Long-term Follow-up in Toxic Solitary Autonomous Thyroid Nodules Treated with Radioactive Iodine

Dyde A. Huysmans, Frans H. Corstens, Peter W. Kloppenborg

Departments of Nuclear Medicine and Medicine and Division of Endocrinology University Hospital Nijmegen, Nijmegen, The Netherlands

The long-term effects of radioiodine treatment on thyroid function in patients with a toxic solitary autonomous thyroid nodule were evaluated. Fifty-two patients received a therapeutic dose of 20 mCi of iodine-131 (^{131}I). Duration of follow-up was 10 ± 4 yr. Follow-up data included a biochemical evaluation of thyroid function. The failure rate (recurrent hyperthyroidism) was 2%. The incidence of hypothyroidism was 6% and was not related to the dose per gram of nodular tissue. Oral administration of 20 mCi of radioiodine is a simple and highly effective method for the treatment of patients with a toxic autonomous thyroid nodule. The risk of development of hypothyroidism is low if extranodular uptake of ^{131}I is prevented. This can be achieved by not treating euthyroid patients, by no longer using injections of exogenous thyroid stimulating hormone in the diagnostic work-up of the patients and by always performing radioiodine imaging shortly before treatment.

J Nucl Med 1991; 32:27–30

Two subgroups of nodular thyroid diseases with autonomous hyperfunction are currently recognized as clinically distinct entities. Toxic multinodular goiter is a disease in which there is a large multinodular goiter. It predominantly afflicts elderly people. The goiter and autonomous function often precede the onset of hyperthyroidism by many years (*1*). Goetsch's disease or the solitary autonomous thyroid nodule is characterized by a single thyroid adenoma which is functioning autonomously and independently of pituitary stimulation or any other extrathyroidal stimulator. The thyroid hormone secreted by the nodule has a negative feedback on the production of thyroid-stimulating hormone (TSH) by the pituitary gland. By this mechanism, the function of the TSH-dependent extranodular tissue is suppressed to a variable degree (*1*).

Received Feb. 20, 1990; revision accepted Jul. 6, 1990.

For reprints contact: Frans Corstens, M D, Dept. of Nuclear Medicine, University Hospital Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.

Many patients with a solitary autonomously functioning thyroid nodule are euthyroid. Progression to persisting hyperthyroidism occurs in only a small number of patients. Moreover, spontaneous degeneration of the nodule is possible (*2*). Therefore, non-toxic autonomous thyroid nodules are regularly left untreated in The Netherlands.

Radioactive iodine is a generally accepted method for the treatment of hyperthyroidism, especially in patients with a solitary autonomous thyroid nodule. Post-treatment hypothyroidism seems less likely if iodine uptake in the extranodular tissue is sufficiently suppressed, which means that the nodule is the only visible thyroid tissue on iodine scintigraphy.

There are few reports on the long-term follow-up of patients with hyperthyroidism, due to a solitary autonomous thyroid nodule, treated with iodine-131 (^{131}I) (*3–9*). Recently, we have studied the long-term effects of radioiodine treatment on thyroid function in patients with hyperthyroidism due to Goetsch's disease treated in our hospital.

PATIENTS AND METHODS

Iodine-131 Therapy

Between 1970 and 1985, 52 patients with a toxic solitary autonomous thyroid nodule received an oral standard therapeutic dose of 20 mCi (740 MBq) of ^{131}I as sodium iodide at the University Hospital, Nijmegen. The female-to-male ratio was 3.3:1 and the age range was 58.2 ± 11.2 yr (mean ± s.d.). All patients had clinical signs and symptoms of hyperthyroidism as well as elevated levels of thyroid hormones (thyroxine (T_4) 186 ± 44 nmole/l, triiodothyronine (T_3) 4.3 ± 1.1 pmole/l). The 24-hr ^{131}I uptake was 52% ± 12%. Thyroid scans using [^{131}I]sodium iodide, [^{123}I]sodium iodide or (in 9 patients) technetium-99m-pertechnetate showed single hot nodules with total suppression of extranodular tissue in 48 patients and near-total suppression in four. The weight of the nodules was estimated from the thyroid scan using the formula:

$$\frac{1}{6}\pi xy^2,$$

where x is the longest and y is the shortest diameter of the nodule. For each nodule, the total ^{131}I dose delivered was

divided by this estimated nodular weight and multiplied by the 24-hr uptake/100 in order to calculate the ^{131}I dose per gram functional thyroid tissue (*6*). Iodine scintigraphy after injections of exogenous TSH was used to visualize extranodular thyroid tissue. Therapy was postponed at least 4 days after imaging with TSH stimulation. Twelve patients were on antithyroid medication (thiamazole) prior to ^{131}I therapy. They concomitantly used a thyromimetic drug to avoid elevation of the serum TSH level. The antithyroid drug was discontinued for at least three days prior to ^{131}I administration till three days afterwards.

In our laboratory, normal values for the various tests used are: serum T_4 65-140 nmole/l, serum T_3 1.8–2.9 nmole/l, serum free T_4 9–19 pmole/l, serum TSH 0.4–4.0 mU/l, and 24-hr ^{131}I uptake 10%–59%.

Follow-up

The patients were followed for a period of 4–17.5 yr (mean 10 ± 4 yr). Five of them had died of unrelated causes and one patient had emigrated. The last available data from the medical records of these patients were used. All other patients were seen by their own physician or by ourselves. A short medical interview and physical examination were carried out. Serum T_4 and TSH levels were measured utilizing standard methods. Criteria for hyperthyroidism were a serum T_4 level over 140 nmole/l together with a suppressed TSH. Hypothyroidism was diagnosed in patients with a serum T_4 level of less than 65 nmole/l together with a serum TSH level over 4.9 mU/l. In patients with an elevated TSH, the serum-free T_4 level was also measured.

RESULTS

All 52 patients became euthyroid within 6 mo after radioiodine therapy and antithyroid medication was stopped. In one patient, thyrotoxic symptoms recurred 1.5 yr later. Iodine scintigraphy showed the same hot nodule. This patient was successfully treated with a second dose of 20 mCi of ^{131}I. Hyperthyroidism did not recur in any of the other patients.

During the follow-up period, thyroxine therapy was started in six patients. In two of these, therapy was started 3 and 7 yr after radioiodine therapy because of mild clinical and biochemical hypothyroidism (T_4 level, 56 and 58 nmole/l, respectively; TSH level, 16.9 and 19.1 mU/l, respectively). In a third patient, thyroxine therapy was started in another hospital after 15 yr (no further data available). Two other patients became hypothyroid (T_4 level 42 and 60 nmole/l, respectively; TSH level 54 and 33 mU/l, respectively) 2 and 6 yr after they had been treated with ^{131}I. However, they had been treated at an inappropriate moment, while the effects of the injected exogenous TSH were still present. In the sixth patient, thyroxine therapy was started unnecessarily after 3 yr (serum TSH level at the start of thyroxine therapy 1.4 mU/l). The remaining 46 patients, including the patient who had received 20 mCi twice, were, without replacement therapy, clinically and biochemically euthyroid at the end of the follow-up period. Of these patients, six had a slightly elevated serum TSH level (5.20–8.10 mU/l) together with a normal serum T_4 level (80–102 nmole/l), and free T_4 level (8.6–11.5 pmole/l).

The development of hypothyroidism in our series was not related to the dose per gram of nodular tissue corrected for radioiodine uptake (399 ± 242 μCi/g in the 46 patients who remained euthyroid and 408 ± 295 μCi/g in the 6 patients who became hypothyroid ($p \geq 0.10$, Wilcoxon's test). No antithyroid antibodies were present in the patients in whom hypothyroidism developed. The prior use of antithyroid medication, stopped at least three days before ^{131}I administration, in 12 patients seems not to have influenced the development of hypothyroidism. One of these patients became hypothyroid. This patient had a suppressed serum TSH level on the day of therapy.

