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Nuclear Medicine Review 2012, 15, 1: 7–13
10.5603/NMR.2012.0003

ISSN 1506–9680

Original

Iodine isotope (^{131}I) therapy for toxic nodular goitre: treatment efficacy parameters

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[Received 5 I 2012; Accepted 20 I 2012]

Sources of financing: diagnostic evaluation and patient treatment — the National Health Fund; analysis of research results and edition — authors' own resources

Abstract

BACKGROUND: When planning radioactive iodine therapy, it frequently happens, both in Poland and world-wide, that inadequate attention is paid to such easily measurable parameters as: 1) the serum concentration of thyrotropin (TSH) before administering radioiodine, which is a key factor for extranodular (non-autonomous) iodine uptake of the thyroid gland, 2) thyroid gland iodine uptake, and 3) the effective half-life of ^{131}I ($T_{eff.}$). The aim of the study is to evaluate the impact of the above factors on the efficacy of ^{131}I treatment in hyperthyroid patients.
METHODS: The material consisted of 4140 patients: 2190 with autonomous toxic nodules (ATN) and 1950 with toxic multinodular goitres (TMG). The patients were prepared for treatment in such a way that the concentration of TSH did not exceed 0.1 mU/l and $T_{eff.} < 5$ days. The therapeutic activity of ^{131}I was calculated using Marinelli's formula. The selection of absorbed dose value was determined by the degree of suppression of extranodular tissue. Monitoring was performed every eight weeks.
RESULTS: At one year after ^{131}I administration showed that a euthyroid status was achieved in 94%, hypothyroidism was seen observed in 3%, while persistence or recurrence of hyperthyroidism in 3% of ATN patients and, respectively, 89%, 4% and 7% of TMG patients.
CONCLUSIONS: Patients with toxic nodular goitre who are to be treated with radioiodine should have the lowest possible serum concentration of TSH. The suppression of extranodular determines the optimal value of absorbed dose for Marinelli's formula.
Key words: autonomous toxic nodules, toxic multinodular goiter, radioiodine, Marinelli's formula

Nuclear Med Rev 2012; 15, 1: 7–13

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Introduction

In spite of the fact that radioiodine has been employed for the treatment of hyperthyroidism for over sixty years, and although numerous studies all over the world seem to have provided a comprehensive view of various aspects of this therapy, a uniform standard of procedures has not been developed as yet. The lack of agreement as to radioiodine treatment of hyperthyroidism frequently results from the fact that specialists do not make adequate use of knowledge concerning the pathophysiology of the thyroid gland or data on the interaction of ionising radiation with organic matter. Admittedly, we still do not have a method to assess the radiosensitivity of the treated gland, but many hospitals — both in Poland and abroad — neglect other, equally important and easily measurable, parameters such as:

— concentration of thyrotropin (TSH) in the blood serum of patients with toxic nodular goitre before radioiodine administration, crucial for stimulation of extranodular (non-autonomous) iodine uptake by thyroid gland tissue [1–2];
— thyroidal iodine uptake, with particular attention to the dynamics of its change, whose indicator is the effective half-life of ^{131}I ($T_{eff.}$)[3–4].

The above parameters determine the optimal dose of ^{131}I absorbed by the thyroid gland. And it is indisputable that the effect of ionising radiation on thyroid tissue depends on the absorbed dose. Its increase results, among other things, in a reduction of both the hormonal function of the thyroid gland and its size.

The purpose of this study is to evaluate the impact of the above mentioned factors on the efficacy of (^{131}I) treatment in hyperthyroid patients. This evaluation was based on a retrospective analysis of the outcome of over 4,000 radioiodine therapy patients.

Methods

The material consisted of 4140 patients who, between the years 1998 and 2010, underwent radioactive iodine ^{131}I therapy for hyperthyroidism in the Nuclear Medicine Clinic of the Medical University of Bialystok.

