Long term thyroid function after $^{131}$I treatment for toxic adenoma

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ABSTRACT
Radioactive iodine is a widely used treatment for hyperthyroidism caused by solitary autonomously functioning thyroid nodule (toxic adenoma). The aim of this retrospective analysis is to report the long term effects of this therapy on the thyroid function of patients with toxic adenoma treated in our department. Between 1968 and 1996, 160 patients received a single dose of $^{131}$I (range 25-40 mCi) for hyperthyroidism caused by toxic adenoma. In 126 of these (110 females, 26 males), follow-up was feasible either in our Endocrine Outpatient Clinic or through correspondence. The mean observation period was 5.3 years (range 1-21 years, median 4.0). Post treatment evaluation revealed that: a) 57 patients became euthyroid and remained free of disease up to the last visit (mean observation period 5.76–0.52 years, range 1-21 years, median 5 years), b) 69 patients developed hypothyroidism, all within 1 to 12 months (5.9–0.49 months), c) persistence or recurrence of the disease (i.e. thyrotoxicosis) was not observed, d) the $^{131}$I dose, or the $^{131}$I pretreatment TSH levels were not different between patients who developed hypothyroidism and those who became and remained euthyroid. CONCLUSION: $^{131}$I administration in the above-mentioned dose to patients with toxic adenoma: a) was a safe and very effective therapy, and b) led to hypothyroidism which developed within the first year after $^{131}$I administration in 55% of the patients.

Key words: Toxic adenoma, $^{131}$I treatment, hypothyroidism

INTRODUCTION
Solitary, autonomously functioning thyroid nodules are nodules clearly demarcated from the rest of the thyroid tissue, with autonomous function, independent of the physiological pituitary-thyroid feedback mechanism. Autonomous hormonal secretion by the nodule suppresses pituitary TSH production, leading to various degrees of functional reduction of the remaining thyroid tissue. Thus, thyroid scintigraphy (with $^{131}$I or $^{99m}$Tc) depicts a region of increased radionuclide uptake as compared to the normal extranodular thyroid tissue (i.e. hot nodule). The diagnosis of toxic adenoma is established in the presence of a “hot” thyroid nodule along with the complete suppression of the remaining thyroid tissue on scintigraphy, in combination with biochemical evidence of hyperthyroidism. The natural history of a solitary, autonomously functioning thyroid nodule, is variable; in this respect, both stability in size and function and slow increase of the size with development of clinical hyperthyroidism (toxic adenoma), are possible. In rare cases, spontane-
ous degeneration of the nodule may occur.\(^4,5\)

Treatment of toxic adenoma includes in surgical excision or ablation with \(^{131}\)I.\(^6-8\) Both options are equally effective. Iodine administration is widely used and it has certain advantages (easy administration, avoidance of surgical intervention with potential complications, especially in the elderly), while surgery remains the treatment of choice for children and adolescents, as well as for large nodules (\(>3\) cm)\(^9\) which are relatively radioresistant.\(^10\)

In this retrospective study we present our 28-year experience of the therapeutic administration of \(^{131}\)I and its long term effects on thyroid function in patients with toxic adenoma.

**PATIENTS AND METHODS**

**Patients-methods**

Of the total number of patients with toxic adenoma treated in our Department during the period 1968 - 1996, 160 patients were treated with a therapeutic dose of \(^{131}\)I, while the remaining had surgical treatment. Radioiodine treated patients received a single therapeutic dose of \(^{131}\)I. In all patients the pertechnetate \(^{99m}\)Tc (2-3 mCi) or \(^{131}\)I (15-30 \(\mu\)Ci) thyroid scanning revealed a solitary „hot“ nodule with suppressed radioiodine uptake in the exanodular thyroid tissue. The selection of patients for \(^{131}\)I administration was based on the size of the toxic adenoma (\(<3\) cm), unless the presence of a medical condition precluded surgery. With the exception of 20 patients treated in the initial years of our study (before 1980), all patients had received carbimazole (mean dose 15 mg daily for 4-6 months) or/and propranolol, according to the severity of thyrotoxicosis. Most patients were given low dose antithyroid drugs for a rather long period waiting for their admittance to the special ward for radiation treatment of our department. Treatment was discontinued 5 days prior to \(^{131}\)I administration. On the day of \(^{131}\)I administration, 128 patients were euthyroid and 32 were marginally hyperthyroid with slightly increased serum total \(T_3\) and/or suppressed TSH (the latter available in 1980) levels. Post treatment follow-up was feasible for 126 patients (mean 62.6±0.9 years, 97 of them were treated between 1986 and 1996). 85 patients regularly attended our outpatient clinic, while 41 patients were traced through correspondence. For the remaining 34 patients, no follow-up information could be obtained.

