A Comparative Evaluation of the Treatment of Hyperthyroidism

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Synopsis

In order to evaluate the effect of treatment for hyperthyroidism based on a proposed criteria from our institution, the patients with the disease first seen at the Ito Hospital during 1965 were studied on the basis of clinical diagnosis and the follow-up study in 4-5 year period.

Surgery was recommended in the younger ages and radioiodotherapy in the higher ages for both sexes, though there was no inclination for antithyroid therapy in ages. Surgery exhibited the most reliable result among the three major therapies. Hypothyroidism was found more often in females than in males. Incidence of hypothyroidism with radioiodotherapy after the first four years of therapy was about 10% in females, and the result indicated the necessity of further improvement for administering ^{131}I . In case of radioiodotherapy, it is difficult to predict the manifestation of hypothyroidism, because of no relationship between the incidence of hypothyroidism and radiation dose. The follow-up study showed the remission rates with surgery and radioiodotherapy were both 80-90 per cent, whereas the rate with antithyroid therapy was 38 per cent.

After the introduction of radioiodotherapy or antithyroid therapy for hyperthyroidism, the principle of the treatment of the disease has shown so remarkable modification. Among the major therapies for the disease, such as ^{131}I (radioiodotherapy), subtotal thyroidectomy or antithyroid drugs (ATD), each therapy has certain advantages, as well as disadvantages, as compared with each other.

The evaluation for each therapy, however, has so many differences or discrepancies among the specialists. Since no treatment of the disease is completely satisfactory and its etiology is not known, it is not surprising that several types of therapy have been tried.

Surgery had been the only method of treatment for hyperthyroidism at the Ito Hospital until 1955, when radioiodine ^{131}I

also became available for treatment. ATD have been applied since 1947. Prior to 1963, however, they were administered in preparation to surgery and not as independent treatment. Since then we have applied all three kinds of treatment based on our criteria for indication. Our criteria for the choice of treatment with the disease were established in 1956 and have not yet been modified.

In order to examine the clinical situation for the choice of treatment with the disease, all new patients with the disease seen in 1965 at the Ito Hospital were studied in this paper.

Materials and Methods

I. Patients

The 1,124 cases with hyperthyroidism were first seen at the hospital in 1965. Of these cases, 177 were

Table 1. Distribution of the patients with hyperthyroidism, by sex and age-group

Sex	—19	20—	30—	40—	50—	60—	Total
Male	8	44	68	44	12	1	177
(%)	(4.5)	(24.9)	(38.4)	(24.9)	(6.7)	(0.6)	(100.0)
Female	129	233	281	192	93	19	947
(%)	(13.6)	(24.6)	(29.7)	(20.3)	(9.9)	(2.0)	(100.0)

male and 947 were female. The youngest was 9 years of age and the oldest was 76 years old (Table 1).

The 496 cases (44.1 per cent of 1,124 cases) had no history of previous treatment for the disease, whereas the remainders (628 cases) had some kind of previous treatment for the disease elsewhere prior to visiting our clinic.

Out of the 1,124 patients, one of the three major treatments was tried in 1,066 cases. 930 cases (87.2 per cent of the 1,066 cases) were treated in the hospital, and the others were recommended to transfer to other hospitals or quit their regular visit.

II. Diagnosis and grading

The diagnosis of hyperthyroidism was made by a medical history, physical examination, and an abnormal value of two or more of the following tests; basal metabolic rate, resin-sponge uptake, protein bound iodine, and 24-hour thyroidal ^{131}I uptake.

An impression was recorded as to one of three degrees of severity of hyperthyroidism based on all data available, using the designation mild, moderate, or severe. The size and configuration was traced and recorded as large, medium, or small (estimated weight over 50 g, 20–49 g, or less than 20 g respectively). All cases composed of diffuse toxic goiter; toxic nodular goiter was not seen in the series.