Based on scintigraphy and ultrasonography results, the analysed cases were divided into two subgroups. Group I was comprised of 2190 persons with autonomous toxic nodule (ATN), while in group II there were 1950 patients with toxic multinodular goitre (TMG) Eligibility for radioiodine therapy was determined on the basis of typical hyperthyroidism symptoms — both clinical and biochemical, i.e. elevated levels of free triiodothyronine (fT_3) and free thyroxine (fT_4), as well as reduced serum levels of TSH. All nodules detected by USG were diagnosed through fine needle aspiration biopsy in order to exclude malignancy. It was assumed that treatment could be commenced if a patient's TSH level was below 0.1 mIU/L, 24h iodine uptake was higher than 20% (T_{24} > 20%), and the effective half-life of ^{131}I ($T_{eff.}$), calculated from iodine uptake measurements 24 and 48 hours (T_{24} and T_{48}) after the administration of the diagnostic dose, exceeded 5 days. Those patients whose fT_4 had been markedly elevated were pretreated with antithyroid drugs for 2–3 weeks, the pretreatment being discontinued 2–3 days before radioiodine administration [5–6]. The therapeutic activity of ^{131}I was calculated using Marinelli's formula (D) [7]:

$$A = \frac{25 \times m \times D}{T_{24} \times Teff}$$

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

It was assumed that the absorbed dose from Marinelli's formula is closely correlated with the ratio of radioiodine uptake in nodules to radioiodine uptake in the entire gland. This ratio is further referred to as a percentage of radioiodine uptake in nodule (Figures 1–3). The formula for this relation is:

$$D = P \times 400\ Gy,$$

where:
D — absorbed dose
P — percentage of radioiodine uptake in nodules, expressed as a common fraction
400 Gy — maximum absorbed dose for autonomous toxic nodule(s), as agreed in the literature [8]

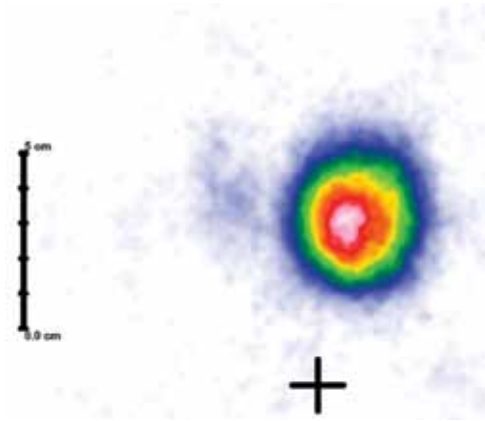

Figure 1. ATN scintigram with 100% radioiodine uptake in nodule (I degree of suppression of extranodular tissue). Calculated absorbed dose used in Marinelli's formula is: D = 400 Gy x 100% → 400 Gy

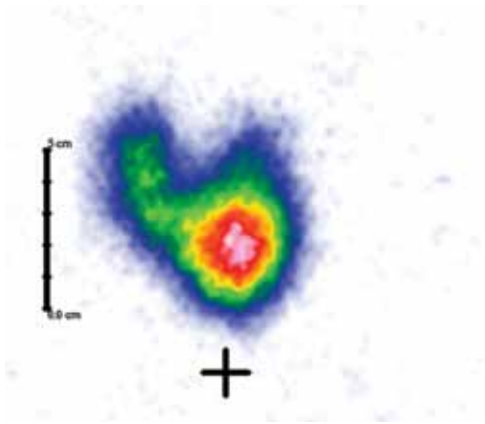

Figure 2. ATN scintigram with 75% radioiodine uptake in nodule (II degree of suppression of extranodular tissue. Calculated absorbed dose used in Marinelli's formula is: D = 400 Gy x 75% → 280 Gy

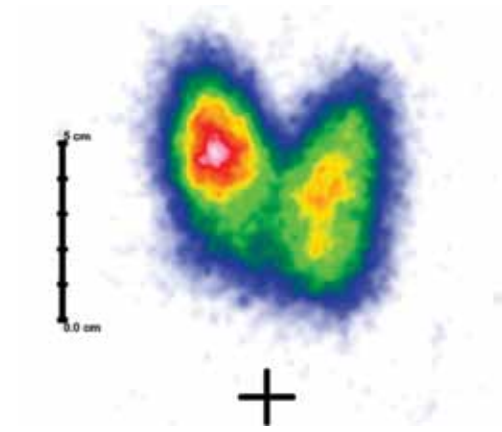

Figure 3. ATN scintigram with 50% radioiodine uptake in nodule (III degree of suppression of extranodular tissue). Calculated absorbed dose used in Marinelli's formula is: D = 400 Gy x 50% → 200 Gy

The volume of the gland assessed by USG was calculated using the usual formula for the volume of a spheroid [9]:

Table 1. General profile of 4140 patients with toxic nodular goitre treated with ^{131}I

Diagnosis	Female		Male		Value p	Age (year) min–max	$\bar{X}$	Value p
	n	%	N	%				
ATN	1883	86	307	14	SI	20–80	59	< 0.05
TMG	1626	83	324	17		34–88	67	

ATN — autonomus toxic nodule; TMG — toxic multinodular goitre; SI — statistically insignificant

$$V = \frac{4\pi \times a \times b \times c}{3}$$

where:
a, b, c — size of thyroid lobes (length, width, thickness)

The calculated ^{131}I therapeutic activities were administered orally in the form of capsules. In Poland, the only available capsules are (MBq): 200, 280, 400, 600 and 800. If the activity calculated from the formula proved to be much higher than that available, and amounted to the maximum ambulatory dose, additional ^{131}I doses were not administered until after 6 months.

The patients underwent medical check-ups every 8 weeks within a year after ^{131}I administration. Additionally, 400 persons were randomly selected from the analysed group and, after 3 and 5 years following radioactive iodine administration, tested for fT_4, fT_3 and TSH blood levels in order to evaluate possible changes in the percentage of euthyroid, hypothyroid and hyperthyroid patients which may have occurred in the time interval.

Statistical analysis

All statistic analyses were performed using the software package Statistica 9 (Stat Soft, Kraków, Poland).

General comparison of the two (ATN, TMG) groups in terms of gender, euthyroidism, hypothyroidism and hyperthyroidism after 1, 3 and 5 years from the commencement of therapy was performed using the χ^2 test, whereas the Mann-Whitney test was used for comparison in terms of age.

In order to assess the proportion of euthyroid, hypothyroid and hyperthyroid patients depending on sex, age, thyroid gland volume, radioiodine effective half-life and uptake in nodule, the χ^2 test was employed separately for both groups.

Friedman's test was used to estimate the difference between fT_4, fT_3, TSH levels at 2 weeks before treatment and those observed in the subsequent months after ^{131}I administration.

Moreover, the logistic regression model was used to evaluate the degree to which independent variables (gland volume, T_{24}, $T_{eff.}$, radioiodine uptake in nodule) affected the likelihood of recovery (i.e. restoring euthyroidism). The influence of the same variables on the probability of hypothyroidism was assessed analogically.

Results

Table 1 presents a summary of the characteristics of the patients who were included in the sample, divided into subgroups based on type of hyperthyroidism, gender and age.

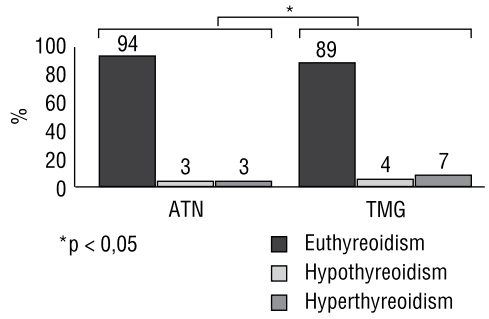

Figure 4. Comprehensive presentation of efficacy of ^{131}I therapy in TNG patients at 1 year after radioiodine administration

The table shows that the proportions of men and women were similar for both groups, but that the TMG patients were older ($p < 0.05$).

The assessment of the overall efficacy of treatment at one year after ^{131}I administration showed that a euthyroid status was achieved in 94%, hypothyroidism was observed in 3%, while persistence or recurrence of hyperthyroidism in 3% of patients with autonomous toxic nodules. In toxic multinodular goitre patients however the efficacy was slightly lower ($p < 0.05$) and amounted to 89%, 4%, 7% respectively. This outcome meant that further treatment was necessary only in 7% of TMG patients and in 3% of ATN cases (Figure 4).

As the time after radioiodine administration elapses, the percentage of hypothyroid patients increases. And thus, 3 years after ^{131}I administration the proportion of such patients in the ATN subgroup was 9%, while 5 years after the treatment it rose to 11%. In the TMG subgroup, the percentage was 11% and 16% respectively. This amounts to an average annual increase of 1.6% (ATN) and 2.4% (TMG) in hypothyroidism among the study sample (Figure 5).

