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Original Article

Fixed 30 mCi (1110 MBq) ^{131}I-iodine therapy in autonomously functioning nodules: Single toxic nodule as a predictive factor of success

ABSTRACT

Aims: The aim of this study is to evaluate the efficacy of a fixed 30 mCi (1110 MBq) ^{131}I-iodine dose for the treatment of hyperthyroidism due to uninodular or multinodular toxic goiter and identify predictors of success. **Materials and Methods:** Fifty-nine patients diagnosed with nonautoimmune toxic goiter were treated with a fixed 30 mCi dose of ^{131}I-iodine and were followed at a tertiary service between 2000 and 2016. The therapy was considered successful if the patient reached euthyroidism or hypothyroidism without needing an extra ^{131}I-iodine dose or antithyroid drugs for at least 1 year after the radioiodine therapy (RIT). **Results:** Patients with a single toxic nodule were younger at diagnosis (52 vs. 63 years; $P = 0.007$), presented a shorter disease duration until RIT (2 vs. 3.5 years; $P = 0.007$), smaller total thyroid volume (20 vs. 82 cm^3; $P = 0.044$), and lower pre-RIT thyroid uptake ($P = 0.043$) than patients with multinodular goiter. No significant difference was seen with antithyroid drug use, thyroid-stimulating hormone and free thyroxine level, and follow-up after RIT. After RIT, 47 patients (79.66%) met the success criteria, and 12 (20.33%) remained hyperthyroid. Among the success group, 32 (68.08%) reached euthyroidism, while 31.92% developed hypothyroidism after 1 year. Patients with single toxic nodules who achieved success after RIT presented smaller nodules (2.8 vs. 5.75 cm; $P = 0.043$), while the pre-RIT thyroid uptake was higher among patients with multinodular toxic goiter who achieved success after RIT (5.5% vs. 1.5%; $P = 0.007$). A higher success rate was observed among patients with a single toxic nodule than those with a toxic multinodular goiter (92.3% vs. 55%; $P = 0.001$), and a single toxic nodule presentation was found to be an independent predictor of success ($P = 0.009$). **Conclusions:** The fixed 30 mCi ^{131}I-iodine dose was particularly effective in the group of patients with single autonomously functioning nodule rather than the group with multiple nodules. A single toxic nodule was an independent predictor of treatment success.

Keywords: Fixed ^{131}I-iodine dose, hyperthyroidism, radioiodine therapy

INTRODUCTION

Worldwide, toxic nodular goiter (TNG) is a common thyroid pathology entity, and it is associated with substantial morbidity. Treatment is based on ablation through thyroidectomy or radioactive iodine (^{131}I); however, antithyroid drugs are often used to control hyperthyroidism before the chosen therapy.[1-3] Thyroidectomy is indicated in the presence of bulky substernal goiters with compressive symptoms,[4] while radioiodine therapy (RIT) is especially recommended for elderly patients with high surgical risk and smaller goiters.[5] RIT is also a safe and low-cost option that has been used for over 60 years with high cure success rates and minimal side effects.[6,7] Hyperthyroidism control is the primary goal of RIT, whether it results in euthyroidism

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or hypothyroidism since untreated hyperthyroidism can be associated with a 20% increase in the mortality rate, as well as a higher frequency of arrhythmia and heart failure.[8-11] Functioning nodules show relative resistance to radioiodine action, thus requiring higher doses of ^{131}I-iodine than those administered to patients with Graves' disease. Nevertheless, there is no consensus on the optimal dose of ^{131}I-iodine when considering the therapeutic efficacy, incidence of hypothyroidism, nodule size, pretreatment thyroid uptake, and previous use of antithyroid drugs.[12] The superiority of any dose-adjusted individually using thyroid volume or other complex calculations compared with the use of a fixed-dose protocol is not well established. The calculated dose of ^{131}I aims to optimize therapeutic outcomes by providing the lowest radiation dose to the rest of the body and is used in many centers. In those cases, scintigraphy and iodide uptake tests, together with nodule iodine uptake, must be determined to estimate the dose to be delivered to the entire gland.[13,14] The use of a calculated dose approach increases the complexity and cost of the procedure. The fixed-dose administration simplifies protocols and results in considerable cost savings. Based on the literature, we have implemented a protocol in which a fixed dose of 30 mCi has been used for over 20 years to treat TNG.

