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Long-term follow-up studies on Iodine-131 treatment of hyperthyroid Graves' disease based on the measurement of thyroid volume by ultrasonography

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In the present series of studies, the long-term (four year) effect of 80 Gy of ^{131}I treatment was evaluated in patients with hyperthyroid Graves' disease whose thyroid volumes have been accurately estimated with a high resolution ultrasound scanner. One year after ^{131}I treatment, 23.1% (3 out of 13 patients) remained hyperthyroid, 69.2% (9 out of 13) became euthyroid, and 7.7% (1 out of 13) were in a hypothyroid state. Since three patients in a hyperthyroid state one year after treatment were subsequently treated with either antithyroid drugs or additional ^{131}I treatment, the remaining ten patients (9 euthyroid and 1 hypothyroid patients) have been followed up for three more years. Two patients developed a hypothyroid state three years after treatment and one patient four years after treatment. Overall, 60% (6 out of 10 patients) were in a euthyroid state and 40% (4 out of 10) in a hypothyroid state, four years after 80 Gy ^{131}I treatment. There was no significant difference between eu- and hypothyroid groups in the sex ratio, age, radiation dose, therapeutic dose, thyroid gland volume, 24-hr ^{131}I uptake, the effective half-life of ^{131}I in the thyroid or the duration of hyperthyroidism.

In our preliminary studies, the incidence of late hypothyroidism in our ^{131}I treatment is similar to those previously reported. These suggest that uncertain factor(s), such as inhomogeneity of iodine distribution in the thyroid, unequal sensitivity of the thyroid cells to the radiation, and/or persistent destructive effects of the autoimmune process may influence the long-term effect of ^{131}I treatment of Graves' disease.

Key words: radioiodine therapy, Graves' disease, thyroid volume

INTRODUCTION

Iodine-131 (^{131}I) treatment is now generally regarded as the first choice in the treatment of patients with hyperthyroid Graves' disease who do not remit following a course of antithyroid drugs. The appropriate therapeutic dosage of ^{131}I should ideally be calculated, according to Werner's formula, with the estimated weight of the thyroid gland, the 24-hour thyroidal radiation uptake and the effective half-life of radioiodine in the thyroid gland taken into account.[1] Since our previous studies have indicated that the thyroidal radioiodine uptake and the effective half-life of the therapeutic dose of radioiodine can be precisely predicted from those of the tracer dose of radioiodine when administering lithium carbonate,[2] the determination of the accurate estimation of the weight of the thyroid gland seems to be critical in achieving success in the ^{131}I treatment of Graves' patients. Indeed, the determination of thyroid volume has previously been performed by palpation and thyroid scintigraphy, both of which are reported to be generally inaccurate.[3,4] However, the high resolution ultrasonic scanner that we have developed has been reported to be capable of very

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accurate determining the weight of the thyroid glands,[5] and has previously been introduced by our group for ^{131}I treatment of Graves' disease.[6] Our studies have provided evidence that in our short-term follow-up studies (one year after treatment) the therapeutic radiation dosage should be increased as the gland size does, even if the gland size is accurately estimated by this ultrasound: all hyperthyroid Graves' patients with large thyroid glands (>sixty grams) remained hyperthyroid, whereas 80% of hyperthyroid Graves' patients with small thyroid glands (>forty grams) became euthyroid one year after 80 Gy ^{131}I treatment.[6] But no long-term follow-up of ^{131}I treatment based on accurate thyroid size has yet been performed. This may be important because the high incidence of late hypothyroidism is one of major disadvantages of ^{131}I treatment, regardless of the methods used.[7–12] The present studies were, therefore, designed to investigate the long-term effect of ^{131}I treatment of hyperthyroid Graves' patients whose thyroid volume was accurately determined by the ultrasound. Our preliminary studies revealed that the incidence of late hypothyroidism is similar to those previously reported[7–12] and is not correlated with age, sex ratio, radiation dose, therapeutic dose, thyroid gland size, 24-hour uptake. the effective half-life or duration of hyperthyroid gland size, 24-hour uptake, the effective half-life or duration of hyperthyroidism.

PATIENTS AND METHODS

Thirteen patients (2 males and 11 females, 50.1±8.3 years old) with hyperthyroid Graves' disease have been treated with ^{132}I treatment according to the following protocol, and have been followed up for 4 years in Nagasaki University Hospital. Ten out of 13 patients were those mentioned in our previous report who had been followed up for one year after ^{131}I treatment.[6] The remaining three patients were not available for the present series of studies. The majority of these patients had adverse reactions to antithyroid drugs.