Tables 2 and 3 show that neither gender nor age had a significant influence on the final outcome of hyperthyroidism treatment. The best therapeutic results, i.e. the highest euthyroidism rate and the lowest persistent hyperthyroidism rate, were obtained in patients with autonomous adenoma and with considerable suppression of healthy tissue surrounding the nodule.

It was also established that a correlation exists between therapeutic outcome and the effective half-life of ^{131}I. The highest efficacy was obtained in patients treated with radioiodine which had at least a 7-day effective half-life.

The lowest proportion of hypothyroidism and, at the same time, the lowest efficacy was observed in patients with large and very large glands (above 60 ml).

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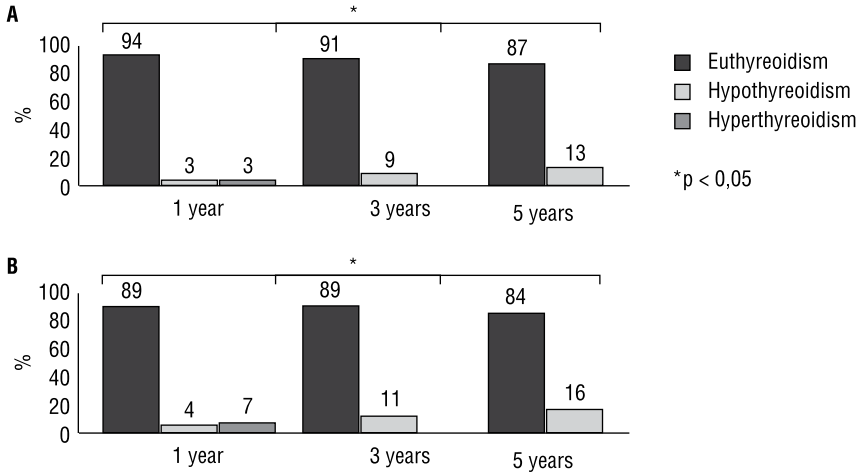

Figure 5. Efficacy dynamics of ^{131}I therapy in ATN(a) and TMG(b) over time

Table 2. Results of treatment of 2190 patients with ATN according to gender, age, volume of thyroid, effective ^{131}I half-life and radioiodine uptake in nodule

	Outcome			
	Euthyreoidism	Hypothyreoidism	Hyperthyreoidism	Value p
Gender				
Female	1802 (94%)	57 (3%)	58 (3%)	SI
Male	251 (92%)	11 (4%)	11 (4%)	
Age (year)				
< 40	285 (93%)	9 (3%)	13 (4%)	
40–60	403 (92%)	13 (3%)	22 (5%)	SI
> 60	1358 (94%)	43 (3%)	44 (3%)	
Thyroid volume [cm3]				
20–30	780 (89%)	87 (10%)	9 (1%)	
30–60	1040 (95%)	22 (2%)	33 (3%)	< 0.005
60–90	195 (89%)	1 (0.5%)	23 (10.5%)	
Effective half-life 131I -Teff. (day)				
5–7	197 (90%)	11 (5%)	11 (5%)	< 0.005
> 7	1833 (94%)	118 (5.5%)	20 (0.5%)	
Percentage of radioiodine uptake				
I° [80–100%]	532 (99%)	3 (0.5%)	3 (0.5%)	
II° [60–80%]	811 (92%)	40 (4.5%)	31 (3.5%)	< 0.005
III° [40–60%]	647 (84%)	77 (10%)	46 (6%)	

SI — statistically insignificant

The least beneficial effects were seen in multinodular goitres with a low rate of radioiodine uptake in nodules, relative to the uptake in the entire thyroid gland.

The logistic regression model was used to demonstrate that three factors have a significant impact on restoration of euthyroidism: percentage of radioiodine uptake in nodule, T_{24} and $T_{eff.}$ levels and the volume of the thyroid gland. To be more precise, the chances of achieving euthyroidism grow 3.6 times when radioiodine uptake in nodule is moved up one level, 2-fold when T_{24} and $T_{eff.}$ concentrations rise, and 1.5 times when the volume of the thyroid increases (Table 4). Whereas, hypothyroidism is most likely to develop when the rate of radioiodine uptake in nodules is low. With a 1% rise in the rate of radioiodine uptake in nodule, the probability of hypothyroidism occurring after treatment drops 0.31 times (Table 5).

