Abstract. Hypothyroidism is often observed after radiiodine treatment in Graves' disease, but it is considered a rare complication in single hyperfunctioning thyroid nodule ('hot' nodule). This concept has been recently challenged, but the available data are conflicting. In the present study we therefore assessed the development of permanent hypothyroidism in 126 patients with thyroid hot nodule treated with \( ^{131} \text{I} \) (180 mCi/g of estimated nodule weight, total dose 5.5–28.9 mCi). Follow-up ranged between 1 to 11 years. Hypothyroidism was observed in 5 (4%) patients, corresponding to a cumulative incidence by life-table analysis of 4.8% ten years after treatment. No relationship was found between the development of hypothyroidism and the size of the nodule or the total amount of administered dose. Fifty-six patients with euthyroid hot nodule at the time of treatment had higher cumulative incidence of hypothyroidism after 10 years (9.7%) than those with toxic adenoma (1.5%) (0.1 > \( P > 0.05 \) by logrank test). When the patients were analyzed according to the presence or absence of serum antithyroglobulin and/or antithyroid microsomal autoantibodies, the prevalence of hypothyroidism after \( ^{131} \text{I} \) treatment was higher (4/25 = 16%) in patients with significant serum antibody titres (≥ 1/400 by passive haemagglutination), when compared to that observed in subjects with negative antibody tests (1/101 = 1.0%). Life-table analysis showed in antibody positive patients a cumulative incidence of hypothyroidism after 10 years of 18.0% vs 1.4% in antibody negative patients (\( P < 0.001 \) by logrank test). In conclusion, the present data provide the first evidence that coexistent thyroid autoimmunity is a significant risk factor for the development of hypothyroidism in patients with hot nodule treated with radiiodine.

Administration of radioactive iodine is a widely used therapy of hyperthyroidism. The most important drawback to this treatment is the late development of hypothyroidism. While this complication is frequently observed in Graves' disease (Nofal et al. 1966; Douglas 1973; Sridama et al. 1984; DeGroot et al. 1984), it is generally believed that hypothyroidism occurs very rarely in patients with solitary autonomous thyroid nodules ('hot' nodule). (Skillern et al. 1962; Gorman et al. 1978). The precise incidence of hypothyroidism after radiiodine therapy in patients with hot nodules cannot be clearly established from previous investigations (Eller et al. 1960; Skillern et al. 1962; Molnar et al. 1965; Horst et al. 1967; McCormack & Sheline 1967; Ramsay et al. 1972; Hamburger 1975; Ng Tang Fui & Maisey 1979; Fontana et al. 1980; Goldstein & Hart 1983; Ross et al. 1984). Even recent studies provide conflicting results: Goldstein & Hart (1983) reported a 36% prevalence of hypothyroidism, while no case of thyroid insufficiency was observed by Ross et al. (1984).

In the present study we evaluated the incidence of permanent hypothyroidism in a large series of
patients with hot nodule treated with $^{131}$I with particular regard to the potential role of serum thyroid autoantibodies in the development of the thyroid failure. The relevance of thyroid autoimmunity as risk factor for hypothyroidism after $^{131}$I has been studied in Graves' disease with conflicting results (Sridama et al. 1984; Lundell & Jonsson 1973; Lundell & Holm 1980). To our knowledge, however, no similar study has been carried out in patients with hot nodule.

Materials and Methods

One hundred thirty-eight consecutive patients treated with $^{131}$I in our institution between 1972 and 1983 for single thyroid hot nodule were considered in this retrospective study. They consisted of 114 females and 24 males ageing 34–84 years (mean 51 years).

The diagnosis was made on the basis of a single thyroid nodule without enlargement of the remaining gland which was hot by standard $^{131}$I scan with functional suppression of the extranodular tissue. No evidence of Graves' ophthalmopathy or pretibial myxoedema was observed in all subjects before and after $^{131}$I therapy. Clinical and biochemical evidence of hyperthyroidism was found in 82 patients, while the remaining 56 patients were clinically euthyroid, with circulating thyroid hormones within the normal range, but undetectable basal and thyrotropin releasing hormone (TRH) stimulated serum thyrotropin (TSH).

