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Radioiodine therapy for Graves' disease — retrospective analysis of efficacy factors

Radiojodoterapia w chorobie Gravesa-Basedowa — czynniki wpływające na skuteczność leczenia w oparciu o analizę retrospektywną

Piotr Szumowski, Saeid Abdelrazek, Agnieszka Kociura Sawicka, Małgorzata Mojsak, Jerzy Kostecki, Monika Sykała, Janusz Myśliwiec

Department of Nuclear Medicine, Medical University of Bialystok, Poland

Abstract

Introduction: Radioiodine (^{131}I) isotope therapy is the method of choice in the treatment of Graves' disease relapse. The efficiency of this method is dependent on many factors; therefore, the present paper aims to identify the parameters that have a crucial impact on the efficacy of radioiodine therapy for Graves' disease.

Material and methods: The authors performed a retrospective analysis of the medical documentation of 700 Graves' disease sufferers treated with ^{131}I. The patients were divided into three groups depending on the thyroid-absorbed dose of ^{131}I: group I — 100 Gy, II — 150 Gy, and III — 200 Gy. The authors assessed the influence of gender, age, presence of orbitopathy, TRab titres, thyroid mass, iodine uptake after 24 and 48 hours, and the absorbed dose on the treatment efficacy at one year post-^{131}I administration.

Results: The volume of thyroid gland ($P < 0.002$) and the thyroid-absorbed dose ($P < 0.001$) were the only factors that had a significant impact on the outcome of the treatment. The likelihood of hyperthyroidism persisting (odds ratio: 3.71, 95% confidence interval: 2.4–5.87) was greatest in patients from group I. In group II, with thyroid volume amounting both to 25 mL and to 25–50 mL, the percentage of hyperthyroidism was lowest (1 and 0%). However, with thyroid volume > 50 mL, the percentage of hyperthyroidism was lowest in group III (10%).

Conclusions: The absorbed dose of ^{131}I and the volume of the thyroid gland are two parameters that have a significant influence on the efficacy of radioiodine therapy for Graves' disease. 150 Gy is the optimal dose for glands < 50 mL. A goitre > 50 mL requires an absorbed dose of 200 Gy in order to minimise the risk of recurrent hyperthyroidism. **(Endokrynol Pol 2015; 66 (2): 126–131)**

Key words: *Graves' disease; radioiodine therapy; absorbed dose*

Streszczenie

Wstęp: Metodą z wyboru w leczeniu nawrotów choroby Gravesa-Basedowa jest terapia izotopowa radiojodem (^{131}I). Efektywność tego leczenia zależy od wielu czynników, dlatego też celem pracy było wskazanie parametrów mających decydujący wpływ na skuteczności radiojodoterapii choroby Gravesa-Basedowa.

Materiał i metody: Przeanalizowano retrospektywnie dokumentację medyczną 700 pacjentów z chorobą Gravesa leczonych ^{131}I. Ze względu na dawkę pochłoniętą ^{131}I w tarczycy, pacjentów podzielono na trzy grupy (grupa I — 100 Gy, II — 150 Gy, III — 200 Gy). Zbadano zależność płci, wieku, obecności orbitopatii, miana TRAb, masy tarczycy, jodochwytności tarczycy po 24 i 48 godzinach, dawki pochłoniętej na efektywność leczenia, po roku od podania ^{131}I.

Wyniki: Objętość tarczycy ($P < 0{,}002$), dawka pochłonięta w tarczycy ($P < 0{,}001$) miały jedynie istotny wpływ na wyniki terapii. Największe ryzyko utrzymywania się hipertyreozy (iloraz szans [OR] 3,71, 95% przedział ufności [CI] 2,4–5,87) wystąpiło u pacjentów z grupy I. W grupie II przy objętości tarczycy 25ml jak i 25-50ml odsetek hiperytreozy był najmniejszy (1 i 0%). Natomiast przy objętości tarczycy > 50 ml odsetek hipertyreozy był najmniejszy w grupie III (10%).

