Endokrynologia Polska
DOI: 10.5603/EP2015.0038
Tom/Volume 66; Numer/Number 4/2015
ISSN 0423–104X

Large multinodular goitre — outpatient radioiodine treatment

Wole guzowate olbrzymie — ambulatoryjne leczenie radiojodem

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Abstract

Introduction: 131-I treatment of nodular, especially nontoxic, goitre is still reserved mainly for elderly patients, whose numerous concomitant diseases disqualify them from surgery. Therapy often involves isolation and is available only in selected centres, which may be located far from some patients' places of residence, which is inconvenient for elderly people.
The aim of the study was to assess the effectiveness of outpatient fractionated 131-I treatment of patients with large nodular goitres, as well as to evaluate complications and the factors affecting treatment results.
Material and methods: The study included 35 patients with a large nodular goitre. Thyroid volume and treatment results were evaluated using US and CT neck examination.
Results: Mean thyroid volume prior to treatment was 104.36 mL (range 36.23–301.09 mL). An average administered 131-I activity was 1806 MBq (range 800–4000). The average reduction of goitre volume was 43.18% (range –17.23–89.66%). Final treatment results correlated with the thyroid size reduction obtained three months after treatment (r = 0.74; p = 0.001). Symptoms of transient hyperthyroidism were observed in 8.57% of patients, in 5.4% Graves disease was induced (including severe Graves' orbitopathy in 2.7%), and in 2.86% TRAb increase without development of hyperthyroidism was observed. The treatment results were not influenced by initial thyroid volume (r = –0.01; p = 0.95). An increase in thyroid volume during the treatment was reported in 20% of patients, with a mean increase of 22.3% (range 0.63–55.03%). Post-treatment hypothyroidism was diagnosed in 42.9% of patients. One patient was diagnosed with salivary gland damage.
Conclusions: Fractionated 131-I treatment of large nodular goitres is an effective method, the results of which are comparable to those obtained from the administration of one-time high doses of radioiodine. **(Endokrynol Pol 2015; 66 (4): 301–307)**

Key words: *radioiodine; radioiodine treatment; goitre; nontoxic goitre*

Streszczenie

Wstęp: Leczenie 131-I wola guzowatego olbrzymiego, szczególnie obojętnego, nadal zarezerwowane jest głównie dla pacjentów w starszym wieku, z licznymi chorobami towarzyszącymi dyskwalifikującymi ich z leczenia zabiegowego. Terapia, szczególnie w przypadku dużych rozmiarów wola wiąże się z izolacją po podaniu 131-I, a leczenie jest możliwe tylko w wybranych ośrodkach często oddalonych od miejsca zamieszkania, co jest utrudnieniem dla osób starszych.
Celem pracy była ocena skuteczności leczenia wola olbrzymiego 131-I w warunkach ambulatoryjnych dawkami frakcjonowanymi z analizą czynników wpływających na efekt terapii oraz oceną jej powikłań.
Materiały i metody: Analizą objęto 35 osób z wolem guzowatym olbrzymim. Ocenę objętości tarczycy i efektów leczenia wykonano z użyciem badań USG oraz CT szyi.
Wyniki: Średnia objętość wola przed leczeniem wynosiła 104,36 mL (zakres 36,23–301,09), a średnia podana aktywność 131-I to 1806 MBq (zakres 800–4000). Uzyskano redukcję objętości wola średnio o 43,18% (zakres –17,23–89,66%). Ostateczny efekt leczenia korelował z poziomem redukcji uzyskanym po 3 miesiącach leczenia (r = 0,74; p = 0,0010). Efekt leczenia nie zależał od wyjściowej wielkości wola (r = –0,01; p = 0,95). Objawy przejściowej nadczynności tarczycy obserwowano u 8,57% leczonych, u 5,4% wyindukowano chorobę Gravesa-Basedowa (u 2,7% ciężką orbitopatię) u 2,86% zaobserwowano wzrost miana przeciwciał przeciw receptorowi TSH bez objawów nadczynności tarczycy. Przejściowo powiększenie tarczycy w trakcie leczenia obserwowano u 20% leczonych, a objętość gruczołu wzrosła średnio o 22,3% (zakres 0,63–55,03). Niedoczynność tarczycy po zakończeniu leczenia stwierdzono u 42,9% pacjentów. W jednym przypadku obserwowano, nieopisywane wcześniej po stosowaniu małych dawek 131-I, popromienne uszkodzenie ślinianek.
Wnioski: Leczenie wola guzowatego olbrzymiego frakcjonowanymi dawkami 131-I jest leczeniem skutecznym, o efektach porównywalnych do stosowania dużych jednorazowych dawek radiojodu. **(Endokrynol Pol 2015; 66 (4): 301–307)**

Słowa kluczowe: *radiojod; jod radioaktywny; leczenie radiojodem; wole obojętne; wole olbrzymie*

This work was supported by the National Science Centre (NCN) from funds for science in 2009-2013 as research project number N N402 477137.