Radioiodine was orally administered at the dose of 5.5–28.9 mCi, (mean ± sd: 12.6 ± 4.1) corresponding to 180 µCi/g of estimated nodule weight. No patients received thyroid hormone therapy before or shortly after $^{131}$I treatment.

In all cases clinical and biochemical assessment of thyroid function was carried out before and at various time intervals after treatment, with a follow-up period ranging between 1 and 11 years (3.0 ± 2.2 years, mean ± sd).

Serum thyroxine ($T_4$) concentrations were determined by competitive binding protein method or by radioimmunoassay. Serum triiodothyronine ($T_3$) was determined by radioimmunoassay. Free $T_4$ index ($F_{4\text{T}}$) and free $T_3$ index ($F_{3\text{T}}$) were calculated in all cases on the basis of $T_3$ resin uptake test. Serum TSH concentrations were determined by radioimmunoassay using materials provided by N.I.H. (Martino et al. 1976) until 1977 and then using commercial kits. Anti-thyroglobulin (anti-Tg) and anti-thyroid microsomal antibody (anti-M) were detected by passive haemagglutination using commercial kits (Thyroid Test Kit for anti-Tg antibody and Microsome Test Kit for anti-M antibody, Fujizoki Pharmaceutical Co, Tokyo, Japan). Antibody tests were performed according to the manufacturer's instruction: serial 4-fold dilutions from 1:100 to 1:102400 were carried out by means of the Takatsy microtitration apparatus. Since often sera with positive haemagglutination titres corresponding to the lowest dilution employed (1:100) gave inconsistent results in

![Graph](https://via.placeholder.com/150)

Cumulative incidence of permanent hypothyroidism in 126 patients with thyroid hot nodule after $^{131}$I treatment. The number in parenthesis represents number of patients included in the study at various time intervals after treatment.
Cumulative incidence of permanent hypothyroidism after \(^{131}I\) treatment in 126 patients with thyroid hot nodule divided according to the thyroid status before therapy; (○—○) indicates hyperthyroid and (△—△) euthyroid hot nodules. The number in parenthesis represents the total number of patients examined at various time intervals.

repeated tests, only titres \(\geq 1:400\) were considered as indicative of unequivocally elevated autoantibody levels. A similar cut off of autoantibody titres has been recently used for the assessment of thyroid antibody incidence in amiodarone-treated subjects (Martino et al. 1984). Hyperthyroidism was diagnosed on the basis of clinical features associated with elevated FT₄I (> 11) and/or FT₃I (> 208) with undetectable basal and TRH stimulated serum TSH. The diagnosis of hypothyroidism was made by clinical criteria associated with the presence of a reduced FT₄I (< 4) and elevated serum TSH \((\geq 6 \mu U/ml)\).

**Statistical analysis**

Differences in the frequency of hypothyroidism in the study groups were assessed by \(\chi^2\) test. The cumulative incidence of hypothyroidism was calculated by life-table analysis (Peto et al. 1977), and the difference between the groups of patients was assessed by logrank test (Peto et al. 1977).

**Results**

Hyperthyroidism recurred between 6 and 15 months after \(^{131}I\) treatment in 12 patients. They received further doses of \(^{131}I\) and were therefore excluded from this study. Permanent hypothyroidism was observed in 5 (4%) of the remaining 126 patients 1 to 2 years after therapy. As shown in Fig. 1, the cumulative incidence of hypothyroidism in these patients was 4.8% after 2 years and did not show any further increase thereafter; in all five patients the degree of hypothyroidism was mild. No relationship was found between the development of hypothyroidism, the size of the nodule (as assessed by physical examination and thyroid scan), and the total amount of administered radioiodine (mean \(\pm SD\) values of \(^{131}I\) in patients who developed hypothyroidism was 12.9 \(\pm\) 3.1, range 11.0–15.5 mCi, while in the remaining patients the dose was 12.4 \(\pm\) 4.2, range 5.5–28.9 mCi).

When the patients were divided according to the thyroid status before \(^{131}I\) therapy, hypothyroidism was observed in 4 of 56 (7.1%) euthyroid patients, and only in 1 of 70 (1.4%) hyperthyroid patients \((0.1 > P > 0.05\) by \(\chi^2\) test). The cumulative incidence of hypothyroidism at the end of the tenth year calculated by life-table analysis was 9.7% in euthyroid and 1.5% in thyrotoxic patients (Fig. 2). Again, this difference was near to, but did not reach the level of statistical significance \((0.1 > P > 0.05\) by logrank test).