Wnioski: Dawka pochłonięta ^{131}I, objętość tarczycy to parametry mające istotny wpływ na skuteczności radiojodoterapii choroby Gravesa-Basedowa. Optymalną dawką pochłoniętą w tarczycy z objętością < 50 ml jest 150Gy. Wole (> 50 ml) wymaga dawki pochłoniętej 200Gy celem zminimalizowania nawrotu hipertyreozy. **(Endokrynol Pol 2015; 66 (2): 126–131)**

Słowa kluczowe: *choroba Gravesa-Basedowa; radiojodoterapia; dawka pochłonięta*

Introduction

The treatment of Graves' disease (GD), which affects 25 out of 100,000 people in Poland, involves using antithyroid drugs for at least 1.5 years. If no remission is achieved, radical treatment methods are used, including surgery or, more frequently these days, radioiodine (^{131}I) therapy. The to-date history of radioiodine treatment for GD justifies the claim that the radioisotope method is inexpensive, relatively safe (in 3–15% of patients, it can exacerbate the pre-existing orbitopathy), convenient (per os administration of, in most cases, one capsule of ^{131}I),

Piotr Szumowski M.D., Ph.D. Department of Nuclear Medicine, Medical University of Bialystok, Poland, M. Skłodowskiej-Curie St. 24A, 15–276 Białystok, tel.: +48 85 746 87 70, fax: +48 85 746 87 71, e-mail: piotrmjs@wp.pl

non-invasive, and efficient (cures hypothyroidism after first course of treatment in 75–90% of cases) [1–3].

Nevertheless, there are several reasons for which the effects of treating Graves' disease by means of radioiodine are less predictable than in the case of toxic goitre. First of all, it is an autoimmune disorder, in which hyperthyroidism is caused by antibodies acting against thyrocytes, and not by the gland itself. This makes the choice of correct therapeutic activity of radioiodine fairly difficult [4]. What is more, because of increased vascularisation and greater metabolic activity of thyrocytes in GD, the turnover of radioiodine is usually accelerated during treatment [5]. As a result, the effect of the ^{131}I ionising radiation on thyrocytes is shorter, and this lowers the efficacy of radioiodine therapy. Treatment outcomes are also dependent on the volume of the thyroid gland [1, 6].

In view of the above, the authors undertook an attempt to assess the efficiency of ^{131}I therapy for Graves' disease, on the basis of a retrospective analysis of medical documentation of patients treated at the Department of Nuclear Medicine of the University Clinic Hospital in Białystok in the years 2004–2014.

Material and methods

The sample comprised 700 GD patients, 524 of whom were women and 176 were men. The average age of the women and men was 50 ± 16 and 53 ± 18 years, respectively. All the subjects were administered ^{131}I in order to eliminate hyperthyroidism, having previously undergone unsuccessful pharmacological treatment with thyrostatic drugs (for a period no shorter than 1.5 years). Before the administration of therapeutic ^{131}I, the patients had undergone routine eligibility screening, involving the assessment of standard clinical symptoms of Graves' disease, biopsies of existing thyroid nodules (to rule out malignancy), USG of the thyroid and oculomotor muscles (if active orbitopathy was suspected), the estimation of TSH receptor antibodies (TRAb) via radioimmunoassay TRAK Human Brahms (norm < 2 IU/L), iodine uptake tests: 24-hour (T_{24}) and 48-hour (T_{48}) ones, as well as thyroid scintigraphy with a gamma camera (Nucline™ Th, Mediso).

The principle was assumed that the studied patients could commence treatment if their serum levels of free thyroxin (fT_4), free triiodothyronine (fT_3), and thyrotropin (TSH) were within normal range, the 24-h iodine uptake in the thyroid was higher than 20%, and active orbitopathy had been excluded (after physical examination and oculomotor muscles USG).

The therapeutic activity of ^{131}I for each patient was calculated using Marinelli's formula[7]:

$$A = \frac{25 \cdot m \cdot D}{T_{24} \cdot T_{eff}}$$

where: A — ^{131}I therapeutic activity (MBq); 25 — unit conversion coefficient; m — volume of thyroid gland calculated from USG (mL); D — absorbed dose of ^{131}I (Gy); T_{24} — 24-h ^{131}I uptake (%); T_{eff} — effective ^{131}I half-life in thyroid gland (days) = $T_{biolog} \times T_{phys} / T_{biolog} + T_{phys,}$ where T_{biolog} (rate of iodine excretion from the thyroid), T_{phys} (physical half-life of radioactive iodine).

The patients were divided into three groups according to the thyroid-absorbed dose of ^{131}I: group I — 100Gy, II — 150Gy, and III — 200Gy. The differences in the quantity of those doses resulted from the fact that patients were treated over a 10-years period, from 2004 until 2014, by various doctors, who adopted varied assumptions as to the thyroid-absorbed dose of radioiodine.

The calculated therapeutic activities of ^{131}I were administered per os in the form of gel capsules. In Poland, the only available capsules are (MBq): 200, 280, 400, 600, and 800. Whenever hyperthyroidism recurred after the first dose of radioiodine, an additional dose was not administered until after six months.

