Radioiodine Therapy for Multinodular Toxic Goiter

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Background: Radiolabeled iodine 131 therapy is used for treatment of multinodular toxic goiter, but long-term follow-up studies are lacking.

Methods: A prospective study of 130 consecutive patients (115 women) treated with 131I for multinodular toxic goiter and followed by evaluation of thyroid volume (determined using ultrasound) and thyroid function variables.

Results: The patients were observed for a median of 72 months (range, 12-180 months). Sixty-six patients received antithyroid drug pretreatment; 64 did not. Iodine 131 treatment (3.7 MBq/g thyroid tissue corrected to a 100% 24-hour 131I uptake) was given as a single dose in 81 patients, 2 doses in 38, and 3 to 5 doses in 11. One or 2 treatments cured 119 patients (92%), and 68 (52%) became euthyroid within 3 months after 131I treatment. The median 131I dose was 370 MBq (range, 93-1850 MBq). Forty-nine patients needing more than 1 131I dose had a reduction in median thyroid volume from 56 mL (range, 21-430 mL) to 44 mL (range, 15-108 mL), representing a 24% reduction related to the insufficient 131I dose. In all patients, the initial median thyroid volume of 44 mL (range, 16-430 mL) decreased to 25 mL (range, 8-120 mL) (P<.005), representing a median reduction of 43%, 24 months after the last 131I dose. Hypothyroidism evaluated using life-table analysis developed in 6% of patients who did not receive antithyroid pretreatment and 20% who did (P<.005) after a median of 42 months (range, 3-60 months), the total hypothyroidism frequency being 14% within 5 years of treatment.

Conclusions: Ninety-two percent of patients with multinodular toxic goiter were cured with 1 or 2 treatments. The thyroid volume was reduced by 43%, with few side effects. Iodine 131 should be the choice of treatment in patients with multinodular toxic goiter.

Arch Intern Med. 1999;159:1364-1368

MULTINOULAR goiter is a common cause of hyperthyroidism, especially in areas of mild to moderate iodine deficiency.1 In these patients, hyperthyroidism cannot be expected to be permanently cured by antithyroid drug treatment. Radiolabeled iodine 131 therapy is in principle an attractive treatment modality, since the suppressed extranodular thyroid tissue is partly protected, and in recent years, the popularity of this treatment has increased. Therefore, it is of great importance to evaluate the long-term effects and possible side effects of this treatment. A 1-year follow-up of 70 patients was published from our department in 1986, demonstrating a 35% reduction of thyroid volume, and hypothyroidism developed in only 1 patient.2 Studies evaluating the long-term effects of 131I treatment in patients with Graves disease,3-7 autonomously functioning solitary hot or toxic thyroid nodules,8-12 and multinodular nontoxic goiter have been performed.13-15 However, few studies6,7,17 have described the long-term effects of 131I treatment in patients with multinodular toxic goiter, and a precise evaluation of the long-term changes in thyroid volume is not available.

We therefore wanted to evaluate the long-term changes in thyroid function and volume using a precise and accurate ultrasonic technique18 in a large, prospective group of consecutive patients with multinodular toxic goiter treated with 131I. We used an algorithm for 131I dose calculation, taking volume and 24-hour 131I uptake into consideration.

RESULTS

Clinical data for the 130 patients are given in Table 1. The median follow-up was 72 months (12-180 months). Patients pretreated with antithyroid drugs did not differ significantly from those not receiving antithyroid pretreatment with regard to age, sex, 131I dose, follow-up, or the proportion needing more than 1 131I dose. The patients receiving antithyroid pretreatment had significantly lower FT4I and FT3I at the time of 131I treatment than patients not receiving antithyroid pretreatment (Table 1). Thyroid function variables before antithyroid pretreatment were not available in all patients and are therefore not given. The pretreated group had a significantly higher 24-hour 131I uptake (Table 1). The median initial thyroid volume was higher in the pretreated group (59 mL [16-
PATIENTS AND METHODS

The study population consisted of 130 consecutive patients treated with 131I for a multinodular toxic goiter and observed for a minimum of 1 year. Sixty-six patients were pretreated with antithyroid drugs, whereas 64 were not. Another 15 patients were treated in this period but were unavailable for follow-up within 12 months (7 were given antithyroid pretreatment). The patients were seen from November 1, 1979, through April 31, 1994. Type of thyroid gland was determined using technetium Tc 99m-pertechnetate scintigraphy and ultrasound, whereas the diagnosis of hyperthyroidism was based on the clinical picture, elevated free triiodothyronine (T3) index (FT3I) and/or free thyroxine (T4) index (FT4I), and suppressed serum thyrotropin level.