III. Selection of treatment

Our criteria on the choice of treatment for hyper-

thyroidism was shown in Table 2. Relations between the status of patient and the kind of treatment were as follow:

a) History of previous treatment

Among the 628 previously treated cases, 563 were treated with ATD administration, 26 with ^{131}I administration, and 39 with surgery.

b) Recommendation of treatment by age

Figure 1 shows the distribution of patients for each treatment by age-group. ATD treatment was given to most of age-groups, ranging from 11 to 33 per cent. Under the age-group of 30–39, the majority of cases were recommended for surgery, and patients over 40 were mostly recommended for ^{131}I administration.

c) Size of thyroid enlargement by treatment

Surgery was more performed for the patients with large goiter as well as medium size of goiter, whereas ATD was mainly performed for small size of thyroid enlargement. This was shown in Table 3.

d) Severity of hyperthyroid status by treatment

Figure 2 shows the relation between severity of hyperthyroidism and their selected treatment. ATD treatment was performed mainly for mild cases. ^{131}I administration was, on the other hand, performed mainly for most severe cases. Surgery was mainly performed for the moderate cases.

e) Duration of hyperthyroid status by treatment

Duration of the disease in each group of three treatments was shown in Table 4. About half of the patients less than 3 years duration of the disease

Table 2. Criteria for the selection of the treatment for hyperthyroidism

Subject	ATD	^{131}I	Surgery
Age	any age	middle and over	younger age
Size of goiter	small	medium or small	large or medium
Severity of hyperthyroidism	mild	severe or moderate	severe or moderate
Duration of illness	short duration	long duration	no consideration
Marital status and pregnancy	no consideration	post reproductive age	younger age
Social factors	accessibility to regular medical care	no consideration	early return to job
Complications	no consideration	no consideration	to avoid

Fig. 1 Selection of treatment by sex and age-group

Table 3. Size of thyroid enlargement

Size	ATD	¹³¹ I	Surgery	Observation	Total
Large	12(6)	39(18)	163(75)	4(2)	218(100)
Medium	85(15)	189(33)	293(51)	10(2)	577(100)
Small	138(48)	105(36)	24(8)	24(8)	291(100)
No detail	12(32)	5(13)	1(3)	20(53)	38(100)
Total	247(22)	338(30)	481(43)	58(5)	1,124(100)

(); percentage

Fig. 2 Relation of severity to the selection of treatment

Table 4. Duration of hyperthyroidism

Duration	ATD	¹³¹ I	Surgery	Observation	Total
Less than 1 year	156(22)	206(29)	332(46)	21(3)	715(100)
1 year to less than 3 years	50(20)	73(30)	109(44)	15(6)	247(100)
3 years and over	40(25)	58(37)	39(25)	21(13)	158(100)
No detail	1	1	1	1	4(100)
Total	247(22)	338(30)	481(43)	58(5)	1,124(100)

(); percentage

Table 5. Performance of treatment, by sex

Indication Performance	Male			Female		
	ATD	¹³¹ I	Surgery	ATD	¹³¹ I	Surgery
ATD	25 (89)	0	0	188 (86)	2 (1)	5 (1)
¹³¹ I	0	49 (91)	0	0	269 (95)	3 (1)
Surgery	0	0	80 (90)	0	1 (0)	308 (79)
No treatment	3 (11)	5 (9)	9 (10)	31 (14)	12 (4)	76 (19)
Total	28 (100)	54 (100)	89 (100)	219 (100)	284 (100)	392 (100)

() ; percentage

were treated with surgery. Patients more than 3 years duration of the disease were predominantly treated with ¹³¹I treatment.

f) Complicated disorders

Although there were patients with complication of cardiovascular disorders (44 cases), hypertension (238 cases), diabetes mellitus (13 cases), and periodic paralysis (36 cases), no consideration was actually taken for the selection of treatment. In the case of patients with psychiatric disorders (21 cases), treatment was chosen after the consultation with psychiatrists.

