Thyroid volume is the key predictor of hyperthyroidism remission after RAIT in pediatric patients

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Research Article

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Abstract

Graves’ disease (GD) is the leading cause of hyperthyroidism in pediatric patients. Radioiodine therapy (RAIT) is widely used to treat GD, however, the predictors of efficacy of RAIT in childhood and adolescence are still not completely clear.

Our purpose was to determine the most significant predictors of efficacy of RAIT in pediatric patients.

The study enrolled 144 patients (124 females; 20 males) aged 8 to <18 years old who received the primary dosimetry-guided RAIT for GD. The parameters analyzed included gender, age, thyroid volume according to ultrasound examination before and 12 months after treatment, thyroid stimulating hormone (TSH), free triiodothyronine (FT3) free thyroxine (FT4), TSH receptor antibodies (TRAB) levels at baseline and twelve months after RAIT, 10-20-Min 99mTc thyroid uptake (%), maximum thyroid $^{131}$I uptake (%), specific $^{131}$I uptake (MBq/g) and therapeutic $^{131}$I activity (MBq). Fisher’s exact test, Mann-Whitney U-test, Wilcoxon signed–rank test, ROC–analysis and Youden index were used for statistical analysis.

Six months after RAIT, hypothyroidism was achieved in 119 (82.6%) patients, euthyroid state was achieved in 6 (4.2%), and hyperthyroidism persisted in 19 (13.2%). Thyroid volume decreased from 17.6 [14.6; 24.1] to 9.25 [7.62; 13.34] mL 12 months after the treatment (p<0.001). The main predictor that showed a statistically significant difference between the groups of patients who achieved and did not achieve remission of GD hyperthyroidism after RAIT was the initial thyroid volume. Using Youden index the optimal cut-off point of the initial thyroid volume in 45.4 ml was determined.

Conclusion: The efficacy of the dosimetry-guided RAIT in pediatric patients with GD was 82.6% after 12 months, and one of the major predictors of RAIT success was an initial smaller thyroid volume.

What Is Known

- Radioiodine therapy is a common, effective and safe treatment for children with Graves’ disease.

What is New:

- One of the most important predictors of the onset of hypothyroidism after radioiodine therapy is the initial volume of the thyroid gland in a child. In patients with a thyroid volume of less than 45.4 ml, radioiodine therapy may be the preferred treatment.

Introduction

Hyperthyroidism is an actual problem in pediatric endocrinology. The most common cause of hyperthyroidism in children and adolescents is Graves’ disease (GD). The highest incidence is in the ages of 10–15 years, with a strong female predominance. Hyperthyroidism is well treated with antithyroid drugs (ATDs). However, studies show that only about 30% of pediatric patients achieve long-term remission after 2 years of ATDs therapy [1]. Radioiodine therapy (RAIT) is a safe, effective and widely
used treatment for hyperthyroidism. However, up to now there are no accurate predictive factors of successful RAIT in pediatric patients. In the present study, we report our own experience of treating pediatric patients with Graves hyperthyroidism by dosimetry-guided RAIT. We analyzed the efficacy of the RAIT and also identified the predictive parameters of treatment success.

**Methods**

The prospective, nonrandomized, single-centre explorative study was conducted between 2016 and 2021 at the Endocrinology Research Center (ERC), Moscow, Russia.

**Patient examination**

All patients underwent clinical, hormonal and instrumental examination. Basic anthropometric (sex, age, height, weight, body mass index) and anamnestic data were collected. Clinical and hormonal examination included determination of the serum levels of thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4) and TSH receptor antibodies (TRAB). Hormonal analysis was performed in the hormonal analysis laboratory using an ARCHITECT i2000 immunoassay analyzer (ABBOTT).