Sixty-six patients received antithyroid drugs before 131I treatment (propylthiouracil [n = 54], methimazole [n = 8], and carbimazole [n = 4]). In these patients, antithyroid drug treatment was discontinued 5 days before 131I therapy and was not resumed after 131I treatment. Sixty-four patients did not receive antithyroid pretreatment. Pretreatment was based on the degree of hyperthyroidism and the clinical status of the patients.

Permanent hypothyroidism was defined as decreased FT4I accompanied by an elevated serum thyrotropin concentration. Euthyroidism was defined as FT4I and FT3I within the reference range. The 131I dose was calculated as 3.7 MBq/g total thyroid mass (evaluated using ultrasound), corrected to 100% uptake of 131I after 24 hours. The maximum single dose given was 740 MBq.

Serum concentrations of T4 (reference range, 56-129 nmol/L [4-10 µg/dL]) and T3 (reference range, 1.0-2.5 nmol/L) and T4 resin uptake (reference range, 0.80-1.25 arbitrary units) were determined using in-house methods (assay variation was 6%, 10%, and 5%, respectively). The FT4I (reference range, 62-158 arbitrary units) and FT3I (reference range, 0.8-2.8 arbitrary units) were calculated as the total hormone concentration times the T3 resin uptake. Serum concentrations of thyrotropin were determined using different commercial assays as described previously.3 Ultrasonic scanning and calculation of total thyroid volume (reference range, 9.6-27.6 mL) was performed as previously described10 using a compound scanner (type 3401 and type 1846; Bruehl and Kjaer, Nærum, Denmark).

Thyroid function variables and the size of the thyroid on ultrasonography were determined before and 3/4, 1/2, 3, 6, and 12 months after treatment, and thereafter, once every year. In patients becoming hypothyroid, no further volume or thyroid function data were included in the data evaluation after hypothyroidism was diagnosed.

Results are given as median and range or 25th and 75th percentiles. When percentage of change in thyroid volume is used, the median values of the individual changes are given. For statistical evaluation, Wilcoxon test for paired design, Mann-Whitney test for unpaired design, χ2 test, and life-table analysis were used. The level of significance was chosen as P<.05.

Table 1. Clinical Data in Patients With Multinodular Toxic Goiter Treated With Iodine 131a

<table>
<thead>
<tr>
<th></th>
<th>Patients Receiving Antithyroid Drug Pretreatment (n = 66)</th>
<th>Patients Not Receiving Antithyroid Drug Pretreatment (n = 64)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65 (31-81)</td>
<td>64 (41-85)</td>
<td>.92</td>
</tr>
<tr>
<td>No. of men/women</td>
<td>10/56</td>
<td>5/59</td>
<td>.14</td>
</tr>
<tr>
<td>FT4I, arbitrary units</td>
<td>84 (33-253)</td>
<td>179 (124-441)</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>FT3I, arbitrary units</td>
<td>2.0 (0.7-5.0)</td>
<td>4.0 (1.5-12.4)</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Thyroid volume, mL</td>
<td>59 (16-430)</td>
<td>43 (18-125)</td>
<td>.09</td>
</tr>
<tr>
<td>Initial 131I dose, MBq</td>
<td>290 (93-925)</td>
<td>315 (111-740)</td>
<td>.97</td>
</tr>
<tr>
<td>24-h 131I uptake, %</td>
<td>57 (13-86)</td>
<td>45 (28-76)</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Total 131I dose, MBq</td>
<td>370 (85-1550)</td>
<td>385 (130-1547)</td>
<td>.82</td>
</tr>
<tr>
<td>No. of 131I doses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>41</td>
<td>40</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>3-5</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

aFT4I indicates free thyroxine index; FT3I, free triiodothyronine index. Unless otherwise indicated, data are given as median (range).

