Incidence of Hypothyroidism Occurring Long After Iodine-131 Therapy for Hyperthyroidism

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We have studied the long-term incidence of hypothyroidism in 4,473 formerly hyperthyroid patients given I-131 therapy between 1951 and 1975. The mean age at the first I-131 treatment was 56 yr. Six percent developed hypothyroidism within one year of therapy, and 72% within 26 yr. Prior antithyroid medication did not affect the incidence of hypothyroidism. Patients cured with one dose of I-131 had a lower cumulative long-term incidence of hypothyroidism than those requiring more than one dose.

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Hypothyroidism is common following radioiodine therapy for hyperthyroidism (*1–4*). After the first post-therapy year, there is an annual increase of approximately 3% in the number of patients who develop hypothyroidism (*2,5*). This study was designed to provide data to determine whether the annual increase of the cumulative incidence of hypothyroidism after I-131 therapy for hyperthyroidism levels off with very long observation periods, or whether it continues steadily until eventually all patients at risk become hypothyroid.

MATERIALS AND METHODS

Between 1951 and 1975 I-131 therapy was given at our institution to 4,473 patients (3,765 women and 708 men) with hyperthyroidism. Of these, 583 patients (13%) had previous thyroid surgery, and 763 patients (17%) had received antithyroid medication for at least 3 wk immediately before the I-131 therapy. Iodine-131 was usually avoided in patients under 40 yr of age unless surgery or antithyroid drugs had been contraindicated or the patients had not responded to either of these. Patients with solitary hyperfunctioning thyroid nodules (n = 80) were excluded.

The mean age at the time of the first I-131 treatment was 56 yr for the women, 53 yr for the men, and 56 yr overall (range 14–91 yr). Seven patients (0.2%) were less than 20 yr of age and 436 (10%) were less than 40.

Data were obtained from hospital records. There were 2,332 patients with diffuse goiters and 2,123 with nodular glands. For 18 patients the information as to goiter type was inadequate. Goiter size was estimated by palpation and supported by thyroid imaging. Five percent of the thyroids were judged normal in weight ($\leq$30 g), 86% were between 31 and 60 g, and 9% were larger.

The principles of I-131 treatment for hyperthyroidism at Radiumhemmet have been described (*1,2*) and were unchanged throughout the study. We tried to deliver a radiation dose of 6,000–10,000 rad (60–100 Gray) per treatment. The lower doses were given to patients with diffuse goiters and higher doses for the nodular type.

The mean I-131 dose administered and the retained dose in the thyorid 24 hr later, as calculated from pretherapy diagnostic doses, are shown in Table 1. The mean effective half-time of the nuclide in the gland, also assessed from the diagnostic procedures before treatment, was 5.4 days in the diffuse goiters and 5.7 days in the nodular. Fifty-six percent of the patients received one treatment, 28% two, 10% three, and 6% more than three

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TABLE 1. MEAN ADMINISTERED ACTIVITY OF I-131 AND MEAN TOTAL I-131 ACTIVITY IN THE THYROID GLAND AT 24 HR AFTER ADMINISTRATION

		Type of thyroid gland			
		Diffuse		Nodular	
		Women	Men	Women	Men
Mean administered I-131 activity per treatment:	mCi	4.9	5.1	10.1	11.0
Total	mCi	8.1	9.8	17.2	20.2
Mean total I-131 activity in thyroid gland*	mCi	5.1	5.9	10.1	11.1

* As estimated from diagnostic doses before therapy.

treatments. Table 2 shows the distribution of the total doses of I-131 administered.

The cure rates after I-131 therapy were similar for patients with diffuse or nodular goiters (Table 3). Patients premedicated with antithyroid drugs had a lower cure rate (Table 3), but since the exact duration of pretreatment is not known, our data on this point are incomplete.

Following I-131 treatment, patients were examined at 2–4-mo intervals during the first year, and usually at 6–12-mo intervals subsequently. The follow-up period started at the time of the first I-131 treatment and continued until December 1977 or until hypothyroidism or death if either occurred sooner. Table 4 shows the duration of follow-up.

Diagnoses of hypothyroidism were based on clinical findings and confirmed by thyroid function tests. To avoid permanent replacement therapy for patients with transient hypothyroidism, thyroid hormone was not instituted within the first 4–6 mo after I-131 therapy whenever the clinical status permitted.

The incidence of hypothyroidism was analyzed by the standard life-table technique. The statistical analysis used was the log-rank test.