This study aimed to evaluate the rate of success after RIT and identify factors related to outcomes of hyperthyroidism treatment with a single fixed 30 mCi (1110 MBq) I^{131}-iodine dose in patients with uninodular or multinodular toxic goiter.

MATERIALS AND METHODS

Study design

This is a retrospective study involving 59 patients with nonautoimmune hyperthyroidism due to TNG followed at the Thyroid Disease Unit at the Clinics Hospital of the University of Campinas between 2000 and 2016. All participants received a fixed dose of 30 mCi (1110 MBq) of ^{131}I-iodine as a therapeutic option after treatment with antithyroid drugs to control hyperthyroidism. The ethical committee approval for the study was obtained according to the Declaration of Helsinki, Human Research Ethics Committee in Lausanne, No 204/14. CAAE 20028813.4.0000.5404.

Clinical data collected were sex, age, age at diagnosis, age at RIT, disease duration, antithyroid drugs use (methimazole or propylthiouracil), and total thyroid volume estimated by ultrasound and thyroid uptake just before RIT, follow-up of the thyroid status after RIT (euthyroidism, hypothyroidism, or hyperthyroidism). Biochemical data collected were serum thyroid-stimulating hormone (TSH) (reference values RV 0.41–4.5 mUI/L), free thyroxine (FT4) (RV 0.9–1.8 m/dl), antithyroglobulin antibodies (TgAb) (RV <115 mUI/L), anti-thyroperoxidase antibodies (TPOAb) (RV <35 UI/mL), and thyroid-stimulating hormone receptor antibody (TRAb) (RV <1.58 UI/mL), all measured by electrochemiluminescence immunoassay. Hyperthyroidism was confirmed by elevated serum levels of FT4 and suppressed levels of serum TSH. Thyroid autoimmunity was excluded by serum TgAb, TPOAb, and TRAb.

All patients underwent thyroid scintigraphy with ^{99m}Tc-pertechnetate for uptake evaluation and cervical ultrasonography before the ablative treatment. They were treated with propylthiouracil or methimazole and referred to the Nuclear Medicine Division in euthyroid conditions or with mild elevated FT4 levels and TSH levels below the lower limit. All patients were instructed to stop taking propylthiouracil or methimazole three days before RIT. On the day following RIT, the previous antithyroid drug was reintroduced and gradually withdrawn according to thyroid function results. It is essential to state that the RIT was done in a setting that allows patients to receive up to 50 mCi (1850 MBq) in outpatient nuclear medicine clinics.

All patients were regularly followed every 3–4 months at the Thyroid Disease Unit. Thyroid function was assessed with TSH and FT4, and patients were clinically evaluated to search for changes in thyroid volume and consistency. Euthyroidism and hypothyroidism without the use of antithyroid drugs 1 year after RIT was considered a successful treatment. Treatment failure was determined as hyperthyroidism that could not be controlled without antithyroid medications. These were later submitted to a new RIT.

Exclusion criteria

Exclusion criteria were: patients using propranolol, corticosteroids, amiodarone, or exposed to iodinated contrasts up to 3 months before evaluation. Heart failure (class III or IV), severe liver disease, advanced chronic kidney disease (stage 4 or 5) or hemodialysis, any infection, and those severely ill.