All 126 patients received a therapeutic dose of 25-40 mCi \(^{131}\)I (mean 33.9±0.6, median 30 mCi). Patients were previously informed about the possibility of post-treatment hypothyroidism and the resulting need for life-long replacement therapy with thyroxin. Post treatment follow-up ranged from 1 to 21 years, (mean 5.3±0.4, median 4 years) and consisted of clinical and biochemical assessment, with TSH, \(T_3\) and \(T_4\) measurements, approximately every 2 months during the first year and at longer intervals afterwards, or until hypothyroidism was detected and life-long treatment with l-thyroxin was initiated. During the follow-up period, no patient had evidence of other disease on clinical grounds and routine biochemical screening, and none was taking medication known to interfere with thyroid function.

Serum TSH was measured by a radioimmunoassay (RIA) during the 1970s, (normal range 1-10 mU/L) an immunoradiometric assay (IRMA, International CIS, Gif-sur-Yvette, France, normal range 0.5-4.5 mU/L) from 1985-1995 and a sensitive IRMA method (Henning, Berlin, GMBH) with analytical sensitivity of 0-03 mU/L (normal range 0.3-4.0 mU/L) thereafter. \(T_3\) and \(T_4\) were measured using commercial RIA kits.

**Statistical analysis**

Unpaired t-test was performed for comparisons of the means of several parameters. Probability at the 5% level (P<0.05) was considered statistically significant. All results are expressed as mean±standard error of the mean. The statistical calculations were performed with the SPSS+5 version (Statistical Package for Social Science, +5, SPSS Inc, Chicago).

**RESULTS**

From the 160 patients with hyperthyroidism due to toxic adenoma, none was found hyperthyroid 2 months following \(^{131}\)I treatment (1st follow up visit). From the 126 patients with long term follow up (mean 5.3±0.4, median 4 years) post \(^{131}\)I administration, 69 (54.8%) developed hypothyroidism within the 1st post treatment year (mean 5.9±0.5 months, median 4). In 22 of these individuals hypothyroidism was evident in their 1st follow up visit (2 months after treatment). The remaining 57 patients (45.2%), who were euthyroid at 12 months, remained so for the whole follow-up period (5.76±0.5, median 5 years). No clinical and biochemical evidence of hypothyroidism and no relapse of the hyperthyroidism was observed during this period. More specifically, for 52 euthyroid patients follow-up was longer than 2 years and for 33 patients longer than 5 years.

No differences were observed between patients who
became hypothyroid and those who remained euthyroid after $^{131}$I treatment for toxic adenoma, as regards age at the time of treatment, the $^{131}$I dose administered, the size of the adenoma, or pre $^{131}$I treatment TSH levels. Of the 57 patients who remained euthyroid after treatment, 54 were euthyroid on the day of $^{131}$I administration, while 3 were subclinically hyperthyroid.

Of the 69 patients who developed hypothyroidism, 40 (58.4%) were euthyroid on the day of $^{131}$I administration and 29 (41.6%) were subclinically hyperthyroid. Hypothyroidism developed earlier in patients who were euthyroid before $^{131}$I administration (within 3.63±0.64 months) than in the subclinically hyperthyroid patients, who became hypothyroid within 6.82 ±0.57 months (P=0.001). No difference was found between the two patient groups of individuals with post radiation hypothyroidism as regards age at the time of treatment, $^{131}$I dose administered and size of the adenoma (smaller or larger than 3 cm). None of our patients developed any malignancy during the follow up period.