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Introduction

Over the last two decades radioiodine treatment of toxic and nontoxic nodular goitres has gained considerable popularity. However, surgery still remains the preferred method. In toxic goitre one of the options is antithyroid drug treatment. Nevertheless, it cannot be used permanently due to its negative impact on the thyroid volume, causing further goitre growth [1, 2]. 131-I treatment, especially in nontoxic goitre, has thus far been reserved mainly for elderly patients, whose numerous concomitant diseases disqualify them from surgery [3, 4]. Without hyperthyroidism-related symptoms, patients with long-standing nontoxic nodular goitres and those on antithyroid drug therapy are not willing to undergo any other treatment, even relatively non-invasive 131-I administration, especially when it involves post-treatment isolation. The administration of rhTSH shortens the hospitalisation period, yet in many countries no reimbursement is given for rhTSH nodular goitre treatment [5, 6]. Moreover, this method is available only in selected centres that offer hospitalisation. The centres are often located a considerable distance from elderly patients' place of residence, which causes great inconvenience to them.

The aim of the study was to assess the effectiveness of outpatient fractionated 131-I treatment of patients with large nodular goitres, with evaluation of the treatment complications and the factors affecting treatment results.

Material and methods

The study included 37 patients with nodular goitres (25 euthyroid, 10 with subclinical hyperthyroidism), who did not give their consent to surgical treatment, were disqualified from surgery due to their concomitant diseases, or were diagnosed with post-surgical goitre regrowth. The study was conducted in the Department of Endocrinology and Internal Medicine and the Outpatient Endocrinology Clinic of the Medical University of Gdansk (MUG) between 2009 and 2012. The treatment was conducted in the Department of Nuclear Medicine of the same University. The scheme of the study and treatment was approved by the MUG Independent Bioethics Commission. During the study, two patients were excluded from evaluation after they were diagnosed with radioiodine-induced Graves disease, and in one of them symptoms of severe Graves orbitopathy were observed. Prior to the treatment, the patient did not show any symptoms of Graves hyperthyroidism, she had negative TRAb, and she was a smoker.

Table I. *Basic characteristics of the study group*
Tabela I. *Charakterystyka podstawowa badanej grupy*

Study group N = 35		
Age (years)	median (range)	65.63 (49.00–84.00)
Duration of symptoms (years)	median (range)	15.83 (1.00–50.00)
L-T4 dosage [μg/day]	median (range)	9.23 (0–75.0)
Previous L-T4 therapy	N (%)	6 (17.1%)
Previous strumectomy	N (%)	6 (17.1%)
Family history	N (%)	13 (37.1%)
Smokers	N (%)	17 (48.6%)
Pressure on or dislocation of trachea	N (%)	21 (60.0%)
Substernal goitre	N (%)	17 (48.6%)
Euthyroid	N (%)	25 (71.4%)

The final group consisted of 35 patients (33 women, 2 men) with large nodular goitre, who were administered 131-I. The characteristics of the patient group is shown in Table I.

131-I treatment

Radioiodine was administered orally, with an activity of 800 MBq per capsule. The radioiodine activity was determined using modified Marinelli's formula [7]:

$$A = (C \times V \times 100)/U$$

A — administered 131-I activity [MBq]; C — constant, usually between 3 and 5 [MBq/g of thyroid tissue], in the study the assumed value was 4.44 MBq/g; V — thyroid mass [g] (based on US study); U — thyroid 131-I uptake (RAIU) 24 hours after 131-I administration (%).

The calculated 131-I activity was fractionated, with a single administered activity of 800 MBq. In the case of calculated activities < 800 MBq a full dose (800 MBq) was administered. In the case of calculated activities > 800 MBq, 800 MBq was administered in repeated doses. In order to avoid the "thyroid stunning" effect, consecutive radioiodine doses were administered every three months.