Imaging evaluation

Scintigraphy and thyroid uptake of ^{99m}Tc-pertechnetate

The evaluation of thyroid uptake of ^{99m}Tc-pertechnetate was performed before RIT as previously standardized in our patient population.[15] Patients were instructed to follow a low-iodine diet intake and avoid iodine-rich personal hygiene products 15 days before RIT. Scintigraphy and thyroid uptake were performed 20 minutes after the intravenous injection of 10 mCi (370 MBq) of ^{99m}Tc-pertechnetate. Thyroid uptake

was calculated using the methodology previously described by Maisey *et al*.[16] and adapted for scintillation chambers.[17] According to the service standardization, reference values for the uptake of pertechnetate-^{99m}Tc are 0.35%–1.7%.[15]

Ultrasonography

Thyroid volume was assessed by an ultrasound performed at the radiology service before the RIT. The exam was acquired in a multiple linear frequency devices with a 10–12 transducer MHz for morphological analysis and 4.5–7 MHz for Doppler analysis. The thyroid volume was calculated by the ellipsoid method, in which the volume of each lobe was a product of the width, height, and depth measurements in centimeters multiplied by 0.52 as a correction factor.[18]

Statistical analysis

Descriptive analysis was made by providing measures of position and dispersion, median and interquartile range for continuous data, and frequencies and percentages for categorical variables. The Kolmogorov–Smirnov test assessed normality. The Chi-square or Fisher exact tests were used, when necessary, to verify association, or compare proportions. The Mann–Whitney U-test was used to compare continuous variables between both groups (hyperthyroid vs. hypothyroid and euthyroid patients). To identify associated factors to RIT success, we performed univariate and multivariate logistic regression analysis. Factors showing $P < 0.1$ in univariate analysis were included in the multivariate model, which was also adjusted by age. Results were considered significant if the $P < 0.05$. All calculations were done with the SPSS (IBM Inc.) version 20.0.

RESULTS

Comparative analysis of characteristics and outcome after radioiodine therapy between single and multiple toxic nodular goiters

Patients' demographic characteristics and outcomes after the radioiodine treatment are summarized in Table 1. Patients with a single toxic nodule were younger at diagnosis (52 vs. 63 years; $P = 0.007$), presented a shorter disease duration until RIT (2 vs. 3.5 years; $P = 0.007$), smaller total thyroid volume (20 vs. 82 cm^3; $P = 0.044$), and lower pre-RIT thyroid uptake ($P = 0.043$) when compared to patients with multinodular goiter. No significant difference was seen with antithyroid drugs use, TSH and FT4 level, and follow-up after RIT. The fixed 30 mCi ^{131}I-iodine dose was considered successful in 47 patients (79.66%) and a failure in 12 (20.33%) 1 year after RIT. Among patients classified as successful, 32 (68.08%) reached euthyroidism, and 31.92% progressed to hypothyroidism after 1 year. Patients with a single toxic nodule presented a rate of euthyroid, hypothyroidism, and hyperthyroid of 61.5%, 30.8%, and 7.7%, respectively. Regarding patients with toxic multinodular goiter, the rate of euthyroidism, hypothyroidism, and hyperthyroidism was 40%, 15%, and 45%, respectively. A higher success rate was observed among patients with a single toxic nodule than those with a toxic multinodular goiter (92.3% vs. 55%; $P = 0.001$). As expected, the single nodule groups presented a lower failure rate when compared to the multinodular group (7.7% vs. 45%; $P = 0.003$). There was no significant statistical difference in the proportion of success 1 year after RIT between patients with pre-RIT TSH <0.4 IU/mL versus TSH >0.4 IU/mL ($P = 0.31$).

Table 1: Comparative analysis of characteristics and outcome after radioiodine therapy between patients with toxic adenoma and toxic multinodular goiter

Variables	Uninodular (%)	Multinodular (%)	*P*
Sex			
Male	3 (7.7)	3 (15)	0.398
Female	36 (92.3)	17 (85)	
Age at diagnosis (years old)	52 (39-62)	63 (56-67)	0.007
Thyroid volume (cm^3)	20 (13-56)	82 (19-140)	0.044
Medication			
Methimazole	26 (74.3)	18 (94.7)	0.157
Propylthiouracil	5 (14.3)	1 (5.3)	
Disease duration up to RIT (years)	2.0 (1.0-4.0)	3.5 (2.0-10.75)	0.007
Pre-RIT assessment			
T4L (ng/dl)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.768
TSH (IU/mL)	0.0 (0.0-1.0)	0.0 (0.0-3.25)	0.261
Pre-RIT uptake (%)	2.0 (1.0-3.0)	2.0 (2.0-8.25)	0.043
Outcomes after RIT			
Success	36 (92.3)	11 (55)	0.001
Failure	3 (7.7)	9 (45)	
Hypothyroidism	12 (30.8)	3 (15)	0.003
Euthyroidism	24 (61.5)	8 (40)	
Hyperthyroidism	3 (7.7)	9 (45)	
Follow-up after RIT (months)	15 (4-36)	17 (7.75-24)	0.058
Success treatment regarding TSH pre-RIT (IU/mL)			
<0.4	22/24 (91.7)	6/12 (50)	0.310
>0.4	10/10 (100)	5/8 (62.5)	

