

Analysis of demographic and clinical factors affecting the outcome of radioiodine therapy in patients with hyperthyroidism

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Abstract

Introduction: The influence of demographic and clinical factors on the outcome of ¹³¹I therapy in hyperthyroid patients has been examined, based on a retrospective evaluation of results obtained in patients submitted to ¹³¹I treatment at the Department of Nuclear Medicine and Oncological Endocrinology, Medical University of Lodz (Province Hospital, Zgierz). The goal of the study was to analyse such factors as the age and sex of patients, disease duration, as well as the hormonal status before ¹³¹I application, which could have an influence on the effects of therapy with radioiodine ¹³¹I.

Material and methods: The study involved 500 randomly selected patients with hyperthyroidism, treated with ¹³¹I radioiodine. The following 3 groups were defined: group 1 – patients with multinodular goitre (MNG), *n* = 200; group 2 – patients with a single autonomous nodule of the thyroid (AFTN), *n* = 100; group 3 – patients with Graves' disease (GD), *n* = 200. The local ethics committee (in the Polish Mother's Memorial Hospital – Research Institute, Lodz) approved the study.

Results: The obtained results indicate that the efficacy of therapy with ¹³¹I applied in patients with MNG, AFTN and GD does not depend on either patient sex or patient age. The length of antithyroid treatment before ¹³¹I therapy onset does not appear to have any effect on the therapy outcome, and the baseline thyrotropin concentration seems to be significant only in the case of GD.

Conclusions: The analysed demographic factors do not affect the outcome of ¹³¹I therapy in hyperthyroidism.

Key words: thyroid, hyperthyroidism, ¹³¹I radioiodine therapy.

Introduction

The treatment of hyperthyroidism with radioiodine is an approved and commonly practised therapeutic method, especially in cases of Graves' disease and single toxic adenomas. Since complete cure, following a single therapeutic dose of radioiodine, is not observed in all the treated patients, while hypothyroidism is observed in others, an evaluation has for some years been attempted, trying to identify what factors affect the outcome of ¹³¹I therapy. Also new methods have been sought to improve the to-date results of this therapy.

The goal of the study was to analyse demographic and clinical factors affecting the outcome of treatment with radioiodine in hyperthyroid patients.

Material and methods

The study involved 500 randomly selected patients with hyperthyroidism, treated with ¹³¹I radioiodine at the Department of Nuclear Medicine and Oncological Endocrinology in Zgierz. The local ethics committee (in the Polish Mother's Memorial Hospital – Research Institute, Lodz) approved the study.

In the analysed group of 500 patients, the following 3 groups were defined: group 1 – patients with multinodular goitre (MNG), *n* = 200; group 2 – patients with a single autonomous nodule of the thyroid (autonomously functioning thyroid nodule – AFTN), *n* = 100; group 3 – patients with Graves' disease (GD), *n* = 200.

The patients were assigned to particular groups, following clinical examination, hormonal and immunological tests, sonographic imaging of the thyroid gland and thyroid scintigraphy.

In the studied population, the effects of demographic data, such as the age and sex of patients, and disease duration (in categories: below/above 3 months, below/above 3 years), were analysed, separately for each disease entity, as well as the hormonal status before ¹³¹I application.

The group of patients with multinodular goitre consisted of 171 females (85.5%) aged 34-81 years (mean age: 60.7 years) and 29 males (14.5%) aged 45-79 years (mean age: 61.7 years). The group of patients with a single autonomous nodule consisted of 88 females (88%) aged 32-79 years (mean age: 60.4 years) and 12 males (12%) aged 36-70 years (mean age: 55 years). The group of patients with Graves' disease consisted of 151 females (78.5%) aged 24-81 years (mean age: 48.4 years) and 43 males (21.5%) aged 31-77 years (mean age: 52.9 years).

Prior to radioiodine administration, the hormonal status was evaluated in the patients, based on serum concentrations of free thyroxine (FT₄), free triiodothyronine (FT₃) and thyrotropin (TSH). In each of the above-mentioned 3 groups, the following subgroups were identified:

- A) patients with hormonal euthyroidism after administration of antithyroid drugs (methimazole or propylthiouracil),
- B) patients with TSH suppression (< 0.3 μIU/ml) and normal FT₄ and FT₃ values,
- C) patients with TSH suppression and elevated values of FT₄ and/or FT₃.