Imaging evaluation

US examinations were performed in all patients prior to treatment, as well as 3, 6, and 12 months afterwards. All measurements were taken by the same radiologist using a SIEMENS S2000 (Siemens, Erlangen, Germany) with a 18L6 HD linear transducer (5.5–18 MHz) and 6C2 convex transducer 6C2 (2–6 MHz).

The US estimation of thyroid volume was based on the ellipsoid formula, adding the volumes of both lobes measured using the following formula [8]:

$$V = H \cdot W \cdot D \cdot \frac{\pi}{6}$$

where:

H — height [cm], W — width [cm], D — depth [cm]

All patients with suspicion of malignancy in US additionally underwent FNAB (fine needle aspiration biopsy).

CT thyroid assessment without contrast enhancement was conducted both before and 12 months after the treatment. All examinations were performed with the same GE LightSpeed 32-Slice CT Scanner (GE Healthcare Technologies, Wisconsin, USA) by using the spiral technique. Images were taken in sequences every 5 mm. Thyroid volume was calculated planimetrically using Siemens SYNGO.VIA software.

Evaluation of hormonal function of the gland

Serum concentration of TSH (reference values: 0.35–4.94 μIU/mL), fT4 (reference values: 9.01–19.05 pmol/L), and fT3 (reference values: 2.63–5.7 pmol/L) as well as anti-TPO and anti-TG antibodies (negative < 150 IU/mL and < 4.11 IU/mL, respectively) were measured by immunoassay using an ARCHITECT analyser (Abbott Laboratories, USA). Thyrotropin receptor antibodies (TRAb) antibodies (negative < 1.8 IU/L) were measured by ELISA assay using a EUROIMMUN analyser.

Statistical analysis

Statistical calculations were performed using the StatSoft, Inc. (2011) STATISTICA data analysis software system, version 10.0. (www.statsoft.com) and MS Excel spread sheets. The significance of differences between the two groups was evaluated using tests of statistical significance: Student's *t*-test or the Mann-Whitney U test. The significance of differences between more than two groups was tested using the F-test (ANOVA) or Kruskall-Wallis one-way analysis of variance. In the case of statistically significant differences between the groups, post hoc tests were used (the Tukey range test for the F-test and the Dunn test for Kruskal-Wallis test). In the case of two related variables model, the Student's *t*-test or Wilcoxon signed-rank test were used. The significance of differences between more than two variables in the related variables model was determined with repeated measures analysis of variance or the Friedman test.

In order to determine the interdependence, strength, and direction between the variables, a correlation analysis was used to calculate Pearson correlation coefficients. In all calculations the assumed level of significance was set at $\alpha = 0.05$.

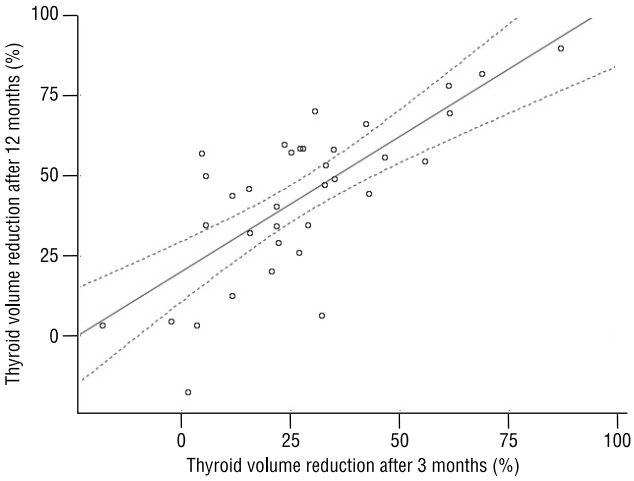

Figure 1. *Correlation between reduction level 3 months after the treatment and total reduction level*

Rycina 1. *Korelacja stopnia redukcji objętości tarczycy po 3 miesiącach po leczeniu z całkowitym stopniem redukcji*

Results

Mean thyroid volume in US was 104.36 mL (range: 36.23–301.09 ml, median: 92.04 mL), and in CT 112.09 mL (range: 35.75–315.97 ml, median: 91.07 mL). No statistically significant difference was observed between US and CT volumetric evaluation either before the treatment (H = 1.74; p = 0.6291) or afterwards (H = 1.09; p = 0.7786). Additionally, using Bland-Atman plots, we assessed previously that in volumetric thyroid measurements US is a comparable method to CT; therefore, in this study US examination was established as a reference method [9].