Data are shown as frequency (%) or median (IQR). IQR: Interquartile range, RIT: Radioiodine therapy, TSH: Thyroid-stimulating hormone, T4: Thyroxine

Comparative analysis regarding the success of radioiodine therapy in single and multiple toxic nodular goiters

In the group of patients with single toxic nodules, those who achieved success (euthyroidism or hypothyroidism) after RIT presented smaller nodules than those who remained hyperthyroid after RIT (2.8 vs. 5.75 cm; $P = 0.043$). The pre-RIT thyroid uptake was higher among patients with multinodular toxic goiter who achieved success after RIT (5.5% vs. 1.5%; $P = 0.007$). No significant difference was found with pre-RIT TSH levels [Table 2].

Table 2: Comparative analysis between patients who achieved success with the treatment (hypo or euthyroidism) and those who remained with hyperthyroidism (failure) with toxic adenoma and toxic multinodular goiter

Variables	Success	Failure	*P*
Uninodular goiter			
Diameter of the functioning nodule pre-RIT (cm)	2.8 (2.20-3.50)	5.75 (4.60-5.75)	0.043
Pre-RIT uptake (%)	1.8 (0.92-3.35)	1.2 (0.69-1.2)	0.248
Pre-RIT TSH (IU/mL)	0.06 (0.01-0.82)	0.11 (0.01-0.11)	0.684
Multinodular goiter			
Thyroid volume pre-RIT (cm^3)	20.00 (13.00-73.50)	42.00 (19.00-106.00)	0.149
Pre-RIT uptake (%)	5.5 (2.30-11.0)	1.5 (0.43-2.60)	0.007
Pre-RIT TSH (IU/mL)	0.27 (0.15-4.10)	0.1 (0.10-1.92)	0.246

Data are shown as median (IQR). IQR: Interquartile range, RIT: Radioiodine therapy, TSH: Thyroid-stimulating hormone

Regression analysis of predictive factors for radioiodine therapy success

The model in univariate logistical regression analysis included the variables age, sex, years of disease until RIT, age at diagnosis, initial free T4, initial TSH, pre-RIT free T4, pre-RIT TSH, pre-RIT thyroid uptake of ^{99m}Tc-pertechnetate, number of functioning nodules, number of nodules, and larger diameter of the functioning nodule assessed by ultrasound. The initial FT4 (odds ratio [OR] =1.55; 95% confidence interval [CL] =0.98–2.47; $P = 0.063$), and uninodular toxic goiter versus multinodular toxic goiter (OR = 9.82; 95%CL = 2.26–42.74; $P = 0.002$) were the factors associated with RIT success. All other factors studied showed $P > 0.1$ in univariate analysis and therefore were not included in the multivariate model. Multiple logistic regression analysis (model included age, number of toxic nodules, and initial FT4) showed that the single toxic nodule was a predictor of treatment success (OR = 7.42, 95%CL = 1.64–33.7; $P = 0.009$).

DISCUSSION

In the present study, we found that a fixed 30 mCi (1110 MBq) ^{131}I-iodine dose efficiently treated TNG, reaching a global success rate of about 79% and 68.1% remaining euthyroid 1 year after RIT. The success rate was 92.3% in patients with a single nodule, while the group with multinodular goiter reached 55%, with 30.8% and 15% of them developing hypothyroidism, respectively. In addition, a smaller functioning nodule diameter was associated with a higher success rate in toxic adenoma. On the other hand, a higher pre-RIT ^{99m}Tc-pertechnetate uptake was associated with treatment success in TMG. Moreover, a single toxic nodule was found to be the main factor related to treatment success.