430 mL] vs 43 mL [18-125 mL]), but the difference was not significant (P = .09; Table 1). However, comparing the initial volume in patients needing more than 1 131I dose, a highly significant difference was seen (74 mL [21-430 mL] in the pretreated group vs 47 mL [23-125 mL] in the group not pretreated) (P<.005).

The median initial 131I dose was 313 MBq (93-925 MBq), whereas the median total dose was 370 MBq (93-1850 MBq). More than 1 dose was given due to persistent hyperthyroidism in 41 patients and to reduce goiter size in 8.

The median time to become euthyroid after 131I therapy was 5 weeks (range, 3 weeks to 24 months) after the last 131I treatment (Table 2). There were no significant differences between patients given antithyroid pretreatment and those who were not. Sixty-eight patients (52%) were euthyroid within 3 months after the first 131I treatment. Eight patients did not become euthyroid after 131I treatment. Three of these 8 patients had 1 131I treatment, 4 patients had 2 treatments, and 1 patient had 3 treatments. These patients did not want subsequent 131I treatment and were given long-term antithyroid drug treatment.

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THYROID VOLUME IN PATIENTS RECEIVING ANTITHYROID PRETREATMENT

Median initial thyroid volume was 59 mL (16-430 mL). Twenty-five of the 66 patients were treated with more than 1 131I dose. In these patients, 131I doses not leading to euthyroidism caused a 27% decrease in thyroid volume from a median of 74 mL (21-430 mL) to 50 mL (13-315 mL) (P, .005), and 24 months after the last 131I dose, a further decrease to 24 mL (8-108 mL) (P, .005). The median volume reduction after more than 1 131I dose was 50%. Thyroid volume before and after 131I therapy in relation to the latest 131I dose is demonstrated in Figure 1. A gradual 45% reduction from a median of 45 mL (13-115 mL) to 24 mL (8-85 mL) 24 months after treatment was observed (P, .005). Hereafter, no further significant changes were observed. Within the observation period, 11 patients became hypothyroid. In these patients, the median thyroid volume was reduced from 24 mL (17-66 mL) to 16 mL (8-72 mL) at the time when hypothyroidism was diagnosed (P = .01). Within the first 3 months after 131I therapy, 68% of the total volume reduction was seen.

THYROID VOLUME IN PATIENTS NOT GIVEN ANTITHYROID PRETREATMENT

Median initial thyroid volume was 43 mL (18-125 mL). Twenty-four of the 64 patients were treated with more than 1 131I dose. In these patients, 131I doses not leading to euthyroidism caused a 21% decrease in thyroid volume from a median of 47 mL (23-125 mL) to 44 mL (15-99 mL) (P = .03), and 24 months after the last 131I dose, a further decrease to 29 mL (8-76 mL) (P < .005). The median volume reduction after more than 1 131I dose was 32%. Thyroid volume before and after 131I therapy in relation to the latest 131I dose is demonstrated in Figure 2. A gradual 40% reduction from a median of 43 mL (15-115 mL) to 27 mL (8-85 mL) 24 months after treatment was observed (P < .005). Hereafter, no further significant changes were observed. Within the observation period, 3 patients became hypothyroid. In these patients, the median thyroid volume was reduced from 19 mL (15-42 mL) to 10 mL (8-12 mL), measured at the time hypothyroidism was diagnosed. Within the first 3 months after 131I therapy, 72% of the total volume reduction was seen.

There was no significant difference between the patients receiving and those not receiving antithyroid drug pretreatment in relation to changes in thyroid volume seen after the 131I dose that cured the hyperthyroidism.

