Original article

Long-term follow up of 1,168 Graves'disease patients post radioiodine treatment

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Background: Current treatments of Graves' disease have their own advantages and disadvantages. Radioactive Iodine (RAI) is an effective treatment but most of the patients will develop hypothyroidism.

Objective: To study the results of treatment of Graves' disease treated with RAI and to identify factors those could influence the outcomes.

Methods: In all, 1,168 Graves' disease patients who were treated with RAI were evaluated on their thyroid function for 1 - 26 years. The results of treatment were recorded in associated with patient's gender, age, estimated gland size, pretreatment antithyroid drug and dose of RAI.

Results: From 1,168 patients, 939 were females (80.4%), 1,098 (94.0%) received RAI from King Chulalongkorn Memorial Hospital, 64 (5.5%) were treated at Rajavithi Hospital. The incidence of hyperthyroid/euthyroid/hypothyroid was 34.3%/29.5%/36.1% , 22.0%/33.1%/44.9% and 2.1%/22.1%/75.8% at 1, 2 and 10 year after RAI therapy, respectively. Premedication with methimazole (MMI) or propylthiouracil (P.T.U.) reduced the effectiveness of RAI ($P < 0.001$). Patients with hypothyroid had younger age than those with hyperthyroid ($P < 0.002$) and euthyroid ($P < 0.001$). Patients with hyperthyroid had larger gland size than those with hypothyroid ($P = 0.004$) and euthyroid ($P < 0.001$) and received higher dose of RAI ($P < 0.001$). There were no differences in treatment outcome between gender and two medical centers.

Conclusions: Premedication with either MMI or P.T.U. reduce RAI efficacy. Patients with larger gland size or older increase rate of treatment failure. Higher dose of RAI may be advisable to increase treatment efficacy.

Keywords: Hyperthyroidism, Graves' disease, radioactive iodine.

Graves' disease is the most common cause of hyperthyroidism, characterized by antibody that acts as an agonist on the thyrotropin receptor of thyroid cells.[1] Treatment options could be either antithyroid drugs (ATD), surgery or radioactive iodine (RAI).[2] The drawback of ATD treatment is 51.0 - 68.0% long term relapse rate[3] and thyroid surgery is the least frequently selected modality.[4] RAI therapy is most popular in North America, 69.0% of physicians recommend it as first line therapy for Graves' disease, compared with 22.0% in Europe and 11.0% in Japan.[5] After RAI therapy, hypothyroidism develops in 80.0 - 90.0% of patients and 14.0% of patients require additional treatment because they had persistent hyperthyroidism.[6]

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The purposes of this study were to investigate the results of treatment of Graves' disease treated with RAI. and to identify factors that could influence the treatment outcomes.

Materials and methods

Enrolled patients: This retrospective study was conducted in Graves' patients who have been treated with RAI and had regular follow-up at thyroid clinic of Sawanpracharak Hospital. This included 1,168 patients, 939 (80.4%) were females, 229 (19.6%) were males. Almost all patients were referred to two large medical centers, 1,098 (94.0%) to King Chulalongkorn Memorial Hospital, 64 (5.5%) to Rajavithi Hospital and 6 (0.5%) to the others. The median time of follow-up was 9 years (1 - 26 years) after RAI treatment.

Baseline disease and treatment characteristics: Patients' data included sex, age (at the time of RAI treatment), estimated gland size (gland size estimation was performed before RAI treatment and was based on physical examination), pretreatment ATD, dose of RAI and thyroid function after RAI therapy.

They were 4 groups of patients divided by the pretreatment medication. **Group 1:** included 951 patients (741 females, 210 males, age 11 - 82 years) who were treated with MMI. **Group 2:** included 150 patients (142 females, 8 males, age 16 - 73 years) who were treated with propylthiouracil (P.T.U.) **Group 3:** included 52 patients (46 females, 6 males, age 17 - 61 years) who were not received any ATD before RAI. **Group 4:** included 15 patients (10 females, 5 males, age 24 - 71 years) who were treated with both MMI and P.T.U.

Post-RAI treatment evaluation: Thyroid function test (FT4, FT3 and TSH) was done monthly in the first 3 months, then every 2 - 3 months in the first year, every 4 months in the second year and then every 6 - 12 months if the patients had euthyroid or hypothyroidism.