IV. Relation between indication and actual treatment

The relation of recommended treatment to performance of the treatment for hyperthyroidism are shown in Table 5. Although about 90 per cent of male patients with the disease were equally treated in each mode, female patients showed a stronger inclination against surgery. The reasons were as follows; of 8 cases in which treatment other than surgery were done, five were treated with ATD administration because of refusal for surgery (3 cases) and of well responded to preoperative ATD administration (2 cases). The other three patients were treated with ¹³¹I administration because of anemia in one case and depression in the remaining two.

V. Method of treatment

a) Antithyroid drugs (ATD)

The cases for this indication were principally treated with methimazole, but some cases were treated with propylthiouracil because of the side effect with methimazole. The initial dose of methimazole was 15 to 30 mg, three times daily, then reduced gradually as the thyroid function tests showed the normal range until the minimum maintenance

dose of 5 mg daily was obtained. Maintenance dose was continued for at least one year. In the case of propylthiouracil treatment, the initial dose was 300 mg in three divided doses daily, and maintenance dose of 50–100 mg daily. The majority of cases were treated on outpatient basis and allowed with their daily activity. Those patients not responding with ATD administration were requested to have one of other treatments in its early stage.

b) Radioiodine (¹³¹I)

¹³¹I was administered orally in a single dose aiming to deliver 6,000 to 8,000 rads to the thyroid. The method of calculating the amount of ¹³¹I to be given was followed by Mc Gavacks formula (1951).

$$\text{Radiation dose (Rads)} = 0.2 \times 93.7$$

$$\times \frac{{}^{131}\text{I uptake/24 hr (\%)} \times \text{effective half life (day)}}{\text{Weight of gland (g)}}$$

$$\times \text{administration dose (mc)}$$

Uptake and effective half life were counted and calculated by a preliminary tracer dose administration. The weight of thyroid gland was assessed by Okubo's formula (1959) which was established on the basis of practical comparison between surgically resected specimen of the hyperthyroid goiter and its scintigram. After the administration of therapeutic dose actual radiation dose delivered to the thyroid was also counted and calculated for confirmation. If the estimated dose of ¹³¹I was not to be delivered to the gland, deficient amount of ¹³¹I was added immediately. In such instance, while ¹³¹I was given twice, number of doses was regarded as a single dose. The cases failed to reach euthyroid status with the above treatment were classified as post-therapeutic hyperthyroid status in the result of follow-up study. ¹³¹I treatment was not recommended for unmarried women and women with future possibility of pregnancy. Those beyond their reproductive age were

Table 6. The Follow-up results of ATD treatment

A. Patients maintaining euthyroid less than 1 year after cessation of medication	84 cases
1. Administration continued	33 cases
2. Treatment altered	35 cases
to iodine-131	20 cases
to surgery	15 cases
3. Under observation	16 cases
B. Patients maintaining euthyroid over 1 year after cessation of medication	51 cases
1. Over 1 year-less than 2 years	16 cases
2. Less than 3 years	16 cases
3. Less than 4 years	12 cases
4. Over 4 years	7 cases
C. Others	112 cases
1. Treatment discontinued	78 cases
2. Transferred to other hospitals	34 cases

usually treated with ^{131}I administration.

c) Surgery

Patients undergoing surgery were prepared by the administration of ATD until euthyroidism was obtained. Lugol solution was given only when the patients had an extremely large goiter or had side effects with ATD administration. The detail of surgical procedure was previously reported by the authors (1969). All cases with surgery were operated only by the first author. Surgery was selected for patients who needed to return to their work as early as possible. The same was true for patients living in remote area, without access to satisfactory medical care.

Follow-up

The follow-up study of the 930 cases treated in the hospital was carried out from July 1969 through June 1970. The patients were requested to visit outpatient clinic for the evaluation of their thyroid function. Thyroid status was evaluated by two function tests, generally resine-sponge up-take and protein bounding iodine as well as physical examination. In a few cases, evaluation was made by questionnaire sent to patients, or by evaluation of the nearby practicing physicians. The follow-up data was obtained in 685 cases (73.3 per cent of the 930 cases), including 9 dead cases. All deaths were not related to hyperthyroidism, except one case with unknown cause.