The best method to define a ^{131}I-iodine dose for TNG treatment is still a matter of debate. The fixed-dose approach has a lower cost and is easier to perform than the calculated method, and showed an excellent success rate in our study. In a prospective study that used the calculated dose to determine the therapeutic activity of ^{131}I, 94% of the patients with a single nodule and 89% with multinodular goiter reached resolution of hyperthyroidism within a year after the procedure;[13] however, this success rate is higher than those demonstrated in other institutions.[19,20] Other authors showed progression to hypothyroidism 1 year after RIT in up to 45% of the patients,[13] which is higher than the 25% rate verified in this study. Similar to previous studies with the calculated dose approach,[13] patients with a single nodule were younger at diagnosis and presented a higher success rate.

There is no consensus regarding the optimal dose of ^{131}I when considering the therapeutic efficacy, incidence of hypothyroidism, nodule size, the magnitude of pretreatment thyroid uptake, and previous use of antithyroid drugs.[12] Studies comparing the effectiveness of treating hyperthyroidism with a fixed-dose based on the gland size assessed only by palpation as opposed to a calculated dose of ^{131}I according to the type of disease (diffuse, multinodular, and solitary adenoma), thyroid volume, and 24-h ^{131}I uptake, demonstrated that the fixed approach, which is much simpler and of lower cost, is as good as the calculated dose approach for the treatment of nodular goiter.[21]

Previous studies have shown lower effectiveness with calculated dose in larger goiters (over 60 cc).[13] In addition, we found that the total thyroid volume was not a predictive factor for treatment success, as opposed to the size of functioning nodule in the single toxic adenoma group, which was significantly smaller in patients whose treatment was successful.

We verified that TSH was not a predictor of success, as has been shown by other authors.[22] Some protocols suggest an ideal TSH <0.1 IU/mL before RIT to minimize the potential damage induced by radiation to the surrounding thyroid parenchyma.[13,23] However, we did not find a relationship between pre-RIT TSH, above or below the lower limit of the

reference values, and the outcome 1 year after RIT. Besides, the frequency of hypothyroidism in patients with pre-RIT serum TSH levels above 0.4 IU/mL was not increased.

Higher ^{99m}Tc-pertechnetate uptake is widely accepted as a condition for a successful treatment with radioiodine.[24] Although controversial, some authors have shown that pretreatment uptake was inversely associated with posttreatment results.[25] In this study, a higher pre-RIT ^{99m}Tc-pertechnetate uptake was associated with a higher success rate only in the multinodular goiter group.

As for the pitfalls of this study, it was a retrospective study with a small casuistic analysis of a single-center, all our patients were evaluated with ^{99m}Tc-pertechnetate uptake instead of radioiodine uptake which only reflects NIS expression, and we did not assess the radiation absorbed dose. Another limitation was the use of total thyroid volume for patients with TMG instead of calculating the volume of all nodules separately; however, this value is often inaccurate, especially due to the difficulty in delimiting each nodule in both scintigraphy and ultrasonography images. One strong point of our study is that it was based on the execution of a defined treatment protocol with a fixed-dose and periodic monitoring of laboratory thyroid function and thyroid clinical evaluation in all patients after radioiodine therapy.

CONCLUSIONS

We demonstrated that a fixed 30 mCi (1110 MBq) ^{131}I-iodine dose was particularly effective for the treatment of single autonomously functioning nodule rather than the group with multiple nodules. In addition, single toxic nodules were evidenced as an independent predictor of treatment success. The administration of higher doses of ^{131}I-iodine, such as 40 or 50 mCi (1480 or 1850 MBq), could raise the rate of treatment success in patients with multinodular toxic goiter. Although, further studies are indispensable to confirm our results.

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Conflicts of interest

There are no conflicts of interest.

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