The lowest total activity administered was 800 MBq and 4000 MBq was the highest. On average, 1806 MBq was administered. All patients were administered activities higher or equal to the calculated activity. The mean absorbed activity calculated on the basis of goitre size, and iodine uptake by the thyroid was 6.16 MBq/g (range: 4.51–9.94 MBq/g of thyroid tissue).

Mean goitre size reduction reported in US examination was 43.18% (range: –17.23–89.66%, median: 47.02%). In only one patient an increase in thyroid volume was observed after the treatment. In absolute values, mean thyroid volume after the treatment was 58.66 mL (range: 10.82–203.32 mL, median: 53.20 mL) and differed significantly from the pre-treatment value (t = 7.50; p = 0.0001).

The evaluation of total goitre reduction with time proved to be the best treatment results achieved a year after the treatment. The volume reduction changed significantly with time (Friedman ANOVA: 30.40; p = 0.0001). The greatest decrease in goitre size (relative reduction) was observed during the first three months

after the treatment. The reduction of goitre size between 3 and 6 months after the treatment, similarly to the relative reduction between 6 and 12 months after the treatment, was significantly lower than the reduction reported during the first 3 months after the treatment (ANOVA F = 8.47; p = 0.0005).

The goitre reduction level obtained 3 months after the treatment correlates with the level obtained at the end of observation (correlation coefficient: 0.74; p = 0.0010) (Fig. 1).

Factors modifying the treatment efficacy were not determined. There was no correlation between goitre reduction and age (r = –0.28; p = 0.1049), L-T4 dosage (r = 0.19; p = 0.2859), pretreatment TSH level (r = 0.09; p = 0.6030), Iodine uptake (r = –0.13 p = 0.4587), total administered 131-I activity (r = 0.14; p = 0.4130), absorbed 131-I activity (r = 0.14; p = 0.3965), goitre duration (r = –0.27 p = 0.1170), and goitre size before treatment (r = –0.01; p = 0.9542). No differences in level of thyroid reduction were observed between patients with positive and negative anti-TPO and anti-TG antibodies (t = 0.44; p = 0.6625 and t = 0.07; p = 0.9423, respectively).

Prior to treatment 25 patients (71.4%) were euthyroid and the remaining 10 (28.6%) were diagnosed with subclinical hyperthyroidism. After the treatment 20 patients (57.1%) remained euthyroid and 15 (42.9%) required L-T4 substitution due to hypothyroidism. Symptoms of transient hyperthyroidism were observed in 3 patients, and in 2 patients Graves disease was induced. The latter two were excluded from the study, yet initially they accounted for 5.4 % of the whole group.

In 2 patients thyroid enlargement was reported 3 months after the completed treatment, with their thyroids increased in volume by 18.42 % and 2.57 %, respectively. In both cases final goitre reduction was eventually observed. US examination during the treatment (between consecutive 131-I administrations) revealed an increased thyroid volume in 7 patients. On average, thyroid increased by 22.3% (range 0.63–55.03%; median 19.58%). In none of the patients increased dyspnoea, stridor, or pressure sensation were observed.

Post-treatment hypothyroidism was reported in 15 patients (42.9%). Patients from this group had initially higher TSH and lower fT4 values than those who remained euthyroid after the treatment (U = 28.00; p = 0.0001 and t = –3.84; p = 0.0005). No correlation was observed between anti-TPO, anti-TG, and TRAb antibodies and the risk of post-treatment hypothyroidism. The evaluation of the other evaluated parameters did not reveal a higher risk of hypothyroidism. There was no difference in goitre size (U = 93.00; p = 0.0597), age (U = 100.00; p = 0.0989), iodine uptake (U = 83.00; p = 0.1297), total administered 131-I activity (t = –0.68; p = 0.4982), goitre duration (U = 122.50; p = 0.3681), and absorbed 131-I activity (t = 1.74; p = 0.0919) between euthyroid and hypothyroid groups.

The number of anti-TPO and anti-TG positive patients significantly increased after treatment (anti-TPO 12 [34.29%] before *vs.* 15 [42.86%] after treatment p=0.0001, anti-TG 14 [40.00%] before *vs.* 24 [68.57%] after treatment p = 0.001). Before treatment, 6 patients (17.14%) had elevated TRAb without clinical and laboratory features of hyperthyroidism. After treatment only 1 person (3.03%), different from those above, presented positive TRAb results. The low percentage of positive results does not allow us to discuss the significance of these changes.