**DISCUSSION**

This retrospective analysis demonstrated that a complete cure of hyperthyroidism was achieved in 100% of the 126 patients with toxic adenoma treated with an ablative dose of $^{131}$I (25-40 mCi, median 30 mCi) and no recurrence was observed during a mean follow-up period of 5.3 years. Hypothyroidism developed in approximately 55% of the patients (n=69), exclusively within the first year after radiiodine treatment, while 45% of the patients (n=57) remained euthyroid for the total duration of the follow-up.

The treatment rate of toxic adenomas and the frequency of post $^{131}$I treatment hypothyroidism vary widely, and this variability seems to correlate with the administered dose of radiiodine but not entirely (Table 1). Hence other factors must be sought for the variable responses. In the present study, we demonstrated higher treatment rates (100%) than the ones reported by others as well as higher incidence of post treatment hypothyroidism (55%), using 25-40 mCi $^{131}$I. O’Brien et al. using 19.7-100 mCi $^{131}$I, reported a 8.7 % recurrence rate of hyperthyroidism in 23 patients with typical toxic adenoma after $^{131}$I, while hypothyroidism developed in approximately 35% of the patients within 3 months to 16.3 years post-treatment. In another study of 29 patients, using 10-40 mCi, the recurrence rate was 52% and hypothyroidism developed in 17% of the subjects in 10 years and 44% in 20 years of follow-up. Finally, in the study by Goldstein & Hart, hypothyroidism occurred in 36% of the 23 patients followed for 8.5 years and treated with a dose of 23±10 mCi. The lower treatment rate and incidence of post radiation hypothyroidism as regards age at the time of treatment, $^{131}$I dose administered and size of the adenoma (smaller or larger than 3 cm). None of our patients developed any malignancy during the follow up period.

<table>
<thead>
<tr>
<th>AUTHORS</th>
<th>n</th>
<th>$^{131}$I dose (mCi)</th>
<th>PERSISTENCE or RECURRENCE of HYPERTHYROIDISM</th>
<th>HYPOTHYROIDISM</th>
<th>FOLLOW UP years mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Brien et al., 1992</td>
<td>23</td>
<td>19.7±1.00</td>
<td>8.7%</td>
<td>35%</td>
<td>3.8 (0.4-16.3)</td>
</tr>
<tr>
<td>Fontana et al., 1980</td>
<td>29</td>
<td>10-40</td>
<td>52%</td>
<td>17%</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Goldstein &amp; Hart, 1983</td>
<td>23</td>
<td>15-55 (23±10)</td>
<td>-</td>
<td>36%</td>
<td>8.5 (4-16.5)</td>
</tr>
<tr>
<td>Eyre-Brook &amp; Talbot, 1982</td>
<td>37</td>
<td>1.2-15</td>
<td>32%</td>
<td>5.4%</td>
<td>6.5</td>
</tr>
<tr>
<td>Blum et al., 1975</td>
<td>14</td>
<td>10-15</td>
<td>100%</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>Ross et al., 1984</td>
<td>45</td>
<td>5-15 (10.3±2)</td>
<td>13.3%</td>
<td>-</td>
<td>4.9±3.2 (0.5-13.5)</td>
</tr>
<tr>
<td>Hagedus et al., 1986</td>
<td>27</td>
<td>7.5</td>
<td>7%</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Mariotti et al., 1986</td>
<td>138</td>
<td>(12.6±4.1)</td>
<td>15%</td>
<td>4%</td>
<td>3.2±2.2 (1-11)</td>
</tr>
<tr>
<td>Ratcliffe et al., 1986</td>
<td>48</td>
<td>10-15</td>
<td>15%</td>
<td>-</td>
<td>3.08 (2-10)</td>
</tr>
<tr>
<td>Huysmans et al., 1991</td>
<td>52</td>
<td>20</td>
<td>2%</td>
<td>6%</td>
<td>10 ±4 (4-17.5)</td>
</tr>
<tr>
<td>Present study</td>
<td>126</td>
<td>25-40</td>
<td>0%</td>
<td>55%</td>
<td>5.3±0.4 (1-21)</td>
</tr>
</tbody>
</table>
the hyperthyroidism in 100% of the patients (15, Table 1). This observation is in concordance with the well known radioresistance of adenomatous tissue due to the presence of medium and large follicles with much more colloid which reduces the effect of beta-radiation of $^{131}$I on the follicular cells$^{10}$.