TABLE 2. PATIENTS DISTRIBUTED ACCORDING TO TOTAL DOSE OF I-131 ADMINISTERED

Total dose (mCi)	Number of patients	Percentage
<10	2523	56.4
10–19.9	1164	26.0
20–49.9	635	14.2
50–99.9	123	2.8
≥100	28	0.6

TABLE 3. CURE RATE AFTER I-131 THERAPY FOR HYPERTHYROIDISM IN RELATION TO TYPE OF GOITER AND ANTITHYROID DRUG PREMEDICATION

Months after I-131 therapy	Percentage of patients cured		
	All diffuse (n = 2332)	All nodular (n = 2123)	All antithyroid premedicated (n = 763)
3	20	11	11
6	58	55	45
9	74	72	65
12	83	82	77

RESULTS

One year after I-131 therapy 6% of the patients were hypothyroid (Fig. 1): 8% for patients with diffuse goiter and 3% for nodular. The cumulative incidence of hypothyroidism during the first 24 yr after therapy rose by an average of 3.0% yearly overall, 3.2% diffuse, and 2.7% nodular. Twenty-four years after I-131 therapy, 72% of patients were hypothyroid (77% diffuse and 64% nodular). The difference between diffuse and nodular types was statistically highly significant ($p \ll 0.001$). The tendency of the curves to level off at the end of the observation periods could be due to the few euthyroid patients followed that long.

For part of the observation period, the incidence of hypothyroidism was somewhat higher in female patients

TABLE 4. NUMBER OF PATIENTS DISTRIBUTED ACCORDING TO DURATION OF FOLLOW-UP

Maximum follow-up (yr)	Number of patients		
	Women	Men	All
<10	2654	458	3112
10–14	582	134	716
15–19	344	71	415
20–24	146	39	185
≥25	38	7	45

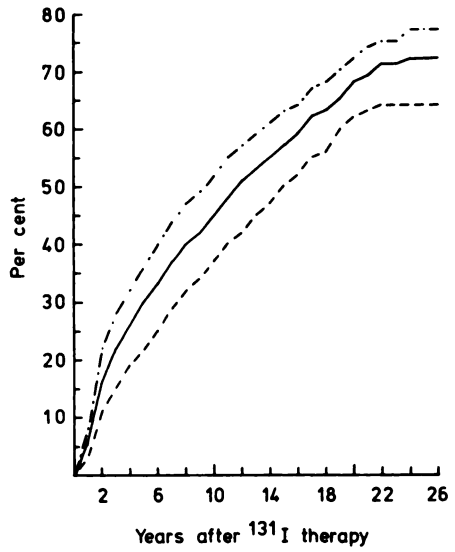

FIG. 1. Cumulative incidence of hypothyroidism after I-131 therapy in 4,473 previously hyperthyroid patients. All patients (——); patients with diffuse goiters (·--·); and patients with nodular (---) glands.

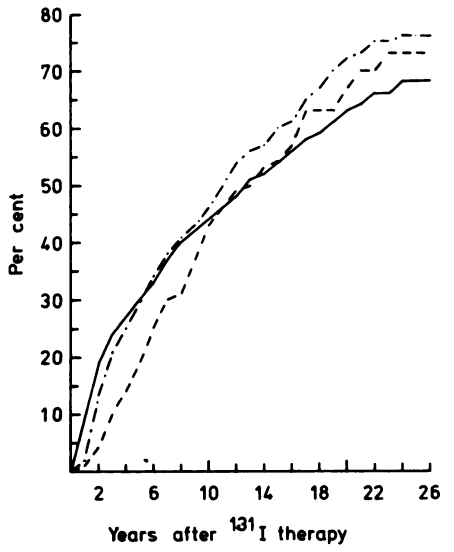

FIG. 2. Cumulative incidence of hypothyroidism after I-131 therapy for hyperthyroidism according to number of treatments. One treatment (——); 2–3 treatments (·--·); more than three treatments (---). Numbers of patients still euthyroid at 20 yr after I-131 therapy were 98, 102, and 31, respectively.

with diffuse thyroid glands than in males ($p < 0.001$). At the end of the observation period this sex difference disappeared. No sex difference was observed in patients with nodular glands. As anticipated, the incidence of hypothyroidism was lowest in patients with goiters larger than 60 g (53% after 22 yr) since this group also contained the patients with large multinodular goiters. There was no major difference in the incidence of hypothyroidism between patients with normal and moderately enlarged glands—74% and 71% hypothyroidism after 22 yr, respectively.

Patients premedicated with antithyroid drugs had an incidence of hypothyroidism similar to that for patients without premedication. The incidence of hypothyroidism in patients with previous thyroid surgery was somewhat higher than for the whole series: 6% after 1 yr and 81% after 24 yr.

Younger patients had a higher incidence of hypothyroidism than older patients (Table 5). This was most obvious in those patients with nodular glands. The higher incidence in the younger patients was also apparent when differences in thyroid weight were considered.

Patients treated with one dose of I-131 had the highest incidence of hypothyroidism within 2 yr after treatment (Fig. 2), and patients treated with more than three doses had the lowest incidence in the first 2 yr ($p < 0.001$). After 2 yr, however, the annual rate of hypothyroidism was lowest for patients treated with one dose ($p < 0.001$).