Instrumental examination included thyroid ultrasound and thyroid scintigraphy. Thyroid ultrasound was performed with a Toshiba Aplio 500, PLT-I204BX 7–18 MHz linear transducer; Aloka prosound alpha 10, UST-5543 4–13 MHz linear transducer; Accuvix A 30, L5-13IS 5–13 MHz linear transducer; Medison SonoAce R5, LN5-12 5.0–12.0 MHz linear transducer; Esaote MyLab 20, LA523 4–13 MHz linear transducer. The ultrasonography was performed in the standard position of the patient lying on the back with the head tilted back and a roller placed under the shoulders. Thyroid was scanned in B-mode and using color-Doppler mapping. We measured three dimensions of both thyroid lobes (length - width - anteroposterior dimension) to calculate thyroid volume according to J. Brunn formula, 1981. Thyroid structure, degree of echogenicity decrease and vascularization increase, presence of nodular neoplasms were assessed.

Thyroid scintigraphy with 99mTc pertechnetate radiopharmaceutical was performed using Discovery NM630 and Discovery NM/CT670 gamma-cameras at the ERC. Radiopharmaceutical (RP) dose was calculated individually using PedDose calculator ([https://www.eanm.org/publications/dosage-calculator](https://www.eanm.org/publications/dosage-calculator)) in [MBq] and [mCi]. Scintigraphy was performed 15–20 min after the RP administration. Subsequently, the functional state of the thyroid was evaluated.

**Dosimetry-guided RAIT**

Dosimetry planning was performed as prescribed by a radiologist using Discovery NM630 SPECT system with the administration of tracer $^{131}$I activity (from 5 to 10 MBq), Patent for Invention № 2722568. Scintigraphy was performed after 2 hours in the "Whole body" mode and after 24 hours in the "Static" mode. The procedure included determining 24-hour $^{131}$I uptake ratio [%], clarification of the thyroid lobes.
volume by scintigraphic signs using the formula $0.163 \times (0.785 \times \text{width of right lobe (cm)} \times \text{length of right lobe (cm)})^{(3/2)}$, calculating thyroid tissue absorbed dose [Gy/h] for 24 hour upon the administration of the proposed therapeutic ablative activity.

RAIT was conducted in the "Active Wards" block in the Department of Nuclear Medicine of ERC. A concilium was held to prescribe therapeutic activity with the involvement of radiologists, pediatric endocrinologists, oncologists, and medical physicists. The patient's medical history, current hormonal profile, specific activity of $^{131}\text{I}$, 99mTc-pertechnetate uptake ratio, response to reduced ATD dosage, presence of Graves' orbitopathy (GO), and presence of contraindications to the treatment were taken into account. Prescribed $^{131}\text{I}$ activity was administered orally in both liquid and encapsulated form, depending on the patient's wishes; the pre-packaging error amounted to 4.2%. Inpatient meal had minimal iodine content. When the acceptable level of exposure rate of an equivalent dose at a distance of 1 meter from the patient's body surface was reached, the patient was discharged.

**Statistical analysis**

Data were statistically processed using IBM SPSS Statistics v.23.0 (IBM, USA, 2015), MedCalc Statistical Software version 20.104 (MedCalc Software bvba, Belgium, 2021).

The distributions of quantitative features are presented as medians and interquartile range (1 and 3 quartiles) - Me [Q1; Q3]. Mann-Whitney $U$-criterion was applied to compare quantitative data differences between two independent groups. Qualitative data are presented as absolute (n) and relative (%) frequency.

The parameters that showed statistically significant differences in univariate analysis were chosen as predictors of hyperthyroidism remission after RAIT. Optimal threshold values for quantitative parameters were assessed by calculating the Receiver Operating Characteristic (ROC) curve and the Youden index. Qualitative variables in independent groups were compared using Fisher's exact test.

A type 1 error rate (less than 5%, $p < 0.05$) was considered statistically significant.

**Ethics**

The study protocol was approved by the local ethical committee of the ERC, protocol No.1 on 2016. Parents or legal guardians of the patients voluntarily signed an informed consent to participate in the study.

**Results**

Our study included 144 children. All patients were diagnosed with Graves' disease.