The efficacy of the treatment was expressed as the percentage of patients with euthyroidism, hypothyroidism, or persistent hyperthyroidism within a year since radioiodine administration.

The study was approved by the Ethics Committee for Medical Research, Medical University of Białystok, and is in accordance with the GCP (Good Clinical Practice). Informed consent was given by all patients participating in the study.

Statistical analysis

The statistical analysis of the results of the study was performed using the software package Statistica 10 (Stat Soft, Tulsa, USA).

A one-way analysis of variance was applied to investigate the influence of gender, age, presence of orbitopathy, TRab titres, absorbed dose, as well as 24-hour and 48-hour iodine uptake on achieving euthyroidism, hypothyroidism, and persistent hyperthyroidism, using the χ^2 test for ordinal variables and the Mann-Whitney test for continuous variables.

Additionally, a one-way analysis of variance helped to assess the relationship between thyroid volume and thyroid-absorbed dose of ^{131}I and the attainment of euthyroidism, hypothyroidism or hyperthyroidism after applied treatment.

Moreover, the logistic regression function was used to evaluate the extent to which particular parameters

Table I. *Characteristics of patients under study with regard to clinical and physical parameters and ^{131}I therapy outcomes*
Tabela I. *Charakterystyka badanych chorych z uwzględnieniem parametrów klinicznych i fizycznych oraz wyników leczenia ^{131}I*

	Hypothyroid	Euthyroid	Hyperthyroid	P
No. of patients	399 (57%)	217 (31%)	84 (12%)	
Sex				0.378
Female (n = 604)	(56%)	(31%)	(13%)	
Male (n = 96)	(57%)	(30%)	(13%)	
Age (years)	43.9 ± 14	46.6 ± 11,5	42.1 ± 13.2	0.094
Graves' orbitopathy				0.142
Absence (n = 581)	57%	31%	12%	
Presence (n = 119)	56%	32%	12%	
TRAb, IU/L	12,8 ± 11,7	10,9 ± 14,8	11,7 ± 9,8	0.186
Thyroid volume [mL]				< 0.002
< 25 (n = 220)	72%	23%	5%	
25–50 (n = 390)	52%	39%	9%	
> 50 (n = 90)	46%	32%	22%	
Absorbed dose, Gy				< 0.001
100 (n = 210)	49%	26%	25%	
150 (n = 387)	52%	37%	11%	
200 (n = 103)	58%	34%	8%	
24-h Uptake (%)	54 ± 9	53 ± 7	55 ± 9	0.349
48-h Uptake (%)	53 ± 11	54 ± 9	52 ± 13	0.212
Teff. (days)	7,5 ± 0,7	7,1 ± 0,9	7,2 ± 0,8	0.087

n — number of patients

contributed to the failure of treatment with ^{131}I (persistent hyperthyroidism). The regression analysis only took into consideration those parameters that were statistically significant for the outcome ($P < 0.05$).

Results

Table I includes the characteristics of the 700 Graves' disease patients under study, with regard to clinical and physical parameters and the results of the treatment with ^{131}I that they had undergone. The overall efficacy of the therapy at one year after ^{131}I administration was as follows: euthyroidism was achieved in 31% of the subjects, hypothyroidism in 57%, while 12% of them experienced relapse or persistence of hyperthyroidism.

The one-way analysis of variance demonstrated that the volume of the thyroid ($P < 0.002$) and the absorbed dose of radioiodine ($P < 0.001$) were significantly associated with an effective cure of hyperthyroidism. The highest percentage of hyperthyroidism (22%) was recorded among the patients with thyroid glands of > 50 mL, whereas the highest rate of euthyroidism (39%) was found in the group of patients whose gland volumes were 25–50 mL. The volume of the thyroid gland < 25 mL seemed to be associated with the highest rate of hypothyroidism and the lowest percentage of hyperthyroidism: 72% and 5%, respectively.

With a thyroid-absorbed dose of 100 Gy, the proportion of euthyroid (26%) and hypothyroid (49%) patients was the lowest. In those treated with 150 Gy and 200 Gy, the percentage of euthyroidism and hypothyroidism was higher and amounted to 37%, 52% and 34%, 58%, respectively (Table I).

It was shown, by means of a logistic regression model, that the likelihood of recurrent hyperthyroidism after ^{131}I treatment was the highest (OR = 3.71) when the absorbed dose was 100 Gy and the thyroid volume exceeded 50 mL (OR = 3.52). The higher the absorbed dose, or the smaller the thyroid volume, the lesser the probability of hypothyroidism relapse. The lowest likelihood of persistence was noted in those patients whose thyroid volumes were below 25 mL and who had received absorbed doses of 200 Gy: OR = 1.1 or OR = 1.54 (Table II).