Discussion

Surgery still remains the gold standard of nodular, especially nontoxic, goitre treatment. It is undoubtedly the method of choice for young patients without any concomitant diseases. In patients with a toxic goitre antithyroid drug treatment resolves metabolic problems, but still does not influence thyroid reduction; on the contrary it stimulates further goitre growth [1]. Apart from those patients who give their consent to surgery and do not have any contraindications, there are also those who need treatment but definitely should not be operated on. This group consists of elderly patients with numerous contraindications and those unwilling to give their consent to surgery. Assuming low goitre growth ratio (on average 10–20% per year), in patients with small goitre and in advanced age, observation and monitoring or, in some cases, antithyroid drug treatment may be sufficient [10]. The need for more invasive therapy starts when cosmetic aspects and symptoms including the compression of the trachea or other structures within the neck appear [11]. In this characterised group the method of choice, in other words the method when there is no alternative because surgical treatment is impossible, remains radioiodine treatment.

Radioiodine treatment allows a goitre reduction of 40–60% within 1–2 years after isotope administration [3, 12–14]. The range of thyroid volume reduction is comparable regardless of whether it is diffuse toxic [15], autonomous solitary toxic thyroid adenoma [16], or diffuse nontoxic [17, 18] and nontoxic multinodular goitre [2]. In EU countries (the United Kingdom, France, Belgium, the Netherlands, and Poland) the maximum radioiodine activity allowed in outpatient treatment is 370–800 MBq [19]. The used 131-I activity is determined by the 131-I uptake and goitre volume. Our study group consisted of elderly patients with long-standing, usually very large goitres, who required the administration of high radioiodine activities. In order to avoid inconvenient isolation and hospitalisation, a high dose of 131-I was fractionated to

activities allowed in outpatient treatment. The administration of lower 131-I activities enables the therapy to be conducted in every centre that uses isotopes. It allows elderly patients to avoid hospital treatment that is available only in selected centres, often located a considerable distance from their place of residence. It seems to be of great importance, especially as the patients often suffer from numerous concomitant diseases, which somehow immobilise them.

In our study, using repeated 131-I doses in outpatient treatment of large nodular goitre, we reported a goitre reduction of approximately 43% a year after the treatment. The outcome did not differ from the results of the studies in which high, single doses were used [3, 14, 20–22].

The results improved with time and were highest a year after the treatment. Studies with a longer observation period report increased goitre reduction in time from 38% during the first year to 44% after 2 years of observation and from 34% to 55%, respectively [12, 22]. The authors of the studies with a longer follow-up report as much as a 71.9 % reduction [21]. Verelst et al. observed the best results after less than a year of treatment with a nearly maximum effect 24 to 30 months after the therapy [23]. Similarly to what Nygaard et al. reported in toxic goitre, we observed the greatest decrease in goitre volume within the first 3 months after the treatment, with a subsequent decrease in reduction degree [2].

An interrelationship never described before but observed in our study is the correlation between the final treatment results and the preliminary results obtained 3 months after the treatment. We found that the results obtained a short time after the treatment can provide a reliable bias for predicting final results. This information may be of great clinical importance, when making a decision regarding the continuation of treatment and the administration of the next 131-I dose.

The dependence of treatment results on the other parameters still remains an unresolved issue. According to Le Moli et al., treatment results depend on the administered 131-I activity [24]. In our study, however, we did not observe any correlation between the administered 131-I activity and the treatment results. Similarly to us, despite using a complicated algorithm to calculate 131-I activity, Bonnema et al. did not show any relation between the administered 131-I activity and the obtained results [20]. Jarlov et al. questioned the sense of precise 131-I activity calculation. Comparing the effects of 131-I toxic goitre treatment in the administration of a fixed dose, based on gland size assessment by palpation only, to the precise calculation of the activity based on the morphology of the gland, iodine uptake, and US estimation of goitre size, they did not observe any differences [25]. Analysing the interdependence between the initial goitre size and treatment results, we did not find any correlation. Based on the publications by Danish researchers, we expected treatment results to decrease with the increase in initial goitre volume [22, 24]. Le Moli et al. showed a correlation of treatment results with goitre duration and patient's age as indirect factors determining the goitre size [24]. In our study, we neither observed a correlation between thyroid volume and treatment results nor a correlation between the treatment results and duration of the disease or the age of the patients. Moreover, we did not find a correlation between the L-T4 dosage administered before the treatment, the hormonal function before surgery, iodine uptake, smoking, positive anti-TG, and anti-TPO antibodies and thyroid volume reduction. Given the obtained results, based on our work, the reason for the observed discrepancies in thyroid volume reduction, ranging from a 17.23% goitre growth to an 89.66% goitre reduction, remains unexplained.