The therapeutic dose of radioiodine (^{131}I) was calculated according to the following formula:[1]

$$\text{Dose of radioiodine given } (\mu\text{Ci}) = \frac{8{,}000 \times \text{grams thyroid weight} \times 8}{120 \times \text{24-hour radioiodine uptake} \times \text{effective half-life}}$$

In the present series of studies, 1 μCi/gram of ^{131}I was thought to deliver 120 rads to the gland.[13] The weight of the thyroid gland, 24-hour ^{131}I uptake and the effective half-life of ^{131}I in the thyroid was determined as follows. Briefly, the weight of the thyroid gland was determined with the high resolution ultrasonic scanner as previously described.[5,6] The estimated thyroid volume obtained with this scanner has been found to be closely correlated with the actual weight at operation (correlation coefficient: 0.98 in Graves' disease and 0.99 in thyroid adenoma).[5] The 24-hour ^{131}I uptake of the tracer dose was measured after an iodine-restricted diet for at least 1 week. The effective half-life of ^{131}I in the thyroid was calculated under the administration of 300–600 mg/day of lithium carbonate as previously described.[2,6] 80 Gy of radioiodine was chosen as a recommended radiation dose as before[6] and was given per os. Each value is shown in Table 1, where the patients were listed according to thyroid volume.

Thyroid function was judged clinically and biochemically. Patients with no signs/symptoms attributable to hyperthyroidism, and normal free thyroid hormone and normal TSH values without medication were considered to be "euthyroid". Those with signs/symptoms of hyperthyroidism, free thyroid hormone values above normal or suppressed TSH were

Table 1 Radioiodine therapy of thirteen patients with Graves' disease

Pt no.	Mge (years)	Sex	Dose (MBq, mCi)	Gland size (g)	24 h uptake (%)	Effective half-life (days)	Per gram dose (MBq/g, μCi/g)	Radiation dose (Gy)
1	42	F	492.1(13.3)	110.4	79.0	5.6	4.46(120.5)	80
2	58	F	223.1 (6.0)	64.9	80.5	7.5	3.44 (92.9)	84
3	47	F	129.5 (3.5)	34.8	70.2	7.7	3.72(100.6)	83
4	56	M	173.9 (4.7)	30.8	73.0	5.1	5.65(152.6)	85
5	55	F	152.4 (4.1)	29.9	66.0	5.8	5.10(137.8)	79
6	48	F	140.6 (3.8)	27.2	67.1	5.7	5.17(139.7)	80
7	50	F	99.9 (2.7)	25.4	69.2	7.3	3.93(106.3)	81
8	45	F	74.0 (2.0)	25.0	84.0	8.0	2.96 (80.0)	81
9	53	F	114.7 (3.1)	24.2	68.0	6.2	4.74(128.1)	81
10	64	M	68.1 (1.8)	24.0	74.1	8.0	2.84 (76.7)	70
11	60	F	111.0 (3.0)	23.1	70.3	5.8	4.81(129.9)	79
12	36	F	48.1 (1.3)	17.8	86.4	7.4	2.70 (73.0)	70
13	37	F	111.0 (3.0)	16.2	46.0	6.9	6.85(185.2)	88

considered to be "hyperthyroid". Patients with symptoms/signs (if present) and TSH levels above normal were considered to be hypothyroid. TSH and free thyroid hormones in sera were measured with commercially available kits.

Echogenicity of the thyroid gland before ^{131}I treatment was also investigated with the high resolution ultrasonic scanner.

Statistical analysis was performed by Wilcoxon analysis. A P-value less than 0.05 was considered to be statistically significant.

RESULTS

Thirteen patients with Graves' disease whose thyroid volume was accurately determined with the high resolution ultrasonic scanner[5] were treated with 80 Gy of ^{131}I and have been followed up for four years. As shown in Figure 1, one year after ^{131}I treatment, 23.1% (3 out of 13 patients, Nos. 1, 2 and 4) remained hyperthyroid, 69.2% (9 out of 13, Nos. 3, 5, and 7–13) became euthyroid, and 7.7% (1 out of 13, No. 6) were in a hypothyroid state. Table 2 shows the analysis of various factors in the three groups (hyper-, eu- and hypothyroid groups) that may influence the early effect of ^{131}I treatment. As we have previously reported,[6] statistically significant differences between hyper- and euthyroid groups were observed in therapeutic doses (296.4±171.3 MBq vs. 101.1±32.5 MBq, $p<0.05$) and thyroid gland volume (64.7±33.59 g vs. 24.2±5.36 g, $p<0.05$).