In order to reveal a process of slowly diminishing thyroid function after radioiodine therapy, we compared serum T_4 levels as measured in 1984 and 1988 in 29 patients who had not become hypothyroid. In 1984, the T_4 level was 90 ± 21 nmole/l, in 1988 93 ± 19 nmole/l ($p \geq 0.10$, Wilcoxon's test). None of these patients showed a decline of the serum T_4 level.

DISCUSSION

In the present study, patients with a solitary autonomous thyroid nodule were treated with radioiodine only when they were clinically and biochemically hyperthyroid. The high mean age (58.2 ± 11.2 yr), the suppression of extranodular tissue, and the rather large size of most nodules are in accordance with the hyperthyroid state (*1,2,10–12*).

All of our 52 patients became euthyroid within 0.5 yr after a standard dose of 20 mCi of ^{131}I and during a mean follow-up period of 10 yr hyperthyroidism recurred in only one patient. This patient received a second dose of 20 mCi of ^{131}I 1.5 yr after the first dose. The failure rate found in our study (2%) is lower than that found in the study of Ratcliffe et al. (*8*). In their study, hyperthyroidism recurred in 7 of 48 patients after a standard oral dose of 15 mCi of ^{131}I. Other authors (*3,4,6,7,13*) not using a standard dose, but a dose adjusted according to the individual size of the nodule, also reported higher incidences of therapy failures (7%–52%; Table 1).

During the follow-up period, thyroxine therapy was started in 6 of our 52 patients. However, in one of these patients thyroxine therapy was started while the patient was not hypothyroid. In two patients, treatment with ^{131}I was given while the effects of injected exogenous TSH were still present. Excluding these three patients the incidence of hypothyroidism in our series is 3/49 or 6%. Other investigators found similarly low percentages, although during shorter follow-up periods. Mariotti et al. (*7*) reported five cases of hypothyroidism after treatment of 126 patients with a dose of 180 μCi

TABLE 1
Failure Rate of ^{131}I Therapy in Patients with Solitary Autonomous Thyroid Nodules and Hyperthyroidism (Primary Therapy Failures and Recurrences)*

Investigator	Number of patients	Failure rate (%)	Follow-up (yr)	Method of calculation	Dose of ^{131}I (mCi)
Fontana	23	52	Life-table method	20,000–80,000 rad	Not mentioned
Heinze	188	9	2.5 ± ?	30,000–40,000 rad	18.9 ± 9.6
Hegedus	27	7	1 (all patients)	100 μCi/g	7.5 ± ?
Mariotti	138	15	3.2 ± 2.2 (1–11)	180 μCi/g	12.6 ± 4.1
Ratcliffe	48	15	3.1 (2–10)	Standard dose	15
Ross	45	13	4.9 ± 3.2 (0.5–13.5)	160 μCi/g	10.3 ± ?
This study	52	2	10 ± 4 (4–17.5)	Standard dose	20

* Mean ± s.d. (range).

of ^{131}I per gram nodular tissue (duration of follow-up 3.2 ± 2.2 yr). Eyre-Brooke et al. (*14*) found two cases of hypothyroidism out of 37 patients treated with 1.2–15 mCi of ^{131}I (mean duration of follow-up 6.5 yr) while none of the 48 patients of Ratcliffe et al. (*8*) developed hypothyroidism after treatment with 15 mCi of ^{131}I (mean duration of follow-up 3.1 yr; range 2–10 yr).

In two studies, rather high incidences of hypothyroidism have been reported. In the study of Goldstein et al. (*5*), 8 of 22 patients became hypothyroid after treatment with 15–55 mCi of radioiodine. However, it has to be noted that 16 of these patients were euthyroid at the time of treatment and 12 of them had incomplete suppression of uptake in the extranodular tissue. Fontana et al. (*4*) reported an incidence of hypothyroidism of 17% at 10 yr and 44% at 20 yr after treatment of 29 patients with 20,000–80,000 rads (these authors used a life-table method). But none of their patients who had (almost) complete suppression of the function of the extranodular parenchyma, developed hypothyroidism.

