less than one year, and 96.7% who received medication more than one year. This association also was not significant (P = 0.10). (Table 2). A good result was seen in 95.9% of patients who received less than 10 mCi RAI and in 97.7% of patients who received 15 mCi, but the correlation was not significant (P = 0.6) (Table 2). Also 100% of patients with normal thyroid size, 97.7% with moderate thyroid size (1.5-2 times more than normal), and 87% with large thyroid size (more than 2 times the normal size) obtained a good result (P = 0.2).

Discussion

RAI is widely used for the treatment of patients with thyroid disorders, particularly hyperthyroidism. However, the outcomes for patients who have received RAI have differed from study to study. In our study, a good result was seen in 96.3% of patients with Graves' disease and 100% of patients with toxic adenomas and multi nodular goiter. A second dose of RAI was needed by 15% of the patients, and a third dose for 5%. Through the year of patient observation, 74.2% of the patients became hypothyroid.

In our study, a good result was seen in more pa-

Table 2. Results according to different variables.

Variables		Good Result		Not Good Result	
		Number	Percentage	Number	Percentage
Sex	Female	109	96.5%	4	3.5%
	Male	44	97.7%	1	2.3%
Age	Less than 35 years	69	93.2%	5	6.8%
	More than 35 years	84	100%	—	—
Pretreatment antithyroid drug duration	Less than 1 year	37	97.4%	1	2.8%
	More than 1 year	116	96.7%	4	3.3%
RAI dose	Less than 10 mCi	69	95.8%	3	4.2%
	More than 10 mCi	84	97.7%	2	2.3%

tients than other studies. This positive result may have been due to a higher absorption of radioactive iodine in our region. Taylor et al studied 225 patients who were treated with 555 MBq (15 mCi) RAI for hyperthyroidism to ablate the thyroid and induce early hypothyroidism. With this fixed dose regimen, only 5.6% failed to become euthyroid within one year of treatment. Ten patients (4.4%) required a second dose of 555 MBq ^{131}I since they were still hyperthyroid 1 year after RAI treatment; 3 of these patients required a third dose.[13]

Our patients received 10 mCi or more RAI on the basis of the size of the thyroid gland determined by physical examination. The optimal method for determining the appropriate iodine-131 treatment dose remains controversial. Techniques have varied from fixed doses[14-16] to more elaborate calculations based upon gland size (estimated either by palpation or imaging), iodine uptake, and sometimes from iodine turnover.[17-20]

Leslie et al. studied 88 patients with Graves' hyperthyroidism who had not previously been treated with radioactive iodine. The patients were randomized to one of four dose-calculation methods: low-fixed, 235 MBq; high-fixed, 350 MBq; low-adjusted, 2.96 MBq (80-Ci)/g thyroid adjusted for 24 h RAI uptake; and high-adjusted, 4.44 MBq (120-Ci)/g thyroid adjusted for 24-hour RAI uptake. Subjects were followed for a mean of 63 months to assess clinical outcomes. Mean treatment doses were similar in the different outcome groups. Leslie et al. could not demonstrate any advantage to using an adjusted dose method. Survival analysis did not demonstrate any difference in the time to outcome between the fixed and adjusted dose methods.[21]

Mazzaferri et al., in their study on 813 hyperthyroid patients, divided them into two groups. The first group received 185 MBq, and the second group received 370 MBq. At the end of their study period, the first group had an incidence of hypothyroidism of 41.3%, and the second group had an incidence of 60.8%.[22]

Most dosimetric methods have the benefit of including a measure of thyroid size in their formulas, thereby administering a dose of RAI proportional to size of the gland. This theoretically increases 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 RAI treatment.[23] Despite these potential benefits of calculated doses, several studies have failed to demonstrate improvements in cure rate over fixed doses.[24-26] Furthermore, there is little evidence that using a calculated dose has any advantage over a fixed-dose regimen in preventing hypothyroidism.[27] Because of this, many centers use a single fixed dose.[28]

We administrated RAI of approximately 15 mCi to patients with toxic mulitinodular goiters and toxic adenomas. Opinions also vary about the need for larger doses of RAI in toxic nodular goiter, as compared with Graves' disease.[29,30] Patients with hyperthyroidism from toxic nodular goiters are perceived to be relatively radio-resistant compared to patients with Graves' disease,[29] although evidence is conflicting. Consistent with this perception, researchers report studies in which they administered relative large but varied doses of RAI (555–1850 MBq) to patients with toxic nodular goiters.[31,32]

In our study, results show no difference in the cure rate between the two different doses of RAI.