Table 1 shows the baseline characteristics of the patients.
Table 1
Baseline characteristics of the patients who underwent Radioiodine therapy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>14.3 [12.1; 17.5]</td>
</tr>
<tr>
<td>Sex, male:female</td>
<td>124 (86.1%): 20(13.9%)</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.61 [1.55; 1.68]</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>54 [47; 60]</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>20.7 [18.7; 22.3]</td>
</tr>
<tr>
<td>Duration of ATDs therapy, months</td>
<td>31.0 [18.0; 52.0]</td>
</tr>
<tr>
<td>Thyroid volume, cm³</td>
<td>20.3 [15.8; 31.0]</td>
</tr>
<tr>
<td>TSH</td>
<td>0.031 [0.006; 0.992]</td>
</tr>
<tr>
<td>FT4</td>
<td>13.1 [8.2; 14.5]</td>
</tr>
<tr>
<td>FT3</td>
<td>5.6 [4.0; 8.1]</td>
</tr>
<tr>
<td>TRABs</td>
<td>9.4 [3.0; 18.2]</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>10 [8.95; 14.65]</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>2.73 [1.95; 2.99]</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.23 [1.10; 1.55]</td>
</tr>
<tr>
<td>total cholesterol, mmol/L</td>
<td>4.32 [3.63; 4.65]</td>
</tr>
<tr>
<td>triglycerides, mmol/L</td>
<td>0.76 [0.52; 1.02]</td>
</tr>
</tbody>
</table>

Notes: BMI – body mass index; ATD – antithyroid drugs; TSH – thyroid stimulating hormone; FT3 – free triiodothyronine; FT4 – free thyroxine; TRABs – TSH receptor antibodies; LDL – low-density lipoproteins; HDL – high-density lipoproteins.

MAIN RESULTS OF THE STUDY

Following 12 months after the treatment, hypothyroidism was achieved in 119 (82.6%) patients, euthyroid state was achieved in 6 (4.2%), and hyperthyroidism persisted in 19 (13.2%). Table 2 presents comparative characteristics of the patient group with hypothyroidism and group with euthyroid state or hyperthyroidism 12 months after RAIT.
Table 2
Comparative baseline characteristics of the group of patients with hypothyroidism 12 months after the Radioiodine therapy and the group that did not respond to the treatment