SIDE EFFECTS

Hypothyroidism occurred significantly more often in patients pretreated with antithyroid drugs (11/66 [17%]) than in those not receiving such treatment (3/64 [5%]) (P = .03).
After evaluation using life-table analysis, hypothyroidism was seen in 14% of the entire group within 5 years. Hereafter, no further cases of hypothyroidism occurred. Life-table analysis showed a hypothyroidism rate of 20% within 5 years in patients treated with antithyroid premedication, whereas patients in the group not given antithyroid drug pretreatment had a significantly lower hypothyroidism rate of 6% (P <.005) (Figure 3). Hypothyroidism was diagnosed after a median of 42 months (3-60 months). No significant differences in time to hypothyroidism, time to serum thyrotropin values greater than 4 μIU/mL, and time from these values to hypothyroidism were seen between patients who were given antithyroid drug pretreatment and those who were not (Table 2). In Table 2, 12 patients are described as having serum values of greater than 4 μIU/mL without progression to overt hypothyroidism. These patients had serum thyrotropin values in the range of 5 to 11 μIU/mL during follow-up (in 1 patient, a single measurement of 17 μIU/mL was found). In all patients, FT3 and FT4 were within the normal range, with no symptoms of hypothyroidism.

Recurrence of hyperthyroidism after a longer period of euthyroidism without antithyroid drugs was seen in 1 patient treated with 400 MBq of 131I. The patient was euthyroid with a slightly suppressed serum thyrotropin level for 10 years; then hyperthyroidism recurred and, after a further 131I dose, the patient again became euthyroid.

None of the patients had symptoms of a radioiodine-induced thyroiditis. An increase (more than 5%) in thyroid volume was seen in 9 patients the first months after 131I treatment. The median increase was 23% (11%-60%). In these 9 patients, the median thyroid volume was 33 mL (19-133 mL) before treatment. The largest increase was seen in a patient with an initial volume of 28 mL. None of these patients had increased pressure symptoms, and none needed surgical intervention. Three patients had a second 131I dose, not because of compression symptoms, but because of continued hyperthyroidism.

In 1 patient, a disseminated follicular thyroid carcinoma was diagnosed 3 years after 131I treatment of 488 MBq. The time from 131I treatment to the diagnosis of a disseminated thyroid follicular cancer is too short to relate the cancer to the 131I treatment.

The magnitude of thyroid volume reduction found in our study is of the same order as that seen after 131I therapy in toxic diffuse and autonomous solitary toxic thyroid adenomas, as well as in nontoxic diffuse and nontoxic multinodular goiter. As in these long-term follow-up studies, we found that the most pronounced reduction is seen within the first 3 months, with a continuous size-reducing effect of 131I on thyroid volume lasting 2 years. One could speculate that if the 131I is only taken up in the hyperfunctioning nodules, the reduction in the thyroid volume would be based on the changes in these nodules, leaving the paranodular tissue unaffected with a potential of growth. The result could be a primary reduction of the thyroid volume followed by a reincrease related to growth of the paranodular tissue. We did not see this secondary regrowth of the thyroid volume in a rather long follow-up, indicating that the 131I affects not only the hyperfunctioning nodules but also the paranodular tissue. To our knowledge, these are the first long-term data on thyroid volume and function in multinodular toxic goiter, using an accurate thyroid size evaluation, and on 131I therapy, taking thyroid size and 131I uptake into consideration.

We demonstrated a cumulated risk for hypothyroidism of 14% within 5 years of 131I therapy. No cases of hypothyroidism were seen beyond 5 years in this follow-up ranging from 1 to 15 years. This pattern of hypothyroidism is different from that seen in patients treated with 131I for Graves disease. In the latter group, hypothyroidism was seen in approximately 20% within 1 year and thereafter with a constant incidence of 2% to 3% per year, eventually reaching 100% if the patients lived long enough. In our study, the incidence of hypothyroidism is similar to that found in patients with other nonimmunological thyroid diseases such as autonomously functioning solitary thyroid nodules and nontoxic multinodular goiter. Few published studies have addressed this issue in groups of patients all treated with 131I for multinodular goiter. Franklyn et al demonstrated hypothyroidism in 11.4% of 44 patients with a 1-year follow-up. Danaci et al investigated 21 patients and found a cumulative 5-year hypothyroidism rate of 24%, giving a fixed dose of 444 MBq. Berg et al gave a calculated dose of 100 Gy, found that 47% were given thyroxine treatment 48 months after treatment. On the other hand, Wiener, studying 88 patients only, found 1 patient with hypothyroidism in a follow-up ranging from 1 to 17 years (average, 5.3 years).