Outcome assessment: The results of treatment of each patient were reported in 3 categories by using the following criteria.

Hyperthyroidism: patient who had high thyroid hormone level and low thyroid stimulating hormone level or who could not stop ATD.

Euthyroid: patient who still had normal thyroid hormone level after ATD withdrawal.

Hypothyroidism: patient who had low free thyroxin and high thyroid stimulating hormone level.

Statistical analysis

Statistical data analysis was performed using Chi-squared test for discrete data and using Student's *t* - test for continuous data. Statistically significance was defined at $P < 0.05$.

Results

Table 1 shows the patients' baseline data in each group. From 1,168 patients: 80.4% were female, 81.4% received MMI, 13.0% received P.T.U. and 4.5% had no premedication.

Table 2 shows the overall results of treatment. The incidence of hypothyroid was 36.1%, 44.9%, 75.8% and 83.1% at 1,2,10 and 15 years after RAI therapy. The incidence of euthyroid was 29.5%, 33.1%, 22.1% and 14.1% while hyperthyroidism were found 34.3%, 22%, 2.1% and 2.8%, respectively. In all, 109 patients (9.3%) received multiple doses of RAI (97 in group 1, 5 in group 2, 1 in group 3 and 6 in group 4).

Table 3 shows statistical analysis of factors that may influence the treatment outcome at 2 years after RAI therapy.

Table 1. Baseline characteristics of the patients.

Characteristic	Group 1 (n = 951)	Group 2 (n = 150)	Group 3 (n = 52)	Group 4 (n = 15)	Total (n = 1,168)
Age (years)	11 - 82	16 - 73	17 - 61	24 - 71	11 - 82
Female sex (No.,%)	741 (77.9)	142 (94.6)	46 (88.5)	10 (66.7)	939 (80.4)
Gland size (grams)	10 - 200	20 - 250	25 - 120	15 - 100	10 - 250
Dose of RAI (mCi)	3 - 29	3 - 30	3 - 30	11 - 27	3 - 30
Duration of follow-up					
1 year	951	150	52	15	1,168
2 years	920	145	50	15	1,130
3 years	877	138	47	13	1,075
4 years	839	132	46	13	1,030
5 years	801	126	43	12	982
6 years	736	115	40	12	903
7 years	668	105	39	12	824
8 years	608	88	38	11	745
9 years	545	73	37	10	665
10 years	462	59	32	9	562
11 years	408	49	26	9	492
12 years	358	44	24	9	435
13 years	307	34	16	9	366
14 years	242	27	9	7	285
15 years	180	19	7	7	213
>15 years	136	15	5	6	162

Table 2. Results of treatment of after RAI therapy.

Duration after RAI	Results of treatment number (%)			Total number
	Hyperthyroid	Euthyroid	Hypothyroid	
3 months	736 (63.0)	291 (24.9)	141 (12.1)	1,168
6 months	511 (43.8)	346 (29.6)	311 (26.6)	1,168
1 year	401 (34.3)	345 (29.5)	422 (36.1)	1,168
2 years	249 (22.0)	378 (33.1)	507 (44.9)	1,130
5 years	78 (7.9)	281 (28.6)	623 (63.4)	982
10 years	12 (2.1)	124 (22.1)	426 (75.8)	562
15 years	6 (2.8)	30 (14.1)	177 (83.1)	213

Table 3. Factors influence treatment outcome at 2-year follow-up.

Factors	Result of treatment number (%)			*P* - value
	Hyperthyroid	Euthyroid	Hypothyroid	
Gender				0.053
Male	62 (28.0)	66 (29.9)	93 (42.1)	
Female	187 (20.6)	308 (33.9)	414 (45.5)	
Age (years) mean (SD)	41.1 (13.1)	42.1(12.4)	38.0 (13.3)	< 0.001*
Gland size (gm) mean (SD)	64.4 (35.3)	49.2 (24.1)	56.2 (35.3)	< 0.001*
Premed				< 0.001*
MMI	196 (21.4)	303 (33.0)	419 (45.6)	
P.T.U.	38 (26.2)	45 (31.0)	62 (42.8)	
no premed	5 (9.6)	22 (42.3)	25 (48.1)	
Both	10 (66.7)	4 (26.7)	1 (6.7)	
Hospital				0.398
Chulalongkorn	238 (22.4)	352 (33.2)	472 (44.4)	
Others	11 (16.2)	22 (32.3)	35 (51.5)	
Dose of RAI (mCi) mean (SD)	12.4 (8.6)	8.5 (4.8)	10.4 (6.6)	< 0.001*

*Post hoc test with LSD

Gender: treatment outcome of male and female were comparable ($P = 0.053$).