Twenty-five patients had serum anti-M antibody titres \(\geq 1/400\) in at least 2 consecutive samples obtained before and after treatment; in three of these patients positive anti-Tg antibodies were also observed. The remaining 101 patients
Serum anti-M antibody titres by passive haemagglutination in 126 patients with thyroid hot nodule before treatment with $^{131}$I. (●) euthyroid and (■) hypothyroid patients at the last control after therapy. For convenience, antibody titres < 1/400 were grouped together in patients who remained euthyroid.

showed consistently negative antibody tests. The individual titres of anti-M antibodies observed in all the study group are reported in Fig. 3. As also shown in Fig. 3, hypothyroidism was observed in 4 (16%) of the 25 thyroid antibody positive and only in 1 (1%) of the 101 thyroid antibody negative patients ($P < 0.005$ by $\chi^2$ test). In Fig. 4 is illustrated the cumulative incidence of hypothyroidism at the end of the tenth year which was 18.0% and 1.4% in antibody positive and antibody negative patients, respectively. Statistical analysis by logrank test showed a highly significant difference between the two groups ($P < 0.001$ by the end of the first 2 years after $^{131}$I therapy.

The outcome of $^{131}$I treatment in all 126 patients subdivided according to the thyroid status and to the presence or absence of circulating thyroid autoantibodies is summarized in Fig. 5. The highest incidence of hypothyroidism occurred in patients with euthyroid hot nodule and positive serum antibodies.

Discussion

The results obtained in the present investigation indicate that permanent hypothyroidism is observed only in a minority of patients treated with $^{131}$I for thyroid hot nodule. This finding is in agreement with the majority of previous studies (Eller et al. 1960; Skillern et al. 1962; Molnar et al. 1965; Horst et al. 1967; McCormack & Sheline.
Outcome of $^{131}$I therapy in 126 patients with thyroid hot nodule subdivided according to the thyroid status before treatment and presence (Ab+) or absence (Ab−) of serum thyroid autoantibodies.

An established risk factor for hypothyroidism after $^{131}$I is the amount of administered dose. Thyroid failure was in fact more frequently observed in patients with hot nodule treated with rather high doses (usually ranging 20–50 mCi) (Fontana et al. 1980; Goldstein & Hart 1983), than in patients who received lower doses (Eller et al. 1960; Molnar et al. 1965; Ng Tang Fui & Maisey 1979; Ross et al. 1984). In our study we used a relatively low dose of radioiodine similar to that employed by Ross et al. (1984) and other investigators (Eller et al. 1960; Molnar et al. 1965; Ng Tang Fui & Maisey 1979). These authors, however, found a lower incidence of hypothyroidism when compared with that observed by us. Since in the present study the $^{131}$I dose administered to patients who developed hypothyroidism or to those who remained euthyroid was similar, other risk factors had to be considered.

The relevance of the thyroid status before radioiodine administration has been advocated to explain the different outcome of $^{131}$I therapy in thyroid hot nodule (Ross et al. 1984), since the suppression of extranodular tissue should be more complete in toxic than in functioning thyroid nodule. In keeping with this concept, Goldstein & Hart (1983) found 36% prevalence of hypothyroidism after $^{131}$I therapy in 22 patients with thyroid hot nodule, 15 of whom were euthyroid at the time of radioiodine administration. In contrast, no case of thyroid insufficiency after $^{131}$I was observed by Ross et al. (1984) in 45 patients with toxic nodule. The results obtained in the present investigation confirm that the euthyroid status at the time of radioiodine treatment may be relevant in the development of post-therapy hypothyroidism.