The primary objective of radioiodine therapy is to eliminate hyperthyroidism, but what is significant for patients is the quickness of therapeutic effect. Figures 6, 7 and 8 illustrate the dynamics of change in mean concentrations of TSH, fT_3 and fT_4 after treatment with ^{131}I.

Both groups revealed a statistically significant decrease ($p < 0.001$) in fT_3 and fT_4 blood levels as early as approximately two months after radioiodine administration. Moreover, the concentration of these hormones continued to remain within normal range throughout the studied period. It should be emphasised that TSH serum values reached normal levels much later than those of fT_3 and fT_4, i.e. after 4 months in the case of solitary nodules and after 7 months in the case of multinodular goitres.

Table 3. Results of treatment of 2190 patients with TMG according to gender, age volume of thyroid, effective ^{131}I half-life and radioiodine uptake in nodule

	Outcome			
	Euthyreoidism	Hypothyreoidism	Hiperthyreoidism	Value p
Gender				
Female	3297 (91%)	108 (3%)	218 (6%)	SI
Male	465 (90%)	21 (4%)	31 (6%)	
Age (year)				
< 40	175 (90%)	8 (4%)	12 (6%)	SI
40–60	210 (90%)	10 (4%)	14 (6%)	
> 60	1424 (91%)	47 (3%)	94 (5%)	
Thyroid volume [cm3]				
20–30	201 (86%)	28 (12%)	5 (2%)	< 0.005
30–60	1100 (94%)	35 (3%)	35 (3%)	
60–90	486 (89%)	3 (0.5%)	57 (10.5%)	
Effective half-life I-131-Teff. (day)				
5–7	210 (90%)	12 (5%)	12 (5%)	< 0.005
> 7	1596 (93%)	103 (6%)	17 (1%)	
Percentage of radioiodine uptake				
I° [80–100%]	213 (98%)	2 (1%)	2(1%)	< 0.005
II° [60–80%]	562 (91%)	31 (5%)	25(4%)	
III° [40–60%]	892 (80%)	134 (12%)	89 (8%)	

SI — statistically insignificant

Table 4. Evaluation of the influence of particular factors (through calculation of adjusted odds ratio) on achieving euthyroidism in patients with TMG and ATN after one-year treatment

	AOR	95% CI	Value p
Thyroid volume	1.5	1.19–2.2	0.005
T24	1.03	1.23–2.47	0.002
Teff.	1.8	1.71–2.56	< 0.001
Percentage of radioiodine uptake	3.6	2.88–4.02	< 0.001

AOR — adjusted odds ratio

Table 5. Evaluation of the influence of particular factors (through calculation of adjusted odds ratio) on achieving hypothyroidism in patients with TMG and ATN after one-year treatment

	AOR	95% CI	Value p
Thyroid volume	0.4	0.25–0.5	0.005
T24	0.98	0.76–0.99	0.002
Teff.	0.87	0.74–0.94	< 0.001
Percentage of radioiodine uptake	0.31	0.2–0.39	< 0.001

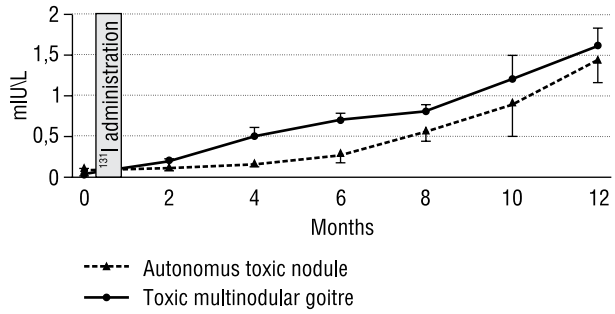

Figure 6. Changes in mean concentrations of TSH in studied patients within 12 months after ^{131}I administration

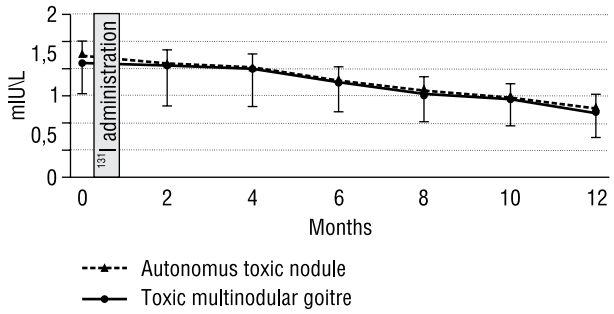

Figure 7. Changes in mean concentrations of fT_3 in studied patients within12 months after ^{131}I administration