Age: patients who developed hypothyroidism had younger age than hyperthyroid group (mean difference = - 3.1 years, $P = 0.002$) and younger than euthyroid group (mean difference = - 4.1 years, $P < 0.001$).

Estimated gland size: patients in hyperthyroid group had larger gland size than in euthyroid group (mean difference = 15.2 gm, $P < 0.001$) and larger than hypothyroid group (mean difference = 8.2 gm, $P = 0.004$).

Pretreatment medication: patients who received ATD (either MMI or P.T.U.) before RAI had incidence of hyperthyroidism more often than those who had no premedication ($P < 0.001$).

Dose of RAI: patients in hyperthyroid group received higher dose of RAI than in euthyroid group and in hypothyroid group (mean difference = 3.9 mCi and 2 mCi respectively, $P < 0.001$).

Institute: there was no difference of treatment outcomes between King Chulalongkorn Memorial Hospital and Rajavithi hospital ($P = 0.398$).

Discussion

Graves's disease is a common endocrine disorder that can cause serious and maybe irreversible complications.[1] Due to high relapse rate (25.0 - 77.0%) after ATD withdrawal, [7, 8] RAI is often recommended. The incidence of hypothyroidism varies in each study, Sridama V, *et al*. studied low dose RAI found the incidence of hypothyroid 12.0% in first year and 76.0% in 11 years.[9] Alexander EK. found hypothyroidism 83.0% in the first year of high dose RAI therapy. [6] Stan MN, *et al*. found 40.0% and 80.0% of patients hypothyroid by 8 weeks and 16 weeks, respectively.[10] Kendall-Taylor P, *et al*. found 64.0% of the patients hypothyroid and 30.0% euthyroid at 1 year.[11] Nordyke RA, *et al*. found

87.0% of patients given 10 mCi of RAI were euthyroid or hypothyroid at 1 year.[12]

In this study, incidence of hypothyroidism was 36.0% at first year, 45.0% at second year and 75.0% at tenth year and incidence of hyperthyroidism was 34.3% at first year, 22.0% at second year and 2.1% at tenth year. The incidence of hyperthyroid at first year is higher than other studies suggesting that our patients received inadequate dose of RAI. Nevertheless, three-fourths of patients developed hypothyroidism at 10 years after RAI therapy.

There was no difference of treatment outcome between 2 large medical centers in Bangkok. About 9.0% of patients needed multiple doses of RAI.

Patients who did not receive premedication had hypothyroid more than patients who received P.T.U. or MMI. This data suggested a potential radio-protective effect of both P.T.U. and MMI. Alexander EK studied 261 Graves' hyperthyroid patients also found both P.T.U. and MMI increased treatment failure.[6] P.T.U. not MMI had been reported to reduce the efficacy of RAI in several but rather small studies (less than 100 patients in each study).[13 - 15] Nevertheless, most endocrinologists treat high risk patients include elderly persons, patients with cardiovascular disease or with severe hyperthyroid symptoms with ATD for several weeks before administeraing RAI.[16]

Patients who remained hyperthyroid after RAI had significantly larger gland size than patients who were euthyroid and who were hypothyroid. Same results had been reported in previous studies.[6, 17]

We found that patients with hypothyroidism were younger than those who became euthyroid or persistent hyperthyroidism. This finding is different from other studies.[6, 15, 18]

The discrepancy may be due to larger gland size, patients who had persistent hyperthyroidism received significantly higher dose of RAI than those who were euthyroid and who were hypothyroid.

Although this was a large populations and long-term follow-up study but all the patients were referred out to receive RAI at other hospitals. However, we did not know the methods of dose calculation and some data were incompletely recorded.

Conclusion

RAI is the effective treatment of Graves' disease and complete ablation of thyroid gland is the goal. Pretreatment with either P.T.U. or MMI reduces RAI efficacy. Patients with large gland size or older persons increase rate of treatment failure. Higher dose of RAI may be advisable to increase treatment efficacy.

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Conflict of interest

The author, hereby, declare no potential conflict of interest.

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