The finding that in our patients who were subclinically hyperthyroid on the treatment day, post radiation hypothyroidism developed less frequently and also later, as compared to patients who were euthyroid, can be explained by the protective effect of the functional suppression of the extranodular thyroid tissue by the hyperfunctioning toxic adenoma leading to a lower iodine uptake of the normal thyroid cells at the time of the $^{131}$I administration. The lack of correlation between TSH levels immediately before treatment and the development of hypothyroidism is probably due to the less sensitive radioimmunoassays for TSH determination during the early years of the study (before 1990). However, most of the patients in our study that remained euthyroid were euthyroid on the $^{131}$I treatment day (54 out of 57) and presumably with normal $^{131}$I uptake potential. Thus the avoidance of hypothyroidism in almost half of our patients can be only partially attributed to the above mentioned protective effect$^{6,7,20}$. Apart from the incomplete suppression of the extranodular normal thyroid, or the possibility of some $^{131}$I uptake by the thyroid tissue which appeared suppressed on the scanning$^{21}$, other factors participate in the development of hypothyroidism as well. It has also been proposed that autonomously functioning micronodules which may accompany toxic adenoma may degenerate and predispose to hypothyroidism post $^{131}$I$^{19}$. Finally, hypothyroidism may be part of the natural history of toxic adenoma due to autoimmune dysfunction of the extranodular thyroid tissue$^{4}$ as it is shown that patients with antithyroid antibodies have a higher incidence of hypothyroidism post $^{131}$I$^{19}$.

In accordance with others$^{13}$, post treatment hypothyroidism in our patients did not correlate with the adenoma size, patient’s age or $^{131}$I dose. None of our patients developed any malignancy during the follow-up period, in agreement with reports of no increased risk for thyroid malignancy$^{23}$, other cancers$^{31}$, and leukemia$^{29}$ post $^{131}$I treatment.

The main argument against the use of $^{131}$I versus the surgical approach in the treatment of toxic adenoma is the possible coexistence of thyroid cancer. Nevertheless our data$^{26}$ and those of others$^{27-29}$ indicate that such a risk is very low (≈1.5%), although rates as high as 2.5-5.4% have been reported$^{30-31}$. It should be noted that the incidence of thyroid carcinoma in the general population following operation or post mortem is reported to range from 0.11$^{26}$ to 2.8%$^{33}$. Nevertheless, lobectomy, which is the surgical treatment of choice for toxic adenoma, offers only partial protection due to the well documented multifocality, especially in papillary carcinoma where microscopical foci of cancer are detected in the opposite lobe in 30-82% of patients$^{21}$.

In conclusion, our findings suggest that treatment of toxic adenoma with $^{131}$I in the dose of 25-40 mCi is a well tolerated therapy, with no side effects, leading to rapid relief of hyperthyroid symptoms. Hypothyroidism is a permanent disease that needs life long treatment and regular follow-up once or twice a year, but it cannot be considered a major side effect, as the replacement therapy with thyroxine is easy, safe and cost-free. In addition, the observation that hypothyroidism in all our patients developed within one year post treatment is of major importance. Since our follow-up is 1-21 years, we suggest that if hypothyroidism does not develop within the first year, the likelihood of developing it later is very small, so that follow-up visits should be less frequent past the first year.

REFERENCES