However, the size of the gland was different in the two groups and hence the results cannot be universally applied. Allahabadia et al. reported that in patients given a single dose of 370 megabequerels , a higher cure rate (84.6% vs. 66.6%) was achieved than when 185 megabequerels were administered. But at one year follow up, patients who received the larger dose had a higher incidence of hypothyroidism (60.8% vs. 41.3%).[33]

Table 3. Incidence of hypothyroidism after RAI according to time.

Time	Number	Percentage
First trimester	38	23%
Second trimester	69	43.7%
Third trimester	6	4.4%
Fourth Trimester	5	3.1%

In the Allahabadia et al. study, age was associated with treatment outcome: younger patients (< 40 years) had a lower cure rate (68.9% vs 79.3%) than patients over 40 years old.[33] In our study, we found a cure rate of 93.2% in patients below 35 and 100% in patients above 35. Compared to the Allahabadia et al. study, a higher percentage of younger patients had a good outcome. According to our results, then, RAI can be offered to younger patients.

We did not observe a significant association between cure rate and sex. This result is consistent with the outcome of many other studies that did not show gender to be a significant prognostic factor in patients' responses to RAI treatment. In contrast, Allahabadia et al. found that males had a significantly lower cure rate than females after one dose of RAI.[33]

Several studies have demonstrated that patients with larger volume thyroid glands are more likely to fail to respond to a single dose of RAI.[33] In our study, the cure rate was lower for patients with smaller thyroid glands, but no significant correlation could be drawn.

Our findings show no significant correlation between pretreatment with antithyroid-drugs and duration of thyroid gland pathology and cure rate. Many studies have shown a reduction in the response rate to RAI[34,35] if patients have received pretreatment with thyroid drugs. Other studies, however, have shown either no effect[36] or an effect confined to propylthiouracil.[37]

For example, Alexander et al. treated 261 patients with hyperthyroidism caused by Graves' disease with ^{131}I [mean dose, 14.6 mCi (540 MBq)]. Patients pretreated with antithyroid medication for greater than 4 months were at higher risk for treatment failure.[38] Some other studies also demonstrated that antithyroid-drug pretreatment may cause an exacerbation or recurrence of hyperthyroidism.[39,40]

On the other hand, Braga and Andrade et al. demonstrated that methimazole pretreatment has no effect on the final result, the time required for cure, or the 1-year success rate of ^{131}I therapy.[41,42] In contrast, Ahmad et al. demonstrated that the frequency of hypothyroidism was lower in patients treated with antithyroid drugs prior to RAI compared with patients who did not received antithyroid drugs.

Ahmed et al. studied risk factors that allow estimates of the probability of developing hypothyroidism following radioactive iodine treatment.[43] Hypothyroidism was reported to occur from 2 months to 20-to-30 years after RAI therapy. As significant independent risk factors, they identified Graves' disease, the presence of thyroid autoantibodies, no antithyroid treatment given prior to RAI, a nonpalpable goiter, and a high RAI dose. The researchers reported that in the absence of all risk factors, the probability of developing hypothyroidism is 11.9%. In the presence of all risk factors, the probability increases linearly to 96.4%.

In our study, hypothyroidism was seen in 74.2% of subjects, mostly in the second trimester post therapy. Similarly, in a study by Nebesio et al., hypothyroidism was observed in 75% patients 40-to-90 days after RAI.[44] By comparison, Ahmad et al. [43] reported that the cumulative incidence of hypothyroidism following RAI treatment was 38.2% after 6 months. The incidence increased to 55.8% after 1 year and to 86.1% at 10 years.[43] In Kendall-Taylor et al. study the modal time to hypothyroidism was three months, and 64% of patients were hypothyroid at one year.[13]

These data suggest that our patients' cure rate was higher than in other studies. The high rate may have been contributed to by two factors: our low sample size and higher RAI absorption in our patients due to regional iodine insufficiency compared to iodine sufficiency in regions where other studies were conducted.

No significant association was observed between cure rate and gender, antithyroid-drug pretreatment, duration of antithyroid-drug pretreatment, or RAI dose. According to our results, the incidence of hypothyroidism was highest in the second trimester following RAI therapy. Because of this, we recommend

that patients be carefully followed in this period.

Study Limitations

A limitation of our study is the sample size which was relatively small. Because of this, our negative results may reflect a lack of power. Further studies to confirm or refute our results with longer follow up times and larger sample sizes are suggested.

Also the hypothesis that the better cure rate was due to higher iodine absorption is not verified due to the lack of an iodine uptake probe. However, an association between gamma-camera calculated thyroid uptake and cure rate is to be studied to determine whether there is a relationship between a higher cure rate and higher ^{131}I absorption.

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