One might think that the amount of administered ^{131}I plays a major role in the development of hypothyroidism after radioiodine treatment in thyrotoxic patients with a solitary autonomous thyroid nodule. However, the data in our study and those of Goldstein et al. (*5*) and Fontana et al. (*4*) strongly suggest that it is not the dose of radioiodine but the presence of incomplete suppression of iodine uptake in the extranodular tissue that determines the incidence of hypothyroidism. Extranodular iodine uptake is, of course, frequently seen in patients with a solitary autonomous thyroid nodule who are not thyrotoxic. In order to prevent the development of hypothyroidism, radioiodine treatment should not be given to these patients. Incomplete suppression of uptake in extranodular tissue is also present after exogenous TSH injections, sometimes even months afterwards. Therefore, to visualize extranodular thyroid tissue, we recommended imaging with thallium-201-chloride or ultrasonography of the thyroid instead of imaging with ^{123}I after pretreatment with injections of exogenous TSH (*15*). The latter procedure is no longer in use in The Netherlands. In our opinion, visualization of suppressed normal thyroid tissue is relevant. If suppressed extranodular tissue is present, we assume that this parenchyma will take over thyroid function after ablation of the nodule with a relatively high dose of 20 mCi of ^{131}I. If there is no extranodular tissue, we routinely administer a lower dose calculated according to the method described by DeGroot (*16*) in order to diminish the risk of post-treatment hypothyroidism.

We conclude that oral administration of 20 mCi of radioiodine is a simple and highly effective method for the treatment of patients with a toxic autonomous thyroid nodule. The risk of development of hypothyroidism is low if the uptake of ^{131}I in the extranodular tissue is prevented. This can be done by not treating euthyroid patients, by no longer using injected exogenous TSH in the diagnostic work-up of the patients, and by always performing radioiodine imaging immediately before treatment. When this pretreatment radioiodine image reveals uptake of iodine in extranodular parenchyma, therapy has to be postponed.

REFERENCES

1. Hamburger J. The autonomously functioning thyroid nodule: Goetsch's disease. *Endocr Rev* 1987;8:439–447.
2. Hamburger J. Solitary autonomously functioning thyroid lesions. Diagnosis, clinical features, and pathogenetic considerations. *Am J Med* 1975;58:740–748.
3. Heinze H, Pfeiffer K, Lichtenstein Z. Radioiodtherapie des autonomen Adenoms. *Dtsch Med Wschr* 1975;100:2203–2208.
4. Fontana B, Curti G, Biggi A, Fresco G. The incidence of hypothyroidism after radioactive iodine therapy for autonomous hyperfunctioning thyroid nodules evaluated by means of life-table method. *J Nucl Med All Sci* 1980;24:85–91.
5. Goldstein R, Hart IR. Follow-up of solitary autonomous thyroid nodules treated with ^{131}I. *N Engl J Med* 1983; 309:1473–1476.
6. Ross D, Ridgway C, Daniels G. Successful treatment of solitary toxic thyroid nodules with relatively low-dose iodine-131 with low prevalence of hypothyroidism. *Ann Intern Med* 1984;101:488–490.
7. Mariotti S, Martino E, Francesconi M, et al. Serum thyroid

autoantibodies as a risk factor for development of hypothyroidism after radioactive iodine therapy for single thyroid 'hot' nodule. *Acta Endocr (Copenh)* 1986;113:500–507.
8. Ratcliffe G, Cooke S, Fogelman I, Maisey M. Radioiodine treatment of solitary functioning thyroid nodules. *Br J Radiol* 1986;59:385–387.
9. Corstens F, Smals A, Buys W, Kloppenborg P. Letter to the editor. *N Engl J Med* 1984;310:1393.
10. Skillern P, McCullagh E, Clamen M. Radioiodine in diagnosis and therapy of hyperthyroidism. *Arch Intern Med* 1962;110:888–897.
11. Blum M, Shenkman L, Hollander C. The autonomous nodule of the thyroid: correlation of patient age, nodule size, and functional status. *Am J Med Sci* 1975;169:43–50.
12. Burman K, Earl J, Johnson M, Wartofsky L. Clinical observations on the solitary autonomous thyroid nodule. *Arch Intern Med* 1974;134:915–919.
13. Hegedus L, Veiergang, D, Karstrup S, Hansen J. Compensated ^{131}I-therapy of solitary autonomous thyroid nodules: effect on thyroid size and early hypothyroidism. *Acta Endocr (Copenh)* 1986;113:226–232.
14. Eyre-Brook I, Talbot C. The treatment of autonomous functioning thyroid nodules. *Br J Surg* 1982;69:577–579.
15. Corstens F, Huysmans D, Kloppenborg P. Thallium-201 scintigraphy of the suppressed thyroid: an alternative for iodine-123 scanning after TSH stimulation. *J Nucl Med* 1988;29:1360–1363.
16. DeGroot LJ. Graves' disease diagnosis and treatment. Multinodular goiter. In: DeGroot LJ, Stanbury JB, eds. *The thyroid and its diseases*, 4th edition. New York: Wiley, 1975:314–367 and 637–665.