Having analysed the interdependencies of the two parameters: absorbed dose and thyroid volume, and their impact on radioiodine therapy outcomes (Table III), one can conclude that in thyroids smaller than 25 mL,

Table II. *Logistic regression model with variables determining the probability of hyperthyroidism relapse at one year after administration of ^{131}I*

Tabela II. *Model regresji logistycznej ze zmiennymi decydującymi o prawdopodobieństwie nawrotu nadczynności tarczycy po roku od podania ^{131}I*

Parameter	OR	95% CI	P
Thyroid volume [mL]			0.001
< 25	1.1	0,8–3,2	
25–50	1.98	1.59–5.59	
> 50	3.52	2.94–5.12	
Absorbed dose of ^{131}I			0.001
In thyroid, Gy			
100	3.71	2,4–5,87	
150	1.84	1,36–5,38	
200	1.54	0,2–3,75	

hyperthyroidism did not recur provided that the absorbed dose was ≥ 150 Gy. Thyroid volumes of 25–50 mL and absorbed doses of 150 Gy meant persistent hyperthyroidism in 2% of the subjects, similarly as with 200 Gy. Meanwhile, the percentage of euthyroid patients was higher in the group who had been given 150 Gy (40%) than among those who had received 200 Gy (35%). In thyroids smaller than 50 mL, the lowest rate of recurrence was observed when the absorbed dose equalled 200 Gy (10% of hyperthyroidism).

Discussion

The history of ^{131}I therapy for Graves' disease dates back to 1940. Since then numerous scientific papers have been written on the subject. Consequently, a number of views, often markedly different, have come into being as regards the efficacy of radioiodine treatment, and more specifically as regards the parameters which influence its efficiency and the methods of calculating the therapeutic activity of ^{131}I.

Some authors focus on gender and age as the factors that determine the outcomes of radioiodine therapy for Graves' disease [8, 9]. Allahabadia et al. claim that men have lower chances of recovery from hyperthyroidism than women (47% of men vs. 74% of women) without, however, providing an unequivocal explanation of this correlation. They also add, as do other authors, that the efficiency of treatment is lower in patients younger than 40 years old. This is because young people usually have larger goitres and higher blood concentrations of antithyroid antibodies (TRAb), which stimulate hyperthyroidism [10]. Our analysis shows, in accordance with what numerous other authors have found, that neither age ($P < 0.094$) nor gender ($p < 0.378$) have a significant influence on the outcomes of the therapy [11–13].

The volume of the thyroid can also have a considerable impact on the therapeutic effects of radioiodine. Markovic et al. used statistical analyses to prove that the chances of recovery are much higher for the patients whose thyroids are smaller than 62 g (only 9.6% of unsuccessful attempts) as opposed to persons with thyroids larger than 62 g (as many as 44% of cases of persistent hyperthyroidism) [14]. Our research has also proven that the volume of the thyroid gland has a significant ($P < 0.002$) bearing on the success of treatment. The efficiency of therapy decreases along with the increasing size of the thyroid, particularly if the volume is considerably greater than 50 ml. Then the

Table III. *Correlation between thyroid volume and absorbed dose of radioiodine and thyrometabolic state after treatment*

Tabela III. *Współzależność objętości tarczycy i dawki pochłoniętej radiojodu na stan tyreometaboliczny po zastosowanym leczeniu*

Absorbed dose (Gy)	Thyrometabolic state	Thyroid volume [mL]		
		< 25	25–50	> 50
100	Euthyroid	16%	27%	21%
	Hypothyroid	83%	49%	37%
	Hyperthyroid	1%	24%	42%
	P < 0.001			
150	Euthyroid	21%	40%	31%
	Hypothyroid	79%	58%	48%
	Hyperthyroid	0%	2%	21%
	P < 0.002			
200	Euthyroid	9%	35%	39%
	Hypothyroid	91%	63%	51%
	Hyperthyroid	0%	2%	10%
	P < 0.001			

rate of hyperthyroidism is highest and amounts to 22%. Among the patients with thyroid volumes of 25–50 mL and below 25 mL, the recorded persistence of hyperthyroidism was 9% and 5%, respectively. This should be attributed to the fact that the larger the thyroid prior to the treatment, the more gland tissue remains intact after treatment with radioiodine, which increases the likelihood of persistent hyperthyroidism.