Similarly to Le Moli et al., we did not observe any longer the cases of subclinical hyperthyroidism after the treatment [24]. In the study, after 131-I treatment 42.9% of the patients required L-T4 substitution, including those with initial post-strumectomy hypothyroidism. Considering TSH as a goitre growth factor, we initiated L-T4 treatment in all patients whose TSH level exceeded 4 μIU/mL, as did Wesche et al. [22]. All patients submitted to L-T4 therapy were classified as hypothyroid, with a possibly overestimated percentage of hypothyroidism cases reported in the study. Post-treatment hypothyroidism risk factors were not determined. We established that the administered 131-I activity did not affect the risk of hypothyroidism, and neither did the thyroid volume, patient's age, iodine uptake, goitre duration, or anti-TPO and anti-TG antibodies. We observed that patients with hypothyroidism after the treatment initially had higher TSH and lower fT4 levels. These results confirm the conclusions drawn by Wesche et al. that subclinical hyperthyroidism is a protective factor against hypothyroidism after 131-I treatment [26].

An early complication following 131-I treatment is transient thyrotoxicosis resulting from thyroid cell damage. In the available literature, the incidence of this complication is estimated at between 0% and 28% [13, 17, 22, 24]. In our study, 8.57% of the patients were diagnosed with hyperthyroidism caused by transient, self-limiting form of thyroiditis. This complication had no clinical implications. However, such risk cannot be excluded, especially in patients with heart rhythm disturbances and heart failure, in whom even transient thyrotoxicosis may significantly deteriorate their condition. In 2 patients the treatment induced autoimmune thyroiditis. In the whole group, the risk of this complication was estimated to be 5.41%. Nygaard et al. presented

similar results (5%) of Graves-like hyperthyroidism incidence after the 131-I treatment in a retrospective study of 191 patients with a nontoxic goitre [27]. Apart from ours, to the authors' best knowledge, there is only one case study that describes GO induction after 131-I treatment of nontoxic goitre [28]. Clinically, at the time of 131-I administration the patient did not show any symptoms of Graves hyperthyroidism or GO. She was a smoker, which theoretically increased the risk of GO [29]. However, even in 131-I treatment of Graves' disease severe GO progression, especially in patients without initial GO symptoms, is rare [30]. In one patient after treatment we observed an increase of TRAb, while a reduction of these antibodies in 6 other patients was noticed. Despite the described TRAb increase following radioiodine therapy for Graves disease [31, 32] and in thyroid cancers [33, 34], autonomous thyroid disease [35], as well as nontoxic goitre [36], we did not obtain such results. Long observation time, assessment at only two time points, or advanced patient's age may be of importance for these results.

It should be taken into consideration that 131-I administration, especially in case of very large or substernal goitres, entails a risk of thyroid enlargement. Numerous authors encourage the use of this method, but tend to undermine the significance of the problem. A week after 131-I administration, Bonnema et al. observed thyroid enlargement in 9 out of 23 patients, with increased thyroid volume of more than 5% of the initial value in 4 cases [20]. Following the nontoxic goitre 131-I treatment, thyroid enlargement of more than 5% was described by Nygaard et al. in 9 out of 130 patients, with the median enlargement being 23% (11–60%) [2]. In our work, thyroid enlargement was observed in 2 patients (5.71%) 3 months after the treatment, but it did not exceed 20% of the initial volume. During the treatment, thyroid enlargement by a maximum of 55% was reported in 7 patients (20%). In none of the patients increased dyspnoea, stridor, or pressure sensation in the neck were observed. Eventually, all patients were reported to have their goitres decreased in size. The above results should not discourage 131-I administration, but rather encourage monitoring patients more frequently during and after the treatment.

A complication after low 131-I activity administration, to the best of our knowledge previously never reported, is radiation parotid gland damage. In our work this complication was observed in one case after the third 131-I administration. This patient had previously been suspected of Sjögren's syndrome but had never been fully diagnosed. In our opinion, previous salivary gland damage may increase the risk of radiation damage of the salivary gland even if the patient is administered low 131-I activities.

Conclusions

Fractionated 131-I treatment of large nodular goitres is safe, effective, and, what needs to be emphasised, convenient method of treatment for the patient. The efficacy of the therapy with a reduction of 43% will not differ from high, single-dose treatment. The therapy is a good alternative to surgery and may be successfully conducted by dose fractionation in every outpatient centre that uses radioisotopes for therapy.

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