<table>
<thead>
<tr>
<th>Predictors</th>
<th>All</th>
<th>Hypothyroidism</th>
<th>Hyperthyroidism/Euthyroid state</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>144 (100%)</td>
<td>119 (82.6%)</td>
<td>25 (17.4%)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>0.415</td>
</tr>
<tr>
<td>Male</td>
<td>20 (13.9%)</td>
<td>17 (14.3%)</td>
<td>3 (12%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>124 (86.1%)</td>
<td>102 (85.7%)</td>
<td>22 (88%)</td>
<td></td>
</tr>
<tr>
<td>Age(^1)</td>
<td>14.3 [12.1; 17.5]</td>
<td>14.5 [11.1; 18.2]</td>
<td>14.1 [11.8; 17.1]</td>
<td>0.675</td>
</tr>
<tr>
<td>Thyroid volume, ml(^1)</td>
<td>20.3 [15.8; 31.0]</td>
<td>18.5 [15.6; 25.1]</td>
<td>46.8 [39.8; 49.8]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Duration of ATDs therapy, months(^1)</td>
<td>31.0 [18.0; 52.0]</td>
<td>33.0 [21.0; 49.4]</td>
<td>26.2 [14.8; 58.0]</td>
<td>0.387</td>
</tr>
<tr>
<td>FT4, pmol/l(^1)</td>
<td>13.1 [8.2; 14.5]</td>
<td>14.1 [9.8; 19.1]</td>
<td>10.2 [5.3; 13.2]</td>
<td>0.021</td>
</tr>
<tr>
<td>FT3, pmol/l(^1)</td>
<td>5.6 [4.0; 8.1]</td>
<td>5.1 [4.2; 6.9]</td>
<td>5.8 [4.0; 10.1]</td>
<td>0.528</td>
</tr>
<tr>
<td>TSH, U/L(^1)</td>
<td>0.031 [0.006; 0.992]</td>
<td>0.030 [0.012; 1.230]</td>
<td>0.049 [0.006; 0.489]</td>
<td>0.513</td>
</tr>
<tr>
<td>TRABs, U/L(^1)</td>
<td>9.4 [3.0; 18.2]</td>
<td>7.0 [2.9; 15.5],</td>
<td>27.0 [5.1; 42.3]</td>
<td>0.041</td>
</tr>
<tr>
<td>99mTc-pertechnetate uptake, %(^1)</td>
<td>0.17 [0.09; 0.22]</td>
<td>0.12 [0.07; 0.19]</td>
<td>0.29 [0.12; 0.40]</td>
<td>0.048</td>
</tr>
<tr>
<td>Therapeutic(^1)131I activity (MBq)(^1)</td>
<td>882 [744; 1084]</td>
<td>871 [742; 1030]</td>
<td>1060 [784; 1155]</td>
<td>0.201</td>
</tr>
<tr>
<td>Maximum thyroid(^1)131I uptake, %(^1)</td>
<td>0.42 [0.39; 0.50]</td>
<td>0.45 [0.35; 0.50]</td>
<td>0.47 [0.44; 0.54]</td>
<td>0.090</td>
</tr>
<tr>
<td>Specific(^1)131I uptake (MBq/g)(^1)</td>
<td>13.2 [10.5; 15.8]</td>
<td>13.8 [12.6; 16.4]</td>
<td>10.3 [7.5; 12.4]</td>
<td>0.01</td>
</tr>
</tbody>
</table>

\(^1\)Data are presented as median and interquartile range

ATD – antithyroid drugs; TSH – thyroid stimulating hormone; FT3 – free triiodothyronine; FT4 – free thyroxine; TRABs – TSH receptor antibodies.
The decrease in thyroid volume 12 months after RAIT varied from 11.8–94.4% (70.6 [56.4; 83.1] %); the volume decrease was statistically significant (p < 0.001, Fig. 1).

No statistically significant changes in TRABs levels were observed after 12 months (baseline: 9.4 [3.0; 18.2] U/L; after 12 months: 11.4 [4.4; 28.5] U/L; p = 0.371).

After the Bonferroni correction, the FT4 level and the value of the 99mTc-Pertechnetate uptake as well as the $^{131}$I specific uptake showed only a statistical trend. The predictor that showed a statistically significant difference between the groups of patients who achieved and did not achieve remission of hyperthyroidism after RAIT was the initial volume of the thyroid.

ROC-analysis was performed for the baseline value of thyroid volume (Fig. 2).

Using Youden index the optimal cut-off threshold for the value of initial thyroid volume was determined, which amounted to 45.4 ml. The sensitivity of the method was 96.64% (95% CI 91.6–99.1), specificity was 92.00% (95% CI 74.0–99.0).

**Discussion**

Therefore, the main factor influencing the possibility of hyperthyroidism remission after RAIT is the volume of the thyroid prior to the treatment. The ROC-analysis and Youden index were used to determine that the RAIT is most effective when the thyroid volume is less than 45.4 ml.

There are several studies in the literature that have examined possible predictors of hyperthyroidism remission after RAIT.

Thyroid volume, that was assigned to hypothyroid status after RAIT, mostly depends on limits of activity that are allowed in medical practice. On the other hand we have publications that observe high 131-I activity treatment in patients up to 250 ml thyroid volume.

The prospective study of RAIT efficacy in 55 child group was done in Endocrinology research centre, that shown 81.8% hypothyroid status, 3.6% euthyroid status and 14.6% hypothyroid status on the 6th month of follow up. Age was an effective predictor OR = 1.305 (CI: 1.063–1.602) [2].