EDITORIAL
The Autonomously Functioning Thyroid Nodule

Plummer in 1913 first reported hyperthyroidism resulting from nodular goiter as distinct from the hyperthyroidism seen in toxic diffuse goiter (Graves' disease) (*1*). He noted that the former type of hyperthyroidism was milder and was not associated with exophthalmos. We now know that Graves' disease is an autoimmune disorder in which thyroid stimulating immunoglobulins are produced resulting in thyroid hyperplasia and increased hormone secretion. In toxic nodular goiter, hyperthyroidism results from nodules which function antonomously, that is independent of the normal pituitary thyroid-stimulating hormone (TSH) control.

Plummer did not differentiate between the two types of toxic nodular goiter, toxic multinodular goiter (TMNG) and toxic autonomously functioning thyroid nodules (AFTN). This difference is useful clinically. Patients with TMNG are more likely to be older and have cardiac complications. A large multinodular goiter with autonomous function is often present for years before the onset of hyperthyroidism (*2*). This presence of autonomous function contraindicates the use of thyroid hormone suppression in patients believed to have nontoxic multinodular goiter since the exogenous thyroid hormone is simply additive to that secreted by the nonsuppressible autonomous nodules.

AFTN can occur at any age (amongst teens as well as the elderly) and are discrete and usually solitary nodules. Hamburger, in an excellent review, called this Goetsch's disease, named after Emil Goetsch who remarkably worked out much of the pathophysiology in 1918 (*3*). There is not total agreement on the pathogenesis of AFTN, but most researchers agree with Miller that the autonomous function develops at a very early stage in the evolution of clinical AFTN (*4*). In patients with palpable AFTN, he demonstrated micronodules possessing autonomous function elsewhere in the gland utilizing microautoradiographic techniques.

Most AFTN are nontoxic and the evolution of toxicity is usually very gradual if it occurs at all. A group of seven authors reported on 312 patients with nontoxic AFTN who were followed 1–5 yr. Only 20 evolved into the toxic state, and in only 15 others was an increase in size reported (*5*). Autonomous nodules 2.5 cm or less rarely cause hyperthyroidism. In 62 toxic AFTN reported by Hamburger, all but 4 were 3.0 cm or greater in size (*6*). In a total of 349 patients with AFTN, he found toxic lesions in 56.5% of patients over 60 yr of age but only in 12.5% in patients under 60. Degeneration of AFTN is also common and is seen on thyroid imaging as a central area of reduced activity surrounded by the functioning tissue. This should not be mistaken for malignancy. Although cancer may occur elsewhere in the gland, or even incidentally as a nonfunctional mass within an AFTN, carcinoma in the autonomously functioning tissue itself is exceedingly rare. In most cases of carcinoma reported in "hot" nodules, the dianosis of autonomous function was not conclusively established. For all practical purposes, one does not need to be concerned about malignancy in the AFTN.

Received Aug. 16, 1990; accepted Aug. 16, 1990.
For reprints contact: Donald A. Meier, MD, Department of Nuclear Medicine, William Beaumont Hospital-Troy, 44201 Deguindre Rd., Troy, MI 48098-1198.