In group 1 (with multinodular goitre), 80 patients (40%) revealed euthyroidism (subgroup A), 40 patients (20%) demonstrated subclinical hyperthyroidism (subgroup B) and 80 patients (40%) were hyperthyroid (subgroup C). In group 2 (with a single autonomous nodule), 12 patients (12%) revealed euthyroidism, 31 patients (31%) demonstrated subclinical hyperthyroidism and

57 patients (56%) were hyperthyroid. In group 3 (with Graves' disease), 60 patients (30%) revealed euthyroidism, 52 patients (26%) demonstrated subclinical hyperthyroidism and 88 patients (44%) were hyperthyroid.

Regarding the duration of treatment with antithyroid drugs before ¹³¹I therapy, 77 patients in group 1 (38.5%) were treated for less than 3 months, 118 patients (59%) for 3 months to 3 years, and 5 patients (2.5%) for more than 3 years. In group 3, 50 patients (25%) were treated for less than 3 months, 131 patients (65.5%) for 3 months to 3 years and 19 patients (9.5%) for more than 3 years. The patients with a single autonomous nodule (group 2) received ¹³¹I without prior treatment with antithyroid medications.

¹³¹I radioiodine was administered during patients' hospitalisation. The administered doses (calculated according to the formula proposed by Marinelli *et al.* [1]) were within the range of dose values used in hyperthyroidism:

- group 1 – MNG – from 236.8 MBq (6.4 mCi) to 1498.5 MBq (40.5 mCi),
- group 2 – AFTN – from 236.8 MBq (6.4 mCi) to 1217.3 MBq (32.9 mCi),
- group 3 – GD – from 111 MBq (3 mCi) to 1198.8 MBq (32.5 mCi).

The effect of radioiodine therapy was evaluated after 6 months on the basis of clinical examination and TSH and thyroid hormone concentrations. The results of treatment were assigned to 2 subgroups in each of the study group – MNG, AFTN and GD:

- effective therapy – euthyroidism or hypothyroidism,
- ineffective therapy – persistent hyperthyroidism.

Additionally, it should be mentioned that the cases of subclinical hyperthyroidism were considered as ineffective treatment, while the cases of subclinical hypothyroidism were included in the group of effective therapy.

The concentrations of FT₃ (pg/ml) and FT₄ in blood serum (pmol/l) were measured by the radioimmunochemical method with standard, commercially available kits (Brahms), and TSH (μIU/ml) concentrations were measured by the IRMA radioimmunochemical method, using a standard, commercially available kit for TSH assay (Brahms).

The concentrations of anti-TPO antibodies (IU/ml) were measured by the RAI immunometric method, using a commercially available anti-TPO test (Brahms), and the concentrations of anti-TSH receptor antibodies were measured by the radioreceptor method (TRAK human kits, Brahms).

Results

In 133 patients (26.6%) – out of 500 – the ¹³¹I therapy was ineffective, i.e., clinical and biochemical hyperthyroidism was further maintained. In

367 patients (73.4%), either euthyroidism or hypothyroidism was obtained.

The following results were obtained in particular groups: in group 1 (multinodular goitre): 25% – ineffective therapy, 75% – effective therapy (19% – hypothyroidism, 56% – euthyroidism); in group 2 (single autonomous nodule): 18% – ineffective therapy, 82% – effective therapy (9% – hypothyroidism, 73% – euthyroidism); in group 3 (Graves' disease): 32.5% – ineffective therapy, 67.5% – effective therapy (27.5% – euthyroidism, 40% – hypothyroidism).

Analysis of demographic data

While analysing demographic data, such as the age and sex of the patients, it was found that all the studied groups were uniform, regarding sex and age distribution in the subgroups of therapy effectiveness.