Allahabadia et al reported that 813 adult patients who received 10 mCi had a higher remission rate (85%) than those who received 5 mCi (67%). Men had a lower rate of achieving the treatment goal than women, and patients under 40 years of age had a lower rate than those over 40 years of age [3].

Aung et al analyzed 655 cases of RAIT for GD over a 10-year period, including 89 repeat courses, and reported that 12 months after the first RAIT, 77% of patients had hypothyroidism, 17% had persistent hyperthyroidism, and 6% had euthyroid state, similarly to our results. Higher FT4 levels at the time of diagnosis (rather than prior to RAIT) were a prognostic sign of treatment failure. At the same time, at higher levels of TRABs (> 40), the rate of RAIT failure was 42%, compared with 12% for patients with an
TRABs level of less than 10. In addition, performing RAIT within 6 months of diagnosis had a failure rate of 11% compared to 23% for those patients who received RAIT more than 6 months after diagnosis [4].

Because of the lower incidence of hyperthyroidism in the pediatric age group, there are a few studies of RAIT outcomes in this population. The largest study involved 304 patients with an average age of 15.6 years at the time of diagnosis, 136 of whom received $^{131}$I at a dose of 200 µCi/g. Hypothyroidism was achieved in 66% of cases. Patients who achieved hypothyroidism were significantly older. In a study of 27 patients who received RAIT, 45% still had hyperthyroidism 6 months after treatment with the 150 µCi of $^{131}$I/g of thyroid tissue, 41% had hypothyroidism and 15% had euthyroid state. Gender, age, thyroid weight (did not specify how it was measured), and total treatment dose were not the predictors of the outcome [5]. A study of 22 patients who received RAIT at a dose of 100 µCi of $^{131}$I/g of thyroid tissue showed that 27% of patients remained hyperthyroid and needed a second course of treatment. The average time to achieve hypothyroidism after the RAIT was 3 months. The authors found no differences in outcomes depending on age, $^{131}$I dose, thyroid size, and duration between diagnosis of GD and RAIT [6].

Our study found no effect of gender, age or duration of hyperthyroidism prior to RAIT on achieving hypothyroidism, which is consistent with some but not all of the studies cited previously. However, we found an effect of thyroid volume on the treatment outcome. The average thyroid volume determined by ultrasound was significantly higher in the case of 25 patients who had hyperthyroidism/euthyroid state after RAIT compared with 119 patients who achieved hypothyroidism (p < 0.0001).

**Conclusion**

RAIT is an effective and safe treatment option for patients with GD. Thyroid size is the most significant predictor of hyperthyroidism remission within one month after RAIT. Meanwhile, there are other factors that may influence the achievement of hypothyroidism. Further studies are needed to determine them.

**Abbreviations**

ATDs
antithyroid drugs
BMI
body mass index
ERC
Endocrinology Research Center
FT3
free triiodothyronine
FT4
free thyroxine
GD
Declarations

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Disclosure of interest. The authors declare that they have no competing interests.

Authors’ contribution.

Marina Sheremeta proposed the idea of the research. The data were collected, analyzed and interpreted by Marina Sheremeta, Alexey Trukhin, Elena Nagaeva, Olga Bezlepkina and Valentina Peterkova. Marina Sheremeta, Alexey Trukhin, Elena Nagaeva, Olga Bezlepkina and Valentina Peterkova drafted the manuscript. Maria Korchagina translated the manuscript. All authors gave final suggestions and contributed to the final approval of the manuscript.

Ethics approval

The study protocol was approved by the local ethical committee of the ERC, protocol No.1 on 2016.

Consent to participate

Informed consent was obtained from the parents and legal guardians.

Consent to publish

N/A
References


Figures
**Figure 1**

Change in thyroid volume within 12 months after Radioiodine therapy.
Figure 2

ROC analysis for baseline thyroid volume before Radioiodine therapy.

AUC = 0.981
P < 0.001