Other authors also add that, besides its volume, the echogenicity of the thyroid gland can contribute to the differences in treatment outcomes. A hypoechogenic thyroid is more sensitive to ionising radiation than a normoechogenic one. This is associated with the fact that normoechogenic thyroids contain more colloid, which absorbs ionising radiation, thus weakening its destructive effect on cellular structures [15, 16].

In the examined population of patients, the outcome of the Graves' disease radioiodine treatment was not correlated with the presence of orbitopathy as well as with the TRAb titres before the radioiodine administration. The above-stated conclusion remains in concord the results presented by other authors. [12–14, 24].

Among researchers into the treatment of Graves' disease there is no agreement as to the method of calculating the therapeutic activity of the radioisotope. Some authors use the old formula created by Marinelli, which takes into account the volume of the thyroid, its iodine uptake capacity, as well as the turnover of radioiodine and its thyroid-absorbed dose [16–18]. Others recommend using an empirically established value of ^{131}I activity per one gram of thyroid tissue; and others apply fixed activities, often administered repeatedly at certain intervals, until effective [19–21]. These varying approaches to the calculation of therapeutic activity stem from the divergent assumptions concerning the thyroid function post-treatment. Ross believes that the therapeutic activity of radioiodine should be fixed: 185MBq, 370MBq, or 555MBq, and that its application should result in hypothyroidism [22]. A similar approach is adopted by the British Nuclear Medicine Society, which assures patients that precise computing of therapeutic activity using a formula does not translate into improved therapeutic outcomes, and thus recommends fixed doses of radioiodine (from 400 to 600 MBq) [23]. The European Association of Nuclear Medicine, on the other hand, opts for Marinelli's formula as a way to calculate the therapeutic activity of radioiodine and prefers post-therapeutic euthyroidism to hyperthyroidism. To achieve such results in Graves' disease treatment, it is crucial that the thyroid-absorbed dose of radioiodine used in the formula should be 150 Gy [6].

Our views on therapeutic activity calculation are largely the same as those expressed by the European Association of Nuclear Medicine. The only difference regards the amount of thyroid-absorbed dose of ^{131}I. Our research has revealed that it is the volume of the thyroid that determines the absorbed dose. We have observed that for thyroids > 50 mL, the highest rate of success, including the attainment of euthyroid state, occurred when the absorbed dose was 200 Gy, whereas for thyroids < 50 mL, the optimum dose was 150 Gy. In the case of patients with thyroids of this volume (< 50 mL), a higher absorbed dose did not have any influence on overcoming hyperthyroidism, but merely increased the rate of hypothyroidism. This is because the smaller the volume of the gland, potentially the less gland tissue should be destroyed by ionising radiation used for anti-thyroid therapy. And, as is known from radiobiology, the destructive capability of ionising radiation is directly proportional to its tissue-absorbed dose. It should, moreover, be remembered that too small an absorbed dose of radioiodine significantly increases the risk of recurrent hyperthyroidism (in our study, the probability of relapse grew nearly four-fold, OR = 3.71, when the lowest dose of 100 Gy was administered).

The literature also indicates the coefficient denoting the ratio between ^{131}I uptake by the thyroid after 6 and 24 hours as a parameter that has a significant impact on the efficacy of radioiodine therapy for Graves' disease [24]. Isgoren et al. and Willegaignum et al. argue that with this coefficient at > 1 (> 0.9 according to the latter author), the rate of recurrence of hyperthyroidism reached 80% (83%). Meanwhile, when the coefficient was < 1 (< 0.9 according to Willegaignum et al.), the treatment failure rate dropped to 7% (17%) [20, 25]. The above coefficient, similarly to Teff. from Marinelli's formula, expresses the turnover of radioactive iodine in the thyroid. In our study, Teff. did not have a significant influence on treatment efficiency (P = 0.087). We account for this by the fact that when the thyroid-absorbed dose of ^{131}I is specified, the varying values of Teff. merely modify the activity of radioiodine that should be applied to achieve the intended therapeutic effect. Therefore, when the turnover of radioiodine in the thyroid is accelerated (Teff. is shortened), the therapeutic activity calculated by means of the formula increases accordingly; and, conversely, when Teff. is lengthened, it decreases.

Conclusion

The thyroid-absorbed dose of radioiodine and the volume of the gland are the key parameters that affect the efficacy of ^{131}I therapy for Graves' disease. For thyroids < 50 mL, 150 Gy is the optimum dose that ensures low risk of hyperthyroidism relapse (to 1%). Large goitres (> 50 mL) require an absorbed dose of 200 Gy so that the risk of relapse is minimised (OR = 1.54, 95% CI 0.2–3.75).

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