The mean age of the patients was as follows:

- group 1: 61.7 ±11.23 years ($x \pm SD$), including the particular subgroups of therapy effectiveness (hyperthyroidism – HYPERT, euthyroidism – EU, hypothyroidism – HYPO): {0 – HYPERT} – 60.3 ±11.21; {1 – EU} – 61.4 ±10.13 and {2 – HYPO} – 61.2 ±10.15;
- group 2: 60.4 ±11.35, including the particular subgroups of therapy effectiveness: {0 – HYPERT} – 62.8 ±9.36; {1 – EU} – 59.2 ±11.15 and {2 – HYPO} – 63.2 ±10.35;
- group 3: 49.5 ±11.16, including the particular subgroups of therapy effectiveness: {0 – HYPERT} – 48.5 ±10.42; {1 – EU} – 52.6 ±11.22 and {2 – HYPO} – 49.3 ±11.10.

No statistically significant differences in the mean age of patients in various groups of therapeutic effectiveness were observed in any of the study groups (the level of significance of the variance analysis test was always considerably higher than 0.05). Analysing sex distribution among the patients in particular therapeutic groups, no statistically significant correlations were found between sex and the effectiveness of ^{131}I treatment. Nor was there statistically significant dependence of the treatment outcome on patient sex in any of the study groups. Contingency tables and related Pearson's χ^2 test were applied for verification of the above phenomenon.

As presented above in Tables I-III, Pearson's χ^2 test and Spearman's rank correlation coefficients, the latter calculated for evaluation of correlations, were statistically insignificant.

Analysis of clinical data

Analysing the importance of the baseline hormonal status (before ^{131}I radioiodine application) on the outcome of radioiodine therapy, the following

Table I. Analysis of treatment effectiveness in MNG group

Sex	Effectiveness of ^{131}I treatment			Statistical analysis
	0	1	Together	
F	41	130	171	$\chi^2 = 0.7, p = 0.4$ $r_s = -0.06, p = 0.4$
M	9	20	29	
F + M	50	150	200	

Table II. Analysis of treatment effectiveness in AFTN group

Sex	Effectiveness of ^{131}I treatment			Statistical analysis
	0	1	Together	
F	17	71	88	$\chi^2 = 0.3, p = 0.6$ $r_s = 0.09, p = 0.3$
M	1	11	12	
F + M	18	82	100	

Table III. Analysis of treatment effectiveness in GD group

Sex	Effectiveness of ^{131}I treatment			Statistical analysis
	0	1	Together	
F	49	108	157	$\chi^2 = 0.6, p = 0.5$ $r_s = -0.05, p = 0.4$
M	16	27	43	
F + M	65	135	200	

Table IV. Correlation between the effectiveness of ^{131}I treatment and hormonal status of MNG patients

Sex	Effectiveness of ^{131}I treatment			Statistical analysis
	0	1	Together	
0	21	59	80	$\chi^2 = 4.4, p = 0.1$ $r_s = 0.08, p = 0.2$
1	14	25	39	
2	15	66	81	
Together	50	150	200	

Table V. Correlation between the effectiveness of ^{131}I treatment and hormonal status of AFTN patients

Hormonal status	Effectiveness of ^{131}I treatment			Statistical analysis
	0	1	Together	
0	10	47	57	$\chi^2 = 0.5, p = 0.7$ $r_s = 0.03, p = 0.7$
1	5	26	31	
2	3	9	12	
Together	18	82	100	

criteria were accepted: "0" – hyperthyroidism (TSH suppression and elevated thyroid hormones), "1" – subclinical hyperthyroidism (TSH suppression and normal thyroid hormones), "2" – euthyroidism (normal TSH and thyroid hormone concentrations), comparing the criteria with the therapeutic outcome (Table IV–VI).

Table VI. Correlation between the effectiveness of ¹³¹I treatment and hormonal status of GD patients

Hormonal status	Effectiveness of ¹³¹ I treatment			Statistical analysis
	0	1	Together	
0	31	57	88	$\chi^2 = 6.2, p < 0.05$ $r_s = 0.11, p = 0.1$
1	22	31	53	
2	12	47	59	
Together	65	135	200	

Table VII. Correlation between the effectiveness of ¹³¹I treatment and duration of antithyroid drug therapy in MNG group

Duration	Effectiveness of ¹³¹ I treatment			Statistical analysis
	0	1	Together	
0	18	59	77	$\chi^2 = 0.3, p = 0.8$ $r_s = -0.03, p = 0.7$
1	31	87	118	
2	1	4	5	
Together	50	150	200	