Three hyperthyroid patients (Nos. 1, 2, and 6) were subsequently treated with either antithyroid drugs or additional ^{131}I treatment (see Fig. 1), and therefore could not be followed up to judge the long-term effect of ^{131}I treatment alone.

Ten other patients who were in a euthyroid or

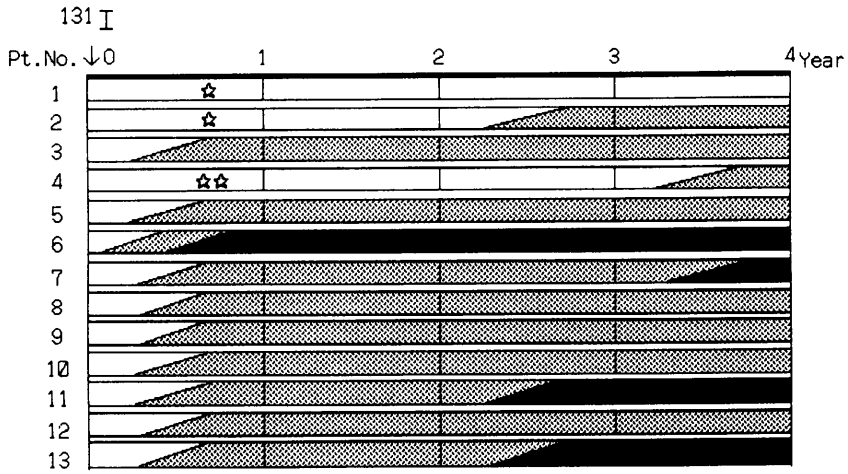

Fig. 1 Alternations of thyroid function in patients with Graves' disease after ^{131}I treatment. *, antithyroid drugs; **, additional ^{131}I treatment. The white, gray and black areas indicate hyperthyroid, euthyroid, and hypothyroid states, respectively. The patients were arranged according to their thyroid volumes.

Table 2 Analysis of several parameters that might influence the efficacy of radioiodine therapy in hyper-, and eu- and hypothyroid groups one year after ^{131}I treatment

		Hyperthyroid	Euthyroid	Hypothyroid
Patient	number (%)	3 (23.1)	9 (69.2)	1 (7.7)
Male: Female		1:2	1:8	0:1
Age	years	52.0±8.7	49.7±9.5	48
Radiation dose	Gy	53.0±2.6	79.0±5.7	80.2
	(rads)	(8,300±265)	(7,900±574)	(8015)
Dose	MBq	*296.4±171.3	101.1±32.5	140.6
	(mCi)	(*8.0±4.6)	(2.7±0.88)	(3.8
Thyroid gland volume	g	*68.7±39.9	24.5±5.6	27.2
24 h ^{131}I uptake	%	77.5±4.0	70.5±11.6	67.1
Effective half-life	days	6.1±1.3	7.0±0.9	5.7
Duration of Hyperthyroidism	months	84.7±134.5	13.2±15.5	6

*; statistical difference ($p<0.01$) between hyper- and euthyroid groups.

Table 3 Analysis of several parameters that might influence the efficacy of radioiodine therapy in eu- and hypothyroid groups four years after ^{131}I treatment

		Euthyroidism	Hypothyroid
Patient	number (%)	6(60.0)	4(40.0)
Male:Female		1:5	0:4
Age	years	50.0±9.6	48.8±9.4
Radiation dose	Gy	77.0±5.6	82.1±4.1
	(rads)	(7,700±564)	(8,200±408)
Dose	MBq	97.8±40.5	115.6±17.5
	(mCi)	(2.6±1.1)	(3.1±0.5)
Thyroid gland volume	g	26.0±5.8	23.0±4.8
24 h ^{131}I uptake	%	74.8±8.5	63.1±11.5
Effective half-life	days	7.2±1.0	6.4±0.8
Duration of hyperthyroidism	months	14.7±19.2	9.3±5.0