On the other hand, another questionnaire was sent to the patients with hyperthyroidism to whom surgery were carried out in our series to ask their judgement of the surgical scar.

Results

a) ATD Treatment

The results of ATD administration is sum-

marized in Table 6. Of 135 followed-up cases, patients achieved remission lasting more than one year was only in 37.5 per cent.

b) ^{131}I Treatment

The results of this treatment revealed that 80.5 per cent (186 cases of 231 followed-up cases) obtained euthyroidism by 4 to 5 years after single dose administration (Table 7). This remission rate was significantly better than that of ATD treatment. It is noteworthy that the remission rate in male was excellent with 90.9 percent with no development of hypothyroidism, whereas in female the rate was not as favorable with 78.8 per cent of euthyroidism and 10.6 per cent of hypothyroidism. Hyperthyroidism persisted in 9.1 per cent of male and 10.6 per cent of female

Table 8 shows the relationship between the actually delivered radiation dose to the thyroid and the thyroid status at the follow-

Table 7. Follow-up status with patients treated with ^{131}I , by sex

Sex	Thyroid Function			Total
	Hyper-thyroid	Eu-thyroid	Hypo-thyroid	
Male (%)	3(9)	30(91)	0	33(100)
Female (%)	21(11)	156(79)	21(11)	198(100)
Total (%)	24(10)	186(81)	21(9)	231(100)

(); percentage

Table 8. Relationship of radiation dose to the thyroid function at the follow-up status in female patients

Radiation Dose	Thyroid Function			Total
	Hyper-thyroid	Eu-thyroid	Hypo-thyroid	
-5000 rads	1	1	1	3(100)
5001-6000 rads	0	4(67)	2(23)	6(100)
6001-7000 rads	2(17)	10(83)	0	12(100)
7001-8000 rads	3(9)	26(76)	5(15)	34(100)
8001-9000 rads	2(5)	32(87)	3(8)	37(100)
9001+ rads	4(6)	58(83)	8(11)	70(100)
No detail	9(25)	25(69)	2(6)	36(100)
Total	21(11)	156(79)	21(11)	198(100)

(); percentage

up in female cases. It seemed that radiation sensitivity of thyroid gland was quite different from case to case. In some cases, hyperthyroidism persisted among patients irradiated with a large radiation dose and in others hypothyroidism resulted despite a small dose of irradiation delivered. Mode of radiation dose delivered to those obtained euthyroidism was 8,640 rads (4,940-17,520 rads), those with persistent hyperthyroidism, 8,000 rads (4,800-13,400 rads) and those developed hypothyroidism, 8,250 rads (3,080-11,020 rads). Thus, no relation could be found between the incidence rate of hypothyroidism and radiation dose.

c) Surgery

Table 9 summarizes the result of surgical treatment in 295 follow-up cases; 75.8 per cent of the 389 cases operated on. Euthyroid was obtained in 93.9 per cent among them. This remission rate was significantly better than that for ATD or ^{131}I treatments. The surgical records were reviewed in regard to the twelve hyperthyroid patients relapsed or persistent; seven cases were presumed due to the large amount of thyroid tissue left behind

Table 9. Follow-up status with patients after surgery, by sex

Sex	Thyroid Function			Total
	Hyper-thyroid	Eu-thyroid	Hypo-thyroid	
Male	5(8)	56(90)	1(2)	62(100)
Female	7(3)	221(95)	5(2)	233(100)
Total	12(4)	277(94)	6(2)	295(100)

(); percentage

and the reasons for the remaining cases were unknown. In the case of hypothyroid patients, it was proved that the remnant of thyroid tissue was too small and histologically lymphoid infiltration was demonstrated in all cases.

In regard to complications of surgery, there were 10 cases of transient tetany and 4 cases of transient unilateral vocal cord paralysis among 389 operated cases. No surgical mortality and postoperative thyroid storm took place.

In term of a questionnaire sent to the patients to whom surgery were carried out for asking their judgement of the surgical scar, answers were obtained in 202 cases among 389 operated cases. The results were as follows; hardly noticeable 29 (14%), slightly noticeable 132 (20%), and extremely evident 8 (4%).