Discussion

The obtained results indicate that the efficacy of ^{131}I treatment for hyperthyroidism in both solitary nodules and multinodular goitres is slightly higher in our Department than in other European institutions of the same type [10–13]. The proportion of patients with autonomous solitary nodules and multinodular goitres who were cured of hyperthyroidism within a year of starting therapy amounted to 94% and 89%, respectively, and remained as high as 80–90% throughout the five-year period following therapy. It seems that the

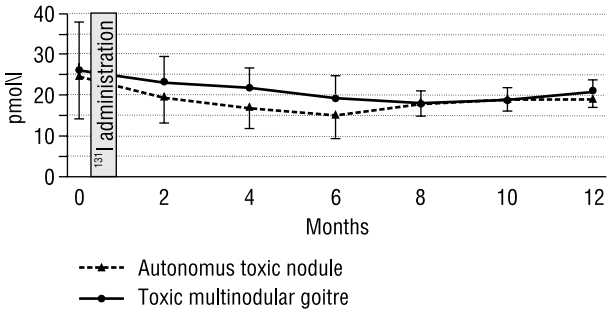

Figure 8. Changes in mean concentrations of fT_4 in studied patients within 12 months after ^{131}I administration

high rate of successful treatment of hyperthyroidism is a result of the clinical protocol designed in our Department.

The overriding objective of our standards of treatment for hyperthyroidism is to obtain the highest possible proportion of euthyroid patients with the fewest possible cases of hypo- or hyperthyroidism. This approach is somewhat different from that employed by other European authors, particularly British ones, for whom the primary goal of treatment is the elimination of hyperthyroidism (achieving either euthyroidism or hypothyroidism), the ratio of euthyroid to hypothyroid glands notwithstanding. For this reason, many studies reveal a fairly high percentage of hypothyroid patients — 15–25% after radioiodine therapy [14–16]. Our results show that the proportion of hypothyroidism in both types of goitre does not exceed 5% a year after therapy and 16% five years after therapy. The reason for the low percentage of post-therapy hypothyroidism in our Department is that we follow certain basic principles.

First and foremost, we take steps to prepare patients for the ^{131}I treatment in such a way that after the radioiodine capsule is ingested, the radiation energy is absorbed entirely, or primarily, by autonomous nodules.

We regard achieving the lowest possible TSH serum value as an essential part of patient preparation. Our Department treats only patients with TSH $<$ 0.1 IU/ml, which minimises iodine uptake and potential radiation-induced damage of the tissue surrounding the nodules [2]. The prerequisite of low TSH is frequently overlooked in other studies. What seems to further confirm this observation is the fact that those studies recommend discontinuation of antithyroid drugs merely days before the planned administration of radioiodine. As is well known, antithyroid drugs medications first of all inhibit the function of autonomous thyroid nodules and, as a consequence, enhance the action of the pituitary gland, which results in elevated TSH secretion thereby stimulating radioiodine uptake in normal tissue and leads to needless damage or destruction. That is why the outcomes presented in the mentioned studies are relatively worse than ours. Namely, they report a higher percentage of hypothyroid patients, amounting even to 45% at one year after radioiodine therapy in our Department, hypothyroidism was observed in 3% of ATN patients and 4% of TMG patients.

Proper qualification of patients with severe hyperthyroid symptoms should involve bringing the levels of the thyroid hormones (thyroxine and triiodothyronine) within the normal range. For this reason, some cases require preliminary but short-term (2–3 days) treatment with antithyroid drugs in order to lower the concentrations of fT_4 and fT_3 in serum and in the thyroid gland itself, but without increasing the TSH blood level. With this condition fulfilled, there is a lower risk of early, transient exacerbation of hyperthyroidism caused by an increased release of thyroid gland hormones from radioactively damaged thyreocytes into the blood stream [2].