hypothyroid state one year after ^{131}I treatment have been followed up for three more years. As shown in Fig. 1, two (Nos. 11 and 13) patients four years after developed a hypothyroid state three years after treatment and one patient (No. 7) four years after. Finally, 67% (6 out of 9 patients in a euthyroid state one year after ^{131}I treatment) remained in a euthyroid state, and 33% (3 out of 9) developed a hypothyroid state four years after treatment. Overall, 60% (6 out of 10) and 40% (4 out of 10) were in a euthyroid and a hypothroid state, respectively, four years after 80 Gy ^{131}I treatment. There was no significant difference between eu- and hypothyroid groups in sex ratio, age, radiation dose, therapeutic dose, thyroid gland volume, 24-hr ^{131}I uptake, the effective half-life of ^{131}I in the thyroid or duration of hyperthyroidism (Table 3). There was also no significant correlation between thyroid echogenicity and the effect of ^{131}I treatment (data not shown). The size of the thyroid gland therefore did not affect the outcome of long-term follow-up of ^{131}I treatment of Graves' disease with relatively small goiters in our protocol.

DISCUSSION

In the present series of studies, the long-term (four years) effect of 80 Gy ^{131}I treatment was evaluated in patients with hyperthyroid Graves' disease whose thyroid volume has been accurately estimated with the new high resolution ultrasound scanner.[5] One year after ^{131}I treatment, 69.2% of patients were euthyroid, indicating that the early effect of ^{131}I treatment in our protocol is similar to those previously reported,[14–20] although it may be meaningless to compare our results to the previous studies, because thyroid volume was not accurately determined in previous studies. As has been recently reported by us and others,[6,11] the therapeutic radiation dose should be graded according the thyroid gland size in order to improve the early effect of ^{131}I treatment.

Four years after ^{131}I treatment, 60% (6 out of 10) patients were in a euthyroid state, but the remaining 40% were in a hypothyroid state. The incidence of late hypothyroidism in the present studies, although the number of patients is very limited, is also similar to those previously reported.[7–12] Since patients with large goiters were still in a hyperthyroid state one year after ^{131}I treatment and were subsequently treated with either antithyroid drugs or additional ^{131}I treatment (see *Results*), only patients with relatively small goiters have been subjected to the long-term follow-up studies, which might have biased the outcome of the long-term follow-up of ^{131}I treatment. Previous studies demonstrate the radioresistance of larger goiters.[6,11] Therefore, in the present studies the actual incidence of late hypothyroidism might be even somewhat lower than we have calculated. In either case, no difference between eu- and hypothyroid groups in several factors that may influence the long-term effect of ^{131}I treatment suggests that other uncertain factor(s), including the inhomogeneity of iodine distribution in the thyroid or unequal sensitivity of the thyroid cells to radiation, may influence the long-term as well as the short-term effects of ^{131}I treatment of Graves' disease. There is, however, at present no way to measure them.

Furthermore, late hypothyroidism is presumably not only due to the long-term effect of radiation, but also due to the persistent destructive effects of the autoimmune process, because late hypothyroidism occurs even in Graves' patients treated with either antithyroid drugs or subtotal thyroidectomy.[12] The fact that there is a much greater incidence of late hypothyroidism during long-term follow-up of ^{131}I treatment in Graves' patients with a positive MCHA test relative to those with negative MCHA[12] supports this possibility. From this point of view, late hypothyroidism is now regarded as an unavoidable complication following not only ^{131}I treatment, but also other therapeutic choices for Graves' disease.

In previous studies,[7–12] many different approaches, including high dose treatment (140–160 μCi/g thyroid), low dose treatment (50–80 μCi/g thyroid) and size-compensated protocol (the therapeutic dose was adjusted to goiter size), have been applied in ^{131}I treatment of Graves' disease, but all have failed to avoid the high incidence of late hypothyroidism. Although the occurrence of hypothyroidism shortly after ^{131}I treatment is related to the radiation dose, delayed hypothyroidism similarly develops regardless of the amount of ^{131}I.[11,12,21] For these reasons, some thyroidologists think that the goal of this therapy is to cure hyperthyroidism rather than to avoid hypothyroidism. However, it is still controversial whether or not the intentional thyroid ablation should be accepted as the standard protocol for ^{131}I therapy.[12] In our clinic, Graves' patients who undergo ^{131}I treatment are mainly those who are relatively old and have suffered adverse effects of antithyroid drugs. Delay in controlling hyperthyroidism is also a serious problem in such patients. We therefore believe that it is more important to improve the relatively early effect of ^{131}I treatment than to avoid late hypothyroidism in such patients.

In conclusion, our preliminary studies reveal that accurate determination of the weight of the thyroid gland cannot lower the incidence of late hypothyroidism in ^{131}I treatment of Graves' disease. Uncertain factor(s) may affect the long-term efficacy of ^{131}I treatment of Graves' disease.

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