Table VIII. Correlation between the effectiveness of ¹³¹I treatment and duration of antithyroid drug therapy in GD group

Duration	Effectiveness of ¹³¹ I treatment			Statistical analysis
	0	1	Together	
0	11	39	50	$\chi^2 = 4.3, p = 0.1$ $r_s = -0.09, p = 0.2$
1	49	82	131	
2	5	14	19	
Together	65	135	200	

The results presented above suggest that only in patients of the GD group did the baseline concentrations of TSH and thyroid hormones ($p < 0.05$) demonstrate some influence on the outcome of radioiodine therapy (Table VI), i.e., the appropriate preparation of patients with antithyroid drugs for ¹³¹I treatment seems to be important to obtain, at least, normal levels of FT₃ and FT₄ hormones.

The duration of disease is another variable which may have affected therapy outcome in the groups with multinodular goitre and Graves' disease; it was divided into the following 3 categories: "0" – up to 3 months, "1" – from 3 months to 3 years, and "2" – above 3 years (Tables VII, VIII).

As presented above, the obtained values of Pearson's χ^2 test, calculated for the contingency tables, turned out to be statistically insignificant, similarly as Spearman's rank correlation coefficients (Tables VII, VIII).

Discussion

The above results demonstrate that the efficacy of therapy with ¹³¹I applied in patients with MNG, AFTN and GD does not depend on either patient sex or patient age. The length of antithyroid treatment before ¹³¹I therapy onset does not appear to have any effect on the therapy outcome, and the baseline TSH concentration seems to be significant only in the case of GD.

¹³¹I therapy is a non-invasive and safe method, used already for more than 50 years, and the primary therapeutic protocol – besides antithyroid drugs and surgery – recommended in hyperthyroidism [2-4]. However, the planned therapeutic effects are not obtained in all patients, so studies have been performed for years to identify new methods improving the to-date therapeutic outcomes.

The goal of the study was to search for and analyse factors which could have any influence on the effects of therapy with ¹³¹I. The effects of radioiodine treatment, unlike those of surgical intervention, are extended in time, while the rate of their occurrence depends on the therapeutic dose of ¹³¹I. The majority of authors report that the period of 6 months after radioiodine administration is sufficient to stabilise thyroid functions [5-7]. Therefore, the effects of radioiodine therapy, applied to 500 hyperthyroid patients, were summarised in our study also after 6 months. After the mentioned period, persistent hyperthyroidism was found in 27% of patients, euthyroidism in 48%, and hypothyroidism in 25% (in other words, the therapy was effective in 73%), using doses from 129 MBq to 1665 MBq, with a mean dose of 740 MBq (3.5 mCi to 45 mCi, mean dose of approximately 20 mCi). In practice, the relatively high percent of hypothyroidism after ¹³¹I therapy is still a problem. However, it is now regarded as a complication of the applied therapy. The percent of persistent hyperthyroidism after radioiodine therapy is different in particular disease entities. The French authors [8] who performed a retrospective evaluation of 100 patients with Graves' disease, following radioiodine therapy, found hypothyroidism in 33% of the treated patients after 6-9 months. In German centres [5, 9, 10] hypothyroidism was found in 30-46% of patients with Graves' disease and in 8-28% of patients with nodular goitre. An Italian group [11] evaluated the incidence of hypothyroidism at as much as 74% in Graves' disease already after 3 months, while no hypothyroidism was observed by the authors in nodular goitre after that period. After one year from the performed ¹³¹I therapy, only 3% of the patients revealed hypothyroidism (the observation included 146 patients with Plummer's disease).

Vijayakumar *et al.* [12] reported, in a group of 147 GD patients, 57% cases of hypothyroidism 5 months after ¹³¹I treatment. Ronga *et al.* [13] reported 2.6% cases of hypothyroidism after many-year observation of 1361 patients (82.4% with AFTN and 17.6% with MNG).

In our study, hypothyroidism occurred in 19% of the patients with MNG, in 9% of patients in the group with AFTN, and in 40% of the patients with GD, which is not different from other results of Polish authors [14, 15].