The role of thyroid autoimmunity in the development of hypothyroidism after $^{131}$I treatment for thyrotoxicosis is still unclear. Recently, Sridama et al. (1984) did not find any significant association between the presence of circulating thyroid autoantibodies and the subsequent deve-
Development of thyroid insufficiency in patients with Graves’ disease after $^{131}$I administration. In contrast, Lundell and co-workers (Lundell & Jonsson 1973; Lundell & Holm 1980) reported significantly higher cumulative incidence of hypothyroidism after radioiodine therapy in patients with diffuse toxic goitre and positive serum thyroid autoantibodies. Only scanty data are available on the relevance of thyroid autoimmunity for the development of hypothyroidism after $^{131}$I in toxic nodular goitre. Lundell & Jonsson (1973) and Lundell & Holm (1980) reported a higher cumulative incidence of thyroid failure after radioiodine treatment in patients with toxic nodular goitre and positive serum thyroid autoantibodies when compared to antibody negative patients, although this difference did not reach the level of statistical significance. Furthermore, it should be noted that in these studies the precise type of toxic nodular (uni- or multinodular) goitre was not reported. Thus, to our knowledge no clear data are available from previous investigations on the potential role of thyroid autoantibodies as risk factor of hypothyroidism after $^{131}$I in solitary hot nodules. The results obtained in this study provided clear evidence that patients with thyroid hot nodule and elevated serum thyroid autoantibodies developed hypothyroidism more frequently when compared to those with negative antibody tests. The mechanism leading to thyroid failure in patients with thyroid hot nodules and serum thyroid autoantibodies cannot be fully established. A combination of radiation damage to the perinodular tissue with destructive autoimmune phenomena due to co-existing lymphocytic thyroiditis could be envisaged. The possibility of a radiation-induced exacerbation of thyroid autoimmunity should also be considered. A transient increase of circulating thyroid autoantibody titres after $^{131}$I administration is a well known phenomenon (O’Gorman et al. 1964; Einhorn et al. 1965; Pinchera et al. 1969; Fenzi et al. 1979) which has been attributed to the release of thyroid autoantigens from the irradiated gland and/or to the destruction of intra-thyroidal radiosensitive T-suppressor lymphocytes (McGregor et al. 1979) with consequent enhancement of immunoglobulin secretion by B-cells infiltrating the gland, which are actively involved in thyroid autoantibody production (Weetman et al. 1982; McLachlan et al. 1983). Whether radioiodine therapy also triggers autoimmune cell mediated reactions is still unknown.

The question of whether our patients with positive serum thyroid autoantibodies and thyroid hot nodule had actually autonomous nodule or Hashimoto’s thyroiditis with prominent uptake in a nodular area should also be considered. Although this problem cannot be unequivocally solved without histological examination of the entire thyroid gland, some lines of evidence suggest that this was not the case. Firstly, all patients had absent TSH response to TRH, indicating that no case of pre-clinical hypothyroidism, frequently observed in Hashimoto’s thyroiditis, was included. Furthermore, in all antibody positive patients a functional recovery of extranodular thyroid tissue, as assessed by $^{131}$I scan, was observed at various time intervals after radioiodine therapy (data not shown). This finding suggests that the absence of radioiodine uptake in the perinodular tissue at the time of treatment was due to a functional suppression and not to already advanced destructive thyroid autoimmune reactions. Third, preliminary evidence has recently been provided in a small number of cases that thyroid autoimmune reactions are associated with toxic adenoma more frequently than previously believed (Grubeck-Loebenstein et al. 1985). Further studies are needed to ascertain whether patients with toxic nodule and positive serum thyroid autoantibodies actually represent a separate subgroup with some degree of pathogenetic overlap with Graves’ disease (Grubeck-Loebenstein et al. 1985).

In our series the curves of cumulative incidence of permanent hypothyroidism were completely flat after 24 months. This finding is somewhat at variance with other reports (Lundell & Johnson 1973; Lundell & Holm 1980; Fontana et al. 1980; Goldstein & Hart 1983; Sridama et al. 1984) of hypothyroidism after radioiodine treatment, in which the cumulative incidence of thyroid failure is also high in the first two years, but thereafter continues to rise, albeit more slowly. The reason for such discrepancy is not immediately clear; besides other explanations, we cannot rule out the possibility that some patients treated more than 24 months previously, who might have became hypothyroid, had been lost from follow-up.

Finally, from the practical point of view, the data of the present investigation indicate that patients with thyroid hot nodule and positive serum thyroid autoantibodies need careful follow-up for early detection of hypothyroidism.


Ross D S, Ridgway E C & Daniels G H (1984): Successful treatment of solitary thyroid nodules with rela-

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