Within one week of the I-131 treatment 12 patients (0.3%) had a severe exacerbation of the hyperthyroid state, with fever, hypertension, and tachycardia. In two of these the diagnosis of thyrotoxic crisis was firmly established. The mean age of these 12 patients did not differ from that of the whole series. The exacerbations appeared after mean I-131 doses of 5.6 mCi in five patients with diffuse thyroid glands, and of 16.4 mCi in

TABLE 5. PERCENTAGES OF PATIENTS DEVELOPING HYPOTHYROIDISM WITHIN 1, 8, AND 16 YR AFTER I-131 THERAPY, IN RELATION TO AGE AT FIRST TREATMENT

Age at first treatment	Type of thyroid gland					
	Diffuse			Nodular		
	1 yr	8 yr	16 yr	1 yr	8 yr	16 yr
<40	10	46	65	3	40	59
40–49	8	49	66	3	42	61
50–59	9	47	66	5	34	55
60–69	8	44	57	2	25	39
≥70	4	35	47	1	21	36

seven patients with nodular glands. Only one episode occurred after 1969.

Two of the 12 patients died (0.04% of all patients); one was 65 yr old and the other 71. Both had associated chronic debilitating diseases: diabetes mellitus and arteriosclerotic heart disease, with cardiac decompensation and uremia, in one; and myocardial infarctions, one old and one recent, in the other. Hence it is impossible to determine the relative contributions of the thyroid disease and the other diseases to these deaths.

DISCUSSION

Hypothyroidism is common after I-131 therapy for hyperthyroidism (*1-5*). The cumulative incidence of hypothyroidism for patients treated at our institution increased with an average of 3% yearly, at least during the first 24 post-therapy years. The slope of the curve resembles those of other studies (*2,3,5*). It seems that most patients—possibly all with diffuse goiter—will eventually develop hypothyroidism if they live long enough.

The annual incidence of hypothyroidism after surgery for hyperthyroidism is less than after I-131 (*3,4*). We have found no published data on the incidence of hypothyroidism after thyroidectomy in patients followed as long as ours, but it seems likely that the cumulative incidence in surgically treated patients would also continue to rise with longer observation periods.

Our study showed no signficant difference between patients who received antithyroid premedication and those who did not. Since the duration of pretreatment (beyond 3 wk) is not known, our data are incomplete on this point.

An incidence of hypothyroidism within several years after the radiotherapy has been reported to be higher for patients cured with one dose of I-131 than for those requiring more than one dose (*2*), findings similar to ours. With a longer observation period, however, the results were reversed.

A correlation exists between the incidence of hypothyroidism and the dose of I-131 delivered to the thyroid gland. The use of lower doses of I-131 has been advocated in an attempt to reduce the incidence of hypothyroidism (*6-9*). However, the incidence of hypothyroidism long after low-dose therapy of I-131 seems not to differ from that following conventional doses (*10*). Hence, lower I-131 doses may only prolong the time needed to eradicate the hyperthyroid state without any ultimate reduction in hypothyroidism.

The cure rate of the present study is consistent with those of other studies (*6,11*). Higher I-131 activities are reported to result in higher cure rates and a decreased need for retreatment, but also to cause hypothyroidism more rapidly (*12-14*).

Twelve patients in this study (0.3%) had a severe exacerbation of the thyroid disease, and for two of these the diagnosis of thyrotoxic crisis was established. Two patients with exacerbations died, but both had associated chronic debilitating diseases that probably contributed to the deaths. These two patients were treated in 1961 and in 1966, i.e., before the era of beta- blocking agents. Today the risk of thyrotoxic crisis after I-131 therapy is almost negligible, because patients with a high risk of this complication can be identified and pretreated with antithyroid drugs and/or beta-blocking agents. If post-therapy exacerbations occur, these can be effectively treated with such agents in combination with corticosteroids.

There seems to be no increased risk of thyroid cancer (*15,16*) or leukemia (*17*) after I-131 therapy for hyperthyroidism. Compared with therapeutic alternatives, I-131 therapy is a safe procedure. Most patients can be treated as outpatients, the recurrence rate is small, and costs are low for the patients and for the community. With relatively few exceptions, we regard I-131 as the treatment of choice for hyperthyroid patients aged 40 yr or more. We advise surgery for patients with rapidly progressing eye symptoms or large goiters, and also for the few in whom malignancy is suspected. The latter group can be reduced by the use of fine-needle biopsy (*18,19*).

To date I-131 therapy for either hyperthyroidism (*20,21*) or thyroid cancer (*22,23*) in children and adolescents has not been associated with harmful effects on the subsequent fertility or birth history of the patients, or on health status and reproductive history of the progeny. Because of the safety record of I-131 therapy for hyperthyroidism, young adults, and possibly also adolescents, could be treated with I-131 more often than is now being generally advocated.

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