When qualifying patients for treatment, it is indispensable that the scintigraphy of the thyroid gland is performed, as well as iodine uptake tests, the results of which can be used for calculating the effective half-life for Marinelli's formula [20]. This kind of diagnostic allows precise imaging of the gland, as well as a quantitative assessment of its functioning. It also enables the physician to calculate the extent to which iodine uptake is prevented in the tissue adjacent to the nodules. The information is essential for establishing the target thyroid absorbed radiation dose, i.e. the basic component of the modified Marinelli formula used for calculating the correct therapeutic activity of capsule. It was assumed that, given a rising proportion of radioiodine uptake in nodules in relation to the uptake in the entire gland (or, in other words, increasing suppression of surrounding tissue), the thyroid absorbed radiation dose should be proportionately higher. The above premise is based on the knowledge of the physical properties of radiation and the fundamental principles concerning the interaction of radiation with matter. Assuming that the medium range of β radiation emitted by ^{131}I in tissue is as low as 0.4 mm, then with fully suppressed normal tissue (I degree of suppression in our study) the entire radiation dose is bound to be taken up by the nodule. Therefore, only the nodule is destroyed, possibly with only a small margin of surrounding tissue [1]. The maximum absorbed dose adopted in our Department is 400 Gy for both autonomous and multinodular goitre, which is a commonly accepted value [8, 21, 22]. In those patients whose normal tissue adjacent to nodules is not fully suppressed (II and III degree in the Department), we used appropriately lower absorbed doses. The above findings seem to be corroborated by the fact that the greatest proportion of euthyroidism was observed in patients with the 1st degree suppression of normal tissue, both in the case of solitary and multinodular goitres. Therefore, Okosieme et al.'s claim that scintigraphy of the thyroid gland which images the distribution of radioiodine in the thyroid tissue does not have any bearing on the outcome of treatment seems to stem from inadequate understanding of the significance of radioisotopic diagnostic investigation for radioiodine therapy of thyroid disorders [3].

The evaluation of the effective half-life and iodine uptake in the thyroid is also crucial because the therapeutic activity of a given absorbed dose is inversely proportional to the values of these parameters (as both of them are in the denominator of the modified Marinelli formula). In other words, when the values of iodine uptake and effective half-life drop, the therapeutic activity of ^{131}I grows. To avoid exceeding national limits for therapeutic activity (800 MBq), we assumed that the lower threshold for iodine uptake in radioiodine therapy patients is 20%, since below this value therapeutic activities calculated by the Marinelli formula — even for medium-sized glands — were frequently higher than 800 MBq [23].

The effective half-life of radioiodine depends on its biological half-life. It is usually the case that the less acute hyperthyroidism was before treatment, the longer the biological half-life of radioiodine. Thus the values of thyroxine and triiodothyronine in patients who are qualified for treatment in our Department are usually only slightly above the norm. In both analysed subgroups, $T_{eff.}$ va-

lues were not lower than 5 days. Having analysed the above data, and having considered the work of such researchers as Gupta and Abos, who use fixed therapeutic doses and do not perform iodine uptake tests in their patients, it can be concluded that one of the reasons for lower treatment efficacy (78% of euthyroidism, 90% in our institution) in patients treated in this way is the fact that the target absorbed doses are not correlated with the iodine uptake capacity, iodine effective half-life in the thyroid or the volume of the gland [17]. Therefore, in the case of post-therapy hypothyroidism, the thyroid absorbed dose was probably too high, while in hyperthyroid patients it might have been too low.

Moreover, when analysing the results we noticed that, contrary to expectations, moderate enlargement of the thyroid gland (i.e. by 30–60 ml) does not adversely affect the efficacy of radiotherapy, but even enhances it (Table 4). This can be explained by the fact that, given mild thyroid enlargement after radiotherapy, the amount of glandular tissue damaged by the first dose of ^{131}I is proportionately greater, which, to a certain extent, prevents hypothyroidism and increases the efficacy of toxic goiter treatment.

Conclusions

Hyperthyroid patients with nodular goitres qualified for radioiodine therapy should have the lowest possible TSH blood levels in order to minimise the risk of post-radiation damage to the gland tissue surrounding the nodule.

Serum concentrations of fT_3 and fT_4 before treatment should be around the upper limit of normal so as to minimise possible exacerbation of transitory hyperthyroidism resulting from a sudden release of hormones from the damaged thyreocytes.

In each case, scintigraphy and iodine uptake tests should be carried out, and the percentage of radioiodine uptake in nodules established, relative to the uptake in the entire gland. Only the knowledge of this ratio makes it possible to determine the appropriate absorbed radiation dose.

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