The persistent hyperthyroidism after ¹³¹I therapy is still a therapeutic problem. The patients in whom no therapeutic effect is achieved need subsequent radioiodine doses to be administered, which, in effect, leads to 100% cure of hyperthyroidism, but in the majority of these patients, hypothyroidism is the resulting adverse effect. As in the case of persistent hypothyroidism, the percentage of persistent hyperthyroidism is higher in GD than in MNG or AFTN and amounts in our material to 32.5%, 25% and 9%, respectively. These results are also similar to the data reported by the earlier mentioned authors.

In our study, the influence of patient sex and age on the therapeutic outcome was evaluated. No statistically significant differences were found in the mean age of the patients in particular subgroups of therapy efficacy. Nor was any correlation found between patient sex and the outcome of the therapy.

Similarly, other authors did not observe any effect of these parameters on the therapeutic efficacy of ¹³¹I treatment [14, 16-19]. In turn, Allahabadia *et al.* [20] observed, after 6 months, a higher percentage of effective therapy in women than in men (76.7% vs. 67.6%), as well as better results in patients above 40 years old, when compared with other patients below 40 (79.3% vs. 68.9%), although it is assumed that the thyroid gland of younger persons is more susceptible to irradiation. Consistently with the above, Vijayakumar *et al.* [12] reported a better effectiveness of ¹³¹I treatment in women than in men (62% vs. 46%, respectively).

The effect of the hormonal status before ¹³¹I administration on the therapy outcome was also analysed, revealing a correlation between TSH and therapy efficacy only in group 3 (GD). These results may suggest that patients with GD should be appropriately pre-treated with antithyroid preparations in order to compensate the biochemical hyperthyroidism, keeping in mind the necessity of drug withdrawal at a proper time point before radioiodine administration.

Sabri *et al.* [21] also pointed attention to the fact that in autoimmune hyperthyroidism, the lower is the baseline TSH concentration, the worse is the efficacy of radioiodine treatment. Urbanek *et*

al. [17] believe, based on their evaluations, that both thyroid hormone and TSH concentrations do not allow for any prognosis of ¹³¹I therapy effects.

In the medical literature, it is quite often discussed how many days before ¹³¹I application antithyroid drugs should be withdrawn [22]. Sabri *et al.* [7] claim that conservative treatment should be withdrawn a minimum one day before radioiodine therapy; Urbanek *et al.* [17], Lind [23], and Kobe *et al.* [24] report that 2 days are enough; Andrade *et al.* [25] propose 4 days, and Braga *et al.* [26] suggest at least 6 days. Ronga *et al.* [13], following 40 years of their experience, suggest the withdrawal of antithyroid treatment in MNG 30 days before radioiodine application. It is to be stressed here that the majority of reports deal with the exact time of antithyroid drug withdrawal before ¹³¹I treatment application rather than with the total period of administration of the drugs in question.

In most of the examined patients presented in this report, antithyroid drugs were withdrawn within 3 days to 3 weeks before ¹³¹I administration (the patients came from various centres in which they were conservatively treated). Only 19 patients – out of 500 patients treated with radioiodine – received a single dose of methimazole and in 14 (73.7%) persistent hyperthyroidism was found. However, these results do not allow for any conclusions that methimazole influences the efficacy of ¹³¹I therapy because that group was very small and not homogeneous with regards to the other variables.

In our study, the duration of disease (more precisely the duration of administration of antithyroid drugs) exerted no effect on the final effectiveness of treatment. In the analysed material, the values of Pearson's χ^2 test were statistically insignificant, similarly as Spearman's rank correlation coefficients.

The most important observation resulting from the presented study is much better effectiveness of ¹³¹I therapy in those GD patients who were – prior to therapy – successfully pre-treated with antithyroid drugs, with subsequent complete normalisation of thyroid hormone concentrations.

In conclusion, our results indicate that the effectiveness of therapy with ¹³¹I in patients with MNG, AFTN and GD does not depend on either patient sex or patient age. The length of antithyroid treatment before ¹³¹I therapy onset does not appear to have any effect on the therapy outcome. Correlation between TSH concentration before ¹³¹I administration and therapy efficacy has been documented only in GD group.

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