We found a significantly higher hypothyroidism rate in patients pretreated with antithyroid drugs compared with patients not given antithyroid premedication (6%). An explanation could be that in patients given antithyroid drugs before 131I treatment, serum thyrotropin was not suppressed at the time of treatment, and the 131I was taken up, not only in the hyperfunctioning nodules but in the whole thyroid gland. In a recent study, Hancock et al found a significantly higher failure rate in patients treated with propylthiouracil until 4 to 7 days before 131I therapy for Graves disease compared with patients not given anti-

Figure 3. Life-table analysis describing the hypothyroidism rate after iodine 131I therapy. Series 1 shows patients pretreated with antithyroid drugs; series 2, patients not pretreated with antithyroid drugs. Numbers indicate number of observations.
thyroid pretreatment, or patients whose therapy was discontinued for more than 1 week, suggesting that antithyroid drugs have a radioprotective effect. Corresponding results have been found by us and by others.\textsuperscript{21,22} In our study, we could not demonstrate a similar radioprotective effect of antithyroid pretreatment, as evidenced by a similar volume reduction in both groups as well as similar time to achieve euthyroidism and similar fraction of patients needing more than 1 dose of \textsuperscript{131}I. However, the patients were not randomized to receive or not receive antithyroid pretreatment. The patients receiving antithyroid drug pretreatment were those with the most severe disease. To illuminate these questions, a randomized prospective study is warranted.

Using a relatively low dose of \textsuperscript{131}I calculated according to \textsuperscript{131}I uptake and thyroid volume, we found that 52% of our patients were cured within 3 months of therapy. This figure is lower than that found for Graves disease\textsuperscript{3} and solitary autonomous thyroid nodules,\textsuperscript{22} where cure rates of 75% are seen using corresponding doses. However, only 8 patients (6%) were not cured following this regimen. An increase in \textsuperscript{131}I dose should theoretically reduce the number of initial failures and thus treatment, reduce thyroid volume even more, and possibly lead to a higher incidence of hypothyroidism. Again, prospective studies are needed to substantiate this.

A potential major side effect of \textsuperscript{131}I treatment is cancer, and several studies have addressed this question.\textsuperscript{24-32} All of these studies conclude that there is no evidence of cancer induced by \textsuperscript{131}I, when given in doses to treat benign thyroid diseases in adults. When \textsuperscript{131}I treatment is given to patients with Graves disease, all thyroid cells receive a high amount of radiation, which reduces their ability to replicate. In nodular goiter, the paranodular tissue receives only a small amount of radiation, and it has recently been proposed that this tissue would be at risk for subsequent neoplastic transformation.\textsuperscript{23} This hypothesis could be supported by the results of a 1998 study by Ron et al.,\textsuperscript{23} in which they found a small but statistically significant increase in thyroid cancer risk in patients with toxic nodular goiter. However, the major increase in mortality was seen in the first 5 years after treatment, indicating that the thyroid cancer was present before \textsuperscript{131}I treatment. If this hypothesis was to be correct, one would also expect an increased number of thyroid cancers in patients examined with diagnostic doses of \textsuperscript{131}I. It has not been possible to demonstrate such a correlation.\textsuperscript{27}

We saw a cure rate of 52% within 3 months after 1 \textsuperscript{131}I treatment for multinodular toxic goiter. One hundred nineteen patients (92%) were cured with 1 or 2 treatments. The median thyroid volume was reduced by 43%, and hypothyroidism was only seen in 14% within 5 years of treatment. Radioiodine, therefore, should be the choice of therapy in these patients.

Accepted for publication October 8, 1998.

This study was supported by grants from Agnes and Kнут Marks Foundation, Copenhagen, Denmark.

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