Discussion

Among the three major treatment for hyperthyroidism, namely ATD, ^{131}I , and subtotal thyroidectomy, the last one was the only treatment for this disease in the past. Administration of iodine provided transient control of the disease and reduction of vascularity of the gland. Astwood (1943), however, introduced the thiourea in the treatment of hyperthyroidism; but high recurrence rates and frequent toxic reaction made the antithyroid drug unsatisfactory for definitive therapy. About the same time, ^{131}I became

available for treatment of this disease. Radioiodotherapy appeared ideal due to lack of operative risks, good control of symptoms, and although other methods of treatment revealed drawbacks, this form of treatment was accepted predominantly. Later, however, follow-up studies disclosed radioactive iodine treatment resulted in high incidence of post-therapeutic hypothyroidism.

In ATD treatment, the term of medication is generally so long that it is not so easy to achieve the completion of the therapy as physician expects. Some patients discontinue the medication by their judgement and others would continue incomplete medication. The remission rate of ATD administration in our study was lower than the following reports; Solomon *et al.*, (1953) 45%, McCullagh and Cassidy (1953) 66%, Trotter (1961) 45%, Reveno and Rosenbaum (1964) 57%, Hershman *et al.*, (1966) 54%, and Shizume (1969) 49%. In regard to our low remission rate, it might be argued that the selection of cases or method of administration was not appropriate: Mild cases with smaller goiter and shorter duration of illness were more likely treated with ATD as was shown in Figure 2 and Table 3. As to the administration of ATD, methimazole was administered ranging from 15 to 30 mg three times daily as the initial dose, and in most cases 20 mg. This dose seems to be small compared with the above other reports. Recently we have found to increase our initial dose to 30 mg or more daily. Furthermore, cases which failed to respond quickly to ATD or presented difficulty of maintaining euthyroidism by administration of the maintenance dose, were switched to other mode of therapy at an earlier stage.

Solomon *et al.*, (1953), Reveno and Rosenbaum (1964), and Shizume (1969) emphasized that the smaller goiter responds more favorably to ATD administration than the larger one. It was, however, difficult to show in our result since cases with larger goiter were not treated with ATD in our series. As Hershman *et al.*, (1966) and

Shizume (1969) stated, there was a tendency that remission was more often obtained in cases with goiter which diminished in size during the period of treatment.

The high incidence of hypothyroidism developed after ^{131}I treatment has been in debate. Segal *et al.*, (1961) reported 17.9% of hypothyroid among the followed-up cases after 5 years of ^{131}I administration, Green and Wilson (1964) 18.8% after 5 years, and Zellmann *et al.*, (1968) 20.6% after 4 years. However, the incidence of hypothyroidism reported in Japan seems to be relatively lower than Occidental ones; Shizume reported 5.1% of hypothyroidism among the followed-up cases after 4 years of ^{131}I administration, and Hara and Kitabatake 9.9% after 5 years. In our series, 9.1% of hypothyroidism was confirmed among the followed-up cases after 4 to 5 years of ^{131}I administration. The difference in frequency between Japanese and Occidental reports may derived from the difference of radiation dose and/or racial sensitivity to ^{131}I .

Among the three major treatment of hyperthyroidism in our study, the remission rate of surgical treatment was most satisfactory as stated in the results. Maruta *et al.*, (1966), Noguchi and Noguchi (1967), Kuma and Kuma (1963), and Ezaki *et al.*, (1968) of Japan also reported similar results as ours. However, the authors of those reports with excellent results were believed to be experienced in thyroid surgery. It is the fact that the results are not always satisfactory unless surgery is performed by experienced thyroid surgeons.

Since scar formation is inevitable and the majority of patients with hyperthyroidism are young women, the appearance of scar constitutes an important problem for them.

From the cosmetic point of view, the result of the inquiry on the patients to whom surgery were carried out revealed that about two thirds of the cases were not much concerned with the scar.

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